Anesthesiology
67:336-340, 1987

Isoflurane When Compared to Enflurane and Halothane Decreases the Frequency of Cerebral Ischemia During Carotid Endarterectomy

John D. Michenfelder, M.D., Thoralf M. Sundt, M.D.,† Nicolee Fode, R.N., M.S.,‡ Frank W. Sharbrough, M.D.§*

Data from the records of patients who underwent 2223 carotid endarterectomies at the Mayo Clinic between January 1, 1972, and December 31, 1985, were abstracted to compare the effects of isoflurane, enflurane, and halothane on the critical cerebral blood flow (CBF) (*i.e.*, the CBF below which the majority of patients develop EEG ischemic changes within 3 min of carotid occlusion), the incidence of EEG ischemic changes, and the neurologic outcome. In a total of 2196 of these procedures, the patient received one of the three volatile anesthetics and, in 2010 of these, both the EEG and the CBF were monitored. Chronologically, halothane was the primary agent from 1972–1974; enflurane progressively replaced halothane during 1975–1981; and isoflurane was used almost exclusively since 1982. This analysis confirmed a previous study that the critical CBF during isoflurane anesthesia (703 procedures) was approximately 10 ml · 100 g^{-1} · min^{-1}, as contrasted to that of approximately 20 ml · 100 g^{-1} · min^{-1} during halothane anesthesia (467 procedures). This analysis also established that the critical CBF during enflurane anesthesia (840 procedures) was approximately 15 ml · 100 g^{-1} · min^{-1}. The incidence of EEG ischemic changes was significantly less ($P < 0.001$) during isoflurane anesthesia (18%) than during either enflurane (26%) or halothane (25%) anesthesia. This difference occurred despite the fact that the preoperative risk status was greater in the patients given isoflurane. There was no difference in neurologic outcome between the three anesthetics, and none was expected, since all patients with EEG changes were immediately shunted, if possible. The authors conclude that relative to halothane and enflurane, isoflurane does offer a degree of cerebral protection for transient incomplete regional cerebral ischemia during carotid endarterectomy. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Brain: electroencephalogram; protection. Surgery: carotid endarterectomy.)

IN A RECENT prospective study, Messick *et al.*[1] determined the critical cerebral blood flow (CBF) in 31 patients undergoing carotid endarterectomy during isoflurane anesthesia (critical CBF was defined as that flow below which the majority of patients developed ipsilateral EEG changes of ischemia within 3 min of carotid occlusion). They found the critical CBF to be approximately 8–10 ml · 100 g^{-1} · min^{-1} which was strikingly lower than that previously reported during halothane anesthesia (approximately 18–20 ml · 100 g^{-1} · min^{-1}).[2] Understandably, this report stimulated speculation as to whether a lower critical CBF with isoflurane implied or reflected a degree of cerebral protection, at least as compared to halothane. Since that report was not concerned with outcome (*i.e.*, either the incidence of EEG ischemic changes or occurrence of neurologic deficits) no claims regarding protection were made.

Recently too, Nehls *et al.*[3] addressed the question of isoflurane brain protection in a primate model of regional cerebral ischemia. They compared neurologic outcome in animals treated with either thiopental or isoflurane, and reported that the latter group fared worse. They concluded that isoflurane was not protective in transient incomplete regional cerebral ischemia, at least as compared with thiopental.

In an effort to address this question of possible isoflurane brain protection in our patients who underwent carotid endarterectomy, we retrospectively reviewed our experience in patients operated upon in the past 14 yr and who received either halothane, enflurane, or isoflurane.

Methods

Since 1972, one of us (TMS) has stored on a computer the abstracted records of all neurosurgical patients who underwent carotid endarterectomy at the Mayo Clinic. Between January 1, 1972, and December 31, 1985, a total of 2223 procedures were done. Available preoperative data included information necessary to determine the patient's risk status. Available intraoperative data included all CBF, blood gas, and relevant arterial blood pressure measurements, EEG findings, and anesthetic technique. Available postoperative data included information necessary to determine outcome.

