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Isoflurane, Halothane, and Regional Cerebral Blood Flow at Various Levels of Pa_{CO_2} in Rabbits

Mark S. Scheller, M.D., Michael M. Todd, M.D.,† John C. Drummond., M.D.‡*

The effects of halothane and isoflurane on regional cerebral blood flow (CBF) were studied in 18 New Zealand White rabbits anesthetized with nitrous oxide (N_2O) and morphine sulfate (MS) at three different levels of Pa_{CO_2}. CBF was measured using the hydrogen clearance technique. Monitored variables were intracranial pressure (ICP), central venous pressure, heart rate, mean arterial pressure, electroencephalogram, arterial blood gases, end-tidal (ET) volatile anesthetic, and ET CO_2. Addition of 1 MAC halothane to the N_2O/MS background anesthetic caused flow to increase significantly in all three regions studied (cortex, dorsal hippocampus, white matter) at all three levels of Pa_{CO_2} (low: 20–25 mmHg; normal: 35–40 mmHg; high: 50–55 mmHg). Addition of 1 MAC isoflurane to the background anesthetic caused CBF to decrease significantly in all regions during hypocapnia. During normocapnia, CBF was unchanged with the addition of 1 MAC isoflurane in all regions and during hypercapnia, CBF increased significantly only in the dorsal hippocampus following addition of 1 MAC isoflurane to the MS/N_2O background anesthetic. Volatile anesthetic administration was associated with significant, although small, increases in ICP at all Pa_{CO_2} levels. We conclude that 1 MAC concentrations of halothane and isoflurane have opposite effects on CBF when added to a N_2O/MS anesthetic during hypocapnia and that the effects of isoflurane on regional CBF are dependent on Pa_{CO_2} in rabbits under the anesthetic conditions of this experiment. (Key words: Anesthetics, volatile: halothane; isoflurane. Brain: blood flow; CO_2 response. Carbon dioxide: hypercarbia; hypocarbia.)

ISOFLURANE AND HALOTHANE are known cerebral vasodilators, and their administration can cause potentially dangerous increases in cerebral blood flow (CBF), cerebral blood volume (CBV) and hence intracranial pressure (ICP) in some neurosurgical patients.[1,2] However, data indicate that these changes can be modified by manipulation of Pa_{CO_2}[2,3] and that such manipulation may lead to differing responses depending on the selected agent. For example, studies by Adams *et al.* in humans have indicated that hyperventilation *prior* to halothane administration was required to attenuate the increases in lumbar cerebrospinal fluid pressure (CSFP) caused by halothane. By contrast, *simultaneous* hyperventilation was adequate to offset the CSFP effects of isoflurane.[2,3] Recently, Drummond *et al.* found that both halothane and isoflurane (both agents administered in the presence of 75% N_2O) steepened the slope of the CBF/Pa_{CO_2} response curve compared with controls (N_2O analgesia alone), with halothane shifting the curve to higher CBF values than isoflurane.[4] Furthermore, they also observed that CBF was lower during hypocapnia in animals anesthetized with isoflurane (+75% N_2O) than in N_2O-sedated control animals.

These various observations suggest that Pa_{CO_2} may play an important role in determining both the qualitative and quantitative cerebrovascular responses to administration of these agents. However, a direct comparison of the effects of these agents on CBF under conditions of altered Pa_{CO_2} has not been done. Therefore, to better define the role of Pa_{CO_2} in determining the cerebrovascular effects of halothane and isoflurane, we have undertaken the following study.

