Preservation of the Ratio of Cerebral Blood Flow/ Metabolic Rate for Oxygen during Prolonged Anesthesia with Isoflurane, Sevoflurane, and Halothane in Humans

Yasuhiro Kuroda, M.D.,* Mari Murakami, M.D.,* Junko Tsuruta, M.D.,* Toshisuke Murakawa, M.D.,† Takefumi Sakabe, M.D.‡

Background: In several animal studies, an increase in cerebral blood flow (CBF) produced by volatile anesthetics has been reported to resolve over time during prolonged anesthesia. It is important to investigate whether this time-dependent change of CBF takes place in humans, especially in clinical situations where surgery is ongoing under anesthesia. In this study, to evaluate the effect of prolonged exposure to volatile anesthetics (isoflurane, sevoflurane, and halothane), the CBF equivalent (CBF divided by cerebral metabolic rate for oxygen (CMRO2)) was determined every 20 min during anesthesia lasting more than 4 h in patients.

Methods: Twenty-four surgical patients were assigned to three groups at random to receive isoflurane, sevoflurane, or halothane (8 patients each). End-tidal concentration of the selected volatile anesthetic was maintained at 0.5 and 1.0 MAC before surgery and then 1.5 MAC for the 3 h of surgical procedure. Normothermia and normocapnia were maintained. Mean arterial blood pressure was kept above 60 mmHg, using phenylephrine infusion, if necessary. CBF equivalent was calculated every 20 min as the reciprocal of arterial-jugular venous oxygen content difference.

Results: CBF equivalent at 0.5 MAC of isoflurane, halothane, and sevoflurane was 21 ± 4, 20 ± 3, and 21 ± 5 ml blood/ml oxygen, respectively. All three examined volatile anesthetics significantly (P < 0.01) increased CBF equivalent in a dose-dependent manner (0.5, 1.0, 1.5 MAC). At 1.5 MAC, the increase of CBF equivalent with all anesthetics was maintained increased with minimal fluctuation for 3 h. The mean value of CBF equivalent at 1.5 MAC in the isoflurane group (45 ± 8) was significantly (P < 0.01) greater than those in the halothane (32 ± 8) and sevoflurane (31 ± 8) groups. Electroencephalogram was found to be relatively unchanged during observation periods at 1.5 MAC.

Conclusions: These results demonstrate that CBF/CMRO2 ratio is markedly increased above normal and maintained during prolonged inhalation of volatile anesthetics in humans. It is impossible to determine whether these data indicate a stable CBF or whether CBF and CMRO2 are changing in parallel during the observation period. The unchanged electroencephalographic pattern suggests that the former possibility is more likely and that the increase of CBF produced by volatile anesthetics is maintained over time without decay, which has been reported in several animal studies. It also is suggested that isoflurane possesses greater capability to maintain global CBF relative to CMRO2, than does halothane or sevoflurane. (Key words: Anesthetics, volatile: halothane; isoflurane; sevoflurane. Brain: blood flow; oxygen consumption. Surgical stimulation: anesthetic interaction with time.)

IT has been reported in several animal studies, with some exceptions, that the increase in cerebral blood flow (CBF) produced by isoflurane and halothane resolves over time despite the maintenance of stable depth of anesthesia. The mechanism for this gradual return of CBF to preanesthetic level is unclear, but it does not appear to be ascribed to a change in cerebral metabolic rate for oxygen (CMRO2). Because of technical difficulties, repeated measurements of CBF with a short time interval were not performed in humans for a prolonged period during surgical anesthesia. Using transcranial Doppler, Bironnette et al. demonstrated that pulsatility and blood flow velocity remained stable during 2 h isoflurane anesthesia in children.
The discrepancies among the previous reports, including animal experiments and human studies, prompted us to determine CBF equivalent (CBF divided by CMRO2), which can be repeatedly measured under constant end-tidal concentration of volatile anesthetics during prolonged surgery. We therefore designed this study to (1) examine the effect of time course on CBF equivalent every 20 min and (2) compare the effect of isoflurane, sevoflurane, and halothane on CBF equivalent.

