Studies on the Cerebral Circulation of the Baboon in Acutely Induced Hypertension

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SUMMARY The upper limit of autoregulation of cerebral blood flow was investigated in eight young baboons with the intracarotid 133 Xe clearance method. Blood pressure was increased by intravenous angiotensin infusion. Autoregulation was effective during blood pressure increase from normotensive levels to a mean pressure of 130 to 139 mm Hg. At this pressure, cerebrovascular resistance reached a maximum. With further blood pressure increase, autoregulation was broken, and the vascular resistance dropped significantly. This flow increase was restricted to the fast component of the 133 Xe clearance curve, leaving the slow component unchanged.

Introduction

CEREBRAL BLOOD FLOW (CBF) is normally autoregulated: that is, it remains relatively constant over a wide range of perfusion pressure. It has been demonstrated that there is an upper blood pressure limit of autoregulation beyond which CBF increases with increasing perfusion pressure. This has been called the hypertensive "breakthrough" of autoregulation and has been postulated to be of relevance in the pathogenesis of acute hypertensive encephalopathy. The present investigation describes in greater detail the events occurring in the cerebral circulation at, and beyond, the upper limit of autoregulation. In particular, the fast and slow components of the 133 Xe clearance curves and their respective contributions to the observed increase in total CBF were examined. Further, attempts were made to maintain blood pressure above the point of "breakthrough" for prolonged periods of time. Following sustained hypertension, blood pressure was returned to normotensive levels and the pattern of CBF was examined throughout.

Methods

The study was carried out in eight young baboons (Papio cynocephalus or Papio anubis) weighing 7 to 14 kg. The animals were sedated with phencyclidine (12 mg i.m.) and then anesthetized with sodium thiopental before being paralyzed with suxamethonium (100 mg i.v. or i.m.). They were then intubated and connected to an intermittent positive-pressure respirator pump (Starling) which delivered a mixture of 75% N₂O and 25% O₂ in open circuit. Phencyclidine (2 to 4 mg i.m.) and suxamethonium (50 to 100 mg i.m.) were administered at 30-minute intervals. Body temperature was controlled (36°C to 38°C) by heating lamps. A catheter was placed in one common carotid artery via the lingual artery, and the pressure measurement and blood sampling. A femoral vein was cannulated for saline and drug administration. The animal was then allowed to stabilize for one hour before being studied.

Aortic and sinus pressures were measured with Statham strain gauge transducers. 133 Xe, dissolved in saline, was injected via the lingual artery catheter and the clearance of the isotope was measured by a lead-collimated detector placed over the denuded skull in the parietal region. CBF was calculated by the height/area (H/A) equation. The linearly displayed clearance curve was manually transformed into a semilogarithmic coordinate system for compartmental analysis and calculation of the relative weight of gray matter. These calculations were carried out by the technical staff at a later date.
After two to five determinations of resting CBF, blood pressure was gradually increased in increments of 10 to 20 mm Hg by the slow intravenous infusion of angiotensin II amide (Hypertensin, CIBA). At each blood pressure level, a steady state was maintained for at least five minutes prior to, and ten minutes during, the measurement of CBF. Immediately after each injection of 133Xenon, blood samples were drawn for determination of arterial and, in some animals, cerebral venous Pco2, pH, Po2 and O2 saturation. When necessary, the respirator was adjusted to maintain arterial Pco2 within physiological limits (38 to 42 mm Hg). The hemoglobin concentration was measured frequently throughout each experiment.

CBF was measured two to three times per hour for four to six hours. Further measurement was hindered by tachyphylaxis to the pressor effect of angiotensin. The amount of this drug infused initially was about 0.05 μg per minute, and in the later stages had to be increased to 50 to 100 μg per minute in order to maintain the required level of hypertension. On a few occasions, norepinephrine was added to the infusate to maintain blood pressure. Cardiac arrhythmia developed in most animals during induced hypertension, a complication that was effectively controlled by atropinization. The amount of saline infused during an experiment amounted to 400 to 700 ml overall. This balanced the fluid losses of the animals, as shown by the constancy of the plasma sodium and potassium were followed and were found to remain constant.

Measurement of CBF was done in some animals during intracarotid infusion of angiotensin in doses of 0.01 and 0.05 μg per minute, which were just insufficient to induce an increase in systemic blood pressure. This control study was done prior to the sustained elevation of blood pressure.

Stochastic CBF measurements from seven of the eight animals of the present study were included in either of two previous works, where the upper limit of autoregulation was demonstrated in the baboon⁴ and where a comparison was made between the upper limit in normotensive and chronically hypertensive baboons.⁵

### Results

The measured values of mean arterial blood pressure (MAP), CBF calculated by the height:area equation (CBF H/A), fast and slow component flow (Fg and Fw) and the Paco2 were grouped into 10 mm Hg blood pressure intervals. The relative weight of fastly perfused tissue (Wg) and cerebral blood flow (CBF) was also calculated, the latter as MABP:CBF (H/A). In each pressure interval, the values of these parameters were compared with the values at MABP 100 to 109 mm Hg, which was taken to be baseline. Student's t-test and the non-parametric Mann-Whitney test were used (table 1, fig. 1). Below 100 mm Hg, too few measurements were obtained to warrant statistical treatment.

