Upper Limit of Autoregulation of Cerebral Blood Flow in the Baboon


ABSTRACT

The upper limit of autoregulation of cerebral blood flow was studied in ten young baboons. Blood pressure was increased by infusing angiotensin, and cerebral blood flow was measured by the intracarotid 133Xe injection method. Autoregulation was maintained until blood pressure was 30-40% above resting values. At this blood pressure level, cerebrovascular resistance reached a maximum. Any additional increase in blood pressure resulted in an increase in cerebral blood flow and a decrease in cerebrovascular resistance; this situation is designated the "breakthrough of autoregulation." In four baboons subjected to unilateral sympathetic denervation, autoregulation of cerebral blood flow was studied bilaterally; no difference in the upper limit of autoregulation was found between the intact and the sympathectomized hemisphere. The breakthrough of autoregulation supposedly plays an important role in the pathogenesis of acute hypertensive encephalopathy. The old concept of hypertensive cerebral vasospasm has been revised in recent years, and it is now generally recognized that acute hypertensive encephalopathy is caused by focal overdistention of brain arterioles with lesions of the blood-brain barrier. However, whether this condition is associated with a high cerebral blood flow in the clinical syndrome has not been investigated.

KEY WORDS induced hypertension breakthrough of autoregulation hypertensive encephalopathy cerebrovascular resistance angiotensin 133Xe clearance

When blood pressure rises, cerebral blood flow is held constant by autoregulatory constriction of the cerebral resistance vessels. Some recent communications have described the existence of an upper limit of autoregulation. When blood pressure rises beyond this limit, autoregulation is exhausted; a forced arteriolar dilation and an increase in cerebral blood flow occur. This situation is called the "breakthrough of autoregulation" (1) and has been observed in hypercapnic dogs (2), in man by the arteriovenous oxygen difference method (3), and, in a limited study, in man by the intracarotid 133Xe injection method (4). Signs of forced vasodilation in the brain during acute hypertension have been observed in recent studies of the blood-brain barrier (5-7).

Previous studies on the upper limit of autoregulation of cerebral blood flow are open to criticism because of the unphysiological experimental conditions (2), the use of an indirect method for assessment of cerebral blood flow (3), and the limited number of experiments performed (4). The present study was undertaken to obtain conclusive evidence on the upper limit of autoregulation. Normocapnic baboons were used, and cerebral blood flow was measured by the intracarotid 133Xe injection method. The involvement of sympathetic nerves in the regulation of cerebral blood flow during acutely induced hypertension was also evaluated.

Methods

The study was carried out in ten young adult baboons (Papio cynocephalus or Papio anubis) weighing 10-14 kg. Three of the baboons were studied 2 weeks after a unilateral cervical sympathectomy, and one baboon was studied immediately after an acute cervical sympathetic block. The baboons were anesthetized with phencyclidine (12 mg, im) and suxamethonium chloride (7.5 mg/kg, iv). They were intubated and connected to an intermittent positive-pressure respiratory pump (Starling) which delivered a mixture of 75% N2O-25% O2 in open circuit. Phencyclidine (2 mg, im) and suxamethonium chloride (100 mg, im) were administered at 30-minute intervals. Blood temperature was controlled (36-38°C) by a heating lamp.

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Cerebral blood flow was measured by the intracarotid $^{133}$Xe injection method and calculated by the height/area equation (8). A catheter for $^{133}$Xe injection was inserted via the linguofacial trunk into the common carotid artery; all other branches of the external carotid artery were ligated. The scalp and the occipital and temporal muscles were removed. In the four baboons subjected to unilateral sympathetic denervation and in two other baboons, cerebral blood flow was measured bilaterally with detectors placed over the occipital bone (Fig. 1); this procedure avoided the ophthalmic circulations. Cross talk between the hemispheres was tested by unilateral $^{133}$Xe injection and bilateral counting; it was 4-12%, as judged from the initial count heights. In the four remaining baboons, cerebral blood flow was studied unilaterally with the detector placed over the parietal region.