Materials and Methods

The study protocol was approved by the Ethical Committee for Human Study of the Yamaguchi Rosai Hospital, and informed consent was obtained from each patient. Twenty-four ASA physical status I or 2 patients (10 males, 14 females) were randomly assigned to three groups receiving isoflurane, sevoflurane, or halothane during elective surgery. Ages of the patients ranged from 22 to 80 yr. Preoperative examinations revealed neither cardiopulmonary nor neurologic disorders in all patients. Surgical procedures included major orthopedic and abdominal surgery. Atropine sulfate (0.5 mg) was given intramuscularly 30 min before induction. Anesthesia was induced with the selected volatile anesthetic in an air-oxygen mixture adjusted to obtain FIO2 of 0.35, and inspired concentration of volatile anesthetic was increased to 3–4% over 3–4 min. Tracheal intubation was facilitated with intravenous administration of 8 mg vecuronium bromide. After intubation, end-tidal concentration of the selected volatile anesthetic was adjusted to an age-appropriate level12-15 of 0.5 MAC, then increased to 1.0 MAC before surgery and maintained at 1.5 MAC for the surgical procedure. Actual end-tidal concentrations (22–39, 40–59, 60–80 yr) for 1.0 MAC were as follows: 1.27, 1.15, 1.04 (isoflurane); 0.82, 0.75, 0.67 (halothane); and 1.96, 1.71, 1.48 (sevoflurane), respectively. Patients' lungs were mechanically ventilated to maintain normocapnia, and FIO2 was kept at 0.35. The end-tidal concentrations of carbon dioxide and volatile anesthetic were continuously monitored with a calibrated infrared gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland). Apart from vecuronium, no other drugs were administered during the surgical procedure except phenylephrine, to maintain cerebral perfusion pressure (CPP; see below). The nasopharyngeal temperature was monitored by a calibrated thermistor probe and kept at 36.0–37.0°C using a cooling-warming water mattress. Bilateral unipolar (ear-lap as a reference electrode), frontal, and occipitotemporal electroencephalograms (EEG) were monitored and recorded continuously (Neuropac 8, Nihon Kohden, Tokyo, Japan). The electrocardiogram also was monitored. A 22-G Teflon indwelling catheter was placed in the radial artery, and an 18-G Medicut catheter was placed in the right jugular bulb for blood sampling and pressure measurement. The position of the jugular bulb catheter tip was confirmed by x-ray. 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 (Lifescope 14, Nihon Kohden, Tokyo). The difference between mean arterial blood pressure and mean jugular venous pressure was defined as CPP. CPP was maintained greater than 60 mmHg with a continuous infusion of phenylephrine (0.2–0.9 µg·kg⁻¹·min⁻¹), if necessary. Arterial and internal jugular venous blood samples were obtained every 20 min and analyzed for oxygen tension (PO2), carbon dioxide tension (PCO2), bicarbonate ion concentration, and pH with a blood gas analyzer (ABL505, Radiometer, Copenhagen, Denmark) at 37.0°C. Hemoglobin oxygen saturations and hemoglobin concentrations were measured spectrophotometrically (OSM3, Radiometer). Oxygen content was calculated from the hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen (estimated from PO2 and oxygen solubility). CBF equivalent was calculated as the reciprocal of arterial-jugular venous oxygen content difference.

Data Analysis

Data are expressed as mean ± SD. Between-group comparisons of demographic data and intraoperative

<table>
<thead>
<tr>
<th>Table 1. Demographic and Intraoperative Data</th>
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<td>Age (yr)</td>
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<td>Weight (kg)</td>
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<td>Male/female</td>
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<td>Fluid infusion volume (ml)</td>
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<td>Urine volume (ml)</td>
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<td>Blood loss (g)</td>
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Values are expressed as mean ± SD. There were no significant differences among three groups.
fluid balances were made by one-way analysis of variance (ANOVA). Gender distribution between groups was compared by chi-square analysis. Physiologic variables were compared by the two-way ANOVA for repeated measures. For the statistical analysis on CBF equivalent and internal jugular venous PO₂ (PjvO₂), the data were separated into two parts, the initial dose-response data (0.5, 1.0, 1.5 MAC) and the time course data at 1.5 MAC. Two-way ANOVA for repeated measures was applied on each part. Bonferroni's post hoc test was applied for between-group comparisons as indicated. Statistical significance was assumed when \( P < 0.05 \).

**Results**

A summary of demographic data is shown in table 1. There were no significant differences among three groups of demographic data and intraoperative fluid balances. Heart rate ranged from 54 to 120 beats/min with different agents. Hemoglobin concentration was stable (8.6–14.9 g/dl), as was PaO₂ (66–210 mmHg) and nasopharyngeal temperature (35.9–37.4°C). There were no significant differences among groups in these variables.

