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

By Svend Strandgaard, John V. Jones, Eric T. MacKenzie, and A. Murray Harper

ABSTRACT

The effect of arterial hypertension on cerebral blood flow was studied by the intracarotid 133Xe clearance method in baboons. The arterial blood pressure was raised in gradual steps with angiotensin. Baboons with renal hypertension of 8-12 weeks duration were studied along with normotensive baboons. In initially normotensive baboons, cerebral blood flow remained constant until the mean arterial blood pressure had risen to the range of 140 to 154 mm Hg; thereafter cerebral blood flow increased with each rise in mean arterial blood pressure. In the chronically hypertensive baboons, cerebral blood flow remained constant until the mean arterial blood pressure had been elevated to the range of 155 to 169 mm Hg. Thus, in chronic hypertension it appears that there are adaptive changes in the cerebral circulation which may help to protect the brain from further increases in arterial blood pressure.

Normally, cerebral blood flow is autoregulated: an intrinsic mechanism maintains the blood supply to the brain constant during changes in perfusion pressure (1-3). When blood pressure rises, the cerebral arterioles constrict; when blood pressure falls or intracranial pressure rises, they dilate. Thus, blood flow through the brain tissue is unchanged. It is now recognized that there is an upper as well as a lower blood pressure limit for autoregulation of cerebral blood flow (4, 5). Below a mean arterial blood pressure of 50-70 mm Hg, autoregulatory vasodilation is inadequate to compensate for the reduction in perfusion pressure, and thereafter cerebral blood flow decreases. Conversely, when the arterial blood pressure rises excessively, cerebral blood flow increases.

In hypertensive patients, the tolerance to acute hypotension is decreased (6). The lower limit of cerebral blood flow autoregulation in such hypertensive patients may be as high as a mean arterial blood pressure of 100-125 mm Hg (7). This fact is thought to be due to hypertensive changes in cerebral arterioles which minimize their ability to dilate.

The present study was undertaken to investigate the upper blood pressure limit of cerebral blood flow autoregulation in chronic arterial hypertension.

Methods

Goldblatt Operations.—Systemic hypertension was established by a constriction of one renal artery in six young baboons (Papio cynocephalus or Papio anubus; average weight ~ 10 kg). The kidney, either right or left, was reached through a loin incision under halothane anesthesia. A silk ligature was placed around the renal artery, which was put into spasm by gentle pulling. The ligature was then tied loosely; when the spasm resolved, the ligature caused a pronounced stenosis of the artery. Hypertension developed in about 50% of the operated baboons. The presence of a renal artery stenosis was then verified by angiography.

Blood Pressure Monitoring.—To measure their blood pressure, the baboons were sedated with phencyclidine (12 mg, im) once a week after the Goldblatt operation. Arm-cuff measurement by auscultation or palpation yielded values in good agreement with intra-aortic systolic blood pressure measured on a strain-gauge transducer from an arterial catheter.

After the Goldblatt operation, systolic blood pressure rose from about 120 mm Hg to 180-200 mm Hg in 1-3 weeks. This blood pressure level remained unchanged during the 8-12-week observation period. The optic fundi were examined regularly, but none of the baboons developed signs of hypertensive retinopathy other than universal arterial narrowing.

Cerebral Blood Flow Measurements.—Along with the six hypertensive baboons, seven normotensive baboons were studied as controls. Baboons that remained normotensive after a Goldblatt operation were not used as controls. Three of the normotensive baboons had been included in a previous study (5).