Materials and Methods

New Zealand White rabbits (n = 18) weighing 2.95 ± .21 kg were anesthetized in a plastic box using 4% halothane in oxygen. After endotracheal intubation, halothane was discontinued and morphine sulfate (MS) 10 mg/kg and pancuronium 1 mg were given intravenously followed by an infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ MS and 1 mg/h pancuronium. The animals were placed in the sphinx position with the head fixed in a stereotactic head frame (interaural line 12 cm above the surface of the table). Ventilation was controlled with 70% N_2O in oxygen at a rate of 30 breaths/min and tidal volume of 17 ml/kg. Pa_{CO_2} was adjusted by adding CO_2 to the inspired mixture and all surgical preparation was carried out with the animal normocapnic after local infiltration of 0.25% bupivicaine. Catheters were placed through the left groin into femoral vessels for the measurement of arterial pressure and central venous pressure (CVP). Burr holes 2 mm in diameter were drilled in the right and left parietal areas and right frontal area with care taken not to damage the dura or underlying brain. The posterior musculature of the neck was separated in the midline and a 21-g needle was placed in the cisterna magna for the measurement of ICP. A drop of cyanoacrylate cement was used to seal the dura. Three platinum needle electrodes measuring 0.3 mm in diameter (Grass Instrument Company) were then stereotactically placed into cortical grey matter, dorsal hippocampus, and white matter through the burr holes (see appendix). The deep electrodes (dorsal hippocampus and white matter) were coated with nylon containing nail polish (Hard As Nails®) except for 1 mm at the tip. A

* Neuroanesthesia Research Fellow.
† Assistant Professor of Anesthesiology.
‡ Assistant Clinical Professor of Anesthesiology.
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Address reprint requests to Dr. Scheller.

Ag–AgCl reference electrode was placed in the musculature of the midback.

Monitored variables were mean arterial pressure (MAP), heart rate (HR), CVP, ICP, end tidal (ET) volatile anesthetic (measured at the distal end of the endotracheal tube), ET CO_2, and a single lead, bipolar electroencephalogram (EEG) (recorded using fronto–occipital needle electrodes implanted in extracranial tissue). Both ET CO_2 and ET volatile anesthetic were measured using infrared analyzers (Beckman LB-II®). Esophageal temperature was kept at 37° C with a servocontrolled heat lamp and heating pad. Normal saline was infused intravenously at 5 $ml \cdot kg^{-1} \cdot h^{-1}$ to replace estimated evaporative and third-space losses. CBF was determined using the hydrogen clearance technique.[5] Hydrogen gas (3% inspired) was administered until the tissues were saturated as evidenced by steady-state platinum electrode potentials. Hydrogen was then discontinued, and washout curves were recorded. CBF was calculated using the T ½ method[6] after discarding the first 36 s of each wash-out curve, a time sufficient to insure that arterial hydrogen content was less than 5% of saturated levels (determined by prior, unpublished work in this laboratory).

After the surgical preparation was complete, the animals were left undisturbed at normocapnia for 1 h before any measurements were made. This insured that ET halothane concentration was less than 0.08% prior to any measurements. Animals were then assigned, on an alternating basis, to receive either halothane (n = 9) or isoflurane (n = 9) (one volatile anesthetic per animal). Pa_{CO_2} was next adjusted to one of three levels: low (20–25 mmHg); normal (35–40 mmHg); or high (50–55 mmHg). Control (N_2O/MS) CBF determinations were made after target Pa_{CO_2} had been maintained for at least 10 min. After control (N_2O/MS) measurements were completed, the selected volatile anesthetic was introduced cautiously over a 15-min wash-in period and maintained at 1 MAC§ ET concentration for 10 min before measurements were repeated. Angiotensin II (Sigma, human form) was infused intravenously to maintain MAP at control levels during volatile anesthetic administration. After CBF measurements were completed at a given Pa_{CO_2} level, volatile anesthetic administration was discontinued, and the animal was returned to normocapnia until the ET volatile anesthetic concentration was less than 0.08% before proceeding to the next Pa_{CO_2} level. In this manner, the CBF response to volatile anesthetic administration was determined at all three levels of Pa_{CO_2}. Both the halothane and isoflurane groups contained equal numbers of the six possible sequences in which the Pa_{CO_2} levels could be ordered (*e.g.*, low–normal–high, high–low–normal, etc.).

