Cerebral Blood Flow in Cats After an Acute Hypertensive Insult With Damage to the Blood-Brain Barrier

BY J. L. PANNIER, M.D., AND I. LEUSEN, M.D.

Abstract: Cerebral blood flow was measured with the 133Xenon clearance method in anesthetized cats under controlled ventilation. An acute pressure increase in the carotid system increases the cerebrovascular permeability to Evans blue, indicating damage to the blood-brain barrier. In these conditions the reactivity of cerebral blood vessels toward changes in the acid-base balance is altered: the CO₂ reactivity is less pronounced, while the effect of increasing the plasma [HCO₃⁻] is more pronounced than in normal cats. Autoregulatory capacity toward moderate alterations in arterial blood pressure or in intracranial pressure is well maintained in these conditions.

Additional Key Words: hypertension, autoregulation, intracranial pressure

Evidence, summarized by Lassen, suggests that the cerebrovascular response to CO₂ alterations is the result of extravascular pH changes occurring in brain tissue. In view of this hypothesis, the different diffusion characteristics of CO₂ and HCO₃⁻ through the blood-brain barrier could explain the contrast between the marked effects of acute respiratory changes and the inconsistent effects of acute metabolic changes in blood pH on cerebral blood flow (CBF). Accordingly, a lesion of the blood-brain barrier could be expected to alter the reactivity of the cerebral vessels toward changes in the acid-base balance. This possibility was investigated in anesthetized cats in which the blood-brain barrier was acutely damaged by an abrupt hypertensive insult.

Methods

The experiments were carried out on adult cats. Under light thiopental anesthesia, the trachea was cannulated; polyethylene catheters were introduced in a femoral vein, femoral artery, and thyroid artery; the surface of the skull was widely exposed, and a needle was placed in the cisterna magna or in a lateral cerebral ventricle. After completion of the surgical preparation the animals were paralyzed with gallamine (Flaxedil®, 5 mg per kilogram per hour) and mechanically ventilated with a gas mixture containing 67.5% N₂O, 25% O₂, and 7.5% N₂. Procaine (2%) was applied locally on the surface of the skin wounds.

Body temperature was kept constant, arterial blood pressure was continuously recorded, and the mean pressure was obtained by electrical integration. Intracranial pressure was measured via the intracisternal needle unless otherwise specified. The methods used for the determination of acid-base parameters in arterial blood plasma and in cerebrospinal fluid (CSF) were previously described. CSF pH was calculated using the values given by Mitchell et al. for the solubility of CO₂ and for pK' in CSF, and a CSF Pco₂ value derived from the arterial Paco₂ according to Pontén and Siesjo. Control cats and cats with a damaged blood-brain barrier were studied.

DAMAGE TO THE BLOOD-BRAIN BARRIER

The cats were ventilated for ten minutes with 65% N₂O, 10% CO₂ and 25% O₂. About 1.5 to 2 ml of citrated blood were manually injected very rapidly into a carotid artery via the thyroid catheter during temporary occlusion of the common carotid just below the thyroid artery. This procedure is analogous to the method used to damage the blood-brain barrier in dogs described by Haggendal and Johansson, and results in an abrupt but transient pressure increase in the carotid artery up to a level of about 30 cm Hg (measured in a few preliminary experiments). The permeability of the cerebral vessels was studied at the end of the experiment with Evans blue dye as previously described. After the hypertensive insult, the cats were ventilated again with 67.5% N₂O, 7.5% N₂, and 25% O₂ for one hour before the beginning of each study.

