The Role of the Carotid Body in Mediating the Cerebrovascular Response to Altered Arterial Carbon Dioxide Tension

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SUMMARY The role of the carotid bifurcation chemoreceptors in mediating the cerebrovascular response to altered arterial PCO₂ has been suggested to be large. In the present study the cerebrovascular response to raised PCO₂ was measured in a group of baboons before and after bilateral inactivation of the carotid bodies. The results suggest that these chemoreceptors do play a part in the cerebral vasodilator response to raised PCO₂.

Introduction

RECENT EVIDENCE1 has suggested that the carotid bifurcation chemoreceptors have an important role in mediating the cerebral vasodilator response to raised arterial carbon dioxide (Paco₂). The implication in this work was that the peripheral chemoreceptor provides an input to an autonomic nervous pathway via the brain stem to act on the cerebral resistance vessels.2 This attractive hypothesis may assist in ascribing a role to the rich autonomic innervation of the cerebral vessels. However, there is also substantial evidence that changes in cerebral resistance following alteration of Paco₂ are mediated by a local effect of the CO₂ on the resistance vessels or by pH changes in the extracellular space around them.3-5 The chemoreceptor-mediated CO₂ response was reported to be large.1 As this study was carried out at only one level of hypercapnia, we have designed the present study to define the cerebrovascular response to a wide range of arterial Pco₂ values, both before and after bilateral inactivation of the carotid bifurcation chemoreceptors.

Methods

Seven adult baboons (Papio ursinus, weighing 9 to 16 kg) were sedated with 0.2 mg per kilogram Ketamine hydrochloride (Ketalar, Parke Davis) by intramuscular injection. Full anesthesia was induced with an intravenous injection of 20 to 30 mg per kilogram of pentobarbitone sodium (Nembutal, Abbott). The animals were then intubated and anesthesia was maintained with a 3:2 mixture of O₂ and N₂O. Small amounts of additional barbiturate were given as required. A femoral artery was catheterized for measurement of arterial blood pressure with a Statham P23AA transducer, and for withdrawal of arterial blood samples for determination of Pco₂, Po₂, and pH on an Instrumentation Laboratories 313 blood gas analyzer. The right carotid bifurcation was exposed and a fine catheter inserted retrograde into the lingual artery. Then the external carotid artery and its remaining branches were ligated. Cerebral blood flow (CBF) was measured by an intracarotid ¹³³xenon technique. A bolus of 30 to 50 mCi of ¹³³Xe in 0.2 ml of saline was injected into the internal carotid via the lingual catheter. The cerebral uptake and clearance of ¹³³Xe were monitored using a 5 cm in diameter sodium iodide detector mounted posteriorly over the parietal region. A high degree of collimation was used to exclude possible radiation arising from orbital non-cerebral tissue. This was confirmed by the absence of a third flow component from the clearance curves. The curve data were recorded in digital form with a Nuclear Enterprise data logging system and were analyzed manually and by computer into two exponential components representing flow through cerebral gray and white matter compartments.

All animals were intubated and ventilated using a Harvard variable phase respirator. Samples of tidal air were constantly circulated through a Godart Capnograph for continuous monitoring of tidal percent CO₂. This, together with the pulsatile and mean blood pressures and the analogue xenon washout curves, was recorded on a Beckman dynograph recorder. Throughout, the animals were kept at a constant body temperature by radiant heating. The bladder was catheterized and allowed to drain freely.

CO₂ REACTIVITY

After a 30-minute stabilization period two control CBF measurements were made with the arterial Pco₂ within the range of 30 to 39 mm Hg. This was designated normocapnia for this altitude. CBF then was measured after the Pco₂ had been raised stepwise by adding CO₂ to the inspired air, always returning to the original baseline between steps. In this way CBF was measured in the ranges of 30 to 39, 40 to 49, 50 to 59 and 60 to 69 mm Hg. When the normal response to altered Paco₂ had been determined, further surgery was carried out to bilaterally destroy and denervate the carotid bodies. When this had been completed, the animals were left for at least one hour to recover before further measurements were made. Then the CBF was measured with stepwise changes in Paco₂, as before.

AUTOREGULATION

In four animals, the CBF was measured during stepwise alteration of mean arterial blood pressure within the range...
of 50 to 200 mm Hg. Blood pressure was changed by withdrawal or infusion of blood from the animals. This procedure was carried out with the \( \text{Paco}_2 \) in the range of 40 to 49 mm Hg after bilateral destruction of the carotid baroreceptor areas and section of the carotid sinus nerve.

