

## Direct Cerebral Vasodilatory Effects of Sevoflurane and Isoflurane

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**Background:** The effect of volatile anesthetics on cerebral blood flow depends on the balance between the indirect vasoconstrictive action secondary to flow-metabolism coupling and the agent's intrinsic vasodilatory action. This study compared the direct cerebral vasodilatory actions of 0.5 and 1.5 minimum alveolar concentration (MAC) sevoflurane and isoflurane during an propofol-induced isoelectric electroencephalogram.

**Methods:** Twenty patients aged 20–62 yr with American Society of Anesthesiologists physical status I or II requiring general anesthesia for routine spinal surgery were recruited. In addition to routine monitoring, a transcranial Doppler ultrasound was used to measure blood flow velocity in the middle cerebral artery, and an electroencephalograph to measure brain electrical activity. Anesthesia was induced with propofol 2.5 mg/kg, fentanyl 2 µg/kg, and atracurium 0.5 mg/kg, and a propofol infusion was used to achieve electroencephalographic isoelectricity. End-tidal carbon dioxide, blood pressure, and temperature were maintained constant throughout the study period. Cerebral blood flow velocity, mean blood pressure, and heart rate were recorded after 20 min of isoelectric encephalogram. Patients were then assigned to receive either age-adjusted 0.5 MAC (0.8–1%) or 1.5 MAC (2.4–3%) end-tidal sevoflurane; or age-adjusted 0.5 MAC (0.5–0.7%) or 1.5 MAC (1.5–2%) end-tidal isoflurane. After 15 min of unchanged end-tidal concentration, the variables were measured again. The concentration of the inhalational agent was increased or decreased as appropriate,

and all measurements were repeated again. All measurements were performed before the start of surgery. An infusion of 0.01% phenylephrine was used as necessary to maintain mean arterial pressure at baseline levels.

**Results:** Although both agents increased blood flow velocity in the middle cerebral artery at 0.5 and 1.5 MAC, this increase was significantly less during sevoflurane anesthesia ( $4 \pm 3$  and  $17 \pm 3\%$  at 0.5 and 1.5 MAC sevoflurane;  $19 \pm 3$  and  $72 \pm 9\%$  at 0.5 and 1.5 MAC isoflurane [mean  $\pm$  SD];  $P < 0.05$ ). All patients required phenylephrine (100–300 µg) to maintain mean arterial pressure within 20% of baseline during 1.5 MAC anesthesia.

**Conclusions:** In common with other volatile anesthetic agents, sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect. However, this effect is less than that of isoflurane. (Key words: Anesthesia; cerebral blood flow; inhalational; transcranial Doppler ultrasonography.)

INHALATIONAL anesthetic agents have been shown to produce a dose-dependent increase in cerebral blood flow (CBF). The magnitude of this increase is dependent on the balance between the agent's intrinsic vasodilatory action and the vasoconstriction secondary to flow-metabolism coupling.<sup>1-3</sup> Therefore, in order to expose the intrinsic vasodilatory action of a particular agent, the vasoconstriction secondary to flow-metabolism coupling has to be abolished. By using propofol to induce isoelectricity of the electroencephalogram (EEG), Matta *et al.*<sup>2</sup> demonstrated that isoflurane and desflurane produce more cerebral vasodilatation than an equipotent dose of halothane.

Sevoflurane, a recently introduced inhalational anesthetic agent, is very similar to isoflurane in its cardiovascular effects.<sup>4,5</sup> Although sevoflurane has been shown to have similar cerebral vascular effects to isoflurane in animals,<sup>6,7</sup> this has not been a consistent finding in humans.<sup>8-11</sup> This study compared the intrinsic vasodilatory effect of 0.5 and 1.5 minimum alveolar concentration (MAC) sevoflurane and isoflurane in humans.

