The Effect of Graded Hypocapnia and Hypercapnia on Regional Cerebral Blood Flow and Cerebral Vessel Caliber in the Rhesus Monkey: Study of Cerebral Hemodynamics Following Subarachnoid Hemorrhage and Traumatic Internal Carotid Spasm

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Abstracts

The Effect of Graded Hypocapnia and Hypercapnia on Regional Cerebral Blood Flow and Cerebral Vessel Caliber in the Rhesus Monkey: Study of Cerebral Hemodynamics Following Subarachnoid Hemorrhage and Traumatic Internal Carotid Spasm

Correlative cerebral blood flow (CBF) and vessel diameter studies were performed during graded PaCO₂ change in control monkeys and in monkeys subjected to subarachnoid hemorrhage and internal carotid artery spasm.

In the control series CBF increased linearly between PaCO₂ values of 30 mm Hg and 60 mm Hg. An increase in PaCO₂ from 40 mm Hg to 62 mm Hg produced a mean CBF increase of 74% while a reduction of PaCO₂ to 25 mm Hg resulted in a decrease of 40%. Cerebral gray matter was more responsive to PaCO₂ change than white matter. Caliber of the larger capacitance vessels did not provide an adequate index of the status of cerebral circulation.

In the experimental series both SAH and traumatic internal carotid artery spasm caused a decreased hemodynamic responsiveness to PaCO₂. However, when PaCO₂ was raised to 60 to 65 mm Hg, marked increases in cerebral perfusion occurred (breakthrough phenomenon). In general, a poor correlation between CBF and vessel diameter studies was found in the postinsult period.

The studies indicated: (1) SAH caused an increase in cerebrovascular resistance and a decrease in CBF, (2) hemodynamic responses to PaCO₂ change, although diminished, were not abolished in the acute period after SAH, (3) hypercapnia (PaCO₂ > 60 mm Hg) significantly increased cerebral perfusion whether or not vasospasm was alleviated, and (4) the small distal cerebral vessels were more reactive to PaCO₂ change and were more intimately associated with regulation of cerebral perfusion.

Additional Key Words: cerebrovascular resistance, PaCO₂, cerebral angiography, 133Xenon cerebral vasospasm

Introduction

It is well accepted that carbon dioxide has the most profound effect on cerebrovascular tone of any substance yet investigated. Numerous clinical and experimental studies have shown that increase in PaCO₂ causes an increase in cerebral blood flow (CBF) in normal brain tissue, and that a decrease in PaCO₂ causes a decrease in CBF. However, the effect of carbon dioxide on cerebral hemodynamic responses in ischemic brain tissue have provided inconsistent results and interpretations.

The present study was designed to concurrently investigate cerebral perfusion (CBF) and intradural vessel reactivity (angiography) responses to graded
carbon dioxide tension change in control monkeys and in monkeys subjected to subarachnoid hemorrhage and traumatic internal carotid artery spasm.

**Methods**

Seventeen juvenile and adult rhesus monkeys (Macaca mulatta) weighing 2.0 kg to 3.6 kg were utilized in the study. Sedation which facilitated introduction of flexometallic endotracheal tubes was achieved by intravenous sodium pentobarbital (20 to 30 mg per kilogram). Anesthesia was maintained with nitrous oxide and oxygen from a reservoir in a ratio of 2:1. The animals were curarized and artificially ventilated with a Harvard variable phase mechanical respirator. Additional aliquots of intravenous curare were given as required throughout the experiments.

Esophageal temperature was maintained near 37°C by an infrared light bulb positioned above the animal. Mean blood pressure (MBP) was continuously measured by a Statham transducer connected to a catheter positioned in the aorta via the femoral artery. In several animals intracranial pressure (ICP) was monitored using a Numoto transducer connected to a threeway stopcock through which heparinized arterial blood samples were taken during each CBF study for determination of pH, Paco₂, and Pao₂.

Regional cerebral blood flow (rCBF) was measured by the extracranial technique described by Ingvar and Lassen. Regional clearance rates of Xenon (3.0 to 3.5 mCi) dissolved in 0.25 to 0.50 ml sterile saline was injected over a two to three-second period into the internal carotid artery. Correct multidetector placement was achieved by applying a plastic template with six radiopaque markers to the lateral surface of the skull (fig. 1).

Partial hemispheric flow (pHBF) was measured in the hemisphere contralateral to the side of Xenon injection by a one-inch diameter scintillation detector, mounted in a one-inch diameter lead collimator positioned over the parietal area. A sampling time of four seconds was used and the output data were processed by an onsite digital computer.

