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 thought¹,² and are probably both directly on cerebral vascular walls³,⁴ and indirectly by action on brain stem neurones.⁵ 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,⁶-⁸ and is affected by changes in cerebral perfusion pressure.⁹ Cervical sympathectomy is said to increase CBF response to PaCO₂ changes, whereas sympathetic nerve stimulation abolishes reactivity to CO₂.¹⁰ 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 i1²¹ 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

Cerebral Vascular Reactivity to CO\textsubscript{2} in Human Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>No. of determinations</th>
<th>Control</th>
<th>CO\textsubscript{2}</th>
<th>Control</th>
<th>CO\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>8</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>CMRO\textsubscript{2} (ml O\textsubscript{2}/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>
<td></td>
<td></td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td>P\textsubscript{aCO\textsubscript{2}} (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>
<td></td>
<td></td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td>(A-V)O\textsubscript{2} (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>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ \Delta \text{CBF}/\Delta \text{P}_{a\text{CO}_2} \] (ml/min/mm Hg) | 15.9 ± 3.2 | 21.5 ± 3.7 |
\[ \Delta \text{CBF}/\text{CBF}/\Delta \text{P}_{a\text{CO}_2} \times 100 \] (%/mm Hg) | 3.9 ± 0.7 | 4.6 ± 0.7 |

Values are means ± SE.

CMRO\textsubscript{2} = cerebral oxygen consumption.

CVR = cerebral vascular resistance.

(A-V)O\textsubscript{2} = arterial-cerebral venous oxygen difference.

\[ \Delta \text{CBF}/\Delta \text{P}_{a\text{CO}_2} \] = index for relative reactivity (see text).

CBF = cerebral blood flow.

MAP = mean arterial pressure.

P\textsubscript{aCO\textsubscript{2}} = arterial carbon dioxide tension.

ApH = arterial pH.

\[ \Delta \text{CBF}/\Delta \text{P}_{a\text{CO}_2} \] = index for absolute reactivity of cerebral vessels to CO\textsubscript{2}.

the I\textsuperscript{181} iodo-antipyrine method.\textsuperscript{11} Following the control CBF determination, the patient inhaled 8% CO\textsubscript{2}-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 O\textsubscript{2} and CO\textsubscript{2} content by the manometric method of Van Slyke and Neill.\textsuperscript{12} CMRO\textsubscript{2} was calculated from the product of CBF and the mean of the arterial-cerebral venous O\textsubscript{2} differences taken before and after each procedure. Blood P\textsubscript{O2}, P\textsubscript{CO2}, and pH were determined by IL meter.

To assess cerebrovascular reactivity to increased P\textsubscript{aCO\textsubscript{2}}, two indices were devised. Absolute response of CBF to CO\textsubscript{2} was calculated by \[ \Delta \text{CBF}/\Delta \text{P}_{a\text{CO}_2} \], relative response by \[ \Delta \text{CBF}/\text{CBF}/\Delta \text{P}_{a\text{CO}_2} \times 100 \]. Corrected CBF was obtained by the equation

\[ \text{cCBF} = \text{CBF} + \frac{\Delta \text{CBF}}{\Delta \text{P}_{a\text{CO}_2}} (40-\text{P}_{a\text{CO}_2}) \]

where CBF and \text{P}_{a\text{CO}_2} 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 \text{P}_{a\text{CO}_2} between \text{P}_{a\text{CO}_2} of 20 to 80 mm Hg.\textsuperscript{10}

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 CO\textsubscript{2} 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. Extracerebral 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 N\textsubscript{2}O technique\textsuperscript{14} with a 15-minute period of gas inhalation. Thirty minutes after the control observation, the animals were given 8% CO\textsubscript{2}-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 O\textsubscript{2} and CO\textsubscript{2} contents and P\textsubscript{O2}, P\textsubscript{CO2}, and pH. CBF during CO\textsubscript{2} inhalation was calculated using the reciprocal of
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(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-

![Figure 1](http://stroke.ahajournals.org/)

**FIGURE 1**

Relationship between cerebral oxygen consumption and absolute reactivity of cerebral blood flow to high PaCO₂ in humans. Absolute reactivity was expressed as the ratio of the change of CBF per unit of PaCO₂ (ml/min/mm Hg of PaCO₂).
TABLE 2

