Cerebral Circulation and Metabolism during Enflurane Anesthesia in Humans

Takefumi Sakabe, M.D.,* Tsuyoshi Maekawa, M.D.,† Seigo Fujii, M.D.,‡ Toshizo Ishikawa,§ Akio Tateishi, M.D.,¶ Hiroshi Takeshita, M.D.**

The effects of enflurane anesthesia on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR\textsubscript{O\textsubscript{2}}) were studied in 17 patients. The patients were divided into two groups according to the depth of anesthesia. Cerebral perfusion pressure was maintained above 60 mmHg with phenylephrine. In Group 1 (arterial enflurane concentration, 15 mg/dl), patients were studied before surgery, while in Group 2 (enflurane concentration, 27 mg/dl), the measurements were performed before and during surgery. In Group 1, mean CBF and CMR\textsubscript{O\textsubscript{2}} were 53 and 2.6 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}, respectively. These values were not significantly different from CBF (46 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}) and CMR\textsubscript{O\textsubscript{2}} (5.1 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}) values previously obtained in awake patients. In Group 2 before surgery, mean CBF and CMR\textsubscript{O\textsubscript{2}} were 61 and 2.6 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}, respectively, and were significantly different from the awake values, while the EEG showed frequent spikes and suppression. In Group 2 during surgery, mean CBF and CMR\textsubscript{O\textsubscript{2}} did not differ from the values obtained before surgery, despite significant EEG changes. The results indicate that enflurane is a cerebral vasodilator and causes an increase in CBF and a decrease in CMR\textsubscript{O\textsubscript{2}}, in humans at an anesthetic level characterized by frequent spikes and suppression on the EEG. (Key words: Anesthetics, volatile; enflurane. Brain: blood flow, oxygen consumption.)

The cerebral effects of enflurane have been well documented in both electrophysiological and behavioral studies. However, the effects of enflurane on cerebral blood flow (CBF) and oxygen consumption (CMR\textsubscript{O\textsubscript{2}}) have not been investigated thoroughly in humans. Wollman et al. reported that CBF remained unchanged, while CMR\textsubscript{O\textsubscript{2}} decreased by 50% at a level of anesthesia characterized by frequent EEG spike activity separated by periods of electrical silence. However, subsequent study from the same laboratory, though published in abstract form only, revealed that enflurane, 1.1 MAC and 1.6 MAC, increased CBF by 97% and 80% from the awake values if blood pressure was supported.††

Methods

Seventeen ASA I or II patients (male, four; female, 13) who were undergoing elective surgery were studied. Age of patients ranged from 25 to 58 yr. The study was approved by the Hospital Committee on Human Study. Preoperative examination revealed no cardiopulmonary or neurologic disorders in all patients. Atropine sulfate, 0.5 mg, was given intramuscularly 30 min before induction. Anesthesia was induced with enflurane in oxygen, and the inspired concentration of enflurane was increased to 4% over 3–4 min. Endotracheal intubation was facilitated with intravenous administration of pancuronium bromide, 6–8 mg. After intubation, enflurane concentrations was changed to either 2% in group 1 (seven patients) or 3.5% in group 2 (10 patients). In all patients ventilation was controlled mechanically to maintain normocapnia, and nitrogen was added to adjust the F\textsubscript{O\textsubscript{2}} to 0.33. A 21-gauge teflon indwelling catheter was placed in the radial artery and an 18-gauge Medicut\textsuperscript{®} catheter was placed in the jugular bulb for blood sampling and pressure measurement. The position of the jugular bulb catheter tip was confirmed by x-ray. In Group 1, measurements were made 30 min after starting enflurane inhalation, 2%. In Group 2, measurements were made 30 min after enflurane inhalation, 3.5%, (before surgery) and then 15–30 min after the start of abdominal surgery (during surgery). The rectal temperature was monitored by a calibrated thermistor probe and was kept at 36.8 ± 0.2° C using a cooling–warming water mattress. The end-expired carbon dioxide concentration was monitored continuously with an infra-red gas analyzer (Datex, Norrocap, Denmark). Bilateral unipolar, frontal, and occipitotemporal electroencephalograms (EEG) were monitored and recorded continuously (Nihon Koden, MAF5, 0003-3022/83/1200/0532 $01.05 © The American Society of Anesthesiologists, Inc.
TABLE 1. Physiologic Variables and Anesthetic Concentration during Enflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Enflurane concentration mg/dl</th>
<th>MAP mmHg</th>
<th>Pao2 mmHg</th>
<th>Paco2 mmHg</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>7</td>
<td>A 14.5 ± 0.8</td>
<td>81 ± 2*</td>
<td>135 ± 7*</td>
<td>38 ± 1</td>
<td>7.37 ± 0.02*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V 14.5 ± 0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2 (before surgery)</td>
<td>10</td>
<td>A 27.3 ± 1.0</td>
<td>76 ± 3*</td>
<td>191 ± 32*</td>
<td>35 ± 1</td>
<td>7.41 ± 0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V 27.0 ± 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2 (during surgery)</td>
<td>10</td>
<td>A 27.3 ± 0.9</td>
<td>80 ± 3*</td>
<td>177 ± 31*</td>
<td>37 ± 1</td>
<td>7.40 ± 0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V 27.3 ± 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake†</td>
<td>13</td>
<td>A —</td>
<td>95 ± 4</td>
<td>473 ± 12</td>
<td>35 ± 1</td>
<td>7.45 ± 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values are mean ± SE.
A = Arterial blood; V = Jugular bulb blood.
* Significantly different from awake value (P < 0.05).
† Data from our laboratory (Br J Anaesth 48:545–550, 1976), FiO2 during measurement = 0.85.