On completion of the experiment, 3 ml of 3% Evan's Blue dye was injected intravenously. The distal (relative to the animal) ends of the implanted electrodes were then touched with a thermocoagulating current for 2 s. After waiting 10 min, animals were killed with KCl and the brains were removed and placed in formalin. At a later date, brains were dissected, and electrode tip placement was verified by observing Evan's Blue dye in the appropriate brain structures.

Statistical Analyses

Cardiovascular variables, arterial blood gases, and ICP were compared within each group at each level of Pa_{CO_2} before and after the addition of either halothane or isoflurane with *t* tests for paired data. Arterial blood gases and MAP, which were held constant during the period of volatile anesthetic administration, were compared at each level of Pa_{CO_2} between groups with unpaired *t* tests. Because the only variables that changed significantly within groups following volatile anesthetic administration were ICP and CVP, the magnitude of the changes in CVP and ICP induced by volatile anesthetic administration was compared between groups with unpaired *t* tests at each level of Pa_{CO_2}. Angiotensin II doses necessary to maintain MAP at prevolatile anesthetic values between groups at each level of Pa_{CO_2} were similarly evaluated.

CBF

Differences between mean regional CBF changes associated with administration of the two anesthetics were examined using the BMDP Statistical Software Package (1983) program 4V.[8] A repeated measures design for one grouping factor (anesthetic) and one within factor (CO_2) was used. Additional tests between mean regional CBF changes between groups were done at each level of Pa_{CO_2} using the same program.[9] Differences in initial CBF for each area of the brain at each level of Pa_{CO_2} between groups were compared using a Student's *t* test. For each level of Pa_{CO_2}, within each anesthetic group and for each area of the brain, confidence limits around the mean changes in regional CBF were calculated using the Bonferroni correction for multiple comparisons. Confidence intervals that did not include zero indicated that after the administration of the volatile anesthetic, CBF decreased significantly ($P < 0.05$) if the mean change was negative and increased significantly if the mean change was positive.

Results

Eighteen rabbits were studied, nine with each volatile anesthetic. There were no intergroup differences in either

§ MAC for both halothane and isoflurane had been previously determined for the rabbit in this laboratory according to the method of Eger *et al.*[7] Halothane and isoflurane MAC values in the rabbit are 1.4% and 2.05%, respectively.

TABLE 1. Measured Variables

		Hypocapnia		Normocapnia		Hypercapnia	
		Control	Volatile Anesthetic Agent	Control	Volatile Anesthetic Agent	Control	Volatile Anesthetic Agent
MAP (mmHg)	H	93 ± 13	91 ± 11	95 ± 12	90 ± 12	91 ± 14	89 ± 10
	I	84 ± 11	86 ± 11	88 ± 8	87 ± 8	87 ± 10	87 ± 10
ICP (mmHg)	H	.6 ± 1.1	1.7 ± 1.3*	1.5 ± .5	2.6 ± 1.0*	2.3 ± 7	4.6 ± .9*
	I	.6 ± 2.2	1.4 ± 1.7*	1.7 ± 1.7	3.3 ± 1.8*	1.9 ± 2.3	4.6 ± 2.8*
CVP (mmHg)	H	1.1 ± 1.1	3.6 ± 2.1*†	1.3 ± .9	4.1 ± 1.4*†	1.7 ± 1.3	4.7 ± 2.0*†
	I	1.5 ± .9	2.1 ± .8*	1.8 ± .5	2.4 ± 1.0*	2.2 ± .9	3.0 ± .7*
HR (beats/min)	H	227 ± 28	214 ± 21	225 ± 19	235 ± 24	207 ± 24	225 ± 21
	I	219 ± 37	217 ± 31	199 ± 33	201 ± 26	200 ± 35	193 ± 25
Pa_{CO_2} (mmHg)	H	22 ± 1.5	21 ± 1.5	37 ± 1.5	37 ± 2	51 ± 1.5	52 ± 1.5
	I	22 ± 1.5	21 ± 1.5	37 ± 1.5	37 ± 2	51 ± 1.5	53 ± 1.5
Pa_{O_2} (mmHg)	H	98 ± 18	101 ± 18	100 ± 15	100 ± 16	105 ± 16	97 ± 18
	I	107 ± 16	107 ± 17	109 ± 20	106 ± 19	107 ± 18	110 ± 19
*p*H	H	7.52 ± .06	7.54 ± .05	7.38 ± .03	7.38 ± .03	7.23 ± .03	7.23 ± .03
	I	7.56 ± .05	7.57 ± .05	7.40 ± .03	7.40 ± .03	7.25 ± .03	7.25 ± .04
Angiotensin II ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	H	.75 ± .36		.81 ± .32		.78 ± .29	
	I	.36 ± .2		.38 ± .40		.51 ± .30	