The abdominal aorta was catheterized via the left femoral artery for blood pressure monitoring with Statham strain-gauge transducers. The femoral vein was used for intravenous infusions. Arterial PCO$_2$ was measured frequently using the micro-Astrup method, and the baboons were maintained at normocapnia by adjusting the respirator. The CO$_2$ reactivity of cerebral blood flow was tested in some baboons prior to the autoregulation study. It was within the normal range; cerebral blood flow rose about 2.75 ml/100 g min$^{-1}$ per mm Hg rise in arterial PCO$_2$. The efficacy of the acute sympathetic block was demonstrated by supramaximally stimulating the cervical sympathetic trunk at a pulse width of 100 seconds and a frequency of 15 Hz. Block was complete when the erector pilae on the baboon's shoulder no longer responded to electric stimulation. The completeness of chronic unilateral cervical sympathectomy was determined after the termination of the cerebral blood flow study; both middle cerebral arteries were processed by the histochemical method of Falck (9). The fluorescence in the denervated artery was considerably diminished compared with that in the artery on the other side.

After an initial estimate of cerebral blood flow had been made, systemic blood pressure was increased in steps by intravenous infusion of angiotensin II (Hyptensin, CIBA). The blood pressure was elevated 10-20 mm Hg over approximately 5 minutes in each step and was held steady for at least 5 minutes prior to and during the 10 minutes required to estimate cerebral blood flow. Thus, cerebral blood flow was measured every 20-30 minutes. Atropine (0.1 mg, im) was given at 2-hour intervals to prevent cardiac arrhythmia.

**Results**

Autoregulation curves from eight hemispheres in the six baboons with intact sympathetic nerves are shown in Figure 2. The curves from eight hemispheres in the four baboons subjected to unilateral cervical sympathetic denervation are shown in Figure 3. Resting mean arterial blood pressure in the baboons was 75-100 mm Hg. With increasing blood pressure, cerebral blood flow was kept effectively constant up to 120-150 mm Hg. In all baboons except one, cerebral blood flow then increased by an average of about 50%. No difference in the upper limit of autoregulation was observed between the intact and the sympathectomized hemispheres in the same baboon. No baboon showed a decrease in cerebral blood flow with an increase in blood pressure.

The data are analyzed more closely in Tables 1 and 2. When the increase in blood pressure was calculated as a percent of the resting level, the upper limit of autoregulation was reached after a 40% increase in mean arterial blood pressure in the baboons with intact cervical sympathetic nerves. At first, the increase in cerebral blood flow beyond this limit was not associated with a change in cerebrovascular resistance, but then a decrease in
Cerebrovascular resistance to resting pressure levels occurred; such a decrease signifies vasodilation. Arterial PCO₂ was 41.5 mm Hg at the highest level of mean arterial blood pressure compared with 39.6 mm Hg at the resting level of mean arterial blood pressure. This slight increase in arterial PCO₂ cannot explain the high flows at high blood pressure. Similar figures were found in the four baboons subjected to unilateral sympathetic denervation, but the number of measurements was too small to permit statistical calculations.

**Discussion**

The cerebral resistance vessels of the baboons in the present study showed a normal CO₂ reactivity and a normal autoregulation to moderate blood pressure increases; therefore, these vessels were physiologically intact after experimental preparation. The necessary precautions were taken to avoid isotope counting from extracerebral tissues. Anesthetic agents that have been reported to have little influence on cerebral blood flow were used. Cerebral blood flow values for patients anesthetized with N₂O and O₂ supplemented with neuroleptic drugs are on the same order as those for conscious patients (10); N₂O anesthesia does not influence the autoregulatory response to an angiotensin-induced blood pressure increase in normal man (11).

