Anesthesiology
65:462–467, 1986

A Comparison of the Direct Cerebral Vasodilating Potencies of Halothane and Isoflurane in the New Zealand White Rabbit

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

Halothane is commonly viewed as a more potent cerebral vasodilator than isoflurane. It was speculated that the lesser vasodilation caused by isoflurane might be the result of the greater reduction in cerebral metabolic rate (CMR) that it causes, and that the relative vasodilating potencies of halothane and isoflurane would be similar if the two agents were administered in a situation that precluded volatile-agent–induced depression of CMR. To test this hypothesis, cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMR_{O_2}) were measured in two groups of rabbits before and after the administration of 0.75 MAC halothane or isoflurane. One group received a background anesthetic of morphine and N_2O, which resulted in an initial CMR_{O_2} of 3.21 ± 0.17 (SEM) ml · 100 g^{-1} · min^{-1}; second group received a background anesthetic of high-dose pentobarbital, which resulted in an initial CMR_{O_2} of 1.76 ± 0.16 ml · 100 g^{-1} · min^{-1}. In rabbits receiving a background of morphine sulfate/N_2O, halothane resulted in a significantly greater CBF (65 ± 10 ml · 100 g^{-1} · min^{-1}) than did isoflurane (40 ± 5 ml · 100 g^{-1} · min^{-1}). Both agents caused a reduction in CMR_{O_2}, but CMR_{O_2} was significantly less during isoflurane administration. By contrast, with a background of pentobarbital anesthesia, CBF increased by significant and similar amounts with both halothane and isoflurane. With halothane, CBF increased from 22 ± 2 ml · 100 g^{-1} · min^{-1} in the control state to 39 ± 3, and with isoflurane from 24 ± 2 to 38 ± 2 ml · 100 g^{-1} · min^{-1}. CMR_{O_2} was not depressed further by either halothane or isoflurane. These results suggest that the relative effects of halothane and isoflurane on CBF are dependent on the CMR present prior to their administration. When the preexistent CMR is not markedly depressed, isoflurane decreases CMR and causes less cerebral vasodilation than does halothane. When initial CMR is depressed, halothane and isoflurane have similar vasodilating potencies. (Key words: Anesthetics, volatile: halothane; isoflurane. Brain: blood flow; metabolism; oxygen consumption.)

In several species,[1–6] halothane has been shown to cause greater increases in cerebral blood flow (CBF) than isoflurane and, accordingly, halothane is widely viewed as the more potent cerebral vasodilator. Isoflurane, however, has been shown to cause a more marked depression of the cerebral metabolic rate for oxygen (CMR_{O_2}).[1,2,6] The authors speculated that the metabolic differences between halothane and isoflurane might explain the differing effects of these two agents on CBF. We reasoned that the change in CBF caused by a volatile agent might represent the interaction of at least two separate but simultaneous effects: 1) a direct effect on cerebral vascular smooth muscle resulting in relaxation (intrinsic vasodilation); and 2) a "coupled" vasoconstrictive effect occurring as a result of the reduction in cerebral metabolic rate (CMR) caused by the volatile agent. Given a constant arterial carbon dioxide tension and mean arterial pressure (MAP), the change in CBF caused by a volatile agent would be determined by the summation of these two influences. We speculated that the intrinsic effects of the two volatile agents might in fact be quite similar, and that the differences in the CBF effects of halothane and isoflurane might be explained by the greater reduction in CMR_{O_2} caused by isoflurane. If true, this leads to a prediction regarding the CBF effects of halothane and isoflurane: If the effects of both halothane and isoflurane on CMR could be reduced or eliminated, then the vasodilating potency of isoflurane would be similar to that of halothane. To test this hypothesis, the effects of halothane and isoflurane on CBF were compared in two groups of New Zealand white rabbits. The animals received one of two different background anesthetics. One regimen provided a greater background CMR_{O_2}, and the other markedly decreased the background CMR_{O_2}. The rationale was that in the second group, the antecedent suppression of CMR_{O_2} caused by the barbituate might prevent or at least attenuate volatile anesthetic-induced metabolic suppression (and the associated "coupled" vasoconstriction) and thereby unmask for direct comparison the intrinsic vasodilating effects of the two agents.

