Effect of $\text{Pa}_\text{CO}_2$ on Blood Flow and Microvasculature of Ischemic and Nonischemic Cerebral Cortex

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Abstract:
Effect of $\text{Paco}_2$, on Blood Flow and Microvasculature of Ischemic and Nonischemic Cerebral Cortex

The right middle cerebral artery (MCA) was occluded in cats; after subsequent craniectomy cortical blood flow (CBF) was measured bilaterally with $^{85}$Kr, and photographs of the superficial microvasculature were made. Ventilation was controlled, and $\text{Paco}_2$, was altered by changing the concentration of $\text{CO}_2$ in the inspired air. In nonischemic cortex CBF varied as an exponential function of $\text{Paco}_2$, and the caliber of superficial arterial vessels ($50$ to $200$ $\mu$ in diameter) increased with increasing $\text{Paco}_2$. In ischemic cortex, changes of $\text{Paco}_2$, produced no change of CBF in six of ten animals studied within one day of occlusion; in four of these six, there was no change in the caliber of arterial vessels. In the four other animals of this group, there was a paradoxical response (an increase of $\text{Paco}_2$ produced a decrease of CBF of ischemic cortex), and in two of these four animals, there also was a paradoxical response of the caliber of arterial vessels. In eight animals allowed to survive 5 to 12 days after MCA occlusion, the arterial vessels of ischemic cortex regained some reactivity: a normal response of CBF to changes of $\text{Paco}_2$ was found in four, and appropriate changes of vessel caliber were found in all eight. The ischemia-induced impairment of the reactivity of cortical vessels to changes of $\text{Paco}_2$ casts doubt on the usefulness of $\text{CO}_2$ inhalation for the treatment of strokes of humans.

ADDITIONAL KEY WORDS autoregulation carbon dioxide inhalation cerebral circulation cerebral ischemia and infarction cerebral metabolites diffusible indicator methods experimental stroke isotope clearance methods regional cerebral blood flow

Normal cerebral tissue has the intrinsic ability to regulate its blood supply in accordance with metabolic needs, despite changing external influences such as systemic blood pressure (1-4). Thus, the brain is capable of autoregulation of its blood flow (5). One of the metabolic factors important in the autoregulation of cerebral blood flow is carbon dioxide or bicarbonate production, mediated either as tissue $\text{CO}_2$ tension or as tissue pH (6-8). The $\text{CO}_2$ tension of arterial blood ($\text{Pa}_\text{CO}_2$) perfusing the brain also is important in the regulation of cerebral blood flow (1, 9-13).

Although the influence of $\text{Pa}_\text{CO}_2$ probably is due to a direct effect on arterial blood vessels of the brain (14-16), there may be an indirect effect mediated through brain stem structures (17) or through other neural (18) or humoral (19) mechanisms.

Because $\text{CO}_2$ has been shown to cause dilatation of the superficial arterial vessels of the cerebral cortex (20) and because cerebrovascular resistance, calculated mathematically, varies inversely with cerebral blood flow...
during changes of $P_{aCO_2}$ (1, 9), it has been assumed that the effects of $P_{aCO_2}$ on cerebral blood flow are the result of changes of the caliber of arterioles and small arteries of the brain. However, vascular diameter and cerebral blood flow have not been measured simultaneously in studies previously reported.

Autoregulation of cerebral blood flow for changes of blood pressure is easily impaired or abolished by anything that interferes with the integrity of cerebral tissue, such as trauma (2) or ischemia (4, 21-23). Similarly, trauma (24), ischemia (21, 22, 24, 25), and disturbances of the autonomic nervous system (26) can affect the responses of cerebral blood vessels to changes of $P_{aCO_2}$. The present study was designed to assess the effects of changes of $P_{aCO_2}$ on both blood flow and blood vessel diameter of nonischemic and ischemic cerebral cortex.

Methods

EXPERIMENTAL PROCEDURES

Thirty-one cats were used for this study. In 27 cats the right middle cerebral artery (MCA) was occluded by the extradural approach previously described (27). After bilateral craniectomy cortical blood flow (CBF) was measured from both hemispheres simultaneously by external detection of the beta activity of krypton-85 injected into the brachiocephalic artery (4). The data were obtained in digital form, and a kinetic analysis was used (4, 28). Macrophotographs of the superficial vasculature of both cerebral hemispheres were made at the times of measurements of CBF (29). In addition, the surface vessels were observed through an operation microscope.

