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Neurologic Outcome in Rats Following Incomplete Cerebral Ischemia during Halothane, Isoflurane, or N_2O

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Using rats in which incomplete cerebral ischemia was induced, the authors evaluated the effects of halothane (H) and isoflurane (I) on neurologic outcome compared to nitrous oxide (N_2O) controls. Incomplete cerebral ischemia was produced by right carotid artery occlusion combined with hemorrhagic hypotension. Neurologic outcome was evaluated using a graded deficit score from 0 to 5 (0 = normal, 5 = death associated with stroke). Two levels of cerebral ischemia were tested. At moderate ischemia with hypotension of 30 mmHg, an F_{IO_2} of 0.3, and ischemic periods of 30 or 45 min, N_2O produced a deficit of 4.7–5.0 and a mortality rate of 90–100%. In contrast, halothane (1 MAC) and isoflurane (1 MAC) resulted in similar deficit scores (H = 1.1–1.8, I = 1.4–1.6) and mortality rates (H = 17–30%, I = 17–20%). Cerebral blood flow (CBF) measured with radioactive microspheres showed a 60–65% decrease in the ischemic hemisphere at this level of hypotension. With severe ischemia with hypotension = 25 mmHg, F_{IO_2} = 0.2, and a 30-min period of ischemia, deficit scores increased to 3.0 and 3.9 with 1 MAC halothane and 1 MAC isoflurane, respectively. Mortality rates also increased to 40% with halothane and 70% with isoflurane. Increasing the concentration of halothane or isoflurane to 2 MAC did not significantly improve outcome. Brain histology demonstrated extensive neuronal damage in striatal, hippocampal, and neocortical regions of N_2O control treated rats, and less damage with little difference between H-and I-treated rats at each level of ischemia. Using this model of incomplete cerebral ischemia, halothane and isoflurane provided significantly better neurologic and histologic outcomes when compared to N_2O controls, with little difference between the two volatile anesthetics. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane; isoflurane. Brain: blood flow; EEG; ischemia.)

ANESTHETICS MAY PROVIDE protection from brain ischemia because of their ability to decrease neuronal metabolism and oxygen demand.[1,2] This is of particular importance during incomplete cerebral ischemia when blood supply to the brain is decreased and electroencephalogram (EEG) activity is still present. Two inhalation anesthetics that decrease cerebral oxygen consumption ($CMRO_2$) are halothane and isoflurane.[3,4] It has been suggested that isoflurane may provide more brain protection than halothane because it decreases $CMRO_2$ more at the same anesthetic level while maintaining a normal cerebral energy state.[5,6] Isoflurane has also been reported in humans to permit a lower blood flow than halothane before appearance of EEG signs of ischemia.[7] Isoflurane produces little change in cerebral blood flow (CBF) at 1 MAC, while halothane produces a decrease in cerebral vascular resistance and increase in CBF.[6–9] However, the cerebral vasodilatory effects of halothane may be detrimental by increasing intracranial pressure (ICP), augmenting tissue edema, and producing steal from the ischemic zone. At the same time, recent reports suggest that isoflurane may not provide as much protection from brain ischemia as previously proposed.[10] ¶

In the experiments reported in this paper, cerebral protection provided by isoflurane and halothane was compared to that during a control-state using nitrous oxide (N_2O) in rats with incomplete cerebral ischemia.[11]

Materials and Methods

These experiments were performed after approval from the institutional animal care committee. One hundred and forty-two male Sprague-Dawley rats weighing 350–450 g were used in these studies. For surgery, the rats were anesthetized in a jar containing halothane or isoflurane and ventilated with anesthetic levels of halothane or isoflurane following tracheal intubation. Catheters were inserted into the right femoral artery and vein for continuous blood pressure recording and drug administration, and into the right subclavian vein for blood withdrawal. The right carotid artery was isolated and a loose ligature placed around it for later clamping. Screw electrodes were placed on the skull for EEG recording. At completion of surgery, the wounds were infiltrated with 0.5% bupivicaine. The inhalational anesthetic was then adjusted to the appropriate inspired concentration for 30 min before initiation of ischemia. Cerebral ischemia was produced for 30 or 45 min by the combination of carotid artery occlusion and hemorrhagic hypotension. Mean blood pres-