Table 2 lists CPP, PaCO₂, and phenylephrine doses at selected times during the study. CPP in the sevoflurane group was significantly \( (P < 0.05) \) greater than those in the halothane and isoflurane groups. Nevertheless, CPP in all groups was maintained within physiologic range. The total number of patients given phenylephrine was five, six, and five in the isoflurane, halothane, and sevoflurane groups, respectively. PaCO₂ was unchanged for 4 h, and there were no significant differences among three groups.

Figure 1 shows the time course of the changes of CBF equivalent and PjvO₂. CBF equivalents at 0.5 MAC of isoflurane, halothane, and sevoflurane were 21 ± 4, 20 ± 3, and 21 ± 5 ml blood/ml oxygen, respectively. CBF equivalent and PjvO₂ significantly \( (P < 0.01) \) increased in a dose-dependent manner at volatile anesthetic concentrations of 0.5, 1.0, and 1.5 MAC. At 1.5 MAC, the increase of CBF equivalent and PjvO₂ with all anesthetics was maintained increased with minimal fluctuation for 3 h. The average value of the CBF equivalent during 3 h at 1.5 MAC was significantly \( (P < 0.01) \) greater in the isoflurane group (45 ± 8 ml blood/ml oxygen) than in the halothane (32 ± 8) and sevoflurane (31 ± 8) groups. The average value of PjvO₂ in the isoflurane group (55 ± 5 mmHg) was significantly

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**Table 2. Physiologic Variables**

<table>
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<tr>
<th>Time</th>
<th>MAC</th>
<th>CPP (mmHg)</th>
<th>PaO₂ (mmHg)</th>
<th>Phenylephrine (mg·kg⁻¹·min⁻¹)</th>
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<tr>
<td></td>
<td>0.5</td>
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<td>60</td>
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<td>240</td>
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<td></td>
<td>Emergence</td>
<td>80 ± 10</td>
<td>81 ± 12</td>
<td>92 ± 21</td>
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Values are mean ± SD. The values in parentheses of phenylephrine dose indicate the number of patients given phenylephrine.

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Fig. 1. Time course of the changes of cerebral blood flow (CBF) equivalent and internal jugular venous oxygen tension (Pjvo2). Values are expressed as mean ± SD. CBF equivalents at 0.5 MAC of isoflurane, halothane, and sevoflurane were 21 ± 4, 20 ± 3, and 21 ± 5 ml blood/ml oxygen, respectively. CBF equivalent and Pjvo2 significantly (P < 0.01) increased in a dose-dependent manner volatile anesthetic concentrations (0.5, 1.0, 1.5 MAC). Once anesthetic concentration reached 1.5 MAC, the increase in CBF equivalent and Pjvo2 in all groups were maintained increased with minimal fluctuation. When compared at 1.5 MAC, the average value of CBF equivalent in the isoflurane group (45 ± 8 ml blood/ml oxygen) is significantly (P < 0.01) greater than that in the halothane (32 ± 8) and sevoflurane (31 ± 8) groups. When compared at 1.5 MAC, the average value of Pjvo2 in the isoflurane group (55 ± 5 mmHg) is significantly (P < 0.01) greater than that in the sevoflurane group (48 ± 6), but it was not significantly different from that in the halothane group (50 ± 4).

(P < 0.01) greater than that in the sevoflurane group (48 ± 6), but it was not significantly different from that of the halothane group (50 ± 4).

Representative EEG patterns at 1 and 4 h are shown in figure 2. At 1.5 MAC, EEG recordings showed frequent burst (sharp or spike wave, 50–100 μV) and suppression in the isoflurane group, whereas in the halothane and sevoflurane groups, 13–15-Hz (50–100 μV) and 9–13-Hz activities (70–100 μV) were predominant, respectively. These EEG patterns at 1.5 MAC, examined without knowing the sequence of each recording, proved to be relatively unchanged with time during observation period.

Fig. 2. Representative electroencephalograms at 1 and 4 h of anesthesia at 1.5 MAC. Electroencephalogram (EEG) recordings showed frequent burst (sharp or spike wave, 50–100 μV) and suppression in the isoflurane group, whereas in the halothane and sevoflurane groups, 13–15-Hz (50–100 μV) and 9–13-Hz activities (70–100 μV) were predominant, respectively. There were no apparent changes in EEG pattern with time in all three groups.
Discussion

This study demonstrated in humans that CBF equivalent§ increased in a dose-dependent manner with all three volatile anesthetics examined. The elevated global CBF relative to oxygen demand was maintained during prolonged (4 h) anesthesia. The results also showed that the CBF equivalent at 1.5 MAC in the isoflurane group was significantly greater than in the halothane and sevoflurane groups.