Regional CBF and pHBF were calculated using the compartmental (C), stochastic (H/A) and initial-slope-index (ISI) methods. In each case Paco₂ corrected and uncorrected flow values were determined. In addition, mean hemispheric blood flow (mHBF) derived by averaging rCBF values from detectors 1, 2, 3 and 5 was utilized in the statistical analysis. Theoretical considerations have been published previously.

**CEREBRAL ANGIOGRAPHY**

Cerebral angiography was performed during hypocapnia, normocapnia and hypercapnia in control and experimental monkeys by forceful injection of 1 to 1.5 ml meglumine iothalamate (Conray 60) into the internal carotid artery. Only lateral angiograms were performed and care was taken to maintain magnification factors constant during each experiment. Angiography was always carried out immediately following cerebral perfusion studies. Three to five films were taken at specified Paco₂ levels and the films showing the arterial phase most distinctly were selected for measurement. A Vernier calibrated lens system was used to measure intradural vessel diameters (intraluminal) at predetermined, fixed locations. Because of the small size of the intradural arteries in the monkey, only the intradural internal carotid (IDICA), proximal pericallosal (PPA), distal pericallosal (DPA) and the middle cerebral (MCA) arteries were measured and statistically analyzed. For each Paco₂ value two to three films were usually selected for measurement studies and average vessel diameter values obtained.

**Measurements**

At the onset of each experiment the stroke volume of the respirator was adjusted to produce a Paco₂ near 40 mm Hg. Hypercapnia was induced in a graded manner by addition of CO₂ gas to the anesthetic mixture until a maximum Paco₂ value of 80 mm Hg was reached. Graded hypocapnia to Paco₂ changes were in steps of 5 to 10 mm Hg and 10 to 15 minutes were allowed following each change for stabilization of hemodynamic responses.

**CEREBRAL BLOOD FLOW**

Regional cerebral blood flow (rCBF) was measured by the intra-arterial technique described by Ingvar and Lassen. Xenon (3.0 to 3.5 mCi) dissolved in 0.25 to 0.50 ml sterile saline was injected over a two to three-second period into the internal carotid artery. Regional clearance rates of Xenon (rCBF) were measured using a collimated six-detector scintillation counter assembly constructed in our laboratory. Extracerebral contamination with Xenon was minimized by direct internal carotid artery injection and ligation of the external carotid artery. Correct multidetector placement was achieved by applying a plastic template with six radiopaque markers to the lateral surface of the skull (fig. 1).

Partial hemispheric flow (pHBF) was measured in the hemisphere contralateral to the side of Xenon injection by a one-inch diameter scintillation detector, mounted in a one-inch diameter lead collimator positioned over the parietal area. A sampling time of four seconds was used and the output data were processed by an onsite digital computer.

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Experimental Design

CONTROL SERIES

The effect of hypocapnia and hypercapnia on rCBF and vessel reactivity (as determined by serial angiography) was determined in nine monkeys over a five to six-hour experimental period.

Upon completion of surgery, angiography and CBF studies were carried out during normocapnia (Paco2 40 ± 5 mm Hg). Usually, two to four baseline CBF studies were performed at 30-minute intervals prior to induction of hypocapnia and hypercapnia. In several animals graded hypocapnia to 20 mm Hg was induced immediately following the baseline normocapnic studies, while in others stepwise hypercapnia to 80 mm Hg was induced first. In general, angiography was carried out during normocapnia at the onset of each experiment and at the extreme hypocapnic and hypercapnic values.

Upon completion of each experiment, the animals were reversed with atropine and neostigmine, and anesthesia was discontinued. Over the following one to three-hour period they were observed and their clinical and neurological state assessed using a five-grade neurological system. Grade 1 — alert, active and vocal ("croaking"), no evidence of neurological deficit, accepts food and water; Grade 2 — mildly obtunded, not as active or vocal, no significant neurological deficit; Grade 3 — moderately obtunded, neurological deficit (i.e., hemiparesis, cranial nerve palsy), usually assume semisupine position but will sit up when stimulated, responds to all forms of stimulation (auditory, touch, pain); Grade 4 — severely obtunded, severe neurological deficit (i.e., hemiplegia, quadriplegia), little or no response to painful stimulation, frequently exhibits generalized intermittent clonic seizures of variable duration; Grade 5 — moribund, unresponsive to all forms of stimulation, failing vital signs (failing MBP, arrhythmias, shallow irregular respirations).

EXPERIMENTAL SERIES

Hemodynamic responses to graded Paco2 change were examined in eight animals subjected to two forms of cerebrovascular insult.

