Direct Cerebrovasodilatory Effects of Halothane, Isoflurane, and Desflurane during Propofol-induced Isoelectric Electroencephalogram in Humans


Background: The effect of volatile anesthetics on cerebral blood flow depends on the balance between the agent's direct vasodilator action and the indirect vasoconstrictive action mediated by flow-metabolism coupling. To compare the intrinsic action of volatile anesthetics, the effect of halothane, isoflurane, and desflurane on flow velocity in the middle cerebral artery during propofol-induced isoelectricity of the electroencephalogram was examined.

Methods: In 21 ASA physical status 1–2 patients, anesthesia was induced with 2.5 mg/kg propofol, 3 μg/kg fentanyl, and 0.1 mg/kg vecuronium and maintained with a propofol infusion to preserve an isoelectric electroencephalogram. End tidal carbon dioxide and blood pressure were maintained constant throughout the study period. A transcranial Doppler was used to measure blood flow velocity in the middle cerebral artery, and a catheter was inserted in a retrograde direction into the jugular bulb for oxygen saturation measurements. After 15 min of isoelectric electroencephalogram, arterial and jugular venous blood samples were drawn, and flow velocity in the middle cerebral artery was recorded. Patients were randomly allocated to receive 0.5 MAC halothane, isoflurane, or desflurane, and after 15 min of equilibration, all variables were measured again. The concentration of the volatile agent was increased to 1.5 MAC, and after 15 min of equilibration, the measurements were repeated.

Results: Halothane, isoflurane, and desflurane significantly increased flow velocity in the middle cerebral artery (baseline 28 ± 4, 30 ± 4, and 29 ± 3 cm/s, respectively) at 0.5 MAC (19 ± 1.5%, 21 ± 2%, and 23 ± 3%, respectively; P < 0.05) and at 1.5 MAC (48 ± 3%, 75 ± 7%, and 74 ± 4%, respectively; P < 0.05). Changes in the cerebral arteriovenous oxygen content difference are consistent with these findings.

Conclusions: Halothane, isoflurane, and desflurane have intrinsic, dose-related cerebral vasodilatory effects. Whereas all three agents are similar at 0.5 MAC, isoflurane and desflurane have greater vasodilatory effects than halothane at 1.5 MAC. (Key words: Anesthetics, intravenous: propofol. Anesthetics, volatile: desflurane; halothane; isoflurane. Brain: arteriovenous oxygen content difference; cerebral blood flow velocity. Equipment: electroencephalogram; jugular venous bulb catheter; transcranial Doppler ultrasonography. Sympathetic nervous system, pharmacology: phenylephrine.)

VOLATILE anesthetics have been shown to increase cerebral blood flow (CBF) in a dose-dependent manner. However, as Drummond et al. suggested, this vasodilatory effect may be modified by their effects on cerebral metabolism. Thus, these investigators observed that, in rabbits lightly anesthetized with morphine and nitrous oxide, the addition of halothane causes an increase in CBF, whereas adding isoflurane does not. In contrast, in animals anesthetized with pentobarbital to maximal electroencephalogram (EEG) suppression (isoelectricity), no difference between halothane and isoflurane can be demonstrated. This report highlighted the importance of the background cerebral metabolic activity. Subsequently, Hansen et al. confirmed in rats that the difference in cerebral vascular effect between isoflurane and halothane can be attributed to the balance between the agent's intrinsic vasodilatory action and the indirect effect it has on cerebral metabolism. Hence, isoflurane, intrinsically perhaps a more potent direct vasodilator than halothane, at equipotent doses produces a smaller increase in CBF because of its greater depressant effect on cerebral metabolism. Therefore, the effect of a volatile agent on CBF partly depends on the level of cerebral

This article is accompanied by a Highlight. Please see this issue of Anesthesiology, page 27A

* Acting Assistant Professor of Anesthesiology. Current position: Senior Registrar, Department of Anaesthesia, Addenbrooks Hospital, Cambridge, United Kingdom.
† Assistant Professor of Anesthesiology and Neurological Surgery.
‡ Professor of Anesthesiology and Neurological Surgery.

Received from the Departments of Anesthesiology and Neurological Surgery, University of Washington School of Medicine, Seattle, Washington. Submitted for publication December 9, 1994. Accepted for publication August 2, 1995.

Address correspondence to Dr. Lam: Department of Anesthesiology, Box 559724, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104.