For measurements of CBF and photography, the animals were lightly anesthetized with halothane (concentration in inspired air 0.3 to 0.5%) and paralyzed with tubocurarine injected through a catheter in the femoral vein in doses just sufficient to abolish respiratory movements. Halothane anesthesia was begun two to four hours before measurements of CBF were made, so that the direct effects of the anesthetic on cerebral blood vessels were minimal (30). The animals were ventilated mechanically through a tracheostomy. The respiratory rate and tidal volume were kept constant by a respirator. Water-pumped air was used for inhalation; halothane, $CO_2$, and oxygen were added to the air.

Mean systemic arterial blood pressure (MABP) was monitored with a strain-gauge attached to a catheter placed in the abdominal aorta through the femoral artery; the data were recorded on a polygraph. Heparinized saline was used to keep the catheters open. The rectal temperature was monitored continuously. The electrical activity of the cerebral cortex was recorded from both hemispheres by screw electrodes placed through the intact skull near the craniectomies. Determinations of arterial $P_{aCO_2}$, pH, $P_{aO_2}$, and hematocrit value were made at the time of each measurement of CBF. Measurements of CBF were made up to nine times in each animal, before and after changes of $P_{aCO_2}$ were produced by changing the concentration of $CO_2$ in the ventilating mixture.

Measurements of CBF and macrophotographs of the superficial cortical vasculature were made within 24 hours of MCA occlusion in 15 cats (group 1); CBF measurements were made two to five hours after occlusion in ten of these and on the following day in five. Twelve cats were allowed to survive 5 to 12 days after MCA occlusion before craniectomy was done and blood flow measurements were made (group 2). Pentobarbital given intraperiurally was used for anesthesia for MCA occlusion of animals of group 2.

The neurological status of those cats that survived one day or more after MCA occlusion was assessed daily by examination. At the completion of each experiment, the brain of the animal was removed and inspected to verify MCA occlusion. The brains of those cats that survived one day or more after occlusion were sectioned and inspected to assess the extent and degree of cerebral infarction.

Identical procedures were performed on four additional cats (group 3), including preparation of the MCA to receive the clip used for occlusion and dissection of the arachnoidal investiture of the artery, but the clip was placed next to the MCA rather than on it. CBF measurements and macrophotographs of the superficial cortical microvasculature were made within two to five hours in two of these animals and eight days later in the other two.

ANALYSIS OF DATA

The only data used for analysis were those obtained from experimental preparations that were intact and functioning well. Five animals were hypotensive during the surgical procedure, had excessive bleeding from the skull or dural veins, or had surgical trauma to the brain, and the data from these were discarded. In addition, data from four animals were discarded because the normal responses of CBF to changes of $P_{aCO_2}$ were not found in measurements from the nonischemic cerebral hemispheres. Thus, data from 22 animals were analyzed: ten of group 1, eight of group 2, and four of group 3.

Individual measurements of CBF were not
used for data analysis if the peak of the curve of radioactivity appeared as an excessively high and sharp "spike" (indicating the rapid passage of $^{85}$Kr through large blood vessels rather than through tissue). Measurements made when $P_{a_{CO_2}}$ was less than 80 or greater than 175 mm Hg were discarded. Measurements from nonischemic cortex were discarded if MABP was less than 70 or greater than 150 mm Hg. Because of the known impairment of autoregulation of CBF for changes of MABP that is caused by ischemia (4), measurements of CBF from the ischemic cerebral hemispheres were discarded if fluctuations of blood pressure (caused by changes of $P_{a_{CO_2}}$) resulted in a change of MABP of more than 15 mm Hg from either the preceding measurement or the first measurement of the experiment.

In all, 131 measurements of CBF from the nonischemic hemispheres of 18 animals of groups 1 and 2, 55 measurements from the ischemic hemispheres of the 10 animals of group 1, and 57 measurements from the ischemic hemispheres of the eight animals of group 2 were used for analysis. Coefficients of correlation of CBF with $P_{a_{CO_2}}$ were calculated for these three sets of data in linear, linear-logarithmic (base 10), logarithmic-linear, and logarithmic modes. Equations for straight lines fitted to the three sets of data in the four modes were determined by inspection of a linear plot of CBF versus $P_{a_{CO_2}}$. Therefore, the $I_{ACBF(CO_2)}$ that was chosen was calculated by taking the difference between a pair of CBF measurements ($\Delta$CBF), dividing this difference by the higher of the two values (CBF$_h$), dividing the result by the difference in $P_{a_{CO_2}}$ ($\Delta P_{a_{CO_2}}$), and multiplying this result by 100:

$$I_{ACBF(CO_2)} = \frac{\Delta CBF/CBF_h}{\Delta P_{a_{CO_2}}} \times 100.$$ 

$\Delta$CBF was considered positive if the change of CBF was in the same direction as the change of $P_{a_{CO_2}}$; if the changes were in opposite directions, $\Delta$CBF was taken as negative.