ALTERATIONS IN PLASMA pH

Changes in the acid-base balance were induced with the same experimental protocol as described in previous experiments. To alter the Paco₂, N₂ was replaced by CO₂ without modifying the percent of N₂O and O₂ in the inspired gas mixture. CBF was first measured during ventilation with 0% CO₂. The measurement was repeated after 20 minutes' ventilation with 5% CO₂. The cats were ventilated again with 0% CO₂ and an intravenous infusion of Na₂CO₃ (0.23 M) was started and maintained for 90 minutes (ten cats). CBF was measured 30, 60 and 90 minutes after the start of the infusion, the last measurement being made under 5% CO₂ in-
ALTERNATIONS IN ARTERIAL BLOOD PRESSURE

The influence of changes in mean arterial blood pressure (BP) on CBF was studied in seven cats. After a control observation, the blood pressure was diminished in two steps. First, a decrease of about 3 cm Hg (mean pressure) was induced by the i.v. infusion of the alpha-adrenergic blocking drug phenotolamine (Regitine®, 5 mg per kilogram per hour, followed by 2.5 mg per kilogram per hour), and eventually supplemented by the withdrawal of blood. Second, an additional decrease of about 3 cm Hg was induced by further bleeding (20 to 30 ml) while the infusion of phenotolamine was maintained. In both instances, the blood pressure was lowered progressively over a 10 to 15-minute period and held constant, while the CBF was measured 20 minutes after the beginning of the change in blood pressure.

ALTERNATIONS IN INTRACRANIAL PRESSURE

The influence of alterations in the intracranial pressure (ICP) on CBF was studied in six cats. Intracranial pressure was raised by infusion of artificial CSF into the cisterna magna, and infusion pressure was determined by regulating the height of the reservoir connected to the cisterna magna. ICP was continuously measured from a needle introduced into a lateral cerebral ventricle. Intracranial pressure was increased in two steps, each time by about 3 cm Hg. In both instances, pressure was raised progressively over a ten-minute period, then held constant while the CBF was measured 20 minutes after the beginning of the change in ICP.

MEASUREMENT OF CBF

CBF was measured with the 133Xenon clearance method, as previously described. About 0.25 ml of 133Xenon solution (0.5 mCi) was injected in the carotid system in five seconds via the thyroid artery. Tissue clearance of 133Xenon was monitored for at least ten minutes by means of a single collimated NaI(Tl) crystal (5 cm diameter, 5 cm thick), and an amplifier, pulse height analyzer, and linear ratemeter assembly (Tracerlab). The scintillation detector with the collimator (diameter: 2 cm, length: 6 cm) was placed lateral to the cat’s head at a right angle to the midline and oriented downward with an angle of approximately 30° to 35° to the horizontal plane. The skin and muscles on the superficial and lateral part of the head were removed in order to minimize the influence of isotope uptake in extracranial tissue. A 0.5-second time constant was used to record the first two minutes of clearance; the response time for full scale deflection of the potentiometer chart recorder was 0.4 second (Texas Instruments, Servowriter). CBF was calculated in milliliters per 100 gm per minute according to the stochastic (height over area) method. In some preliminary experiments, the brain:blood partition coefficient (A) was determined for whole brain in the cat with the method described by Veall and Mallett. It was found to approximate unity at normal hematocrit values, which agrees with the observations in dog and man. The results are presented as mean values with standard deviation. Differences between values obtained before and during infusions, or before and during changes in cerebral perfusion pressure within a group of cats, were analyzed using Student’s t-test for paired data. Differences between values obtained in two different groups of cats were analyzed using an unpaired t-test.

