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A Comparison of the Cerebrovascular and Metabolic Effects of Halothane and Isoflurane in the Cat

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Halothane is a well known cerebral vasodilator that can produce dangerous increases in intracranial pressure (ICP) in certain neurosurgical patients. It has been suggested that isoflurane may be a less potent cerebral vasodilator. The authors therefore undertook a direct comparison of the effects of halothane and isoflurane on cerebral blood flow (CBF), cerebral vascular resistance (CVR), intracranial pressure, and cerebral metabolic rate for oxygen (CMR_{O_2}). Studies were carried out in normocarbic mechanically ventilated cats, using the intracarotid ^{133}Xe injection technique to measure CBF. The effects of three doses were examined: 0.5, 1.0, and 1.5 MAC, studied in the continued presence of 75% N_2O. Autoregulation also was tested at 1.0 MAC (plus 75% N_2O) by recording CBF and CVR before and after elevation of blood pressure with angiotensin.

Both agents had similar effects on blood pressure and ICP. However, while halothane produced significant increases in CBF at all doses, with values of 61 ± 5 ml · 100 g^{-1} · min^{-1} (123 ± 8% of control, mean ± SE) at 1.0 MAC, isoflurane anesthesia caused no significant changes in CBF at any level, (*e.g.*, 48 ± 8 ml · 100 g^{-1} · min^{-1} or 94 ± 12% of control at 1.0 MAC). Both drugs produced dose-related decreases in CVR, but the changes were greater with halothane, *e.g.*, CVR at 1.0 MAC halothane = 1.46 ± 0.20 mmHg · ml^{-1} · 100 g · min (47 ± 7% of control) compared with 2.23 ± 0.40 mmHg · ml^{-1} · 100 g · min (72 ± 9% of control). In addition, isoflurane produced greater decreases in CMR_{O_2} than did halothane, and also impaired autoregulation less.

The results indicate that isoflurane possesses cerebrovascular properties that are different from halothane. These differences suggest that isoflurane may come to play an important role in future neuroanesthetic practice. (Key words: Anesthetics, volatile: halothane; isoflurane. Brain: autoregulation; blood flow; intracranial pressure; metabolism.)

IN THE 1960S, MCDOWALL AND CO-WORKERS reported that the administration of halothane to neurosurgical patients resulted in an increase in intracranial pressure (ICP), occasionally to dangerous levels.[1,2] Other investigations have demonstrated that this agent is a potent cerebral vasodilator, capable of producing dose-related decreases in cerebral vascular resistance (CVR) and increases in both cerebral blood flow (CBF) and cerebral blood volume (CBV).[3–6] Halothane will also blunt or abolish the normal autoregulatory responses to changes in arterial pressure,[7,8] and there is evidence suggesting that this latter action renders the blood-brain barrier more susceptible to hypertension-mediated disruption.[9] Since these effects can be detrimental, particularly in patients with pre-existing neurologic injuries, many clinicians have limited their use of halothane in neurosurgical patients.

There is still, however, a clinical need for volatile agents in neuroanesthetic practice, and some workers have suggested that isoflurane may be more suitable. Specifically, in 1974 Murphy *et al.* reported that isoflurane in humans produced smaller increases in CBF than did equivalent concentrations of halothane.‡ Unfortunately, this work was presented only in abstract form and since that time, few direct comparisons of the CBF effects of equipotent doses of isoflurane and halothane have appeared. Furthermore, canine studies suggest that isoflurane may be a more potent vasodilator at least in high concentrations (2 MAC).[10,11] Therefore, in view of the clinical problems with halothane and the potential but incompletely evaluated benefits of isoflurane, we undertook a comparative study of the cerebrovascular and metabolic effects of these two agents in the cat.

