Consistency of Cerebral Blood Flow and Evoked Potential Alterations With Reversible Focal Ischemia in Cats

Naoki Matsumiya, MD, PhD, Raymond C. Koehler, PhD, and Richard J. Traystman, PhD

To enhance the consistency of the ischemic insult caused by reversible transorbital middle cerebral artery occlusion, we investigated the variability of somatosensory evoked potential amplitudes and regional cerebral blood flow in 26 anesthetized cats using four procedures to induce transient ischemia. These procedures included 60 minutes of left middle cerebral artery occlusion with or without left common carotid artery occlusion and 120 minutes of left middle cerebral artery occlusion with or without bilateral common carotid artery occlusion. Blood flow in the left middle cerebral artery territory was markedly and consistently reduced to <20 ml/min/100 g with simultaneous occlusion of the left middle cerebral artery and both common carotid arteries. The standard deviation of blood flow with this procedure (5.4) was less than that with the other three procedures (13-25). The amplitudes of ipsilateral somatosensory evoked potentials were decreased to approximately 20% of control during ischemia with all four procedures. During reperfusion, amplitudes recovered more slowly, to half of control, after both procedures involving 120 minutes of ischemia. After 120 minutes of reperfusion, the range of amplitudes was smallest in the group exposed to middle cerebral artery occlusion with bilateral common carotid artery occlusion. The degree of recovery of the somatosensory evoked potentials correlated with residual blood flow in both the ipsilateral middle cerebral artery territory and in the white matter during ischemia. We conclude that the most consistent model of focal ischemia and reperfusion in cats in which there is partial recovery of somatosensory evoked potentials is occlusion of one middle cerebral artery and both common carotid arteries for 120 minutes. (Stroke 1990;21:908-916)
Materials and Methods

We studied 26 cats of either sex weighing 2.5–4.2 kg. Anesthesia was induced with 50 mg/kg i.m. ketamine and 1.1 mg/kg i.m. acepromazine. The cats were intubated and mechanically ventilated with 70% N2O-30% O2. Anesthesia was maintained by supplementation with the continuous infusion of 21.5 μg/hr fentanyl throughout the experiment. The cats were paralyzed with a 0.3 mg/kg i.v. bolus of pancuronium bromide. After thoracotomy, a catheter was inserted into the left atrium for the injection of radiolabeled microspheres. A catheter placed into the aortic arch via a femoral artery allowed withdrawal of a reference blood sample. The contralateral femoral artery was catheterized for arterial blood sampling and blood pressure recording. Catheters were also placed in both femoral veins for the administration of fluids and drugs. The left CCA in six cats and both CCAs in another six cats were exposed for later occlusion and were kept moist with saline. Mean±SD rectal temperature was maintained at 37.5±0.5°C using a warmed water blanket. End-tidal CO2 concentration was monitored, and the ventilator was adjusted to maintain PacO2 between 32 and 36 mm Hg. Pao2 was maintained above 80 mm Hg and arterial pH was maintained above 7.32 by the administration of NaHCO3 when necessary.

After the cat's head was placed in a stereotactic frame holder, the left MCA was exposed by the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the transorbital approach using microsurgical techniques.

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After the cat's head was placed in a stereotactic frame holder, the left MCA was exposed by the transorbital approach using microsurgical techniques. The orbit was completely exenterated, and the optic foramen was enlarged with a high-speed pneumatic drill. The dura was opened, and the arachnoid was gently dissected from the MCA with the sharp tip of a 25-gauge needle. The MCA was occluded for 60 or 120 minutes, then reversibly occluded near its origin from the intracranial carotid artery using a microvascular clip. The arteries were occluded for 60 or 120 minutes, and reperfusion was allowed to occur for 120 minutes. In cats in which one or both CCAs were occluded, these clips were released before the MCA clip was removed.

Arterial blood pressure was recorded continuously with a Statham pressure transducer (Glen Burnie, Maryland). Arterial pH, PacO2, and Pao2 were measured with a self-calibrating Radiometer electrode system (ABL 3, Copenhagen, Denmark) corrected for the cat's body temperature. Hemoglobin and arterial O2 contents were measured with a CO-oximeter (Instrumentation Laboratones, Lexington, Massachusetts). Regional CBF was measured with radiolabeled microspheres (16±0.5 μm diameter; Du Pont-New England Nuclear Products, Boston, Massachusetts) using the reference withdrawal method. Six radiolabels (gadolinium-153, indium-114, tin-113, ruthenium-103, niobium-95, and scandium-46) were injected in random sequence in each cat. Approximately 1.5–2×10⁸ microspheres were injected at each time into the left atrium over 20 seconds followed by a flush with 5 ml saline. The reference blood sample was withdrawn from the aorta using a withdrawal syringe pump set at 1.94 ml/min beginning 30 seconds before each injection of microspheres and continuing for 2 minutes after the flush with saline.