METHODOLOGICAL TEST: CONTAMINATION FROM EXCRACEREBRAL TISSUES

To estimate the influence of isotope uptake in extracranial tissue on the clearance curves, the distribution of 133Xenon in the tissues after an intracarotid injection was investigated in a preliminary series of experiments on nine cats. The animals were killed with KCl (i.v.) immediately (four cats) or ten minutes (five cats) after the injection of 133Xenon. The two cerebral hemispheres and symmetric samples of jaw muscle on each side of the head were rapidly dissected free, cut into pieces, and put into closed test tubes which were kept in ice water and filled with the tissue samples to a height of < 2 cm. Radioactivity was measured in the tissue samples with a well-type gamma spectrometer (Nuclear Data). The results (activity per gram) are expressed as percent of the activity per gram of tissue in the hemisphere on the side of the injection. In Group 1 (killed immediately following the injection), the mean activity per gram in ipsilateral jaw muscle was 8.9% (SD ± 5.29), in contralateral jaw muscle 0.18% (SD ± 0.19), and in the contralateral hemisphere 9.3% (SD ± 7.01). In Group 2 (killed ten minutes after the injection), the mean activity per gram in ipsilateral jaw muscle was 92.2% (SD ± 64.46), in contralateral jaw muscle 3.7% (SD ± 2.91), and in the contralateral hemisphere 6.7% (SD ± 2.18).

Results

PERMEABILITY OF THE BLOOD-BRAIN BARRIER

The permeability of the cerebral blood vessels for Evans blue was clearly modified in cats who had acute hypertension in the carotid system as described in Methods. Macroscopic inspection of the brains showed areas of Evans blue extravasation in the cerebral cortex and in deep gray nuclei. Blue staining was more pronounced on the side of the autotransfusion than on the other side. The brains of control cats were not found to be colored after the administration of Evans blue.

INHALATION OF 5% CO2

CBF was studied before and during the inhalation of 5% CO2 in 16 control cats and in 16 cats one hour to one hour and three minutes after an acute hypertensive insult (fig. 1). Individual data obtained from control cats are listed in tables 1 and 2, and values from cats with a hypertensive insult in tables 3 and 4 (control values obtained before the i.v. infusion). An increase in Paco2 from 30 mm Hg (SD ± 3.8) to 47 mm Hg (SD ± 4.4) increased CBF from 42 ml/100 gm per minute (SD ± 11.4) to 121 ml/100 gm per minute (SD ± 31.7) in normal cats. An increase in Paco2 from 30 mm Hg (SD ± 3.8) to 46.5 mm Hg (SD ± 6.1) increased CBF from 35 ml/100 gm per minute (SD ± 9) to 74 ml/100 gm per minute.
(SD ± 24.7) in cats who had a hypertensive insult. The difference in mean CBF between the two groups of cats just attained the 5% significance level (P = 0.05) at the lower \( P_{acO_2} \) level, but was highly significant (P < 0.001) at the higher \( P_{acO_2} \) level. Mean increase in CBF as a function of \( P_{acO_2} \) was significantly lower (P < 0.001) in cats who had a hypertensive insult (2.41 ml/100 gm per minute per 1 mm Hg change in \( P_{acO_2} \), SD ± 1.33) than in the control cats (4.85 ml/100 gm per minute per 1 mm Hg change in \( P_{acO_2} \), SD ± 1.94).

ICP, measured in the cisterna magna, increased during the inhalation of 5% CO\(_2\) from 5 cm H\(_2\)O (SD ± 1.6) to 13 cm H\(_2\)O (SD ± 4.5) in control cats, and from 7 cm H\(_2\)O (SD ± 5) to 14 cm H\(_2\)O (SD ± 4.2) in cats who had a hypertensive insult. It should be noted that 0.2 ml CSF was sampled in each cat before these measurements.

**INFUSION OF Na\(_2\)CO\(_3\) — 0.23 M**

The results obtained in this series of experiments on ten cats who had a hypertensive insult are presented in figure 2 and table 3. In each cat two different \( P_{acO_2} \) levels were studied before and during the infusion of Na\(_2\)CO\(_3\). Plasma actual [HCO\(_3\)] was increased from 13 mEq per liter (SD ± 1.4) to 24 mEq per liter (SD ± 2.9) 15 minutes after the beginning of the infusion, and was maintained constant at a level of 25 mEq per liter (SD ± 2.7) throughout the rest of the infusion period. During ventilation with 0% CO\(_2\), CBF was not significantly altered with respect to the control value. \( P_{acO_2} \) and CBF were, respectively, 28 mm Hg (SD ± 2.9) and 31 ml/100 gm per minute (SD ± 7.8) before the infusion, and 31 mm Hg (SD ± 3.5) and 31 ml/100 gm per minute (SD ± 5.2) 60 minutes after the start of the infusion. During ventilation with 5% CO\(_2\), however, CBF was significantly decreased with respect to the control value (P < 0.001). \( P_{acO_2} \) and CBF were, respectively, 48 mm Hg (SD ± 6.2) and 44 ml/100 gm per minute (SD ± 11.5) 90 minutes after the start of the