Angiotensin has no direct pharmacological effect on cerebral blood flow in normal man (12). The use of this drug in testing autoregulation 2 weeks after sympathectomy could be criticized, since angiotensin exerts part of its effect on blood pressure via the sympatheticoadrenal system (13). This effect in combination with denervation hypersensitivity could theoretically give rise to cerebral blood flow changes along with, but not caused by, an increase in blood pressure induced by angiotensin. However, this possibility is rather improbable because no difference in cerebral blood flow response to in-

**TABLE 1**

<table>
<thead>
<tr>
<th>Blood pressure range (%) Increase</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Arterial PCO₂ (mm Hg)</th>
<th>Cerebral blood flow (ml/100 g min⁻¹)</th>
<th>Cerebrovascular resistance (mm Hg/ml/100 g min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Base line</td>
<td>94 ± 11</td>
<td>39.6 ± 1.8</td>
<td>50 ± 12 (NS)</td>
<td>2.00 ± 0.32</td>
</tr>
<tr>
<td>8 10-19</td>
<td>110 ± 10</td>
<td>38.9 ± 1.5</td>
<td>48 ± 12 (NS)</td>
<td>2.43 ± 0.66</td>
</tr>
<tr>
<td>3 20-29</td>
<td>113 ± 5</td>
<td>38.7 ± 1.3</td>
<td>49 ± 3 (NS)</td>
<td>2.41 ± 0.27</td>
</tr>
<tr>
<td>3 30-39</td>
<td>126 ± 13</td>
<td>38.8 ± 1.4</td>
<td>54 ± 18 (NS)</td>
<td>2.65 ± 0.82</td>
</tr>
<tr>
<td>8 40-49</td>
<td>137 ± 13</td>
<td>38.9 ± 1.2</td>
<td>64 ± 22*</td>
<td>2.65 ± 0.82</td>
</tr>
<tr>
<td>5 50-59</td>
<td>150 ± 9</td>
<td>41.3 ± 2.0</td>
<td>74 ± 18†</td>
<td>2.44 ± 0.93</td>
</tr>
<tr>
<td>6 60+</td>
<td>152 ± 14</td>
<td>41.5 ± 1.5</td>
<td>77 ± 7†</td>
<td>1.94 ± 0.28</td>
</tr>
</tbody>
</table>

Data from eight hemispheres in six baboons are presented as means ± SD. Changes in cerebral blood flow were compared with baseline values by the t-test; NS = not significant. The upper limit of autoregulation is reached with a 40% increase in mean arterial blood pressure. Cerebrovascular resistance was calculated as mean arterial blood pressure divided by the corresponding cerebral blood flow. Above the upper limit of autoregulation cerebrovascular resistance decreased to base-line levels, signifying vasodilation. N = number of cerebral blood flow measurements.

*P < 0.05.
†P < 0.001.
duced hypertension was noted between sympathectomized and intact hemispheres. Also in the blood-brain barrier study of Haggendal and Johansson (7), autoregulation was apparently interrupted by an acute mechanically induced hypertension without the use of exogenous pressor agents.

In the present study, cerebral blood flow autoregulation was effective until the blood pressure increased by 30-40%. Above this level it was lost in nine of ten baboons, as evidenced by a pronounced rise in cerebral blood flow. With this breakthrough of autoregulation, the vascular resistance decreased, signifying a forced vasodilation. Similar observations have been made in the kidney (14) and the intestine (15), and this exhaustion of the Bayliss response is probably typical of what happens in autoregulating vascular beds when blood pressure increases high enough.

These findings may be pertinent to the pathogenesis of acute hypertensive encephalopathy. It has been suggested that in this vascular crisis the arterioles react to extreme elevations in blood pressure either with spasm (uncontrolled vasoconstriction) or with the opposite response, forced vasodilation. Evidence for this possibility has been obtained from three different experimental approaches: direct observation of pial vessels (16-20), blood-brain barrier studies (5-7, 16, 17, 21, 22), and cerebral blood flow studies (2-4).

In acute and chronic experimental hypertension, the arterioles in the pia and elsewhere may display a characteristic “sausage-string” appearance with alternately constricted and dilated segments in the same vessel. In the previous work of Byrom (17) on experimental hypertensive encephalopathy in the rat and in other later experiments (18-20), the constricted segments were regarded as being in vasospasm. This vasospasm was thought to damage the brain by hypoxia, causing neurological symptoms and local blood-brain barrier lesions and edema.