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¶ Milde LN, Milde JH: Preservation of cerebral metabolites during incomplete ischemia by isoflurane, halothane, or fentanyl. Anesthesiology Review 13:25, 1986.

sure was maintained at the prescribed hypotensive level ±2 mmHg for the prescibed period of time. Rectal temperature was maintained at 37° C and Pa_{CO_2} between 35 and 45 mmHg by adjusting ventilation. Vecuronium was administered as needed to maintain paralysis. Arterial *p*H was maintained at normal levels by bicarbonate infusion. The electroencephalogram (EEG) was recorded from both the right and left hemisphere during control, ischemic, and recovery conditions using a Grass bioelectric preamplifier connected to a Hewlett-Packard® EEG amplifier. At the end of the ischemic period, the carotid artery was unclamped and the withdrawn blood slowly reinfused into the rat over 10 min. Following a 30-min reinfusion/recovery period, the catheters were removed, the incisions closed, and the tracheas extubated.

Neurologic Outcome

Two graded levels of cerebral ischemia were studied (table 1). In the first series of experiments, moderate ischemia was produced by clamping the carotid artery and decreasing mean arterial blood pressure to 30 mmHg for either 30 or 45 min. The anesthetic treatments for both time periods were as follows: group 1 (controls) = 70% N_2O/30% O_2, group 2 = 1 MAC halothane (1.1% inspired) in 30% O_2 and the balance nitrogen, and group 3 = 1 MAC isoflurane (1.38% inspired) in 30% O_2. These inspired values may represent slightly lower anesthetic levels than those previously reported for MAC in rats, since differences between inspired and end-tidal anesthetic concentrations are only 9% for halothane and 3% for isoflurane in rats with a tracheostomy.[12] In the second experimental series, severe ischemia was produced by clamping the carotid, decreasing blood pressure to 25 mmHg for 30 min, and decreasing the inspired O_2 fraction to 0.2. The anesthetic concentrations in rats in the second set of experiments were: group 1 = 1 MAC halothane, group 2 = 1 MAC isoflurane, group 3 = 2 MAC halothane, and group 4 = 2 MAC isoflurane. Neurological deficits were initially evaluated 3 h after recovery and repeated every 8 h for 3 days. Neurologic exams were performed by an individual blinded to the procedure performed. Deficits were scored from 0 to 5 as follows: 0 = normal, 1 = paw adduction or unusual posture, 2 = circling behavior and unilateral weakness, 3 = stroke-related seizures induced by stimulation, 4 = unstimulated seizures, and 5 = death associated with progressive stroke.

Histopathology

Histopathologic examination of brain tissue was performed using additional groups of rats for each ischemic condition (n = 4 per group). Twelve hours after ischemic recovery, the rats were anesthetized with halothane and killed by transcardial perfusion with 50 ml saline followed by 50 ml of 10% buffered formalin. Although neuronal damage is probably progressive over several days,[13] 12 h was chosen for histological measurement in order to obtain rats from all treatment conditions before they died of the ischemic brain injury. The brains were removed and immersed in 10% formalin for 1–2 weeks. The forebrain and hindbrain, including the cerebellum, were sliced into coronal blocks and imbedded in paraffin wax, and 7–8-μm sections were cut and mounted on slides. These slides were stained using hematoxylin and eosin and examined in the blinded manner by a neuropathologist using light microscopy. Histopathological damage was scored in the ischemic cerebral hemisphere according to the following scale: 0 = no observable neuronal damage, 1 = scattered neuronal cell death, 2 = moderate damage including focal regions in hippocampal, striatal, and cortical areas, 3 = severe damage involving extensive brain tissue regions, and 4 = total infarction.

