Lower Limit of Cerebral Blood Flow Autoregulation in Experimental Renovascular Hypertension in the Baboon

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SUMMARY The effect of chronic renovascular hypertension on the autoregulation of cerebral blood flow was studied in anesthetized baboons. Cerebral blood flow was measured by the intracarotid \(^{133}\text{Xe}\) clearance method. Six baboons with renal hypertension of 8-12 weeks' duration were compared with six normotensive controls. The lower limit of autoregulation was determined following controlled hemorrhage. In the initially normotensive baboons, cerebral blood flow remained constant until mean arterial pressure had decreased to the range of 45-59 mm Hg. Thereafter, cerebral blood flow decreased with each further decrease in mean arterial pressure. In the chronically hypertensive baboons cerebral blood flow autoregulated until the mean arterial pressure had decreased to the range of 75-89 mm Hg. Therefore, the lower limit of autoregulation of cerebral blood flow was shifted to higher absolute levels of mean arterial pressure in baboons with chronic renovascular hypertension presumably due to adaptive changes in the cerebral circulation.

AUTOREGULATION of cerebral blood flow is that mechanism which ensures constant perfusion of the brain during alterations of arterial pressure or intracranial pressure. Recent studies have shown that there are upper and lower limits of arterial pressure beyond which autoregulation is ineffective. During acutely induced increases in arterial pressure, autoregulatory constriction of arterioles and small arteries may be overridden. An increase in cerebral blood flow will result. A decrease in cerebral blood flow is noted with induced hypotension, since autoregulatory vasodilation becomes inadequate ultimately.

In a previous study it was shown that, in baboons with chronic renovascular hypertension, the upper limit of autoregulation of cerebral blood flow was shifted to higher levels of mean arterial pressure, a phenomenon due presumably to structural changes in the cerebral resistance vessels. A similar shift in the lower limit of autoregulation was observed in patients with severe, untreated, essential hypertension. In this latter study cerebral blood flow was assessed with the indirect arteriovenous oxygen difference method, and arterial pressure was decreased by ganglionic blockade together with head-up tilt.

Our present study was undertaken to investigate in greater detail the lower limit of autoregulation in baboons with chronic renovascular hypertension. The direct, \(^{133}\text{Xe}\) clearance method was used to determine cerebral blood flow.

Methods

The detailed methodology has been presented elsewhere, therefore only the salient features will be considered here. Chronic hypertension was produced by unilateral renal artery constriction in six young baboons (Papio cynocephalus or Papio anubis) weighing 8-15 kg. A silk ligature was tied loosely around one renal artery, causing the vessel to go into spasm. When the spasm resolved the ligature caused stenosis of the artery. Following operation the baboons became hypertensive within 1-3 weeks and were then left for a period of at least 2 months before being used in a definitive study.

After the Goldblatt operation the baboons were sedated with phencyclidine (1.2 mg/kg, im) once per week and systolic arterial pressure was measured by arm cuff. Systolic arterial pressure increased from 100 mm Hg to 120 mm Hg in those baboons in which the operation was successful (approximately 60% of the total number that underwent operation). The optic fundi were examined regularly for vessel changes, but the characteristic signs of hypertensive retinopathy, other than arterial narrowing, were not seen.

Along with the six hypertensive baboons, six normotensive baboons were studied as controls. Animals which remained normotensive after a Goldblatt operation were not used as controls. Some of the normotensive baboons were included in a previous study.

Cerebral blood flow was measured by the intracarotid \(^{133}\text{Xe}\) injection method. The baboons were tranquillized with phencyclidine (1.2 mg/kg, im) and anesthesia was induced with sodium thiopentone (7.5 mg/kg, iv). Anesthesia was maintained subsequently with 70% nitrous oxide in oxygen delivered through a Starling positive-pressure respirator. During each investigation, phencyclidine (0.35 mg/kg, im) and suxamethonium (5 mg/kg, im) were given at 30-minute intervals to prevent awareness and to produce
muscular relaxation. Cerebral blood flow was calculated from the $^{133}$Xe clearance curve by the height/area equation. After two to five measurements of baseline cerebral blood flow, arterial pressure was decreased gradually in steps of approximately 20 mm Hg by controlled hemorrhage. At each level, the arterial pressure was allowed to stabilize for at least 5 minutes prior to the measurement of cerebral blood flow. With each cerebral blood flow measurement, arterial and sagittal sinus blood samples were withdrawn for determination of $PCO_2$, pH, $PO_2$, and oxygen saturation. The respirator was adjusted to maintain arterial $PCO_2$ within physiological limits.

**Results**

Following the completion of surgery the baboons were left to stabilize under anesthesia for 1 hour. At the end of this period resting mean arterial pressure was 91 ± 6.7 (SD) mm Hg in the normotensive group and 135 ± 13.4 mm Hg in the hypertensive group. Cerebral blood flow and mean arterial pressure curves for individual normotensive and hypertensive baboons are shown in Figure 1. As arterial pressure was decreased cerebral blood flow remained at first relatively constant in both groups; subsequently it decreased as the lower limit of autoregulation was reached. This lower limit of autoregulation occurred at a higher level of mean arterial pressure in the hypertensive baboons than in the normotensive baboons.