In general, all volatile anesthetics are considered potent cerebral vasodilators and to increase CBF. It is, however, controversial whether the increase of CBF by volatile anesthetics is maintained for a prolonged period of anesthesia. Many animal studies using dogs and goats revealed that isoflurane- and halothane-induced cerebral hyperemia spontaneously decreased over time.1-6 No definitive explanation has been obtained for this gradual decline of CBF. The decrease of CBF over time may be partially explained in one report6 by the decrease of CMRO₂, probably related to the gradual increase in the depth of anesthesia (although the concentration of anesthetic was not measured). However, in most of the studies, CMRO₂ was either unchanged1-5 or increased slightly6 during the measurement period. Immobilization and/or mechanical ventilation has been postulated as the cause,1 but this is not conclusive. The time-dependent changes in the status of autoregulation6 or in the pH of cerebrospinal fluid,4 and the involvement of α-/β-receptor6 failed to reveal the mechanism.

Some reports have failed to observe the gradual decrease in CBF over time. Roald et al. reported that CBF and CMRO₂ remained unchanged during isoflurane anesthesia of 3-4 h in dogs using sagittal sinus outflow technique.7 The authors speculated that the gradual decrease in CBF with time in the previous study2 might have been caused by the changes in the blood rheology due to exposure to air combined with mechanical destruction by a roller pump. McPherson et al. reported that the CBF measured by the technique of radiolabeled microspheres was increased without decay by isoflurane for 4 h in primates, whereas CMRO₂ was unchanged over time.8 Although not conclusive, the different results reported in animals may be due to the


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caused by 1% halothane returned to the preanesthetic level over 150 min of anesthesia. In primates, CBF was increased gradually during 4 h of isoflurane anesthesia, the measurements having been started 15 min after the completion of surgical preparation. Furthermore, in the above-mentioned clinical studies, CBF (and blood flow velocity) was unchanged during 1.5–6 h of anesthesia, while surgical nociceptive stimulation was of minor importance. From these results, it is unlikely that the lack of CBF decay over time in clinical studies, including the current one, is due to the nociceptive stimulation.

The current results also showed that, at 1.5 MAC, isoflurane possesses greater capability to maintain global CBF relative to CMRO₂ than does halothane or sevoflurane. CPP in the sevoflurane group was higher than in the isoflurane or halothane groups at 1.5 MAC. However, CPP in all groups was maintained within physiologic range, and there were no significant changes over time. Provided that autoregulation is attenuated at 1.5 MAC, the values of CBF equivalent in the sevoflurane group might have been a bit exaggerated, and hence, the difference of CBF equivalent between isoflurane and sevoflurane groups might have been underestimated. Therefore, the conclusion is not affected.

Because we did not directly measure CBF or CMRO₂, we are unable to conclude whether our results that isoflurane possesses greater capability to maintain global CBF relative to CMRO₂ than halothane or sevoflurane are due to greater vasodilating capability and/or greater metabolic depressive effects. In isoflurane anesthesia, many studies reported that the increase in CBF, if present at all, is smaller, whereas the decrease in CMRO₂ is greater than the changes observed with halothane. This partly coincides with the experimental results reported by Hansen et al., that isoflurane possesses greater cerebral vasodilating capability relative to CMRO₂ than halothane. Although Smith reported that CBF equivalent was a function of anesthetic depth (MAC) regardless of volatile anesthetics, we postulate that CBF equivalent depends on MAC as well as on volatile anesthetics used.

In summary, the current study demonstrates that global CBF relative to oxygen demand is markedly increased and maintained during prolonged inhalation of volatile anesthetics in humans. It is impossible to determine whether these data indicate a stable CBF or whether CBF and CMRO₂ are changing in parallel during the observation period. The unchanged EEG pattern suggests that the former possibility is more likely and that the increase in CBF produced by volatile anesthetics is maintained over time without decay, which has been reported in several animal studies. The current results also suggest that isoflurane possesses greater capability to maintain global CBF relative to CMRO₂ than does halothane or sevoflurane.

References

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PROLONGED VOLATILE ANESTHESIA AND CBF/METABOLISM