Cerebral blood flow (CBF) was measured by the Kety-Schmidt technique using 15% nitrous oxide as previously reported. After taking arterial and jugular bulb venous blood samples, nitrous oxide 15% was added to the gas mixture and the nitrogen concentration was adjusted to maintain a constant FiO2 at 0.33. Simultaneous arterial and jugular bulb venous blood samples then were obtained at 1, 2, 3, 4, 5, 7, 9, 12, and 15 min after the initiation of nitrous oxide. The concentration of nitrous oxide in the blood was measured by gas chromatography (Shimazu, GC-4APTF, Japan). The CBF was calculated by a modification of the Kety-Schmidt method, which includes prolongation of the nitrous oxide saturation phase and extrapolation of the arterio-venous difference of nitrous oxide concentration to infinity. The arterial and internal jugular venous pressures were measured by strain gauge transducers with the zero point at the mastoid process and were recorded on a polygraph (Nihon Koden, MAP-5, Japan). The electrocardiogram (lead II) also was monitored. The difference between mean arterial pressure (MAP) and mean jugular venous pressure was defined as cerebral perfusion pressure (CPP). Cerebral vascular resistance (CVR) was calculated as the ratio of CPP to CBF. Pao2, Paco2, and pH were measured with a blood gas analyzer (ABL2, Radiometer, Denmark). Oxygen saturation and hemoglobin concentration were measured with an IL CO-oximeter (Model 282, Instrumentation Laboratory, Lexington, MA). Blood glucose concentration was measured by an enzymatic method. These values were measured before and at 5, 10, and 15 min after the start of nitrous oxide inhalation; the mean values of the four samples are reported. Arterial and jugular bulb venous blood concentrations of enflurane were measured with a gas chromatograph (Shimazu, GC-4APTF, Japan) equipped with a flame ionization detector. Enflurane in the blood was extracted into carbon tetrachloride, and the recovery rate of enflurane was 98 ± 1 per cent. The values reported are the mean of three samples taken before and 5 and 15 min after initiating the inhalation of nitrous oxide.

Oxygen content was calculated from the hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from Pao2 and oxygen solubility. CMRO2 and GMRglucose were calculated as the product of CBF and the oxygen or glucose content differences, respectively, between the arterial and the jugular bulb blood. Oxygen-glucose index was calculated as suggested by Cohen et al. CPP was maintained above 60 mmHg with an infusion of phenylephrine (0.005% solution); 0.4 ± 0.1 μg·kg⁻¹·min⁻¹ in Group 1 and 1.3 ± 0.3 and 0.9 ± 0.1 μg·kg⁻¹·min⁻¹ in Group 2 before and during surgery, respectively. Phenylephrine was chosen because it has been shown to have no effect on CBF or CMRO2. If CPP fell below 60 mmHg despite phenylephrine infusion or if CPP fluctuated more than 10% from the mean value obtained during inhalation of nitrous oxide, the data were discarded. In Group 2, in order to quantify the EEG change, the frequency of spikes (greater than 100 μV, less than 0.08 s duration), sharp waves (greater than 100 μV, 0.08–0.2 s duration), spike-and-wave complex, and the percentage of time occupied by the periods of suppression (electrical silence 1 s in duration or longer) were determined during the 15-min period of CBF measurement. The analysis was done visually without knowledge of surgical stimulation.

Statistical differences were tested by one-way analysis of variance with critical-difference testing, except the EEG analysis, which was tested by Wilcoxon's rank sum test. P < 0.05 was considered significant.