All data expressed as mean ± SD.

MAP = mean arterial pressure; ICP = intracranial pressure; CVP = central venous pressure; HR = heart rate; H = halothane; I = isoflurane.

* Significant difference within a group at a given Pa_{CO_2} level ($P < 0.05$).

† Magnitude of increase significantly greater following addition of halothane at a given Pa_{CO_2} level.

weight or sex ratio. Arterial *p*H, Pa_{CO_2}, Pa_{O_2}, MAP, and HR were similar between groups at given Pa_{CO_2} levels, both before and after the addition of the volatile anesthetic (table 1). CVP and ICP were also similar between groups at each Pa_{CO_2} level before adding the volatile anesthetic, but both CVP and ICP increased significantly with the administration of the volatile anesthetic at all levels of Pa_{CO_2}. The magnitude of the increase in CVP with halothane was greater than with isoflurane at all Pa_{CO_2} levels. However, the magnitudes of the ICP increases were not different between the groups.

CBF Changes

CBF data from one cortical electrode in both the halothane and isoflurane groups were discarded because the hydrogen clearance curves could not be adequately interpreted. One electrode intended for white matter in the isoflurane group was found to be in grey matter at autopsy, and data from this electrode were also discarded. There were no intergroup differences in control CBF (N_2O/MS) in any of the three brain regions at any Pa_{CO_2} level.

After the addition of 1 MAC halothane to the N_2O/MS anesthetic, CBF increased significantly in all brain areas at all three Pa_{CO_2} levels. By contrast, the addition of 1 MAC isoflurane to the N_2O/MS anesthetic during hypocapnia decreased CBF in all areas (table 2). During normocapnia, blood flow did not change in any region after the addition of 1 MAC isoflurane, and when isoflurane was administered during hypercapnia, blood flow increased significantly only in the dorsal hippocampus but was unchanged in the cortex and white matter (fig. 1).

EEG Changes—Angiotensin II

With halothane, there was generalized slowing of the EEG and increase in amplitude compared with the control state. However, all of the animals given 1 MAC isoflurane demonstrated a deep-burst suppression pattern. Bursts of electrical activity could be elicited with handclapping or other noise at this anesthetic depth (fig. 2).

The mean doses of angiotensin II required to support MAP at control levels in the halothane and isoflurane groups at the various Pa_{CO_2} levels are listed in table 1. Although generally more angiotensin II was required in the halothane anesthetized animals, these differences did not achieve statistical significance at any Pa_{CO_2} level.

Discussion

Our results indicate that during hypocapnia, 1 MAC isoflurane *decreases* CBF when added to a N_2O/MS anesthetic. This effect was seen in three separate areas of the brain, *i.e.*, cerebral cortex, white matter, and dorsal

TABLE 2. Regional Cerebral Blood Flow (ml · 100 g^{-1} · min^{-1}).

