The Relation Between Cerebral Oxygen Consumption and Cerebral Vascular Reactivity to Carbon Dioxide

BY MASATOSHI FUJISHIMA, M.D., PERITZ SCHEINBERG, M.D., RAUL BUSTO, B.S., AND OSCAR M. REINMUTH, M.D.

Abstract: The mechanisms whereby CO₂ affects cerebral vessels are not as simple as once thought, and are probably both directly on cerebral vascular walls and indirectly by action on brain stem neurones. Furthermore, cerebral vascular reactivity to CO₂ has been reported to be altered by a number of physiological and pathological circumstances. The capacity to dilate to increased PaCO₂ is decreased in cerebral vascular lesions, and is affected by changes in cerebral perfusion pressure. Cervical sympathectomy is said to increase CBF response to PaCO₂ changes, whereas sympathetic nerve stimulation abolishes reactivity to CO₂. Deep anesthesia, hypothermia, or trauma to brain reduces reactivity to cerebral vessels to CO₂, the one common denominator for these states being reduced cerebral metabolism. This report demonstrates that the capacity of cerebral vessels to dilate or constrict in response to changes in PaCO₂ is influenced by cerebral oxygen consumption.

ADDITIONAL KEY WORDS: brain stem neurones, autonomic pathways, cerebral anaerobic metabolism, [¹³¹] iodo-antipyrine, senile dementia, cerebral seizures

The influence of brain metabolism on cerebral vascular reactivity to increased PaCO₂ was observed in 31 human subjects and 35 dogs. Absolute and relative indices of CBF responsivity to CO₂ were correlated with the level of CMRO₂. It was concluded that this is further confirmation that the action of CO₂ on cerebral circulation cannot be only a direct one upon cerebral arteries, for this effect should be independent of CMRO₂. The action of CO₂ on the brain stem secondarily influencing CBF cannot be a consequence of increased cortical neuronal metabolism, for this is not observed during CO₂ inhalation. It is suggested that the CO₂ action on the brain stem may influence cerebral vessels indirectly through autonomic pathways.

Methods
HUMAN EXPERIMENTS
Thirty-one patients with a variety of disease states were studied. None had clinical evidence of brain stem disease. Twenty of the patients had symptomatic cerebral vascular disease and had been studied angiographically. The diagnosis of senile dementia had been made in ten patients and cerebral seizures of unknown etiology in one. They were divided into four groups, ranging from greatly reduced (Group 1) to normal (Group 4) values for cerebral oxygen consumption (CMRO₂). There were six patients in Group 1, 13 in Group 2, eight in Group 3, and four in Group 4. Mean ages were 64, 58, 61, and 51 years respectively.

Cerebral blood flow (CBF) was measured by...
### TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>No. of determinations</th>
<th>Control (6)</th>
<th>CO₂ (8)</th>
<th>Control (13)</th>
<th>CO₂ (14)</th>
</tr>
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</tr>
<tr>
<td>CMRO₂ (ml O₂/min)</td>
<td>19.5 ± 1.3</td>
<td>16.3 ± 1.3</td>
<td>26.3 ± 0.5</td>
<td>27.1 ± 1.0</td>
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<tr>
<td>CBF (ml/min)</td>
<td>339 ± 22</td>
<td>441 ± 35</td>
<td>401 ± 26</td>
<td>592 ± 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>118 ± 8</td>
<td>129 ± 9</td>
<td>106 ± 5</td>
<td>118 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVR (mm Hg/ml/min)</td>
<td>35.8 ± 1.6</td>
<td>31.9 ± 1.2</td>
<td>27.6 ± 2.5</td>
<td>22.8 ± 2.6</td>
<td></td>
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<tr>
<td>Paco₂ (mm Hg)</td>
<td>37.4 ± 1.6</td>
<td>43.5 ± 1.0</td>
<td>37.3 ± 1.2</td>
<td>45.7 ± 1.1</td>
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<tr>
<td>ApH</td>
<td>7.436 ± 0.011</td>
<td>7.386 ± 0.011</td>
<td>7.437 ± 0.017</td>
<td>7.366 ± 0.012</td>
<td></td>
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<tr>
<td>(A-V)O₂ (vol. %)</td>
<td>5.82 ± 0.28</td>
<td>3.81 ± 0.38</td>
<td>6.86 ± 0.39</td>
<td>5.28 ± 0.49</td>
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</tr>
</tbody>
</table>