A "normal" $I_{ACBF(CO_2)}$ was arrived at by determining the mean of 113 values of $I_{ACBF(CO_2)}$ calculated from pairs of CBF measurements obtained from the nonischemic hemispheres of the 18 animals of groups 1 and 2. A mean $I_{ACBF(CO_2)}$ then was calculated for each hemisphere of each animal used in the study. If the mean $I_{ACBF(CO_2)}$ for a hemisphere was greater than 0.5, the response of CBF to changes of $P_{a_{CO_2}}$ was considered to be normal. A mean $I_{ACBF(CO_2)}$ between 0.5 and −0.5 was considered as indicating no response of CBF to changes of $P_{a_{CO_2}}$, and a mean $I_{ACBF(CO_2)}$ less than −0.5 was thought to indicate a paradoxical response—that is, there was a significant change of CBF but in the direction opposite to the change of $P_{a_{CO_2}}$. In this way the reactivity of cortical vessels of the ischemic and nonischemic hemispheres of the animals to changes of $P_{a_{CO_2}}$ was assessed. In addition, a linear plot of CBF versus $P_{a_{CO_2}}$ was made for the data from each hemisphere, and the resulting graphs were inspected.

During analysis of the data, it became apparent that a change of $P_{a_{CO_2}}$ of 10 mm Hg or less occasionally did not produce a change of CBF greater than one that could be accounted for by the limitations and errors of the methods used. (In four animals not included in this series, the mean variation of 12 pairs of consecutive measurements of CBF, without a change of MABP or $P_{a_{CO_2}}$, was 6.5%, with a range of 1.5 to 13.9%
and a standard deviation of 3.7.) Because of this variation and because a small divisor may give a spuriously high result, measurements made after a change of \( P_{\text{aco}_2} \) that was less than 10 mm Hg were not used for calculation of mean \( I_{\Delta \text{CBF}(\text{CO}_2)} \).

Measurements of the caliber of selected arterial vessels of the superficial cortical microvasculature, from 50 to 200 \( \mu \) in diameter, were made directly from the macrophotographs obtained at the time of the measurements of CBF that were used for data analysis. Because of the imprecision of the photographic technique and the complicating factor of possible changes of vessel size due to autoregulation for changes of MABP, changes of caliber were graded only as dilatation, constriction, or no response. A change of arterial caliber was considered normal if it was in the same direction as a change of \( P_{\text{aco}_2} \), that is, if dilatation resulted from an increase of \( P_{\text{aco}_2} \). If a change of caliber was opposite to that of \( P_{\text{aco}_2} \), the response was considered to be paradoxical.

**Results**

**NONISCHEMIC CORTEX**

**Cortical Blood Flow**

The 131 measurements of CBF obtained from the nonischemic hemispheres of the 18 animals of groups 1 and 2 ranged from 0.73 to 3.37 ml/g brain/min at values of \( P_{\text{aco}_2} \) ranging from 12.0 to 99.0 mm Hg (fig. 1). The mean of 39 measurements of CBF at \( P_{\text{aco}_2} \) between 20 and 45 mm Hg was 1.14 \( \pm \) 0.23 (SD). At \( P_{\text{aco}_2} \) between 20 and 80 mm Hg, CBF increased as \( P_{\text{aco}_2} \) increased (figs. 1 and 2). Although the data were insufficient for certainty, changes of \( P_{\text{aco}_2} \) below 20 mm Hg and above 80 mm Hg did not appear to produce further changes of CBF. Linear regression analysis of CBF versus \( P_{\text{aco}_2} \) between \( P_{\text{aco}_2} \) values of 20 and 80 mm Hg showed that the best fitted straight line was a function of the logarithm (base 10) of CBF and the actual values of \( P_{\text{aco}_2} \) (fig. 2), indicating that CBF was an exponential function of \( P_{\text{aco}_2} \). The sensitivity of CBF of nonischemic cortex to changes of \( P_{\text{aco}_2} \), calculated from the fitted line, was approximately 0.021 ml/g/min per 1-mm Hg change of \( P_{\text{aco}_2} \).