The patient's preoperative risk status was determined by a grading system based upon angiographic findings, neurologic status, and general health status[4] (table 1). Grade 1 and 2 patients were neurologically stable without major medical risks (the former group had no angiographically determined risks; the latter did have such risks, usually an opposite carotid artery occlusion or coexisting ipsilateral siphon stenosis). Grade 3 pa-

* Consultant in Anesthesiology, Mayo Clinic; Professor of Anesthesiology, Mayo Medical School.

† Consultant in Neurosurgery, Mayo Clinic; Professor of Neurosurgery, Mayo Medical School.

‡ Instructor of Neurosurgery, Mayo Medical School.

§ Consultant in Neurology, Mayo Clinic; Professor of Neurology, Mayo Medical School.

Received from the Departments of Anesthesiology, Neurosurgery, and Neurology, Mayo Clinic, Mayo Medical School, Rochester, Minnesota 55905. Accepted for publication March 31, 1987. Supported in part by research grant NS-07507 from the National Institutes of Health, Public Health Service.

Address reprint requests to Dr. Michenfelder: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

tients were those with a major medical risk (usually cardiac), and grade 4 patients were those that were not neurologically stable.

CBF measurements were routinely obtained during most of the procedures by the xenon washout method immediately prior to carotid occlusion, immediately after occlusion, and following repair. If a shunt was inserted, post-shunt flow was also measured. CBF values were calculated from the initial slope of the washout curve, and the calculation of CBF was available in less than 2 min following the injection of ^{133}Xe. In all patients, normocarbia (Pa_{CO_2} = 35–40 mmHg) was sought and blood pressure was maintained, when possible, at a normal or modestly elevated level (+20%). The standard 16-lead EEG was also monitored throughout the procedure in most patients.

Except for 27 occasions, all patients received one of three volatile anesthetics: isoflurane, enflurane, or halothane. In virtually all patients, nitrous oxide (approximately 50%) was also administered. Necessarily, there was a chronologic sequence in the administration of the volatile anesthetics. From 1972–1974, halothane was used almost exclusively; between 1974 and 1981, halothane was progressively replaced with enflurane; and, since 1982, isoflurane has been used almost exclusively. In addition, it has become increasingly common to administer small doses of fentanyl (1–3 $\mu g \cdot kg^{-1}$) during anesthetic induction. The latter has almost always been accomplished with thiopental followed by either succinylcholine, pancuronium, vecuronium, or atracurium. There obviously was a chronological sequence for the administration of muscle relaxants as well. Anesthetic depth was deliberately "light" (approximately 1.0 MAC) in order to produce an EEG pattern characterized by symmetrical sustained rhythmic activity of 10–14 Hz that ranged between 25 and 100 μV. This EEG pattern is preferred to sensitively detect changes consistent with ischemia characterized by ipsilateral loss of high frequency activity and altered amplitude.

Following surgical occlusion of the affected carotid artery, a shunt was inserted, if possible, whenever the EEG changed. Likewise, up until 1983–1984, a shunt was inserted in most patients with occlusion CBF values less than 18 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, regardless of the EEG. Since 1983–1984, in the absence of EEG changes, a shunt was only inserted if CBF was below 14–15 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. On the average, insertion of a shunt required 4 min. Neurologic outcome was evaluated in terms of onset of a new permanent neurologic deficit or death due to neurologic complications.

TABLE 1. Classification of Patients

Grade	Neurologically Stable	Major Medical Risk	Angiographic Risk
1	Yes	No	No
2	Yes	No	Yes
3	Yes	Yes	Yes/No
4	No	Yes/No	Yes/No

The CBF values below 20 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ were grouped in increments of 5 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. The precision of the initial slope calculation in low-flow states is impaired. Accordingly, grouping of the low flows is considered a more accurate reflection of the truth. The CBF values, the patient risk status, the incidence of EEG ischemic changes, and neurologic outcome were compared between patients who received isoflurane, enflurane, and halothane anesthesia using the chi-square test of Pearson and the Bonferroni correction for multiple comparisons. A P value of less than 0.05 was considered significant. Where appropriate, contingency tables were prepared showing the actual values and the expected values (in parenthesis) assuming the null hypothesis.[5]