| ΔCBF/ΔPaco₂ (ml/min/mm Hg) | 15.9 ± 3.2 | 21.5 ± 3.7 |
| ΔCBF/cCBF/ΔPaco₂ × 100 (%/mm Hg) | 3.9 ± 0.7 | 4.6 ± 0.7 |

Values are means ± SE.

CMRO₂ = cerebral oxygen consumption.
CVR = cerebral vascular resistance.
(A-V)O₂ = arterial-cerebral venous oxygen difference.
ΔCBF/ΔPaco₂ = index for relative reactivity (see text).
CBF = cerebral blood flow.
MAP = mean arterial pressure.
Paco₂ = arterial carbon dioxide tension.
ApH = arterial pH.
ΔCBF/ΔPaco₂ = index for absolute reactivity of cerebral vessels to CO₂.

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The i² iodo-antipyrine method. Following the control CBF determination, the patient inhaled 8% CO₂-air mixture through a mask for five minutes, during which time CBF was repeated. Arterial and cerebral venous samples were drawn immediately before and after each procedure. The samples were analyzed for O₂ and CO₂ content by the manometric method of Van Slyke and Neill. CMRO₂ was calculated from the product of CBF and the mean of the arterial-cerebral venous O₂ differences taken before and after each procedure. Blood P O₂, P CO₂, and pH were determined by IL meter.

To assess cerebrovascular reactivity to increased PaCO₂, two indices were devised. Absolute response of CBF to CO₂ was calculated by ΔCBF/ΔPaCO₂, relative response by ΔCBF/corrected CBF/ΔPaCO₂ × 100. Corrected CBF was obtained by the equation:

\[
cCBF = CBF + \frac{\Delta CBF}{\Delta PaCO_2} \times (40-PaCO_2)
\]

where CBF and PaCO₂ are the values obtained by actual measurement during the control experiment. The equation is dependent upon the condition of a linear relationship of CBF and PaCO₂ between PaCO₂ of 20 to 80 mm Hg.

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**ANIMAL EXPERIMENTS**

Thirty-five mongrel dogs weighing from 12 to 22 kg were studied. They were anesthetized with intravenous sodium pentobarbital (22 to 44 mg/kg) and intubated. The animals were paralyzed with gallamine and respiration was controlled by mechanical pump. Expired CO₂ was continuously recorded by infrared gas analyzer. One femoral artery was cannulated and connected to a pressure transducer. The other femoral artery and one femoral vein were cannulated for arterial blood sampling and to infuse intravenous fluids. Extracranial contamination of torcular blood was minimized by reflecting the temporal muscles from the skull bilaterally. A hollow metal screw was inserted through a small hole in the confines of the cerebral venous sinuses and connected to a polyethylene tubing to facilitate ease in blood sampling.

CBF was measured by the integrated N₂O technique with a 15-minute period of gas inhalation. Thirty minutes after the control observation, the animals were given 8% CO₂-air mixture to inhale for five to seven minutes. Arterial and cerebral venous bloods were drawn immediately prior to and following the blood flow measurement for determinations of O₂ and CO₂ contents and P O₂, P CO₂, and pH. CBF during CO₂ inhalation was calculated using the reciprocal of...
CEREBRAL OXYGEN CONSUMPTION AND CEREBRAL VASCULAR REACTIVITY TO CARBON DIOXIDE

