Anesthetic Modulation of Cerebral Hemodynamic and Evoked Responses to Transient Middle Cerebral Artery Occlusion in Cats

Mark A. Helfaer, MD, Jeffrey R. Kirsch, MD, and Richard J. Traystman, PhD

We measured cerebral blood flow and somatosensory evoked potentials during transient focal cerebral ischemia in cats to compare the effects of four commonly used anesthetic regimens: ketamine/fentanyl/N2O (fentanyl), pentobarbital, ketamine/α-chloralose (α-chloralose), and ketamine/halothane/N2O (halothane). Six cats in each group were subjected to 60 minutes of left middle cerebral artery occlusion followed by 120 minutes of reperfusion. Although the amplitude of the initial somatosensory evoked potential wave complex was highest in the α-chloralose group (58.6±16.5 μV) and smallest in the halothane group (27.5±5.7 μV), amplitude fell by 75% in all groups upon occlusion. Baseline cerebral blood flow varied substantially between groups (e.g., in the right intersylvian gyrus: fentanyl, 96±12; pentobarbital, 30±5; α-chloralose, 24±3; and halothane, 76±11 ml/min/100 g). Occlusion decreased cerebral blood flow to subcortical (e.g., left caudate) structures in all groups (fentanyl, 29±11%; pentobarbital, 45±12%; α-chloralose, 27±13%; and halothane, 18±5% of baseline). Postischemic hyperemia occurred in the cortical regions of cats anesthetized with pentobarbital or α-chloralose that had reduced cerebral blood flows during occlusion but not in cats anesthetized with fentanyl (cerebral blood flow during occlusion not different from that of cats anesthetized with pentobarbital or α-chloralose) or halothane. After 120 minutes of reperfusion, cerebral blood flow had returned to baseline values in all groups. Recovery of cerebral blood flow and somatosensory evoked potential amplitude at that time did not differ among groups. We conclude that anesthetics alter baseline cerebral blood flow and baseline somatosensory evoked potentials as well as the cerebral blood flow pattern during reperfusion after middle cerebral artery occlusion independent of insult severity. (Stroke 1990;21:795-800)
Brush recorder (Cleveland, Ohio). PaO₂, PacO₂, and Pao₂ were determined with a CO-oximeter electrodes and analyzer (Copenhagen, Denmark). The active electrode and reference system yields a large negative wave (N₁) and a large positive wave (P₁). The amplitude of the initial complex (P₁+N₁) was measured and recorded for each time. Baseline latencies of N₁ were anesthetic-dependent (for fentanyl 11–15, for pentobarbital 13–18, for α-chloralose 15–19, and for halothane 12–15 msec).

We measured brainstem auditory evoked responses to document that MCA occlusion changed the amplitude of the somatosensory evoked potential independent of changes in electrical transit through the brainstem. A small earpiece connected to an NIC-1007 click stimulus generator (Nicolet Instruments, Madison, Wisconsin) was secured in the auditory canal of each cat. Alternating clicks at a rate of 11.9/sec for 200 msec were used as the sound stimulus. There were 256 measurements lasting 10 msec each. The stimulus intensity was 95 dB for each measurement.

In each group CBF, somatosensory evoked potentials, brainstem auditory evoked responses, and blood gases were measured before MCA occlusion (baseline, at least 30 minutes after the end of surgery), after 30 and 60 minutes of ischemia, and after 15, 60, and 120 minutes of reperfusion. To initiate focal cerebral ischemia, a Weck micro–cerebral...
an aneurysm clip (Edward Weck, Inc., Research Triangle, North Carolina) was placed on the left MCA via a transorbital approach. Briefly, the left orbit was exonerated and the bone surrounding the optic foramen was removed using a diamond bit on a high-speed water-cooled drill. The dura was carefully removed, and the MCA was exposed close to its origin from the internal carotid artery. Correct clip placement was assumed when a >75% reduction in P,Ni amplitude occurred within 5 minutes. After 60 minutes of ischemia, reperfusion was initiated by removing the clip from the MCA.

All values are reported as the mean±SEM. Because CBF data sometimes had a skewed distribution and the SD varied among times and among groups, the CBF data were subjected to logarithmic transformation before testing for differences as a function of time within each group. Repeated-measures analysis of variance (ANOVA) was used to define differences in each measurement over time within each group. One-way ANOVA was used to define the effect of anesthetic at each time for each measurement between groups. The Newman-Keuls test was used for post-hoc comparisons. Unless otherwise specified, p<0.05.

**Results**

Although there were small changes in Paco\(_2\) (for fentanyl), Paco\(_2\) (for pentobarbital and \(\alpha\)-chloralose), and hemoglobin concentration (for fentanyl and pentobarbital) during the experiment, there were no differences among groups at any time for arterial pH (7.32–7.36), Paco\(_2\) (32–35 mm Hg), Paco\(_2\) (115–135 mm Hg), hemoglobin concentration (9.5–11.3 g/dl), or mean arterial blood pressure (80–107 mm Hg).

