Effect of Cerebrospinal Fluid Removal on Cerebral Blood Flow and Metabolism in the Baboon

Influence of Tyrosine Infusion and Cerebral Embolism on Cerebrospinal Fluid Pressure Autoregulation

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SUMMARY Cerebral blood flow (CBF) and metabolism were measured before and after withdrawal of 5 to 6 ml of cerebrospinal fluid (CSF) in 17 baboons. The measurements were made before and after infusion of tyrosine, the precursor amino acid of the putative neurotransmitters, dopamine and norepinephrine, in the brain. The same observations were made in another experimental group, i.e., before and after acute cerebral multiembolization induced by microfil emboli.

In the steady state CBF was unaltered following reduction of intracranial pressure by removal of CSF. After infusion of tyrosine, CBF was decreased, and cerebrovascular resistance increased significantly on removal of CSF. Cerebral embolization did not influence changes in CBF at reduced intracranial pressure.

It appears that the cerebral resistance vessels constrict following reduction of intracranial pressure by removal of CSF and that cerebrospinal fluid pressure-CBF autoregulatory mechanisms are resistant to cerebral ischemia induced by middle cerebral artery embolization.

RECENTLY, THE EFFECTS OF withdrawal of cerebral spinal fluid (CSF) on cerebral hemodynamics with stroke and Alzheimer's disease were compared. In that study after CSF removal cerebral blood flow (CBF) decreased in patients with Alzheimer's disease but showed no significant change in patients with stroke. It was postulated that a neurogenic reflex induced by alterations in cerebral venous pressure may vary vasomotor tone of the cerebral arterial system (venoarterial reflex), and this reflex might provide a part of a cerebrospinal fluid pressure-cerebral blood flow (CSFP-CBF) autoregulatory mechanism. Furthermore, it was postulated that the excessive vasoconstriction demonstrated in Alzheimer's disease might reflect an imbalance of the central neurotransmitter system.

These observations led us to test the hypothesis that a cerebral neurogenic venoarterial reflex may regulate the CSFP-CBF autoregulatory mechanism before and after cerebral embolization in the baboon. The hypothesis to be tested was based on the following evidence: First, CBF normally remains constant despite wide changes in CSFP; secondly, the walls of the cerebral veins are thought to be the site most sensitive to changes in CSFP, and thirdly, similar venoarterial reflexes have been regularly observed in many tissues other than the brain. In addition, it was conjectured that differences in the disorder of the various neurotransmitter systems between patients with stroke and those with Alzheimer's disease might account for the different responses following withdrawal of CSF.

In the present experiments changes in cerebral hemodynamics and metabolism were measured before and after reduction of intracranial pressure by removal of CSF in the baboon. The observations were repeated after intravenous infusion of tyrosine, the precursor amino acid of the putative neurotransmitters, dopamine and norepinephrine, in the brain, since this might alter the levels of these neurotransmitters.
mitter substances and possibly influence any neurogenic reflex responses to changes in CSF pressure. These observations were repeated in another experimental group of baboons before and after cerebral embolization had been induced by the intracarotid injection of standardized microfil emboli.4,5

Methods

Seventeen baboons (Papio anubis), weighing 5 to 10 kg, were anesthetized with intravenous pentobarbital, 25 mg/kg body weight. Following tracheostomy nine animals were used for the study of induced embolism on CSF-CBF autoregulation. This group of animals were immobilized by 0.1 mg/kg body weight of pancuronium bromide (Pavulon), and anesthesia was maintained with N2O inhalation, using a Harvard variable speed respirator. Pancuronium bromide was supplemented as required to maintain immobilization. Anesthesia of all eight baboons in the experiments with tyrosine infusion was maintained with pentobarbital and 2 mg/kg body weight of gallamine triethiodide (Flaxedil). End-tidal CO2 was recorded continuously with a Beckman infrared gas analyzer. Catheters were inserted through the femoral artery into the ascending aorta to monitor systemic blood pressure and into one femoral vein to permit continuous intravenous infusion of isotonic saline to maintain mean arterial blood pressure constant, and another was inserted to return blood from the extracorporeal circulation system. An arterial catheter was inserted into the left brachial artery to draw arterial blood into the extracorporeal circulation system. The extracorporeal system included a Guyton analyzer for measuring cerebral arteriovenous (A-V) oxygen differences and oxygen and hydrogen electrodes mounted in flow-through cuvettes for measuring the partial pressure of oxygen (pO2) and hydrogen (pH2).6 Arterial and cerebral venous blood were propelled through the cuvette system and the Guyton (A-V) oxygen analyzer at a constant rate (5 ml/min) and returned to the systemic circulation via the femoral vein.