<table>
<thead>
<tr>
<th>Control</th>
<th>CO₂</th>
<th>Control</th>
<th>CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.9 ± 1.1</td>
<td>34.8 ± 3.1</td>
<td>54.1 ± 4.3</td>
<td>54.7 ± 4.5</td>
</tr>
<tr>
<td>541 ± 30</td>
<td>931 ± 103</td>
<td>952 ± 87</td>
<td>1705 ± 244</td>
</tr>
<tr>
<td>112 ± 4</td>
<td>125 ± 4</td>
<td>112 ± 7</td>
<td>120 ± 8</td>
</tr>
<tr>
<td>21.2 ± 1.2</td>
<td>15.1 ± 2.0</td>
<td>11.2 ± 2.3</td>
<td>6.7 ± 0.5</td>
</tr>
<tr>
<td>37.8 ± 0.6</td>
<td>45.7 ± 1.3</td>
<td>37.9 ± 2.6</td>
<td>44.1 ± 1.4</td>
</tr>
<tr>
<td>7.418 ± 0.016</td>
<td>7.353 ± 0.021</td>
<td>7.399 ± 0.015</td>
<td>7.350 ± 0.044</td>
</tr>
<tr>
<td>6.73 ± 0.33</td>
<td>4.18 ± 0.56</td>
<td>5.86 ± 0.56</td>
<td>3.56 ± 0.73</td>
</tr>
</tbody>
</table>

(A-V)O₂, assuming that CMRO₂ did not change. Indices for cerebrovascular reactivities to CO₂ were calculated similarly to those in Group 1. The animals were grouped according to CMRO₂ values, as in the human experiments.

Results

Human Experiments

Table 1 summarizes the means and standard errors for CBF, mean arterial pressure (MAP), cerebral vascular resistance (CVR), PaCO₂, (A-V)O₂, and pH during normocarbia and during inhalation of 8% CO₂-air mixture in the four different groups of patients. CMRO₂ was not altered in any group by increasing PaCO₂. CVR was significantly reduced only in Groups 3 and 4 during CO₂ inhalation. The absolute response of CBF per mm Hg increase in PaCO₂ was 151.5 ml/min in the patients with normal CMRO₂ as contrasted to 15.9 ml/min in the patients with lowest values for CMRO₂. This correlation between CMRO₂ and absolute reactivity to CO₂ is depicted graphically in figure 1. In response to each increase in PaCO₂ from normal, percent increase in CBF varied from 3.9% in the patients with lowest CMRO₂ to 12.9% in the patients with normal CMRO₂. This correlation is depicted graphically in figure 2.

Animal Experiments

Table 2 demonstrates the mean values and standard errors of the various functions studied in the dogs. The responsivity to CO₂ was much greater in the animals with normal CMRO₂ than in those with low CMRO₂. The percent-age response is likewise related to CMRO₂ as indicated in figures 3 and 4.

Discussion

In this study the absolute and relative indices of CBF responsivity to CO₂ show a close correlation to the level of CMRO₂. It is difficult to conclude that the low cerebral metabolic rate is solely responsible for de-
TABLE 2
Cerebral Vascular Reactivity to CO2 in Dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>CMRO2 (ml O2/min/100gm)</th>
<th>CBF (ml/min/100gm)</th>
<th>MAP (mm Hg)</th>
<th>CVR (mm Hg/ml/min/100gm)</th>
<th>Paco2 (mm Hg)</th>
<th>ApH</th>
<th>(A-V)O2 (vol. %)</th>
<th>ACBF/APaCO2 (ml/min/100gm/mm Hg)</th>
<th>ACBF/cCBF/APaCO2 X100 (%/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.58 ± 0.11</td>
<td>23.2 ± 2.5</td>
<td>129 ± 5</td>
<td>6.28 ± 0.67</td>
<td>7.359 ± 0.021</td>
<td>7.83 ± 0.83</td>
<td>0.19 ± 0.11</td>
<td>0.19 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>CO2</td>
<td>2.40 ± 0.29</td>
<td>30.5 ± 3.6</td>
<td>122 ± 6</td>
<td>4.98 ± 0.91</td>
<td>7.162 ± 0.016</td>
<td>5.83 ± 0.63</td>
<td>0.69 ± 0.16</td>
<td>0.69 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>CO2</td>
<td>44.1 ± 5.2</td>
<td>24.6 ± 1.8</td>
<td>130 ± 5</td>
<td>5.53 ± 0.53</td>
<td>7.390 ± 0.017</td>
<td>10.28 ± 1.04</td>
<td>2.3 ± 0.4</td>
<td>2.3 ± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

Increased CO2 reactivity in the human subjects, since the severity of disease of the cerebral vessels might also play a role. In the animal studies, however, the level of CMRO2 might be dependent upon the depth of anesthesia or level of cerebral metabolic function due to other causes, but not to sclerotic cerebral vessels.