At the end of the experiment the cat was killed with KCl. The brain was removed and placed in 10% buffered formalin for 3–6 days. We used a grid for sectioning the brain so that the CBF gradient could be measured (Figure 1). Regions C3, C4, D2, D3, and E were assumed to be the MCA territory. Regions A1 and A2 were assumed to be the posterior cerebral artery territory. Regions A4 and A5 were assumed to be the anterior cerebral artery territory. We also dissected the caudate nucleus and the bulk of the subcortical white matter that could be easily separated without contamination by gray matter. The reference blood samples and weighed tissue specimens were counted for gamma radioactivity (Minaxi Model 5530, Packard Instrument Co., Inc., Downers Grove, Illinois) with correction for overlap of activity among the isotopes. Regional CBF was calculated as corrected tissue counts multiplied by reference blood sample withdrawal rate divided by counts in the reference blood sample divided by tissue weight. Recent evidence indicates that in cats the micro-
sphere technique overestimates white matter blood flow by a factor of 2 compared with the iodoantipyrine technique. However, white matter blood flow with the two techniques remains linearly correlated, allowing it to be presented validly as a percentage of control. Therefore, white matter blood flow is expressed as a percentage of control although the actual value in milliliters per minute per 100 g is also given in the tables for comparison.

We measured SEPs using a signal averager (Med-80, Nicolet Biomedical, Madison, Wisconsin). After the scalp skin and musculature were dissected laterally, silver ball electrodes with shielded cables were placed into holes drilled approximately 1 cm lateral to the midline and just posterior to the coronal suture on both sides of the cranium. A reference electrode was placed into a hole drilled in the frontal bone. A recording needle electrode was placed into the muscle over the second cervical vertebra (C-2). Stimulator needle electrodes were placed percutaneously on the volar surface of both forelegs. A needle electrode ground was secured to the cat's tongue. For SEPs, 256 stimuli at a voltage twice the motor threshold and lasting 150 μsec were delivered at a rate of 5.9/sec. Bandpass filters were set at 30–1,500-Hz cutoff frequencies, and the evoked responses were averaged. Amplitude was measured to the peak of the first major negative wave (12–14 msec latency) from the peak of the preceding positive wave.

We studied four groups of cats. Cats in groups MCAO-60 (n=6) and MCAO-120 (n=8) underwent left MCA occlusion for 60 and 120 minutes, respectively. Cats in group MCALCGAO-60 (n=6) underwent left MCA occlusion and left CCA occlusion for 60 minutes. Cats in group MCABCCAO-120 (n=6) underwent left MCA occlusion and bilateral CCA occlusion for 120 minutes.

At least 30 minutes after surgery was completed, arterial blood gases and microspheres were injected twice approximately 15 minutes apart before the MCA was occluded. The average of the two SEP and CBF determinations was used as the control value. In groups MCALCGAO-60 and MCABCCAO-120, the left or both CCAs were occluded just after SEP amplitude decreased to <25% of control following MCA occlusion (i.e., after 2–5 minutes). In all groups, rapid reduction of SEP amplitude to <25% of control was used as a criterion for the proper placement of the MCA clip proximal to the lenticulostriate arteries. In groups MCAO-60 and MCALCGAO-60, SEPs were measured 5, 15, 30, and 60 minutes after the induction of ischemia; in groups MCAO-120 and MCABCCAO-120, SEPs were measured 5, 15, 60, 90, and 120 minutes after the induction of ischemia. In all groups SEPs were measured after 15, 30, 60, 90, and 120 minutes of reperfusion. Arterial blood gases were measured and microspheres were injected at the end of ischemia and after 15, 60, and 120 minutes of reperfusion.