Cerebral blood flow was measured by the intracarotid 133Xe injection method. The baboons were anesthesiaed with phencyclidine (12 mg, im) and sodium thiopental (7.5 mg/kg, iv) and maintained on nitrous oxide and...
oxygen delivered through a Starling positive-pressure respirator. During the experiment, phencyclidine (3 mg, im) and suxamethonium (50 mg, im) were given at 30-minute intervals. A catheter was placed in the common carotid artery via the lingual artery; all other branches of the external carotid artery were ligated. The scalp and the temporal muscle were removed, and a catheter was placed in the superior sagittal sinus. A femoral artery was cannulated for blood sampling and pressure measurement; a femoral vein was also cannulated for saline and drug administration. Aortic and sagittal sinus pressures were measured using Statham strain-gauge transducers. 133Xe, dissolved in saline, was injected via the lingual artery catheter, and clearance of the isotope was measured by a lead-collimated NaI detector placed over the denuded skull in the parietal region. Cerebral blood flow was calculated from the clearance curve by the height/area equation (8). After two to five determinations of base-line cerebral blood flow, blood pressure was gradually increased in increments of 10–20 mm Hg (on two occasions 30 mm Hg) by a slow intravenous infusion of angiotensin II amide (Hypertensin, CIBA). At each blood pressure level, a steady state was obtained for at least 5 minutes; cerebral blood flow was then measured, and arterial and sagittal sinus blood samples were drawn for determination of carbon dioxide tension (Pco₂), pH, oxygen tension (Po₂), and oxygen saturation. The respirator was adjusted to maintain arterial Pco₂ within physiological limits. Hemoglobin was measured frequently during each experiment.

Results

Resting mean arterial blood pressure in the normotensive group was 97 ± 12 (SD) mm Hg, and in the hypertensive group it was 136 ± 18 mm Hg. Cerebral blood flow and mean arterial blood pressure curves for individual normotensive and hypertensive baboons are shown in Figures 1 and 2. When blood pressure was increased, cerebral blood flow was at first relatively constant; subsequently, it rose as the upper limit of autoregulation was reached. This upper limit occurred at a higher mean arterial blood pressure level in hypertensive baboons than it did in normotensive baboons.

In Tables 1 and 2, the measured values for cerebral blood flow and arterial Pco₂ have been grouped in 15-mm Hg blood pressure intervals. For statistical evaluation of the results, base-line values of cerebral blood flow were taken from the lowest blood pressure interval for which an acceptable number of observations had been made in different baboons. In the normotensive group base-line mean arterial blood pressure was taken as 95–109 mm Hg (13 observations in five baboons, Table 1), and in the hypertensive group base-line mean arterial blood pressure was 125–139 mm Hg (6 observations in three baboons, Table 2). Cerebral blood flow in normotensive baboons first increased significantly compared with the base-line value in the blood pressure range of 140 to 154 mm Hg. In hypertensive baboons, cerebral blood flow first increased significantly compared with the base-line value in the blood pressure range of 155 to 169 mm Hg.

There was no statistical difference in base-line cerebral blood flow values in the two groups. There was still no statistical difference in cerebral blood flow between the two groups in the lowest overlapping blood pressure range (125–139 mm Hg). Cerebral blood flow values in the next blood pressure range (140–154 mm Hg) were significantly different (P < 0.001).

Discussion

These results show that the six baboons with chronic hypertension consistently had a higher upper limit of autoregulation that did the initially normotensive baboons. The blood pressure in both normotensive and hypertensive baboons was raised with angiotensin, and it could be argued that
angiotensin directly affected the caliber of cerebral vessels. However, two independent investigations in human subjects have indicated that angiotensin does not directly affect cerebral vessels (9, 10). Furthermore, in one other baboon not included in this study in which blood pressure was elevated by the gradual inflation of an intra-aortic balloon, the cerebral circulatory response was the same as that seen in the baboons with angiotensin-induced hypertension.

In hypertensive man, the walls of the resistance vessels are thickenen in the brain and elsewhere (11-13). In benign hypertension, hyperplastic sclerosis develops in the subintimal elastic tissue and muscular media; hyaline degeneration may be associated with a loss of muscle cells in the media. In malignant hypertension, endarteritis fibrosa develops along with fibrinoid arteriolonecrosis (14). In hypertensive arterioles, a state of chronic narrowing has been claimed to be associated with medial thickening but no true hypertrophy (12). Increased sodium and water contents have been demonstrated in the walls of hypertensive vessels (15).

Hemodynamically, the structural vascular changes in hypertension result in a decreased capacity for maximum dilation and an increased maximum response to pressor drugs (16). This phenomenon has been demonstrated in the hand vessels of hypertensive patients (17) and in various experimental animals, including rats with hypertension following renal artery clipping (18). In this latter study, the change in hemodynamic parameters—presumably due to structural vascular adaptation—was complete within 3 weeks after hypertension had been established. The Goldblatt hypertensive baboons in the present study were investigated ~10 weeks after the establishment of hypertension; it can be assumed that morphological adaptation was well advanced.

