The hemodynamic effects of internal carotid artery stenosis and occlusion


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The purpose of this study was to determine in subhuman primates whether hemodynamic mechanisms (as compared with embolic mechanisms) contribute to cerebral ischemia following carotid artery occlusion or stenosis. Following carotid artery occlusion there was loss of cerebral autoregulation: cerebral blood flow (CBF) measured with the xenon-133 technique became passively dependent upon the mean arterial blood pressure (MABP) over an MABP range of 30 to 110 mm Hg. By contrast, autoregulation was preserved in normal animals and in animals with a 90% carotid artery stenosis. Regional CBF was measured with carbon-14-labeled iodoantipyrine autoradiography in normotensive baboons, in hypotensive animals, and in hypotensive animals with carotid artery occlusion or stenosis. With carotid artery occlusion and hypotension, reduced levels of local CBF were seen ipsilaterally in the boundary zones between the anterior and middle cerebral arteries with 35% of the area of an anterior section through the hemisphere displaying a CBF value of less than 20 ml/100 gm/min. Comparable values with hypotension were 21% with carotid artery stenosis, 20% with no proximal vascular lesion, and 1% in normotensive animals. These areas of reduced CBF corresponded with areas of boundary-zone ischemia seen with light microscopy. The study suggests that while hemodynamic ischemia develops with carotid artery occlusion, it does not occur with even a 90% carotid artery stenosis or in normal animals.

KEY WORDS cerebral blood flow ischemia carotid artery occlusion carotid artery stenosis baboon

ISCHEMIC cerebrovascular disease is common, but the mechanisms of its production are often poorly understood. A frequent cause of brain ischemia is embolization, but it is now recognized that hemodynamic mechanisms may operate to produce a reduction in cerebral blood flow (CBF) in some patients. Indeed, Yates originally proposed that in 25% of patients with ischemic cerebrovascular disease a hemodynamic mechanism was responsible for the lesions. Such hemodynamic events are associated with a reduction in cerebral perfusion pressure (CPP), which may be the result of an increase in intracranial pressure or a decrease in mean arterial blood pressure (MABP). These events may occur physiologically (such as during normal sleep) or as a result of a reduction in cardiac output (such as may occur with an arrhythmia or following a myocardial infarction), induction of anesthesia and/or surgery, traumatic shock, or excessive reduction of MABP in the treatment of systemic hypertension.

Occlusive or stenotic disease of the large cerebral arteries may be asymptomatic. Brice, et al., showed that a stenosis of more than 84% of the lumen diameter was needed before a hemodynamic reduction in CBF was produced. However, if a patient with either a tight stenosis or proximal arterial occlusion has a reduction in CPP even in the presence of a good collateral circulation, then hemodynamic ischemia may develop distal to the diseased portion of the vessel. Failure to differentiate embolic from hemodynamic mechanisms may be responsible for the failure of the recent Extracranial-Intracranial (EC-IC) Bypass Study to show that EC-IC bypass reduces the risk of ischemic stroke. Clearly, an EC-IC bypass will do little to prevent embolic stroke, so a hemodynamic cause for ischemic events or strokes must be identified if the procedure is to offer the patient any benefit. Clinical measurements with positron emission tomography (PET) have now shown that areas of brain with increased oxygen extraction ("misery perfusion") are associated with hemodynamic ischemia, and that this abnormality is reversed following EC-IC bypass. Clarification of these different mechanisms of ischemia is therefore important if...
progress is to be made in the management of cerebrovascular disease in man.

The aim of the present study was to determine if hypotension of a degree that is normally well tolerated would produce focal cerebral ischemia when there is stenosis or occlusion of the extracranial arteries. To test this hypothesis, we examined the autoregulation of CBF (measured by the xenon-133 ($^{133}$Xe) technique) in response to reductions of perfusion pressure to 30 mm Hg MABP in normal baboons and in baboons with either stenosis or occlusion of the carotid artery. We also examined the spatial distribution of the ischemia at the lowest level of local CBF (at 30 mm Hg MABP). Carbon-14-labeled iodoantipyrine ($^{14}$C-IAP) autoradiography was used to measure local CBF, and any ischemic brain damage was identified by conventional light microscopy.