Materials and Methods

Adult cats weighing 2.5–4.0 kg were used for all studies. Anesthesia was induced with halothane in oxygen (in a closed plastic box). Pancuronium bromide (0.3 mg/kg) was administered via a peripheral vein and the trachea intubated. Mechanical ventilation was begun at a tidal volume of 15 ml/kg, and a respiratory rate of 20 breaths/min, using an inspired gas mixture containing 1% halothane, 75% N_2O, and 25% O_2. Normocarbia (Pa_{CO_2} 28–32 mmHg)[12] was maintained by the addition of carbon dioxide to the inspired gas mixture. Catheters were placed into the femoral artery, the right atrium (via the femoral vein), and the right lingual artery (for ^{133}Xe injection). The animal was placed in a prone position and the head was fixed in a stereotactic frame with the interaural line 12 cm above the table. Extracranial soft tissue was resected bilaterally to the level of the zygomatic arches to prevent

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‡ Murphy FL, Kennell EM, Johnstone RE et al: The effects of enflurane, isoflurane and halothane on cerebral blood flow and metabolism in man. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, 1974, pp 62–63.

contamination of the ^{133}Xe washout curves by extracranial perfusion. Burr holes were drilled over the left parietal area and the posterior midline and catheters were placed into the subarachnoid space (for measurement of ICP) and into the caudal aspect of the sagittal sinus (to permit sampling of cerebral venous blood). The dura was sealed with Eastman® 910 cement and the skull defects closed with dental acrylic. Brass screws were placed on the left side of the skull for electroencephalographic (EEG) recording (frontal- occipital bipolar lead). All wound edges were infiltrated carefully with 0.25% bupivicaine (total dose 4 ml) and the halothane was discontinued. Analgesia was then maintained with 75% N_2O in oxygen, and stimuli were kept to a minimum (eyes closed, no handling, quiet room).

Monitored variables in all animals included arterial pressure (BP), right atrial pressure (RAP), intracranial pressure (ICP), heart rate, the electrocardiogram, EEG, and expired CO_2 (Beckman® LB-II). All pressures are expressed as the electrical means, and the BP and ICP transducers were positioned at head level to permit accurate calculation of cerebral perfusion pressure (CPP = BP − ICP). Esophageal temperature was kept at 37° C with servo-controlled heat lamps. CBF was determined using the intra-arterial ^{133}Xe injection technique.[13,14] Approximately 300 μCi of ^{133}Xe in 0.3 ml saline were injected as a bolus into the lingual artery catheter, followed by a 0.5-ml saline flush. Activity was recorded with a single collimated scintillation counter positioned over the right posterior-parietal area with the central axis of the probe inclined approximately 20–25° from the horizontal. CBF was calculated using a $T_{1/2}$ method.[15] A xenon blood-brain partition coefficient of 1.0 was assumed, and the first 15 seconds of the washout curve were discarded.[15] Cerebral vascular resistance was calculated as CPP/CBF. Cerebral metabolic rate for oxygen (CMR_{O_2}) was calculated as CBF multiplied by the arterial-sagittal sinus blood oxygen content difference using O_2 contents (Lex-O_2-Con, Lexington Instruments) measured on paired arterial and cerebral venous samples drawn one minute after ^{133}Xe injection. The total volume of blood drawn for each set of determinations was approximately 1 ml.

All animals received a continuous intravenous infusion of normal saline at a rate of 8 $ml \cdot kg^{-1} \cdot h^{-1}$. This had been determined empirically as the amount needed to compensate for evaporative and "third space" losses and to maintain constant arterial pressure, RAP, heart rate, and hematocrit during the experiment.

Experimental Protocol

After surgical preparation and local anesthetic infiltration with bupivicaine were complete, halothane was discontinued and the animals were ventilated with 75% nitrous oxide/25% oxygen until end-tidal halothane concentration (measured using a Beckman LB-II analyzer with the sampling catheter at the *distal* tip of the endotracheal tube) had been <0.05% for more than 20 min. At this point, the analyzer was recalibrated for the desired agent (halothane or isoflurane) and control data obtained. The selected anesthetic (chosen randomly) then was administered by gradually increasing end-tidal concentration (over 5–10 min) to the required level (0.5, 1.0, or 1.5 MAC§) which was then maintained for 15 min. Inspired CO_2 concentration was adjusted as needed to maintain normocarbia, and nitrous oxide administration was unchanged (FI_{N_2O} = 0.75). All values then were recorded and the agent discontinued. When the end-tidal volatile agent concentration had again been below 0.05% for >20 min, "control" data were again obtained, followed by equilibration at the next selected end-tidal level. Thus, a new control point was obtained prior to each anesthetic concentration. All of the six possible experimental sequences were studied with each agent (*e.g.*, 0.5-1.0-1.5 MAC; 1.5-1.0-0.5 MAC; 1.0-0.5-1.5 MAC, etc.). However, since there were nine cats in each group, three sequences were studied twice, and these were matched in the two groups. Only one drug was tested in each animal.

