Abnormal Cerebrovascular Response to Altered PaCO$_2$ in Baboons With Obstructive Jaundice

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SUMMARY The cerebrovascular response to hypercapnia and hyperventilation was studied in normal and jaundiced baboons by the intracarotid $^{13}$Xe injection technique. The baboons with bile duct ligation were found to have decreased CBF at all levels of PaCO$_2$. This difference between normal and jaundiced baboons was 13% at normocapnia rising to 33% with hypercapnia and 37% with hypocapnia. The CBF values all were increased toward normal by use of an alpha-adrenoreceptor blockade (phentolamine).

It is suggested that the obstructive jaundice potentiated an inherent vasoconstrictor alpha-adrenergic mechanism to oppose the effects of CO$_2$. Also, alteration of the PaCO$_2$ may have produced its effects on the cerebral vessels by altering this adrenergic mechanism.

Introduction

ALTHOUGH the intracerebral resistance vessels have been shown to be innervated by both the seventh cranial nerve$^1$ and sympathetic fibers from the cervical ganglia,$^2$ their physiological function in the control of cerebral blood flow (CBF) is unclear.$^3$ In particular, many workers have been unable to demonstrate a change in CBF when the sympathetic ganglia were electrically stimulated or the fibers cut.$^4$ Thus, there is considerable uncertainty concerning the cerebrovascular response to sympathectomies.$^5$

In contrast, the response to increased arterial PaCO$_2$ has been extensively documented. There is much evidence to suggest that the action of increased PaCO$_2$ is to cause cerebrovascular dilatation$^2$ and that this is mainly mediated by a direct effect of the CO$_2$ or of pH on the cerebral resistance vessels.$^4$$^5$

Recently, this predictability of cerebral CO$_2$ reactivity has been used to investigate the function of the sympathetic innervation. Section of the cervical ganglia has been shown to enhance the cerebrovascular response to raised PaCO$_2$ while stimulation reduced the response.$^7$ $^8$ Thus the vasodilatation induced by hypercapnia is opposed by a vasoconstrictor influence originating in the cervical sympathetic ganglia. These sympathetic nerves also may be important in mediating the hypocapnic cerebrovascular constriction as this constriction was reported to be abnormal in subjects with cervical cord transection where there is interruption of the descending sympathetic pathways.$^6$ Also, there is some evidence that sympathectomy reduces the hypocapnic constrictor response.$^10$

In the present experiments a novel model of vascular hypersensitivity to noradrenaline was used to amplify any possible inherent action of the sympathetic nerves on the cerebral vessels. We have previously shown that in obstructive jaundice there is an altered renal vascular sensitivity to infused noradrenaline both in vivo$^{11}$ and in vitro.$^{12}$ This was postulated to be due to some factor in the jaundiced plasma which was capable of sensitizing both renal and femoral arteries to the pressor effects of noradrenaline. We have further tested these animals with obstructive jaundice and have shown that the cerebral circulation is hypersensitive to infused noradrenaline (NA).$^{13}$ In these experiments in normal animals infusion of NA into the internal carotid artery at 8 and 16 $\mu$g per minute produced a mean increase in CBF of 8.4 ± 4.3 and 8.6 ± 6.0 ml per minute, respectively. In jaundiced animals 8 and 16 $\mu$g per minute produced a reduction of 9.5 ± 2.6 and 10.9 ± 4.4 ml per minute, respectively. There was a significant difference between normal and jaundiced baboons at 8 $\mu$g per minute (P<0.005) and 16 $\mu$g per minute (P<0.02). Thus, in these animals with surgically induced obstructive jaundice there appears to be a potentiated response of the cerebral vessels to the sympathetic innervation. We have attempted to further evaluate any possible potentiation by comparing the cerebrovascular response to altered PaCO$_2$ in a group of normal animals and in a group with surgically induced bile duct ligation.
Methods

The cerebrovascular response to altered Paco₂ was studied in nine normal baboons and eight baboons with surgical ligation of the common bile duct two weeks previously. Anesthesia was induced with 0.2 mg per kilogram ketamine hydrochloride (Ketalar, Parke-Davis) administered by intramuscular injection. Full anesthesia was induced with intravenous injection of 20 to 30 mg per kilogram pentobarbitone sodium (Nembutal, Abbott). The animals were then intubated and anesthesia maintained by ventilation with an N₂O mixture. 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 was inserted retrograde into the lingual artery. Then the external carotid artery and its remaining branches were ligated. CBF was measured by an intracarotid ¹³³Xe 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 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. The clearance 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 Goddart Capnograph for continuous monitoring of tidal percent CO₂. This, together with the pulsatile and mean blood pressures, the analogue xenon washout curves, ECG, and EEG, was recorded on a Beckman dynograph recorder. Throughout, the animals were kept at constant body temperature by radiant heating, and the bladder was always catheterized and allowed to drain freely. The EEG was used to standardize the depth of anesthesia so that CBF was measured only during periods when the EEG rhythm was 8 to 12 Hz.