	(n)		Hypocapnia		Normocapnia		Hypercapnia	
			Control	Volatile Anesthetic Agent	Control	Volatile Anesthetic Agent	Control	Volatile Anesthetic Agent
Cortex	(8)	H	59 ± 26	97 ± 51*	84 ± 33	139 ± 94*	112 ± 56	171 ± 78*
	(8)	I	56 ± 25	32 ± 14*	77 ± 32	62 ± 27	87 ± 23	73 ± 22
White matter	(9)	H	18 ± 7	28 ± 13*	25 ± 7	43 ± 16*	41 ± 16	70 ± 35*
	(8)	I	21 ± 7	13 ± 4*	25 ± 6	23 ± 7	34 ± 9	46 ± 24
Dorsal hippocampus	(9)	H	15 ± 5	29 ± 12*	21 ± 8	45 ± 18*	29 ± 7	71 ± 9*
	(9)	I	19 ± 6	12 ± 3*	24 ± 11	24 ± 15	28 ± 10	50 ± 23*

H = halothane; I = isoflurane. All data expressed as mean ± SD.
* Significant difference between control blood flow (N_2O/MS) and blood flow after addition of 1 MAC volatile anesthetic at a given Pa_{CO_2} level ($P < 0.05$). Control flows (N_2O/MS) at a given Pa_{CO_2} were not different in the H and I groups in any brain region at any Pa_{CO_2} level.

hippocampus, and thus appears widespread throughout the brain. During normocapnia, the addition of 1 MAC isoflurane to the N_2O/MS did not significantly change CBF in any of the three regions studied, and introduction of 1 MAC isoflurane during hypercapnia was associated with significant regional flow increases in the dorsal hippocampus only, suggesting a relative redistribution of flow to deeper structures. By contrast, the addition of 1 MAC halothane to the N_2O/MS anesthetic increased CBF significantly in all regions at all Pa_{CO_2} levels.

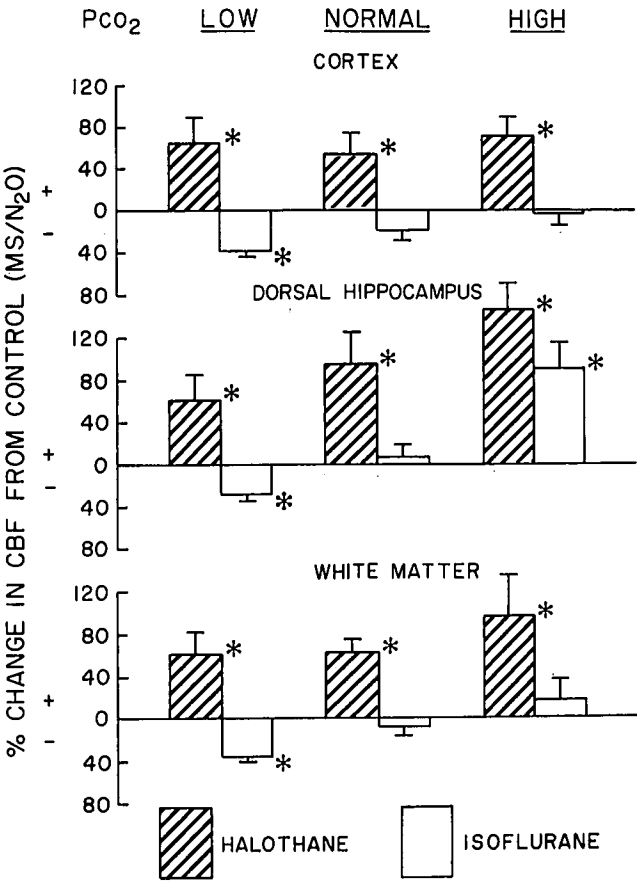

FIG. 1. Per cent change in regional CBF. * denotes significant change in regional CBF following addition of 1 MAC volatile anesthetic to the MS/N_2O background anesthetic.

Like others, we have found that halothane increases CBF during both normocapnia and hypercapnia.[10,11] However, our results indicate that halothane is a more potent vasodilator during hypocapnia than has been reported by others. For example, Alexander *et al.* reported that CBF in halothane-anesthetized volunteers during hypocapnia was not different than had been previously reported in unanesthetized, hypocapnic humans.[12] Likewise, Drummond *et al.* observed that CBF in cats anesthetized with halothane and N_2O was equivalent to that seen in N_2O-sedated animals during hypocapnia.[4] Thus, it is possible there are some inter-species differences with respect to the effects of halothane on CBF during hypocapnia. However, in both of these studies MAP was not supported at control levels. Thus, lower mean blood pressures, perhaps coupled with the known impairment of autoregulation by halothane[13,14,15] may have resulted in CBF values lower than those that might have been observed had MAP been maintained at control levels as was done in the present study.