The effects of these two agents on autoregulation also were examined. After collection of data at the 1.0 MAC level, an infusion of angiotensin II (Sigma Chemical, human form) was started and BP was increased gradually (over 10 min) until it reached a value of 115–130 mmHg. After 10 min of a stable, elevated BP (still breathing 1.0 MAC agent in 75% N_2O) data were again collected. Both the agent and the angiotensin then were discontinued, allowing the cat to return to a control state in preparation for examining another dose. Angiotensin infusions were performed only at the 1.0 MAC level, and only in the event that BP (unsupported) was <110 mmHg. If BP was already >110 mmHg, angiotensin was not given, and no autoregulatory data were obtained in that animal.

Statistical Analysis

Comparisons between the multiple control values were performed using both an analysis of variance and unpaired *t* test (with a Bonferronni correction), while the effects of a given anesthetic concentration (compared with control) were assessed using paired *t* testing. No dose-response comparisons were performed. Intergroup comparisons at a given anesthetic concentration (halothane *vs.* isoflurane) were performed in two ways. First, absolute values were compared with an unpaired *t* test (*e.g.*, CBF at 1.0 MAC

§ MAC values for halothane (1.19%) and isoflurane (1.61%) were determined in this laboratory using the method of Eger *et al.*[16,17]

TABLE 1. Control Values (pre-1.0 MAC)

	Halothane (n = 9)*	Isoflurane (n = 9)*
CBF (ml·100 g^{-1}·min^{-1})	51 ± 4	50 ± 3
HR (beats)	198 ± 10	191 ± 7
$\overline{BP}$ (mmHg)	155 ± 3	152 ± 6
RAP (mmHg)	0.4 ± 0.8	0.9 ± 1.2
ICP (mmHg)	7.4 ± 1.0	5.9 ± 0.7
CPP (mmHg)	148 ± 3	146 ± 5
CVR (mmHg·ml^{-1}·100 g·min)	3.1 ± 0.2	3.0 ± 0.2
CMR_{O_2} (ml·100 g^{-1}·min^{-1})	4.3 ± 0.4	4.4 ± 0.3
Pa_{O_2} (mmHg)	110 ± 4	118 ± 3
Pa_{CO_2} (mmHg)	30.1 ± 0.4	30.5 ± 0.3
*p*H	7.39 ± 0.01	7.37 ± 0.01
Hct (%)	36 ± 1	36 ± 2

* Values (mean ± SE) were obtained in cats ventilated with 75% N_2O, just prior to their exposure to 1.0 MAC agent. Pressures (BP, ICP, RAP, and CPP) are electrical means. There are no intergroup differences.

halothane *vs.* CBF at 1.0 MAC isoflurane). Secondly, the magnitude of the changes (*vs.* control) produced by a given concentration also were compared with an unpaired *t* test (*e.g.*, change in CBF produced by 1.0 MAC halothane *vs.* that occurring with 1.0 MAC isoflurane). Please note that while data in the figures are expressed as "per cent of control" (to make intergroup comparisons easier for the reader) statistical evaluations of the degree of change were carried out only on arithmetic differences.