Results

CBF AND EEG

Both the CBF and EEG were monitored in 2010 of the 2196 procedures in which one of the three volatile anesthetics was administered. The baseline preocclusion CBF values differed significantly among anesthetics and risk grades (table 2). At each risk grade, the CBF values were greatest for halothane, intermediate

TABLE 2. Pre-occlusion CBF* *Versus* Anesthetic and Risk Grade (Mean ± SE)†

	Grade‡							
	1		2		3		4	
Anesthetic§	n	CBF	n	CBF	n	CBF	n	CBF
Isoflurane	199	37 ± 1	163	35 ± 2	227	31 ± 1	107	28 ± 1
Enflurane	290	50 ± 1	197	44 ± 1	198	42 ± 1	143	37 ± 2
Halothane	150	62 ± 2	89	59 ± 3	143	51 ± 2	81	48 ± 2

* CBF units: $ml \cdot 100 g^{-1} \cdot min^{-1}$.

† Pre occlusion CBF values were not available in 23 of the 2010 procedures.

‡ For each anesthetic the Grade 1 CBF differs significantly from the Grade 4 CBF ($P < 0.05$).

§ Each anesthetic at each grade differs significantly from one another ($P < 0.05$).

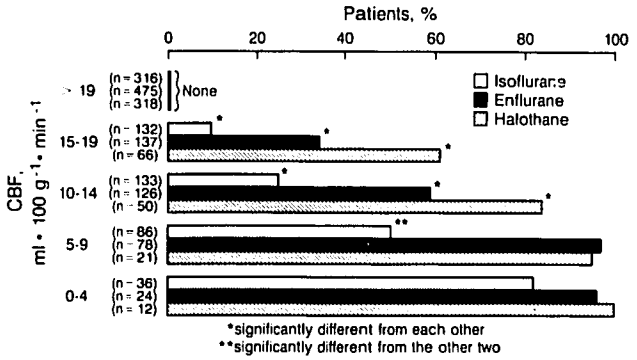

FIG. 1. Percent of cases with EEG changes at different levels of CBF with isoflurane, enflurane, and halothane. Occlusion CBF values are grouped in increments of 5 ml·100 g^{-1}·min^{-1} from 0–4 to >19 ml·100 g^{-1}·min^{-1}. Each bar represents, for each anesthetic, the percentage of cases at that flow increment that manifested EEG ischemic changes within 3 min of carotid occlusion. For each anesthetic at each flow increment, the number of cases (n) is given.

for enflurane, and least for isoflurane. For each anesthetic, the CBF values were numerically less with increasing risk, and this consistently achieved significance when comparing grade 1 *versus* grade 4 patients.

Following carotid occlusion, none of the patients with CBF values exceeding 19 ml·100 g^{-1}·min^{-1} had EEG ischemic changes within 3 min of occlusion. The CBF values that were less than 20 ml·100 g^{-1}·min^{-1} at the time of carotid occlusion were grouped into 5-ml flow increments of 0–4, 5–9, 10–14, and 15–19 ml·100 g^{-1}·min^{-1}. The incidence of EEG ischemic changes within 3 min of carotid occlusion at these CBF levels among the three anesthetics is depicted in figure 1. At flows of 0–4 ml·100 g^{-1}·min^{-1}, most of the patients developed EEG changes within 3 min, and there were no differences among the anesthetics. At flows of 5–9, 10–14, and 15–19 ml·100 g^{-1}·min^{-1}, the incidence of EEG changes with isoflurane was significantly less than that with the other two anesthetics. At flows of 10–14 and 15–19 ml·100 g^{-1}·min^{-1}, the incidence of EEG ischemic changes with enflurane was significantly less than that with halothane. Defining critical CBF as that flow below which more than 50% of patients develop EEG changes within 3 min of carotid occlusion, the approximate critical CBF for isoflurane was 10 ml·100 g^{-1}·min^{-1}, for enflurane was 15 ml·100 g^{-1}·min^{-1}, and for halothane was 20 ml·100 g^{-1}·min^{-1}.