Results

Physiologic variables in each group are summarized in Table 1 and compared with awake values previously obtained in our laboratory. The variations in the blood concentrations of enflurane from the tabulated mean values (Table 1) during measurements were 0.9 ± 0.1 mg/dl (Group 1), 0.9 ± 0.1 mg/dl (Group 2, before surgery) and 1.0 ± 0.1 mg/dl (Group 2, during surgery), respec-
Fig. 1. Representative electroencephalogram during enflurane anesthesia (Group 1). Predominant 12–15 Hz of 50–100 μV waves were observed with higher amplitude in frontal leads than in occipitotemporal leads (anterior dominance). CBF and CMRO₂ were 56.7 ml·100 g⁻¹·min⁻¹ and 3.6 ml·100 g⁻¹·min⁻¹, respectively. Enflurane concentration in the arterial blood was 16.8 mg/dl and PaCO₂ was 39 mmHg.

Fig. 2. Representative electroencephalogram during enflurane anesthesia (Group 2). Frequent spikes and suppression observed before surgery (left) disappeared during surgery (right). CBF and CMRO₂ before and during surgery were 60 ml·100 g⁻¹·min⁻¹ vs. 72 ml·100 g⁻¹·min⁻¹ and 2.6 ml·100 g⁻¹·min⁻¹ vs. 2.4 ml·100 g⁻¹·min⁻¹, respectively. Enflurane concentration and PaCO₂ before and during surgery were 26.5 mg/dl vs. 25.8 mg/dl and 34 mmHg vs. 36 mmHg, respectively.
CEREBRAL VASCULAR AND METABOLIC EFFECTS OF ENFLURANE

TABLE 2. Electroencephalographic Changes with Surgical Simulation during Enflurane Anesthesia (Group 2)

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>During Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spike frequencies/min</td>
<td>17 ± 2</td>
<td>9 ± 2*</td>
</tr>
<tr>
<td>Spike and wave</td>
<td>4 ± 1</td>
<td>1 ± 1*</td>
</tr>
<tr>
<td>Sharp wave</td>
<td>11 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Suppression (%)</td>
<td>10 ± 2</td>
<td>1 ± 1*</td>
</tr>
</tbody>
</table>

The values are mean ± SE.
* Significantly different from the value before surgery (P < 0.05).

The mean CMR glucose tended to decrease in both Groups 1 and 2 as compared with the awake values. There was no significant change in oxygen-glucose index in any group. Jugular venous $P_{O_2}$ was significantly higher in Group 2 than in the awake group.

Discussion

The Kety–Schmidt method for measuring CBF and CMRO$_2$ in awake humans has been used for several decades and values have been reported from numerous laboratories. The range of normal values for CBF and CMRO$_2$ are from 45 to 54 ml·100 g$^{-1}$·min$^{-1}$ and from 3.0 to 3.3 ml·100 g$^{-1}$·min$^{-1}$, respectively.$^8,10,11$ Since our previously reported values are within this reported range and our methodology has not changed, we could not justify the risk and expense of repeating control measurements in awake patients at this time. Accordingly, we used our awake values obtained previously for comparison.

The present study demonstrated that in humans enflurane causes an increase in CBF (when CPP is maintained above 60 mmHg) at a level of anesthesia characterized by frequent spikes and suppression on the EEG. The increase in CBF was accompanied by a reduction in CVR, indicating that enflurane is a cerebral vasodilator. In Group 1, the significant reduction in calculated CVR was largely due to a decrease in CPP rather than any significant change in CBF. Wollman et al.$^4$ reported no significant change in CBF in volunteers during enflurane anesthesia when the EEG showed frequent spikes separated by periods of electrical silence. A subsequent study from the same laboratory by Murphy et al. demonstrated that CBF did not change significantly at 0.6 MAC enflurane but with arterial blood pressure support increased by 37 and 80% at 1.1 and 1.6 MAC, respectively, as compared with the awake values. For comparison, MACs in Groups 1 and 2 in the present study calculated from the arterial blood concentrations of enflurane (assuming a blood gas partition coefficient of 1.91 and a MAC for enflurane of 1.08%$^{12,13}$) were 0.6 and 1.2 MAC, respectively. However, actual MAC values must have been slightly higher because of additional factors, which contribute to the difference in the estimation of arterial and end-tidal anesthetic concentration.$^{14}$ Thus, the anesthetic levels in our patients may have been comparable with those in the study by Murphy et al. and, therefore, the increase in CBF with arterial blood pressure support observed in the present study is in agreement with their results. The decrease in regional CBF reported by Rolly and Van Aken$^5$ could be the result of the combined effects of enflurane, nitrous oxide and meperidine, and/or a decrease in MAP to approximately 60 mmHg.