Materials and Methods

Animal Groups

Thirty adult baboons (Papio cynocephalus), weighing 7 to 16 kg each, were separated into four groups. Group 1 (the normal group) comprised four animals maintained at normotension. Group 2 (the control group) contained 10 animals subjected to hemorrhagic hypotension but no carotid occlusion or stenosis. Group 3 (the stenosis group) included five animals with hemorrhagic hypotension and carotid stenosis. Group 4 (the occlusion group) contained 11 animals that underwent hemorrhagic hypotension and carotid occlusion.

In the animals in Groups 2, 3, and 4, CBF was measured sequentially by the $^{133}$Xe technique at graded reductions in MABP. In Group 1 repeated measurements of CBF were made with $^{133}$Xe at normotension. In five animals in each of Groups 2, 3, and 4, CBF was also measured at the lowest level of MABP (30 mm Hg) using $^{14}$C-IAP autoradiography to obtain an accurate spatial distribution of flow at that level. Detailed neuropathological studies were performed in four Group 2 animals and five Group 4 animals. The fifth animal in Group 2 suffered a cardiac arrest just before perfusion fixation; however, where the physiological variables had remained stable, the sequential $^{133}$Xe CBF measurements were included in the data analysis. Similarly, the physiological variables became unstable just before the instant of CBF measurement with $^{14}$C-IAP in one Group 4 animal, and the autoradiographs were therefore excluded, but the $^{133}$Xe data were still included.

Anesthesia and Surgery

In each group, anesthesia was induced with intravenous thiopentone (7.5 mg/kg) and was maintained throughout the study by a continuous intravenous infusion of phencyclidine (0.01 mg/kg/min). The animals were intubated and ventilated with a mixture of 70% nitrous oxide and 30% oxygen. Intermittent injections of succinyl dicholine (50 mg) were administered intra-

muscularly. End-tidal CO$_2$ was monitored continuously with a capnograph attached to a pen recorder. Normoxia and normocapnia were maintained throughout the experiments. Both the femoral arteries and the femoral veins were cannulated for infusion of drugs and isotopes, monitoring of intravascular pressures, and withdrawal of arterial and venous blood samples.

The left brachial artery was cannulated with a polythene catheter for timed withdrawal of arterial blood samples during $^{14}$C-IAP autoradiography. The lingual artery was cannulated retrogradely after all other branches of the external carotid artery had been ligated. This catheter was used for injection of $^{133}$Xe by previously described techniques. The scalp and temporalis muscle were reflected to minimize extracerebral flow measurements, and six silver-silver-chloride electrodes were positioned parasagittally and screwed into position so as to lie on the dura mater to permit continuous electroencephalographic (EEG) monitoring. The electrodes were immobilized with plaster of Paris and connected to an EEG junction box. Bipolar EEG recordings were made under basal conditions and intermittently thereafter for the duration of the experiment. A global assessment of cerebral activity was obtained according to the analysis described by Prior, et al. A cannula was placed retrogradely in the posterior one-third of the superior longitudinal sinus and was connected to a Statham P23 pressure transducer* with output to a pen recorder. This permitted continuous monitoring of sagittal sinus pressure and withdrawal of cerebral venous samples for cerebral metabolic studies. A collimated 50-mm diameter scintillation detector was placed over the right parietal cortex. Temperature was maintained at 37°C with a heated blanket and infrared lamps. Each measurement of CBF was preceded by the appropriate withdrawal of arterial and venous samples for blood gas analysis, measurement of blood sugar, hematocrit, and the cerebral arteriovenous difference for oxygen content and glucose.

Production of Stenosis or Occlusion

After the completion of surgery the animals were permitted to stabilize for 30 minutes. Baseline measurements of CBF and cerebral metabolic rate (CMR) were made. After completion of these measurements, a 90% stenosis of the common carotid artery was produced in Group 3 animals by external ligation with a silk thread encircling the artery and a silver tube of known external diameter, corresponding to a reduction of 90% of the lumen of the vessel. After the ligature was tied the silver tube was removed, thus allowing the lumen to open to the diameter of the tube. At the end of the experiment in the Group 3 animals, the artery was perfused with contrast medium, excised, and an angiogram was performed to verify the degree of ste-

* Statham P23 pressure transducer manufactured by Statham Instruments, Oxnard, California.
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nosis. By contrast, in Group 4, the common carotid artery was completely occluded by a ligature. Because all branches of the external carotid artery had been ligated, the occlusion or stenosis of the common carotid artery corresponded to an equivalent lesion of the internal carotid artery, there being no collateral supply through the external circulation.