![](image1.png)

**FIGURE 1**
Effect of acute (20-minute) alterations in the arterial \( P_{CO_2} \) (\( P_{acO_2} \)) on cerebral blood flow (CBF) in normal cats \((n = 16)\) and in cats who had an acute hypertensive insult \((n = 16)\). Mean values ± SD.

![](image2.png)

**FIGURE 2**
Effect of an infusion of Na\(_2\)CO\(_3\) (0.23 M) on CBF in cats who had an acute hypertensive insult. \( P_{CO_2} \) arterial \( P_{acO_2} \) \( [\text{HCO}_3^-] \): actual bicarbonate concentration in arterial blood plasma \((\text{white bars})\), and bicarbonate concentration in CSF \((\text{hatched bars})\). The mean values ± SD obtained on 10 cats are presented for the different parameters 40 minutes and 10 minutes before, and 15, 30, 60 and 90 minutes after, the beginning of the Na\(_2\)CO\(_3\) infusion. The animals were ventilated for 30 minutes with 5% CO\(_2\) starting 30 minutes before and 70 minutes after the beginning of the infusion.
CBF IN CATS AFTER ACUTE HYPERTENSIVE INSULT

TABLE 1

Effect of Acute (20-Minute) Alterations in the Arterial P_{CO_2} on Cerebral Blood Flow in Normal Cats

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Individual data obtained from control cats infused with Na_2CO_3 are listed in table 3.

infusion, [HCO_3] in CSF was significantly (P < 0.001) increased 60 minutes after the start of the infusion, from 21 mEq per liter (SD ± 0.7) to 25.5 mEq per liter (SD ± 2). Using the mean values and the method of calculation described in Methods, CSF pH increased from 7.41 to 7.46 during ventilation with 0% CO_2, and from 7.24 to 7.31 during ventilation with 5% CO_2.

Arterial blood pressure was practically unchanged during these experiments, the mean pressure being 15 cm Hg (SD ± 2.1).

Individual data obtained from control cats infused with Na_2CO_3 are listed in table 3.

TABLE 2

Effect of an Infusion of Na_2CO_3 (0.23 M) on CBF in Normal Cats During the Inhalation of 5% CO_2

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<th>Cat no.</th>
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INFUSION OF NaCl — 0.29 M

In order to study the influence of the general experimental procedure, control experiments were carried out with 0.29 M NaCl solutions. The experimental protocol was similar to that of the previous experiments, and the values obtained on six cats who had an acute hypertensive insult are shown in figure 3 and table 4. Plasma actual [HCO_3] (15 mEq per liter, SD ± 2.1), CSF [HCO_3] (22.2 mEq per liter, SD ± 1.6) and arterial blood pressure (14.5 cm Hg, SD ± 2.4) were generally unchanged during these experiments. CBF also was not systematically influenced by the NaCl infusions.

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TABLE 3
Effect of an Infusion of Na₂CO₃ (0.23 M) on CBF in Cats Who Had an Acute Hypertensive Insult

<table>
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Values obtained at two different Paco₂ levels before and during the infusion.

During ventilation with 0% CO₂, Paco₂ and CBF were, respectively, 33 mm Hg (SD ± 3) and 40 ml/100 gm per minute (SD ± 8.9) before the infusion, and 32 mm Hg (SD ± 2.5) and 39 ml/100 gm per minute (SD ± 4.9) 60 minutes after the start of the infusion.