Anesthetics affected baseline CBF. Global CBF was higher for the fentanyl (66±5 ml/min/100 g) and halothane (63±6 ml/min/100 g) groups than for the pentobarbital (27±4 ml/min/100 g) and \(\alpha\)-chloralose (28±1 ml/min/100 g) groups.

MCA occlusion reduced CBF variably, depending on the anesthetic used. rCBF to the left caudate nucleus decreased significantly for all four groups (Figure 1). On the contrary, rCBF to the intersylvian gyrus decreased significantly only in the fentanyl, pentobarbital, and halothane groups (Figure 2). Absolute rCBF to the intersylvian gyrus during occlusion was higher for the halothane group than for the other groups, but there was no difference among the fentanyl, \(\alpha\)-chloralose, and pentobarbital groups. MCA occlusion also significantly decreased rCBF to the left ectosylvian gyrus for the fentanyl, \(\alpha\)-chloralose, and halothane groups (Figure 3), the left lingula gyrus for all four groups (data not shown), the left precruciate gyrus for the pentobarbital, \(\alpha\)-chloralose, and halothane groups (data not shown), and the left thalamus for the fentanyl and halothane groups (data not shown). rCBF to the brainstem and the right-sided brain regions were not decreased by MCA occlusion (data not shown).

Five of six cats in the pentobarbital group and four of six in the \(\alpha\)-chloralose group had reduced rCBF to the intersylvian gyrus during MCA occlusion (for...
pentobarbital 32±19% and for α-chloralose 22±19% of baseline). All nine of these cats demonstrated reactive hyperemia during reperfusion (for pentobarbital 697±122% and for α-chloralose 801±492% of baseline). After 15 minutes of reperfusion cats in the pentanyl and halothane groups did not demonstrate hyperemia relative to their high baseline values.

In all regions, rCBF eventually returned to baseline values. In the pentobarbital, α-chloralose, and halothane groups, rCBF returned to baseline in all regions by 60 minutes of reperfusion. In the fentanyl group, rCBF in the left thalamus did not return to baseline until 120 minutes of reperfusion; it had returned to baseline in all other regions by 60 minutes of reperfusion. No group demonstrated hyperemia at 120 minutes of reperfusion. Expressed as a percentage of baseline, there were no differences among groups in the recovery of rCBF for any region at 120 minutes of reperfusion.

The latencies of waves I, III, and V of the brainstem auditory evoked responses did not differ among groups, nor were they affected by MCA occlusion (data not shown).

The absolute voltage of the baseline P1N1 amplitude varied across groups (for fentanyl 32.0±9.4, for pentobarbital 29.3±9.9, for α-chloralose 38.6±16.5, and for halothane 27.5±5.7 μV). MCA occlusion significantly decreased P1N1 amplitude to <25% of baseline for all groups (Figure 4). In each cat, the reduction in P1N1 amplitude correlated closely with a reduction in subcortical (i.e., caudate nucleus) rCBF. In many cats a large reduction in P1N1 amplitude occurred with no or only a small change in cortical (intersylvian) rCBF.

Reperfusion was associated with recovery of the P1N1 amplitude, which did not differ among groups, but which remained significantly less than the baseline value (Figure 4).

Discussion

There are a number of models of focal cerebral ischemia that differ in the physiologic and electro-

physiologic variables measured, the extent and length of ischemia produced, and the anesthetics used. We found that anesthetics affect baseline CBF (fentanyl and halothane blood flows were greater than those of pentobarbital and α-chloralose) and amplitude of the somatosensory evoked potential (highest with α-chloralose). In all groups MCA occlusion reduced ipsilateral subcortical (e.g., caudate nucleus) rCBF, which was associated with a decrease in the amplitude of the somatosensory evoked potential but had a variable effect on the distribution of the reductions in cortical rCBF. The fentanyl and halothane groups had the most regions with decreased rCBF during MCA occlusion. Occlusion did not affect rCBF to the brainstem or to contralateral (i.e., right-sided) regions. Reactive hyperemia was observed in cats anesthetized with pentobarbital or α-chloralose that demonstrated reduced cortical rCBF during MCA occlusion but not in cats anesthetized with fentanyl or halothane. The presence of hyperemia did not correlate with the severity of ischemia since cats anesthetized with fentanyl had CBF reduced to the same extent as cats anesthetized with pentobarbital or α-chloralose but did not exhibit hyperemia. No group demonstrated delayed hypoperfusion after 120 minutes of reperfusion. There were no differences in the recovery of somatosensory evoked potential amplitude among the groups.

Somatosensory evoked potentials have been used both clinically and experimentally to noninvasively measure the adequacy of CBF. We used the forepaw somatosensory evoked potential as a noninvasive indicator that MCA occlusion reduced CBF.