As blood pressure was increased, CBF, Fg and Fw remained constant up to the MAP range 130 to 139 mm Hg. At this pressure level, CVR reached a maximum value which was significantly greater than the baseline value. At higher pressures, CBF and Fg increased significantly, CVR decreased and Fw remained unchanged. Wg rose steadily with increasing blood pressure, to reach values significantly different from baseline at the highest pressure range (MABP > 160 mm Hg). At this pressure level, CVR had returned to baseline values. The Paco2 was constant throughout the experiment.

The upper limit of autoregulation judged from the individual pressure:flow curves of the eight animals was 115 to 145 mm Hg with a mean value of 130 mm Hg (fig. 2). When blood pressure was decreased after having been beyond the upper limit of autoregulation, four of the animals showed a persistent cerebral hyperemia, while four returned to the resting flow level. In the former group, blood pressure was kept above the upper limit for 60 to 114 minutes, in the latter for 10 to 50 minutes. In the former group, resting blood pressure and resting CBF were comparatively higher than in the latter, and the animals of the former group showed a tendency to an increase in Fw beyond the upper limit of autoregulation. The cerebral hyperemia following a prolonged "breakthrough" was restricted to the fast flow component. None of the animals showed any tendency to a flow decrease during the experiment.

Infusion of angiotensin in the internal carotid artery in concentrations of 0.01 μg per minute and 0.05 μg per minute had no detectable influence on CBF.

### Discussion

The present study could be criticized in that the use of angiotensin as a pressure agent might also have a direct effect upon the cerebral resistance vessels. However, the in-

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<table>
<thead>
<tr>
<th>MAP (range)</th>
<th>MAP</th>
<th>CBF (H/A) (100 gm/min)</th>
<th>Fg (ml/100 gm/min)</th>
<th>Fw (ml/100 gm/min)</th>
<th>Wg (%)</th>
<th>CVR (mm Hg/ml/00 gm/min)</th>
<th>Paco2 (mm Hg)</th>
<th>No. of observations</th>
<th>No. of animals</th>
</tr>
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<tbody>
<tr>
<td>100-109</td>
<td>103 ± 2 56 ± 9</td>
<td>83 ± 18</td>
<td>30 ± 7</td>
<td>51 ± 5</td>
<td>1.87 ± 0.29</td>
<td>39.8 ± 1.7</td>
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<tr>
<td>110-119</td>
<td>114 ± 3 56 ± 8</td>
<td>94 ± 15</td>
<td>32 ± 8</td>
<td>52 ± 4</td>
<td>2.19 ± 0.40</td>
<td>39.4 ± 2.1</td>
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<tr>
<td>120-129</td>
<td>124 ± 4 57 ± 11</td>
<td>128 ± 12</td>
<td>28 ± 8</td>
<td>54 ± 4</td>
<td>2.23 ± 0.36</td>
<td>39.2 ± 2.0</td>
<td>7</td>
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</tr>
<tr>
<td>130-139</td>
<td>134 ± 4 57 ± 8</td>
<td>175 ± 17</td>
<td>29 ± 7</td>
<td>53 ± 5</td>
<td>2.30 ± 0.32</td>
<td>39.9 ± 2.9</td>
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<tr>
<td>140-149</td>
<td>145 ± 3 72 ± 7</td>
<td>105 ± 12</td>
<td>35 ± 12</td>
<td>56 ± 4</td>
<td>2.00 ± 0.19</td>
<td>38.9 ± 0.9</td>
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<tr>
<td>150-159</td>
<td>153 ± 3 82 ± 9</td>
<td>110 ± 17</td>
<td>33 ± 6</td>
<td>56 ± 5</td>
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<tr>
<td>160+</td>
<td>167 ± 6 88 ± 11</td>
<td>120 ± 18</td>
<td>32 ± 7</td>
<td>58 ± 5</td>
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<td>40.3 ± 1.5</td>
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Measured values of mean arterial blood pressure (MAP) and cerebral blood flow (CBF H/A), fast and slow component flow (Fg and Fw, respectively), relative weight of fastly perfused tissue (Wg) and arterial carbon dioxide tension (Paco2) and calculated values of cerebrovascular resistance (CVR) are shown as mean ± 1 SD in 10 mm Hg MAP intervals. The values as each MAP level were compared with the baseline values at MABP 101 to 109 mm Hg by means of Student's t-test and the non-parametric Mann-Whitney test (MW-test). NS = not significant.