During ventilation with 5% CO₂, Paco₂ and CBF were, respectively, 47 mm Hg (SD ± 3.4) and 68 ml/100 gm per minute (SD ± 22.9) before the infusion, and 50 mm Hg (SD ± 3.9) and 69 ml/100 gm per minute (SD ± 18.8) 90 minutes after the start of the infusion.

ARTERIAL BLOOD PRESSURE
The influence of lowering arterial blood pressure on CBF was studied in seven cats who had a hypertensive insult (fig. 4). The results are presented in function of cerebral perfusion pressure (CPP), defined as the difference between mean arterial blood pressure (BP) and intracranial pressure (ICP). Lowering CPP from 15.4 cm Hg (SD ± 0.8) to 12.5 cm Hg (SD ± 0.4) and subsequently to 9.1 cm Hg (SD ± 0.6), induced by decreasing BP from 16.2 cm Hg (SD ± 1.1) to 13.3 cm Hg (SD ± 0.5) and subsequently to 9.7 cm Hg (SD ± 0.5) had no significant influence (P > 0.4) on hemispheric blood flow, which was, respectively, 33 ml/100 gm per minute (SD ± 10), 32 ml/100 gm per minute (SD ± 16) and 31 ml/100 gm per minute (SD ± 11). ICP was only slightly modified during these experiments, and decreased slightly from 0.9 cm Hg (SD ± 0.4) to 0.7 cm Hg (SD ± 0.3). Paco₂ was 32 mm Hg (SD ± 3) before and 33.7 mm Hg (SD ± 3.4) after the changes in arterial blood pressure.

INTRACRANIAL PRESSURE
The influence of raising intracranial pressure on CBF was studied in six cats who had a hypertensive insult (fig. 5). A decrease of CPP from 16 cm Hg (SD ± 0.7) to 13 cm Hg (SD ± 0.9) induced by raising ICP from...
CBF IN CATS AFTER ACUTE HYPERTENSIVE INSULT

### Table 4

**Effect of an Infusion of NaCl (0.29 M) on CBF in Cats Who Had an Acute Hypertensive Insult**

<table>
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<th>Pco₂ (mm Hg)</th>
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<th>Pco₂ (mm Hg)</th>
<th>CBF (ml/100 gm per min)</th>
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Mean values obtained at two different Paco₂ levels before and during the infusion.

0.5 cm Hg to 3.5 cm Hg (SD ± 0.5) was accompanied by a slight decrease in CBF from 35 ml/100 gm per minute (SD ± 6.4) to 34 ml/100 gm per minute (SD ± 5.5), which was not significant at the 5% level (0.05 < P < 0.10). A further lowering of CPP to 10.2 cm Hg (SD ± 1) realized by a further increase in ICP to 6 cm Hg (SD ± 1.2) induced a further decrease in CBF from 34 ml/100 gm per minute (SD ± 5.5) to 30

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**FIGURE 4**

Effect of alterations in arterial blood pressure on CBF in cats who had an acute hypertensive insult. Mean arterial blood pressure (BP), intracranial pressure (ICP) and CBF are shown as a function of cerebral perfusion pressure (CPP). Mean values ± SD obtained on seven cats.

**FIGURE 5**

Effect of alterations in intracranial pressure on CBF in cats who had an acute hypertensive insult. Same parameters as in figure 4. Mean values ± SD obtained on six cats.
ml/100 gm per minute (SD ± 3.6), which was significant (0.02 < P < 0.05).

Alterations in arterial blood pressure were variable and not systematic, mean pressure was 16.4 cm Hg (SD ± 0.7) before, and 16.2 cm Hg (SD ± 2) after, the changes in ICP. Paco2 was 30.6 mm Hg (SD ± 4) before, and 32.5 mm Hg (SD ± 4.7) after, the changes in ICP.

