

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

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Background: The effect of volatile anesthetics on cerebral blood flow depends on the balance between the agent's direct vasodilatory 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 ($19 \pm 1.5\%$, $21 \pm 2\%$, and $23 \pm 3\%$, respectively; $P < 0.05$) and at 1.5 MAC ($48 \pm 3\%$, $75 \pm 7\%$, and $74 \pm 4\%$, 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.¹ 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.¹ 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.² 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.² Therefore, the effect of a volatile agent on CBF partly depends on the level of cerebral

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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,³ 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.⁴

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 $\mu\text{g}/\text{kg}$ fentanyl, and muscle relaxation was achieved with 0.1 mg/kg vecuronium. After tracheal intubation, the lungs were ventilated with an oxygen/air mixture ($\text{F}_{\text{I}\text{O}_2} = 0.50$) to achieve normocapnia ($\text{Pa}_{\text{CO}_2} 38 \pm 2$ mmHg). Anesthesia was maintained with propofol infusion set at 250–300 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and fentanyl infusion set at 2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, 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.⁵ 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.⁶ 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 [$V_{\text{mca}} = 1/3(\text{systolic} - \text{diastolic velocity}) + \text{diastolic velocity}$]. 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 ($\text{F}_{\text{I}\text{O}_2} = 0.5$). 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} .⁷

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.⁷ Moreover, the period during which volatile anesthetics were given was approximately 1 h, a duration deemed too short to effect time-related changes.

Table 1. Patient Demographic Data

Group	Halothane (n = 7)	Isoflurane (n = 7)	Desflurane (n = 7)
Age (yr)	33 ± 11	35 ± 7	32 ± 8
Weight (kg)	84 ± 16	80 ± 12	79 ± 10

Values are mean ± SD.

Data Analysis

Demographic data were analyzed using analysis of variance. The CBF equivalent (CBF_E) was calculated from the reciprocal of the cerebral arteriovenous oxygen content difference ($AVDO_2$): $AVDO_2 = \text{hemoglobin concentration} \times 1.39 \times (Sa_{O_2} - S_{jv}O_2) + 0.003 \times (Pa_{O_2} - P_{jv}O_2)$ vol%, where Sa_{O_2} is arterial oxygen saturation, $S_{jv}O_2$ is the jugular bulb oxygen saturation, Pa_{O_2} is arterial oxygen tension, and $P_{jv}O_2$ is the jugular bulb oxygen tension.

CBF velocity and CBF_E 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 V_{mca} and CBF_E 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

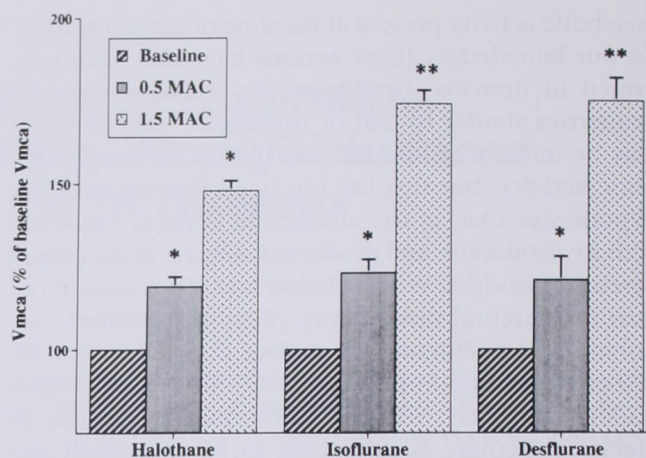


Fig. 1. The effect of 0.5 and 1.5 MAC halothane, isoflurane, and desflurane on V_{mca} . The V_{mca} is expressed as a percentage of baseline value. * V_{mca} was significantly higher than baseline during halothane, isoflurane, and desflurane anesthesia at 0.5 and 1.5 MAC using analysis of variance for repeated measures at $P < 0.05$. ** V_{mca} was significantly higher during isoflurane and desflurane than halothane anesthesia at 1.5 MAC using analysis of variance for repeated measures at $P < 0.05$.

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, Pa_{O_2} , or Pa_{CO_2} during the study period. During the study, hematocrit was between 35% and 37%; Pa_{O_2} was between 235 and 289 mmHg; Pa_{CO_2} 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 $AVDO_2$

Group	Halothane (n = 7)			Isoflurane (n = 7)			Desflurane (n = 7)		
	Baseline	0.5 MAC	1.5 MAC	Baseline	0.5 MAC	1.5 MAC	Baseline	0.5 MAC	1.5 MAC
MAP (mmHg)	80 ± 2	82 ± 2	81 ± 2	90 ± 3	89 ± 3	89 ± 3	84 ± 3	85 ± 3	85 ± 2
V_{mca} (cm/s)	28 ± 4	34 ± 4*	42 ± 6†	30 ± 4	37 ± 7*	52 ± 7†‡	29 ± 3	35 ± 4*	51 ± 5†‡
$AVDO_2$ (vol%)	6.3 ± 0.8	5.3 ± 0.6*	4.2 ± 0.7†	5.7 ± 0.6	4.6 ± 0.5*	3.2 ± 0.4†‡	6.6 ± 0.6	5.4 ± 0.6*	3.7 ± 0.4†‡
CBF_E (1/vol%)	0.165 ± .03	0.196 ± 0.15*	0.244 ± 0.05†	0.184 ± 0.02	0.224 ± 0.04*	0.326 ± 0.05†‡	0.16 ± 0.01	0.197 ± 0.2*	0.286 ± 0.03†‡
% CBF_E (change from baseline)	0	18 ± 3*	48 ± 3†	0	24 ± 3*	73 ± 4†‡	0	23 ± 3*	79 ± 7†‡

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).