The neck was dissected, and a catheter was inserted via the left lingual artery to permit intracarotid injection of a 2 ml hydrogen bolus for measuring hemispheric blood flow. Another catheter was inserted into the left lateral sinus via the facial vein to draw cerebral venous blood into the extracorporeal circulation system. A specially made T-shaped catheter was inserted into the left common carotid artery to produce multiple cerebral infarcts. Secondly, immediately after this procedure, carotid injection of a cylindrical embolus 7 mm in length and 1.6 mm in diameter was then made through the same catheter in order to produce selective segmental occlusion of the trunk of the middle cerebral artery. We have found it possible by this method to produce both cerebral multieMBOLISM and middle cerebral artery occlusion in the same experimental animal. The localization of cerebral emboli in the cerebral vessels was confirmed at the termination of each experiment at necropsy.

In the experimental group of nine baboons submitted to cerebral embolization, 5 to 6 ml of CSF were withdrawn in the steady state and 60 minutes after embolization.

Results

Tyrosine Infusion Group

Effect of Tyrosine Infusion on CSF Autoregulation

Successful CBF hemodynamic and metabolic changes induced by withdrawal of CSF before and after intravenous infusion of tyrosine are shown in table 1. Before the tyrosine infusion CBF showed a tendency to increase after withdrawal of CSF; however, this trend did not reach the level of statistical significance. Control values for CBF increased significantly after the tyrosine infusion compared with control values before the infusion. After the tyrosine infusion the effect of withdrawal of CSF on CBF (CSFP-CBF autoregulation) was altered since CBF now decreased significantly from 32.2 to 30.1 ml/100 gm brain/min (P < 0.01) as a result of withdrawal of CSF. Cerebral metabolic rate for oxygen was unaltered by withdrawal of CSF both before and after the tyrosine infusion. Cerebral vascular resistance

\[
\text{CVR} = \frac{\text{CPP}}{\text{CBF}}
\]

where CPP = Cerebral perfusion pressure, CBF = Cerebral blood flow, and CVR = Cerebral vascular resistance.
(CVR) was not changed by withdrawal of CSF before tyrosine infusion; however, after the tyrosine infusion, as CSF was withdrawn, CVR increased significantly from 2.6 to 3.0 mm Hg/ml/100 gm brain/min ($P < 0.02$).

**Effect of Withdrawal of CSF on Cerebral Hemodynamics**

Mean arterial blood pressure (MABP) did not change by withdrawal of CSF either before or after tyrosine infusion (table 1). Control values for MABP after tyrosine infusion decreased significantly compared with the control values before infusion. Superior sagittal wedge pressure decreased by withdrawal of CSF from 235 to 192 mm Hg before the tyrosine infusion and from 231 to 175 mm Hg after the tyrosine infusion. CSFP of course decreased significantly from 123 to −6 mm Hg before tyrosine infusion and from 118 to 1 mm Hg after tyrosine infusion.

Paco2 was unaltered by the procedures, i.e., there was no significant change before or after the tyrosine infusion or during CSF removal. Likewise, Pao2 did not change during the same procedures (table 2).

**Cerebral Embolism Group**

**Effect of Cerebral Embolism on CSFP-CBF Autoregulation**

Before and after cerebral embolization, reduction of intracranial pressure by removal of CSF did not alter CBF (table 3). Before cerebral embolism CBF showed no significant change as a result of withdrawal of CSF, from 32.8 to 33.4 ml/100 gm brain/min. One hour after embolism, CBF also did not show any significant change after CSF removal: from 30.4 to 31.0 ml/100 gm brain/min. Likewise, reduction of intracranial pressure did not alter cerebral oxygen metabolism or cerebral vascular resistance before and after cerebral embolization.