Group 1 — Subarachnoid Hemorrhage (SAH)

In four monkeys SAH was induced by injection of 4 ml fresh autogenous blood, over a 20-second period, through a circumferentially beveled needle positioned (under fluoroscopy) in the chiasmatic cistern. Cerebral hemodynamic responses (CBF and angiographical studies) to graded Paco2 change were tested prior to and after SAH. Hemorrhage was always induced during normocapnia. The first postsubarachnoid hemorrhage CBF study was performed three minutes after the insult and was immediately followed by angiography. Usually, one or two additional CBF studies were carried out in the normocapnic state. During graded Paco2 change CBF was measured at approximately 30-minute intervals. Additional angiographical studies were performed whenever marked CBF changes occurred with Paco2 change and at the extreme hypocapnic and hypercapnic values. The concurrent presubarachnoid and postsubarachnoid hemorrhage CBF and vessel diameter (angiography) studies permitted correlative analysis to be performed.

Group 2 — Traumatic Spasm of the Internal Carotid Artery (TSICA)

Four animals displayed marked spasm of the origin of the internal carotid artery. This vasoconstriction was produced by manipulation of the artery during catheterization and was demonstrated by angiography carried out during normocapnia at the onset of each experiment. Cerebral vessel reactivity and CBF studies were performed after stepwise changes in Paco2 were induced. The hemodynamic responses were compared with the responses observed in the control animals.

Upon termination of each experiment the animals were observed for one to three hours and neurologically assessed. They were then killed and the brains removed for gross pathological examination. Histological examination performed on two specimens (one SAH and one with TSICA) revealed no abnormalities, due to the acuteness of the postinsult period.

Results

CONTROL SERIES

The mean and standard derivations of Paco2 during hypocapnia, normocapnia and hypercapnia were 23.5 ± 5.5 mm Hg, 39.8 ± 2.4 mm Hg, and 61.9 ± 10.3 mm Hg, respectively. Changes in Paco2 significantly (P < 0.01) altered arterial pH values (respiratory alkalosis and acidosis) but produced little change in Paco2. Heart rate and mean blood pressure were not significantly altered (P > 0.05) during induced hypocapnia and hypercapnia. Stability of HR and MBP was due in part to the small stepwise differences in Paco2 and to the time allotted for the cardiovascular responses to normalize. Hypercapnia produced an increase in ICP (increase in cerebral blood volume) whereas hypocapnia caused a slight decrease. Changes in EKG were not observed even at extreme Paco2 levels.

RELATIONSHIP BETWEEN CBF AND Paco2

A total of 84 CBF studies were performed in the Paco2 range of 16 mm Hg to 85 mm Hg in nine control animals. Fifteen studies were carried out during hypocapnia, 35 during normocapnia (40 ± 5 mm Hg), and 33 during hypercapnia.

Considerable variation in CBF response to Paco2 change was found among different animals and in individual animals (fig. 2). Cerebral perfusion increased linearly between Paco2 values of 30 mm Hg and 60 mm Hg and in this range CBF sensitivity was greatest. Cerebral blood flow response to Paco2 diminished considerably below 30 mm Hg and values below 25 mm Hg were frequently associated with a small increase in CBF. Response to Paco2 values above 65 to 75 mm Hg was attenuated and no further increase in cerebral perfusion occurred above a Paco2 value of 80 mm Hg.

Linear regression analysis for CBF was carried out for each of the several calculated flow values in Paco2 range of 10 to 80 mm Hg and these results are shown in figure 3. An excellent correlation between the stochastic (H/A) and initial-slope-index (IST)
EFFECT OF HYPOCAPNIA AND HYPERCAPNIA ON rCBF

Methods for CBF calculation was found and these two methods of calculation have been used for purposes of statistical analysis. As shown in figure 3, gray matter flow (Fg) was more sensitive to PaCO2 change than white matter flow (Fw).

Mean stochastic and initial-slope-index rCBF, mHBF, and pHBF values during hypocapnia, normocapnia and hypercapnia are given in table 1. Induced hypocapnia, to a mean PaCO2 value of 23.5 ± 5.5 mm Hg from the mean normocapnic value (39.8 ± 2.4 mm Hg), caused a 40% decrease in mHBF, whereas hypercapnia (mean 61.9 ± 10.3 mm Hg) produced a 74% increase. During normocapnia rCBF did not vary significantly (P > 0.05) from one