Anesthesiology. V 83, No 5, Nov 1995
EFFECT OF VOLATILE ANESTHETICS ON CBF VELOCITY DURING ISOELECTRIC EEG

metabolic activity present at the time of administration. To our knowledge, these actions have not been confirmed in humans. Desflurane has cerebral vascular properties similar to that of isoflurane, and its effect may be influenced similarly by the background metabolic activity, but this has not been investigated. We hypothesize that, in the absence of cortical electrical activity, isoflurane and desflurane may be more potent cerebral vasodilators than halothane. To examine the intrinsic cerebral vasodilatory effect of halothane, isoflurane, and desflurane, we studied their effect on CBF velocity during propofol-induced EEG suppression (isoelectric EEG), when cerebral metabolism due to electrical activity is presumed to be maximally depressed.

Methods and Materials

After human subjects committee approval and written informed consent were obtained, we examined the cerebral vascular effects of halothane, isoflurane, and desflurane in 21 patients (ASA physical status 1 or 2) undergoing general anesthesia for peripheral orthopedic procedures of at least 4 h duration. Patients with neurologic, cardiovascular, or respiratory disease and those medicated with psychotropic drugs were excluded. With routine monitors in place (electrocardiograph, pulse oximetry, and noninvasive blood pressure), anesthesia was induced with 2.5 mg/kg propofol and 3 \( \mu \)g/kg fentanyl, and muscle relaxation was achieved with 0.1 mg/kg vecuronium. After tracheal intubation, the lungs were ventilated with an oxygen/air mixture \((F_{O_2} = 0.50)\) to achieve normocapnia \((PaCO_2 = \pm 2 \text{ mmHg})\). Anesthesia was maintained with propofol infusion set at 250–300 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1}\) and fentanyl infusion set at 2 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1}\), and muscle relaxation was maintained with repeated doses of vecuronium. A catheter was inserted into a radial artery to monitor mean arterial pressure (MAP) and for repeated blood gas sampling. A 13.3-cm 16-G catheter (Angiocath, Becton Dickinson, Sandy, VT) was placed retrogradely into the jugular bulb via the right internal jugular vein using an aseptic technique described previously. The catheter was connected to a low-pressure flush system (normal saline at 3 ml/h). The position of the catheter was confirmed radiographically. Blood flow velocity \( (V_{mca}) \) was measured by insonating the right middle cerebral artery (MCA; ipsilateral to the jugular bulb catheter) through the temporal window, using a 2 MHz pulsed transcranial Doppler probe (Multidop by DWL, Sipplingen, Germany). The technique has been described previously. Briefly, the probe was secured in position so that the angle of insonation remained constant throughout the study. Doppler signals from the right MCA were identified and measured at a depth of 45–50 mm. The maximum shift in frequency spectra (spectral outline) of the Doppler signals was converted to mean \( V_{mca} \) by built-in computer software using a standard mathematical algorithm \( [V_{mca} = 1/3 (systolic - diastolic velocity) + diastolic velocity] \). This was averaged over four or five cardiac cycles. Brain electrical activity (EEG) was monitored using a two-channel frontooccipital montage, with filters set at 0.5–30 Hz (Spacelabs model 94800, Redmond, WA), and the raw unprocessed EEG signals were displayed. A phenylephrine infusion was used to maintain MAP between 70 and 90 mmHg.

During a period of stable surgical stimulation (mid-surgery) characterized by a stable \( V_{mca} \), the propofol infusion rate \((250–300 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) was adjusted to induce maximal EEG suppression, with display of “isoelectricity” and complete absence of burst activity. Once this was achieved, the infusion rate was kept constant. After 15 min of isoelectric EEG, normotension, and normocapnia, control arterial and jugular bulb venous blood samples were drawn, and MAP and \( V_{mca} \) were recorded. The patients were randomly allocated to receive halothane, isoflurane, or desflurane in an air/oxygen mixture \((F_{O_2} = 0.5)\). After 15 min of unchanged end-tidal concentration at 0.5 MAC (minimum alveolar concentration for halothane was 0.76%, isoflurane 1.15%, and desflurane 6.0%), MAP and \( V_{mca} \) were recorded, and another set of arterial and jugular bulb blood gases was drawn. Concentration of the inhaled agent was increased to 1.5 MAC, and after a 15 min steady end-tidal equilibration, the measurements and blood draws were repeated. Jugular venous blood samples were drawn at a rate no greater than 2 ml/min and were immediately analyzed using an automated blood gas analyzer (Nova Biomedical, Waltham, MA). Throughout the study, the phenylephrine infusion was adjusted to maintain MAP as near the value before introduction of the inhaled agent as possible. We previously demonstrated that phenylephrine \( per se \) had no effect on \( V_{mca} \).