**Results**

**CO\(_2\) Reactivity — Control**

In the control animals, increasing the arterial \( \text{Paco}_2 \) level resulted in a progressive rise in CBF. A typical chart recording of the clearance curves of \(^{133}\text{Xe}\) from the baboon brain, the respiratory tidal air percent CO\(_2\) content, and the pulsatile and mean systemic blood pressures is shown in figure 1. As the end-expired CO\(_2\) was increased stepwise from 39 mm Hg to 47 mm Hg and, after briefly returning to the control level, to 58 mm Hg, a steepening of the \(^{133}\text{Xe}\) washout curve is evident, indicating increments in cerebral perfusion. Figure 2 shows the mean gray matter CBF from the seven animals calculated from similar clearance curves obtained while the arterial \( \text{Paco}_2 \) was maintained in the ranges of 30 to 39, 40 to 49, 50 to 59 and 60 to 69 mm Hg. Between 30 to 39 and 50 to 59 mm Hg a linear change in CBF occurred with a mean increase in CBF of 3.1 ml per minute per 100 gm of tissue per unit change in \( \text{Paco}_2 \). Beyond these limits, a further change in \( \text{Paco}_2 \) produced less change in CBF giving the CBF per \( \text{Paco}_2 \) curve a sigmoid shape.

**CO\(_2\) Reactivity — Experimental**

The mean values of CBF obtained after removal of the carotid bodies are also shown in figure 2 as open circles. With normocapnia (30 to 39 mm Hg), the mean blood flow in this experimental situation was almost identical to the normal mean. Increments of \( \text{Paco}_2 \) from the 30 to 39 mm Hg range to the 50 to 59 mm Hg range produced a smaller increase in CBF of 1.63 ml per minute per 100 gm of tissue per unit change of \( \text{Paco}_2 \) in comparison to the 3.1 ml per minute per 100 gm of tissue for the normals. This attenuation of response to raised CO\(_2\) was statistically significant in the 50 to 59 and 60 to 69 mm Hg ranges (P < 0.05).

In some experiments, changes in arterial blood pressure did occur when hypercapnia was induced. To consider these, the cerebrovascular resistance (CVR) was calculated (mm Hg/ml-min\(^{-1}\)) and the mean CVR found for each range of \( \text{Paco}_2 \). These are shown in table 1. A slight fall in CVR was found during hypercapnia in the experimental group, which was significantly different from the normal at the highest level of \( \text{Paco}_2 \) (P < 0.05). Thus, removal of the carotid bodies tends to produce a smaller decrease in CVR and a smaller increase in CBF with hypercapnia. This indicates an

<table>
<thead>
<tr>
<th>( \text{Paco}_2 ) (mm Hg)</th>
<th>CBF (ml/min/100 gm)</th>
<th>CVR (mm Hg/ml-min(^{-1}))</th>
<th>MBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>30-39</td>
<td>59.1 ± 6.6</td>
<td>2.10 ± 0.1</td>
<td>118.2 ± 4.0</td>
</tr>
<tr>
<td>40-49</td>
<td>38.0 ± 7.4</td>
<td>1.46 ± 0.1</td>
<td>113.7 ± 3.6</td>
</tr>
<tr>
<td>50-59</td>
<td>121.1 ± 14.4</td>
<td>1.17 ± 0.1</td>
<td>117.0 ± 6.1</td>
</tr>
<tr>
<td>60-69</td>
<td>125.4 ± 17.0</td>
<td>0.97 ± 0.1</td>
<td>107.4 ± 4.1</td>
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<tr>
<td>Carotid body removed</td>
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<tr>
<td>30-39</td>
<td>58.0 ± 2.9</td>
<td>2.12 ± 0.1</td>
<td>136.6 ± 9.3</td>
</tr>
<tr>
<td>40-49</td>
<td>67.2 ± 9.7</td>
<td>1.87 ± 0.3</td>
<td>132.8 ± 14.3</td>
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<tr>
<td>50-59</td>
<td>90.7 ± 9.0</td>
<td>1.33 ± 0.1</td>
<td>122.4 ± 10.5</td>
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<tr>
<td>60-69</td>
<td>101.8 ± 5.1</td>
<td>1.19 ± 0.1</td>
<td>116.4 ± 7.2</td>
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attenuated vasodilator response of the cerebral vasculature, and that the bodies may normally play a part in the vasodilatation, particularly at the high $P_{\text{aco}_2}$ values.