For 113 pairs of CBF measurements made from the nonischemic cerebral hemispheres of animals of groups 1 and 2, the mean \( I_{\Delta \text{CBF}(\text{CO}_2)} \) was 1.17 \( \pm \) 0.15 (SE). For values of \( P_{\text{aco}_2} \) between 20 and 80 mm Hg, \( I_{\Delta \text{CBF}(\text{CO}_2)} \) did not vary with \( P_{\text{aco}_2} \) in any systematic way.

In individual animals CBF of the nonischemic hemispheres increased with increasing \( P_{\text{aco}_2} \) and decreased with decreasing \( P_{\text{aco}_2} \) (figs. 3, 4, and 5).

**Superficial Cortical Microvasculature**

In all animals of groups 1 and 2, arterial vessels of the superficial microvasculature of the nonischemic cerebral hemispheres changed in caliber appropriately with changes of \( P_{\text{aco}_2} \) and CBF; that is, with a decrease of \( P_{\text{aco}_2} \) and CBF, the caliber of the arterial vessels decreased, and with an increase of \( P_{\text{aco}_2} \) and...
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CBF, the caliber increased (figs. 6 and 7). Inspection of nonischemic cortex with the operation microscope revealed no detectable change of the velocity of flow in arterial vessels, although flow in venous vessels could be seen to be faster at higher than at lower levels of PA\textsubscript{CO\textsubscript{2}}. The color of the blood in veins frequently changed from blue or bluish black to reddish blue or bright red at higher levels of PA\textsubscript{CO\textsubscript{2}} and the surface of the cortex itself appeared redder and more vascular (4, 29). At high levels of PA\textsubscript{CO\textsubscript{2}}, a moderate degree of swelling of the nonischemic hemispheres was evident.

ISCHEMIC CORTEX

Cortical Blood Flow

Values of the 55 measurements of CBF obtained from the ischemic hemispheres of the ten animals of group 1 ranged from 0.31 to 1.60 ml/g/min at PA\textsubscript{CO\textsubscript{2}} ranging from 15.0 to 99.0 mm Hg (fig. 8, upper). The mean of 14 measurements at PA\textsubscript{CO\textsubscript{2}} between 25 and 44 mm Hg was 0.92 ± 0.19 (sd); this was lower than CBF of nonischemic cortex, but because of variations from animal to animal, the difference was not statistically significant.

The shallow slope of the fitted straight line, the small correlation coefficient, and the relative unreliability of the correlation coefficient indicated that there was no correlation between PA\textsubscript{CO\textsubscript{2}} and CBF of the acutely ischemic cerebral cortex.

The mean I\textsubscript{ACBF(CO\textsubscript{2})} for the ischemic hemispheres of the ten animals of group 1 was \(-0.57 ± 0.18\) (SE). None of the ten animals had a normal response of CBF to changes of PA\textsubscript{CO\textsubscript{2}} (table 1); I\textsubscript{ACBF(CO\textsubscript{2})} ranged from \(-1.37\) to 0.28. In six animals there was no response of CBF to changes of PA\textsubscript{CO\textsubscript{2}} (fig. 3); four animals had a paradoxical response (fig. 4).

In the eight animals of group 2, CBF values from ischemic cortex ranged from 0.28 to 2.14 ml/g/min at PA\textsubscript{CO\textsubscript{2}} ranging from 14.0 to 91.0 mm Hg (fig. 8, lower). The mean of 18 measurements at PA\textsubscript{CO\textsubscript{2}} between 25 and 44 mm Hg was 0.94 ± 0.37 (sd). This also was lower than the CBF of nonischemic cortex, but the difference was not statistically significant. There was likewise no statistically significant difference between the values obtained from ischemic cortex of animals of group 1 and those of group 2.

