Abnormal Cerebrovascular Response to Altered PaCO₂ 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 133 Xe injection technique. The baboons with bile duct ligation were found to have decreased CBF at all levels of PaCO₂. 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 CO₂. Also, alteration of the PaCO₂ 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 and sympathetic fibers from the cervical ganglia, their physiological function in the control of cerebral blood flow (CBF) is unclear. In particular, many workers have been unable to demonstrate a change in CBF when the sympathetic ganglia were electrically stimulated or the fibers cut. Thus, there is considerable uncertainty concerning the cerebrovascular response to sympathomimetics.

In contrast, the response to increased arterial PCO₂ has been extensively documented. There is much evidence to suggest that the action of increased PaCO₂ is to cause cerebrovascular dilatation and that this is mainly mediated by a direct effect of the CO₂ or of pH on the cerebral resistance vessels.

Recently, this predictability of cerebral CO₂ 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 PaCO₂ while stimulation reduced the response. 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. Also, there is some evidence that sympathectomy reduces the hypocapnic constrictor response.

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 and in vitro. 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). In these experiments in normal animals infusion of NA into the internal carotid artery at 8 and 16 μg 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 μg 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 μg per minute (P<0.005) and 16 μg 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 PaCO₂ in a group of normal animals and in a group with surgically induced bile duct ligation.
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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 Goddard 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](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.\(^2\) When blood flow was studied with an indicator washout technique,\(^3\) 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.\(^7\) Also, alpha-adrenergic blockade has been
shown to potentiate the cerebral vasodilator response to increased $\text{Paco}_2$,
while complete interruption of sympathetic nerves in tetraplegic man reduces the vasoconstrictor
response to lowered $\text{Paco}_2$.

All of these studies point to a sympathetic vaso-
constrictor 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 cerebrovascular dilatation with hyper-
capnia rather than the enhanced response previously shown.
These workers have proposed that the sympathetics are
cerebral vasodilators and assist in the reaction to hyper-
capnia. 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 $\text{Paco}_2$ 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 $\text{CO}_2$ response during symp-
pathetic stimulation, and suggests that the present finding of
a reduced CBF to elevated $\text{Paco}_2$ is due to increased sympathetic tone. The work of Kawamura et al. suggests
that the cerebral vasodilator response to raised arterial $\text{Paco}_2$ 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 jaun-
dice was due to enhancement of normal cerebrovascular
sympathetic tone.

In the present experiments the difference between the
jaundiced and normal CBF values was not constant at all
levels of $\text{Paco}_2$. At normocapnia the jaundiced values were
lower than the normals by 13%. With hypercapnia this
difference increased by 33%. This implies a larger sym-
pathetic vasoconstrictor tone with increasing $\text{CO}_2$ in the jaundiced animals. It has been suggested that the sym-
pathetic nerves medulate the $\text{CO}_2$ response, and that the
cerebrovascular dilatation is partially related to a reduction in
sympathetic tone. Also, there is evidence to suggest that
hypercapnia vasoconstriction is partly mediated by a neural
reflex involving an autonomic brain stem center. The pre-
sent 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 $\text{CO}_2$
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 vaso-
constriction 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 situa-
tion when the effects of sympathetic nervous system are
potentiates, the cerebral $\text{CO}_2$ reactivity is altered by an
alpha-receptor mediated vasoconstriction. Furthermore, it
appears that an increased $\text{Paco}_2$ induces cerebrovascular dilatation partly by a decrease in sympathetic tone. Also, a
decreased $\text{Paco}_2$ may cause cerebral vasoconstriction partly
by sympathetic tone.

The possibility arises that the reduced CBF and reduced
response to raised $\text{CO}_2$ 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 $\text{CO}_2$. Thus, the reduced response found in obstruct-
ive 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 vasoconstrictor response to lower $\text{Paco}_2$. 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 $\text{CO}_2$ reac-
tivity. 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

1. McNaughton F: The innervation of the intracranial blood vessels and
2. Lassen NA: Control of cerebral circulation in health and disease. Cir-
culation Research 34:749-760, 1974
14:261-268, 1964
6. Betz E, Heuser D: Cerebral cortical blood flow during changes of acid-
control of cerebral blood flow in the baboon. Circulation Research
25:77-93, 1969
pathetic nervous activity on cerebral blood flow. Arch. Neurol. 27:1-6, 1972
vasoconstriction with hyperventilation in tetraplegic man. Lancet
1:457-460, 1972
10. Falck B, Nielsen KC, Owman C: Adrenergic innervation of the pial cir-
11. Bloom D, Bonzon L, Rosendorff C: Renal blood flow in obstructive
12. Bloom D, McCalden TA, Rosendorff C: The effects of jaundiced plasma
13. Bloom D, Eddelman BH, McCalden TA: Modification of the cerebro-
reactivity of the fast and slow clearing compartments. Stroke 5:607-611, 1974
erivation on cerebral $\text{CO}_2$ sensitivity. Stroke 5:13-18, 1974
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