Data are presented as mean±SD (or mean±SEM where noted). To assess the consistency of regional CBF and SEP amplitudes, variances among groups were compared using the two-tailed F test. One-factor analysis of variance (ANOVA) was used to compare values among the four groups at each time. If ANOVA demonstrated significant (p<0.05) differences among groups, Duncan's multiple range test was used to compare group means. To assess changes over time within each group, repeated-measures ANOVA was performed and group means at each time were compared with control values using the paired t test with Bonferroni's correction.

Results

Table 1 shows arterial pH, blood gases, O2 content, and mean arterial blood pressure values at the time of each microsphere injection in each group. Blood gases and mean arterial blood pressure did not change significantly during the experiment. Arterial O2 content decreased slightly after 60 and 120 minutes of reperfusion.

Mean CBFs in each brain region in each group are summarized in Table 2. There was no difference in control values among the four groups in any region. There was also no difference between left and right CBF in homologous regions. In group MCAO-60, CBF decreased significantly in all left regions after 60 minutes of ischemia. CBF in the MCA territory and white matter were reduced to 28% and 46% of control, respectively. In only one cat in this group was end-ischemic CBF in the MCA territory below 20 ml/min/100 g. After 15 minutes of reperfusion, CBF in the left white matter increased significantly above control values (hyperperfusion), while CBF in the left posterior and anterior cerebral artery territories remained significantly below control values. All regional CBF values had returned to control by 120 minutes of reperfusion. In the right regions CBF did not decrease.

In group MCALCGAO-60, the regional responses to 60 minutes of occlusion were similar to those of group MCAO-60. CBF in all left regions decreased significantly (Table 2). CBF in the MCA territory and white matter were reduced to 34% and 59% of control, respectively. In two of the six cats, CBF in the left MCA territory decreased to <20 ml/min/100 g. As in group MCAO-60, the left white matter showed transient hyperperfusion but no delayed hypoperfusion during reperfusion. CBF in the left MCA territory showed delayed hypoperfusion by 120 minutes of reperfusion. In the right regions, CBF remained unchanged. These values of CBF for each region did not differ from those in group MCAO-60 at any time. Therefore, tandem left MCA and left CCA occlusion for 60 minutes does not produce any circulatory effects in addition to those created by 60 minutes of left MCA occlusion alone.

In group MCAO-120, CBF of all left regions had decreased by 120 minutes of occlusion (Table 2). CBF in the MCA territory and white matter de-
creased to 32% and 48% of control, respectively. In four of the eight cats in this group, CBF in the MCA territory decreased to <20 ml/min/100 g. In contrast to the two groups experiencing 60 minutes of occlusion, no significant postischemic hyperemia was detected. In the left anterior cerebral artery territory, hypoperfusion was evident during reperfusion. CBF in the right MCA territory had decreased significantly by the end of the occlusion. CBF in all other right regions remained unchanged.

In group MCABCCAO-120, CBF in all left regions had decreased significantly after 120 minutes of occlusion (Table 2). CBF in the left MCA territory and white matter decreased to 8% and 23% of control, respectively. In contrast to the other three groups, CBF in the left MCA territory had decreased to <20 ml/min/100 g in all six cats by the end of the occlusion. CBF in the left MCA territory, white matter, and caudate nucleus returned to control values after 15 minutes of reperfusion and did not show hyperperfusion. As in group MCAO-120, post-ischemic hypoperfusion occurred in the left anterior cerebral artery territory. In the right regions, CBF in the MCA territory, white matter, and posterior cerebral artery territory decreased but remained above 20 ml/min/100 g at the end of the occlusion. During reperfusion, they returned to control values.

At the end of the occlusion, CBF was reduced most consistently in group MCABCCAO-120 (Figure 2). In this group, SD of the left MCA territory (Table 2) was less than that in group MCAO-60 (p<0.01), group MCALCCAO-60 group (p<0.01), and group MCAO-120 (p<0.01). For the percentage change of left white matter CBF (Figure 2), SD of group MCABCCAO-120 (Table 2) was also less than that of group MCAO-60 (p<0.025), group MCALCCAO-60 (p<0.025), and group MCAO-120 (p<0.005).

After 15 minutes of reperfusion, left white matter CBF in groups MCAO-120 and MCABCCAO-120 was lower than that in group MCALCCAO-60. In other regions there were no significant differences among groups at any time.

