A Model of Acute Focal Ischemia
in the Territory of the
Anterior Cerebral Artery in Baboons

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Background and Purpose: We developed a model of acute focal ischemia in the territory of the anterior cerebral artery in baboons to study the ischemic pattern following occlusion and changes in regional cerebral blood flow.

Methods: In nine anesthetized animals, a Scoville clip was placed on the proximal segment of the common anterior cerebral artery via a unilateral transorbital approach. Regional cerebral blood flow was measured by hydrogen clearance in the cortex and corpus callosum. Postexperimentally, arteries were selectively injected.

Results: The resulting ischemia involved both hemispheres symmetrically and the corpus callosum. Cortical flows were significantly reduced within a region 15 mm from the midline on each side (p < 0.01). A gradient of cortical flow reduction was produced between 10 and 25 mm from the midline. This area defines the boundary region between the territories of the anterior and middle cerebral arteries, and is identified as the "penumbra" of the ischemic core, which itself lies within 10 mm of the midline. Blood flows in the corpus callosum decreased from an average of 21.0 to 6.7 ml/100 g/min in the body (p < 0.01) and from 22.5 to 10.7 ml/100 g/min in the genu (p < 0.05).

Conclusions: This ischemic model has close physiological and morphological relevance to stroke-related clinical circumstances, in particular the acute conditions of focal cerebral ischemia associated with vascular surgery. It also provides a new framework for experimental investigation of the ischemic penumbra. (Stroke 1992;23:40-44)
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FIGURE 1. Normal distribution of common anterior cerebral artery (ACA) injected with red material. ① Both A i segments join to form common ACA; ② common ACA ascends superficially in front of anterior perforated substance and lamina terminalis; ③ the major trunk courses around genu of corpus callosum as common pericallosal artery; ④ and ⑤ branches come off to cortical striate area. The corpus callosum (④) and septum pellucidum (②) are supplied by perforating branches of common ACA.

recording technique were similar to those described previously. Anesthesia was induced with thiopentone (5 mg/kg i.v.) for intubation and cannulation, then maintained using propofol (2,6-diisopropylphenol, 30 mg/kg per hour i.v.), and the animals were ventilated with air. Blood gases were monitored and maintained in the normal range. The rCBF was measured by the hydrogen clearance method as described previously, and groups of cortical flow electrodes were positioned in the precentral area of both convexities at different distances from the midline (5, 10, 15, 20, 25, and 45 mm) to cover the territories of both anterior and middle cerebral arteries. Deep electrodes for measurement of flow in the corpus callosum were inserted stereotactically into the genu and body of the corpus callosum 4–11 mm from the midline bilaterally in six baboons. These white matter placements were confirmed in three experiments by examination of brain slices and in other experiments by measurements of blood flow during electrode insertion, with fast and slow clearances indicating that the electrodes were in the gray and white matter, respectively. A large Ag-AgCl electrode was placed in the mouth to act as the reference for the hydrogen clearance system.

The animal was placed supine with the neck extended. The head was turned about 15° to the left to allow a proper view of the medial region of the right orbital fossa. A circular incision was made around the bony margins of the orbit. Dissection was performed back on the orbital walls toward the apex of the muscle cone; the contents of the orbit were excised. A high-speed air drill was used to make a craniectomy of about 15×15 mm involving the medial sphenoid aid, the subfrontal bone, and part of the anterior clinoid process. The craniectomy was extended to the olfactory groove of the frontal base. Bleeding from the bony edges of the craniectomy and the epidural space of the olfactory groove was arrested with bone wax, monopolar and bipolar coagulation, and the use of Surgicel (absorbable hemostatic gauze; Johnson & Johnson Ltd., Slough, UK) and surgical patties. Under the operating microscope (Carl Zeiss), the medial part of the optic foramen and part of the anterior clinoid process were removed. The dura was opened and removed. The ipsilateral olfactory nerve just under the exposure was a clear sign of correct positioning. The arachnoid was opened medially over the proximal ACA trunk. The ipsilateral terminal segment of the internal carotid and middle cerebral arteries were unexposed to avoid potential traumatic vasospasm. With dissection medially along the proximal segment of ACA, the junction of the two ACAs joining to form a common ACA could be exposed easily with gentle retraction of the medial part of the frontal lobe. A Scoville clip was placed on the common ACA within 5 mm distal to the junction. Perforating vessels from the proximal segment of both ACAs were kept patent to avoid ischemia of the deep nuclei and the medial part of the internal capsules.

The mean systemic blood pressure was monitored continuously in all experiments. Blood flow was measured during three periods: control, 5 minutes after the common ACA occlusion, and 30 minutes after the occlusion.