Methods

Twenty-four New Zealand white rabbits of either sex, weighing 3.1 ± 0.2 (SD) kg, and approximately 6 months of age, were studied. Each animal received one of two maintenance anesthetic regimens. Group 1 animals (n = 12) received morphine sulphate and nitrous oxide, and Group 2 animals (n = 12) received pentobarbital. Within each group, six animals received halothane and six received isoflurane.

In both groups, animals were placed in a plexiglass box and anesthesia was induced with 4% halothane in oxygen. The animals were intubated, paralyzed with pancuronium (2 mg, iv) and mechanically ventilated (tidal volume = 15 ml · kg^{-1}; rate = 20 breaths/min). Carbon dioxide was

* Assistant Clinical Professor of Anesthesiology.
† Associate Professor of Anesthesiology.
‡ Assistant Professor of Anesthesiology.
§ Professor of Anesthesiology and Neurosurgery.

Received from the Department of Anesthesiology (Neuroanesthesia Research), University of California at San Diego, La Jolla, California. Accepted for publication June 4, 1986. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1984. Dr. Drummond was a Parker B. Francis Investigator in Anesthesiology.

Address reprint requests to Dr. Drummond: Neuroanesthesia Research, M-029, University of California at San Diego, La Jolla, California 92093.

added to the inspired gas mixture to maintain normocapnia (Pa_{CO_2} 38–42 mmHg) throughout the study. Anesthesia was initially maintained with 1.25–1.5% halothane and 60% nitrous oxide in oxygen. Immediately after placement of aortic and right atrial catheters *via* femoral vessels, the administration of the background intravenous anesthetic agent began. One group received morphine sulphate 10 $mg \cdot kg^{-1}$ as a slow intravenous injection over 2–3 min, followed by 2 $mg \cdot kg^{-1} \cdot h^{-1}$ as a continuous infusion. Halothane was discontinued at the beginning of morphine administration, and the animals continued to breathe 60% N_2O and 40% O_2. During the subsequent volatile anesthetic, phenylephrine was infused as needed to maintain MAP within 10 mmHg of the control (prevolatile agent) level. A second group received an intravenous loading dose, 60 $mg \cdot kg^{-1}$ of pentobarbital. As pentobarbital administration began, halothane and nitrous oxide were discontinued and the latter was replaced with 60% nitrogen. The loading dose was completed over a period of 30–45 min and at its conclusion an infusion of pentobarbital was begun at 45 $mg \cdot kg^{-1} \cdot h^{-1}$. A single fronto–occipital channel of surface EEG was monitored continuously. Throughout the study, phenylephrine was infused as needed to maintain MAP within 10 mmHg of the prevolatile agent value and/or to maintain an MAP greater than or equal to 65 mmHg. Both groups received a maintenance infusion of lactated Ringer's solution at 6 $ml \cdot kg^{-1} \cdot h^{-1}$.

In all animals, the cranial portion of the preparation began simultaneously with the placement of the vascular catheters. The dura was exposed in the midline between the occiput and the first cervical vertebra and a 19-gauge needle was passed through the atlanto–occipital membrane into the cisterna magna to permit recording of intracranial pressure (ICP). A limited craniectomy was performed over the confluence of the cerebral venous sinuses and a 23-gauge needle was placed nonocclusively in the latter structure to permit sampling of cerebral venous blood. The skull surface was exposed and platinum-alloy needle electrodes (diameter 250 μm) were positioned stereotactically *via* 3 mm burr holes in frontal and parietal cortex and in the left dorsal hippocampus. The cortical electrodes were inserted to a depth of 2 mm beyond initial dural contact. The dorsal hippocampal electrode was nylon coated with the distal 1 mm exposed. It was positioned according to previously established coordinates,[7] which have been verified in this laboratory.[8] A silver–silver chloride reference electrode was placed subcutaneously over the midback. Esophageal temperature was controlled to 37.5° C with a heat lamp and a warming blanket. Blood pressure and ICP (both referenced to head level) were recorded continuously. The ECG and pan-tidal carbon dioxide and volatile agent concentrations (Beckman LB-II® infrared analyzers) were monitored continuously.

