Neurological Deficit and Cerebral Infarction after Temporary Middle Cerebral Artery Occlusion in Unanesthetized Cats

PHILIP R. WEINSTEIN, M.D., GARY G. ANDERSON, B.S., AND DAVID A. TELLES, B.S.

SUMMARY  Forty-four unanesthetized cats underwent temporary middle cerebral artery (MCA) occlusion with an implanted, externally controlled balloon cuff occluder. The occlusion was reversed to allow reperfusion of the MCA after 2 min to 24 hr of ischemia. Fourteen cats had temporary occlusions lasting 2 min to 3 hr; their neurological deficits improved or resolved after reperfusion, and brain sections showed only scattered microscopic areas of necrosis. After a 4-hr occlusion, five of nine cats (55%) recovered completely within 24 hr; two had persistent deficit when sacrificed, 10 days later, and each had a circumscribed infarct. All 18 cats undergoing 5-, 6-, 8-, and 24-hr occlusions sustained permanent neurological deficits. Three 3-hr occlusions at 2-day intervals in three cats resulted in permanent deficits and infarcts that were 25% larger than those after single 8-hr occlusions. Ten cats underwent permanent MCA occlusion; three deteriorated neurologically and died, and the survivors showed no improvement. Infarcts after 5-, 6-, and 8-hr occlusions followed by reperfusion were 66% smaller (p < 0.05) than those after permanent occlusion; reperfusion after 24 hr of occlusion did not reduce infarct size. Hemorrhagic infarction occurred after two permanent occlusions, but after only one 5-hr temporary occlusion. The results obtained with this method of temporary regional ischemia indicate that restoration of flow after 1–8 hr, but not after 24 hr, of MCA occlusion resulted in less severe neurological deficit and smaller infarcts than did permanent occlusion. The infarct size correlated with the duration of MCA occlusion (p < 0.05) rather than with the degree of deficit during occlusion.

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Methods

Occluder Implantation and Function

Adult cats were anesthetized with intramuscular injections of ketamine (100 mg/kg) and acepromazine (2 mg/kg). An endotracheal tube was inserted and the head of the cat was placed in a stereotactic frame. The cats were ventilated with a Harvard 607 animal respirator to maintain normal arterial pO2 and pCO2 levels; isotonic fluids were administered intravenously during surgery. Using sterile microsurgical technique, the right orbit was exenterated and the optic foramen and orbital fissure were enlarged with a dental drill to expose the dura overlying the origin of the MCA from the internal carotid artery.† Under the operating microscope, the arachnoid was dissected and an inflatable vessel occluder† was positioned around the MCA proximal to or incorporating adjacent branches (fig. 1). The occluder catheter was tunneled under the scalp but remained accessible through a small subcutaneous portal overlying the occiput. Under direct visualization, the balloon was inflated by injection of sterile water with a 1-ml syringe and then deflated to verify that it functioned properly. The balloon volume required to interrupt MCA flow completely was recorded. The dural incision was covered with Gelfoam soaked in Bacitracin-Neomycin solution, and the orbit was filled with methyl methacrylate dental cement. Intramuscular injections of penicillin and streptomycin were given daily for 5 days after surgery. The cats were allowed to recover for 7–10 days. Neurological examinations were performed daily during the recov-

*The Experimental Protocols used in this study were approved by the Animal Care Subcommittee of the Research and Development Committee and the staff veterinarian at the Tucson Veterans Administration Medical Center, Tucson, Arizona. All procedures are consistent with regulations published in the Guide for Care and use of Laboratory Animals, National Institutes of Health (DHEW Publication No (NIH) 78–23, Revised 1978).

†The balloon cuff occluder was supplied by Heyer-Schulte, Inc., Goleta, California 93017.

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Figure 1. (A) Occluder with balloon inflated. The pair of parallel prongs is passed over the vessel in the subarachnoid space. (B) Transorbital exposure of the origin of the right middle cerebral artery (arrowhead) at 24 X magnification under the operating microscope.

ery period; neurological function was graded using the criteria listed in table 1.

After the cats had recovered from the implantation procedure, a single 1-min test occlusion was performed in each cat. The rapid onset of neurological deficit of grade 3 to grade 9 was considered to indicate that the balloon cuff had occluded the MCA. Neurological recovery within minutes after deflation of the balloon cuff was considered to indicate reversal of the occlusion and reperfusion of the MCA.