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
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<tbody>
<tr>
<td>Regional Cerebral (rCBF), Mean Hemispheric (mHBF) and Partial Hemispheric (pHBF) Blood Flow Responses (H/A and ISI Analysis) to PaCO2 Change in Control Animals</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>rCBF</th>
<th>Hypocapnia PaCO2 (23.5 ± 5.5)</th>
<th>Normocapnia PaCO2 (39.8 ± 2.4)</th>
<th>Hypercapnia PaCO2 (61.9 ± 10.3)</th>
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<tbody>
<tr>
<td>H/A</td>
<td>ISI</td>
<td>H/A</td>
<td>ISI</td>
</tr>
<tr>
<td>P1</td>
<td>23.7 ± 7.0</td>
<td>23.3 ± 5.1</td>
<td>23.7 ± 17.9</td>
</tr>
<tr>
<td>P2</td>
<td>26.3 ± 6.1</td>
<td>26.7 ± 6.3</td>
<td>41.5 ± 16.9</td>
</tr>
<tr>
<td>P3</td>
<td>25.3 ± 4.2</td>
<td>23.5 ± 4.9</td>
<td>39.8 ± 13.6</td>
</tr>
<tr>
<td>P4</td>
<td>19.3 ± 4.4</td>
<td>25.5 ± 7.7</td>
<td>22.3 ± 6.3</td>
</tr>
<tr>
<td>P5</td>
<td>27.3 ± 6.0</td>
<td>27.9 ± 8.8</td>
<td>38.1 ± 12.8</td>
</tr>
<tr>
<td>P6</td>
<td>22.2 ± 5.2</td>
<td>23.7 ± 6.1</td>
<td>29.9 ± 9.1</td>
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<tr>
<td>mHBF</td>
<td>25.7 ± 5.9</td>
<td>25.4 ± 6.7</td>
<td>39.3 ± 15.3</td>
</tr>
<tr>
<td>pHBF</td>
<td>23.2 ± 4.7</td>
<td>23.5 ± 4.4</td>
<td>35.3 ± 13.6</td>
</tr>
</tbody>
</table>

FIGURE 2

Computer printout showing the relationship between cerebral blood flow (ISI method) and PaCO2 change in nine control animals (PaCO2 range 10 to 80 mm Hg).
cerebral area to another, although flow in the central area (Probe 2) appeared to be consistently higher. During normocapnia, flows in the cerebellum (Probe 6) and in orbitomaxillary tissue (Probe 4) were lower than cerebral tissue by 20% and 35%, respectively. Cerebral tissue flows were more influenced by PaCO₂ change than were the cerebellar or orbital tissues, thus suggesting a greater responsiveness.

Mean hemispheric blood flow and vessel caliber responses to severe hypocapnia and hypercapnia in individual control animals are shown in Table 2. Six animals were made hypocapnic and all exhibited a decrease in mHBF. Hypercapnia was induced in eight animals and all showed a marked increase in mHBF.

### Table 2

<table>
<thead>
<tr>
<th>M#</th>
<th>PaCO₂</th>
<th>H/A</th>
<th>ISI</th>
<th>IDICA</th>
<th>PPA</th>
<th>DPA</th>
<th>MCA</th>
<th>PaCO₂</th>
<th>H/A</th>
<th>ISI</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>14.5</td>
<td>3.6*</td>
<td>18.4</td>
<td>3.6*</td>
<td>0.673</td>
<td>0.615</td>
<td>0.670</td>
<td>38</td>
<td>56.6</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>27.5</td>
<td>5.2*</td>
<td>28.4</td>
<td>4.9*</td>
<td>0.913</td>
<td>0.855</td>
<td>0.780</td>
<td>45</td>
<td>45.7</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>31.2</td>
<td>1.4*</td>
<td>29.8</td>
<td>2.3*</td>
<td>0.938</td>
<td>0.700</td>
<td>0.780</td>
<td>40</td>
<td>34.5</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>18.9</td>
<td>1.9*</td>
<td>17.6</td>
<td>1.6*</td>
<td>1.145</td>
<td>0.912</td>
<td>0.890</td>
<td>40</td>
<td>37.5</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>28.5</td>
<td>3.1†</td>
<td>26.8</td>
<td>3.8†</td>
<td>1.005</td>
<td>0.830</td>
<td>0.860</td>
<td>40</td>
<td>43.6</td>
</tr>
<tr>
<td>6</td>
<td>22.1</td>
<td>0.8</td>
<td>1.6†</td>
<td>0.935</td>
<td>0.722</td>
<td>0.785</td>
<td>0.843</td>
<td>0.830</td>
<td>40</td>
<td>27.3</td>
</tr>
<tr>
<td>7</td>
<td>18.9</td>
<td>1.9*</td>
<td>17.6</td>
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<td>0.843</td>
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<td>0.785</td>
<td>39</td>
</tr>
</tbody>
</table>

**IDICA** = intradural internal carotid artery, **PPA** = proximal pericallosal artery, **DPA** = distal pericallosal artery, **MCA** = middle cerebral artery.