CO₂ Reactivity

Initially 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 or lowered by adding CO₂ to the inspired air or by hyperventilating, respectively, always returning to the original baseline between steps. In this way measurements of CBF were obtained in the Paco₂ ranges of 20 to 29, 30 to 39, 40 to 49, 50 to 59 and 60 to 69 mm Hg, respectively. This cerebrovascular reactivity to CO₂ was determined in a group of normal baboons and in a group of baboons with bile duct ligation. In the ligated group the procedure was repeated after alpha-adrenergic blockade had been achieved with an intravenous 15-mg injection of phentolamine (Ciba).

Statistics

A comparison of the mean CBF found in the normal and jaundiced animals at the same level of Pco₂ was made using Student's t-test.

Results

Clinical Effects of Bile Duct Ligation

The majority of animals had clinical jaundice within two weeks of bile duct ligation. There was no evidence of weight loss, ascites or features suggesting a general debility in the animals used. Also, there were no behavioral changes suggestive of hepatic encephalopathy.

CO₂ Reactivity — Normal Animals

In the normal animals increasing the arterial Pco₂ level resulted in a progressive rise in CBF. A typical chart record-
ing of the $^{133}$Xe clearance curves, 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 returning briefly to the control level) to 58 mm Hg, a steepening of the $^{133}$Xe washout curve is evident indicating increasing cerebral perfusion.

In figure 2 the closed circles show the mean gray matter cerebral blood flows for the nine normal animals when the Paco$_2$ was altered. At normocapnia (30 to 39 mm Hg) a mean CBF of 59.1 ± 6.6 ml per minute per 100 gm of tissue was recorded. With stepwise increments in Paco$_2$ this mean increased to 88.0 ± 7.4, 121.1 ± 14.4 and 125.4 ± 17.0 ml per minute per 100 gm of tissue at Paco$_2$ values of 40 to 49, 50 to 59, 60 to 69 mm Hg, respectively. A decrease in Paco$_2$ to the 20 to 29 mm Hg range resulted in a decrease in mean CBF to 55.1 ± 5.4 ml per minute per 100 gm of tissue.

**Gray matter cerebral blood flow (mls/min/100g of tissue)**

![Graph showing cerebral blood flow vs Paco2](image)

**Figure 2** The mean values of CBF at the various levels of Paco$_2$ are shown for the normal animals (closed circles), the jaundiced animals (open circles), and the jaundiced animals after alpha-receptor blockade (open triangles).

**CO$_2$ Reactivity — Jaundiced Animals**

Figure 2 also shows the mean gray matter CBF values recorded in the same Paco$_2$ ranges as open circles. The mean CBF in the jaundiced animals was lower than the normals at all levels of Paco$_2$. At normocapnia (30 to 39 mm Hg) a mean of 53.0 ± 3.4 ml per minute per 100 gm of tissue was recorded but this was not significantly different from the normal value. With hypercapnia a significantly lower mean CBF was recorded in the ranges 40 to 49, 50 to 59, and 60 to 69 mm Hg (P<0.005, P<0.05, and P<0.05, respectively). The values were 54.6 ± 3.3, 77.9 ± 6.3, and 92.2 ± 12.1 ml per minute per 100 gm of tissue, respectively. Thus, the jaundiced animals displayed an attenuated response to hypercapnia.

Reduction of the Paco$_2$ values into the range 20 to 29 mm Hg by hyperventilation produced a fall in CBF to 34.8 ± 3.6 ml per minute per 100 gm of tissue in the jaundiced group. This was significantly different from normal (P<0.025). Thus, hypocapnia produces a larger fall in CBF in the jaundiced animals.

**Alpha-Adrenergic Blockade**

From in vitro experiments we have previously shown that jaundiced plasma produces a hypersensitivity of the renal and femoral arteries to the pressor effects of noradrenaline. This may have accounted for the shift in the curve from normal to jaundiced and may be reversed by alpha-adrenergic blockade. In the present experiments this was tested by redefining the CBF/Paco$_2$ curve in the jaundiced animals after a 15-mg i.v. injection of the alpha-adrenergic blocking agent, phentolamine.

Figure 2 shows the mean CBF (open triangles) recorded at various Paco$_2$ ranges after alpha blockade in the jaundiced animals. A return toward normal is evident in the CBF/Paco$_2$ curve. The response to raised CO$_2$ was significantly increased after alpha blockade of the jaundiced animals in the 40 to 49 mm Hg Paco$_2$ range (P<0.05).