Discussion
Cerebral blood flow is seldom measured in cats by the intracarotid injection of 133Xenon with external monitoring of the desaturation curves through the intact skull, probably because the absence of a permeable internal carotid artery and the presence of a rich anastomotic network connecting the extracerebral and intracerebral blood vessels (rete mirabile)

seem to preclude any specific injection to the brain by way of the carotid arteries in this species. In a preliminary series of experiments (see Methods section), the distribution of 133Xenon in cerebral and extracerebral tissues was studied after an intracarotid injection of the isotope. Activity in ipsilateral muscle tissue is relatively important, and would be expected to contaminate the desaturation curves, especially toward the end of the clearance curves. It is essential therefore to remove the soft tissues in the field of the crystal on the side of the injection. Activity in muscle on the opposite side is small, and amounts to approximately 0.2 and 4% of the activity (per gram) in the hemisphere on the side of the injection, respectively, one and ten minutes after an injection. Considering the fact that the thickness of this muscle layer is maximally half of one cerebral hemisphere, and considering the absorption of 81 kev radiation in tissues between crystal and muscle, only 25% (or less) of the activity from the contralateral muscle mass would be detected taking the activity from the ipsilateral hemisphere as reference. Hence, contamination of the clearance curves from this source would amount approximately to 0.05 and 1%, respectively, one and ten minutes after the injection, which can be neglected.

These experiments seemed to indicate that the combination of an intracarotid injection of 133Xenon, with removal of the soft tissues on the surface of the skull and with suitable collimation, allows measurement of CBF in cats. Furthermore, flow is measured mainly in the hemisphere on the side of the injection, at least in normal cats, since the contralateral hemisphere contains only about 6% to 10% of the activity (per gram tissue) in the hemisphere on the side of the injection.

Several authors have shown that acute or chronic arterial hypertension may damage the blood-brain barrier function. The Evans blue extravasation in the brains of cats who had an abrupt pressure increase in the carotid system indicates an increased cerebrovascular permeability to proteins in these conditions, which confirms the findings of Håggendal and Johansson, who produced a damage to the barrier in dogs with a similar procedure. Evans blue is bound to plasma proteins, especially to albumins, and is generally considered as a protein-tracer in this type of experiment.

Intraluminal pressure in the common carotid artery, in which the blood was injected, increased to about 30 cm Hg during the injection, but the way this pressure-pulse was propagated and damped over the cerebrovascular tree is unknown.

Besides the increase in pressure, the rapidity of the pressure rise and the administration of CO2 during the procedure should favor the occurrence of a lesion of the blood-brain barrier in these conditions.

The results of the present experiments seem to indicate that the reactivity of the cerebral blood vessels is altered in cats who had a hypertensive insult. CBF is about 15% lower than in control cats at normocapnia, and the increase in CBF during hypercapnia is less pronounced (fig. 6).

A lesion of the blood-brain barrier could lead to an extravasation of plasma proteins with edema formation during the experiment. A decreased CPP resulting from an increased ICP could then explain a decreased CBF if the pressure-autoregulation mechanisms were also impaired in these conditions. This could not only explain the lower CBF in control conditions, but also the decreased CO2 reactivity, since the administration of CO2 could further impair the integrity of the blood-brain barrier and favor edema formation. However, measurements of ICP and the study of pressure autoregulation in these cats do not support this interpretation. ICP was of the same order of magnitude in normal cats and in cats who had a hypertensive insult, both during the inhalation of 0% CO2 (respectively, 5 and 7 cm H2O) and during the inhalation of 5% CO2 (respectively, 13 and 14 cm H2O). The rise in ICP during the inhalation of 5% CO2 is probably somewhat attenuated by the sampling of CSF between the two measurements in all cats. Such a rise in ICP (to a value of approximately 1 cm Hg) and the corresponding decrease in CPP would not affect CBF in the experimental groups, since it was shown that CBF is barely influenced by alterations in the ICP between 0.5 and 3.5 cm Hg in these cats (fig. 6). A further increase in the ICP to 6.5 cm Hg was accompanied by about 10% decrease in mean CBF but the limit of the autoregulation capacity was not adequately defined in the present experiments.