Cerebral Hemodynamic Changes by Removal of CSF Before and After Cerebral Embolization

Although cerebral embolization reduced MABP significantly from 103 to 96 mm Hg ($P < 0.02$), reduction of intracranial pressure by removal of CSF did not alter MABP either in the steady state or after embolism (table 3). Superior sagittal wedge pressure decreased significantly ($P < 0.01$) from 318 to 227 mm Hg before cerebral ischemia was induced and from 338 to 197 mm Hg after embolization. Likewise, CSFP decreased from 148 to 22 mm Hg before embolization and from 137 to 13 mm Hg after cerebral embolization.

Paco2 did not show any significant changes by withdrawal of CSF, being maintained between 40.8 and 41.4 mm Hg before embolization and from 42.3 to 41.6 mm Hg after embolization. Pao2 showed no significant change during the procedures (table 2).

**Discussion**

The literature will be briefly reviewed concerning the effects on CBF of manipulating CSFP. A considerable number of experiments have been made on the effects of raised intracranial pressure on CBF. In the earliest investigations Wolff and Forbes,11 using the skull window technique in the cat, observed that the pial arteries and veins dilated as CSFP was increased and that this continued until the intracranial pressure was restored to normal. More recently, it has been shown experimentally that CBF remains constant when intracranial pressure is increased to levels of 50 mm Hg or 100 mm Hg by infusion of artificial CSF into the cisterna magna. The first clinical study to be reported concerned the effects of increased intracranial pressure on CBF in a series of patients with brain tumor.

**Table 2  Arterial Pao2 and Paco2 Before and After Withdrawal of CSF**

<table>
<thead>
<tr>
<th>Pao2 (mm Hg)</th>
<th>Before infusion</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C*</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>96.0 ± 11.5</td>
<td>(N = 8)</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>36.5 ± 3.1</td>
<td>(N = 8)</td>
</tr>
</tbody>
</table>

*E = values showing effect of CSF withdrawal.

Table 2: Arterial PaO2 and PaCO2 Before and After Withdrawal of CSF.
CBF appeared to be unaffected by increases of CSFP up to 33 mm Hg but above this level tended to decrease.14

There are few references which deal with the effect of lowering CSFP on CBF. Early but prescient observations were made by Forbes and Nason in 1935. They found that reduction of intracranial pressure by removal of CSF caused dilatation of the pial veins and venules but prompt constriction of the pial arteries.14 Haggendal et al. observed in dogs that CBF was maintained constant even when CSFP became negative.15

The first clinical study on the effects of lowering CSFP on CBF was reported by Shenkin et al.16 They showed that reduction of increased intracranial pressure by removal of CSF in patients with brain tumor caused no change in CBF. More recently, it was reported from this laboratory that lowering CSFP by removal of CSF in patients with benign intracranial hypertension17 or stroke did not alter CBF.

Several points of interest may be summarized from these studies. First, it is apparent that CBF remains constant unless CSFP exceeds certain critical levels. Second, it is evident that changes in CSFP in either direction cause the pial veins and venules to dilate. On the other hand, the pial artery responses to changes in intracranial pressure appear to be different; they dilate when pressure is increased but constrict when pressure is decreased. It appears paradoxical that the pial veins dilate as a result of both reduced and increased states of CSF pressure, while the pial arteries behave quite differently in response to the two situations. The question to be considered is whether dilatation of the pial veins produces pial arterial constriction during intracranial CSF hypertension and pial arterial dilatation during intracranial CSF hypertension as a neurogenic reflex response. The precise answer is not known. However, it is possible that in these two situations the intraluminal pressures in the cortical veins are different, although they appear to be dilated on external observation. For example, during intracranial hypertension with elevated CSFP, the pial venous dilatation may result from compression and closure of the veins near the sinuses, accompanied by distention and high intraluminal venous pressure. On the other hand, during reduced intracranial and CSF pressure, although the pial veins dilate, their intraluminal pressure may remain low. In the latter situation the cerebral veins probably dilate in order to maintain intracranial volume constant. Thus, if the intraluminal venous pressures are different in the two situations, then the arterial constriction and dilatation could be explained on the basis of a neurogenic reflex.