Preliminary Studies

Sham operations were performed in four cats to verify that the surgical procedure did not cause neurological deficit or infarction. Two of these cats underwent transorbital exposure of the MCA without implantation of the occluder; the other two cats underwent transorbital implantation of the occluder without inflation of the balloon cuff. None of the cats had a postoperative neurological deficit or a cerebral infarct. Three occlusions lasting 1–5 min were performed in four other cats at 48-hr intervals to verify that the neurological response to the production and reversal of MCA occlusion was reproducible. These cats showed no significant variation in deficit grade during occlusion and suffered no cumulative neurologic effect; pathologic examination revealed only scattered microscopic areas of infarction.

Cerebral angiograms were obtained in two cats after contrast material was injected through a transfemoral catheter into the right carotid artery. These studies demonstrated normal MCA perfusion after occluder implantation, MCA occlusion after balloon inflation, and reperfusion of the MCA without stenosis or vasospasm after balloon deflation.

Cerebral blood flow (CBF) studies were performed in four cats by intraarterial injection of 1 mCi of xenon-133 after surgical exposure of the right carotid artery. Isotope washout curves obtained with a gamma camera demonstrated an average reduction of 50% in mean hemispheric flow during occlusion; after reperfusion, CBF increased 20–30% above the baseline level, indicating reactive hyperemia. The absence of any significant difference in preocclusion CSF between right and left hemispheres suggests that flow was not impaired by implantation of the occluder. Because CBF and angiographic studies required anesthesia, blood flow and perfusion could not be assessed in the unanesthetized experimental groups.
Complications such as MCA branch hemorrhage or occlusion of the balloon cuff occluder. In 5 cats, intraoperative neurological deficit after occluder implantation and delayed recovery could be observed.

Experimental Studies

Fifty-nine cats underwent transorbital implantation of the balloon cuff occluder. In 5 cats, intraoperative complications such as MCA branch hemorrhage or spasm occurred. All of these cats exhibited persistent neurological deficit after occluder implantation and were excluded from further study. In the remaining 54 cats, the occluder was implanted without complication and no postoperative deficit was observed. These cats were divided into seven experimental groups and underwent MCA occlusion of various durations (table 2): (A) 1-60 min; (B) 1-3 hr; (C) 4 hr; (D) 5-8 hr; (E) 24 hr; (F) three-hr occlusions at 48-hr intervals; (G) permanent occlusion by permanent balloon inflation or by bipolar cauterization and transection of the MCA.

Pathological Analysis and Verification of Occluder Function

Before sacrifice, the cats were anesthetized and both carotid arteries were cannulated. In 5 cats that had a neurological deficit of less than grade 4 during occlusion, occluder function was verified by injecting Evans blue dye into the right carotid artery with the balloon inflated. Absence of dye distal to the site of occlusion at the time of brain removal was considered proof that MCA flow had been blocked by the occluder. In all other cats, restoration of MCA patency after release of the occluder was verified by injecting dye into the right carotid artery with the balloon deflated. The presence of dye in the MCA branches distal to the occluder was considered proof that MCA flow had been restored. After the brains were removed, MCA patency was again checked by inspection under the operating microscope. Finally, MCA segments taken from the occluder site were examined histologically and by scanning electron microscopy (SEM) of the luminal surfaces.

When the dye injections had been completed, the brains were perfusion fixed with 10% formalin, removed by craniectomy, immersed in 10% formalin for 10–14 days, inspected, and photographed. Four coronal sections 4 mm thick centered at the anterior notch of the optic chiasm were cut in a miter box. Histological preparations were made with hematoxylin-eosin and luxol-fast blue cresyl-violet stains. In each coronal section, the infarct area was grossly outlined under a dissecting microscope.

None of the cats in the preliminary studies were included in the experimental studies.

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<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Duration of occlusion</th>
<th>Average deficit grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td>1-60 min</td>
<td>5.7±1.2</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>1-3 hr</td>
<td>6.2±2.0</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>4 hr</td>
<td>6.0±2.1</td>
</tr>
<tr>
<td>D</td>
<td>12</td>
<td>5-8 hr</td>
<td>7.0±1.4</td>
</tr>
<tr>
<td>E</td>
<td>6</td>
<td>24 hr</td>
<td>6.7±0.5</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>3 hrs × 3</td>
<td>7.6±1.5</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>permanent</td>
<td>7.2±1.8</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
infarct areas were coagulation necrosis and glial proliferation or inflammatory cell infiltration, as well as moderate or severe ischemic neuronal alterations as described by Little et al. The infarcts were outlined on slides of coronal sections, projected, and traced onto paper. Infarct size was measured with a Zeiss MOP-3 electronic planimeter and calculated as a percentage of hemispheric area. The infarct areas in the four sections from each cat were then averaged.