CBF was determined intermittently using the hydrogen clearance technique.[9–11] Following tissue saturation by breathing 3–5% hydrogen, the hydrogen was omitted from the inspired gas mixture and the current between the platinum and the reference electrodes was recorded during the ensuing "washout." CBF was calculated by the $T_{1/2}$ method.[9] The first 36 s were discarded in order to exclude from analysis that portion of the curve during which arterial hydrogen content was greater than 5% of saturated levels (unpublished data from this laboratory). The CMR_{O_2} was calculated as the product of the arterial–cerebral venous oxygen content difference (Lex-O_2-Con) × CBF. CBF for the purpose of this calculation was the mean of the three individually recorded CBF values (dorsal hippocampus and two cortical). This value is referred to herein as $\overline{CBF}$.

The time course of study was identical for both experimental groups. After surgical preparation, there was a 90-min equilibration period. During and subsequent to this period, noise and contact with the animal were avoided. At the end of the equilibration period, CBF and CMR_{O_2} were determined, and a volatile agent (halothane or isoflurane on an alternating basis) was introduced and increased gradually over 10 min to a 0.75 MAC end-tidal value. The MAC values employed for the rabbit for halothane and isoflurane were 1.38% and 2.05%, respectively.[12] The 0.75 MAC end-tidal value was maintained for 15 min and then a second CBF/CMR_{O_2} determination was performed. In the pentobarbital group, the volatile agent was then omitted and the EEG was observed for an additional 60 min to confirm ongoing isoelectricity. This was done to permit the inference that the pentobarbital levels during the preceding exposure to the volatile agent were sufficient to produce isoelectricity without the influence of the inhaled agent.

Within each group, the data obtained before and during the administration of the volatile anesthetic were compared using Student's *t* test for paired data with the Bonferroni correction for multiple comparisons. Comparisons between groups employed a one-way analysis of variance.§

Results

The data are presented in tables 1 (morphine/N_2O, Group 1) and 2 (pentobarbital, Group 2). There were no statistical differences between the two cortical blood flow measurements (frontal and parietal) in either group and the value presented in tables 1 and 2 as "Cortex" represents the mean of the two values obtained. In all instances, the end-tidal halothane concentration was less

§ BMDP Statistical Software. Los Angeles, Univeristy of California Press, 1983.