### Materials and Methods

With local ethical committee approval and written informed consent, 20 patients, aged 20–62 yr, American

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Society of Anesthesiologists physical status 1 or 2, requiring general anesthesia for routine spinal neurosurgical procedures, were recruited. Routine monitoring consisting of electrocardiography, noninvasive blood pressure measurement (Dinamap; Critikon, Tampa, FL), and pulse oximetry was instigated before the induction of anesthesia with propofol 2.5 mg/kg, fentanyl 2  $\mu$ g/kg, and atracurium 0.5 mg/kg. After tracheal intubation, the lungs were ventilated with an air/oxygen mixture (inspired oxygen fraction 0.5) to mild hypocapnia (end-tidal carbon dioxide concentration 30–35 mmHg; measured with Capnomac Ultima; Datex, Helsinki, Finland). Esophageal temperature was measured continuously after the induction of anesthesia. Brain electrical activity was measured using a two-channel bipolar frontal montage (A-1000 EEG monitor; Aspect Medical Systems, MA), which displayed unprocessed EEG and burst suppression ratio. The burst suppression ratio is defined as the percentage of epochs in the past 63 s in which the EEG signal is considered suppressed; a burst suppression ratio of 100% implies EEG silence. The EEG electrodes were attached to the patients' foreheads with self-adhesive, low-impedance electrodes, and the impedance was confirmed at less than 10,000  $\Omega$  before measurements were made. A 2-MHz transcranial Doppler ultrasound probe (DWL Multidop; Sipplingen, Germany) was used to measure the time-averaged mean blood flow velocity in the middle cerebral artery ( $V_{mca}$ ). Once the best signal was obtained at a depth between 45 and 55 mm, the probe was secured in position using a specially designed frame so that the angle of insonation remained constant throughout the study period. Baseline anesthesia was maintained with a propofol infusion at a rate sufficient to achieve EEG isoelectricity (a rate of 200–300). After a 20-min period of stable propofol infusion and isoelectric EEG,  $V_{mca}$ , mean arterial pressure (MAP), end-tidal  $CO_2$  concentration, heart rate, and esophageal temperature were measured. Patients received either sevoflurane or isoflurane in the first of two random doses adjusted for age,<sup>12</sup> *i.e.*, either 0.5 MAC sevoflurane (0.8–1.0%) or 1.5 MAC sevoflurane (2.4–3.0%), or 0.5 MAC isoflurane (0.5–0.7%) or 1.5 MAC isoflurane (1.5–2.0%). After a 15-min period of unchanged end-tidal concentration (Capnomac Ultima; Datex), the measurements were repeated. The concentration of sevoflurane or isoflurane was increased or decreased as appropriate, and after a further 15-min period of unchanged end-tidal concentration, all measurements were repeated. All measurements were performed before the start of surgery. An infusion

**Table 1. Physiologic Values during Direct Cerebral Vasodilatory Tests**

	Sevoflurane (n = 10)	Isoflurane (n = 10)
Baseline		
ET <sub>CO<sub>2</sub></sub> (mmHg)	33 ± 12	34 ± 3
MAP (mmHg)	78 ± 12	84 ± 12
HR (beats/min)	69 ± 12	64 ± 9
$V_{mca}$ (cm/sec)	23 ± 3	26 ± 6
0.5 MAC anesthesia		
ET <sub>CO<sub>2</sub></sub> (mmHg)	32 ± 12	34 ± 3
MAP (mmHg)	74 ± 6	83 ± 12
HR (beats/min)	69 ± 12	65 ± 12
$V_{mca}$ (cm/sec)	24 ± 3*	31 ± 6*
$V_{mca}$ (% increase from baseline)	4 ± 3*	19 ± 3*
1.5 MAC anesthesia		
ET <sub>CO<sub>2</sub></sub> (mmHg)	32 ± 12	34 ± 3
MAP (mmHg)	75 ± 9	83 ± 9
HR (beats/min)	67 ± 9	62 ± 12
$V_{mca}$ (cm/sec)	27 ± 3*	44 ± 12*
$V_{mca}$ (% increase from baseline)	17 ± 3*	72 ± 12*

Values are mean ± SD.

