Regional Cerebral Blood Flow Response to Hypocapnia in the Contralateral Hemisphere of Patients With Acute Cerebral Infarction

BY ELDAD MELAMED, M.D., SYLVAN LAVY, M.D., AND ZIPPORA PORTNOY, M.SC.

Abstract: The rCBF response to hypocapnia induced by active short-term hyperventilation was determined in the contralateral hemispheres of ten patients with acute unilateral cerebral infarction. Overall rCBF reduction occurred in only two patients. Regional or widespread abnormal responses to Paco2 reduction manifested as either no change or a paradoxical increase in the rCBF were observed in eight patients. The hemispheric mean rCBF reduction following hypocapnia was diminished as compared with control subjects. Our findings suggest that an impairment of the chemical control of rCBF may occur in the non-infarcted hemisphere during the early period following the onset of cerebral infarction. The pathophysiological mechanisms which may underlie this abnormal rCBF reactivity to Paco2 reduction are considered.

Introduction

Several studies have shown that in patients with unilateral cerebral infarction, the regional cerebral blood flow (rCBF) may be reduced not only in the infarcted hemisphere but in the contralateral one as well. Abnormalities in the homeostatic mechanisms may occur in the infarcted hemispheres of experimental animals and man and are well documented. They include loss of autoregulation and disruption of the chemical control, i.e., the normal cerebrovascular reactivity to Paco2 changes. However, little is known about the regulation of the rCBF in the non-infarcted hemisphere. Loss of autoregulation in the opposite hemisphere has been demonstrated in a small number of patients with cerebral infarction. On the other hand, the normal rCBF reactivity to Paco2 changes was found to be preserved in the non-affected hemisphere of experimental animals with unilateral cerebral ischemia. Lack of data seems to indicate that this subject warrants further study. The present study therefore was undertaken to investigate the rCBF reactivity to Paco2 changes in the contralateral hemispheres of patients with acute cerebral infarction. It was determined by the rCBF response to hypocapnia induced by a short period of active hyperventilation.

Methods

Ten patients hospitalized with acute unilateral cerebrovascular accident in the territory of the internal carotid arterial system were studied. Their ages ranged from 42 to 69 years, with a mean of 57.5 years. There were six men and four women. In each patient the diagnosis of unilateral cerebral infarction was established on the basis of the history, careful neurological examination, lumbar puncture, serial EEG recordings, and Tc99m brain scans. Cerebral angiograms were performed in three cases and disclosed internal carotid artery occlusion in two patients (Cases 2 and 7 — table 1) and middle cerebral artery occlusion in one patient (Case 1 — table 1). No evidence of previous or present ischemic involvement of the opposite hemisphere was found in any of the patients.

rCBF was determined over the hemisphere contralateral to the cerebral infarction. The study was performed as closely as possible, and within 72 hours following the onset of the acute stroke. At the time of the measurement none of the patients were stuporous or in coma. The patients were unanesthetized and no premedication had been administered. The method used was that of the intracarotid injection of 133Xe. The clearance of the radioisotope was followed by 15 to 22 scintillation detectors applied externally over the studied hemisphere. Mean arterial blood pressure was measured and arterial blood samples for Paco2 and pH determinations were drawn immediately prior to each injection of the radioisotope. The initial slope, two minutes' rCBF, was computerized and adjusted to hemoglobin levels.

The normal rCBF values obtained in our laboratory are: 55 ± 5 ml/100 gm/min for those aged below 50; 50 ± 5 ml/100 gm/min for the 50 to 59 age group, and 40 ± 4 ml/100 gm/min for those above 60.

The first rCBF measurement was carried out in the resting state. After an interval of 15 minutes, a second study was performed, following two to three minutes of active hyperventilation.