Sohler15 reported no effect on the pial vessels of cats and monkeys, observed through a permanent cranial window, of pentobarbital in doses of 25 to 45 mg/kg. Geiger and Magnes16 observed no effect on CBF in cats of similar doses of pentobarbital. On the other hand, Gleichmann et al.17 demonstrated that
there is a variable response in different dogs to the same dose of pentobarbital, with substantial reduction in CMRO$_2$ in some animals. They also observed that diffuse EEG abnormalities appeared consistently in the animals with diminished CMRO$_2$. We believe that the reduced CMRO$_2$ in some of our animals was a function of their individual response to anesthesia.

There are other experimental data which confirm the correlation between rate of cerebral metabolism and responsivity of cerebral vessels to changes in Pa$_{CO_2}$. Radioisotope or impedance techniques for recording flow changes have shown that the increase in flow which accompanies increased Pa$_{CO_2}$ is not uniform in all parts of the brain and is much greater in gray than in white matter. Flohr et al. observed that absolute reactivity of CBF to CO$_2$ varies in different parts of the central nervous system, being 3.05 ml/100gm/min/mm Hg of Pa$_{CO_2}$ in the prosencephalon, 2.84 in the cerebellum, 2.26 in the brain stem, 0.91 in the cervical cord, and 0.54 in the thoracic cord. There is a reasonable correlation between these figures and the comparable levels of tissue metabolism in the areas measured.

Similarly Shalit et al. and Fujishima et al. have shown that brain stem lesions produced directly by cold probe or by pontine infarction following experimental occlusion of the basilar artery caused reduction in CBF and CMRO$_2$ and diminished to absent response of cerebral vessels to increased Pa$_{CO_2}$.

The mechanism whereby a reduction in brain metabolism diminishes the response of cerebral vessels to CO$_2$ is not clear, but must reflect upon the mode of action of CO$_2$ on the
cerebral circulation. We had concluded from previous studies\(^2\) that the action of CO\(_2\) is not only directly on the vessel wall, but must also be secondary to some other effect of CO\(_2\) on the brain. If the effect of CO\(_2\) were only on the vessel wall it should be independent of CMRO\(_2\). It cannot be argued that the cerebral vessels are already partially dilated by decreased CMRO\(_2\), which should result in decreased tissue P\(_{CO_2}\) and consequent vasoconstriction rather than vasodilatation. Furthermore, if the decreased CMRO\(_2\) were secondary to tissue hypoxia, anaerobic glycolysis would occur, with associated increase in tissue lactate/pyruvate ratio and increased hydrogen ion concentration, thereby decreasing cerebral vascular resistance. This was not observed in these patients or experimental animals, nor is there evidence that cerebral anaerobic metabolism occurs in deep barbiturate anesthesia in animals.\(^2\)

The composite evidence leads to the conclusion that some action of CO\(_2\) on the brain stem contributes to its effect upon cerebral circulation. If this action is upon the reticular activating substance or other neural structures in the medulla, pons, or mesencephalon, whereupon these structures are stimulated to increased activity by CO\(_2\) with cortical activation and increased cortical metabolism which secondarily increases CBF, then changes in P\(_{PCO_2}\) should alter CMRO\(_2\) as well as CBF. The existing evidence indicates that this is not the case.

An alternative pathway whereby CO\(_2\) action on the brain stem can influence CBF is through autonomic pathways, perhaps in cranial nerves V, VII, or X, and ultimately by way of the neural innervation of cerebral vessels. Though this explanation requires convincing proof, it fits existing data better than any other, and there is already some evidence which points to the effect of autonomic nervous stimulation or section upon cerebral vascular response to CO\(_2\).\(^1\)

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