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 cerebrospinal fluid (CSF) on cerebral hemodynamics in patients with stroke and Alzheimer's disease were compared.1 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 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 neurotrans-
messenger 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.4,7

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 CSFP-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 (pH). Arterial and cerebral venous blood were propelled through the arterial catheter 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 permit the injection of emboli without interrupting carotid blood flow. The left external carotid artery was ligated, and the vagus nerve and cervical sympathetic chains were meticulously preserved during these surgical procedures.

Intracranial pressure was measured through a catheter inserted into the cisterna magna via the spinal subarachnoid space after high thoracic laminectomy. Intracranial venous pressure was measured through a catheter wedged into the anterior portion of the superior sagittal sinus. Heparin, 3000 IU, was injected intravenously before starting the extracorporeal circulation pump.

All pressures were continuously recorded with Statham pressure transducers. Cerebral arteriovenous (A-V) differences were measured continuously with the Guyton analyzer. PaO₂ and PacO₂ were monitored continuously by a mass spectrometer as well as estimated periodically by the use of a Corning 165 gas analyzer. EEG and EKG were recorded throughout the experiment with a Grass 4-channel electroencephalograph.

Cerebral blood flow was measured by the hydrogen bolus technique.4,6 The clearance curves were recorded by means of a hydrogen electrode monitored in the cuvette and calculated by stochastic analysis. Cerebral perfusion pressure (CPP) was estimated by subtracting the superior sagittal wedge pressure (SSWP) from the mean arterial blood pressure (MABP). Cerebral vascular resistance (CVR) was calculated using the formula:

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

In the experimental group in which the effects of tyrosine infusion were measured, eight baboons were used, and 12.5 mg/kg body weight of tyrosine, dissolved in 100 mg of normal saline, were infused intravenously for an interval of 30 minutes. Withdrawal of CSF was made in the steady state and 40 minutes after completion of tyrosine infusion.

Preparation for Experimental Embolism

The emboli were prepared according to the method described by Molinari.4,7 Multiple cerebral infarctions were produced in the baboon by two steps as follows: First, 20 particles of Microfil, 1.4 mm in diameter and 1.0 mm in length, were injected through the T-shaped catheter in the common carotid artery in order 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 CSFP 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
Effect of Withdrawal of CSF on Cerebral Hemodynamics

Mean arterial blood pressure (MABP) did not change by withdrawal of CSF 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 significantly by withdrawal of CSF from 235 to 192 mm Hg before the tyrosine infusion and from 231 to 175 mm Hg after 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, Paco2 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. One hour after cerebral embolization, reduction of intracranial pressure did not alter cerebral oxygen metabolism or cerebral vascular resistance before and after cerebral embolization.

Cerebral Embolization Effects on CBF, Cerebral Metabolism, Hemodynamics, and CVR Before and After Tyrosine Infusion

Effect of Withdrawal of CSF on Cerebral Embolism

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).

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

* C = control values; E = values showing effect of CSF withdrawal.

<table>
<thead>
<tr>
<th></th>
<th>Before tyrosine infusion</th>
<th>After tyrosine infusion</th>
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<tbody>
<tr>
<td></td>
<td>C*</td>
<td>E</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>96.0 ± 11.5 (N = 8)</td>
<td>97.3 ± 9.1</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>36.5 ± 3.1 (N = 8)</td>
<td>36.9 ± 2.7</td>
</tr>
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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, 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 concerns the effects of increased intracranial pressure on CBF in a series of patients with brain tumor;
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 CBF on CSF. 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.\(^{16}\) 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 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 neurovascular reflex.

<table>
<thead>
<tr>
<th>Table 3: Effect of Withdrawal of CSF on CBF, Metabolism, Hemodynamics, and CVR Before and After Cerebral Embolization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before ischemia</strong></td>
</tr>
<tr>
<td>CBF (ml/100 gm brain/min)</td>
</tr>
<tr>
<td>CMRO(_2) (ml/100 gm brain/min)</td>
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<tr>
<td>CSFP (mm H(_2)O)</td>
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<tr>
<td>MABP (mm Hg)</td>
</tr>
<tr>
<td>SSWP (mm H(_2)O)</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/100 gm brain/min)</td>
</tr>
</tbody>
</table>

(C = control values; E = values showing effect of CSF withdrawal.†Statistically significant compared with control values.‡Statistically significant compared with steady state values.)

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.\(^{16,18}\) 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.

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 CBF change following withdrawal of CSF appeared to occur within a few seconds.\(^{1}\) Similar, rapidly occurring neurovascular reflexes have been observed in many organs other than brain and are generally regarded as neurogenic reflexes. The present experiments may be viewed as further support for the neurogenic neurovascular reflex hypothesis since after tyrosine infusion CSFP autoregulatory constriction became excessive, indicated by a significant reduction in CBF and a significant increase of cerebral vascular resistance as CSF was withdrawn. Tyrosine is the precursor amino acid for the putative neurotransmitters, dopamine and norepinephrine, in the brain, and increased tyrosine blood levels may influence neurotransmitter levels in the brain. Dopamine has been reported to have a cerebral vasodilatory effect with an increase of CBF,\(^{21,22}\) while norepinephrine has a well-known vasoconstrictor effect on cerebral arteries.\(^{23,24}\) The decrease of CBF and excessive increase of cerebral vascular
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 neurotransmission, as available dopamine, thereby causing a significant increase in systemic arterial pressure (SSWP) and cerebrovascular resistance.

We now consider certain differences between CSFP-CBF autoregulation and blood pressure-CBF autoregulation. The mechanisms accounting for the responses of cerebral vessels to changes in blood pressure are still a matter of debate. However, several neurogenic pathways which may influence CBF are well established, assuming that cerebral blood pressure autoregulation is controlled, at least in part, by neurogenic mechanisms. These are pathways from the vascular sympathetic ganglia, the cerebral venous sinuses, and the cranial nerves such as the facial, glossopharyngeal, or vagal nerves.

The anatomical pathways of the hypothetical venoarterial reflex have not been identified. Miller et al. demonstrated that CSFP-CBF autoregulation is correlated with the presence or absence of blood pressure-CBF autoregulation. Mchedlishvili et al. observed that the venoarterial reflex from cerebral venous sinuses was not abolished even after bilateral extirpation of the superior and inferior cerebral ganglia. The observed result in the present study that the reflex was preserved even after embolic occlusion of middle 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 embolization 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 vascular constriction 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.1 Since it is relatively easily detected polarographically it would appear to be ideal for measurement of blood flow in very discrete regions.5, 4 Since the essential measurement is of a clearance rate, there is no need for quantitative calibration of electrode sensitivity, and the only demand for stabil-

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