Role of the Carotid Body in Speeding the Cerebrovascular Response to Altered Paco2 in Baboons

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SUMMARY The alterations in cerebral perfusion with graded hypercapnia were measured in the baboon using the intra-carotid 133 xenon clearance technique. In addition, the tidal percent of CO2 and the blood flow in the common carotid artery were measured using a capnograph and an electromagnetic flowmeter respectively. The delay times between the induced increments in tidal respiratory percent of CO2 and the beginning of the blood flow increments were assessed, together with the rate of increment of the blood flow at each level of hypercapnia. The changes in cerebral perfusion, delay time and rate of blood flow increase with hypercapnia were measured before and after bilateral denervation and destruction of the carotid bifurcation receptors.

Hypercapnia normally caused an increased cerebral perfusion which was attenuated when carotid receptor function was destroyed. This change was only significantly different from normal with the highest value of Pco2. Before removal of carotid receptor function the mean delay time was 13.7 ± 1.2 seconds and the rate of increment in carotid flow was 29.7 ± 8.4 ml/min per min. These values were similar at all levels of hypercapnia. After carotid receptor removal the mean delay time was significantly increased at 35.8 ± 9.0 seconds while the rate of flow increment was unchanged at 36.0 ± 5.2 ml/min per min. These results in the baboon suggest that the carotid bifurcation receptors provide a quantitatively small but fast mechanism mediating the cerebrovascular dilator response to hypercapnia.

IN 1974, Ponte and Purves suggested that the cerebral vasodilator response to a raised arterial Pco2 is mediated, at least in part, by carotid and aortic chemoreceptors. Since then many workers have investigated the role of a neural reflex in cerebral hypercapnic vasodilatation. Hoff, Mackenzie and Harper5 showed that, in the baboon, section of the seventh cranial nerve had no effect on the cerebral response to either hypercapnia or hypoxia. Similarly, Linton, Miller and Cameron7 found in the rabbit that the carotid sinus had no influence on the response to hypercapnia. Other recent studies also failed to demonstrate any role for the carotid chemoreceptors in the control of cerebral blood flow in the dog or cat.6

On the other hand, James and MacDonell6 have shown in the dog that stimulation of the vascularly isolated carotid bifurcation with hypercapnic or hypertensive blood caused alteration in cerebral blood flow. We have recently shown that the carotid body chemoreceptors do play a quantitatively small role in the cerebrovascular dilator response to hypercapnia.7 However, this role became apparent only at high Paco2 values and was quantitatively smaller than that reported previously by Ponte and Purves.1 Also, we have suggested that the hypercapnic cerebral vasodilatation is mediated by a quantitatively small but fast reflex arising in the peripheral chemoreceptors.7 If this is true, it may explain some of the variation in the literature as different authors may have made their measurements at different times after induction of the chemoreceptor stimulation. The present study was designed to test the hypothesis that hypercapnic cerebral vasodilatation occurs more quickly when the carotid chemoreceptors are intact than when they are destroyed.

Methods

Cerebral blood flow was measured in five pentobarbital anesthetized baboons as previously described.7 All animals were intubated and ventilated using a Harvard positive pressure respirator. The response of the cerebral circulation to stepwise increments in Paco2 was measured as before. In addition to these measurements of cerebral perfusion with 133 xenon, the blood flow in the common carotid (with ligation of the external carotid) was measured using an electromagnetic flowmeter. The flowmeter probe was placed around the common carotid a short distance away from the bifurcation. The diameter of the probe was chosen to fit snugly around the artery. The probe was then connected to a Biotronex electromagnetic (EM) flowmeter, which gave a continuous write-out of pulsatile and mean EM blood flow on a Beckman dynograph recorder. In addition, the pulsatile and mean arterial blood pressure, the analogue 133 xenon clearance curve and the tidal percent of CO2 were recorded. Throughout each experiment arterial blood samples were analysed for Pco2, Po2 and pH on an Instrumentation Laboratories 313 blood gas analyzer.

The 133 xenon clearance curves were used to calculate the changes in cerebral perfusion when CO2 was added to the inspired air. In addition, the continuous record of tidal percent of CO2 and carotid EM blood flow allowed the delay time (seconds) between the initiation of the tidal CO2 increment and the initiation of the increase in EM flow to be measured. The rate of increase in flow was also measured as the slope of the EM flow record. All measurement of delay and slope of the EM flow record were made by two independent observers working from the original Beckman dynograph traces which were coded with random numbers. The mean of their two observations is used in the results.