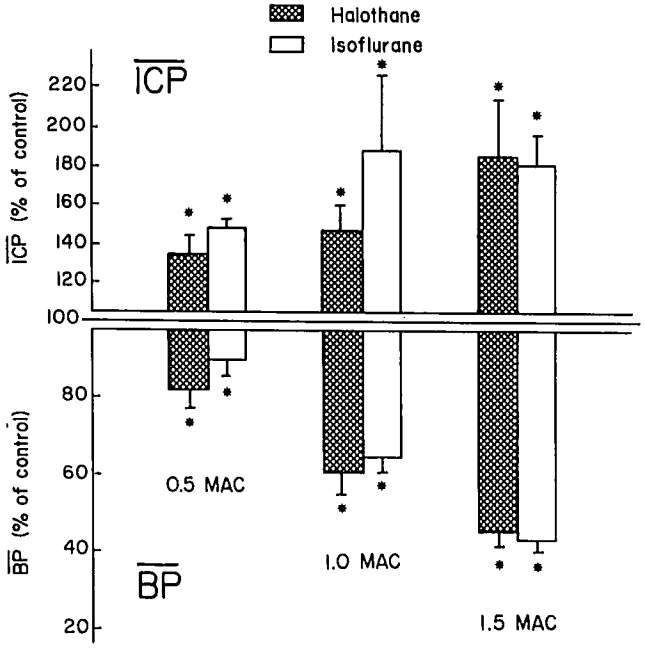

FIG. 1. ICP and BP. Both agents produced significant changes in both ICP and BP (* $P < 0.05$ *vs.* control), but there were no intergroup differences (halothane *vs.* isoflurane). Values are mean ± SE.

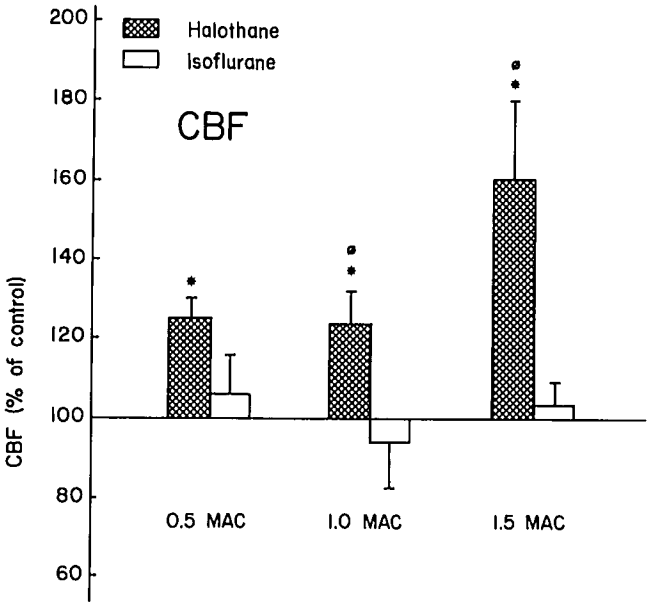

FIG. 2. CBF. CBF was increased significantly with all three concentrations of halothane (* $P < 0.05$ *vs.* control), but was unchanged during isoflurane anesthesia. In addition, CBF with 1.0 and 1.5 MAC halothane was greater than with equi-MAC isoflurane (0 = $P < 0.05$, halothane *vs.* isoflurane).

Results

Eighteen cats were used (nine in each group). There were no intergroup differences in weight or sex ratio. The lowest observed Pa_{O_2} was 93 mmHg (range 93–138 mmHg), Pa_{CO_2} values were between 29 and 32 mmHg,[12] while *p*H ranged from 7.33 to 7.42. There were no changes in any of these variables produced by drug administration. There were no changes in hematocrit.

Three sets of control data were recorded in each cat, with a new set obtained prior to testing each dosage level (*i.e.*, pre-0.5 MAC, pre-1.0 MAC, etc.). For the sake of brevity, only the data obtained prior to the 1.0 MAC exposure are summarized in table 1. There were no intergroup differences in control values (halothane *vs.* isoflurane) at any MAC level.

The observed changes in BP and ICP are summarized in figure 1, with results expressed as per cent of control. Both agents produced comparable, dose-related decreases in BP, reaching 75 ± 7 mmHg (46 ± 4% of control) (mean ± SE) in animals breathing 1.5 MAC halothane, and 68 ± 4 mmHg (44 ± 3%) with 1.5 MAC isoflurane. Both drugs also produced similar increases in ICP, reaching values of 11.6 ± 1.7 mmHg (185 ± 29% of control with 1.5 MAC halothane and 10.9 ± 0.7 mmHg (181 ± 18% of control) with 1.5 MAC isoflurane.