Experimental Protocols

Hypotension and Its Management. Staged hemorrhagic hypotension was achieved by withdrawal and reinfusion of warmed autologous blood from the descending aorta via a cannula in one of the femoral arteries. The MABP was simultaneously monitored through the opposite femoral artery, and the level of MABP was strictly maintained between predetermined limits, depending upon the initial baseline pressure after ligation or occlusion (thus, for our analysis (in mm Hg): 130 = 125–134; 120 = 115–124; 110 = 105–114; 100 = 95–104; 90 = 85–94; 80 = 75–84; 70 = 65–74; 60 = 55–64; 50 = 45–54; 40 = 35–44; and 30 = 25–34). The MABP was maintained within the appropriate band while baseline blood gases were measured to insure normoxia and normocapnia. The MABP was maintained at this stable level throughout the 10 minutes of the $^{133}$Xe CBF measurement.

Physiological Variables. Arterial blood gas levels, hematocrit and blood sugar, CMR for $O_2$ and glucose, temperature, and MABP were measured within each band and recorded.

Comparison of CBF and Pathology at 30 mm Hg MABP. With MABP in the 30-mm Hg band, CBF was first measured by the $^{133}$Xe technique. Thereafter, in five animals in each of Groups 2, 3, and 4, CBF was immediately measured by $^{14}$C-IAP autoradiography. An additional nine animals (four Group 2 and five Group 4 animals) were prepared for neuropathological study by maintaining MABP at 30 mm Hg for 30 minutes, followed by reinfusion of the heparinized blood and a 2-hour period of reperfusion at normotension.

Measurement of CBF. Cerebral blood flow was measured by determining the cerebral clearance rate of a bolus of $^{133}$Xe injected into the internal carotid artery via the right lingual artery by means of a scintillation detector positioned over the exposed bone in the right parietal region. The height/area method of analysis of CBF was used. The CBF measurements were made when the MABP had become stable for at least 10 minutes within the range selected. Serial measurements were made at each band of MABP to a low mean pressure level of 30 mm Hg.

The quantitative $^{14}$C-IAP autoradiographic technique was used to measure local CBF; this method has been described previously in baboons. Briefly, $^{14}$C-IAP (250 μCi in 5 ml saline) was infused intravenously over 30 seconds followed by a 5-ml bolus of saturated KCl. The tracer concentration in the arterial blood during infusion of tracer was determined by scintilla-

tion counting of 15 to 18 timed arterial blood samples collected on filter discs from a free-flowing catheter inserted into the brachial artery. Immediately after the animal's death, the brain was rapidly removed via a circular craniotomy, rinsed in saline, cooled in isopentane at (−20°C), and cut with a brain knife into two 15-mm thick coronal blocks (15 to 30 mm anterior and 5 to 20 mm posterior to the interaural line). The blocks were separated along the midline, frozen in isopentane (at −45°C), and sectioned in a cryostat (at −22°C). More than 80 semiserial sections were exposed to Kodak GR X-ray film for approximately 2 weeks. Ten calibrated standards (44 to 1475 nCi/gm) were also exposed with each film. A Model 720 Quantimet densitometer was used to measure: 1) the mean optical density for each structure examined (an average of at least 12 measurements from four consecutive autoradiographic images); 2) the mean optical density of the entire coronal section (an average measurement from three consecutive sections); and 3) the area of the entire coronal section and the area of the section with a blood flow of less than 20 ml/100 gm/min (an average from three consecutive sections). Local tissue concentrations of tracer were determined by relating the optical density of the calibrated standards to that of the regions examined. Local CBF was calculated from the concentration of tracer in the tissue and the concentration in the arterial blood during the infusion period.