TABLE 3. Frequency of EEG Change within 3 Min of Occlusion *Versus* Anesthetic

	EEG Change	No EEG Change	Total
Isoflurane*	126 (161)†	577 (542)	703
Enflurane	219 (192)	621 (648)	840
Halothane	115 (107)	352 (360)	467
Total	460	1550	2010

* $P < 0.001$.

† Parenthetical values in this and subsequent tables represent expectations assuming the null hypothesis.

TABLE 4. Frequency of Shunt Placement

	Shunt	No Shunt	Total
Isoflurane*	260 (295)	443 (408)	703
Other	577 (549)	730 (758)	1307
Total	837	1173	2010

* $P < 0.05$.

When the overall incidence of EEG changes, regardless of CBF, was compared between the three anesthetics, isoflurane was again associated with a significantly lower incidence (18%) than was halothane and enflurane (table 3). In this analysis, there was no difference between enflurane and halothane (26 and 25%, respectively).

The frequency of placement of a shunt was also decreased in those patient's given isoflurane from 44% (enflurane and halothane groups combined) to 37% (table 4). This presumably reflects both the altered criteria in recent years (flow less than 14–15 ml·100 g^{-1}·min^{-1}) and the decrease in frequency of EEG changes.

PATIENT RISK STATUS AND NEUROLOGIC OUTCOME

For comparison of the anesthetics, the preoperative risk status was divided into two major groups: those patients that were neurologically stable (groups 1 and 2), and those that either had a major medical risk or were not neurologically stable (groups 3 and 4). In those patients given isoflurane, the risk status was greater than the combined risk status in those given enflurane or halothane (table 5).

When the incidence of neurologic complications was compared between the anesthetics, there were no significant differences (table 6).

Discussion

This retrospective study again confirmed the fact that the volatile anesthetics differ in their cerebral vascular effects, such that halothane is a potent vasodilator relative to isoflurane, while enflurane is intermediate. Also demonstrated by this study is the impact of cerebrovascular pathology on CBF. For each anesthetic, the base-

TABLE 5. Patient Risk *Versus* Anesthetic

	Grades 1 and 2	Grades 3 and 4	Total
Isoflurane*	353 (378)	350 (325)	703
Other	729 (704)	578 (603)	1307
Total	1082	928	2010

* $P = 0.017$ (uncorrected).

line (pre-occlusion) CBF was progressively less as the risk grade increased.

The primary purpose of this study was to determine whether there was evidence that the lower critical CBF associated with isoflurane anesthesia reflects a cerebral protective effect in those patients in whom EEG changes did not occur. That the critical CBF is less with isoflurane was again established in this study, and the value determined for the critical CBF was in agreement with that reported by Messick *et al.*[1] in their prospective study (approximately 10 ml · 100 g^{-1} · min^{-1}). Similarly, the critical CBF for halothane (approximately 20 ml · 100 g^{-1} · min^{-1}) was the same as that previously reported.[2] The critical CBF for enflurane (approximately 15 ml · 100 g^{-1} · min^{-1}) had not previously been reported.

There were no differences among the anesthetics as regards neurologic outcome. From the outset, we considered that this would be the likely finding, since, when possible, a shunt was immediately inserted in all patients who developed EEG changes in order to abort an untoward neurologic outcome. In addition, we knew that the numbers of patients with postoperative neurologic deficits would be relatively small. Only 61 patients developed new permanent neurologic complications (2.8%), and a significant difference among the anesthetics was not even suggested.