CEREBROVASCULAR CHANGES

The impact of the two agents on CBF and CVR is summarized in figures 2 and 3. With each concentration

of halothane, CBF increased significantly, reaching values of 60 ± 4 (124 ± 5% of control), 61 ± 5 (123 ± 8%), and 73 ± 8 ml · 100 g^{-1} · min^{-1} (159 ± 20%) at 0.5, 1.0, and 1.5 MAC, respectively. By contrast, CBF was never significantly different from control values during isoflurane administration, reaching levels of only 51 ± 7 (105 ± 9%), 48 ± 8 (94 ± 12%, and 51 ± 5 ml · 100 g^{-1} · min^{-1} (103 ± 6%) at the three concentrations. Intergroup comparisons demonstrate that the CBF changes produced by 1.0 and 1.5 MAC isoflurane were significantly less than that observed with equi-MAC halothane. Both drugs produced decreases in CVR. With halothane, CVR reached 2.13 ± 0.20 mmHg · ml^{-1} · 100 g · min (65 ± 5% of control) at 0.5 MAC, and 1.46 ± 0.20 mmHg · ml^{-1} · 100 g · min (47 ± 7%) and 0.93 ± 0.10 mmHg · ml^{-1} · 100 g · min (27 · 2%) at 1.0 and 1.5 MAC, respectively. By contrast, isoflurane produced significantly smaller decreases at all concentrations, reaching 2.81 ± 0.03 mmHg · ml^{-1} · 100 g · min (88 ± 7% of control) at 0.5 MAC, 2.23 ± 0.40 mmHg · ml^{-1} · 100 g · min (72 ± 9%) at 1.0 MAC, and 1.34 ± 0.30 mmHg · ml^{-1} · 100 g · min (40 ± 4%) at 1.5 MAC.

Autoregulation (Fig. 4)

Autoregulation was tested in seven cats in each group. In animals breathing 1.0 MAC halothane, increasing BP from 85 ± 7 mmHg to 120 ± 2 mmHg increased CBF from 64 ± 6 ml · 100 g^{-1} · min^{-1} to 83 ± 9 ml · 100 g^{-1} · $dmin^{-1}$ ($P < 0.05$). With isoflurane, BP was increased from 94 ± 5 mmHg to 120 ± 2 mmHg, but CBF did not change significantly (49 ± 10 ml · 100 g^{-1} · min^{-1} *vs.* 53 ± 10 ml · 100 g^{-1} · min^{-1}).

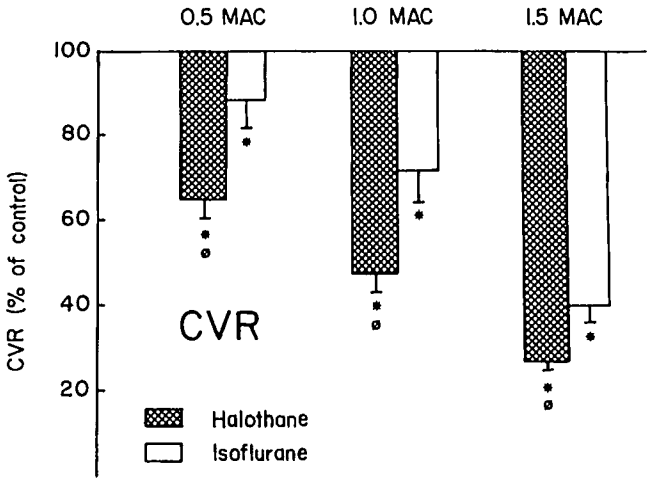

Fig. 3. CVR. Both drugs produced significant decreases in CVR at all three concentrations tested (* $P < 0.05$ *vs.* control). However, the decreases produced by halothane were greater than those seen with isoflurane at all three levels (0 = $P < 0.05$, halothane *vs.* isoflurane).