An example of SEP waveforms from a cat in group MCABCCAO-120 is illustrated in Figure 3. The first major negative wave over the left cortex with right foreleg stimulation decreased during ischemia and recovered only partially during reperfusion. Recordings over C-2 were unaffected, indicating intact brain death in all six cats.
peripheral nerve transmission. This observation was confirmed in all four groups. Contralateral SEPs were not diminished despite bilateral CCA occlusion.

In all groups ipsilateral SEP amplitude was suppressed to 13%–22% of control during ischemia, and there was no difference among groups (Figure 4). After 15 and 30 minutes of reperfusion, recovery of SEP in groups MCAO-120 and MCABCCAO-120 was significantly less than in group MCALCCAO-60 \( (p<0.05) \). After 60, 90, and 120 minutes of reperfusion, however, SEP amplitudes were no longer significantly smaller. SEP amplitudes after 120 minutes of reperfusion showed considerable variation: from 39% to 95% of control in group MCAO-60, from 41% in group MCABCCAO-120 was approximately half that of 71% in group MCALCCAO-60 and 84% in group MCAO-120. However, SD in group MCABCCAO-120 \( (16.6) \) was not significantly different from that in groups MCAO-60 \( (24.8, \ p<0.25) \), MCALCCAO-60 \( (28.2, \ p<0.25) \), or MCAO-120 \( (34, \ p<0.10) \). There were no differences among groups in contralateral SEP amplitude (Figure 4).

When data from all four groups were pooled, the correlation coefficients between recovery of left SEP after 60, 90, and 120 minutes of reperfusion and CBF in the left MCA territory at the end of ischemia were 0.40, 0.41, and 0.39, respectively; all were significant. The correlations between recovery of left SEP amplitude and percentage change in left white matter CBF were also significant. Their correlation coefficients were 0.43, 0.45, 0.58, 0.56, and 0.46 after 15, 30, 60, 90, and 120 minutes of reperfusion, respectively.

### Table 2. Regional Cerebral Blood Flow Before, During, and After Ischemia in Cats

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Ischemia 15</th>
<th>Ischemia 60</th>
<th>Ischemia 120</th>
<th>Reperfusion (min) 120</th>
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<td>106±27*</td>
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<td>65±26</td>
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<td>165±27</td>
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<td>91±43</td>
<td>27±16*</td>
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<td>54±14*</td>
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<tr>
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<td>45±13*</td>
<td>87±17†</td>
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<tr>
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<td>78±14‡</td>
<td>73±12</td>
<td>116±37</td>
<td>79±27</td>
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Values are mean±SD ml/min/100 g unless noted. MCAO-60, left middle cerebral artery occlusion \( (n=6) \); MCALCCAO-60, left middle cerebral artery and left common carotid artery occlusion for 60 minutes \( (n=6) \); MCAO-120, left middle cerebral artery occlusion for 120 minutes \( (n=8) \); MCABCCAO-120, left middle cerebral artery and bilateral common carotid artery occlusion for 120 minutes \( (n=6) \); MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery.

*\( p<0.005 \), †\( <0.01 \), ‡\( <0.05 \), respectively, different from ipsilateral control by repeated-measures analysis of variance.
Discussion

Four major conclusions can be drawn from our studies on the effects of unilateral MCA occlusion with and without ipsilateral or bilateral CCA occlusion for 60 or 120 minutes followed by 120 minutes of reperfusion. First, variability of CBF in the ipsilateral MCA territory and white matter at the end of ischemia in the group with 120 minutes of MCA occlusion plus bilateral CCA occlusion is less than in the other groups. Variability in SEP recovery was also less in this group. Second, only in this group did CBF in the ipsilateral MCA territory decrease consistently to below the critical level of CBF that others have shown to be associated with infarction.2-5 White matter CBF during ischemia in this group was also lower than that in the other groups. Third, recovery of SEP amplitude during reperfusion was slower in both groups with 120 minutes of occlusion than in either group with 60 minutes of occlusion. Fourth, recovery of SEP amplitude after reperfusion was correlated with the level of residual CBF during ischemia in both the left MCA territory and the white matter, although there was considerable variability.

