Cerebrovascular CO$_2$ Reactivity in Normotensive and Hypertensive Man

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SUMMARY Cerebrovascular reactivity to CO$_2$ inhalation and voluntary hyperventilation was studied in seven normotensive subjects and nine hypertensive patients without clinical or angiographical signs of arteriosclerosis. Cerebral blood flow (CBF) was measured by the intracarotid $^{133}$Xe clearance method and calculated as the initial slope index. Three to five CBF measurements were made in each patient in the Paco$_2$ range of 20 to 55 mm Hg. No difference was observed in reactivity between hypertensive and normotensive patients, either during CO$_2$ inhalation or during hyperventilation. The shape of the CBF:Paco$_2$ curve suggested a decrease in reactivity below a Paco$_2$ of 30 to 35 mm Hg in both groups. Above a Paco$_2$ of 35 mm Hg, exponential regression analysis yielded a mean reactivity of 6 ± 2%, whereas below a Paco$_2$ of 30 mm Hg it was about 2%. The rise in CBF during CO$_2$ inhalation was not influenced by the intravenous infusion of a small dose of trimethaphan which blocked the concomitant rise in blood pressure.

rCBF was measured three to five times in each patient with a 15-minute interval between the measurements. Following one measurement in the resting state, 5% to 10% CO$_2$ in room air was inhaled via a face mask for 1.5 minutes prior to and two minutes during one or two subsequent rCBF measurements. In three normotensive subjects and four hypertensive patients, rCBF measurement during CO$_2$ inhalation was repeated during intravenous infusion of a small dose of trimethaphan camsylate (Arfonad, Roche), 0.4 to 1.7 mg per minute. This had little influence upon resting blood pressure, but completely abolished the rise in blood pressure caused by CO$_2$ inhalation. Then the patients were asked to perform voluntary hyperventilation. In half of the cases, end-tidal CO$_2$ was monitored with a capnograph (Godart N.V., type 119) and was found to be constant during hyperventilation. The latter was maintained for 1.5 minutes prior to and two minutes during rCBF measurement. Some patients hyperventilated at two or three different Paco$_2$ levels. In some cases, the order of CO$_2$ inhalation and hyperventilation was reversed.

The mean arterial blood pressure (MABP) was monitored continuously from the catheter in the internal carotid artery by means of a strain-gauge transducer (Statham, P23Db). Arterial blood was sampled from the catheter immediately prior to and two minutes during one or two subsequent rCBF measurements. In three normotensive subjects and nine hypertensive patients, either during CO$_2$ inhalation or during hyperventilation. The rise in CBF during CO$_2$ inhalation was not influenced by the intravenous infusion of a small dose of trimethaphan which blocked the concomitant rise in blood pressure.

IN CHRONIC ARTERIAL HYPERTENSION the cerebrovascular reactivity to blood pressure variations is abnormal. This reactivity, the autoregulation of cerebral blood flow (CBF), is reset to higher pressure levels with both the lower and upper limits of the autoregulatory plateau being found at higher pressures than that in normotensives. In this context it was felt to be of interest to study in hypertensive man another important cerebral vasomotor regulatory function, viz., the cerebrovascular reactivity to variations in arterial carbon dioxide tension (Paco$_2$). We report here such studies in a group of fairly young patients having no clinical or angiographical signs of cerebrovascular disease.

Methods

The study was carried out in seven normotensive subjects and nine hypertensive Japanese patients without any neurological deficits. Clinical data are given in table 1. The nature of the study was carefully explained to the patients, and consent was obtained. They fasted approximately 17 hours before the study. Neither premedication nor general anesthesia was applied. All patients had bilateral carotid angiography, and no significant arteriosclerosis or other abnormality of the cerebral vessels was discovered. The study of regional cerebral blood flow (rCBF) was done in connection with one of the carotid angiograms. In one of the normotensive subjects, rCBF was studied in both hemispheres with an interval of one week.

Prior to the first rCBF measurement, 5,000 units of heparin were injected intravenously. rCBF was measured by the intracarotid $^{133}$Xe method, using a 16-channel system of collimated NaI detectors (Meditronic Cerebrograph Model 165). Approximately 3 mCi of $^{133}$Xe dissolved in 2 to 3 ml of saline were injected as a bolus into the internal carotid artery. By means of a computer (JEC-7D), rCBF was calculated from the initial slope of the first two minutes of the semilogarithmically transformed $^{133}$Xe clearance curves. Mean hemispheric CBF was calculated by the sum of the clearance curves from all 16 detectors.