**AUTOREGULATION**

Table 1 shows the mean values for CBF, CVR, and arterial blood pressure (MBP) at the four levels of $P_{\text{aco}_2}$ used. There was no significant change in mean blood pressure when the $P_{\text{aco}_2}$ was altered. The MBP after removal of the bodies, however, was slightly higher than before. Although these increased pressures fall well within the autoregulatory range known for the normal baboon, it is possible that without an intact carotid sinus these limits may be altered. These higher blood pressures, therefore, may fall outside the altered autoregulatory range and may have produced a forced vasodilatation at higher levels of $P_{\text{aco}_2}$, thereby masking the attenuation of the hypercapnia dilatation. This could be of particular importance at the 40 to 49 mm Hg level of $P_{\text{aco}_2}$, as no statistical difference was found between normal and experimental at this level. To investigate this, a further series of experiments was carried out to determine the autoregulatory limits of blood pressure in baboons in which the carotid chemoreceptors and baroreceptors had been bilaterally ablated. No significant change in CBF was found at $P_{\text{aco}_2}$, 45 mm Hg when the MBP was varied between 90 and 140 mm Hg, as shown in figure 3. This implied that autoregulation was well maintained at this $P_{\text{aco}_2}$, even after our experimental procedure. Thus, the higher mean arterial blood pressure in this situation is unlikely to affect the magnitude of the CBF response to a $P_{\text{aco}_2}$ of 40 to 49 mm Hg.

**Discussion**

It has been well established that changes in the $P_{\text{aco}_2}$ of arterial blood profoundly affect CBF. A rise in $P_{\text{aco}_2}$ from normal produces a marked increase in CBF, while a fall produces a decrease in CBF. The mechanism by which altered $P_{\text{aco}_2}$ affects the cerebral resistance vessels has been suggested to be a direct action of the altered $P_{\text{aco}_2}$ and/or the accompanying altered pH on the cerebral arteriolar smooth muscle cells. While this mechanism may be the major contribution to the CBF response in a quantitative...

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**Figure 2**  
The graph shows the mean values of gray matter CBF (ml/min/100 gm of tissue) obtained at varying levels of arterial $P_{\text{aco}_2}$ (mm Hg) in the normal baboon (closed circles) and after bilateral removal of the carotid bodies (open circles). Vertical lines represent ± 1 SE of the means.

**Figure 3**  
Gray matter cerebral blood flows recorded at various levels of mean arterial blood pressure in four baboons (after bilateral removal of the carotid bodies) are shown. Autoregulation of the blood flow is suggested over the blood pressure range of 90 to 150 mm Hg.
sense, evidence is accumulating that some neurally mediated reflex mechanism also is important.

Dilatation of cerebral blood vessels can be achieved by stimulation of the seventh cranial nerve. This was thought to be mediated via the brain stem. It also has been established that a vasodilator innervation exists on at least the large extracerebral vessels, and it may be that these vessels are of considerable importance in the control of blood flow through the brain. Also, some areas of the cerebral microvasculature have been shown to have a vasodilator innervation. Thus the neural connections exist to provide an autonomic reflex pathway from the peripheral chemoreceptors via the brain stem to the cerebral vessels. The importance of the pons and mesencephalon has been demonstrated in mediating the cerebrovagal dilatation to raised arterial PCO₂. Lesions in these areas produced an attenuated CBF response to the raised CO₂, while lesions in other areas of the lower medulla, transection of the spinal cord at C1, and extensive frontal and occipital lobectomies had no effect. These workers concluded that "a neural factor should be taken into account in future hypotheses of cerebral circulatory regulation." Similar studies have further demonstrated the influence which the brain stem can have on overall CBF.

Previous attempts to identify a peripheral CO₂ receptor capable of influencing CBF have not been successful. Kedrov and Naumenko have reported that when blood flow to the brain is supplied only through the vertebral arteries (the common carotid having been ligated) the CO₂ reactivity was the same as in the normal animal. However, it is not clear how much cerebral ischemia was caused by the carotid ligation and this may have potentiated the action of any subsequent increase in arterial PCO₂. More recent observations indicate that when the carotid, vagus and aortic nerves are sectioned, the cerebral response to CO₂ is attenuated. These observations suggested that the carotid bifurcation and aortic arch chemoreceptors may mediate the cerebral response to CO₂. As the carotid chemoreceptors lie in the arteries serving the brain, it was thought that these had more influence on the cerebral vessels than the aortic bodies. This was confirmed by surgically isolating the carotid chemoreceptors and stimulating them with blood of a different CO₂ tension. The surgery involved in this study was complex and may have influenced the magnitude of the result.