The measurement of CBF with autoradiography was made at an MABP of 30 mm Hg approximately 10 minutes after the last $^{133}$Xe CBF measurement was completed, and after the physiological variables had been remeasured. In the same animals, the intermediate blocks of brain tissue that were not frozen in isopentane were used for the determination of CBF by the tissue sampling method. For this, $2 \times 2 \times 2$-mm blocks of tissue were dissected and placed into preweighed containers for scintillation counting. Each container was weighed again after the sample had been inserted, and then emissions were counted in the scintillation counter. Local CBF was calculated from the concentration of $^{14}$C-IAP as determined by the emission count and the sample weight related to the concentration in the arterial blood.

Measurement of Cerebral Metabolic Rate. Arterial and venous oxygen content measurements were made at each band of MABP during the $^{133}$Xe CBF study. The CMRO$_2$ was calculated using the measured $O_2$ content in the peripheral arterial blood and the superior longitudinal sinus venous sample, and the corresponding CBF measurement was made with the $^{133}$Xe technique. For the CMR of glucose, similar arterial and venous measurements were obtained and the glucose measurement was made on the Beckman glucose meter.†

† Beckman glucose meter manufactured by Beckman Instruments, Inc., Fullerton, California.
At the end of the procedure, the animals were given heparin (1000 mg/kg) and the brain was fixed with a transcardiac perfusion of 2 liters of FAM fixative (40% formaldehyde/glacial acetic acid/absolute methanol in a ratio of 1:1:8) preceded by flush-perfusion with heparinized saline. After perfusion, the brains were stored in the same fixative for 12 to 24 hours. The brain was removed and immersion-fixed in FAM for a further 24 hours. The hindbrain was then detached by a cut at right angles to its long axis and sectioned into slices 6 mm thick, and the cerebellum was cut into two slices perpendicular to the dorsal surface of each hemisphere. Large representative bilateral blocks of brain were embedded in paraffin wax and stained with hematoxylin and eosin and a method combining cresyl violet and Luxol fast blue. The histological sections were examined by one of us (D.I.G.) without full knowledge of the animal's history. Any microscopic abnormalities were recorded on a series of line diagrams.

**Statistical Analysis**

All values are expressed as mean ± standard error of the mean. Comparisons were made using Student's paired t-test or nonpaired t-tests as appropriate, with Bonferroni's correction for multiple comparisons.

**Results**

**Hemorrhagic Hypotension and Arterial Stenosis**

Graded hemorrhagic hypotension was achieved in all animals in Groups 2, 3, and 4. Of six animals in which carotid stenosis was produced, five were shown to have a 90% stenosis on angiogram and these five form Group 3. The other animal, in which the lumen was completely occluded, was omitted from the analysis.

**Physiological Variables**

There were no significant differences in the physiological variables between either the stenotic or the occluded animals and the control group at any level of MABP, from 30 to 110 mm Hg, aside from a marginally elevated PaCO2 in the occluded group at 90 mm Hg. The EEG reflected a stable depth of anesthesia (Stages I to III) throughout, except at the lowest level of MABP (30 mm Hg) when Stages IV and V were evident in some animals.

**CBF and Metabolic Changes with Graded Hypotension**

In control animals (Group 2, without occlusion or stenosis), a typical autoregulation curve was found with a consistent level of CBF from 50 to 110 mm Hg, inclusive. In animals with carotid occlusion (Group 4), \(^{133}\)Xe measurements of CBF in the ipsilateral hemisphere became passively pressure-dependent with loss of autoregulation (Fig. 1). When the mean CBF was compared at each level of MABP, the values in Group 4 animals differed significantly from the control group at 40 and 50 mm Hg (p < 0.05). By contrast, in animals with stenosis (Group 3), the pattern of autoregulation was preserved as it was in control animals (Fig. 2). There were no significant differences between the mean CBF values of the animals with stenosis and the control group. The CMRO2 fell below normal when MABP was 30 mm Hg. At each band of MABP, the mean
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**TABLE 1**