For example, for monkey #1, the 14.5 hypocapnia value and the 95.5 hypercapnia value were compared to the 56.6 normocapnia value and were both found significantly different at the 1% level.

To test vessel reactivity to PaCO₂ change, angiographical studies were performed in nine animals. Angiograms were obtained in five animals during hypcapnia, in nine during normocapnia, and in seven during hypercapnia. Vessel caliber measurements were made at predetermined, fixed locations on the arteries (Fig. 4).

The effect of contrast material on vessel diameter during each angiographical sitting (constant MBP and PaCO₂) in control and experimental animals was analyzed by measuring the change in vessel caliber with each successive Conray injection. Although a small increase in vessel caliber between the first and subsequent Conray injections was frequently present, the induced vasodilation did not reach levels of statistical significance (P < 0.01).

Of the five monkeys subjected to severe hypcapnia two exhibited a marked reduction in vessel diameter, while two others displayed mild constriction. In one animal (monkey #3) vasoconstriction was absent (Table 2). In general, CBF studies performed just prior to angiography correlated well with the angiographical findings.
Correlative CBF and angiographical studies were performed in seven animals during induced hypercapnia. As shown in table 2, all CBF values were significantly increased above normocapnic values whereas vessel diameter changes were variable. Consistent increases in vessel diameters were observed in the more distal vessels (i.e., DPA), suggesting greater responsiveness of smaller vessels to Paco₂ change.

**NEUROLOGICAL ASSESSMENT**

None of the control animals displayed neurological deficit at the termination of the experiments and were classified as Grade 1 or 2. These animals were utilized for subsequent studies.

**Experimental Series**

**GROUP 1 — SUBARACHNOID HEMORRHAGE**

In four animals the effects of hypocapnia, normocapnia and hypercapnia on physiological parameters, before and after subarachnoid hemorrhage, were studied (table 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>Hypocapnia</th>
<th>Normocapnia</th>
<th>Hypercapnia</th>
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<tbody>
<tr>
<td>SAH</td>
<td>Pre-SAH</td>
<td>Post-SAH (n=2)</td>
<td>Pre-SAH (n=12)</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>30.0 ± 2.00</td>
<td>39.3 ± 1.40</td>
<td>40.3 ± 3.10</td>
</tr>
<tr>
<td>pH</td>
<td>7.48 ± 0.04</td>
<td>7.39 ± 0.04</td>
<td>7.35 ± 0.06</td>
</tr>
<tr>
<td>PaO₂</td>
<td>135.00 ± 7.10</td>
<td>120.00 ± 11.50</td>
<td>126.50 ± 14.70</td>
</tr>
<tr>
<td>HR</td>
<td>107.50 ± 3.50</td>
<td>168.30 ± 36.90</td>
<td>145.50 ± 36.90</td>
</tr>
<tr>
<td>MBP</td>
<td>110.00 ± 5.00</td>
<td>121.70 ± 19.80</td>
<td>124.00 ± 17.60</td>
</tr>
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</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>Group</th>
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SAH = subarachnoid hemorrhage; TS (ICA) = traumatic spasm of internal carotid artery.

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Lateral angiograms of a control monkey during normocapnia (A), hypocapnia (B), and hypercapnia (C). The sites at which vessel diameter measurements were made are indicated. Percent changes in rCBF (white values) in the various cerebral regions (probes 1, 2, 3 and 5) are indicated. Black values indicate percent changes in vessel diameters.

being affected to a greater degree. As shown in our previous studies, little subsequent variation in rCBF was observed in the post-SAH period during normocapnia. The average reduction in CBF varied from 15% (monkey #11) to 35% (monkey #13).

Vessel Caliber Responses

Serial angiographical studies were performed (during normocapnia) at the onset of the experiments and after insertion of the needle into the chiasmatic cistern. No significant variation (P > 0.05) in intradural vessel diameter was produced by needle insertion. Post-SAH angiograms were obtained immediately after completion of the first CBF study and at the extreme PaCO₂ values. Additional angiographical studies were carried out whenever marked changes in CBF occurred during induced increases in PaCO₂.

Subarachnoid hemorrhage produced a decrease in intradural vessel caliber in all animals. The degree of vasospasm differed among different animals and also in different vessels in the same animal (table 4). In all animals marked reflux into the opposite ICA and vertebral arteries occurred, suggesting increased cerebrovascular resistance.