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whether or not trimethaphan was given. (Tables with the
detailed data will be sent by the authors on request.)

The individual CBF-Paco₂ curves of the patients are
shown in figure 1. In figure 2, all measurements are plotted
in a semilogarithmic system. From this graph it would
appear that the relationship between CBF and Paco₂ cannot
be satisfactorily described by one exponential function but
rather by two merging into each other at Paco₂ of 30 to 35
mm Hg.

In table 2, the least square method has been used to
calculate individual values for cerebrovascular CO₂ reac-
tivity. The calculations are based on the equations suggested
by Olesen et al.²⁻³ If

\[
\text{CBF} = e^k \cdot \text{Paco}_2 + b
\]

where k and b are constants, then the CBF values at two
different Paco₂ values will be

\[
\text{CBF}_1 = e^k \cdot \text{Paco}_2^1 + b \quad \text{and} \quad \text{CBF}_2 = e^k \cdot \text{Paco}_2^2
\]

and

\[
\ln \frac{\text{CBF}_1}{\text{CBF}_2} = k \cdot \text{Paco}_2^1 - k \cdot \text{Paco}_2^2
\]

or

\[
\frac{\text{CBF}_1}{\text{CBF}_2} = e^{k \cdot (\text{Paco}_2^1 - \text{Paco}_2^2)}
\]

or

\[
\text{CBF}_1 = \text{CBF}_2 \cdot e^{k \cdot (\text{Paco}_2^1 - \text{Paco}_2^2)}
\]

Table 1

**Clinical Data in Normotensive (#1 Through 17) and Hypertensive (#8 Through 16) Patients**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, sex</th>
<th>Clinical BP (mm Hg)</th>
<th>Known duration of hypertension (years)</th>
<th>Treatment</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18, M</td>
<td>125/80</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19, F</td>
<td>105/55</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29, M</td>
<td>120/70</td>
<td>0</td>
<td>Mild tranquilizer</td>
<td>Occipital neuralgia</td>
</tr>
<tr>
<td>4</td>
<td>37, F</td>
<td>115/75</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>35, M</td>
<td>140/75</td>
<td>0</td>
<td>Mild tranquilizer</td>
<td>Myogenic headache</td>
</tr>
<tr>
<td>6</td>
<td>33, M</td>
<td>135/80</td>
<td>0</td>
<td>Psychoneurosis, myogenic headache</td>
<td>Meninge's disease</td>
</tr>
<tr>
<td>7</td>
<td>47, F</td>
<td>120/70</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>27, M</td>
<td>150/60</td>
<td>2</td>
<td>Hydralazine, reserpine</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>9</td>
<td>63, M</td>
<td>200/100</td>
<td>2</td>
<td></td>
<td>Essential hypertension, gastric ulcer</td>
</tr>
<tr>
<td>10</td>
<td>51, M</td>
<td>165/95</td>
<td>7</td>
<td></td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>11</td>
<td>29, M</td>
<td>170/110</td>
<td>15</td>
<td></td>
<td>Renovascular hypertension</td>
</tr>
<tr>
<td>12</td>
<td>42, F</td>
<td>225/120</td>
<td>23</td>
<td>Hydralazine, clonidine, methyldopa, benzothiazide</td>
<td>Essential hypertension, myoma uteri</td>
</tr>
<tr>
<td>13</td>
<td>34, M</td>
<td>175/120</td>
<td>5</td>
<td></td>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td>14</td>
<td>62, F</td>
<td>160/100</td>
<td>14</td>
<td></td>
<td>Essential hypertension, migraine</td>
</tr>
<tr>
<td>15</td>
<td>34, M</td>
<td>160/100</td>
<td>18</td>
<td></td>
<td>Essential hypertension, mild diabetes mellitus</td>
</tr>
<tr>
<td>16</td>
<td>41, F</td>
<td>190/115</td>
<td>6</td>
<td>Hydralazine, methyldopa, benzothiazide</td>
<td>Essential hypertension</td>
</tr>
</tbody>
</table>

![Figure 1](http://stroke.ahajournals.org/content/7/5/508/F1.large.jpg)

**Figure 1.** Individual CBF-Paco₂ curves from normotensive (left panel: circles) and hypertensive (right panel: triangles) patients. Resting values shown by closed circles or closed triangles.