In the present study the chemoreceptors have been shown to be responsible for 38% to 48% of the cerebrovascular response to raised CO₂. At moderately raised levels of CO₂ the CBF response was not significantly altered by removal of the carotid bodies. Only at Paco₂ values greater than 50 mm Hg was the dilator response significantly reduced. The present data, therefore, would suggest that the carotid bodies do have a small but significant role at high Paco₂ levels. It may be that the bodies provide a fast but small CBF dilatation which is normally followed by a slower but greater dilatation when the extracellular fluid around the cerebral arterioles falls in pH. This theory is in keeping with the role of the carotid bodies in the control of respiration. Also, it has been shown that when the Paco₂ is raised, cerebral vessels dilate earlier than the blood vessels of the extremities.

Three possible factors may have complicated our experiments. First, the ablative procedures in the carotid bifurcation area may have stimulated the sympathetic nerves running with the internal carotid to produce cerebral vasoconstriction in opposition to the CO₂-induced dilatation. However, the animals were always left to recover for at least one hour before subsequent CO₂ reactivity was studied. Also, if a sympathetic vasoconstriction had been induced it would have been apparent at all levels of PCO₂. As the measurements at normocapnia were not significantly different from the controls, we felt this explanation was improbable.

The second influence may have been due to abnormal autoregulation of the cerebral vessels. The mean blood pressures recorded after removal of the carotid bodies were higher than normal. If the removal of the bodies and general denervation of the carotid bifurcation area had attenuated the autoregulatory behavior of the cerebral vessels, then a forced vasodilatation may have occurred to augment the CO₂-induced dilatation. However, in our study we could find no evidence of this as the autoregulation was intact over the blood pressure range of 90 to 150 mm Hg at a Paco₂ of 40 to 49 mm Hg.

Third, it may be argued that due to the four-hour to six-hour experimental time, the attenuated CO₂ response may have been coincidental with the removal of the carotid bodies but was actually due to the passage of time and physiological deterioration of the animal. We feel that this explanation is unlikely as we varied the order of CO₂ concentrations so that the response to high CO₂ was tested often early in the experiment. In addition, at no stage was there any detected fall in systemic blood pressure, major alteration in acid-base balance, or cardiac arrhythmia to indicate such deterioration.

Thus, the cerebral vasodilatation in response to raised arterial PCO₂ may be mediated by both a local effect of the CO₂ on the cerebral resistance vessels and by some reflex arising from the carotid body chemoreceptors. This reflex is probably relayed via the brain stem either to inhibit cerebral vasoconstrictor tone or, more likely, to activate dilator nerves.

References
SUMMARY The rehabilitation outcome of 25 elderly hemiplegic patients discharged from the rehabilitation facilities of an acute general hospital and admitted to a long-term facility hospital was evaluated. Only those patients who had been on a rehabilitation program and were discharged after an average of 11 weeks because of lack of progress or severity of their functional and/or neurological disability were considered for this study. Twenty-two patients were wheelchair bound on admission and severely dependent in most self-care activities. Improvement in function and performance occurred in ten patients, while 13 patients remained unchanged. Among the improved patients, eight became ambulatory and independent in activities of daily living (ADL), eight became independent from a wheelchair level, and eight returned home or to the community. The average stay of the patients in the chronic rehabilitation care facility was seven months, although all the patients reached their maximum level of performance within six months. It appears from this study that some hemiplegic patients require a long and intensive rehabilitation program.

Methods

All hemiplegic patients admitted to the rehabilitation facilities of the Bird S. Coler Hospital from July, 1970, to June, 1973, were screened.‡ An average of 80 stroke patients were treated annually. Twenty-five patients were noted to have been transferred because of lack of progress in the functional and/or neurological picture after 8 to 43 weeks of therapy in the acute general hospital, the average being 11 weeks. After being placed on treatment, each patient’s hospital course was reviewed at three-month intervals, and the functional level assessed according to the following categories: Category 1: independent in activities of daily living (ADL) and ambulatory, Category 2: independent in ADL but nonambulatory, and Category 3: dependent in ADL and nonambulatory. There were 15 patients with rightsided hemiplegia and ten with left-sided hemiplegia. Eight patients had a moderate degree of aphasia, predominately expressive type. The average age of these patients was 67.

Results

Eleven of the 25 patients gradually progressed to become fully independent in ambulation and ADL (Category 1), 13 patients remained in Category 3, and one patient became independent from a wheelchair level (Category 2). The average stay was seven months (range: 2 to 14 months), any improvement occurring during the first three to six months; no further functional improvement was evident in any patient after six months.

Twelve patients returned to the community where they lived before the stroke (mostly home); eight patients (Category 3) were transferred to a chronic custodial institution; three were re-admitted to an acute general hospital because of other medical problems; and two died while waiting for disposition (myocardial infarction).
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