Area of hemisphere shown on autoradiography to have CBF below 20 ml/100 gm/min*

<table>
<thead>
<tr>
<th>Autoradiograph</th>
<th>Animal Group</th>
<th>% Area of Hemisphere With CBF &lt; 20 ml/100 gm/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior left</td>
<td>normal</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>19.7 ± 5.9†</td>
</tr>
<tr>
<td></td>
<td>stenosis</td>
<td>20.9 ± 2.2†</td>
</tr>
<tr>
<td></td>
<td>occlusion</td>
<td>28.6 ± 5.6†</td>
</tr>
<tr>
<td>anterior right</td>
<td>normal</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>23.2 ± 8.3†</td>
</tr>
<tr>
<td></td>
<td>stenosis</td>
<td>27.2 ± 3.7†</td>
</tr>
<tr>
<td></td>
<td>occlusion</td>
<td>35.0 ± 3.3†</td>
</tr>
<tr>
<td>posterior left</td>
<td>normal</td>
<td>4.6 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>23.7 ± 4.0†</td>
</tr>
<tr>
<td></td>
<td>stenosis</td>
<td>23.1 ± 2.2†</td>
</tr>
<tr>
<td></td>
<td>occlusion</td>
<td>27.4 ± 5.8†</td>
</tr>
<tr>
<td>posterior right</td>
<td>normal</td>
<td>5.9 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>23.4 ± 2.2†</td>
</tr>
<tr>
<td></td>
<td>stenosis</td>
<td>33.2 ± 6.3†</td>
</tr>
<tr>
<td></td>
<td>occlusion</td>
<td>32.4 ± 2.4†</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means obtained at a mean arterial blood pressure of 30 mm Hg. CBF = cerebral blood flow.
† Significant difference from normal (one-tailed Student's t-test with Bonferroni's correction: p < 0.01).

metabolism values of the occluded and the control animals did not differ significantly from each other, nor was there a significant difference between stenosed and control animals, except for one value of CMRO₂ at 60 mm Hg in an animal with occlusion (Fig. 3). The CMR of glucose similarly remained constant in Groups 2 to 4 with no significant differences between occluded and control animals being detected except for one reading at 80 mm Hg (Fig. 3).

**Patterns and Distribution of Oligemia**

Examination of the autoradiographs obtained at 30 mm Hg MABP at the levels of the caudate nucleus and through the visual cortex revealed that there was a profound reduction in local CBF in the arterial boundary zones between the anterior and middle cerebral arteries on the ipsilateral side in those animals with carotid artery occlusion. This pattern of oligemia was not present in animals with stenosis nor in those subjected to just hemorrhagic hypotension. Area analysis of the ipsilateral hemisphere revealed that in normal animals only 1.4% ± 0.2% of the hemisphere had a flow of less than 20 ml/100 gm/min. The area measured with "ischemic flow" (less than 20 ml/100 gm/min) exceeded this flow in all animals in Groups 2, 3, and 4 (Table 1). The largest area of ischemic flow was seen in the animals with occlusion plus hypotension (35%), followed by animals with stenosis plus hypotension. The area of ischemic flow was greatest in the anterior sections of the ipsilateral (right) hemisphere in occluded animals (Fig. 4). A similar large area was seen posteriorly in both the stenosed and the occluded animals. Analysis of the autoradiographs (Fig. 5) by densitometer revealed reductions in CBF of the ipsilateral hemisphere in the parietal, visual, and occipital cortex of occluded animals and in the parietal cortex of stenosed animals.
TABLE 2

<table>
<thead>
<tr>
<th>Brain Area</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rt</td>
<td>Lt</td>
<td>Rt</td>
</tr>
<tr>
<td>cingulate cortex</td>
<td>69±14</td>
<td>99±17</td>
<td>73±5</td>
</tr>
<tr>
<td>parietal cortex</td>
<td>50±12</td>
<td>60±8</td>
<td>39±7</td>
</tr>
<tr>
<td>visual cortex</td>
<td>61±12</td>
<td>66±10</td>
<td>84±6</td>
</tr>
<tr>
<td>insular cortex</td>
<td>66±18</td>
<td>77±14</td>
<td>49±3</td>
</tr>
<tr>
<td>occipital cortex</td>
<td>42±8</td>
<td>48±11</td>
<td>34±9</td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>60±12</td>
<td>71±15</td>
<td>37±8</td>
</tr>
<tr>
<td>putamen</td>
<td>62±10</td>
<td>72±14</td>
<td>56±5</td>
</tr>
<tr>
<td>globus pallidus</td>
<td>42±8</td>
<td>44±9</td>
<td>32±2</td>
</tr>
<tr>
<td>thalamus</td>
<td>37±8</td>
<td>38±9</td>
<td>31±2</td>
</tr>
<tr>
<td>corpus callosum</td>
<td>14±3</td>
<td>14±3</td>
<td>12±1</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means for five animals in each group. Group 2: hemorrhagic hypotension; Group 3: hemorrhagic hypotension and stenosis; Group 4: hemorrhagic hypotension and occlusion.