The hypertensive sausage-string phenomenon was observed in the intestinal arterioles of the rat by Giese (23). It was associated with the penetration of a macromolecular tracer, colloid carbon, through the arteriolar walls. This penetration invariably took place in the dilated segments of the vessels, never in the constricted segments. Furthermore, Johansson et al. (5) demonstrated hypertensive blood-brain barrier damage within a few minutes after a sudden pronounced rise in blood pressure. These authors (5) indicated that this damage was probably caused by overstretching of the vessel walls and not by spasm, since hypoxic blood-brain barrier damage probably occurs only after several hours. Byrom (16) presented evidence that local cerebral edema in the rat with acute hypertensive encephalopathy is very often topographically related to an arteriole with necrosis in the wall; this lesion is typically caused by overstretching and not by spasm. Therefore, contrary to his earlier concepts, Byrom (16) has now suggested that the critical event in acute hypertensive encephalopathy might be pressure-forced vasodilation with the formation of brain edema through the walls of overdistended segments of arterioles. Thus, focal brain edema and not ischemia is now thought to cause the clinical symptoms.

The results from the cerebral blood flow studies in man (3, 4), dog (2), and baboon must be added to the evidence in favor of the forced vasodilation hy-

### Table 2

Effect of Raising Blood Pressure on Bilateral Cerebral Blood Flow in Four Baboons Subjected to Unilateral Sympathetic Denervation

<table>
<thead>
<tr>
<th>Blood pressure range (% increase)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Arterial P&lt;sub&gt;CO&lt;/sub&gt;&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</th>
<th>Cerebral blood flow (ml/100 g min&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>Cerebrovascular resistance (mm Hg/ml/100 g min&lt;sup&gt;-1&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8  Base line</td>
<td>96 ± 8</td>
<td>39.5 ± 1.9</td>
<td>51 ± 12</td>
<td>1.99 ± 0.54</td>
</tr>
<tr>
<td>4  10-19</td>
<td>112 ± 9</td>
<td>39.6 ± 1.3</td>
<td>54 ± 14</td>
<td>2.22 ± 0.71</td>
</tr>
<tr>
<td>2  20-29</td>
<td>115 ± 4</td>
<td>39.1 ± 1.3</td>
<td>48 ± 14</td>
<td>2.13 ± 0.51</td>
</tr>
<tr>
<td>5  30-39</td>
<td>132 ± 11</td>
<td>39.8 ± 1.6</td>
<td>66 ± 20</td>
<td>2.21 ± 0.76</td>
</tr>
<tr>
<td>3  40-49</td>
<td>126 ± 8</td>
<td>40.0 ± 1.0</td>
<td>61 ± 16</td>
<td>2.64 ± 1.02</td>
</tr>
<tr>
<td>4  50+</td>
<td>154 ± 7</td>
<td>41.5 ± 1.7</td>
<td>68 ± 32</td>
<td>1.92 ± 0.23</td>
</tr>
</tbody>
</table>

Cerebral blood flow increased when blood pressure rose above 30-40% of the base-line value. The number of data points was too small for statistical considerations. No difference was seen between sympathectomized and intact hemispheres.

N = number of cerebral blood flow measurements.
pothesis. These results show the existence of an upper limit of autoregulation beyond which cerebral blood flow increases considerably. Lassen and Agnoli (1) have suggested that this breakthrough of autoregulation may be important in the pathogenesis of acute hypertensive encephalopathy. Like hypertensive segmental arteriolar dilation, the breakthrough in autoregulation should be viewed as the effect of a very high transmural pressure on the vessel wall.

The role of the sympathetic nerves supplying cerebral blood vessels is not clear (24). Some workers (25, 26) have claimed that these nerves play an important role in cerebral blood flow regulation. Other investigators (12, 27) have suggested that these nerves influence the outflow tract of the brain circulation but not the intracerebral vessels. Eklöf et al. (28) have found that autoregulation is uninfluenced by chronic sympathetic denervation in the rhesus monkey. Recently, Alm and Bill (29) studied cerebral blood flow with the microsphere method in cats and found no changes during cerebral sympathetic stimulation. Byrom (17) found the same course of acute hypertensive encephalopathy in the rat whether or not the rat had been subjected to a cervical sympathectomy.

In the present study, the few measurements made following sympathetic denervation showed no conclusive evidence of an effect on the upper limit of autoregulation of cerebral blood flow.

References


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