TABLE 1. Physiologic Variables in Group 1 Studies

	1	2		3	4		ANOVA	
	Morphine/N_2O	Morphine/N_2O + Halothane	*t* test 1 *vs.* 2	Morphine/N_2O	Morphine N_2O + Isoflurane	*t* test 3 *vs.* 4	1 *vs.* 3	2 *vs.* 4
CBF (ml · 100 g^{-1} · min^{-1})								
Cortex	59 ± 12	74 ± 13	$P < .02$	51 ± 11	41 ± 7	NS	NS	$P < .04$
Dorsal hippocampus	33 ± 4	46 ± 5	$P < .002$	27 ± 3	36 ± 6	NS	NS	NS
$\overline{CBF}$	50 ± 8	65 ± 10	$P < .004$	43 ± 7	40 ± 5	NS	NS	$P < .04$
ICP (mmHg)	2.0 ± 0.2	3.0 ± 0.2	$P < .02$	2.5 ± 0.4	3.5 ± 0.4	$P < .05$	NS	NS
MAP (mmHg)	91 ± 3	84 ± 3	NS	91 ± 2	86 ± 2	$P < .02$	NS	NS
CVR (mmHg · 100 g^{-1} · min^{-1})	1.99 ± 0.28	1.37 ± 0.15	$P < .004$	2.30 ± 0.38	2.18 ± 0.26	NS	NS	$P < .02$
CMR_{O_2} (ml · 100 g^{-1} · min^{-1})	3.31 ± 0.22	2.75 ± 0.22	$P < .001$	3.11 ± 0.27	1.82 ± 0.23	$P < .001$	NS	$P < .001$
P_{O_2} (mmHg)	139 ± 7	142 ± 4	NS	149 ± 9	145 ± 8	NS	NS	NS
P_{CO_2} (mmHg)	40 ± 0.5	40 ± 1	NS	39 ± 1	39 ± 0.5	NS	NS	NS
*p*H	7.41 ± .02	7.38 ± .02	NS	7.39 ± .01	7.37 ± .02	NS	NS	NS
Phenylephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.04 ± .04	2.7 ± .78	$P < .02$	0	2.0 ± .45	$P < .003$	NS	NS

Values are mean ± SEM. n = 6 in all groups. NS = not significant. CBF = cerebral blood flow; $\overline{CBF}$: = See "Methods"; ICP = intracranial pressure; MAP = mean arterial pressure; CVR = cerebral vascular resistance; CMR_{O_2} = cerebral metabolic rate for oxygen.

than or equal to 0.05% prior to performing the control (prevolatile agent) CBF and CMR_{O_2} measurements.

GROUP 1 (MORPHINE/N_2O)

There were no differences between the halothane and isoflurane subgroups at the time of the initial control measurements (columns 1 and 3, table 1) for any of the physiologic variables (CBF, CMR_{O_2}, ICP, cerebral vascular resistance [CVR], arterial blood gases, or phenylephrine dose). With the administration of the volatile anesthetic (columns 2 and 4, table 1), $\overline{CBF}$ increased significantly ($P < 0.004$) in the animals that received halothane but was unchanged in those that received isoflurane. CVR mirrored the $\overline{CBF}$ changes; specifically, CVR decreased significantly in the halothane subgroup and was unchanged with isoflurane. In spite of the differences in the CBF effects of the two volatile agents, ICP increased by similar amounts with both halothane and isoflurane. While these ICP changes were significant ($P < 0.05$), the increases were small (approximately 1 mmHg).

The CMR_{O_2} decreased significantly ($P < 0.001$) with the administration of both halothane and isoflurane. The decrease, however, was larger with isoflurane and the CMR_{O_2} at 0.75 MAC of that agent (1.82 ± 0.23 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) was significantly ($P < 0.001$) less than