Cerebral Vascular Reactivity to CO₂ in Dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of dogs</th>
<th>Control</th>
<th>1/2</th>
<th>CO₂</th>
<th>Control</th>
<th>2/8</th>
<th>CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO₂</td>
<td>(ml O₂/min/100gm)</td>
<td>1.58 ± 0.11</td>
<td>—</td>
<td>2.40 ± 0.29</td>
<td>—</td>
<td>44.1 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>CBF</td>
<td>(ml/min/100gm)</td>
<td>23.2 ± 2.5</td>
<td>30.5 ± 3.6</td>
<td>24.6 ± 1.8</td>
<td>44.1 ± 5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>(mm Hg)</td>
<td>129 ± 5</td>
<td>122 ± 6</td>
<td>130 ± 5</td>
<td>132 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVR</td>
<td>(mm Hg/ml/min/100gm)</td>
<td>6.28 ± 0.67</td>
<td>4.98 ± 0.91</td>
<td>5.53 ± 0.53</td>
<td>3.27 ± 0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>(mm Hg)</td>
<td>35.0 ± 0.8</td>
<td>60.7 ± 2.1</td>
<td>33.7 ± 2.0</td>
<td>60.0 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApH</td>
<td></td>
<td>7.359 ± 0.021</td>
<td>7.162 ± 0.016</td>
<td>7.390 ± 0.017</td>
<td>7.197 ± 0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A-V)O₂</td>
<td>(vol. %)</td>
<td>7.83 ± 0.83</td>
<td>5.83 ± 0.63</td>
<td>10.28 ± 1.04</td>
<td>6.00 ± 0.74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ΔCBF/ΔPaCO₂
(ml/min/100gm/mm Hg) | 0.19 ± 0.11 | 0.69 ± 0.16 |
ΔCBF/ΔPaCO₂ X 100 (%/mm Hg) | 1.9 ± 0.5 | 2.3 ± 0.4 |

CREASED 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.

Sohler et al. 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 Magnes observed no effect on CBF in cats of similar doses of pentobarbital. On the other hand, Gleichmann et al. demonstrated that

FIGURE 2

Relationship between cerebral oxygen consumption and relative reactivity of cerebral blood flow to high PaCO₂ in humans. Relative reactivity was expressed as percentage increase of control CBF per unit of PaCO₂ (% CBF/mm Hg of PaCO₂).

FIGURE 3

Relationship between cerebral oxygen consumption and absolute reactivity (ml/min/100 gm/mm Hg of PaCO₂) of CBF to high PaCO₂ in anesthetized dogs.
there is a variable response in different dogs to the same dose of pentobarbital, with substantial reduction in CMRO₂ in some animals. They also observed that diffuse EEG abnormalities appeared consistently in the animals with diminished CMRO₂. We believe that the reduced CMRO₂ 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 PaCO₂. Radioisotope or impedance techniques for recording flow changes have shown that the increase in flow which accompanies increased PaCO₂ 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 CO₂ varies in different parts of the central nervous system, being 3.05 ml/100gm/min/mm Hg of PaCO₂ 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 CMRO₂ and diminished to absent response of cerebral vessels to increased PaCO₂.

The mechanism whereby a reduction in brain metabolism diminishes the response of cerebral vessels to CO₂ is not clear, but must reflect upon the mode of action of CO₂ on the
cerebral circulation. We had concluded from previous studies that the action of CO₂ is not only directly on the vessel wall, but must also be secondary to some other effect of CO₂ on the brain. If the effect of CO₂ were only on the vessel wall it should be independent of CMRO₂. It cannot be argued that the cerebral vessels are already partially dilated by decreased CMRO₂, which should result in decreased tissue PCO₂ and consequent vasoconstriction rather than vasodilatation. Furthermore, if the decreased CMRO₂ 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.

The composite evidence leads to the conclusion that some action of CO₂ 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 CO₂ with cortical activation and increased cortical metabolism which secondarily increases CBF, then changes in Paco₂ should alter CMRO₂ as well as CBF. The existing evidence indicates that this is not the case.

An alternative pathway whereby CO₂ 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 CO₂.

**Acknowledgment**

The authors wish to thank Mercedes Santiso, Sharon Talib, and Arturo Monteil for their technical assistance.

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Stroke, Vol. 2, May-June 1971
The Relation Between Cerebral Oxygen Consumption and Cerebral Vascular Reactivity to Carbon Dioxide
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Stroke. 1971;2:251-257
doi: 10.1161/01.STR.2.3.251
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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