Vessel reactivity was tested in one animal sub-
**TABLE 4**

Mean Hemispheric Blood Flow (H/A and ISI Analysis) and Vessel Caliber (mm) Responses to Hypocapnia and Hypercapnia Individual Animals Subjected to SAH

<table>
<thead>
<tr>
<th>M #</th>
<th>Pre-SAH</th>
<th>Post-SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>40</td>
<td>29.4 ± 6.0</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>20.7 ± 1.3</td>
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<tr>
<td>12</td>
<td>35</td>
<td>20.8 ± 2.6</td>
</tr>
<tr>
<td>13</td>
<td>39</td>
<td>19.7 ± 2.0</td>
</tr>
</tbody>
</table>

- **Hypocapnia**
  - Post-SAH
  - PaCO₂: 32
  - H/A: 17.9 ± 1.4
  - ISI: 18.1 ± 1.7

- **Hypercapnia**
  - Post-SAH
  - PaCO₂: 40
  - H/A: 26.1 ± 2.3
  - ISI: 26.4 ± 2.5
  - P < 0.01

- **Normocapnia**
  - Post-SAH
  - PaCO₂: 21
  - H/A: 26.5 ± 1.5
  - ISI: 26.4 ± 2.5

**Group 2 — Traumatic Spasm of the Internal Carotid Artery**

In four animals the effect of PaCO₂ change on pH, PaO₂, HR and MBP was measured and the results are given in table 5. Average PaCO₂ values during hypocapnia, normocapnia and hypercapnia were 23.0 ± 6.6 mm Hg, 39.5 ± 2.1 mm Hg, and 63.3 ± 11.5 mm Hg, respectively. Mean HR and MBP values were reduced in hypocapnia and increased during hypercapnia but not to levels of statistical significance.

**Relationship Between CBF and PaCO₂**

Mean hemispheric blood flow (H/A and ISI) values in four monkeys displaying traumatic spasm of the internal carotid artery averaged 29 ± 4.5 ml/100 gm per minute. Response to induced hypocapnia was tested in three animals (table 5) and a decrease in CBF was observed in two (significant decrease present in one animal). In the fourth animal (monkey #16), a minute amount of air was injected into the internal carotid artery at the onset of the experiment and in this animal induced hypocapnia increased CBF from the normocapnic values (paradoxical response).

In four animals CBF studies were performed during hypercapnia. In three a significant increase in CBF occurred, although in one animal marked elevation was not exhibited until a PaCO₂ value of 85 mm Hg was reached.

**Vessel Diameter Responses to PaCO₂ Change**

Angiographical studies were obtained in two animals during hypocapnia and generalized vessel constriction demonstrated in both cases. Severe vasoconstriction was associated with marked CBF reduction and mild constriction with a smaller CBF decrease.

**Neurological Assessment**

The animals were assessed neurologically and three were classed as Grade 3 and one Grade 4. The animals were killed and the brains removed for verification of subarachnoid hemorrhage.