The same study was performed in eight control subjects.
Resting Hemispheric Mean rCBF and CVR in the Non-Infarcted Hemisphere

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/sex</th>
<th>Resting Paco₂ (mm Hg)</th>
<th>Hemispheric mean rCBF (ml/100 gm/min)</th>
<th>% reduction from normal rCBF levels*</th>
<th>CVR mm Hg (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56 M</td>
<td>30</td>
<td>26.1</td>
<td>42.0</td>
<td>3.56</td>
</tr>
<tr>
<td>2</td>
<td>68 M</td>
<td>34</td>
<td>27.6</td>
<td>23.3</td>
<td>4.56</td>
</tr>
<tr>
<td>3</td>
<td>65 F</td>
<td>31</td>
<td>28.6</td>
<td>20.6</td>
<td>3.50</td>
</tr>
<tr>
<td>4</td>
<td>69 M</td>
<td>33</td>
<td>17.8</td>
<td>50.6</td>
<td>6.74</td>
</tr>
<tr>
<td>5</td>
<td>53 M</td>
<td>42</td>
<td>32.6</td>
<td>27.6</td>
<td>4.69</td>
</tr>
<tr>
<td>6</td>
<td>53 F</td>
<td>36</td>
<td>33.2</td>
<td>26.3</td>
<td>2.77</td>
</tr>
<tr>
<td>7</td>
<td>44 F</td>
<td>37</td>
<td>33.1</td>
<td>33.8</td>
<td>2.81</td>
</tr>
<tr>
<td>8</td>
<td>64 F</td>
<td>37</td>
<td>51.8</td>
<td>W.N.L.†</td>
<td>2.45</td>
</tr>
<tr>
<td>9</td>
<td>42 M</td>
<td>32</td>
<td>50.7</td>
<td>W.N.L.†</td>
<td>3.02</td>
</tr>
<tr>
<td>10</td>
<td>61 M</td>
<td>43</td>
<td>39.7</td>
<td>W.N.L.†</td>
<td>3.45</td>
</tr>
<tr>
<td>Mean values</td>
<td>57.5</td>
<td>35.5</td>
<td>34.1</td>
<td>—</td>
<td>3.76</td>
</tr>
</tbody>
</table>

*Degree of reduction from lowest limit of normal rCBF levels, matched for age.
†Within normal limits.
‡Mean values calculated from measurements in eight control subjects.

with no evidence of organic cerebral disease. Their ages ranged from 38 to 65, with a mean of 51 years.

Cerebrovascular resistance (CVR) was calculated as the ratio between the mean arterial blood pressure (MABP) and the hemispheric mean rCBF. This is an approximation since the intracranial pressure and, therefore, the cerebral perfusion pressure could not be determined at the time of the study. However, in none of the patients was there any evidence of increased intracranial pressure. The MABP levels ranged from 92 to 153 mm Hg. No significant differences were observed between the MABP levels in the resting state and following hyperventilation in either the patients or the control groups.

Results
The results obtained are presented in tables 1 and 2 and in figures 1 and 2. In seven patients, the resting hemispheric mean rCBF was found to be reduced in the hemisphere contralateral to the cerebral infarc-

Post-Hyperventilation rCBF Alterations in the Non-Infarcted Hemisphere

<table>
<thead>
<tr>
<th>Case No.</th>
<th>ΔPaco₂ (mm Hg)</th>
<th>Hemispheric mean rCBF (ml/100 gm/min)</th>
<th>% rCBF*</th>
<th>% rCBF†</th>
<th>Post-hyperventilation regional alterations‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>23.8</td>
<td>-8.9</td>
<td>-0.74</td>
<td>Regional increase</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>28.3</td>
<td>+2.5</td>
<td>+0.19</td>
<td>Global increase or no change</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>27.6</td>
<td>-3.5</td>
<td>-0.43</td>
<td>Regional increase or no change</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>14.8</td>
<td>-16.9</td>
<td>-1.53</td>
<td>Regional increase or no change</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>21.3</td>
<td>-34.7</td>
<td>-1.73</td>
<td>Global reduction</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>33.6</td>
<td>+1.2</td>
<td>+0.80</td>
<td>Global increase or no change</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>37.0</td>
<td>+11.7</td>
<td>+1.46</td>
<td>Global increase</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>44.6</td>
<td>-13.9</td>
<td>-1.26</td>
<td>Regional no change</td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>50.9</td>
<td>+0.4</td>
<td>-0.03</td>
<td>Global increase</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>28.6</td>
<td>-28</td>
<td>-1.4</td>
<td>Global reduction</td>
</tr>
<tr>
<td>Mean values</td>
<td>13</td>
<td>31.05</td>
<td>—</td>
<td>-0.46§</td>
<td>—</td>
</tr>
<tr>
<td>Control**</td>
<td>15</td>
<td>28.5</td>
<td>-35</td>
<td>-2.48</td>
<td>Global reduction</td>
</tr>
</tbody>
</table>