The most profound reduction in CBF was in the parietal cortex in the ipsilateral hemisphere of animals with occlusion, although this did not differ significantly from the mean CBF in the corresponding area in animals with hemorrhage but with no occlusion or stenosis (Table 2). Similarly, tissue sample analysis revealed that there was a reduction in CBF in the parietal, visual, and frontal cortex of the ipsilateral hemisphere of animals with occlusion. There was also a CBF reduction in the caudate nucleus and in the globus pallidus with this measurement technique (Table 3). A less severe reduction in CBF was seen in the ipsilateral hemisphere of animals with stenosis in the parietal cortex (Tables 2 and 3). None of these differences reached statistical significance.

Correlation of Autoradiographic and Tissue Flow Measurements

The relationship between CBF measured by $^{14}$C-IAP and by tissue sampling is shown in Fig. 6. The least-squares best fit linear regression line corresponded to

$$y = 17 + x$$

(n = 355, r = 0.59, p < 0.001). Mean values for tissue samples are shown in Table 3.

Neuropathological Findings

Perfusion fixation appeared to be good in all animals examined, and there were no cytological artifacts. Microscopic examination was undertaken in only four animals in Group 2 (hemorrhagic hypotension). The fifth animal in that group experienced a cardiac arrest immediately prior to perfusion fixation. Abnormalities were few and limited to small foci of necrosis in the superficial layers of the crests of the parasagittal gyri. These were interpreted as damage secondary to heating from drilling and placement of the EEG electrodes. There were no other histological abnormalities in this group, and in particular there was no evidence of ischemic damage in other brain areas.

In addition to the EEG electrode artifacts seen in Group 2, microscopic examination of specimens from Group 4 (hemorrhagic hypotension and carotid occlusion) revealed neurons with features of an ischemic cell process in the brains of three animals. The nerve cells in these animals showed evidence of microvacuolation (potentially reversible) and ischemic nerve cell change, both with and without incrustations (irreversible), as described previously for FAM-fixed material. On two of the three animals with ischemic brain damage, the lesions were localized to the boundary zones between the distribution of the right anterior and the middle cerebral arteries and extended furthest in the sides and depths of the intraparietal and parieto-occipital sulci. In one of these two animals, there was a small focus of neuronal necrosis in the superolateral quadrant of the right cerebral hemisphere. In the third animal with ischemic brain damage, there was extensive necrosis in the lateral part of the striatum and in the cortex of the lateral convexity of the right cerebral hemisphere (within the distribution of the middle cerebral artery). In none of these three animals with ischemic brain...
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**TABLE 3**
*Tissue sample measurements of local cerebral blood flow (ml/100 gm/min)*