By contrast, we knew that approximately 25% of our patients developed EEG ischemic changes within 3 min of carotid occlusion. The occurrence of such an EEG change is a measure of outcome, and is considered a clinically relevant event which may or may not be manifested ultimately by a neurologic deficit. It is a part of a possible continuum which may be initiated by carotid occlusion progressing from EEG change to transient deficits, to permanent deficits, and ultimately to coma and death. Obviously, the vast majority of those patients that did have EEG ischemic changes did not have a demonstrable postoperative deficit. By the same token, every patient that did have a postoperative deficit (whether transient or permanent) did have intraoperative EEG ischemic changes. Accordingly, it is valid to consider the frequency of EEG ischemic changes that occurred with the different anesthetics to be a measure of outcome and an appropriate indicator of possible brain protection. In this regard, isoflurane was associated with a significantly lower incidence of EEG ischemic changes (18%) than were either enflurane or halothane (26 and 25%, respectively). These data are further enhanced by the fact that the preoperative risk status was worse in the patients given isoflurane than was the combined risk status of those patients given either enflurane or halothane. We believe that these data justify the conclusion that, among currently available volatile anesthetics and within the confines of this study, isoflurane offers a measurable degree of relative brain protection in the event of transient incomplete regional cerebral ischemia.

TABLE 6. Permanent Neurologic Complication *Versus* Anesthetic*

	Neurologic Complication	None	Total
Isoflurane	25 (22)	759 (762)	784
Enflurane	21 (26)	898 (893)	919
Halothane	15 (14)	478 (479)	493
Total	61	2135	2196

* $P < 0.25$.

It should be noted that, in terms of clinical results, this relative protection provided by isoflurane was of little or no importance. One would predict this to be the case so long as selective shunting based upon EEG changes is used. Perhaps the most important clinical contribution of isoflurane to this group of patients was the reduction in the number of shunts used from 44 to 37%. This reduction was accounted for by both the decrease in the critical CBF and the decrease in the incidence of ischemic EEG changes. If there is a morbidity associated with shunt placement, this would be a meaningful contribution.

As noted, there was a distinct chronological sequence in our use of the volatile anesthetics. There was no suggestion that this sequence influenced the results (numerically, there was a higher incidence of EEG changes for enflurane then for halothane, even though halothane use preceded enflurane). Furthermore, it is not obvious what sort of learning process might in any way have influenced the frequency of onset of EEG changes immediately following carotid occlusion. Still, as is the case for most retrospective studies, this must be considered a weakness.

Our conclusions do not truly conflict with the conclusions that Nehls *et al.*[3] came to as a result of their study of regional ischemia in primates. In that study, they compared isoflurane to thiopental (and not to other volatile anesthetics), and reported a worse outcome in animals given isoflurane. As pointed out in an accompanying editorial,[6] the variables that were unavoidably introduced into that study caused the conclusions to be highly specific ones which may or may not apply generically to a comparison of thiopental and isoflurane in patients with regional cerebral ischemia. Specifically, in that study, the thiopental-treated animals received large doses of vasodilators (nitroprusside and hydralazine) and, despite this, their blood pressures were significantly higher (15–20 mmHg) than was the blood pressure in the isoflurane-treated animals. Since increased blood pressure combined with cerebral vasodilators may be important determinants of outcome in regional cerebral ischemia, it is not possible to conclude that isoflurane is worse than thiopental in the absence of these variables.

Certainly, the evidence that barbiturates provide protection in the event of incomplete regional ischemia is consistent and convincing, based upon a host of animal studies[7] and one human study.[8] In the case of isoflurane, the evidence for protection has been from animal studies only, and then only in circumstances of incomplete global ischemia or hypoxia.[9,10] Although this retrospective study does demonstrate a *relative* protective effect for isoflurane in patients with incomplete regional ischemia (relative to enflurane and halothane), it by no means permits any conclusions relative to thiopental protection. The latter is the "gold standard," and should not be abandoned in favor of isoflurane in those specific circumstances where pharmacologic brain protection may be indicated. Obviously, more studies comparing thiopental and isoflurane are needed before any such change in practice could be recommended. By the same token, in those circumstances where a volatile anesthetic is to be administered and where the possibility exists that incomplete cerebral ischemia (whether global or regional) may develop, it seems appropriate that isoflurane should be the agent selected.