There was a statistically significant correlation between CBF of chronically ischemic cerebral cortex and PA\textsubscript{CO\textsubscript{2}}, although the change of CBF for a corresponding change of PA\textsubscript{CO\textsubscript{2}} was not so great as that of nonischemic cerebral cortex (fig. 2). The sensitivity of CBF of ischemic...
Superficial cortical microvasculature of cat studied five days after MCA occlusion. (A) Nonischemic cortex: $P_{aCO_2} = 39$ mm Hg; $CBF = 1.74$ ml/g/min. (B) Nonischemic cortex: $P_{aCO_2} = 91$ mm Hg; $CBF = 2.54$ ml/g/min; $I_{ACBF(CO_2)} = 0.61$. Note dilatation of arterial vessels (arrows) and apparent increase of vascularity. (C) Ischemic cortex, same time as (A): $P_{aCO_2} = 39$ mm Hg; $CBF = 1.39$ ml/g/min. (D) Ischemic cortex, same time as (B): $P_{aCO_2} = 91$ mm Hg; $CBF = 1.97$ ml/g/min; $I_{ACBF(CO_2)} = 0.57$. Despite ischemia arterial vessels are dilated (arrows).

### TABLE 1

Response of Blood Flow of Ischemic Cerebral Cortex to Changes of $P_{aCO_2}$

<table>
<thead>
<tr>
<th>$I_{ACBF(CO_2)}$</th>
<th>Ischemic 1 day or less</th>
<th>Ischemic 5 days or more</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 &gt; $I_{ACBF(CO_2)}$</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>0.5 &gt; $I_{ACBF(CO_2)}$</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>$I_{ACBF(CO_2)}$ &lt; 0.5</td>
<td>10</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>

Cortex of animals of group 2, calculated from the fitted line, was 0.008 ml/g/min per 1-mm Hg change of $P_{aCO_2}$ or approximately one-third that of nonischemic cortex.
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**FIGURE 7**

Superficial cortical microvasculature of cat studied five days after MCA occlusion (same animal as in fig. 5). (A) Nonischemic cortex: \(\text{Pa}_{\text{O}_{2}} = 22\) mm Hg; \(\text{CBF} = 0.95\) ml/g/min. (B) Nonischemic cortex: \(\text{Pa}_{\text{O}_{2}} = 45\) mm Hg; \(\text{CBF} = 1.42\) ml/g/min; \(I_{\Delta \text{CBF}(\text{CO}_{2})} = 1.44\). Note dilation of arterial vessels (arrows). (C) Ischemic cortex, same time as (A): \(\text{Pa}_{\text{CO}_{2}} = 22\) mm Hg; \(\text{CBF} = 0.86\) ml/g/min. (D) Ischemic cortex, same time as (B): \(\text{Pa}_{\text{CO}_{2}} = 45\) mm Hg; \(\text{CBF} = 0.98\) ml/g/min; \(I_{\Delta \text{CBF}(\text{CO}_{2})} = 0.53\) (change of CBF from (C) is within range of error of method). Note failure of arterial vessels to dilate (arrows).

**TABLE 2**

Relationship of Changes of Caliber of Arterial Vessels of Ischemic Cerebral Cortex to Changes of CBF Caused by Changes of Pa\textsubscript{CO\textsubscript{2}}

<table>
<thead>
<tr>
<th>Changes of vessel caliber</th>
<th>Normal</th>
<th>No response</th>
<th>Paradoxical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_{\Delta \text{CBF}(\text{CO}_{2})} &gt; 0.5) (normal response)</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>(0.5 &gt; I_{\Delta \text{CBF}(\text{CO}_{2})} &gt; -0.5) (no response)</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>(I_{\Delta \text{CBF}(\text{CO}_{2})} &lt; -0.5) (paradoxical response)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>

The mean \(I_{\Delta \text{CBF}(\text{CO}_{2})}\) for the ischemic hemispheres of the eight animals of group 2 was 0.67 ± 0.24 (SE). In this group of animals, no paradoxical response of CBF to changes of \(\text{P}_{\text{CO}_{2}}\) was noted (table 1); the range of \(I_{\Delta \text{CBF}(\text{CO}_{2})}\) was from −0.37 to 1.81. Four ani-
mals had a normal response of CBF to changes of $P_{aCO_2}$; the other four had no response (fig. 5).

**Superficial Cortical Microvasculature**

In the four animals of group 2 with a normal response of CBF of the ischemic hemisphere to changes of $P_{aCO_2}$, changes of $I_{ACBF}(CO_2) > 0.5$), normal responses to changes of $P_{aCO_2}$ were found in arterial vessels of the superficial microvasculature (table 2, fig. 6). Of the ten animals of groups 1 and 2 that had no response of CBF to changes of $P_{aCO_2}$, five (two from group 1 and three from group 2) had appropriate changes of vessel caliber with changes of $P_{aCO_2}$, and the other five (four from group 1 and one from group 2) had no detectable change (fig. 7). Photographs were available from only three of the four animals that had a paradoxical response of CBF of ischemic cortex to changes of $P_{aCO_2}$; in one there was no change of the caliber, and in two there was a paradoxical change (constriction with an increase of $P_{aCO_2}$) in association with the paradoxical response of CBF.