We did not randomize the order of study (always from 0.5 to 1.5 MAC) because we previously observed that \( V_{mca} \) is stable under these experimental conditions. Moreover, the period during which volatile anesthetics were given was approximately 1 h, a duration deemed too short to affect time-related changes.
Table 1. Patient Demographic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Halothane (n = 7)</th>
<th>Isoflurane (n = 7)</th>
<th>Desflurane (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33 ± 11</td>
<td>35 ± 7</td>
<td>32 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 ± 16</td>
<td>80 ± 12</td>
<td>79 ± 10</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Data Analysis
Demographic data were analyzed using analysis of variance. The CBF equivalent (CBFe) was calculated from the reciprocal of the cerebral arteriovenous oxygen content difference (AVDO₂): AVDO₂ = hemoglobin concentration × 1.59 × (SaO₂ − SjvO₂) + 0.003 × (PaO₂ − PjvO₂) vol%, where SaO₂ is arterial oxygen saturation, SjvO₂ is the jugular bulb oxygen saturation, PaO₂ is arterial oxygen tension, and PjvO₂ is the jugular bulb oxygen tension.

CBF velocity and CBFe data were analyzed using one-way analysis of variance for repeated measures for intragroup comparisons and two-way analysis of variance for repeated measures for intergroup comparisons. A P-value of <0.05 was considered statistically significant. When significance was found, a post hoc test (Tukey’s) was used to delineate where the differences lay.

To examine the validity of CBF velocity as a measure of CBF, the percentage increase in Vmax and CBFe were subjected to linear correlation analysis.

Results
The main findings of the study are shown in tables 1 and 2 and figures 1 and 2. Unless otherwise stated, all values are mean ± SEM. The three groups were similar in age and weight. There was no significant difference among the groups in the patients’ body temperature, heart rate, mean blood pressure, PaO₂, or PaCO₂ during the study period. During the study, hematocrit was between 35% and 37%; PaO₂ was between 235 and 289 mmHg; PaCO₂ was between 37 and 40 mmHg and did not vary by more than 1 mmHg within each anesthetic group. The position of the jugular bulb catheters was confirmed radiographically, and the tip of the catheter was found to be in a satisfactory position in all patients.

Table 2. Mean Arterial Blood Pressure, Flow Velocity, and AVDO₂

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline 0.5 MAC 1.5 MAC</th>
<th>Baseline 0.5 MAC 1.5 MAC</th>
<th>Baseline 0.5 MAC 1.5 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane (n = 7)</td>
<td>80 ± 2 82 ± 2 81 ± 2</td>
<td>90 ± 3 89 ± 3 89 ± 3</td>
<td>84 ± 3 85 ± 3 85 ± 2</td>
</tr>
<tr>
<td>Isoflurane (n = 7)</td>
<td>28 ± 4 34 ± 4* 42 ± 6†</td>
<td>30 ± 4 37 ± 7* 52 ± 7†</td>
<td>29 ± 3 35 ± 4* 51 ± 5††</td>
</tr>
<tr>
<td>Desflurane (n = 7)</td>
<td>6.3 ± 0.8 5.3 ± 0.6* 4.2 ± 0.7†</td>
<td>5.7 ± 0.6 4.6 ± 0.5* 3.2 ± 0.4†</td>
<td>6.6 ± 0.6 5.4 ± 0.6* 3.7 ± 0.4††</td>
</tr>
<tr>
<td>AVDO₂ (vol%)</td>
<td>0.165 ± 0.03 0.196 ± 0.15* 0.244 ± 0.05†</td>
<td>0.184 ± 0.02 0.224 ± 0.04* 0.326 ± 0.05††</td>
<td>0.16 ± 0.01 0.197 ± 0.2* 0.286 ± 0.03††</td>
</tr>
<tr>
<td>CBFe (1/100%)</td>
<td>0 18 ± 3* 48 ± 3†</td>
<td>0 24 ± 3* 73 ± 4††</td>
<td>0 23 ± 3* 79 ± 7††</td>
</tr>
<tr>
<td>%CBFe (change from baseline)</td>
<td>0 18 ± 3* 48 ± 3†</td>
<td>0 24 ± 3* 73 ± 4††</td>
<td>0 23 ± 3* 79 ± 7††</td>
</tr>
</tbody>
</table>

All Values are mean ± SEM.

* Significantly different from baseline (P < 0.05, ANOVA for repeated measures).
† Significantly different from baseline and 0.5 MAC (P < 0.05, ANOVA for repeated measures).
‡ Significantly different from halothane at 1.5 MAC (P < 0.05, two-way ANOVA for repeated measures).