TABLE 1. Experimental Ischemic Groups for Testing Neurologic Outcome

Treatment	Hypotensive Level (mmHg)	Duration of Ischemia (min)	F_{IO_2}
Experiment one (moderate ischemia)			
N_2O (70%)*	30	30	0.3
Halothane (1 MAC)	30	30	0.3
Isoflurane (1 MAC)	30	30	0.3
N_2O (70%)	30	45	0.3
Halothane (1 MAC)	30	45	0.3
Isoflurane (1 MAC)	30	45	0.3
Experiment two (severe ischemia)			
Halothane (1 MAC)	25	30	0.2
Isoflurane (1 MAC)	25	30	0.2
Halothane (2 MAC)	25	30	0.2
Isoflurane (2 MAC)	25	30	0.2

* Values in parenthesis represent inspired concentration or MAC values.

Cerebral Blood Flow and Metabolism

Cortical CBF was measured in additional groups of rats during three separate test conditions: control anesthesia, during ischemia, and following recovery. Ischemia was produced by unilateral carotid occlusion and 30 min of hypotension to 30 mmHg with F_{IO_2} = 0.3. Rats were prepared as described above. Also, the left ventricle was catheterized *via* the right subclavian artery, using pressure pulses to monitor proper catheter placement. This method of catheter placement allows brain perfusion by both carotid arteries with microsphere injection during control and recovery periods.[14]

The skull was then exposed, a small hole drilled over the posterior sagittal sinus, and a catheter inserted to obtain sagittal sinus blood samples. At the completion of surgery, the inspired anesthetic concentration was maintained at either 1 MAC halothane, 1 MAC isoflurane, or 70% N_2O for 30 min. The first microsphere test was made under these control conditions. The carotid artery was then clamped and the blood pressure decreased to 30 mmHg for 30 min by phlebotomy. A second CBF determination was made 25 min after the start of the ischemic period. A third microsphere test was performed during recovery 15 min after reinfusion of shed blood.

Microspheres

Fifteen micrometer microspheres labeled with cobalt-57, tin-113, and scandium-146 (New England Nuclear) were used in these studies. Stock solutions containing 500,000 microspheres/ml were suspended in isotonic saline with 0.01% Tween-80. Microspheres were vortexed for 1 min, and 0.2 ml were withdrawn (100,000 microspheres), injected into the left ventricle *via* the subclavian catheter (dead space = 0.06 ml), and flushed in with 0.2 ml saline over 20 s. Starting immediately before each microsphere test and continuing 45 s after the end of each injection, blood was withdrawn from a femoral artery at 0.4 ml/min.

Arterial and sagittal sinus blood samples were taken at the end of each microsphere test for measurement of blood gases, *p*H, and oxygen content. Blood gas tensions were measured with an IL 1303 blood gas analyzer. Arterial-sagittal sinus O_2 content was measured using an IL 280 CO-oximeter combined with oxygen dissolved in the plasma of each sample. Mean arterial blood pressure was measured continuously from the femoral artery catheter to ensure that blood pressure did not change appreciably during the microsphere test.

At the end of the third microsphere test, each rat was killed, and the brain was removed and sectioned into left and right cortical and subcortical samples and weighed. Cortical tissue typically contained a small percentage (less than 10%) of white matter. The activity of each microsphere in brain and blood samples was analyzed using a Nuclear Chicago® 1035 gamma counter and a Nuclear Data 600 multi-channel analyzer. CBF was analyzed according to the methods of Heymann *et al.*[15] Cerebral cortex oxygen consumption ($CMRO^2$) was calculated in each rat by multiplying cortical blood flow times arterial-sagittal sinus O_2 content.

Statistics

Data are reported as mean ± SE. Non-parametric neurologic outcome data were compared using a Kraskal-Wallis test to compare N_2O with isoflurane and halothane at hypotensive levels of 30 mmHg, and a Mann-Whitney U test to compare paired outcome data at 30 and 25 mmHg. A Bonferoni correction was used to obtain a significance of $P < 0.05$ when multiple comparisons were made. Parametric data were analyzed using a two-way analysis of variance with repeated measures, and differences between means involving multiple tests were compared using Scheffe's tests.