Studies in the dog indicated that hemispheric CBF was either increased or unchanged with enflurane.$^{15,16}$ This difference also could be explained by the fact that the reduction in CPP was greater in the report where CBF did not increase.$^{16}$ From these considerations, we believe that the effect of anesthetics on CBF must be evaluated when CPP is maintained.

Wollman et al.$^4$ found a 50% reduction in CMRO$_2$ with enflurane anesthesia, while the EEG showed frequent spikes and suppression. This is the largest decrease ever reported in humans for a volatile anesthetic. However, Murphy et al., from the same laboratory subsequently reported that CMRO$_2$ was unchanged or slightly decreased during enflurane anesthesia (0.6, 1.1, 1.6 MAC), though they did not present the actual values. Therefore, one cannot draw any definite conclusions from their studies regarding the cerebral metabolic effects of enflurane in

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TABLE 3. Cerebral Circulation and Metabolism during Enflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CPP mmHg</th>
<th>CBF ml·100 g$^{-1}$·min$^{-1}$</th>
<th>CMRO$_2$ mmol·100 g$^{-1}$·min$^{-1}$</th>
<th>CVR mmHg·ml·100 g$^{-1}$·min$^{-1}$</th>
<th>CMR glucose mg·100 g$^{-1}$·min$^{-1}$</th>
<th>Oxygen-Glucose Index (%)</th>
<th>Jugular Venous $P_{O_2}$ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>7</td>
<td>75 ± 2*</td>
<td>53 ± 3</td>
<td>2.8 ± 0.1</td>
<td>1.4 ± 0.1*</td>
<td>4.2 ± 0.6</td>
<td>100 ± 13</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(before surgery)</td>
<td>10</td>
<td>66 ± 3*</td>
<td>61 ± 4*</td>
<td>2.6 ± 0.1*</td>
<td>1.1 ± 0.1*</td>
<td>3.9 ± 0.4</td>
<td>96 ± 9</td>
<td>48 ± 2*</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(during surgery)</td>
<td>10</td>
<td>71 ± 3*</td>
<td>67 ± 4*†</td>
<td>2.6 ± 0.1*</td>
<td>1.1 ± 0.1*†</td>
<td>3.9 ± 0.4</td>
<td>97 ± 7</td>
<td>51 ± 2†</td>
</tr>
<tr>
<td>Awake</td>
<td>15</td>
<td>90 ± 3*</td>
<td>46 ± 2</td>
<td>3.1 ± 0.2</td>
<td>2.0 ± 0.1</td>
<td>5.0 ± 0.5</td>
<td>88 ± 10</td>
<td>41 ± 2†</td>
</tr>
</tbody>
</table>

The values are mean ± SE.
* Significantly different from awake value (P < 0.05).
† Significantly different from Group 1 (P < 0.05).
‡ Data from our laboratory (Br J Anaesth 48:545–550, 1976).

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humans. In the present study, however, a 17% reduction in CMRO$_2$ was observed at the level of anesthesia characterized by frequent spikes and suppression on the EEG. In the canine studies cerebral metabolic depression with enflurane was also reported, and the reduction in CMRO$_2$ was dose related but nonlinear. Therefore, our observation of no significant differences in CMRO$_2$ between group 1 and the awake group may reflect a nonlinear response of cerebral metabolic depression with enflurane.

With surgical stimulation, CMRO$_2$ and CBF remained unchanged, despite the EEG changes. In our laboratory we previously demonstrated in the dog that EEG desynchronization, as produced by electrical stimulation of a peripheral nerve, was accompanied by an increase in CMRO$_2$. With deepening of anesthesia, CMRO$_2$ remained unchanged, as did the EEG with stimulation during halothane or methoxyflurane anesthesia. This animal study led us to anticipate that the EEG changes in group 2 during surgery might be accompanied by a significant change in CMRO$_2$. However, this was not the case. This might be due to differences in the area of the brain where the CBF and CMRO$_2$ were measured. Namely, in the canine studies, cerebral hemispheric CBF and CMRO$_2$ were measured, while in humans CBF and CMRO$_2$ of the whole brain were measured. However, unchanged CMRO$_2$ does not necessarily mean unaltered neuronal function. Instead, it is more likely that redistribution of blood flow coupled with metabolic change occurred with surgical stimulation.

The present study showed that the balance between oxygen supply and demand in the whole brain was well maintained during enflurane anesthesia when CPP was maintained above 60 mmHg. Enflurane caused an increase in CBF and a decrease in CMRO$_2$ during surgical depth of anesthesia.

References

15. Michenfelder JD, Cucchiara RF: Cerebral oxygen consumption during enflurane anesthesia and its modification during induced seizures. Anesthesiology 40:575-580, 1974