If there were no CSFP autoregulatory mechanism, an increase in intracranial pressure would decrease cerebral perfusion pressure (CPP) and CBF. Likewise, in the absence of CSFP autoregulation, a decrease in intracranial pressure would increase cerebral perfusion pressure and CBF.18-19 However, in the normal animal with intact CSFP autoregulation, dilatation of the pial veins occurs when CSFP is increased or decreased, but the pial arteries constrict when CSFP is decreased and dilate when CSFP is increased and thereby maintain CBF constant. Therefore, it is the pial arteries (or resistance vessels) which ultimately regulate blood flow in response to changes in intracranial pressure.

The hypothesis was advanced and some support adduced that CSFP-CBF autoregulation appears to function by means of a venoarterial neurogenic reflex which is sensitive to intracranial pressure change reflected in the thin-walled veins.1 When intracranial pressure is reduced, the thin-walled veins tend to dilate, but intracranial venous pressure decreases, as shown in the superior sagittal wedge pressure of the present experiment. On the other hand, when intracranial pressure is increased, collapse of the thin-walled veins is prevented by some intracranial venous pressure regulation mechanism and intraluminal venous pressure increases.20 Thus, it may be concluded that the thin-walled veins which are most sensitive to changes in intracranial pressure (fig. 1) could indeed be the site for initiation of a venoarterial reflex.

Other evidence to support this hypothesis has been derived from perusal of continuous records of cerebral arteriovenous oxygen differences in man during CSF removal where it was noted that the latent period for the development of CSFP autoregulatory constriction became extended. This is consistent with the idea that this response is due to changes in intracranial pressure, and it is possible that other factors may also be involved. For example, after CSF removal, the cerebral arterial and venous pressure is decreased, which may result in a decrease in cerebral blood flow. However, when CSF is replaced, the cerebral arterial and venous pressure is increased, which may result in an increase in cerebral blood flow. Therefore, it is possible that other factors may also be involved in the development of CSFP autoregulatory constriction.

<table>
<thead>
<tr>
<th>TABLE 3 Effect of Withdrawal of CSF on CBF, Metabolism, Hemodynamics, and CVR Before and After Cerebral Embolization</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>CBF (ml/100 gm brain/min)</strong></td>
</tr>
<tr>
<td><strong>CMRO2 (ml/100 gm brain/min)</strong></td>
</tr>
<tr>
<td><strong>CSFP (mm H2O)</strong></td>
</tr>
<tr>
<td><strong>MABP (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>SSWP (mm H2O)</strong></td>
</tr>
<tr>
<td><strong>CVR (mm Hg/ml/100 gm brain/min)</strong></td>
</tr>
<tr>
<td><strong>Before ischemia</strong></td>
</tr>
<tr>
<td><strong>After ischemia</strong></td>
</tr>
<tr>
<td><strong>G</strong>  <strong>E</strong></td>
</tr>
<tr>
<td><strong>G</strong>  <strong>E</strong></td>
</tr>
<tr>
<td><strong>32.8 ± 2.7 (N = 9) 33.4 ± 3.9</strong></td>
</tr>
<tr>
<td><strong>2.3 ± 0.7 (N = 8) 2.3 ± 0.6</strong></td>
</tr>
<tr>
<td><strong>148 ± 52 (N = 9) 22 ± 40</strong></td>
</tr>
<tr>
<td><strong>103 ± 14 (N = 9) 102 ± 14</strong></td>
</tr>
<tr>
<td><strong>315 ± 33 (N = 5) 227 ± 59†</strong></td>
</tr>
<tr>
<td><strong>2.6 ± 0.4 (N = 8) 2.6 ± 0.6</strong></td>
</tr>
<tr>
<td><strong>338 ± 39 (N = 5) 197 ± 33‡</strong></td>
</tr>
<tr>
<td><strong>2.8 ± 0.5 (N = 5) 2.7 ± 0.5</strong></td>
</tr>
</tbody>
</table>

*G = control values; E = values showing effect of CSF withdrawal.
†Statistically significant compared with control values.
‡Statistically significant compared with steady state values.
EFFECT OF WITHDRAWAL OF CSF IN STEADY STATE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>CSF Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-VO2</td>
<td>5.7 vol%</td>
<td>6%</td>
</tr>
<tr>
<td>SSWP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BP</td>
<td>60 mmHg</td>
<td>55 mmHg</td>
</tr>
<tr>
<td>P0/CO2</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>P0/O2</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>AI-CO2</td>
<td>6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Withdrawal of CSF (6cc)

FIGURE 1. To illustrate typical continuous recordings of cerebral arteriovenous differences for oxygen (A-VO2) recorded with the Guyton oxygen analyzer, sagittal sinus wedge pressure (SSWP), systemic arterial pressure (BP), cerebral venous and arterial PCO2 and PO2, alternately sampled by a mass spectrometer, alveolar CO2 (PCO2) and intracranial pressure (ICP) in the steady state and following removal of CSF. Note the rapid reduction in SSWP following withdrawal of CSF without remarkable change in cerebral A-VO2 differences.