Baseline = air/oxygen, fentanyl + propofol; ET<sub>CO<sub>2</sub></sub> = end-tidal CO<sub>2</sub>; MAP = mean arterial blood pressure; HR = heart rate;  $V_{mca}$  = mean cerebral blood flow velocity in the middle cerebral artery; MAC = minimum alveolar concentration.

\* Significantly different versus baseline ( $P < 0.05$ ).

of 0.01% phenylephrine was used as necessary to maintain MAP at baseline levels.

### Statistical Analysis

Results with each agent were compared using analysis of variance. The Scheffé test was used for a multiple-comparisons procedure in order to delineate where the differences were.  $P < 0.05$  was considered to be statistically significant. All values are expressed as mean ± SD unless otherwise stated.

### Results

The main findings of the study are shown in table 1. The mean propofol infusion rate required to achieve EEG burst suppression was  $258 \pm 47 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The mean weight in the sevoflurane group was greater than the isoflurane group ( $81 \pm 14$  vs.  $68 \pm 6$  kg, respectively). There were no significant changes in end-tidal  $CO_2$  concentration, heart rate, or MAP during the study period and the esophageal temperature was maintained at or above 36°C in all patients. All patients required phenylephrine (100–300  $\mu$ g) to maintain MAP within 20% of baseline during 1.5 MAC anesthesia. Both sevoflurane and isoflurane significantly increased  $V_{mca}$

from baseline. This increase was significantly less during sevoflurane anesthesia ( $4 \pm 3\%$  at 0.5 MAC sevoflurane and  $17 \pm 3\%$  at 1.5 MAC sevoflurane *vs.*  $19 \pm 3\%$  at 0.5 MAC isoflurane and  $72 \pm 9\%$  at 1.5 MAC isoflurane;  $P < 0.05$ ).

## Discussion

This study demonstrates that, in common with other inhalational anesthetic agents,<sup>2</sup> sevoflurane increases CBF velocity in a dose-dependent manner during propofol-induced EEG silence (maximal metabolic suppression). However, the magnitude of this increase with 0.5 and 1.5 MAC sevoflurane is significantly less than equipotent concentrations of isoflurane under similar conditions.

Transcranial Doppler (TCD) ultrasonography provides an indirect measure of CBF if the angle of insonation and vessel diameter remain constant.<sup>13</sup> We used a specially designed frame to hold the TCD probe in position to ensure a constant angle of insonation throughout the study period.<sup>13</sup> Available evidence suggests that the diameter of the middle cerebral artery is not significantly affected by changes in carbon dioxide tension, blood pressure, or the administration of anesthetic or vasoactive agents.<sup>14-16</sup> Furthermore, the use of TCD ultrasonography to estimate changes in CBF if desflurane, halothane, or isoflurane are administered during propofol-induced EEG suppression has been demonstrated in a recent study.<sup>2</sup> Therefore, it is reasonable to assume that during sevoflurane anesthesia changes in  $V_{mca}$  reflect changes in CBF.

Propofol produces cerebral vasoconstriction indirectly by reducing cerebral metabolism.<sup>17</sup> In dogs, propofol has been shown to decrease EEG activity and cerebral metabolism associated with a decrease in CBF.<sup>18</sup> Once the EEG becomes isoelectric, there is no further reduction in cerebral metabolism despite increasing doses of anesthetic. It is therefore reasonable to assume that under the baseline conditions of this study, with an isoelectric EEG, the addition of sevoflurane would cause no further reductions in cerebral metabolism. Any increases in CBF would therefore be caused by the intrinsic vasodilatory properties of sevoflurane on the cerebral vasculature.