Results

Neurologic Outcome

Changes in blood pressure, heart rate, blood gas tensions, and *p*H during carotid ligation with hypotension to 30 mmHg are shown in table 2. Baseline blood pressure was lower in the rats receiving the volatile anesthetics compared to N_2O controls. Small variations in arterial blood gases and *p*H were observed during hypotension, consistent with the fact that ventilation was adjusted and sodium bicarbonate infused to compensate for these changes. Neurologic deficit scores and mortality rates for these experiments are shown in figure 1. Isoflurane- and halothane-treated rats had significantly fewer stroke-related problems than N_2O controls. However, there was no statistical difference between the volatile anesthetics. Increasing the duration of ischemia from 30 to 45 min did not significantly alter deficit scores or mortality.

Cardiovascular and blood gas values for 1 and 2 MAC halothane and isoflurane at more severe ischemia (25 mmHg hypotension for 30 min with FIO_2 = 0.2) are shown in table 3. Rats treated with 1 MAC isoflurane had higher baseline blood pressures than did animals with 1 MAC halothane. Also, rats treated with 2 MAC halothane and isoflurane had lower initial blood pressures than during 1 MAC. Pa_{O_2} values were lower than the first set of experiments because the inspired O_2 fraction was 0.2 rather than 0.3. Deficit scores and mortality rates are shown in figure 2. The more severe ischemic challenge produced greater stroke-related deficits for both halothane and isoflurane, but there was no significant difference between these two anesthetics at each ischemic level. Doubling the anesthetic concentration of halothane and isoflurane did not significantly change either mortality or deficit scores at 25 mmHg hypotension.

The EEG changes produced during ischemia were consistent with the presence of incomplete ischemia. N_2O produced high-frequency, low-amplitude activity that changed to high-amplitude, slow wave activity in both right and left cerebral hemispheres during hypotension/ischemia. The right hemisphere, ipsilateral to

TABLE 2. Arterial Blood Pressure, Heart Rate, Blood Gas Tensions, and pH during 30 and 45 Min of Unilateral Ischemia

	n	Blood Pressure (mmHg)	Heart Rate (min^{-1})	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	pH	Blood Volume (ml)
30 Min/30 mmHg Hypotension							
70% N_2O							
Control	10	126 ± 2†	381 ± 31	35.3 ± 1.8	140 ± 5	7.40 ± .02	
Hypotension		30 ± 1*	400 ± 17	38.8 ± 2.7	154 ± 10	7.34 ± .04*	14.8 ± .5†
Recovery		125 ± 3	407 ± 14	42.0 ± 2.4*	130 ± 11	7.35 ± .04	
1 MAC Halothane							
Control	12	99 ± 4	355 ± 18	37.5 ± 1.7	117 ± 6	7.41 ± .02	
Hypotension		30 ± 1*	298 ± 11	34.3 ± 1.9	155 ± 6*	7.38 ± .02	9.7 ± .6
Recovery		96 ± 3	339 ± 6	39.9 ± 1.4	117 ± 9	7.42 ± .02	
1 MAC Isoflurane							
Control	12	98 ± 8	356 ± 16	39.0 ± 3.3	127 ± 15	7.40 ± .01	
Hypotension		30 ± 1*	383 ± 20	34.2 ± 1.4	133 ± 10	7.38 ± .03	9.7 ± .7
Recovery		126 ± 2	346 ± 6	43.6 ± 1.0	140 ± 8	7.40 ± .02	
45 Min/30 mmHg hypotension							
70% N_2O							
Control	8	121 ± 5†	364 ± 34	38.0 ± 1.7	109 ± 8	7.41 ± .01	
Hypotension		30 ± 1*	383 ± 20	34.2 ± 1.4	133 ± 10*	7.38 ± .03	13.3 ± .8†
Recovery		131 ± 3	387 ± 19	45.8 ± 2.7*	103 ± 14	7.31 ± .03*	
1 MAC Halothane							
Control	10	95 ± 4	312 ± 8	39.3 ± 1.7	127 ± 6	7.40 ± .01	
Hypotension		30 ± 1*	320 ± 14	36.4 ± 2.1	151 ± 9*	7.35 ± .03*	9.7 ± .5
Recovery		98 ± 2	321 ± 33	42.9 ± 1.4	119 ± 6	7.38 ± .01	
1 MAC Isoflurane							
Control	10	104 ± 4	331 ± 16	37.2 ± 1.1	144 ± 9	7.45 ± .01	
Hypotension		30 ± 1*	333 ± 16	35.7 ± 1.7	146 ± 10	7.39 ± .03*	9.7 ± .5
Recovery		98 ± 9	356 ± 12	42.6 ± 2.3	127 ± 13	7.40 ± .02	

Data presented as mean ± SE. Blood volume indicates amount of blood withdrawn to produce hypotension.