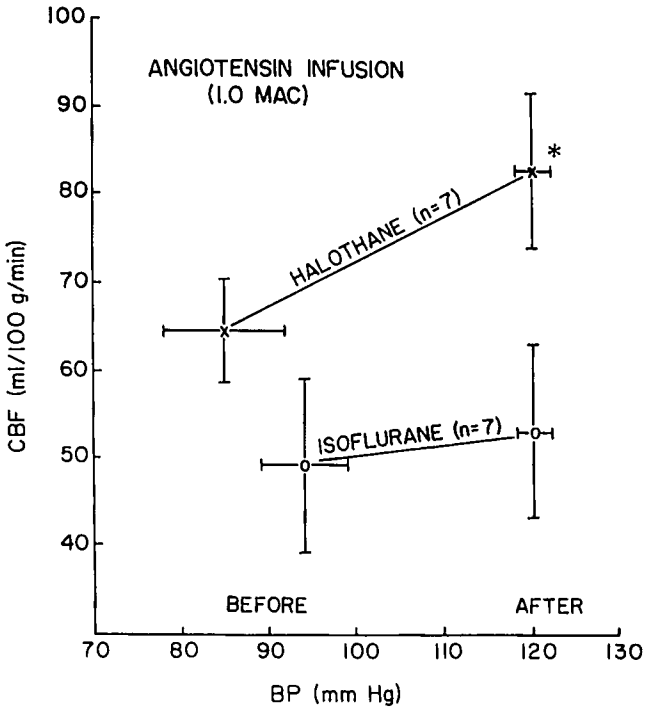

Fig. 4. Autoregulation testing during 1.0 MAC anesthesia plus 75% N_2O. CBF was measured before and again after increasing BP to a value of approximately 120 mmHg using angiotensin [from pre-infusion, 1.0 MAC values of 85 ± 7 mmHg (halothane) and 94 ± 5 mmHg (isoflurane)]. BP elevation produced a significant increase in CBF only in the halothane group (* $P < 0.05$). In addition, CBF in the halothane group (BP = 120 mmHg) was greater than with isoflurane (0 = $P < 0.05$).

An additional index of autoregulatory function is the slope of the lines shown in figure 4 (*i.e.*, ΔCBF/ΔBP). These values were: 0.80 ± 0.26 ml · 100 g^{-1} · min^{-1} · $mmHg^{-1}$ (halothane) and 0.16 ± 0.07 ml · 100 g^{-1} · min^{-1} · $mmHg^{-1}$ (isoflurane) ($P < 0.05$).

Cerebral Metabolic Rates for Oxygen (CMR_{O_2}, Fig. 5)

Both agents produced significant, dose-related decreases in CMR_{O_2}. For halothane, CMR_{O_2} values were 3.7 ± 1.3 (83 ± 3% of control), 3.1 ± 0.3 (73 ± 5%), and 2.9 ± 0.3 ml · 100 g^{-1} · min^{-1} (71 ± 5%) at 0.5, 1.0, and 1.5 MAC, respectively, while for isoflurane, values of 3.1 ± 0.5 (69 ± 6% of control), 2.4 ± 0.4 (55 ± 6%), and 2.3 ± 0.3 ml · 100 g^{-1} · min^{-1} (53 ± 3%) were obtained at 0.5, 1.0, and 1.5 MAC levels. Intergroup comparisons confirmed that the decreases produced by isoflurane were significantly larger than with equi-MAC halothane.

CMR_{O_2} values were not affected by angiotensin infusion (data not shown).