*Degree of post-hyperventilation hemispheric mean rCBF reduction or increase from resting hemispheric mean rCBF.
†Degree of rCBF reduction or increase per 1 mm Hg reduction of Paco₂.
‡Regional — limited rCBF alterations. Global — widespread or whole hemispheric rCBF alterations.
§Calculated from all values.
‖Calculated only from those showing rCBF reduction.
**Mean values calculated from measurements in eight control subjects.
by hyperventilation, a global homogeneous rCBF reduction occurred over the entire non-infarcted hemisphere in only two patients (fig. 1). This normal type of response to Paco, decrease was observed in the hemispheres of all control subjects. In the other eight patients, abnormal responses were noted, i.e., the hypocapnia induced no change and/or a paradoxical increase in the rCBF. In four patients, the abnormal response occurred only in limited hemispheric areas, while the other regions showed a rCBF decrease. In the remaining four patients, the abnormal reaction to Paco, reduction was more widespread and even global, taking place over the major part of, or the entire, non-infarcted hemisphere (fig. 2, table 2).

No significant differences were found between the resting rCBF values measured from the areas which later showed reduction, no change, or paradoxical increase in rCBF in response to hypocapnia.

**Discussion**

Arterial Paco, is an important factor in the control and regulation of the rCBF. Thus, hypocapnia reduces the cerebral vascular resistance and leads to cerebral vasodilatation and increased rCBF, whereas hypocapnia induces a CVR increase with cerebral vasoconstriction and rCBF reduction. These responses to Paco, alterations are believed to be mediated through pH changes in the cerebral arteriolar walls.

The normal circulatory response to a short period of active hyperventilation which lowers the arterial CO2 tension is an overall rCBF reduction. In the present study, this normal type of rCBF reactivity was observed in the hemispheres of all of the control subjects. However, it was demonstrated in the contralateral hemisphere of only two patients with unilateral cerebral infarction. In eight patients, the rCBF response to hyperventilation-induced hypocapnia was found to be impaired in the non-infarcted hemispheres. There was no change and/or paradoxical increase in the rCBF which was either regional or widespread in the latter group of patients.

Considering the hemispheric mean rCBF values, it was demonstrated that the responsiveness of the cerebral vasculature to Paco, reduction was diminished in the non-infarcted hemisphere of our patients as compared with that of the control subjects. This is due, in part, to the inclusion of the regional abnormal responses in the calculation of the hemispheric mean rCBF. However, several additional factors are known to affect the Paco,-rCBF relationship. Absent or reduced response of the rCBF to acute changes in Paco, have been demonstrated in patients with low MABP levels. In the present series, however, these levels were either normal or high.

The level of the resting rCBF is important in the cerebrovascular reactivity to Paco, changes. Thus, at a lower baseline rCBF, smaller change in rCBF occurs with an acute reduction in Paco,. This is probably due to a state of vasoconstriction with increased cerebrovascular resistance which exists at lower rCBF levels. The mechanical constriction of the cerebral vessels limits further rCBF reduction in response to hypocapnia. Diminished rCBF responsiveness to acute Paco, decrease also has been found to be associated with low cerebral metabolic rate. Reduced cerebral metabolic rate, increased cerebrovascular resistance, and low baseline rCBF may provide, therefore, an explanation for the diminished rCBF response to hypocapnia observed in the non-infarcted hemispheres. The pathophysiological mechanism inducing a paradoxical rCBF increase in the contralateral hemisphere following acute Paco, reduction in some of our patients, however, is less clear. Furthermore, no significant differences were found between the resting rCBF values measured from hemispheric areas which later showed rCBF increase or decrease in reaction to the hypocapnia. It is evident therefore that the type of regional vascular reactivity to Paco, reduction was not dependent on the pre-hyperventilation rCBF levels.