Anesthesiology. V 83, No 5, Nov 1995
EFFECT OF VOLATILE ANESTHETICS ON CBF VELOCITY DURING ISOELECTRIC EEG

(at the level of and just medial to the mastoid bone). The propofol infusion rate required to maintain maximal EEG suppression (isoelectric EEG) varied between 250 and 300 µg·kg⁻¹·min⁻¹ and averaged 277 ± 8 µg·kg⁻¹·min⁻¹. Once maximal EEG suppression was achieved, the propofol infusion rate was kept constant. All patients required phenylephrine infusion to support the MAP with induction of maximal EEG suppression, and the infusion rate increased during administration of the inhaled agents to maintain MAP constant at the level before the inhaled agents were administered.

There was no difference in Vmca between the three groups during propofol-induced maximal EEG suppression; they were 28 ± 4, 30 ± 4, and 29 ± 3 for halothane, isoflurane, and desflurane, respectively. All three inhaled anesthetic agents significantly increased Vmca at 0.5 MAC (19 ± 1.5%, 21 ± 2%, and 23 ± 3%, respectively; P < 0.05) and at 1.5 MAC (18 ± 3%, 75 ± 7%, and 74 ± 4%, respectively; P < 0.05; fig. 1). The changes in CBFi were similar. Although the increase in Vmca at 0.5 MAC was not significantly different among the agents, isoflurane and desflurane increased Vmca significantly more than halothane at 1.5 MAC (P < 0.05). The increase in Vmca correlated well with the increase in CBFi (1/AVDO₂), at both 0.5 MAC and 1.5 MAC, for all three agents (r = 0.99, P < 0.0001; fig. 2).

Discussion

In patients with propofol-induced maximal EEG suppression (isoelectric EEG), halothane, isoflurane, and desflurane have similar cerebral vasodilatory effects at 0.5 MAC. However, at 1.5 MAC, halothane produces less cerebral vasodilatation than isoflurane or desflurane. These findings are at variance to the common belief that halothane is the most potent cerebral vasodilator of the inhaled anesthetics. When the influence of metabolism-mediated vasoconstriction is eliminated, isoflurane and desflurane are more potent intrinsic cerebral vasodilators.

Transcranial Doppler ultrasonography allows measurement of CBF velocity as an estimate of CBF in a noninvasive and continuous manner.³⁶ Admittedly, CBF velocity is not a direct measure of CBF. However, there is sufficient evidence to support the contention that changes in Vmca reflect corresponding changes in CBF.⁶⁻⁹ Further evidence of the validity of the change in Vmca as a measure of relative change in CBF is the close correlation observed in this study between the percentage increase in Vmca and the percentage increase in CBFI (fig. 2). During steady-state anesthesia, when cerebral metabolic requirement for oxygen is presumed constant, changes in 1/AVDO₂ reflect changes in CBF (CBF × AVDO₂ = cerebral metabolic requirement for oxygen = constant). As maximal EEG suppression was maintained throughout our study and the body temperature stayed constant, our experimental conditions fulfilled the conditions for a steady cerebral metabolic requirement for oxygen. Had there been any significant dilatation of the insonated portion of the MCA, the increase in CBFI would have been greater than the corresponding increase in Vmca. Although Vmca is an index of regional flow, and AVDO₂ is a global measure of balance between oxygen extraction and blood flow, provided the regional distribution of flow stays constant, changes in this derived variable of CBFI should reflect changes in Vmca. Moreover, under normal conditions, the MCA carries between 70% and 75% of the ipsilateral carotid blood flow.⁹

The normal Vmca varies from 35 to 90 cm/s with an average of about 60 cm/s during the awake and resting state.¹⁰ This range of Vmca probably reflects the individual’s difference in MCA diameter, baseline CBF, and the varying angle of insonation. The Vmca observed during propofol-induced maximal EEG suppression was

![Figure 2](image_url)

Fig. 2. A plot of the percent increase in cerebral blood flow equivalent (1/AVDO₂) versus percent increase in Vmca. Data from the 21 patients studied are pooled and subjected to linear correlation analysis. The best fit line and 95% confidence limits are shown (r = 0.99, P < 0.0001).
less than previously reported during propofol anesthesia but is consistent with the cerebral vasoconstrictive effect of propofol, and the difference can be attributed to the larger dose and profound metabolic suppression in the current study.