Strandgaard and co-workers (7) have shown that in hypertensive patients there is decreased tolerance to an acute reduction in blood pressure. As in the present study, autoregulation existed in these hypertensive patients and the lower limit was shifted to the right on the blood pressure axis. This fact might be explained by thickening of the brain arterioles, limiting their capacity for autoregulatory dilution when blood pressure is decreased. During long-term antihypertensive treatment, the lower limit of cerebral blood flow autoregulation has been observed to shift back toward normal in some, but not all, patients investigated (Strandgaard, unpublished observations).

In this study, we found a similar shift to the right of the upper limit of cerebral blood flow autoregulation in baboons with renovascular hypertension of 8-12 weeks duration. This phenomenon suggests that the structural changes in arteriolar walls which make hypertensive subjects less tolerant of low blood pressure, at the same time, make them more tolerant of high blood pressure.

The demonstration of an upper limit of cerebral blood flow autoregulation above which further increases in blood pressure result in increases in cerebral blood flow has led to a changed concept of the pathogenesis of acute hypertensive encephalopathy (4). This vascular crisis has previously been thought to be caused by cerebral vasospasm, but according to current evidence it is more probably due to prolonged forced dilation of the cerebral vessels at very high blood pressures. If the shift of the upper limit of cerebral blood flow autoregulation found in this study is also present in long-term human hypertension, it would, to some extent, protect the patient against the harmful cerebral

**TABLE 1**

<table>
<thead>
<tr>
<th>MABP range (mm Hg)</th>
<th>CBF (ml/100 g min⁻¹)</th>
<th>Arterial Pco₂ (mm Hg)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>95-109</td>
<td>57 ± 8</td>
<td>39.7 ± 0.6</td>
<td>13</td>
</tr>
<tr>
<td>110-124</td>
<td>57 ± 8</td>
<td>39.5 ± 0.6</td>
<td>12</td>
</tr>
<tr>
<td>125-139</td>
<td>60 ± 9</td>
<td>38.3 ± 2.1</td>
<td>9</td>
</tr>
<tr>
<td>140-154</td>
<td>76 ± 10*</td>
<td>39.2 ± 0.8</td>
<td>8</td>
</tr>
<tr>
<td>155-169</td>
<td>86 ± 8*</td>
<td>40.2 ± 2.0</td>
<td>5</td>
</tr>
</tbody>
</table>

All values are means ± sd. MABP = mean arterial blood pressure, CBF = cerebral blood flow, Pco₂ = carbon dioxide tension, and N = number of observations.

* P < 0.001 compared with the base-line value (t-test).

**TABLE 2**

<table>
<thead>
<tr>
<th>MABP range (mm Hg)</th>
<th>CBF (ml/100 g min⁻¹)</th>
<th>Arterial Pco₂ (mm Hg)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>125-139</td>
<td>55 ± 4</td>
<td>39.0 ± 2.1</td>
<td>6</td>
</tr>
<tr>
<td>140-154</td>
<td>55 ± 4</td>
<td>41.0 ± 2.4</td>
<td>7</td>
</tr>
<tr>
<td>155-169</td>
<td>61 ± 1*</td>
<td>39.0 ± 1.5</td>
<td>7</td>
</tr>
<tr>
<td>170-184</td>
<td>71 ± 9*</td>
<td>39.4 ± 2.7</td>
<td>6</td>
</tr>
<tr>
<td>185-199</td>
<td>82 ± 11†</td>
<td>38.4 ± 3.5</td>
<td>5</td>
</tr>
</tbody>
</table>

All values are means ± sd. Abbreviations are the same as they are in Table 1.

* P < 0.01 compared with the base-line value (t-test).
† P < 0.001 compared with the base-line value (t-test).
effects of further blood pressure rises and explain why some hypertensive patients can tolerate very high blood pressure without developing acute hypertensive encephalopathy.

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