CBF was not systematically affected by alterations in arterial blood pressure between 16.5 and 10 cm Hg (fig. 4), which suggests an absence of major deficits in the pressure autoregulation mechanisms in these cats, at least in this pressure range. No "false" autoregulation apparently is involved, since ICP changed only minimally during the changes in blood pressure.

An efficient autoregulation toward alterations in
CBF IN CATS AFTER ACUTE HYPERTENSIVE INSULT

blood pressure in the presence of a reduced response of CBF to a rise in Paco₂, as described in the present experiments, was previously observed in patients and seems to indicate that these two mechanisms are not necessarily impaired simultaneously. These phenomena, however, must be interpreted with caution as long as only a limited range of perfusion pressures are investigated, especially since some abnormalities of autoregulation can be observed only when the limits of the autoregulation capacity are studied.

The influence of prolonged alterations in the plasma [HCO₃⁻] on CBF in cats with a lesion of the blood-brain barrier is of special interest in view of the pH hypothesis of CBF regulation. Carbon dioxide is assumed to act by changing the pH somewhere in the brain tissue, probably at the level of the arteriole wall. Carbon dioxide can diffuse freely through the blood-brain barrier which, on the other hand, is relatively impermeable to bicarbonate. The different diffusion characteristics of CO₂ and HCO₃⁻ through this barrier are supposed to explain the contrast between the marked effects of acute respiratory changes and the inconsistent effects of acute metabolic changes in blood pH on CBF. Accordingly, a lesion of the blood-brain barrier would be expected to alter the reactivity of the cerebral blood vessels to changes in the acid-base balance if the permeability for bicarbonate ions is altered.

In the present experiments, the effect of an increase in plasma [HCO₃⁻] was investigated in cats who had a hypertensive insult during prolonged (90 minutes) infusions of Na₂CO₃ solutions in normocapnic and hypercapnic conditions. Paco₂ was kept at a normal level during the first 70 minutes of the infusion to avoid the effect of a sustained increase in the Paco₂ on CBF and CSF [HCO₃⁻]. In normocapnia, CBF was barely influenced when the plasma [HCO₃⁻] was increased with 12 mEq per liter during 60 minutes, but during hypercapnia, 90 minutes after the start of the infusion, it showed a 40% reduction (fig. 2 and table 3). In the same experiments, the CSF [HCO₃⁻] was significantly increased (about 4.5 mEq per liter) 60 minutes after the beginning of the infusion. The decreased CBF and the increased CSF [HCO₃⁻] during the prolonged infusions of Na₂CO₃ cannot be explained by the general experimental protocol (anesthesia, time, initial hypercapnia, efficacy of solutions) as indicated by control experiments with NaCl infusions (fig. 3 and table 4).

The increased CSF [HCO₃⁻] suggests an increase of the [HCO₃⁻] of the cerebral interstitial fluid. This would imply a more alkaline pH at any Paco₂ level, which would tend to decrease CBF during prolonged infusions of Na₂CO₃. However, the fact that CBF did not change from control during the inhalation of 0% CO₂ 60 minutes after the start of a carbonate infusion, despite a rise in CSF [HCO₃⁻], casts some doubt on this interpretation. To clarify this point, it must be emphasized that CBF is probably influenced by several factors in these experimental conditions, so that any change in CBF probably must be considered only as a net effect of different mechanisms often opposing each other.

The administration of hypertonic solutions could tend to increase CBF, according to several authors, but this effect seems to depend greatly on the experimental circumstances and apparently not be a complicating factor in the present study, as shown by control experiments with NaCl. Hemodilution can also increase CBF and the relative importance of this effect (insofar as a hypoxic component is involved) seems to increase with increasing alkalization; it is more important at the lower Paco₂ levels and especially when alkaline solutions are infused in hypocapnic conditions. Finally, in analogy with the flattening of the Paco₂ response curve of CBF at low Paco₂ levels, observed by many investigators and with results obtained previously on anesthetized rats, it can be expected that the vasoconstricting effect of a certain increase in the [HCO₃⁻] of cerebral interstitial fluid, if present, would be quantitatively less important at low Paco₂ levels (about 30 mm Hg) than at intermediate values of Paco₂ (45 to 50 mm Hg).