Resistance in the present experiments, caused by CSF removal, may possibly be accounted for by an induced imbalance of the monoaminergic neurotransmitter systems following tyrosine infusion. It should be borne in mind, however, that 30 minutes after the infusion of tyrosine, CBF showed a significant increase despite a reduction in MAP. This observation is considered consonant with enhanced dopaminergic neurotransmitter function regulating blood pressure autoregulation and may be explained as follows: Mean arterial blood pressure became significantly reduced after the tyrosine infusion had been substituted for the isotonic saline infusion, thereby stimulating the blood pressure autoregulatory vasodilator mechanism, which may have been enhanced by an increase in available dopamine, thereby causing a significant increase in CBF. It is also possible that the infusion of tyrosine may have resulted in increased CBF brought about from intravenous infusions of tyrosine. The hypothesis that CSFP-CBF autoregulation is correlated with the presence or absence of blood pressure-CBF autoregulation. Mchedlishvili et al.28 observed that the venoarterial reflex from cerebral venous sinuses was not abolished even after bilateral extirpation of the superior and inferior cerebral arteries, together with the observations by Mchedlishvili et al., suggest that the CSFP venoarterial reflexes in the brain are resistant to cerebral ischemia, unlike the blood pressure autoregulatory mechanisms which are readily disordered by cerebral ischemia.

In conclusion, some evidence has been presented that venoarterial reflex mechanisms influence CSFP autoregulation in the brain. It was shown that the cerebral resistance vessels promptly constrict following reduction of intracranial pressure by withdrawal of CSF. This CSFP autoregulatory mechanism is resistant to cerebral ischemia in the distribution of the carotid artery but is altered by intravenous infusions of tyrosine. The hypothesis that CSFP autoregulation is influenced by neurotransmitter systems appears to be supported since tyrosine infusion may be expected to influence monoaminergic cerebral vasoconstriction when CSF is removed.

References
Use of Hydrogen for Measurement of Regional Cerebral Blood Flow

PROBLEM OF INTERCOMPARTMENTAL DIFFUSION

JAMES H. HALSEY, JR., M.D., NORMAN F. CAPRA, PH.D.,
AND RICHARD S. MCFARLAND, B.A.

SUMMARY The extreme diffusibility of hydrogen, compared with xenon or krypton, may create serious artifacts when it is used to measure local blood flow with a tissue electrode. The errors are greatest when hydrogen is given by intra-arterial slug injection, and when the electrode is within 2 mm of another tissue compartment, CSF, or air. These all appear to be a consequence of intercompartmental diffusion which can occur at rates of the same order of magnitude as clearance from the tissue by blood flow. No matter how small the electrode, the ultimate spatial resolution of the method appears to be about 2 mm unless quantitative account is taken of diffusion. An important precaution in use of the method is to obtain homogeneous tissue saturation by prolonged inhalation administration.

HYDROGEN IS FREELY diffusible between blood and brain and is metabolically inert, making it a useful indicator for blood flow measurements based on the Fick principle. Since it is relatively easily detected polarographically it would appear to be ideal for measurement of blood flow in very discrete regions. Since the essential measurement is of a clearance rate, there is no need for quantitative calibration of electrode sensitivity, and the only demand for stability is that sensitivity not change significantly for the duration of a single clearance curve, which usually is less than 15 minutes.

With these virtues, the method is understandably enjoying wide use in regional cerebral blood flow studies, basing the calculation on the same mathematical models and assumptions as those used for the '*Xenon and '*Krypton methods developed by Ingvar and Lassen. The purpose of this paper is to point out an important limitation in this application, a consequence of the much greater diffusibility of the hydrogen molecule, and to define some tentative precautions which seem appropriate.

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