<table>
<thead>
<tr>
<th>Brain Area</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rt</td>
<td>Lt</td>
<td>Rt</td>
</tr>
<tr>
<td>cingulate cortex</td>
<td>42±10</td>
<td>44±7</td>
<td>46±5</td>
</tr>
<tr>
<td>parietal cortex</td>
<td>53±21</td>
<td>54±11</td>
<td>58±6</td>
</tr>
<tr>
<td>visual cortex</td>
<td>37±8</td>
<td>41±8</td>
<td>67±8</td>
</tr>
<tr>
<td>insular cortex</td>
<td>34±7</td>
<td>59±19</td>
<td>36±3</td>
</tr>
<tr>
<td>frontal cortex</td>
<td>33±7</td>
<td>58±16</td>
<td>37±2</td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>37±9</td>
<td>46±9</td>
<td>30±3</td>
</tr>
<tr>
<td>putamen</td>
<td>44±6</td>
<td>52±7</td>
<td>43±6</td>
</tr>
<tr>
<td>globus pallidus</td>
<td>26±5</td>
<td>25±4</td>
<td>22±3</td>
</tr>
<tr>
<td>thalamus</td>
<td>49±17</td>
<td>41±8</td>
<td>41±6</td>
</tr>
<tr>
<td>corpus callosum</td>
<td>13±3</td>
<td>13±2</td>
<td>10±1</td>
</tr>
<tr>
<td>medulla</td>
<td>18±3</td>
<td>13±1</td>
<td>26±10</td>
</tr>
<tr>
<td>cerebellar hemisphere</td>
<td>28±8</td>
<td>31±6</td>
<td>26±5</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means for five animals in each group. Group 2: hemorrhagic hypotension; Group 3: hemorrhagic hypotension and stenosis; Group 4: hemorrhagic hypotension and occlusion.

Discussion

These studies have demonstrated that in subhuman primates normal autoregulation is lost following carotid artery occlusion, but is preserved even with a tight proximal extracerebral artery when combined with hypotension. This was demonstrated both on autoradiographic maps of local CBF and histologically. Although autoregulation normally allows the brain to withstand degrees of hypotension, occlusion of a large proximal extracerebral artery when combined with hypotension interferes with this normal physiological homeostatic mechanism, and ischemia results.

Previous studies in baboons have also indicated that autoregulation is lost following carotid artery occlusion, but those studies did not demonstrate the distribution of the ischemia that occurred at low levels of MABP, and did not attempt to evaluate autoregulation with carotid artery stenosis. The present study was designed to show the pattern of ischemia using 133Xe autoradiography. Previous work has indicated that carotid artery occlusion and hypotension in rats produces ischemia mainly in the deeper layers of the neocortex, the thalamus, and the caudate nucleus. In the subhuman primate, the boundary zones between the anterior and the middle cerebral arteries (in our anterior sections) and between the anterior and the posterior cerebral arteries (in our posterior sections) are the areas most vulnerable to ischemia. This selective vulnerability is probably anatomically determined from the arterial supply, as was suggested by Ginsberg, et al. Autoradiography was performed at the time of maximal reduction in MABP to confirm whether this was so in baboons. The utilization of the 133Xe technique of measuring CBF, which allows sequential determination of CBF, and the 14C-IAP autoradiography method, which has excellent spacial resolution, has made it possible to demonstrate this pathophysiological process both in time and in space in the same animal. It is therefore clear that following carotid artery occlusion and at the lower limit of autoregulation, perfusion pressure failure produces a hemodynamic disturbance due to the unique vascularization of the cortex that is fundamental in the pathogenesis of the boundary-zone pattern of ischemic brain damage.

Metabolic changes, as determined by serial measurements of CMR of O2 and glucose, indicate that the differences between occluded and control animals were primarily hemodynamic and not the result of differences in levels of anesthesia or cortical activity. This was also confirmed by continuous EEG monitoring in all animals. The differences were also not due to any changes in the physiological variables, which were similar in the Group 2, 3, and 4 animals.

The autoradiographs in this study have demonstrated the pattern of flow in normal animals and have shown that cortical and basal ganglia regions have the highest flow values. With hypotension, there is a patchy reduction in flow in the basal ganglia. The autoradiographic flows measured with the densitometer corresponded well with the tissue-sample flow values obtained from the gamma counter and the tissue weights. Also the autoradiographic flows corresponded with the 133Xe flow values for lateral cortex and white matter at the time of the autoradiograph when the MABP was low. The methodological validation of the 14C-IAP autoradiographic method in baboons has been reported re-

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cently from this laboratory. The three methods of flow measurement reported in the present study all corresponded well with each other. To eliminate any bias which can be introduced in the interpretation of autoradiographic flow, the flow band analysis method was used here. With this technique, the computer records the total area of the caudate nucleus and the hemisphere at predetermined levels on each side, and then measures the percentage of the total with a CBF below any particular threshold. In the present study, a threshold of 20 ml/100 gm/min was chosen because this is generally accepted as being a flow below which membrane failure and structural evidence of ischemic brain damage occur. This flow band analysis clearly showed that the largest reductions in flow occurred in the ipsilateral anterior frontal regions. This finding corresponds with the "target" area of the occluded carotid artery, and correlates with what would be expected with boundary-zone ischemia.