Considering these factors, the failure of baseline CBF to change during carbonate infusions, despite a rise in CSF [HCO₃⁻], does not mean that an alkalization of cerebral interstitial fluid is without effect on CBF. However, in the conditions of the present study, this effect could be less pronounced and more opposed by other factors at the 0% CO₂ level than at the 5% CO₂ level.

The results obtained during the carbonate infusions are in agreement with the observations of Fencl et al. when both studies are compared within the same CSF pH range. Only the results obtained during the inhalation of 5% CO₂ can be used in this respect, since the CSF pH values calculated before and after the carbonate infusion during the inhalation of 0% CO₂ (pH 7.41 and 7.46) are out of the range of the CSF pH values where these authors made their observations (between pH 7.26 and 7.35).

The mechanisms of HCO₃⁻ exchange between blood and CSF are still largely unknown, and different observations indicate that CSF [HCO₃⁻] is largely independent of blood [HCO₃⁻]. The extravasation of Evans blue in the brains of cats who had an acute pressure rise in the carotid system seemed to indicate that the normal regulatory mechanisms at the level of the blood-brain barrier were seriously impaired in these conditions. The blood-brain barrier might be more permeable for bicarbonate favoring the increase in CSF [HCO₃⁻] during the infusions of Na₂CO₃. Some lesions of the blood-brain barrier, such as the application of hypertonic solutions, increase the permeability toward both the Evans blue albumin complex and HCO₃ ions, but other lesions do not indiscriminately...
Effect of an infusion of Na$_2$CO$_3$ (0.23 M) on CBF in normal cats (n = 10; left panel), and in cats who had an acute hypertensive insult (n = 10; right panel). Mean values ± SD obtained at two different PaCO$_2$ levels before and during the infusion. The individual values for normal cats are listed in table 2, and values for cats with a hypertensive insult in table 3.

It is interesting to compare the results of the present experiments with the results obtained in similar experimental conditions in normal cats (fig. 6). When the same changes in plasma [HCO$_3^-$] and in PaCO$_2$ are induced within the same time interval (infusions of Na$_2$CO$_3$, 0.23 M), the depression of CBF at the higher PaCO$_2$ level seems in general more pronounced in cats who had a hypertensive insult (40%, SD ± 12.5) than in normal cats (18.2%, SD ± 22). Although the scatter of the individual data is very important, the difference between both groups appears statistically significant (P < 0.05) with an unpaired t-test and with a Wilcoxon test. This difference is not readily explained in view of the pH hypothesis for CBF regulation, since the accumulation of [HCO$_3^-$] in cisternal CSF during the carbonate infusion is not significantly higher in cats with a damaged blood-brain barrier (increase of 4.3 mEq per liter, SD ± 2.18) than in normal cats (increase of 2.85 mEq per liter, SD ± 1.1). However, the asymmetric character of the blood-brain barrier lesion, demonstrated by the Evans blue experiments, may well invalidate any quantitative correlation between the [HCO$_3^-$] in cisternal CSF and the measured CBF in cats who had a hypertensive insult, since the flow measurement is essentially unilateral (see Methods) while the cisternal CSF is obviously drained from both sides. The increase in the [HCO$_3^-$] of cerebral interstitial fluid in the most affected hemisphere during the carbonate infusions, if related to the lesion of the blood-brain barrier, might be more pronounced than could be suspected from measurements on cisternal CSF.

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Cerebral Blood Flow in Cats After an Acute Hypertensive Insult With Damage to the Blood-Brain Barrier
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