The changes in cerebral perfusion, delay time and slope with hypercapnia were measured in the 5 baboons before and after bilateral denervation of the carotid bifurcation by microdissection and electrocoagulation. The animals were then left for at least 60 minutes before proceeding, to allow for recovery from the surgery. Then the cerebral blood flow (perfusion, delay and rate of rise) responses to hypercapnia were again determined.

At the end of each experiment, the success of this denervation process was tested by assessing the carotid sinus baroreceptor response to a raised arterial blood pressure and the

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carotid body chemoreceptor response to bolus injections of an acidic buffer solution. The baroreceptor reflex was monitored by the degree of bradycardia produced after an intravenous injection of 10 µg of angiotensin II (Hypertensin, CIBA). The chemoreceptor reflex was monitored by the tachypnoeic response to injection of an acidic buffer solution (Instrumentation Laboratories) into the carotid sinus after disconnecting the animal from the respirator.

In normal animals an intravenous injection of angiotensin resulted in an increase in systemic blood pressure. At this high blood pressure the heart rate slowed bringing the blood pressure toward normal. In these animals where the carotid bifurcation had been denervated this bradycardia at high blood pressure was not observed.

The carotid bifurcation chemoreceptors were tested in a similar way. With spontaneous breathing, bolus injections of the acidic solution normally increased the rate of ventilation. In the animals with carotid denervation no alteration in the frequency of spontaneous ventilation was found when 2 ml of solution at pH 6.84, 4 ml at pH 6.84 or 4 ml at pH 4.0 were injected into the carotid bifurcation. There was no alteration in general systemic pH or Pco2 following these injections and thus the pH change was confined to the carotid bifurcation and the cerebral circulation.

These tests were used to indicate that the surgical denervation of the carotid bifurcation was successful in preventing the carotid body–respiratory reflex.

**Statistics**

The mean values of cerebral perfusion obtained before and after denervation were compared at the same levels of Paco2 by a Student’s paired t-test.

The mean values of delay time and slope obtained before and after denervation were compared with a Student’s paired t-test. An F test was also performed to investigate the distribution of data before and after the denervation. Where the distributions were found to be significantly altered, the Wilcoxon rank sum test was used to compare the pre and post denervation data.

**Results**

**Cerebral Perfusion**

When CO2 was added to the inspired air the 183 xenon clearance from the brain became faster indicating an increased cerebral perfusion. The mean value of grey matter cerebral blood flow (CBF) when the Paco2 was within the range 30–39 mm Hg, was 41.9 ± 2.7 ml/min per 100g of tissue. When the CO2 was increased into the ranges 40–49, 50–59, and 60–69, this CBF increased to 69.2 ± 6.0, 103.9 ± 15.1, and 130.9 ± 10.0 ml/min/100g respectively. These mean CBF values (closed circles) plus and minus one standard error are shown in figure 1 plotted against Paco2.

After denervation of the carotid bifurcation the mean value of CBF with the Paco2 at 30–39 mm Hg was 41.6 ± 3.2 ml/min/100g. This was not significantly different from the normal value. With hypercapnia, as before, the mean CBF increased to 75.3 ± 13.0, 88.9 ± 9.4, and 88.4 ± 10.3 ml/min/100g. These values are shown in figure 1 as open circles. No significant difference between the normal and denervated results were found while the Paco2 was at 30–39, 40–49, or 50–59 mm Hg. However, at 60–69 mm Hg the denervated mean CBF values were significantly smaller than the normals (paired t-test, P < 0.05, n = 5).

**Delay and Slope**

An original recording showing the tidal percent of CO2 and the pulsatile and mean carotid blood flows before and after denervation is shown in figure 2. The block of traces on the left shows the recording before denervation and that on the right is a post-denervation record. Before denervation, when CO2 was given to increase the Paco2 from 34.4 to 68.7 mm Hg, the blood flow increased soon after the increment of the tidal CO2. The mean estimate of this delay by the two independent observers was 12.0 seconds and is shown as the block marked "D." After denervation the CO2 was given to increase Paco2 from 35.6 to 68.6 mm Hg. The tidal CO2 increase was as rapid as before but the blood flow record showed a long delay before it began to increase. The estimate of this delay (shown by the block marked "DELAY") was 38.0 seconds.

These delay time measurements were made at each level of hypercapnia before and after denervation. The time was not significantly altered by the degree of hypercapnia either before or after denervation. However, there was a significant increase in the mean delay time in the animals without carotid bifurcation function. Before denervation the carotid
blood flow increase was delayed after the increase in tidal CO₂ by 13.7 ± 1.2 sec (mean ± SEM). After denervation this delay was significantly prolonged to 35.8 ± 9.0 sec. (t = 2.71, P < 0.01). The distributions were, however, found to be significantly different (F = 30.84, P < 0.001). Further analysis of the data by the Wilcoxon rank sum test showed a score of 110 which indicates a significant difference in delay times (P < 0.01).