* $P < 0.05$ hypotension and recovery compared to control for each anesthetic.

† $P < 0.05$ difference between groups.

carotid ligation, also showed periods of quiesence during ischemia. During the recovery phase, neither hemisphere returned to normal, but maintained high-amplitude, low-frequency activity. Both halothane and isoflurane produced a slowing of frequency and an increase in amplitude during steady-state conditions compared to N_2O controls, and these changes were greater with the higher concentrations of each anesthetic. Greater EEG suppression was observed during ischemia with 2 MAC halothane or isoflurane anesthesia than with lower concentrations, but the EEG returned to the original anesthetic state during the recovery period.

HISTOPATHOLOGY

With hypotensive levels of 30 mmHg, only scattered neuronal damage was observed on the side of carotid

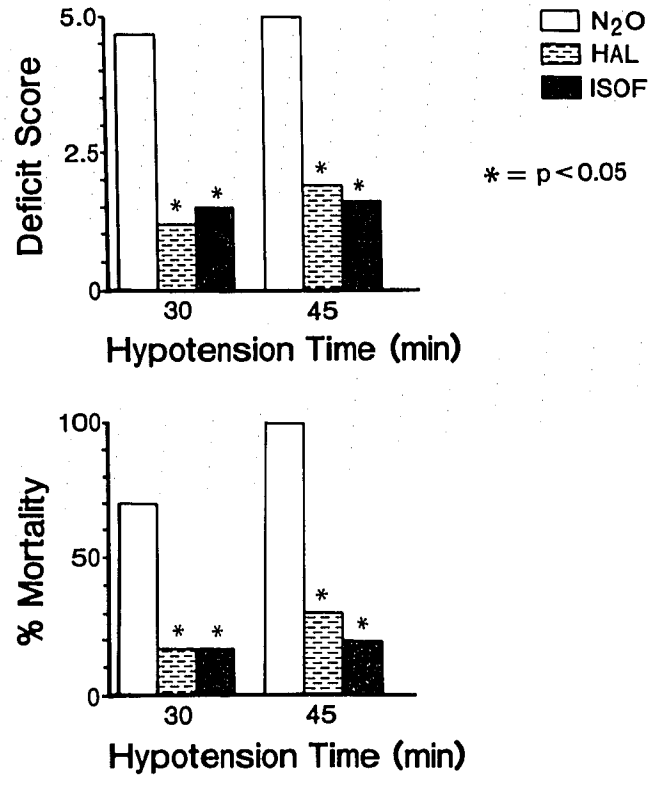

FIG. 1. Neurologic deficit scores and mortality following 30 and 45 min of incomplete cerebral ischemia produced by unilateral carotid occlusion with hypotension to 30 mmHg and $FIO_2 = 0.3$. Deficit scores range from 0 = no deficit to 5 = death associated with stroke. The significance value indicates a difference compared to N_2O-treated rats. Number of rats in each group presented in table 1.

TABLE 3. Arterial Blood Pressure, Heart Rate, Blood Gas Tensions, and pH during 30 Min of Ischemia With 1 and 2 MAC Halothane and Isoflurane