We were not able to demonstrate changes in CBF in any brain region during normocapnia in our isoflurane-anesthetized animals. This is consistent with the findings of Todd and Drummond, who also found no CBF increases with 1.0 MAC isoflurane during normocapnia in cats.[13] Also, Murphy *et al.*¶ reported no significant CBF increases in humans during 1.1 MAC isoflurane anesthesia during normocapnia, although flow increased significantly at higher concentrations of isoflurane. These human data

¶ Murphy FL, Kennell EM, Johnstone RE, Lief PL, Jobes DR, Tompkins BM, Gutsche BB, Behar MG, Wollman H: 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 61–62.

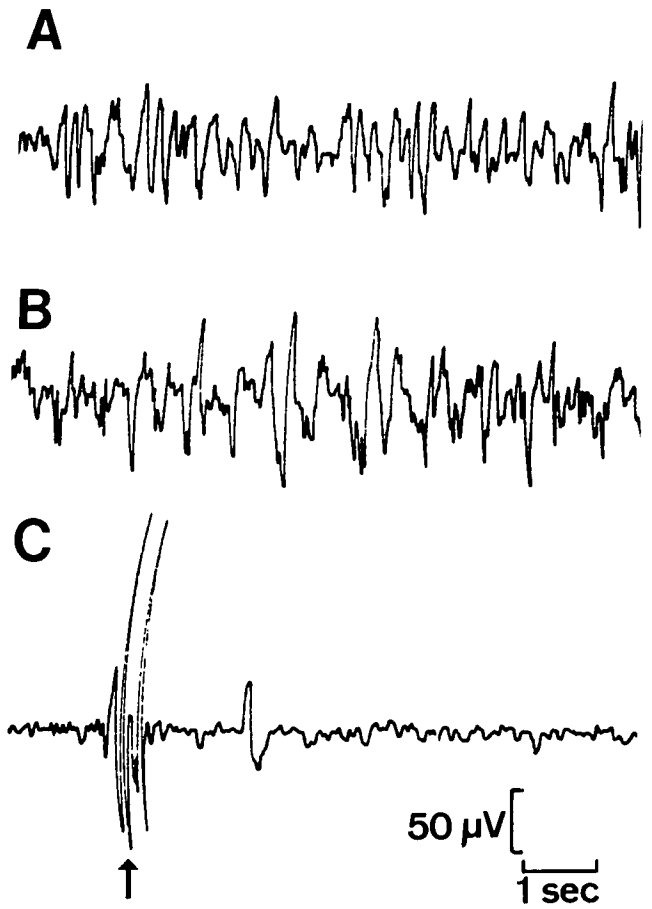

FIG. 2. Typical EEG recordings during the various anesthetic states. (*A*) Background MS/N_2O. (*B*) 1 MAC halothane added to MS/N_2O background. (*C*) 1 MAC isoflurane added to MS/N_2O background. *Arrow* indicates EEG response to handclap.

agree with those reported from experiments in dogs where CBF increases were found with the administration of nearly 2 MAC ET isoflurane, but not with lower doses.[16] Thus, data from the present study are consistent with findings of different investigators using a variety of animal and human models with regard to the effects of isoflurane on CBF during normocapnia. With regard to the decrease in CBF noted during hypocapnia with the addition of isoflurane in the present study, it is consistent with the findings of Drummond *et al.*, who observed lower CBF in cats anesthetized with isoflurane (in the presence of 75% N_2O) than in N_2O-sedated animals.[4]