EFFECT OF HYPOCAPNIA AND HYPERCAPNIA ON rCBF

<table>
<thead>
<tr>
<th>ICA</th>
<th>PPA</th>
<th>DPA</th>
<th>MCA</th>
<th>P_{aCO_2}</th>
<th>H/A</th>
<th>ISI</th>
<th>IDICA</th>
<th>PPA</th>
<th>DPA</th>
<th>MCA</th>
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<tr>
<td>283</td>
<td>1.158</td>
<td>0.918</td>
<td>0.878</td>
<td>60</td>
<td>44.1 ± 11.1*</td>
<td>53.2 ± 15.8*</td>
<td>0.600</td>
<td>0.647</td>
<td>0.743</td>
<td>0.603</td>
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<tr>
<td>330</td>
<td>0.922</td>
<td>0.705</td>
<td>0.738</td>
<td>66</td>
<td>36.1 ± 3.5*</td>
<td>41.8 ± 6.6</td>
<td>0.600</td>
<td>0.647</td>
<td>0.743</td>
<td>0.603</td>
</tr>
<tr>
<td>553</td>
<td>0.930</td>
<td>0.803</td>
<td>0.803</td>
<td>50</td>
<td>33.3 ± 9.1</td>
<td>37.2 ± 7.1*</td>
<td>1.155</td>
<td>0.883</td>
<td>0.838</td>
<td>0.860</td>
</tr>
<tr>
<td>768</td>
<td>0.785</td>
<td>0.688</td>
<td>0.773</td>
<td>60</td>
<td>33.3 ± 9.1</td>
<td>37.2 ± 7.1*</td>
<td>1.155</td>
<td>0.883</td>
<td>0.838</td>
<td>0.860</td>
</tr>
<tr>
<td>385</td>
<td>0.885</td>
<td>0.828</td>
<td>0.920</td>
<td>83</td>
<td>50.2 ± 6.2†</td>
<td>50.0 ± 5.0†</td>
<td>1.108</td>
<td>1.083</td>
<td>1.210</td>
<td>0.963</td>
</tr>
<tr>
<td>355</td>
<td>0.910</td>
<td>0.913</td>
<td>1.025</td>
<td>62</td>
<td>82.2 ± 20.0†</td>
<td>83.8 ± 23.9*</td>
<td>1.163</td>
<td>1.093</td>
<td>1.082</td>
<td>1.110</td>
</tr>
<tr>
<td>135</td>
<td>0.912</td>
<td>0.828</td>
<td>0.938</td>
<td>81</td>
<td>74.0 ± 20.2*</td>
<td>86.7 ± 24.7*</td>
<td>1.163</td>
<td>1.093</td>
<td>1.082</td>
<td>1.110</td>
</tr>
<tr>
<td>040</td>
<td>1.088</td>
<td>0.917</td>
<td>1.040</td>
<td>70</td>
<td>83.2 ± 10.2†</td>
<td>88.6 ± 7.1†</td>
<td>1.080</td>
<td>1.048</td>
<td>1.055</td>
<td>1.025</td>
</tr>
<tr>
<td>397</td>
<td>0.783</td>
<td>0.753</td>
<td>0.800</td>
<td>81</td>
<td>61.5 ± 9.9</td>
<td>70.3 ± 7.1</td>
<td>0.935</td>
<td>0.962</td>
<td>0.818</td>
<td>0.730</td>
</tr>
</tbody>
</table>

**STOCHASTIC:**

**CONTROL:**

\[ H/A = 0.96 \times P_{aCO_2} + 2.8 \]

**PRE-SAH:**

\[ H/A = 1.36 \times P_{aCO_2} - 19.9 \]

**POST-SAH:**

\[ H/A = 0.39 \times P_{aCO_2} + 13.3 \]

**ISI:**

**CONTROL:**

\[ ISI = 1.08 \times P_{aCO_2} - 1.0 \]

**PRE-SAH:**

\[ ISI = 1.53 \times P_{aCO_2} - 23.7 \]

**POST-SAH:**

\[ ISI = 0.47 \times P_{aCO_2} + 9.8 \]

**FIGURE 5**

Regression line analysis for stochastic (H/A) and initial-slope-index (ISI) flows in the \( P_{aCO_2} \) range in 10 to 80 mm Hg for control, pre-SAH and post-SAH monkeys.
TABLE 5

Mean Hemispheric Blood Flow (H/A and ISI Analysis) and Vessel Caliber Responses to Hypocapnia and Hypercapnia in individual Animals Subjected to Traumatic Internal Carotid Artery Spasm

<table>
<thead>
<tr>
<th>M#</th>
<th>Paco₂</th>
<th>H/A</th>
<th>ISI</th>
<th>IDICA</th>
<th>PPA</th>
<th>DPA</th>
<th>MCA</th>
<th>Paco₂</th>
<th>H/A</th>
<th>ISI</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>19</td>
<td>24.5 ± 4.3*</td>
<td>22.3 ± 5.1†</td>
<td>1.025</td>
<td>0.950</td>
<td>0.822</td>
<td>0.723</td>
<td>40</td>
<td>32.4 ± 3.1</td>
<td>33.7 ± 3.1</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
<td>29.0 ± 8.8</td>
<td>35.2 ± 13.0</td>
<td>0.875</td>
<td>0.610</td>
<td>0.713</td>
<td>0.773</td>
<td>40</td>
<td>34.4 ± 2.7</td>
<td>37.1 ± 2.7</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>32.5 ± 8.8</td>
<td>32.4 ± 7.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>19.4 ± 5.3</td>
<td>25.3 ± 6.3</td>
</tr>
<tr>
<td>17</td>
<td>36</td>
<td>22.7 ± 5.5</td>
<td>29.6 ± 6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.
†P < 0.01.

*Test analysis: H/A and ISI hypocapnia and hypercapnia values were compared to the corresponding normocapnia values by a tailed t-test.