The extent of CBF diminution with MCA occlusion and the exact distribution of ischemia is the subject of considerable disagreement. Important potential modulators of the CBF response to MCA occlusion and reperfusion are systemic factors, differences in anesthetics, and differences in location of the MCA clip. For example, it is likely that a clip on the distal MCA will not occlude the lenticulostriate perforators and thus will not produce the same distribution of ischemia as would a more proximal occlusion. In our study, physiologic parameters were well controlled, and MCA occlusion was proximal to the lenticulostriate arteries in all cats so that we could evaluate the role of anesthetics alone.

In spite of reduced amplitudes of the somatosensory evoked potential during reperfusion, latencies of the brainstem auditory evoked response were unchanged from baseline. This suggests that the etiology of somatosensory evoked potential amplitude reduction results from higher brain structures. Cortical (gray matter) rCBFs below which amplitude is substantially (>25%) reduced have been reported to be in the range of 6–16 ml/min/100 g. We achieved such values in the cortex supplied by the MCA with all anesthetics except halothane. Several investigators have suggested that the loss of somatosensory evoked potentials during MCA occlusion correlates better with subcortical (thalamic,
white matter) than with cortical ischemia. Likewise, in our studies, a reduction in somatosensory evoked potential amplitude to 25% of baseline was closely associated with a reduction in subcortical (i.e., caudate nucleus) but not cortical rCBF. rCBF to the thalamus was reduced during MCA occlusion in cats anesthetized with fentanyl or halothane but not pentobarbital or α-chloralose.

Isolated MCA occlusion causes partial focal cerebral ischemia because collateral vessels continue to provide blood flow. The fact that MCA occlusion caused larger reductions in subcortical than in cortical rCBFs may indicate a more extensive collateral circulation in the cortex rather than a decreased vulnerability to ischemia of gray than white matter. Other physiologic variables that may affect this model (such as Paco2, hemoglobin concentration, and body temperature) were well controlled.

We chose a model of transient focal ischemia with reperfusion over one of permanent ischemia so that we could evaluate the pattern of reperfusion with different anesthetics. We did not consistently observe reactive hyperemia followed by hypoperfusion, which has been reported in models of transient global ischemia. Some investigators have demonstrated reactive hyperemia after 1 hour of MCA occlusion in animals anesthetized with pentobarbital or α-chloralose but not with different durations of ischemia. Other investigators, however, have been unable to demonstrate hyperemia following any duration of focal ischemia. In our study, five of six cats anesthetized with pentobarbital and four of six anesthetized with α-chloralose had reduced cortical rCBF after 60 minutes of ischemia; all nine cats demonstrated hyperemia during reperfusion. It is possible that our inability to demonstrate reactive hyperemia in cats anesthetized with fentanyl or halothane relates to the times we chose to measure CBF. Specifically, reactive hyperemia may occur before 15 minutes of reperfusion and, therefore, we may have missed it. As in our study, others have demonstrated that in cats, reactive hyperemia (when present) is sustained for at least 15 minutes of reperfusion following either global or focal ischemia.

One possible explanation for the lack of hyperemia in cats anesthetized with fentanyl or halothane is their high baseline CBF. One proposed mechanism for hyperemia after focal ischemia is an alteration in the ratio of blood pressure to hematocrit. This explanation is supported by Coyer et al, who demonstrated that volume expansion and hemodilution provided a means of significantly elevating rCBF in the gray matter. However, this explanation cannot account for our data, for we maintained blood pressure and hemoglobin concentration constant in all groups. Delayed hypoperfusion did not occur with any of our anesthetics and has not been demonstrated by other experimenters after transient focal ischemia. Likewise, when CBF was expressed as a percentage of baseline values, there was no difference in recovery among groups. Differences among groups in absolute CBF values during reperfusion can be accounted for by previously described effects of anesthetics on CBF. For example, animals anesthetized with halothane have greater CBFs than animals anesthetized with pentobarbital.

In summary, our data suggest that monitoring somatosensory evoked potentials is more useful in diagnosing subcortical than cortical ischemia in the distribution of the MCA. It is clear from our data that the regional cerebrovascular response to transient MCA occlusion depends on the anesthetics used. This may make it difficult to compare studies from different laboratories unless the studies were done in an identical fashion. Differences in the exact distribution of CBF reductions during MCA occlusion (more regions have decreased rCBFs with fentanyl and halothane) and the presence of hyperemia during reperfusion may be due to different baseline CBFs but does not appear to be due to differences in the intensity of the ischemic insult among groups.

Acknowledgments

The authors thank Candace Berryman for her excellent secretarial assistance, Mary North and Eleonora Aldersen for their technical assistance, and Dr. Raymond C. Koehler for critical review of the manuscript.

References

11. Wollman H, Alexander SC, Cohen PJ, Chase PE, Melman E, Behar MG: Cerebral circulation of man during halothane...


**KEY WORDS** • cerebral ischemia • anesthesia • cats
Anesthetic modulation of cerebral hemodynamic and evoked responses to transient middle cerebral artery occlusion in cats.
M A Helfaer, J R Kirsch and R J Traystman

Stroke. 1990;21:795-800
doi: 10.1161/01.STR.21.5.795

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/21/5/795

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/