Certainly, in addition to the animal studies concerned specifically with brain protection, there are other experimental data to support speculation that isoflurane may have the potential to protect the brain. Isoflurane is the only volatile anesthetic that can abolish EEG activity at concentrations that are tolerated hemodynamically (about 2 MAC). At that concentration, the brain appears to be metabolically similar to the brain exposed to barbiturates (to the point of an isoelectric EEG).[11,12] Cerebral metabolic rates in both instances are reduced 50–60%, and brain energy stores are unaffected. If the basis for protection is solely metabolic, one would predict, at deep anesthetic levels, equivalent protection for isoflurane and thiopental. However, in the patients involved in this study, only light levels of anesthesia were deliberately sought; and, based upon the EEG, the level of anesthesia was similar for all three groups. From animal studies, one would expect a similar level of cerebral metabolic suppression in all three groups, as well.[13] If such is the case, then speculation regarding metabolic differences to account for differences in the incidence of EEG ischemic changes seems unwarranted. Accordingly, other factors must influence the degree of protection. Isoflurane in contrast to thiopental is a mild cerebral vasodilator. This may be undesirable in regional ischemia and result in an unfavorable distribution of the cerebral blood flow. By contrast, the cerebral vasoconstriction that occurs with thiopental may cause a favorable distribution of flow in the ischemic area. However, when comparing isoflurane to either enflurane or halothane, it is the least potent cerebrovasodilator. Accordingly, it might cause a relatively less unfavorable redistribution of flow during incomplete regional ischemia, thus accounting for its relative protective effects. Although a number of other mechanisms have been postulated for pharmacologic brain protection, none has been established as valid, and any speculative comparison between isoflurane and the other anesthetics as regards these possible mechanisms would be largely meaningless.

In summary, this retrospective study confirms the fact that the critical CBF during isoflurane anesthesia is lower than that with either enflurane or halothane. Furthermore, this effect on critical CBF does correlate with a degree of cerebral protection relative to the other volatile anesthetics, since the incidence of EEG ischemic changes was significantly less than that observed with the other agents. Nonetheless, this is insufficient evidence to justify any recommendation for the use of isoflurane (in preference to barbiturates) in those specific circumstances where pharmacologic brain protection may be indicated.

References

1. Messick JM, Casement B, Sharbrough FW, Milde LN, Michenfelder JD, Sundt TM: Correlation of regional cerebral blood flow (rCBF) with EEG changes during isoflurane anesthesia for carotid endarterectomy: Critical rCBF. ANESTHESIOLOGY 66:344–349, 1987
2. Sharbrough FW, Messick JM Jr, Sundt TM: Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. Stroke 4:674–683, 1973
3. Nehls DG, Todd MM, Spetzler RF, Drummond JC, Thompson RA, Johnson PC: A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. ANESTHESIOLOGY 66:453–464, 1987
4. Sundt TM: Occlusive Cerebrovascular Disease. Philadelphia, W. B. Saunders Co., 1987, pp 227
5. Glantz SA: Primer of Biostatistics. New York, McGraw-Hill Book Co., 1981, p 123
6. Michenfelder JD: Does isoflurane aggravate regional cerebral ischemia? ANESTHESIOLOGY 66:451–452, 1987
7. Michenfelder JD, Milde JH: Cerebral protection by anaesthetics during ischaemia (a review). Resuscitation 4:219–233, 1976
8. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. ANESTHESIOLOGY 64:165–170, 1986
9. Newberg LA, Michenfelder JD: Cerebral protection by isoflurane during hypoxemia or ischemia. ANESTHESIOLOGY 59:29–35, 1983
10. Newberg LA, Milde JH, Michenfelder JD: Systemic and cerebral effects of isoflurane-induced hypotension in dogs. ANESTHESIOLOGY 60:541–546, 1984
11. 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
12. Michenfelder JD: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. ANESTHESIOLOGY 41:231–236, 1974
13. Stullken EH Jr, Milde JH, Michenfelder JD, Tinker JH: The non-linear responses of cerebral metabolism to low concentrations of halothane, enflurane, isoflurane and thiopental. ANESTHESIOLOGY 46:28–34, 1977