TABLE 2. Physiologic Variables in Group 2 Studies

	1	2		3	4		ANOVA	
	Pentobarbital	Pentobarbital + Halothane	*t* test 1 *vs.* 2	Pentobarbital	Pentobarbital + Isoflurane	*t* test 3 *vs.* 4	1 *vs.* 3	2 *vs.* 4
CBF (ml · 100 g^{-1} · min^{-1})								
Cortex	24 ± 3	44 ± 5	$P < 0.006$	26 ± 3	43 ± 3	$P < 0.0008$	NS	NS
Dorsal hippocampus	17 ± 2	30 ± 2	$P < 0.009$	16 ± 2	28 ± 0	$P < 0.004$	NS	NS
CBF	22 ± 2	39 ± 3	$P < 0.002$	22 ± 2	38 ± 2	$P < 0.0004$	NS	NS
ICP (mmHg)	0.5 ± 0.2	2 ± 0.4	$P < 0.007$	0.5 ± 0.2	2 ± 0.2	$P < 0.002$	NS	NS
MAP (mmHg)	70 ± 0.5	71 ± 1	NS	71 ± 2	68 ± 3	NS	NS	NS
CVR (mmHg · 100 g^{-1} · min^{-1})	3.37 ± 0.28	1.91 ± 0.11	$P < 0.006$	3.36 ± 0.44	1.74 ± 0.11	$P < 0.006$	NS	NS
CMR_{O_2} (ml · 100 g^{-1} · min^{-1})	1.76 ± 0.27	1.66 ± 0.14	NS	1.75 ± 0.17	1.47 ± 0.24	NS	NS	NS
P_{O_2} (mmHg)	179 ± 13	185 ± 14	NS	196 ± 19	199 ± 19	NS	NS	NS
P_{CO_2} (mmHg)	39 ± 0.5	40 ± 1	NS	39 ± 1	39 ± 0.5	NS	NS	NS
*p*H	7.37 ± 0.02	7.33 ± 0.02	NS	7.38 ± 0.02	7.38 ± 0.02	NS	NS	NS
Phenylephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	1.07 ± 0.4	2.7 ± 0.3	$P < 0.0007$	1.6 ± 0.5	3.9 ± 0.8	$P < 0.01$	NS	NS

Values are mean ± SEM. n = 6 in all groups. NS = not significant. See table 1 for other abbreviations.

that observed with halothane (2.75 ± 0.22 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$).

There was a trend toward a reduction in MAP in both subgroups, although that decrease was significant ($P < 0.02$) only for isoflurane. None the less, MAP during the administration of the two volatile agents was not different, *i.e.*, halothane 84 ± 3 mmHg and isoflurane 86 ± 2 mmHg. There were no differences in arterial blood gas variables at any study period. The rate of phenylephrine infusion increased in both subgroups during volatile agent administration, but there was no difference between the halothane and isoflurane subgroups.

Group 2 (Pentobarbital)

The dose of pentobarbital employed was sufficient to induce and maintain EEG isoelectricity throughout the period of study in all animals. Again, there were no differences between the control measurements in the halothane and isoflurane subgroups (columns 1 and 3, table 2) for any physiologic variable. With the administration of halothane and isoflurane (columns 2 and 4, table 2), $\overline{CBF}$ increased by significant ($P < 0.002$) and similar amounts in both subgroups. This latter observation is in sharp contrast with the results obtained in those receiving morphine/N_2O, wherein $\overline{CBF}$ increased following halothane administration but was unchanged with isoflurane.

ICP increased by significant ($P < 0.002$) and similar amounts in both subgroups and CVR decreased ($P < 0.006$). The CMR_{O_2} was not significantly altered by the administration of either volatile anesthetic, although there was a trend suggesting a small decrease in CMR_{O_2} during isoflurane administration. MAP, PaO_2, Pa_{CO_2}, and *p*H did not differ at any measurement interval.

Discussion

The intent of the present protocol was to produce, in those receiving pentobarbital, a degree of CMR_{O_2} depression in the control condition that would preclude further significant reduction of CMR_{O_2} by a superimposed volatile anesthetic. That this could be achieved was suggested by studies of the cerebral effects of thiopental[13] and isoflurane.[14] In those studies, it was observed with both anesthetics that CMR_{O_2} reached similar minimum values simultaneously with the occurrence of electrocerebral silence. The administration of additional anesthetic beyond that necessary to produce EEG isoelectricity resulted in no further reduction in CMR_{O_2}. The present protocol employed a moderate pentobarbital "overdose" in Group 2 animals to achieve and maintain EEG isoelectricity with the intent of establishing a similar CMR_{O_2} plateau. The statistical constancy of CMR_{O_2} throughout the pentobarbital (Group 2) studies indicates that a CMR_{O_2} plateau was achieved and that halothane and isoflurane did not, in fact, produce further significant suppression of CMR_{O_2}.