	n	Blood Pressure (mmHg)	Heart Rate (Min^{-1})	$Paco_2$ (mmHg)	Pao_2 (mmHg)	pH	Blood Volume (ml)
1 MAC halothane							
Control	10	80 ± 5	302 ± 8	37.1 ± 1.1	92 ± 4	7.41 ± .01	
Hypotension		25 ± 1*	304 ± 13	37.1 ± 1.2	101 ± 3	7.34 ± .03*	8.9 ± .7
Recovery		100 ± 3*	356 ± 11*	42.5 ± 1.0*	69 ± 4*	7.39 ± .02	
1 MAC isoflurane							
Control	10	101 ± 3†	341 ± 16	36.6 ± 1.7	84 ± 4	7.45 ± .02	
Hypotension		25 ± 1*	312 ± 9	35.6 ± .9	97 ± 5*	7.38 ± .01*	9.1 ± .3
Recovery		105 ± 5	346 ± 10	41.6 ± 1.0*	74 ± 5*	7.39 ± .01	
2 MAC halothane							
Control	10	61 ± 2	270 ± 12	35.3 ± .7	84 ± 3	7.41 ± .01	
Hypotension		25 ± 1*	293 ± 10	37.2 ± 1.2	88 ± 2	7.36 ± .01*	7.1 ± .8
Recovery		79 ± 6*	306 ± 11	41.7 ± 1.5*	71 ± 3*	7.37 ± .01	
2 MAC isoflurane							
Control	10	66 ± 3	312 ± 12	37.6 ± 2.2	80 ± 4	7.43 ± .01	
Hypotension		25 ± 1*	350 ± 13	37.8 ± 1.7	89 ± 4	7.37 ± .02*	9.7 ± .6
Recovery		88 ± 4*	366 ± 16	43.1 ± 1.2*	64 ± 3*	7.39 ± .02	

Mean ± SE.
* $P < 0.05$ hypotension and recovery compared to control for each anesthetic.
† $P < 0.05$ halothane *vs.* isoflurane at each treatment.

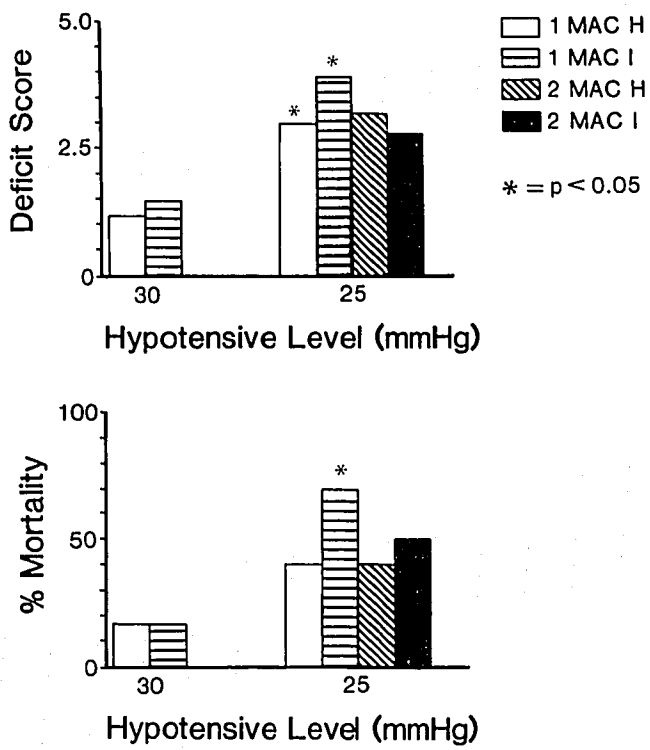

FIG. 2. Neurologic deficit scores and mortality with 1 and 2 MAC halothane or isoflurane following moderate (30 mmHg, FIO_2 = 0.3) and severe (25 mmHg, FIO_2 = 0.2) cerebral ischemia. The values for moderate ischemia are repeated from figure 1. The significance value indicates a difference between moderate *versus* severe ischemia at 1 MAC halothane or 1 MAC isoflurane level. There is no significant difference between 1 and 2 MAC halothane or 1 and 2 MAC isoflurane at 25 mmHg. Number of rats in each group presented in table 2.