It has been shown by Brierley, et al., that a single period of profound arterial hypotension (MABP 25 mm Hg) in the rhesus monkey can result in patterns of brain damage resembling those described in patients dying after hypotensive anesthesia, dental surgery, carotid occlusion, and cardiovascular accidents. The neocortex around the parieto-occipital sulci, representing the common boundary zone between the territories of the anterior, middle, and posterior cerebral arteries, is the most vulnerable region of the brain since it is the most remote from the origin of each major artery. The pattern of ischemic brain damage identified in the animals in this work and in other studies can be attributed to major decreases in perfusion pressure in these arterial boundary zones, where CBF falls to a critical level in those parts of each arterial territory that are most remote from the parent stems.

It is interesting to note in this present investigation that evidence of ischemic brain damage in three of five of the occluded animals was present at an average MABP of 30 mm Hg and at a time when mean CBF, as measured by 133Xe, was not less than 20 ml/100 gm/min. However, as shown by the autoradiograph studies, CBF was considerably less in the boundary zones themselves at this mean arterial pressure. This may therefore simply reflect the global nature of CBF measurement with 133Xe, compared with the high-resolution localized type of measurements with C14-IAP autoradiography.

The clinical importance of this study is that, with carotid artery occlusion, any lowering of MABP that would normally be well tolerated may lead to severe ischemia. Therefore, patients with carotid artery occlusion may be at greater risk from any cardiac disorder that results in a decrease in cardiac output. For example, myocardial ischemia, arrhythmia, or shock, which may not ordinarily produce focal cerebral ischemia or syncope, many produce severe ischemia in patients with carotid artery occlusion. There is sufficient clinical evidence to suggest that this may indeed be the case: in patients undergoing surgery, hypotension is associated with cerebral ischemia; rapid lowering of MABP in patients with hypertension may produce profound cerebral ischemia leading to death; and in normal sleep there is a fall in MABP. It is interesting to note that as many as 60% of strokes are thought to occur during sleep or are recorded on rising in the morning. It is conceivable that in patients with carotid artery occlusion, this normal physiological fall in MABP is poorly tolerated. There is also evidence that in some patients cerebral ischemia is orthostatically produced. If tight carotid artery stenosis does not cause a reduction in CBF with hypotension, then in man carotid artery stenosis is more likely to produce embolic infarction, while ischemia related to carotid artery occlusion is more likely to be hemodynamic. Previous work has indicated that stenosis of greater than 84% is required before significant alterations in flow occur, but that study did not take into account the collateral circulation. Our study certainly suggests that even tight carotid artery stenosis in otherwise normal subhuman primates does not produce altered autoregulation, whereas carotid artery occlusion does.

This finding correlates with observations on PET scanning that carotid artery occlusion in man can cause reduced local CBF and poor collateral reserve. Similarly, areas with poor collateral circulation seen on PET scanning and with high oxygen extraction ("misery perfusion") may be present in some patients. The correct identification of these patients with symptoms of hemodynamic ischemia may be necessary if any future study of EC-IC bypass is undertaken. The post-operative studies of Samson, et al., have certainly suggested that reversal of "misery perfusion" is possible with EC-IC bypass in these patients.

These clinical findings and the results of the present study in subhuman primates indicate that carotid artery occlusion may lead to hemodynamic ischemia. By contrast, even with tight carotid artery stenosis, the collateral circulation in normal baboons is sufficient to maintain autoregulation so that low levels of MABP may be well tolerated. Under these circumstances the pattern of any brain damage will be determined by the resulting changes in hemodynamics in the collateral circulation. While this particular animal model may be an incomplete replica of the disease process in man, we believe that the findings in this study are of clinical relevance to patients with internal carotid artery occlusion or stenosis.

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References

Hemodynamic results of ICA flow defects


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