**Discussion**

It is well established that the cerebral circulation responds to an increase in arterial blood carbon dioxide tension (Paco$_2$) by increasing. When blood flow was studied with an indicator washout technique, it was shown that the CO$_2$ reactivity was greater for cerebral gray matter than for white matter. In the present study a comparison of the gray matter flow CO$_2$ reactivity between a group of normal and jaundiced animals was made. The results suggest that the normal CO$_2$ induced dilatation was opposed by an alpha-adrenoreceptor mediated constriction and that the normal cerebrovascular constriction with lowered CO$_2$ was assisted by this mechanism. We have previously demonstrated (in vitro) that plasma from animals with obstructive jaundice potentiates the pressor effects of noradrenaline. Therefore, we suggest that the cerebrovascular alpha-receptor mediated mechanism found in the present study was due to the potentiation of normal cerebral sympathetic activity.

Other workers have shown that the cerebrovascular response to CO$_2$ is altered by sympathetic nerve stimulation or section. Also, alpha-adrenergic blockade has been
shown to potentiate the cerebral vasodilator response to increased Paco2, while complete interruption of sympathetic nerves in tetraplegic man reduces the vasoconstrictor response to lowered Paco2.

All of these studies point to a sympathetic vasoconstrictor innervation to the cerebral vessels but this has recently been disputed. Stone, Raichle and Hernandez (1974) using a flowmeter have shown that sympathectomy causes a reduced cerebral vasodilatation with hypercapnia rather than the enhanced response previously shown. These workers have proposed that the sympathetics are cerebral vasodilators and assist in the reaction to hypercapnia. The present evidence, however, would support the sympathetic cerebral vasoconstrictor theory.

In the present experiments the cerebral blood flows recorded in the jaundiced animals were lower than those found in the normal animals at all levels of Paco2, and reverted toward normal with alpha-adrenergic blockade. This situation is similar to that found by Harper et al., who demonstrated a reduction in the CO2 response during sympathetic stimulation, and suggests that the present finding of a reduced CBF response to elevated Paco2 is due to increased sympathetic tone. The work of Kawamura et al. suggests that the cerebral vasodilator response to raised arterial Pco2 is opposed by an alpha-adrenergic mechanism in normal baboons. We have shown a similar effect in the present experiments with bile duct ligation and it may be that the attenuation of hypercapnia response found in jaundiced was due to enhancement of normal cerebral sympathetic tone.

In the present experiments the difference between the jaundiced and normal CBF values was not constant at all levels of Paco2. At normocapnia the jaundiced values were lower than the normals by 13%. With hypercapnia this difference increased by 33%. This implies a larger sympathetic vasoconstrictor tone with increasing CO2 in the jaundiced animals. It has been suggested that the sympathetic nerves modulate the CO2 response, and that the cerebral vasodilatation is partially related to a reduction in sympathetic tone. Also, there is evidence to suggest that hypercapnia vasodilatation is partly mediated by a neural reflex involving an autonomic brain stem center. The present results could be explained if, in the normal animals, hypercapnia produces the cerebral dilatation partly via the brain stem to decrease cerebral sympathetic vasoconstrictor tone. In the jaundiced animals this component of the CO2 dilatation may have been abolished by the adrenergic vascular hypersensitivity previously described.

With hypercapnia the difference between normal and jaundiced baboons also increased from the normocapnic 13% to a 37% difference at 20 to 29 mm Hg. The reduction of hypocapnic cerebral vasoconstriction in tetraplegic man would suggest that the hypocapnic cerebral vasoconstriction is partly mediated by an increased sympathetic tone to the cerebral vessels. In the present experiments, this increase in tone may be potentiated in jaundiced animals and so produce the exaggerated response to hypocapnia.

These experiments, therefore, demonstrate that in a situation when the effects of sympathetic nervous system are potentiated, the cerebral CO2 reactivity is altered by an alpha-receptor mediated vasoconstriction. Furthermore, it appears that an increased Paco2 induces cerebral vasodilatation partly by a decrease in sympathetic tone. Also, a decreased Paco2 may cause cerebral vasoconstriction partly by sympathetic tone.

The possibility arises that the reduced CBF and reduced response to raised CO2 in the jaundiced animals may be due to some pathological change in the cerebral arteries. This is unlikely as alpha blockade in jaundice increases the response to raised CO2. Thus, the reduced response found in obstructive jaundice would appear to be related to an alpha-receptor adrenergic mechanism. Furthermore, a generalized pathological vessel disorder would be expected to similarly attenuate the cerebral vasoconstricor response to lower Pco2. The present results indicate the reverse and this further supports the theory of hyperactivity of the sympathetic system.

A further alternative is that alterations of brain metabolism consequent upon liver dysfunction may be responsible for the lowered CBF and disturbed CO2 reactivity. This, in our opinion, is the less likely explanation as our experimental animals showed little clinical evidence of cerebral dysfunction.

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References

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