ligation in rats anesthetized with halothane or isoflurane. This damage was observed in the caudate, hippocampus, and deeper layers of the cortex. No damage was observed in brain stem or cerebellar regions with any ischemic challenge. After hypotension to 30 mmHg, halothane and isoflurane produced histological scores of 1.4 and 1.6, respectively, indicating modest neuronal damage. Ischemia during 70% N_2O produced extensive neuronal necrosis in hippocampus, caudate, and deep cortical layers, and a histopatholgical score of 2.8. This damage was usually focal in nature, and was quite often associated with vacuoles suggesting the presence of edema. After hypotension to 25 mmHg, neuronal damage was more extensive for both halothane and isoflurane. Again, the caudate, hippocampus, and cerebral cortex were primarily involved, but the necrosis was more extensive and less focal than with moderate ischemia. The amount of ischemic histological damage appeared similar between 1 MAC halothane-and isoflurane-treated rats (histopathological score = 2.4 and 2.7, respectively). There was only scattered neuronal necrosis contralateral to carotid ligation in all treatments. In two cases in which 2 MAC halothane was administered, the infarct included almost the entire hemisphere ipsilateral to carotid ligation, sparing only the inferior medial temporal region, which receives its blood supply from the posterior cerebral artery. The histopathologic score was lower following 2 MAC isoflurane (2.8) as compared to 2 MAC halothane (3.2), but this difference was not significant.

Cerebral Blood Flow and Metabolism

Cortical CBF changes produced by the anesthetics and ischemia are shown in figure 3. N_2O produced similar CBF compared to halothane and isoflurane during control conditions, and there was little difference in flow between right and left hemispheres. Carotid ligation combined with hypotension decreased CBF more in the right *versus* left cortex to a level approximately 30–40% of control values. CBF returned toward control levels during the recovery period, although there was considerable variability. During steady-state conditions before ischemia, $CMRO_2$ was lower ($P < 0.05$) with 1 MAC halothane (9.2 ± 1.2 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) and 1 MAC isoflurane ($7.2 \pm 0.7$ ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) compared to N_2O (12.7 ± 1.6 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$). $CMRO_2$ decreased significantly ($P < 0.05$) in all groups during ischemia ($N_2O = 8.2 \pm 1.2$ ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, 35% decrease; H = 6.0 ± 0.5 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, 35% decrease; I = 5.8 ± 1.0 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, 19% decrease) and returned to control levels in the recovery period ($N_2O = 11.6 \pm 1.7$ ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, H = 7.8 ± 1.6 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, I = 8.0 ± 0.7 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$).

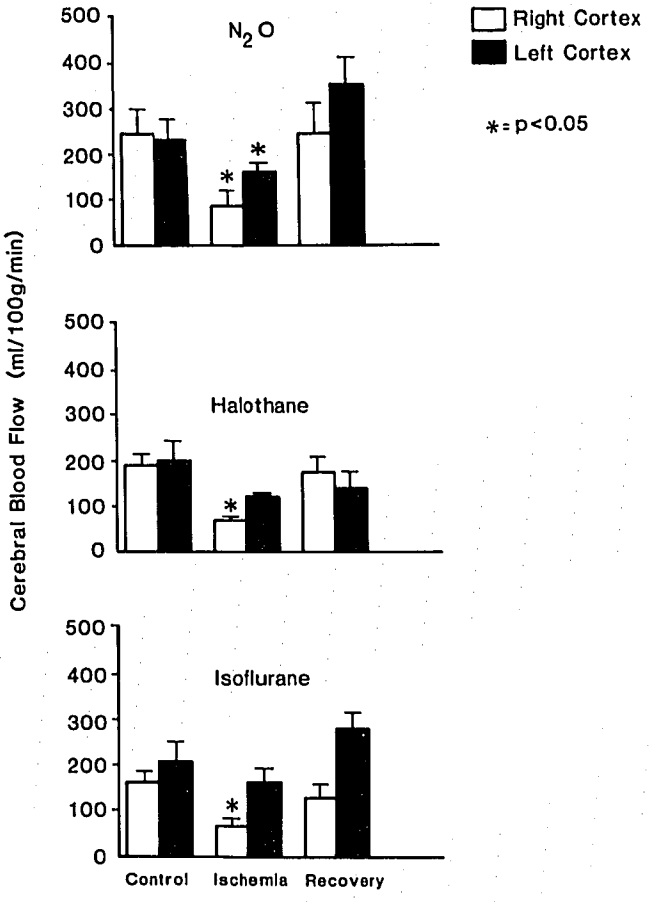

FIG. 3. Cortex CBF during 1 MAC halothane and isoflurane anesthesia compared to 70% N_2O controls (n = 4 per group). Each rat received three tests, one during steady-state conditions before ischemia, one 25 min after the start of ischemia, and the last test 15 min into the recovery period. Significance values indicate a change from pre-ischemic conditions in each treatment group.