A number of methodologic considerations merit comment. In particular, in experiments such as these, the choice of background anesthesia is of critical importance. Ideally, the background anesthetic should have minimal effects on cerebral metabolic rate for oxygen (CMR_{O_2}) and the cerebral vasculature, but still insure the animal is adequately anesthetized and unstressed. The N_2O/MS background anesthetic used here undoubtedly resulted in some cerebrovascular and cerebral metabolic changes from the awake state. However, without measuring CBF and CMR_{O_2} in the unstressed, awake animal and comparing the measurements with those obtained during the background anesthetic, it is not possible to know to what degree cerebral metabolism or blood flow has been altered. We chose a N_2O/MS background primarily because we felt it clinically relevant to the way we administer volatile anesthetics during neurosurgical procedures, that is, adding the volatile anesthetic to a narcotic-based N_2O anesthetic to control depth or blood pressure. The dose of MS that we used was determined by preliminary studies of awake animals given various bolus doses of MS. Animals given 10 mg/kg MS intravenously as a bolus injection would not attempt to right themselves when placed on their sides and would tolerate a tail clamp with no sign of discomfort. We found that a subsequent infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ (in the presence of 70% N_2O) yielded stable CBF determinations over time with excellent cardiovascular stability. We chose to paralyze the animals to remove any variability in ventilation parameters that might be caused by chest-wall rigidity or attempted spontaneous respiration, especially during hypercapnia.

Lastly, angiotensin II was used to control blood pressure during administration of the volatile anesthetic. Angiotensin II is thought to have little or no effect on the cerebral vasculature when administered intravenously,[17] although infusions of high concentrations directly into the carotid artery have been associated with generalized cerebral vasoconstriction in rabbits.[18] Because generally more angiotensin II was required in the halothane animals than in the isoflurane animals, any bias introduced by angiotensin II would have been in the direction of lower observed flows in the halothane animals compared with the isoflurane animals. Therefore, the differences we observed between halothane and isoflurane might have been more pronounced had there been a way to eliminate the direct cerebrovascular effects of angiotensin II.

CVP and ICP increased significantly in both groups at all Pa_{CO_2} levels after the addition of the volatile anesthetic. ICP increases with the addition of halothane would be expected since CBF increased, and this is generally associated with an increase in CBV.[19] However, because blood flow decreased significantly in all regions in the isoflurane group during hypocapnia, it is surprising that ICP still increased. Increases in the size of the cerebrospinal fluid (CSF) compartment or the nonvascular volume of brain tissue can also cause an elevation of ICP, but the time course of the change was too short to be explained by either one of these mechanisms. It is possible that the increases in CVP that occurred in both the halothane and isoflurane animals resulted in elevated jugular venous pressure and thus increases in cerebral venous blood volume and hence ICP. However, if this were the case, we might have expected to see higher ICPs in the halothane group (which we did not) because the magnitude of the

CVP increases was significantly greater in those animals compared with the isoflurane animals. Todd and Drummond also noted equivalent ICP increases in cats given halothane or isoflurane, despite differences in the effects of the two anesthetics on global CBF in their animals during normocapnia, although they did not report changes in CVP.[13] Thus, it is possible that the increases in CBV that are known to occur with both halothane and isoflurane[20,21] are independent of the effects of these agents on CBF. Future studies, simultaneously examining the effects of these agents on CBV and CBF during hypocapnia, would help to clarify this issue. The increases in CVP following the addition of the volatile anesthetic may be explained by a combination of the direct myocardial depressant effects of the volatile anesthetics as well as the recognized action of angiotensin II to increase preload, probably as a result of redistribution of blood from splanchnic beds to the central circulation.[22] This property of angiotensin II may explain why greater increases in CVP were seen following the addition of halothane than with isoflurane, because generally more angiotensin was required to maintain MAP at prevolatile anesthetic levels in animals given halothane compared with those receiving isoflurane.