Table 1A and B shows the measured values for cerebral blood flow and arterial $PCO_2$ in the normotensive and hypertensive baboons. In the normotensive group, the baseline mean arterial pressure was taken as 90–104 mm Hg (12 observations in six baboons) (Table 1). In the hypertensive baboons, baseline mean arterial blood pressure was 135–149 mm Hg (eight observations in four baboons). All blood pressure groupings contained observations from at least four baboons. Cerebral blood flow in normotensive baboons first decreased significantly, compared to the baseline value, in the arterial pressure range 45–59 mm Hg. In hypertensive baboons, cerebral blood flow first decreased significantly, compared to the baseline value, in the blood pressure range 75–89 mm Hg.

There was no statistical difference in baseline cerebral blood flow values in the two groups. There was still no statistical difference in cerebral blood flow between the two groups in the first overlapping arterial pressure range (90–104 mm Hg). Cerebral blood flow values in the next arterial pressure range (75–89 mm Hg) were significantly different ($P < 0.01$) and remained so as arterial pressure was reduced further.

**Discussion**

These results show that in baboons with chronic renovascular hypertension there is a shift of the lower limit of autoregulation toward higher levels of mean arterial pressure. Thus, they confirm and extend similar findings observed in humans with long-standing, severe essential hypertension, in whom cerebral blood flow was assessed by the indirect arteriovenous oxygen difference method and arterial pressure was decreased by the infusion of a ganglionic blocking agent (trimethaphan camyslate) combined with head-up tilt.

In chronic hypertension structural vascular adaptation takes place, with thickening of the walls of resistance vessels including those of the brain. This results in a decreased capacity for maximal dilation, which results from a greater wall to lumen ratio, and is the most probable explanation for the shift of the lower limit of autoregulation observed in the present study. Autoregulation during decreases of arterial pressure is dependent on effective vasodilation and, should this capacity be impaired, then the lower limit of

**Table 1 Cerebral Blood Flow and Arterial Carbon Dioxide Tension in Baboons during Hypotension Induced by Controlled Hemorrhage**

<table>
<thead>
<tr>
<th>MABP, range (mm Hg)</th>
<th>CBF (ml/100 g per min)</th>
<th>Arterial PCO$_2$ (mm Hg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>90–104</td>
<td>54.0 ± 11.1</td>
<td>39.6 ± 2.3</td>
<td>12</td>
</tr>
<tr>
<td>75–89</td>
<td>55.4 ± 8.7</td>
<td>40.2 ± 1.6</td>
<td>9</td>
</tr>
<tr>
<td>60–74</td>
<td>49.8 ± 10.4</td>
<td>40.1 ± 2.2</td>
<td>10</td>
</tr>
<tr>
<td>45–59</td>
<td>42.4 ± 10.3*</td>
<td>40.8 ± 1.9</td>
<td>7</td>
</tr>
<tr>
<td>30–44</td>
<td>32.2 ± 10.6*</td>
<td>40.8 ± 2.2</td>
<td>5</td>
</tr>
</tbody>
</table>

All values are means ± SD. MABP = mean arterial pressure; CBF = cerebral blood flow; n = number of observations.

* $P < 0.05$, compared to the baseline value (t-test).

† $P < 0.001$.

![Figure 1: Autoregulatory curves of cerebral blood flow (CBF) from six normotensive (upper) and six hypertensive (lower) baboons expressed as a percent of resting value plotted against mean arterial blood pressure (MABP).](image-url)
autoregulation will occur at higher absolute levels of systemic arterial pressure.

The adaptive cardiovascular changes in rats during experimental renal hypertension have been shown to be complete within 3 weeks after clipping of one renal artery. In our present study the baboons were left for a total duration of approximately 3 months after the initial Goldblatt operation had been performed, and for at least 2 months after the establishment of hypertension. Although no histometric studies were conducted, it might be expected that morphological adaptation of the vessels would be well advanced. Certainly, arterial narrowing was seen on inspection of the retinæ, and in three of the hypertensive baboons which were examined left ventricular hypertrophy was present post mortem.

The sympathetic innervation of the cerebrovascular bed can influence cerebral blood flow, especially at the lower limit of autoregulation. In normotensive baboons, when hemorrhagic hypotension is accompanied by superior cervical ganglionectomy, or by α-adrenergic blockade, the lower limit occurs at approximately 35 mm Hg. To what extent the sympathetic perivascular nerves might influence the lower limit of autoregulation in hypertensive baboons remains to be studied, but the observations in humans, when a ganglionic blocking agent was used, indicate that the greater part of the shift of autoregulation in chronic hypertension is due to structural adaptive changes in the vessel walls. In these persons the lower limit of cerebral autoregulation was shifted to higher levels of mean arterial pressure as compared to normotensive controls despite the use of a sympathetic ganglionic blocking agent to lower the arterial pressure.

A shift of the upper limit of autoregulation to higher mean arterial pressures in hypertensive, as compared to normotensive baboons, was seen in a previous investigation. Thus, the results of the present study and this earlier study have shown that, even after brief periods of chronic hypertension, both the upper and lower limits of autoregulation have shifted to higher levels of mean arterial pressure. The lower limit of autoregulation does, however, appear to be displaced to a greater extent than the upper limit, although there is wide individual variation. The two separate series of experiments have shown that, in hypertensive baboons, cerebral autoregulation was maintained between the arterial pressure ranges of 155–169 mm Hg and 90–104 mm Hg. In the normotensive baboons autoregulation was maintained between the arterial pressure ranges of 140–154 mm Hg and 45–59 mm Hg. Thus there is a narrowing of the autoregulatory plateau in hypertensive baboons as compared to normotensive controls. Such results are consistent with a structural explanation for the observed changes in autoregulation.

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References

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