Discussion

Our results show that, in a model of incomplete ischemia in rats, both halothane and isoflurane reduce the severity of neurologic insult compared with N_2O control. However, there was no difference in outcome between the two volatile anesthetics following either a moderate or severe ischemic challenge. This occurred in spite of measured differences in $CMRO_2$ between the volatile anesthetics during control, pre-ischemic conditions. In addition, doubling the anesthetic depth of halothane and isoflurane did not significantly improve outcome. This supports previous reports,[16] ¶ and suggests that, while halothane and isoflurane may provide brain protection from ischemia compard to N_2O, this effect may not be strictly related to their ability to depress $CMRO_2$.

In previous studies, it has been shown that N_2O does not markedly change CBF or cerebral metabolism in rats,[17,18] and may produce increases in $CMRO_2$ in other animals compared to unanesthetized controls.[19,20] In contrast, halothane may depress $CMRO_2$ 25–30%[6] and isoflurane up to 50% of control values.[4,6,21] Both halothane and isoflurane provide protection in a hypoxic mouse model,[5,22] but there is little data which compares neurologic outcome between the two anesthetics with ischemia. Recent studies have compared isoflurane to N_2O or thiopental. In dogs submitted to incomplete cerebral ischemia by hemorrhagic hypotension, Newberg and Michenfelder[5] reported that 3% end-expired isoflurane produced less depletion of brain energy charge and less accumulation of brain lactate compared to N_2O controls. In rats with near complete cerebral ischemia, Warner *et al.*[23] found that 3–4% inspired isoflurane resulted in the same degree of brain histopathology as did 70% N_2O. Together, these reports suggest that isoflurane will protect the brain from energy state depletion under incomplete ischemic conditions, but will not protect neurons from injury if the ischemic challenge is severe enough to produce brain electrical silence.[23] In a focal ischemic model produced by middle cerebral artery occlusion (MCAO) in baboons, Nehls *et al.*[10] showed that 2% isoflurane did not protect animals from neurologic or histopathologic damage as well as did thiopental. One problem in that study was that baboons receiving thiopental were hypertensive, requiring the use of vasodilators, while isoflurane-anesthetized animals received phenylephrine to raise blood pressure. It is possible that the use vasodilators or phen-

ylephrine may have contributed to a difference in outcome. More recently, Milde *et al.*[24] repeated these studies in pigtailed monkeys and found that, when vasodilators were not used and blood pressures were similar during ischemia, there was no difference in outcome between thiopental and isoflurane (although animals in both studies were severely damaged). Does isoflurane provide more protection than halothane? Milde and Milde[5] have shown that, in dogs, isoflurane and halothane produce a similar decrement in brain energy state during a challenge of incomplete ischemia. Our results indicate that isoflurane and halothane produce a better outcome from incomplete ischemia compared to N_2O, but there is no difference between the two volatile anesthetics.

One potential problem regarding the use of N_2O as a control state is that pre-ischemic blood pressure was higher in rats receiving N_2O (121–125 mmHg) than in those receiving either halothane (95–99 mmHg) or isoflurane (98–104 mmHg). A hypotensive level of 30 mmHg, therefore, represents a greater decrease in blood pressure and, possibly, a greater ischemic challenge in N_2O-treated rats. However, the percentage decrease in cortical CBF in the ischemia hemisphere was similar with N_2O (60%), halothane (62%), and isoflurane (59%). This indicates that the relative ischemia was similar with each of the three treatment conditions, and that a difference in outcome must be due to other factors.

In summary, results here show that isoflurane and halothane produce significantly better brain protection than N_2O during incomplete cerebral ischemia. While these protective effects may be related to the cerebral metabolic depressant action of both halothane and isoflurane, our results suggest that other factors may also be important. Other possible factors include a cellular action of these drugs that is not dose-related, or an ability to modulate post-ischemic neuronal injury and edema formation.

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