*P < 0.01, P < 0.05; **P < 0.001, P < 0.05; ***P < 0.001, P < 0.005; MW-test = NS.
Fusion of angiotensin in the internal carotid artery had no effects on CBF in this investigation, confirming results found in man11 and in the rabbit.12 High doses of angiotensin cannot be adequately tested by intracarotid infusion, as any effect of the drug on the cerebral vasculature is masked by the autoregulatory response elicited by the rise in systemic blood pressure. Angiotensin exerts part of its effects on the cardiovascular system via the adrenergic nerves.12 These nerves have a weak constrictor effect on the larger cerebral resistance vessels in the baboon only discernible during pre-existing vasodilation.12 Thus, there is little evidence that angiotensin constricts cerebral vessels, and no evidence that it dilates these vessels.

The increase in CBF which occurred beyond the upper limit of autoregulation in the present study was confined to the fast flow component. As the flow increase was accompanied by a small but significant increase in the relative weight of fastly perfused tissue, the latter cannot be strictly identical to anatomical gray matter. It may be recalled from autoradiographical studies that the "fast flow component" represents the average of a wide range of flow values in gray matter,14 a fact that would tend to make detailed analysis of such small weight changes as in the present study less worthwhile. It seems safe to conclude, though, that the forced

**Figure 1.** The effect of acute angiotensin-induced hypertension on the cerebral circulation in eight young baboons. CBF as calculated by the H/A equation is constant until the mean blood pressure (MAP) goes beyond the range 130 to 139 mm Hg. The flow increase at higher pressure is restricted to the fast flow component (Fg), leaving the slow component (Fw) unchanged. CVR, calculated as MAP/CBF (H/A), reaches a maximum at MAP 130 to 139 mm Hg, to fall as autoregulation is broken. The relative weight of fastly perfused tissue (Wg) increases slightly but steadily during blood pressure increase. The values are given as mean ± 1 SE in 10 mm Hg blood pressure intervals.

**Figure 2.** The effect of prolonged acute angiotensin-induced hypertension on the autoregulation of CBF in eight young baboons. Blood pressure was increased beyond the upper limit of autoregulation and maintained there as long as possible. — — = blood pressure increase, ○—○ = subsequent blood pressure decrease. For plotting, CBF values at identical pressures in one animal have been averaged.

Left: Four animals who returned to resting CBF levels when blood pressure was decreased. Duration of "breakthrough" — 10 to 50 minutes. Right: Four animals who showed persistent cerebral hypoxemia when blood pressure was decreased. Duration of "breakthrough" — 60 to 114 minutes.
vasodilatation and flow increase at high blood pressure in this study was restricted largely to the gray matter, while autoregulation was maintained in the bulk of the white matter. The reason for this might be that restoring vascular resistance is comparatively higher in white matter than in gray matter. With autoradiography in the rabbit during acutely induced hypertension, Dinsdale et al. found localized small areas of CBF decrease in the general pattern of CBF increase. An important limitation of the 133Xenon method of the present study is that such discrete areas of low flow, if developing during induced hypertension, would remain undetected. They would, however, influence Wg in the opposite direction of the change that was actually found.

The finding that “breakthrough” of CBF autoregulation is restricted to gray matter agrees well with other studies, in which damage to the blood-brain barrier caused by abruptly induced hypertension was confined to the cortex and deep gray matter. It may explain why Grubb and co-workers could raise the mean blood pressure in rhesus monkeys to about 180 mm Hg without any rise in the blood volume of subcortical brain tissue; on the contrary, a continuous decrease in subcortical cerebral blood volume was found during rising blood pressure, as expected when autoregulation is effective.

When blood pressure was decreased after “breakthrough” in the present study, half of the animals regained a normal CBF level, while the other half showed a persistent cerebral hyperemia. The latter had the longest duration of “breakthrough,” and it is likely that the persistent hyperemia was caused by overstretching of the walls of the cerebral resistance vessels.

Clinical Implications

It has recently been proposed that the “breakthrough” of CBF autoregulation may play an important role in the pathogenesis of acute hypertensive encephalopathy. High intra-arterial pressure, especially caused by sudden elevation or maintained over long periods, causes focal or general cerebral vasodilatation with overstretching of the vessel walls and damage to the blood-brain barrier. This causes plasma protein extravasation with the formation of perivascular edema. In late phases, brain edema may become generalized, and the initially high CBF may decrease below normal.

Opposed to this view stands the traditional concept of hypertensive uncontrolled cerebral vasoconstriction with consequent brain ischemia. Critically low CBF values, however, have not been shown to occur at high blood pressure.

The present study is in support of the “breakthrough” hypothesis. Flow increases caused by acute hypertension have been shown to be restricted to the cerebral gray matter, or strictly speaking to the vastly perfused tissue compartment. Persistent hyperemia may follow when blood pressure is reduced. This finding suggests that treatment with hyperventilation, resulting in hypocapnia, might be beneficial used along with blood pressure reduction in the management of acute hypertensive encephalopathy.

References

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Stroke. 1976;7:287-290
doi: 10.1161/01.STR.7.3.287

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