Intravenous anesthetics, such as the barbiturates, produce cerebral vasoconstriction indirectly by reducing cerebral metabolism. Maximal metabolic reduction coincides with the onset of maximal suppression in the EEG (isoelectric EEG with absence of burst activity), beyond which no further reduction in cerebral metabolic requirement for oxygen or CBF occurs with further administration of barbiturates. We used propofol to induce maximal EEG suppression because there is ample evidence suggesting that the CBF and metabolic effects of propofol are similar to those of barbiturates. At the same time, the pharmacokinetic profile of propofol allows prompt awakening and recovery at the end of the surgical procedure. Atrru et al. showed that, in dogs, low and moderate doses of propofol decrease EEG activity and cerebral metabolism with an associated decrease in CBF. Furthermore, when the EEG becomes isoelectric, increasing the dose of propofol was not accompanied by further reduction in cerebral metabolism.

At 1.5 MAC, isoflurane and desflurane administration resulted in a larger percentage increase in \( V_{\text{mca}} \) than with halothane (fig. 1). This is corroborated by a similar change in \( \text{CBF}_F \). Although we cannot rule out the possibility of a minor change in vessel diameter with volatile anesthetics, one would need to invoke differential dilatation of the MCA with halothane but not with isoflurane and desflurane to account for such a large difference. Not only would this be inconsistent with the \( \text{CBF}_F \) findings, but the close correlation between \( V_{\text{mca}} \) and \( \text{CBF}_F \) would not have been observed (fig. 2). We believe our observations to be valid.

Drummond et al. were the first investigators to establish the importance of background cerebral metabolic activity as a determinant of cerebral vascular effects of volatile anesthetics. Subsequently, Hansen et al. observed that, at equipotent levels of 1 MAC, halothane was associated with a higher cerebral metabolic rate and thus a higher CBF than isoflurane in rats. Whereas Drummond et al. found no difference between halothane and isoflurane when the cortical electrical activity is maximally suppressed, the findings from Hansen et al. suggest that isoflurane may be a more potent intrinsic cerebral vasodilator than halothane. We have extended these observations to humans and confirmed the validity of the "dual action hypothesis" as an explanation of the influence of inhalation anesthetics on the cerebral vasculature. Briefly, this hypothesis states that inhalation agents have a direct cerebral vasodilatory action independent of cerebral metabolism and an indirect effect consequential of the normal flow-metabolism coupling, which causes cerebral vasoconstriction when the cerebral metabolic rate is decreased by the addition of halothane, isoflurane, or desflurane. Thus, the net effect of adding an inhalation agent on CBF depends on the balance between its vasodilatory and cerebral metabolic depressant effects. When cerebral metabolism already is depressed, the agent only increases CBF by dilatation of cerebral vessels. However, should the agent be administered to patients who are in a "light plane of anesthesia," its cerebral metabolic depressant effect leads to a decrease in CBF. As we maintained maximal suppression of the EEG before the introduction of the inhaled agent, it is reasonable to assume that no further reduction in cerebral metabolism would result from the addition of halothane, isoflurane, or desflurane to the inspiratory gases. Indeed, the observed increase in \( V_{\text{mca}} \) and \( \text{CBF}_F \) indicated that all three agents are direct cerebral vasodilators. Their cerebral vasodilatory action is similar at 0.5 MAC, but halothane appears to have less cerebral vasodilatory effect than either isoflurane or desflurane at 1.5 MAC.

Our data in humans are qualitatively in agreement with the findings of Drummond et al. and Hansen et al., and the discrepancy can be attributed to difference in species studied. Desflurane, with cardiovascular and cerebral vascular properties similar to those of isoflurane, is more potent than halothane. Although clinical studies generally reported that isoflurane is the least potent cerebral vasodilator among the inhaled anesthetics, our findings are not contradictory, because isoflurane is also a more potent depressant of cerebral metabolism than halothane and is therefore associated with a more potent indirect vasoconstrictive action if significant cerebral metabolic activity is present at the time of administration.

We conclude that, in patients with propofol-induced maximal EEG suppression, the addition of an inhalation agent results in an increase in \( V_{\text{mca}} \) as a result of direct cerebral vasodilatation and that isoflurane and desflurane are more potent intrinsic vasodilators than halothane. These observations confirm in humans the previous observations in animal studies that the cerebro-
vascular action of inhalation anesthetics depends on the existing cerebral metabolic rate. The clinical importance of these findings remains unclear, but the fact that the influence of volatile anesthetics on CBF depends on the existing cerebral metabolic activity may explain some of the inconsistent CBF findings previously reported.

The authors thank the staff orthopaedic surgeons, for permission to study their patients, and Lee Amorin, for his technical assistance.

References

4. Michenfelder JD. The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 41:231–236, 1974

Anesthesiology, V 83, No 5, Nov 1995