Other changes of the superficial microvasculature, such as a decrease of the velocity of the flow of blood in veins, an increase of the aggregation of formed blood elements, and the appearance of red venous blood, also occurred in relation to changes of CBF (4, 29). Swelling of the ischemic cerebral hemispheres developed as frequently and to the same degree as that of the nonischemic cerebral hemispheres; brain swelling at higher levels of $P_{aCO_2}$ was more evident in animals that had an increase of CBF.

**MISCELLANEOUS RESULTS**

In all four animals of group 3 (arterial clip placed next to but not on MCA), the responses of CBF, including $I_{ACBF}(CO_2)$, and of the caliber of arterial vessels of the superficial cortical microvasculature to changes of $P_{aCO_2}$ were normal. Thus, manipulation of the blood vessels at the base of the brain, without occlusion and the development of ischemia, did not affect the reactivity of vessels of the surface of the brain. In one animal in which measurements were made immediately after manipulation of the basal vessels, CBF of the hemisphere on the side of manipulation was lower than that of the opposite side, as reported previously (31).

The neurological deficits and the sizes of cerebral infarcts of animals of group 2 were similar to those reported previously (27). Electrocoorticographic findings (ECoG) likewise were similar to those previously reported (4); the ECoG of the ischemic hemispheres of animals of group 2 were similar to those of animals of group 1 despite the differences between the two groups in the responses of CBF and arterial diameter to changes of $P_{aCO_2}$. There was no evident relationship between the severity of neurological deficit, the extent of cerebral infarction, or the changes of ECoG and the response of CBF or of arterial caliber to changes of $P_{aCO_2}$.

**Discussion**

**NONISCHEMIC CORTEX**

It has generally been assumed that the increase of cerebral blood flow occurring with an increase of $P_{aCO_2}$ is due to a decrease of cerebrovascular resistance (CVR) resulting from dilatation of cerebral vessels. However, in only one previous study (20) has the
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diameter of superficial arterial vessels been measured during changes of PA$_{CO_2}$; in other studies (1, 9), changes of vascular diameter have been inferred from changes of CVR calculated mathematically. The present study is the first in which measurements of CBF and of the caliber of arterial vessels of the cortex have been made simultaneously with changes of PA$_{CO_2}$. Because perfusion pressure of the brain was not measured, CVR could not be calculated; however, the assumption that increased CBF and decreased CVR are related to dilatation of cerebral vessels is strengthened by the present study. This study does not provide information to resolve the controversy about whether the arterial dilatation and increase of CBF are due to a direct effect of CO$_2$ or of pH on arterial vessels (14) or to an indirect effect mediated through the brain stem (17).

ISCHEMIC CEREBRAL CORTEX

The data reported here show clearly that arterial vessels of the cerebral cortex fail to react to changes of PA$_{CO_2}$ when there is cortical ischemia. The lack of reactivity is manifested both by impairment of the normal response of CBF to changes of PA$_{CO_2}$ and by impairment of the normal dilatation of arterial vessels in response to increasing levels of PA$_{CO_2}$. The lack of reactivity of these arterial vessels probably is not caused by "maximal dilatation" due to local accumulation of CO$_2$ or acidic metabolites. Not all arterioles of the superficial cortical microvasculature dilate with ischemia (29), and in the study reported here, certain arterioles of the ischemic cortex of five animals retained some ability to dilate in response to an increase of PA$_{CO_2}$, although CBF did not change (table 2). Cortical vessels may be less than normally reactive for various reasons, such as ischemic damage to the vessel wall, constriction resulting from ischemia (29), changes of autonomic factors, and, in some vessels, maximal dilatation.