We can only speculate as to why halothane and isoflurane resulted in such disparate effects on CBF during hypocapnia. Although we did not measure CMR_{O_2}, it is likely that CMR_{O_2} was decreased more with isoflurane than with halothane because this has been shown to occur in other species when these agents are administered in equi-MAC concentrations.[13] Furthermore, the EEGs of the isoflurane-anesthetized animals demonstrated a deep-burst suppression pattern, while those of the halothane-anesthetized group remained active, also suggesting greater metabolic depression with isoflurane (see fig. 2). In normal brain, CBF and CMR_{O_2} are coupled such that decreases in CMR_{O_2} lead to decreases in CBF. To what degree coupling remains intact during administration of the volatile anesthetics has not been defined. However, in a study by Kuramoto *et al.*, which examined CBF/CMR_{O_2} responses in dogs, it was demonstrated that coupling remained intact during 1 MAC halothane administration.[23] Therefore, if a volatile anesthetic had no direct vasodilating properties, one might observe a reduction in CBF due solely to reduction of CMR_{O_2} with administration of the volatile anesthetic. Similarly, coupled vasoconstriction might be expected to attenuate the intrinsic vasodilating properties of these volatile anesthetics. This may explain why isoflurane does not appear to be as potent a vasodilator as halothane during normocapnia, because its greater degree of metabolically mediated flow reduction may counteract its intrinsic vasodilating properties. The vasoconstriction caused by hypocapnia would be expected to attenuate the inherent vasodilating properties of volatile anesthetics (without affecting CMR_{O_2}) such that CBF changes during hypocapnia would depend more on the CMR_{O_2}-reducing effects of the agents. In the present study then, a greater degree of metabolic depression with isoflurane compared with halothane may explain the reduction of CBF observed during hypocapnia with isoflurane administration. Halothane is clearly a more potent vasodilator than isoflurane in our model, although whether this is due to its intrinsic vasodilating properties or simply its lesser degree of CMR_{O_2}-reducing ability at equi-MAC doses cannot be deduced from these data.

In summary, 1 MAC halothane and isoflurane were observed to have opposite effects on CBF when added to a N_2O/MS anesthetic during hypocapnia in rabbits, with isoflurane decreasing CBF and halothane increasing CBF. The addition of 1 MAC halothane to the N_2O/MS anesthetic under conditions of normocapnia and hypercapnia increased CBF in all brain regions studied, whereas the addition of isoflurane increased flow only during hypercapnia and only in the dorsal hippocampus. Despite these differences in effects on CBF, both anesthetics caused small but significant increases in ICP at all Pa_{CO_2} levels studied.

If these data are relevant to the practice of human anesthesia, they suggest that the addition of isoflurane to a N_2O/MS anesthetic may be preferable to the addition of halothane in situations where increases in CBF are to be avoided but where a volatile anesthetic is deemed desirable. This lends support to the growing body of evidence that many characteristics of isoflurane make it theoretically more suitable for use in neurosurgical patients than halothane. However, these results may apply only to the background anesthetic state studied here and the concentrations of volatile anesthetics used. Cerebrovascular responses to other concentrations of volatile anesthetics or during other background anesthetics may be different than those observed in the present study. Furthermore, these studies were performed in animals with normal intracranial compliance and may not necessarily reflect the responses that would occur in the presence of compromised intracranial compliance or an abnormal brain. Also, similar ICP increases occurred in both the halothane and isoflurane groups during hypocapnia, despite flow changes in opposite directions. Thus, while our findings regarding the CBF effects of isoflurane might suggest that it may be more appropriate than halothane for use in circumstances of impaired intracranial compliance, the apparently paradoxical ICP effects we observed during hypocapnia remain unexplained. These ICP effects warrant both further study and continued caution in the clinical use of isoflurane in neuroanesthetic practice.

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Appendix

Placement of Electrodes

We chose three representative areas of the brain for electrode placement. Parietal cortex (cortical), dorsal hippocampus (deep grey), and subcortical white matter (white matter). Stereotactic coordinates for these electrodes were as follows (measurements made from the inion and sagittal suture and after contact with the dura): cortical—15 mm anterior, 7 mm lateral, and 1.5 mm deep; dorsal hippocampus—15 mm anterior, 4 mm lateral, and 4 mm deep; white matter—22 mm anterior, 6 mm lateral, and 3.5 mm deep. These coordinates have been modified slightly from those found in a standard stereotactic atlas[24] because we used smaller animals than those for which the atlas was written.

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