**Statistical Analysis**

The unpaired t test and parametric analysis were used to determine the statistical significance of differences in infarct size and grade of neurological deficit between groups.

**Results**

**Occluder Function**

In three of 54 cats, inflation of the occluder failed to produce immediate and sustained onset of neurological deficit. Surgical exploration showed that the balloon cuff had been displaced away from the MCA, and the placement was corrected. Otherwise, there was no significant difference in the average grade of neurological deficit 1 hr after MCA occlusion in groups A–G, although individual variation was observed. In two cats, the occluder malfunctioned and the neurological deficit did not reverse after the balloon was deflated. These cats were reassigned to the permanent occlusion group (group G).

Dye injections and MCA inspection at autopsy showed no evidence of vessel thrombosis from implantation or inflation and deflation of the occluder, even after 24-hr occlusions. Histologic sections of the MCA from the occluder site showed no evidence of necrosis or fibrosis of the vessel wall. Arachnoid inflammatory reaction and fibrosis were minimal. SEM studies showed focal subendothelial folding and neoendothelial cell proliferation consistent with mild mechanical trauma to the vessel wall. No intraluminal platelet or fibrin deposition was seen.

**Neurologic Function and Infarct Size**

The results of MCA occlusion in each group are summarized in table 2. Circling and tonic head and eye deviation to the right were observed immediately after MCA occlusion. Within 1 min, left limb weakness, slipping or falling to the left, poor forepaw placement, and diminished withdrawal to sensory stimuli on the left were seen. The severity of deficit during MCA occlusion varied from grade 2 to grade 9; detailed results for one group are shown in table 3. The level of dysfunction remained stable throughout the occlusion, except in four cats that showed slight improvement of 1–2 grades. A total of 25 cats in various groups had grade 8–9 deficits associated with mild lethargy and somnolence, but all cats were arousable during and after temporary MCA occlusion. Progressive deterioration to coma and death occurred only in three cats that never recovered from anesthesia after surgical transection of the MCA.

**Table 3 Detailed Results of 4-Hour MCA Occlusion (Group C)**

<table>
<thead>
<tr>
<th>Deficit grade</th>
<th>During occlusion</th>
<th>After reperfusion</th>
<th>At sacrifice</th>
<th>Average infarct size (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>10.75 ± 3.8</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>24.5 ± 12.3</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>24.5 ± 8.8</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>19.5 ± 20.0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5.75 ± 10.8</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>14.0 ± 18.0</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>6.0 ± 3.7</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>9.5 ± 11.8</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.

**Groups A and B**

In the eight cats subjected to a single 1–60-min occlusion (group A), complete neurological recovery was observed within 1–20 min (average, 7 min) after deflation of the occluder. In the six cats subjected to 3-hr MCA occlusion (group B), recovery was complete but occurred more slowly, requiring up to 24 hr in some cases. In both groups, only microscopic areas of ischemic neuronal alteration or infarction averaging 3–8% of hemispheric area were seen.

**Group C**

Nine cats underwent 4-h MCA occlusion. Detailed results in this group are presented in table 3. Seven cats recovered completely, five within 24 hr and two within 48 hr. A grade 1 deficit persisted until the time of sacrifice in two cats. All nine cats had infarcts. The average size was 12.8 ± 8.5% of hemispheric area (table 2). The infarcts were 65% smaller than those in cats that underwent permanent occlusion (p < 0.001). Two cats that had infarct areas of 19.5 ± 20% and 14.0 ± 18% had grade 9 deficits during occlusion and grade 6 deficits after 1 hr of reperfusion, but had no residual deficit at the time of sacrifice.

**Group D**

Twelve cats underwent 5-, 6-, or 8-h MCA occlusion (table 2). The average neurological deficit during occlusion was grade 7. Only one cat had a complete neurological recovery, which occurred within 48 hr after a 5-hr occlusion. Neurological deterioration was not observed after reperfusion in group D, but the average neurological improvement after release of the occluder was less than one grade, compared with a five-grade improvement in group C. In the five cats that had 8-hr occlusions, the residual deficits (grade 1–2) were not significantly greater than those in the seven cats that had 5- and 6-hr occlusions. Infarcts after 5–8-hr occlusions were 66% smaller (p < 0.05) than after 24-hr or permanent occlusions. The average infarct size after 5–8-hr occlusion (14.4 ± 9.7%) (fig. 2) was not significantly larger than that after 4-hr occlusion (12.8 ± 8.5%). Considerable variability was
observed among sections from some brains as well as among averages of sections from individual brains within groups. For example, single brain sections from five cats in group D (5–8-hr occlusion) contained infarcts measuring more than 40% of hemisphere area, but the average infarct size after 8-hr occlusion (16.5 ± 4.0% of hemisphere area) was not significantly larger than that after even a 4-hr occlusion. Thus, there was no statistically significant difference in infarct size between 4-, 5-, 6-, and 8-hr occlusions.