The results obtained in animals that received morphine sulphate and nitrous oxide as a background anesthetic were consistent with previous rabbit studies performed in our laboratories[8] and with numerous other studies[1–6] that have indicated that halothane produces greater increases in CBF than isoflurane. By contrast, in the circumstances of CMR_{O_2} suppression produced by pentobarbital, halothane and isoflurane were equipotent cerebral vasodilators. We suspect that the explanation for the disparity between the CBF effects of isoflurane in the two groups lies with the thesis presented in the introduction, *i.e.*, that, given a constant Pa_{CO_2} and MAP, the cerebral vasodilation caused by a volatile agent is a result of the summation of two separate effects: 1) a direct or intrinsic vasodilating effect (mechanism unknown), which is very similar for the two agents; and 2) a secondary "coupled" vasoconstrictive effect occurring as a result of the depression in CMR caused by the volatile anesthetic. This latter effect should normally be greater with isoflurane because this agent is known to be a more potent CMR depressant than halothane.[1,2,5] This may account for the lesser net cerebral vasodilation apparent with isoflurane under most circumstances, including those of pretreatment with morphine/N_2O in the present study. With initial pentobarbital treatment, further CMR depression by either anesthetic was precluded by the antecedent barbiturate-induced suppression of CMR_{O_2}, and we suspect that, accordingly, only the intrinsic vasodilating effect was operative. The identical CBF increases that occurred with exposure to halothane and isoflurane in this circumstance suggest that the magnitude of this direct or intrinsic effect on cerebral vascular smooth muscle is quite similar for halothane and isoflurane.

The ICP changes in those receiving morphine sulphate/nitrous oxide treatment present an apparent contradiction. Whereas CBF increased with the administration of halothane but not with the administration of isoflurane, ICP increased during anesthesia with both anesthetics. We have observed this dissociation of ICP and CBF effects during isoflurane administration previously,[5,8] and its explanation remains a matter of speculation. CBF is known to be an important determinant of the volume of the contents of the intracranial compartment (*via* the effect of CBF on cerebral blood volume.[15]) Changes in CBF, however, probably reflect only the influence of changes in the caliber of cerebral resistance vessels, and cerebral blood volume may also be modified by changes in the status of capacitance vessels.[16] The relative effects of halothane and isoflurane on the latter are undefined in the rabbit. Similarly, alterations in cerebrospinal fluid (CSF) dynamics may be important in deter-

mining the ICP effects of a given anesthetic regimen[17–19] and the influence of volatile anesthetics on CSF dynamics have not been examined in the rabbit. It may be relevant that unexplained ICP increases which are inconsistent with the anticipated CBF effects of isoflurane have also been observed in humans with intracranial mass lesions.[20]

The CMR_{O_2} method employed in the present study is not without limitations. The CBF value used in the calculation was the mean of the three regional values (dorsal hippocampus, parietal cortex, and frontal cortex). This approach was selected to weight the CBF value to reflect the relatively large contribution of the cerebral cortex to total sagittal sinus blood flow.[21] The CBF value obtained may not, however, accurately represent CBF in the compartment traversed by the blood that was sampled from the sagittal sinus. Nonetheless, while the absolute values may be inaccurate, the CMR_{O_2} data obtained should accurately reflect trends.

The suggestion that drug-induced changes in CMR are important in determining the net CBF effects of a volatile anesthetic has been made previously, and Smith reported observations supporting this notion.[22,23] However, Smith proposed that volatile agents were not direct cerebral vasodilators, but rather that CBF changes were a secondary response to the combined influences of alterations in CMR and a volatile-agent–induced change in the set point of unspecified regulatory mechanisms seeking to keep cerebral venous P_{O_2} constant. By contrast, our theory proposes a direct or primary effect on cerebral vascular smooth muscle combined with secondary effects due to changes in CMR_{O_2}. The present data are consistent with either theory and cannot serve to clarify the exact mechanism of the vasodilating effects of volatile agents.