![Figure 2](http://stroke.ahajournals.org/content/7/5/508/F2.large.jpg)

**Figure 2.** All CBF values measured at various Paco₂ levels shown in a semilogarithmic coordinate system. Symbols as in figure 1.
k is the slope of the ln CBF: Paco₂ relationship, and is calculated in table 2. e⁻ⁿ is the change in CBF that will be caused by a 1 mm Hg change in Paco₂. Based on this, Olesen et al. have introduced the concept of percent reactivity, e.g., in the first case in table 2:

\[ e^{-0.09} = 1.06 \text{ or 6%} \]

As shown by the r values in table 2, the correlations between ln CBF and Paco₂ above 35 mm Hg were very satisfactory. In the Paco₂ range 35 to 55 mm Hg, the mean CO₂ reactivity in the whole material was 6 ± 2%. No significant difference was found in the reactivity to CO₂ inhalation between normotensive and hypertensive patients using the t-test or the Mann-Whitney test for statistical comparison. Below a Paco₂ of about 30 mm Hg, the CO₂ reactivity in either group was about 2%. In most cases, only one or two CBF measurements were available at hypocapnia.

### Discussion

In the present study, the subjects were kept at each Paco₂ level for 1.5 minutes prior to and for two minutes during CBF measurement. This is enough to ensure a steady state, as changes in CBF caused by a sudden Paco₂ change are largely completed within 30 seconds. It also may be noted that trimethaphan has no direct pharmacological effect on CBF in man.

Our data suggest that the relationship between CBF and Paco₂ in the Paco₂ range 20 to 55 mm Hg can be roughly described by two exponential functions with a gradual change in slope at relatively moderate hypocapnia (Paco₂ 30 to 35 mm Hg). In earlier, less detailed studies in awake man, it was consistently found that the response in CBF is greater to CO₂ inhalation than to hyperventilation. Based on these data, an exponential shape of the CBF: Paco₂ curve has been invoked in the Paco₂ range in question. The earlier studies, however, are compatible with the present one, where more CBF measurements have been made at moderate hypocapnia.

From the present study it is clear that the increase in CBF caused by CO₂ inhalation is not even in part dependent on the concomitant increase in blood pressure. In other words, autoregulation is preserved at the level of hypercapnia attained. Hypercapnic flow increase then may be attributed solely to periarteriolar acidosis. A number of factors, on the other hand, may contribute to the decrease in cerebrovascular CO₂ reactivity observed below a Paco₂ of 30 to 35 mm Hg. In rats anesthetized with nitrous oxide and undergoing progressive hyperventilation, brain intracellular pH ceased to increase when Paco₂ went below 30 mm Hg, due largely to intracerebral lactate formation. The mental arousal of active hyperventilation will counteract the hypocapnic flow decrease. At more pronounced hypocapnia, impending brain hypoxia will counteract further flow decrease. As reviewed by Olesen, the Bohr effect will operate during hyperventilation and add to the threat of cerebral hypoxia. Finally, it may be that adenosine contributes to the modification of cerebral vasoconstriction at hypcapnia, as it has recently been shown in rats that this substance is formed in the brain along with lactate during hyperventilation.

When the effect of a pharmacological substance or a function test on the brain circulation is to be assessed, changes caused by Paco₂ variations must be taken into consideration and, if possible, corrected. Olesen et al. found a mean 4% CO₂ reactivity in patients with a recent history of stroke or brain tumor. The corresponding figure in the present study is 6%, with occasional figures as high as 11% in younger patients. As pointed out by Olesen et al., the approximation exemplified in Equation (8) is only valid for correction purposes with small Paco₂ differences, i.e., 2 to 3 mm Hg. At greater Paco₂ differences, the exponential Equation (7) may be used. However, it emerges from the present study that the correction procedure should not include CBF measurements at Paco₂ less than 30 to 35 mm Hg.

No difference was observed in the cerebrovascular CO₂ reactivity between hypertensive and normotensive subjects. The patients were selected so as to exclude cerebral arteriosclerosis, which is known to impair the CO₂ response independent of coexisting hypertension. The decrease response to hyperventilation found in hypertensive patients in another study may have been related to cerebral arteriosclerosis. Hypertensive vascular disease per se is located in the arterioles which are narrowed with thickened walls, and this causes a shift to high pressure of both the lower and upper limits of CBF autoregulation. In a similar fashion, the ability to maximal dilatation of resistance vessels is decreased in the forearms of hypertensive patients. Maximum CO₂-induced vasodilatation was not reached in the present study, but would be expected to be decreased in the hypertensive patients. On the other hand, the present results show that cerebrovascular resistance is completely adapted to the hypertension in the Paco₂ range 20 to 55 mm Hg.

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