Cerebral anoxia is known to occur during hypocapnic hyperventilation as a result of cerebral vasoconstriction with rCBF reduction and a shift of the oxyhemoglobin dissociation curve to the left with impairment of oxygen transfer to the cerebral tissue. Paco, reduction is accompanied by a decreased aerobic and increased anaerobic utilization of glucose. Also, in experimental animals, hyperventilation has been associated with a rise of lactic acid concentration in the cerebrospinal fluid and brain tissues. It is possible that in some of our patients a state of brain tissue hypoxia and attendant acidosis was already present in the non-infarcted hemisphere as a result of low baseline rCBF. During the first stage of hyperventilation, the Paco, reduction may have led to further cerebral vasoconstriction and rCBF decrease with aggravation of the brain tissue hypoxia and acidosis. This would result in reduction of the pH in the arteriolar walls with vasodilatation during the later stages of the hyperventilation reflected as no change, or as a paradoxical increase in rCBF. The regional or widespread abnormal responses to the hypocapnia may have been dependent on the degree of the pre-hyperventilation hypoxia in the various regions of the non-infarcted hemisphere. This is probably not the sole mechanism since it is difficult to explain the occurrence of abnormal responses to hypocapnia in the two patients (Cases 8 and 9) with normal baseline rCBF in their non-infarcted hemispheres.
Paulson et al. demonstrated loss of autoregulation in the contralateral hemispheres of two patients, five and six days respectively, after the onset of cerebral infarction, with a normal rCBF response to hypocapnia. Furthermore, the impaired autoregulation was found to be restored during the hypocapnia. These findings suggested a state of "dissociated vasoparalysis" — loss of autoregulation with preserved chemical control in the non-infarcted hemisphere. It seemed, therefore, that autoregulation is the most sensitive mechanism in the regulation of cerebral blood flow and is more readily impaired than the chemical control. Our study, however, was performed during the early stages of the stroke and no later than three days after its onset. It is possible that the observed abnormal rCBF response to hypocapnia is, indeed, transient and limited to this early period. All of these data suggest that a state of "complete vasoparalysis" may be present in the contralateral hemispheres of some patients soon after the onset of acute cerebral infarction. Further studies of the autoregulation and additional aspects of the chemical control in the non-infarcted hemisphere are needed in order to substantiate this hypothesis. Meanwhile, our findings constitute additional evidence that the contralateral hemisphere is involved in the circulatory abnormalities caused by cerebral infarction.

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References

31. Gote J: The influence of oxygen affinity of blood and...
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Overall rCBF reduction in response to hyperventilation-induced hypocapnia.

Following a short period of hyperventilation inducing a Paco decrease, a reduction in the hemispheric mean rCBF occurred in six patients, whereas an increase was noted in four (table 2). Since various degrees of Paco changes were achieved by this procedure in the various patients, calculation of the degree of rCBF alteration per 1 mm Hg reduction of Paco offers a better basis for comparing the results. It follows that in four patients there was a post-hyperventilation mean rCBF increase ranging from 0.03% to 1.46% per 1 mm Hg of Paco, decrease. In six patients, a post-hyperventilation mean rCBF decrease ranging from 0.74% to 1.73% per 1 mm Hg of Paco, reduction was noted (table 2). If values from all of the patients are considered, the mean post-hyperventilation CBF change per 1 mm Hg of Paco, decrease is —0.46%. If the four patients showing post-hyperventilation CBF increase are excluded from the calculation, the mean change was —1.18% per 1 mm Hg of Paco, decrease. On the basis of either calculation, it is evident that the mean rCBF response to hyperventilation in the hemisphere contralateral to the cerebral infarction is much lower than the one obtained for the control group which was —2.48% per 1 mm Hg of Paco, reduction (table 2).

If the individual regional flow values are considered, it appears that following hypocapnia induced


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