Group E
Six cats were subjected to 24-hr MCA occlusions. No immediate neurological improvement or worsening was observed upon reperfusion of the MCA, and slight recovery of no more than one grade to an average of 5.5 occurred by the time of sacrifice. There was no significant difference in the severity of neurological deficit after 10 days or in infarct size between cats in group E and those subjected to permanent occlusion. The average infarct size after 24-hr occlusion was 30 ± 10.3%.

Group F
Three cats had three 3-hr occlusions at 48-hr intervals. In two of the cats, neurological deficit grades were higher after each repeat occlusion, and all three had persistent neurological deficits (average of grade 4) at the time of sacrifice. The average infarct size (21.8 ± 20% of hemisphere area) was 42% larger (p < 0.02) than that in cats subjected to a single 4-hr occlusion and 25% larger than after single 8-hr occlusions, but 52% smaller than that resulting from permanent MCA ligation.

Group G
Seven anesthetized cats underwent permanent MCA occlusion by surgical transection. Three of these cats died within 24 hr. The average neurological deficit grade of the survivors at sacrifice 10 days later was 5.5. In two awake cats reassigned to group G because the occluder failed to deflate and in one cat intentionally subjected to permanent occluder inflation, the average deficit was grade 5.0. Improvement of only one grade occurred during the 10-day observation period. The average infarct size in group G was 41.9 ± 22% of hemisphere area. There was no difference in infarct size between cats subjected to surgical transection and those subjected to permanent balloon occlusion.

Neuropathological Correlation
Although infarct size did not correlate with neurological deficit grade during MCA occlusion or with time required for maximal recovery after MCA reperfusion, it did correlate with the severity of neurological deficit at sacrifice. Infarct sizes in groups C–G averaged 43 ± 10% in cats with grade 5–9 deficits at sacrifice and 14 ± 7.7% in cats with deficits of grade 0–4 at sacrifice (p < 0.001). This correlation was not present in each cat; detailed results in a single group are shown in table 3. In cats with substantial infarcts and minor deficits at sacrifice, it appeared that anterior and parasympathetic cortical involvement was extensive, while basal ganglia and internal capsule areas were spared (fig. 2A). Conversely, when extensive deficits were associated with small infarcts, the basal ganglia and internal capsule appeared to be involved, while much of the cortex was spared.

Hemorrhagic infarction was seen after one 5-hr temporary occlusion and two permanent ligations. Thus, hemorrhage did not occur as frequently after MCA reperfusion in groups C, D, and E as it did in group G after MCA transection or permanent cuff occlusion (4% vs. 20%, p < 0.001). In cats with hemorrhagic infarcts, the average neurological deficit at the time of sacrifice was grade 7.5 and infarct sizes averaged 62.5 ± 29.2%. Midline shift caused by hemispheric edema was seen after two permanent ligations and one 8-hr temporary occlusion. Encephalomalacia caused dilatation of the right lateral ventricle in 13 brains with infarct areas of 8.3% to 80.8% on individual sections.

Discussion
The possibility of using medical therapies and surgical techniques for cerebral revascularization to protect the brain against the effects of acute ischemia has provided the impetus for additional studies to relate the severity and duration of neurological deficit to the threshold of brain tolerance of temporary ischemia and to ascertain the effects of reperfusion.3,4 Our method of reversible MCA occlusion in awake cats provides a model for carrying out such studies. Although neurological deficit produced by externally controlled permanent vessel occlusion has been evaluated in awake cats,9,10 the effects of reperfusion after temporary occlusion without anesthesia have been studied mostly in primates.9,11,12 Our method produced temporary ischemia for up to 24 hr without causing vessel damage or thrombosis at the site of occlusion, and may be a less
traumatic technique than those involving the use of vessel clips or suture snare.s The disadvantage of our method is that complete interruption and restoration of MCA blood flow cannot be verified directly.