Although a number of studies have employed the transorbital MCA occlusion technique to produce focal cerebral ischemia in cats, the size of the infarct varies, in part because the size and degree of ischemia vary.2-3 There is a reasonably well-defined threshold of 10–20 ml/min/100 g for irreversible cortical damage.2-3 Thus, one essential criterion for a
reliable model of focal cerebral ischemia is a consistent reduction of CBF to below this threshold. In our study, only simultaneous occlusion of the left MCA and both CCAs for 120 minutes consistently decreased CBF in the left MCA territory to below this critical level. Our results are in agreement with those of others who have demonstrated that in cats optimal infarction with reversible occlusion occurs with combined unilateral MCA and bilateral CCA occlusion for 2 hours.8-9 It should be emphasized that these results are applicable to reversible focal ischemia in cats. With permanent MCA occlusion, concurrent unilateral CCA occlusion may be sufficient to enlarge the vulnerable area, as has been demonstrated in rats.16

We observed reduced CBF in the ipsilateral anterior and posterior cerebral artery territories in all four groups, consistent with previous studies.3,17 However, residual CBF in these regions remained well above 20 ml/min/100 g even with concurrent bilateral CCA occlusion. Thus, these areas were unlikely to be part of the ischemic border zone. The reduced CBF in the non-MCA territories is probably explained by a redistribution of limited blood inflow, leading to widespread disturbances.17

We also observed reduced CBF during ischemia in the right hemisphere with concurrent left MCA and bilateral CCA occlusion for 120 minutes. These reductions were small and were not accompanied by decreases in right SEP amplitudes. Contralateral reduction of CBF has been described experimentally18 and clinically19 and has been attributed to transcallosal diaschisis.19-20 However, contralateral CBF reductions in the other three groups were minor. Thus, contralateral CBF reduction in group MCABCCA0-120 can be largely attributed to the bilateral CCA occlusion.

Hyperfusion is a common response following brief ischemia. Traupe et al17 observed postischemic hyperperfusion after 60 minutes but not usually after 120 minutes of ischemia. Our observations are partially consistent with these in that transient hyperperfusion occurred in the white matter after 60 but not 120 minutes of MCA occlusion. In the MCA territory, hyperperfusion was not statistically significant, possibly because of the relatively high control CBF obtained with the N2O-fentanyl anesthetic regimen. Delayed hypoperfusion has been reported in cats after 60 or 120 minutes of MCA occlusion.17 Although some degree of hypoperfusion was observed in the MCA territory in group MCALCCA0-60, we have no explanation of why this was not observed in the other groups except for the large variability in the individual values and possibly the 10%-20% decrease in arterial O2 content associated with blood sampling.
Electrophysiological disturbances begin to occur at substantially higher CBF values than morphologic alterations.21 Others have found that SEP is a sensitive measure of the onset, size, and location of ischemia12 and that SEP amplitude correlates with CBF below a threshold.22,23 We found that the reduction of SEP amplitude during ischemia was similar among the four groups. This indicates that the reduction of CBF in either the MCA territory or the conducting white matter was sufficient to impair function in the SEP pathway in all four groups. Abolition of SEPs during MCA occlusion may be caused by lesions in the afferent pathway leading to cortical deafferentation rather than by cortical ischemia,10,11 and SEP recovery may be limited by water accumulation in the white matter. Depending on the model, gray or white matter can be more vulnerable.24–26 In our study, the correlation of SEP recovery with subcortical white matter CBF during ischemia was at least as good as that with CBF in the MCA territory. Thus, our data do not distinguish whether white or gray matter limits SEP recovery. Recovery of SEP was slower after 120 minutes of MCA occlusion with and without bilateral CCA occlusion than after 60 minutes of MCA and unilateral CCA occlusion. This difference in the time course of SEP recovery is probably related to the larger and more consistent reduction in CBF as well as to the longer duration of ischemia. After 120 minutes of reperfusion, SEP recovery no longer differed because of the great variation in some groups. However, when data from all four groups were pooled, there was a significant correlation between SEP recovery and residual CBF during ischemia. Therefore, part of the variation in SEP recovery can be explained by the variation in residual CBF in the ischemic core. Hence, minimizing the variation in residual CBF should minimize the variation in SEP recovery. Indeed, in the group with 120 minutes of left MCA and bilateral CCA occlusion SD of residual CBF was less than in the other groups, and although SD of SEP recovery was not significantly less, the difference between SEP recovery values was reduced by one half. Thus, we have demonstrated that with a model of reversible focal ischemia, consistent reduction of CBF in the MCA territory to <20 ml/min/100 g slows recovery of SEP amplitude to one half of its control value with minimal variation.

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References

Key Words • cerebral blood flow • cerebral ischemia • evoked potentials • cats
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