CBF (H/A and ISI) responses to graded hypercapnia in the pre-SAH and post-SAH periods. Note the marked increase in post-SAH CBF when Paco₂ is increased above 65 mm Hg (breakthrough phenomenon).
Vessel diameter measurements were made in three animals during hypercapnia. Increase in PaCO₂ generally caused vasodilation, but the degree of response was variable. In two animals (monkeys #14 and #15, table 5), only the MCA increased in diameter, yet a global increase in CBF occurred. In monkey #17 hypercapnia (PaCO₂ > 60 mm Hg) resulted in generalized marked vasodilation of the larger intradural vessels, although the increase in CBF was not significant until PaCO₂ values of 85 mm Hg were reached. These correlative studies suggest that the caliber of the large intradural vessels, as demonstrated by angiography, do not adequately reflect the status of cerebral tissue perfusion.

Neurological Assessment

Two animals were classified as Grade 4, one as Grade 3 and one as Grade 2. A good correlation between resting CBF (during normocapnia) and neurological grade was present. The Grade 4 animals had the lowest and the Grade 2 animal the highest resting CBF, respectively.

Summary

The effect of graded hypocapnia and hypercapnia on rCBF and cerebral vessel diameters was examined in rhesus monkeys.

Physiological parameters (except for pH change) remained remarkably stable in control and experimental animals. In the control series, cerebral blood flow increased linearly between PaCO₂ values of 30 and 60 mm Hg. Outside this range the CBF response was attenuated, and above values of 80 mm Hg little or no increase in CBF occurred. Increase in PaCO₂ from 40 to 62 mm Hg produced a 74% increase in mHBF while decreasing PaCO₂ to below 25 mm Hg produced a 40% decrease. Cerebral tissues showed a greater responsiveness to PaCO₂ change than did cerebellar or extracranial tissues. Cerebral gray matter was more sensitive to PaCO₂ change than white matter. Vessel diameter measurement did not provide an adequate index of the status of the cerebral circulation.

In the experimental series, cerebral hemodynamic responses to PaCO₂ change were tested in four animals subjected to subarachnoid hemorrhage and four animals with traumatic spasm of the ICA. Both forms of brain insult caused a decreased hemodynamic responsiveness to PaCO₂. However, when PaCO₂ was raised to sufficient levels (60 to 65 mm Hg), marked increases in cerebral perfusion occurred (breakthrough phenomenon). In general, a poor correlation between rCBF and vessel diameter studies (angiography) was found in the postinsult period.

In animals subjected to SAH both vasospasm and decreased cerebral perfusion occurred. Cerebral blood flow response to PaCO₂ change was diminished and the PaCO₂-CBF curve shifted to the right. Above PaCO₂ values of 60 mm Hg a decrease in cerebrovascular resistance was seen and a marked increase in CBF occurred in all animals subjected to SAH. The present studies indicated: (1) that hemodynamic responses, although diminished, were not abolished by SAH, (2) that hypercapnia produced a significant increase in CBF whether or not vasospasm was alleviated, and (3) that small vessels (below radiological resolution) are important in the regulation of cerebral perfusion.

Whether or not vasodilator therapy in ischemic brain disease will alter the clinical course in patients remains speculative. However, the present results are encouraging and further chronic experimental and carefully managed clinical studies are indicated.

Acknowledgments

The authors are especially grateful to Mrs. Joan Harvey who provided technical assistance during experimentation, and to Ms. F. G. Ramcharan for performing the computer analysis.
EFFECT OF HYPOCAPNIA AND HYPERCAPNIA ON rCBF

Pre-SAH and post-SAH lateral angiograms of monkey #10. (A) Pre-SAH normocapnic angiogram, (B) post-SAH angiogram during normocapnia displaying vasospasm, and (C) post-SAH angiogram during hypercapnia (PaCO₂ 66 mm Hg) showing intensified vasospasm even though rCBF increased. rCBF (white values); vessel diameters (black values).

FIGURE 7C

Strok; Vol. 5, March-April 1974
Pre-SAH and post-SAH lateral angiograms of monkey §13. (A) Pre-SAH angiogram during normocapnia. (B) pre-SAH angiogram during hypercapnia showing marked increase in rCBF while vessel diameters are little affected. (C) post-SAH angiogram with vasospasm and decreased rCBF, and (D) post-SAH angiogram during hypercapnia. rCBF is increased above control values even though diameters remain below control dimensions.
References

The Effect of Graded Hypocapnia and Hypercapnia on Regional Cerebral Blood Flow and Cerebral Vessel Caliber in the Rhesus Monkey: Study of Cerebral Hemodynamics Following Subarachnoid Hemorrhage and Traumatic Internal Carotid Spasm


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