The initial slope of the carotid flow increase was also measured before and after denervation. No significant difference between the normal mean value of 29.7 ± 8.4 ml/min per min and the post denervation value of 36.0 ± 5.2 ml/min per min was found.

Therefore, removal of the carotid bifurcation receptors delayed the hypercapnic increase in CBF but did not alter its rate of increase. This delay occurred at all levels of hypercapnia. In contrast, the removal of the carotid receptors attenuated the amplitude of the hypercapnic CBF dilatation only at the highest level of PaCO₂ used.

**Discussion**

The role of the autonomic innervation in the control of cerebral blood flow is not well defined. This is mainly because the effects of nerve section or nerve stimulation are small and variable. It has recently been suggested that the nerves may not act alone but in concert with other vasoactive mechanisms to modulate those mechanisms.

Various authors have investigated this modulation using lesions in the brain stem, section of the cerebral autonomic nerves, pharmacologic blockade of autonomic receptors, or denervation of the carotid body chemoreceptors. In all cases the cerebrovascular response to hypercapnia was altered by interference with the autonomic nervous system.

Considerable controversy has resulted from the observation that denervation of the carotid body chemoreceptors reduces the cerebrovascular dilatation with hypercapnia. Some investigators have been unable to confirm these observations using other techniques. The present results may provide a unifying theory to resolve the controversy. They suggest that the carotid bodies do play a role in the hypercapnic cerebral vasodilatation but that this role is quantitatively a small one. The main function of the carotid bodies in this context may be to provide a sensor for an autonomic-nervous mediated fast dilatation of the cerebral vessels. Thus the conflict in the literature may be due to measurements of blood flow being made at different time intervals after induction of the hypercapnia.

The present findings are in agreement with the role for the carotid body in the control of respiration where the hypercapnia induces a fast autonomic reflex to increase ventilation. The carotid bifurcation receptors have similarly been shown to provide fast reflex control of the general systemic circulation. Carotid baroreceptor stimulation was shown to induce general hemodynamic changes within 10-15 seconds of stimulation. Similarly, carotid chemoreceptor stimulation has been shown to cause reflex vasoconstriction in many vascular beds. The role of the peripheral receptors has further been defined as causing a rapid cardiovascular change to occur. The onset of this rapid component may be estimated from published records at 10-20 seconds after application of the stimulus. In contrast, a vasodilator response to stimulation of the carotid bodies has been shown in some tissues. Therefore, it is possible that the hypercapnic reflex elicited by the carotid bodies can differentially induce either constriction or dilatation in various vascular beds. The cerebrovascular response to hypercapnia is to dilate. This dilatation has been documented as having a rapid and a slow component.

The present evidence would suggest that the rapid component of this cerebral response is due to a reflex arising from carotid body stimulation. The alteration in cerebral blood flow resulting from this fast reflex is quantitatively small. It may be that the hypercapnia induces a cholinergic vasodilation, activation of the intracerebral noradrenergic pathway or alteration in sympathetic tone to the cerebral vessels. Any of these mechanisms seems possible as it has been shown that anti-cholinergic or anti-adrenergic drugs will interfere with the response to CO₂. Previous work with noradrenaline hypersensitive baboons and CO₂ would indicate that changes in sympathetic tone with hypercapnia and hypocapnia do occur. However, it is possible that all three mechanisms are involved simultaneously.

The present results may explain the controversy in the literature concerning the carotid body. However, it may not be the only factor involved, as other chemoreceptors in the circulation, such as the aortic body, may have similar fun-
tions to the carotids. It may be that simultaneous removal of aortic and carotid chemoreceptor function would produce a more marked attenuation of the hypercapnic cerebral vasodilation. However the present observation of the absence of a reflex bradycardia from a pressor dose of angiotensin and after carotid sinus denervation suggests that the primary afferent sensors are located in the carotid. It may also be possible that the surgical trauma involved in denervating both carotid bifurcations may have accounted for the present results. We have, however, reported a similar attenuation of the cerebral vasodilator response to hypercapnia with chronic denervation of the cerebral adrenergic innervation using an intracisternal injection of 6-hydroxydopamine. Thus, it would seem likely that the present results arise primarily from the interruption of an afferent pathway which normally initiates an adrenergic vasodilator efferent pathway to the cerebral vessels.

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