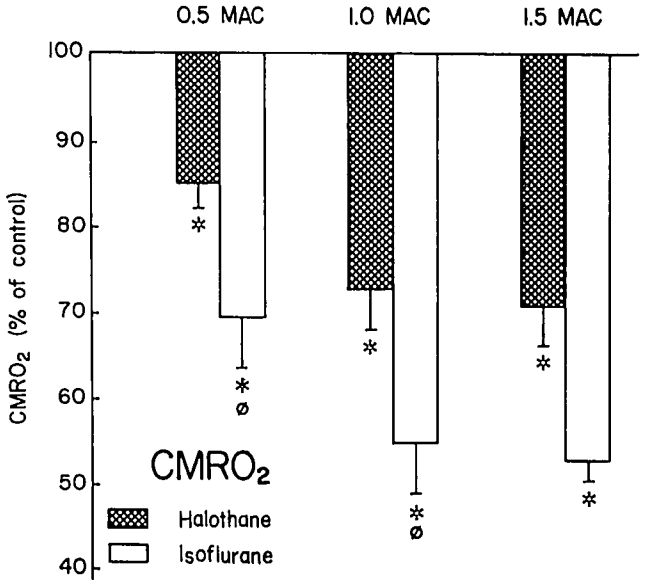

FIG. 5. CMR_{O_2}. Both agents produced significant decreases in CMR_{O_2} at all three concentrations (* $P < 0.05$ *vs.* control). The magnitude of the decrease was greater with isoflurane at all concentrations and absolute CMR_{O_2} values were significantly less with 0.5 and 1.0 MAC isoflurane ($P < 0.05$, halothane *vs.* isoflurane).

EEG Changes

The EEG changes produced by isoflurane and halothane have been described elsewhere.[17-20] It is, however, worth noting that six of nine animals breathing 1.0 MAC isoflurane and all animals at 1.5 MAC isoflurane showed essentially isoelectric EEGs (interrupted by occasional spikes). No animal given halothane ever demonstrated an isoelectric tracing.

Discussion

Halothane has been used in neuroanesthetic practice since the 1950s. Its initially perceived advantages were ease of use and reversibility (compared with ether), the availability of high inspired oxygen concentrations, and smooth control of hemodynamic variables, primarily blood pressure. However, studies of its cerebrovascular effects, particularly its vasodilating properties and the resultant impact on ICP resulted in a curtailment of its use in the early 1970s.[1,2] Most anesthesiologists chose instead to employ combinations of intravenous drugs, usually in conjunction with nitrous oxide. Nevertheless, the need (and desire) for a "better" volatile agent did not disappear, and the report in 1974 by Murphy *et al.*‡ suggested that isoflurane might be such a drug.

It is not yet clear that isoflurane is truly a "better" drug for clinical neuroanesthetic practice, since such a determination would require randomized studies on the clinical outcome of large numbers of neurosurgical patients. However, the present study confirms the belief that the cerebrovascular properties of isoflurane are different from those of halothane. At the three dosage levels tested (0.5, 1.0, and 1.5 MAC in the presence of 75% nitrous oxide) isoflurane had essentially no effect on CBF (compared with the significant increases produced by halothane), and produced smaller decreases in CVR than did halothane. These results are similar to those found in humans by Murphy *et al.*,‡ although they differ from data obtained in dogs.[10,11] This latter discrepancy may stem from the different control states and measurement methods used in the dog (no local infiltration, no N_2O, CBF measured by venous outflow). The current results also indicate that autoregulation was better preserved with isoflurane (at 1.0 MAC). Lastly, isoflurane yielded greater decreases in CMR_{O_2} than did halothane, an observation that may be related to the greater degree of cerebral electrical suppression seen with this agent.[17-20]

In contrast to these differences, there are two initially puzzling findings, both involving the observed changes in ICP. The first concerns the fact that ICP consistantly rose during isoflurane administration, even though no increases in CBF were noted. In fact, ICP increased even in individual cats in which CBF decreased. Since the changes in ICP occurred too quickly to be explained by increases in either tissue water content or cerebrospinal fluid volume, it seems reasonable to attribute them to increases in cerebral blood volume. This in turn suggests that there is some dissociation between the effects of isoflurane (and perhaps halothane) on CBF and CBV. Such dissociation has not been previously reported, and CBF and CBV (and hence ICP) usually increase and decrease in parallel.[21] It is known that CBV does increase during isoflurane anesthesia,[6,22] and it is possible that the drug is acting at a point distal to the arterioles (*e.g.*, producing venodilitation without increasing CBF). Further investigations of this possibility will require simultaneous measurements of CBF and CBV.