Our results, which show extensive but variable neurological deficit even from permanent feline MCA occlusion performed without anesthesia, are in contrast to those of Hayakawa and Waltz. We did not observe, as they did in four of 10 cats, progressive hemiplegia, coma, and death from stroke with our balloon cuff method of occluding the MCA. Because their results were obtained using a snare-ligature technique and because subarachnoid hemorrhage was observed in one of their cats, it is possible that mechanical injury to the vessel, hemorrhage, or vasospasm may aggravate ischemia after suture-loop MCA ligation. Fatal stroke did occur in our study, but only in three of seven cats that underwent MCA transection. It therefore appears that surgical dissection and coagulation during acute MCA occlusion could have been responsible.

Our findings indicate that a 4-hr temporary occlusion of the MCA is required for extensive coagulation necrosis and permanent neurological deficit to occur with our method. After 4 hr of occlusion, but not after longer periods of temporary ischemia, some cats had grossly visible infarcts but no permanent deficits. Therefore, experiments testing therapeutic interventions with this model should be performed with temporary occlusion for at least 5 hr so that neurological deficit and easily measured areas of infarction will be induced more reliably in the untreated control group.

Neuropathological Correlation

The lack of correlation between the severity of neurological deficit and infarct size in some cats confirms previous observations that infarct location is more important than infarct size.15 Deficits of grades 5–9 were usually associated with subcortical infarction involving the thalamus, basal ganglia, and internal capsule. Studies of the cortical distribution of local CBF reduction and metabolic impairment and correlation with histological damage after MCA occlusion in cats have been reported, but the relation to postischemic neurological function and the effect of reperfusion was not evaluated in most of these experiments.12, 14–17 In our study, the slight improvement of one grade or less during 4–8-hr temporary occlusions in two cats suggests that collateral blood flow may have improved spontaneously before the occluder was released.18 The variable neurological and pathologic responses in each group may also be explained by differences in initial collateral flow patterns.16, 19, 20

Reperfusion

An unexpected finding was the similarity in both neurological and pathologic responses to 5-, 6-, and 8-hr temporary occlusions (group D). Additional propagation of the infarct did not appear to occur. Our finding that reperfusion was beneficial in group D but not in group E (24-hr occlusion) suggests the need for studies of 12- and 18-hr temporary occlusions to define more accurately the maximal duration of ischemia after which reperfusion is of no benefit in this model.

Our results indicate that reperfusion after all 5–8-hr occlusions implies that brain tissue in the ischemic penumbra remained viable during occlusion.16, 18 Our results are similar to those reported by Sundt et al. The lack of neurological deterioration after restoration of MCA flow observed by others, even after 8- and 24-hr occlusions, indicates that postischemic reperfusion did not have a deleterious neurological or pathologic effect, perhaps because critical thresholds for decrease in CBF were not reached in functionally important regions.21 These observations suggest that progressive edema, propagation of thrombus, or embolization from the MCA occlusion site did not impair postischemic CBF and recovery potential after reperfusion in our model.1, 22, 23 It is also possible that use of a chronically implanted balloon cuff occluder for temporary occlusion of the MCA in unanesthetized animals produces a less severe vascular injury and ischemic insult than occurs with other methods. Other studies of reperfusion after brief global ischemia in cats suggest that alterations of CBF energy metabolism and ischemic neuronal damage as well as hemorrhage were more extensive after reversal of more severe ischemia in those models.24–25 Considering that hemorrhagic infarction occurred in only two cats in group D and none in Group E, restoration of flow after 4–24-hr temporary MCA occlusion did not appear to increase the risk of hemorrhage in this model, even though in the series of Kamijyo et al. hemorrhage occurred in 40% of the cats subjected to 6-hr MCA clipping and in 60% after 24 hr.26 Clinical and other experimental observations also suggest that revascularization may not increase the risk of hemorrhagic infarction within 6–8 hr after an acute stroke.1, 27

A cumulative neurological and pathological effect of repeated 3-hr occlusions was observed in this study (group F) despite the lack of permanent deficit or extensive infarction after single 3-hr occlusions (group B). This implies that biochemical or structural disturbances after a 3-hr temporary occlusion are not severe enough to cause infarction but may render the brain more susceptible to additional ischemic insults.28, 29

The severity of permanent deficit and the size of infarcts correlated with the duration of MCA occlusion rather than with the severity of neurological deficit during occlusion. We therefore conclude that the grade of neurological deficit during occlusion of the MCA in cats does not accurately predict the outcome after 1 min to 24 hr of temporary regional ischemia.

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