Data from group 1 indicate that the lack of reactivity of cortical vessels is profound and nearly universal during an acute phase of ischemia, and this phase can persist at least as long as one day after the occlusion of a major cerebral artery. In time, however, even if ischemia continues (as in animals of group 2), small vessels can regain some reactivity, and a response of CBF and arterial caliber to changes of PA$_{CO_2}$ can return. Others have shown that cerebral vessels may retain some reactivity to changes of PA$_{CO_2}$ during acute ischemia produced by occlusion of a branch, rather than the main trunk, of a middle cerebral artery (32). The preservation of reactivity may be due to better perfusion through collateral channels when the ischemic zone is small and when blood flow is maintained in other branches of the main cerebral vessel.

The paradoxical response of a decrease of CBF of ischemic cerebral cortex with an increase of PA$_{CO_2}$, found in four animals with acute ischemia (group 1), may also occur after cerebral infarction in humans (22, 25) and has been shown (by qualitative methods for CBF) to occur in dogs (21). The paradoxical response has been termed the "intracerebral steal" by Lassen. Presumably, dilatation of vessels of nonischemic brain in response to increased PA$_{CO_2}$ produces a decrease of CVR and an increase of the proportion of the blood of the head going to nonischemic regions. If the blood supply is constant, blood vessels of ischemic zones, unable to react as well to changes of PA$_{CO_2}$, receive less blood. Increased intracranial pressure, caused by an increase of PA$_{CO_2}$ with a resultant passive increase of CVR, could not account for the paradoxical response of CBF to changes of PA$_{CO_2}$ reported here but, as K. Kogure suggested,* may be important in situations in which the skull is intact (as, for example, in humans with strokes).

A decrease of caliber of arterial vessels of the superficial microvasculature with increased PA$_{CO_2}$ as seen in two animals with a paradoxical response of CBF to changes of PA$_{CO_2}$ probably is not the result of active vasoconstriction but of passive collapse of dilated vessels from a decrease of perfusion pressure caused by a reduction of CVR of nonischemic zones. Such a reduction of pressure in cortical vessels in response to an increase of PA$_{CO_2}$ has been reported in association with ischemia (32) and trauma to the vessels (33). Increased intracranial pressure from increased PA$_{CO_2}$ could cause collapse of arterial vessels of ischemic brain but not in animals with wide craniectomies, as in

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*Personal communication.
this study. The failure of CBF to increase in the ischemic cortex despite dilatation of arterial vessels, seen in five animals, probably is due to even greater dilatation of vessels of nonischemic zones.

The lack of relationship between the severity of the neurological deficit or the extent of the cerebral infarct and the reactivity of cortical vessels in this study and previous ones (4) is a consequence of the measurements of CBF and observations of blood vessels being made outside the zone of maximal ischemia (27).

Although the ECoG obtained from the ischemic hemispheres were different from those obtained from the nonischemic cerebral hemispheres, there was evidence of continuing cerebral function in every animal. Changes in the ECoG were found in all animals of group 2, including those with relatively little ischemia at the time of measurement of CBF and with good responses of CBF to changes of P_{aco2}; thus, the ECoG changes probably were the result of minor permanent damage to neurons caused by earlier ischemia.

It is difficult to relate a study such as this to cerebrovascular disease of man. However, limited studies (22, 25) of patients with strokes have provided results that are quite similar to those reported here. Thus, the use of CO_{2} inhalation for the treatment of strokes of humans must be questioned. During the acute phase of strokes, perhaps comparable to the situation of the animals of group 1, an increase of P_{aco2} is potentially harmful because of the distinct possibility of a paradoxical decrease of blood flow of ischemic brain. In fact, hyperventilation sufficient to cause a decrease of P_{aco2} may be found to be useful (34, 35), particularly if patients with the paradoxical response of CBF to changes of P_{aco2} can be identified by relatively simple clinical methods. In chronic ischemia, or several days after an acute ischemic episode (perhaps comparable to animals of group 2), an increase of P_{aco2} may (or may not) improve blood flow through ischemic zones. At such a time, however, neuronal damage from ischemia most likely has already taken place, and marginal zones may not be helped by an increase of blood flow. Although additional clinical studies of humans must be done, data from this and other reports indicate that there is probably no reason to use CO_{2} inhalation for the treatment of patients with strokes.

Acknowledgment

Technical and instrumentation assistance was provided by Robert Anderson and Robert Ostrom. Dr. T. Yamaguchi assisted in the final experiments. Computer programming and assistance were provided by the Mayo Clinic Computer Facility.

References

EFFECT OF PA\(_{(CO_2)}\) ON BLOOD FLOW


Stroke, Vol. 1, January-February 1970
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doi: 10.1161/01.STR.1.1.27

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