At the end of the experiment, the brain was perfused intra-aortically with saline and formalin. In
FIGURE 2. Common anterior cerebral artery (ACA) supplies a considerable portion of convexity of the hemisphere, up to approximately 2 cm from midline in region of precentral gyrus. Arrows indicate cortical branches of middle cerebral artery (MCA) and posterior cerebral artery (PCA), which were infused retrogradely via leptomeningeal anastomoses across the boundaries (highlighted with white dotted line) between ACA, MCA, and PCA territories.

six baboons, after fixation, different arteries were selectively injected with a red-colored mixture of wood glue, alizarin crimson powder, and 7.5% ammonia water (10 g:1 g:1 ml). The injection pressure was the baboon’s normal arterial pressure (100–120 mm Hg). The injected specimens were kept in formalin and the brains removed after 2 days to allow assessment of abnormality of the anterior part of the circle of Willis, the outline of the anatomical territory of the ACA, the exact position of the applied arterial clip, and the outline of the hypoperfused area. In two baboons, the brains were perfused with carbon black following fixation and sliced coronally at 8–9 mm thickness to allow assessment of the hypoperfusion in the deep structures.

Results

All animals had well-developed A1 segments. In seven animals, both ACAs joined to form a common artery, identified as the common ACA. The distance from the internal carotid bifurcation to the junction of the common ACA ranged from 9 to 12 mm. The other two animals each had an anterior communicating artery and two A2 segments rather than a common ACA. In these two animals, both A2 segments were occluded with one clip. The recurrent artery was single or multiple but usually arose from the proximal two thirds of the A1 segment of the ACA.

As identified by injection, the well-filled large and small arteries indicated the track of major vessels and their distribution (Figure 1). From the junction of the A1 segments, the common ACA ascended in front of the lamina terminalis in the interhemispheric fissure. The major trunk coursed around the genu of the corpus callosum as the common pericallosal artery. Fine perforating branches originating from the common ACA and common pericallosal artery supplied neighboring structures such as the lamina terminalis, septum pellucidum, anterior commissure, and corpus callosum. The cortical branches covered the greater part of the medial surface of both hemispheres from the frontal pole to the striate area anterior to the calcarine fissure and a considerable portion, up to about 2 cm from the midline in the precentral region, of the convexity of the hemisphere (Figure 2). The boundary regions between anterior, middle, and posterior cerebral arteries were fairly sharp, mostly along sulci, and the leptomeningeal anastomoses between the arteries were located in the depths of sulci rather than on the surfaces of gyri. Several cortical branches of the middle cerebral artery were perfused retrogradely through leptomeningeal anastomoses, but fewer similar branches of the posterior cerebral artery were observed.

The differences between control and ischemic brains are illustrated in Figure 3, and these were even clearer in comparisons between the medial surfaces of the hemisphere in the two circumstances. In the brains with common ACAs clipped, there was obvious gross hypoperfusion in the parasagittal convexity and the medial surface of the hemispheres symmetrically, whereas perfusion in the territories of the middle and posterior cerebral arteries appeared normal. The hypoperfused area was similar to the territory of the common ACA shown in Figure 1.

Coronal slices of brain injected with carbon black showed that the hypoperfusion was distributed around the interhemispheric fissure in the shape of a wedge, involving the corpus callosum. The partial black stain of the hypoperfused area indicated some residual blood flow in this region. The medial parts of the basal ganglia and internal capsule were well perfused.

A comparison of rCBF between right and left sides of the brain showed no significant differences between homologous regions of the hemispheres either before or after occlusion, and values from right and left sides were therefore combined for purposes of analysis. The rCBFs in the precentral cortex and corpus callosum are given in Table 1. Cortical blood flow was significantly reduced by the occlusion at distance up to 15 mm from the midline, the data showing a well-defined gradient of flow reduction in the lateral direction with...
FIGURE 3. Comparison between injected normal brain (right) and one made ischemic with common anterior cerebral artery (ACA) occlusion (left). The ischemic region is similar to the region of common ACA distribution as shown in Figure 2.

the densest ischemia close to the midline. In the zone extending from 10 to 25 mm from the midline, the leptomeningeal collateral anastomoses principally determined the flow pattern after occlusion, and this zone may therefore be considered the hemodynamic boundary region in the cortex between the territories of the anterior and middle cerebral arteries. Flow in the corpus callosum was significantly reduced, more so in the body than in the genu. In five experiments, sequential blood flow measurements demonstrated that reduced cortical flow 5 minutes after common ACA occlusion persisted without significant change for 30 minutes after the occlusion whereas the blood pressure remained constant.