Interpretation of the present results is inevitably limited by the simultaneous administration of substantial doses of pentobarbital. In intact subjects, pentobarbital is a cerebral vasoconstrictor, probably resulting from the associated reduction in CMR. However, in isolated cerebral vessel preparations, it causes a smooth muscle relaxation[24] and attenuates the effect of vasoconstrictors.[24–26] The interactions between pentobarbital and vasodilators have not been studied *in vitro*. Accordingly, the possibility exists that the pentobarbital employed here in some way modified the direct effects of the volatile anesthetics on the cerebral vascular smooth muscle. This possibility cannot be excluded. However, it seems unlikely that pentobarbital should have produced any qualitative change in the action of the volatile anesthetic, although the magnitude of change may have been modified.

The protocol allowed variation in arterial pressure by an amount not greater than 10 mmHg, while altogether preventing reduction in MAP below 65 mmHg. The intent was to minimize the effects of alterations in autoregulation caused by the various anesthetics while avoiding the extremely large doses of vasopressor (phenylephrine) that might have been required to hold MAP constant at some arbitrary level in all animals in all groups. However, the phenylephrine may have had some quantitative influence on the results for CBF. Although the cerebral vascular effects of phenylephrine have not been extensively studied, there are data to suggest that phenylephrine is probably a cerebral vasoconstrictor[27] and may thereby have caused some reduction in the observed CBF values. Fortunately, the doses employed were modest, and there were no differences in phenylephrine dose between the subgroups for either the control or the control plus volatile agent measurements. Accordingly, any effect of phenylephrine is likely to have been similar for both halothane and isoflurane and should not impair the merit of this comparison.

The results of the present study were obtained in normal rabbits, and no direct extrapolation to human anesthesia can be made with certainty. However, these results may be relevant to that population of patients with a depressed CMR, (*e.g.*, severe head injury, including those already receiving barbiturates; subarachnoid hemorrhage patients in Hunt-Hess grades 4 and 5; and various encephalopathies). It is possible that in some of these patients, the vasodilating action of volatile anesthetics may be greater than in patients with a more normal CMR. Accordingly, the relative advantage attributed to isoflurane by merit of the lesser increases in CBF that it causes in normal subjects may be less apparent in this population of patients.

In summary, when halothane and isoflurane were added to a background anesthetic consisting of morphine and nitrous oxide (a circumstance in which isoflurane caused a greater reduction of CMR_{O_2} than halothane) only halothane caused an increase in CBF. By contrast, both halothane and isoflurane caused substantial and identical increases in CBF when superimposed on a background of barbiturate-induced EEG isoelectricity (a state that prevented significant volatile-agent–induced depression of CMR_{O_2}). These results are consistent with the suggestion that the intrinsic or direct vasodilating effects of halothane and isoflurane on cerebral vascular smooth muscle may be similar. Furthermore, they are consistent with the suggestion that the lesser cerebral vasodilating effects of isoflurane that have been observed in several models may reflect a greater "coupled" reduction in CBF normally occurring during the administration of isoflurane. The results, in addition, suggest the possibility that the cerebral vasodilating potency of a given volatile agent will vary with the CMR immediately prior to exposure to that volatile agent.

The authors are grateful to Sue Sager Moore for her capable technical assistance, Mark Zornow for his thoughtful review, and Sharon Andrews and Kris Beaver, who carefully prepared the manuscript.