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(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 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and averaged $277 \pm 8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. 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 V_{mca} 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 V_{mca} at 0.5 MAC ($19 \pm 1.5\%$, $21 \pm 2\%$, and $23 \pm 3\%$, respectively; $P < 0.05$) and at 1.5 MAC ($48 \pm 3\%$, $75 \pm 7\%$, and $74 \pm 4\%$, respectively; $P < 0.05$; fig. 1). The changes in CBF_E were similar. Although the increase in V_{mca} at 0.5 MAC was not significantly different among the agents, isoflurane and desflurane increased V_{mca} significantly more than halothane at 1.5 MAC ($P < 0.05$). The increase in V_{mca} correlated well with the increase in CBF_E ($1/\text{AVDO}_2$), 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.⁶ Admittedly, CBF velocity is not a direct measure of CBF. However, there is sufficient evidence to support the contention that changes in V_{mca} reflect corresponding changes in CBF.⁶⁻⁹ Further evidence of the validity of the change in V_{mca} as a measure of relative change in CBF is the close correlation observed in this study between the percentage

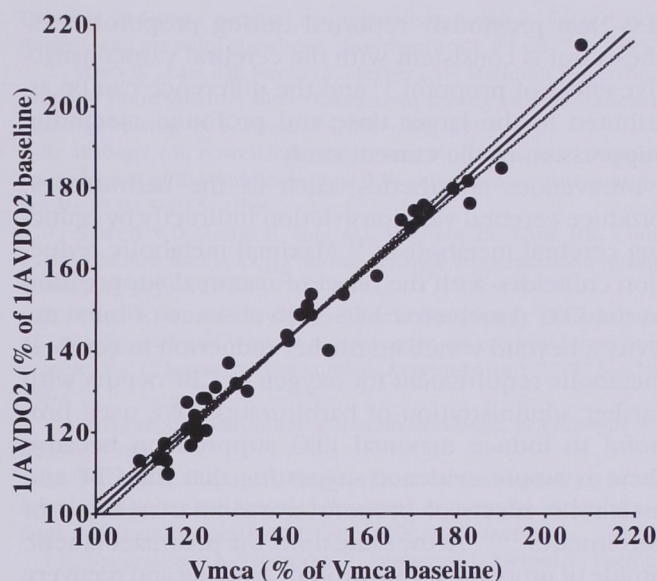


Fig. 2. A plot of the percent increase in cerebral blood flow equivalent ($1/\text{AVDO}_2$) versus percent increase in V_{mca} . Data from the 21 patients studied are pooled and subjected to linear correlation analysis. The best fit line and 95% confidence limits are shown ($r = 0.99$, $P < 0.0001$).

increase in V_{mca} and the percentage increase in CBF_E (fig. 2). During steady-state anesthesia, when cerebral metabolic requirement for oxygen is presumed constant, changes in $1/\text{AVDO}_2$ reflect changes in CBF ($\text{CBF} \times \text{AVDO}_2 = \text{cerebral metabolic requirement for oxygen} = \text{constant}$). 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 CBF_E would have been greater than the corresponding increase in V_{mca} . Although V_{mca} is an index of regional flow, and AVDO_2 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 CBF_E should reflect changes in V_{mca} . Moreover, under normal conditions, the MCA carries between 70% and 75% of the ipsilateral carotid blood flow.⁹

The normal V_{mca} 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 V_{mca} probably reflects the individual's difference in MCA diameter, baseline CBF, and the varying angle of insonation. The V_{mca} observed during propofol-induced maximal EEG suppression was

less than previously reported during propofol anesthesia but is consistent with the cerebral vasoconstrictive effect of propofol,¹⁰ 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.¹¹ 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.³ 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.¹²⁻¹⁴ At the same time, the pharmacokinetic profile of propofol allows prompt awakening and recovery at the end of the surgical procedure. Artru *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.¹²

At 1.5 MAC, isoflurane and desflurane administration resulted in a larger percentage increase in V_{mca} than with halothane (fig. 1). This is corroborated by a similar change in CBF_E . Although we cannot rule out the possibility of a minor change in vessel diameter with volatile anesthetics, one would need to invoke differential dilation 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 CBF_E findings, but the close correlation between V_{mca} and CBF_E 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.¹ 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.² 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.² 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.^{1,2,15} 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 dilation 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_{mca} and CBF_E 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,^{3,16,17} is a more potent direct cerebral vasodilator 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_{mca} as a result of direct cerebral vasodilatation and that isoflurane and desflurane are more potent intrinsic vasodilators than is halothane. These observations confirm in humans the previous observations in animal studies that the cerebro-

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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.

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