The second apparent contradiction is that the ICP changes produced by the two agents were nearly identical, in spite of the differences in CBF. Similar ICP increments might be anticipated if the effects of the two agents on CBV were comparable. However, Artru recently compared the CBV changes produced by halothane and isoflurane and found that the increase was less with isoflurane.[6] In addition, recent work in our laboratory showed that halothane produced a greater degree of acute brain swelling (an indirect measure of increasing CBV) than isoflurane.[22] We suspect, therefore, that the similar ICP changes observed in the current study reflect the fact that these were normal animals, in a head-up posture, with high intracranial compliance. The observed ICP changes were small (3–5 mmHg) and it is probable that

substantial differences in CBV may not have produced detectably different ICP changes. Studies performed in animals whose intracranial compliance is reduced would clarify this situation.

Several of methodologic factors must be considered when interpreting the CBF and CMR_{O_2} data presented. First, it should be noted that while CBF and CMR_{O_2} have been expressed as "whole brain" values, this is not strictly true. Bates and Sundt have shown that the ^{133}Xe methodology used here essentially measures flow only in the hemisphere nearest the scintillation detector.[23] However, the cerebral venous blood samples used for the determination of the $A\text{-}V_{O_2}$ difference (needed for CMR_{O_2} calculations) represent blood from both hemispheres and may represent a different mix of superficial and deep structures than that seen by the flow probe. As a result, the CBF and $A\text{-}V_{O_2}$ difference values may be derived from different tissue compartments, thus introducing some errors into the CMR_{O_2} calculation. However, such errors should be small, particularly in the absence of focal, hemispheric pathology.

A second factor is the use of N_2O. N_2O has its own intrinsic cerebrovascular effects when given alone or when added to a halothane anesthetic.[24,25] However, its influence on the changes produced by isoflurane are unknown. The use of N_2O (along with local anesthetic infiltration of all wounds) represented a compromise between providing the needed analgesia in the control state and having minimal cerebrovascular effects. Nevertheless, the animals were clearly hyperdynamic, and the reader should be cautious about extrapolating these data to anesthetic situations that do not employ N_2O, which utilize any other anesthetic drugs, or in which a lesser degree of baseline stress is present.

Lastly, the experimental design was somewhat atypical. Most prior studies of the dose-related effects of anesthetics on CBF have employed a "stair-step" design, where a control value is followed by repeated measurements made as the concentration of the anesthetic is increased. However, such a design introduces certain problems related to the effects of time and to the possible influence of preceding anesthetic exposure (*e.g.*, Does 20–30 min of exposure to 0.5 MAC agent alter the changes seen at 1.0 MAC, compared with going directly from control to 1.0 MAC?). Furthermore, Albrecht *et al.* recently have shown that CBF begins to normalize within 60 min after the start of halothane administration.[26] This suggests that if a "stair-step" design were used in these experiments, such normalization would tend to attenuate the measured effects of the last level studied (*e.g.*, 1.5 MAC, studied 60–90 min post-control). Admittedly, there are potential problems with the experimental design used here. However, any "drift" in N_2O baseline with time is minimized by the varied sequence of exposures. Furthermore, the fact that the "control" values for all exposure levels are identical (*i.e.*, pre-0.5 MAC, pre-1.0 MAC, etc.) indicates that the approach yields a stable and repeatable baseline. It also implies that the changes produced by brief exposures to these agents is indeed completely reversible.

In summary, this study confirms that there are major differences in the cerebrovascular and metabolic effects of halothane and isoflurane and suggests that the latter may be a more reasonable choice in some neurosurgical settings. Nevertheless, the simple fact that isoflurane produced consistent, dose-related increases in ICP (in spite of the minimal changes in CBF) indicates that it should be used with caution in situations where intracranial compliance is compromised (although other studies suggest that such ICP changes can be blunted by hyperventilation.[27,28]) However, the profound CMR_{O_2} reductions do suggest that it may have some "protective" value in situations of cerebral ischemia/hypoxia. In fact, the patterns of EEG suppression and CMR_{O_2} reduction produced by isoflurane are very much like those seen with the barbiturates,[20] and Newberg *et al.* have shown improved maintenance of metabolic parameters during hypoxia and profound hypotension under isoflurane anesthesia.[29] Therefore, while added work is clearly needed, all of these findings suggest that isoflurane may come to play a large role in future neuroanesthetic practice.

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