Discussion

In the baboon, both ACAs usually join to form a common ACA about 1 cm distal to the internal carotid bifurcation. Clipping the A1 segment on one side alone does not reduce blood flow significantly in the territory of the ACA because there is an excellent collateral supply from the contralateral ACA. To produce focal ischemia in the territory of the ACA in baboons, it is necessary to clip either both ACAs or the common ACA. Bilateral transorbital dissection is unnecessary for this because the midline, where the two A1 segments join to form the common ACA, and even the contralateral A1 segment, can be easily reached by a unilateral approach. Vascular damage or potential traumatic spasm of the middle cerebral artery and internal carotid artery can be avoided because the arachnoid is opened only medially, over the distal A1 segment, and hypoperfusion following the occlusion is thus limited to ACA territory.

The common ACA sends cortical branches bilaterally to the medial hemispheric surfaces and the convexity of the hemisphere near the midline, a major difference from the distribution in humans. Although injection of both internal carotid arteries with a clip placed on the common ACA demonstrated the ischemic area more accurately than injection of the common ACA itself, both methods led to the same conclusions as to the range and shape of the normal common ACA distribution.

Two important cerebral leptomeningeal anastomotic regions of cortical circulation have been demonstrated in this model: one is between the anterior and middle cerebral arteries, the other between the anterior and posterior cerebral arteries. The boundary of the former region was much wider than that of the latter, and the collateral branches were more easily revealed by vascular injection (Figure 2), which indicates that the leptomeningeal collateral circulation between the anterior and middle cerebral arteries is more important and is primarily responsible for the gradient of rCBF after the occlusion (Table 1).

In this model, common ACA occlusion produced an immediate reduction of flow in ACA territory of >50% of control in the corpus callosum and up to 70% in the affected cortex. In contrast, flow in the middle cerebral artery territory was unaffected. If blood pressure remained unchanged, flow values were stable for at least 30 minutes after common ACA occlusion in all the above regions. However,
TABLE 1. Comparison of rCBF in Precentral Cortex and Corpus Callosum Before and After Occlusion of Common Anterior Cerebral Artery

<table>
<thead>
<tr>
<th>Site/position</th>
<th>rCBF before occlusion (n)</th>
<th>rCBF after occlusion (n)</th>
<th>Residual flow (% of control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpus callosum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>50.7±5.3</td>
<td>14.9±5.3*</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>51.7±4.3</td>
<td>19.3±4.6*</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>(8)</td>
<td>(7)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>43.3±3.2</td>
<td>24.1±3.5†</td>
<td>55.7</td>
</tr>
<tr>
<td></td>
<td>(7)</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>45.8±7.2</td>
<td>35.3±8.4</td>
<td>77.1</td>
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<tr>
<td></td>
<td>(4)</td>
<td>(3)</td>
<td></td>
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<td>Body</td>
<td>41.4±5.2</td>
<td>36.0±5.8</td>
<td>87.0</td>
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<tr>
<td></td>
<td>(5)</td>
<td>(4)</td>
<td></td>
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<tr>
<td>Body</td>
<td>39.8±7.3</td>
<td>42.1±7.3</td>
<td>105.8</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Corpus callosum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>22.5±2.2</td>
<td>10.7±2.6†</td>
<td>47.6</td>
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<tr>
<td></td>
<td>(3)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>21.0±1.9</td>
<td>6.7±1.9†</td>
<td>31.9</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SEM, in units of milliliters per 100 grams per minute. rCBF, regional cerebral blood flow; n, number of animals. *p<0.001, †p<0.01, ‡p<0.05 compared with value before occlusion by unpaired t test.

because residual flow in the ischemic cortex was close to the flow threshold for failure of electrophysiological function (i.e., 15–18 ml/100 g/min9,12), locally produced evoked potentials could be made to disappear or reappear by controlled manipulation of the blood pressure. Data relating to motor evoked potentials and transcallosal responses recorded using this ischemic model will be reported separately.

Although the present study was designed to produce an acute ischemic lesion, the question arises whether an infarction would have been produced by common ACA occlusion if the animals had been allowed to recover. On the basis of previous studies in the territory of the middle cerebral artery13 in baboons, we predict that cerebral infarction in the present model would be confined to the ischemic core, lying within a few millimeters of the midline in the territory of the ACA. Flow in the boundary zone, extending to about 25 mm from the midline, is distributed around the threshold of neuronal electrical failure but above the metabolic failure threshold (about 10 ml/100 g/min).9,11,13 This zone is clearly identifiable as the "penumbra"11 of the ischemic core, and the present model provides a new framework for experimental investigation of the ischemic penumbra.

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References


KEY WORDS • cerebral arteries • cerebral ischemia • cerebral blood flow
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