References

1. Theye RA, Michenfelder JD: The effect of halothane on canine cerebral metabolism. ANESTHESIOLOGY 31:1113–1118, 1968
2. Cucchiara RF, Theye RA, Michenfelder JD: The effects of isoflurane on canine cerebral metabolism and blood flow. ANESTHESIOLOGY 40:571–564, 1974
3. Eintrei C, Leszniewski W, Carlsson C: Local application of ^{133}Xenon for measurement of regional cerebral blood flow during halothane, enflurane, and isoflurane anesthesia in humans. ANESTHESIOLOGY 63:391–394, 1985
4. Boarini DJ, Kassell N, Coester HC, Butler M, Sokoll M: Comparison of systemic and cerebrovascular effects of isoflurane and halothane. Neurosurgery 15:400–409, 1984
5. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. ANESTHESIOLOGY 60:276–282, 1984
6. Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth. Analg 63:557–565, 1984
7. Urban I, Richard P: A Stereotaxic Atlas of the New Zealand Rabbit's Brain. Springfield, Charles C Thomas, 1961
8. Scheller MS, Todd MM, Drummond JC: Isoflurane, halothane, and regional cerebral blood flow at various levels of Pa_{CO_2} in rabbits. ANESTHESIOLOGY 64:598–604, 1986
9. Aukland K, Bower BF, Berliner RW: Measurement of local blood flow with hydrogen gas. Circ Res 14:164–187, 1964
10. Young W: H_2 clearance measurement of blood flow: A review of technique and polarographic principles. Stroke 11:552–564, 1980
11. Pastzor E, Symon L, Dorsch NWC, Branston NM: The hydrogen clearance method in assessment of blood flow in cortex, white matter and deep nuclei of baboons. Stroke 4:556–567, 1973
12. Drummond JC: MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: And a test for the validity of MAC determinations. ANESTHESIOLOGY 62:336–338, 1985
13. Michenfelder JD: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. ANESTHESIOLOGY 41:231–236, 1974
14. Newberg LA, Milde JH, Michenfelder JD: The cerebral metabolic effects of isoflurane at and above concentrations that suppress cortical electrical activity. ANESTHESIOLOGY 59:23–28, 1983
15. Grubb RL, Raichle ME, Eichling JO, Ter-Pogossian MM: The effects of change in Pa_{CO_2} on cerebral blood volume, blood flow and vascular mean transit time. Stroke 5:630–639, 1974
16. Artru AA: Relationship between cerebral blood volume and CSF pressure during anesthesia with isoflurane or fentanyl in dogs. ANESTHESIOLOGY 60:575–579, 1984
17. Artru AA: Effects of halothane and fentanyl on the rate of CSF production in dogs. Anesth Analg 62:581–585, 1983
18. Artru AA: The effect of halothane and fentanyl on resistance to reabsorption of CSF. J Neurosurg 60:252–256, 1984
19. Artru AA: Isoflurane does not increase the rate of CSF production in dogs. ANESTHESIOLOGY 60:193–197, 1984
20. Grosslight K, Foster R, Colohan AR, Bedford RF: Isoflurane for neuroanesthesia: Risk factors for increases in intracranial pressure. ANESTHESIOLOGY 63:533–536, 1985
21. Scremin OU, Sonnenschein RR, Rubinstein EH: Cerebrovascular anatomy and blood flow measurements in the rabbit. J Cereb Blood Flow Metabol 2:55–66, 1982
22. Smith AL: Dependence of cerebral venous oxygen tension on anesthetic depth. ANESTHESIOLOGY 39:291–298, 1973
23. Smith AL: The mechanism of cerebral vasodilation by halothane. ANESTHESIOLOGY 39:581–587, 1973
24. Marin J, Lobato RO, Rico ML, Salaices M, Benitez J: Effect of pentobarbital on the reactivity of isolated human cerebral arteries. J Neurosurg 54:521–524, 1981
25. Edvinsson L, McCulloch J: Effects of pentobarbital on contractile responses of feline cerebral arteries. J Cereb Blood Flow Metabol 1:437–440, 1981
26. Altura BT, Altura BM: Pentobarbital and contraction of vascular smooth muscle. Am J Physiol 229:1635–1640, 1975
27. Chikovani O, Corkill G, McLeish I, Ong S, Beilin D: Effect on canine cerebral blood flow of two common pressor agents during prolonged halothane anesthesia. Surg Neurol 9:211–213, 1978