We used the A-1000 EEG monitor to display an unprocessed EEG and to calculate the burst suppression ratio from a two-channel bipolar frontal montage. The burst suppression ratio is defined as the percentage of epochs in the past 63 s in which the EEG signal is considered

suppressed; a burst suppression ratio of 100% implies EEG silence. We were able to achieve an isoelectric EEG with doses of propofol between 200 and 350  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . These doses are similar to those previously described for achieving an isoelectric EEG.<sup>2</sup>

We measured  $V_{mca}$  at constant end-tidal carbon dioxide tensions. Changes in end-tidal carbon dioxide tension have been shown to correlate well with changes in arterial carbon dioxide tension in healthy patients.<sup>19</sup>

Phenylephrine was required in all patients to maintain MAP at baseline values during propofol-induced EEG silence. Phenylephrine has been shown recently not to directly affect intracranial hemodynamics in anesthetized patients.<sup>20</sup>

This study is very similar to the work published by Matta *et al.*,<sup>2</sup> in which the direct cerebral vasodilatory effects of halothane, isoflurane, and desflurane using TCD ultrasonography in humans were demonstrated. The introduction of 0.5 MAC halothane, isoflurane, or desflurane during propofol-induced EEG silence resulted in similar increases in  $V_{mca}$  for all three agents studied. However, if the concentration was increased to 1.5 MAC, the increase in  $V_{mca}$  from baseline was significantly more for isoflurane and desflurane than halothane ( $73 \pm 4$ ,  $79 \pm 7$ , and  $48 \pm 3\%$ , respectively). This demonstrates that under conditions of maximal metabolic suppression, isoflurane and desflurane are more marked cerebral vasodilators than halothane. In this study sevoflurane increased  $V_{mca}$  by 4 and 17% at 0.5 and 1.5 MAC, respectively, suggesting that the direct cerebral vasodilatory effect of sevoflurane is less than that of halothane, isoflurane, and desflurane. These findings agree with previous work published on the effect of sevoflurane on cerebral hemodynamics. Kitaguchi *et al.*<sup>21</sup> investigated the cerebral vascular effects of 0.88 MAC sevoflurane in an oxygen-nitrous oxide mixture in patients with ischemic cerebral vascular disease undergoing extracranial-intracranial arterial anastomosis. CBF was determined by argon desaturation by the Kety-Schmidt method using a mass spectrometer. When the authors compared the data on CBF and cerebral metabolic requirements for oxygen obtained from this study to values in awake patients obtained in a previous study, they reported a reduction of 34% and 52% in CBF and cerebral metabolic requirements for oxygen, respectively. Similarly, previous work at our institution indicated that in the presence of a "light" propofol anesthetic, sevoflurane in humans has negligible effects on  $V_{mca}$  and cerebral metabolic equivalent (CME) at 0.5 MAC and only causes small increases in  $V_{mca}$  and cerebral metabolic equivalent at

1.5 MAC.<sup>9</sup> Cerebral metabolic equivalent = CBF velocity  $\times$  arteriovenous oxygen content difference and was used as a substitute for cerebral metabolic requirements for oxygen, as blood flow velocity was measured and not blood flow.

This "weak" intrinsic cerebral vasodilatory action of sevoflurane may help explain why the cerebral vasculature remains capable of responding to changes in perfusion pressure during sevoflurane anesthesia, but it is abolished during equipotent isoflurane and desflurane anesthesia because of greater cerebral vasodilatation.<sup>10,22</sup> Furthermore, because of this weak intrinsic vasodilatory action, sevoflurane is unlikely to cause a significant increase in intracranial pressure, a feature preferred for agents used in neurosurgical anesthesia. This hypothesis is supported by the recently published data of Artru *et al.*<sup>8</sup> who reported no increases in intracranial pressure during 0.5, 1.0, and 1.5 MAC sevoflurane anesthesia.

We conclude that in common with other volatile anesthetic agents, sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect. However, this effect is less than that reported for halothane, isoflurane, and desflurane at equipotent anesthetic concentrations. These findings suggest that sevoflurane has a cerebral hemodynamic profile favoring its use in neuroanesthesia.

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