Blood Flow Velocity of Middle Cerebral Artery during Prolonged Anesthesia with Halothane, Isoflurane, and Sevoflurane in Humans

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Background: It is not clear whether the increase of cerebral blood flow (CBF) produced by volatile anesthetics is maintained during prolonged anesthesia. In a previous study, the authors found that CBF equivalent, an index of flow–metabolism relationship, was stable over 3 h, suggesting no decay over time in CBF for 3 h during volatile anesthesia in humans. However, it may be possible that CBF changes in a parallel fashion to functional metabolic changes. In this study, to estimate the response of CBF to three volatile anesthetics, the authors used transcranial Doppler (TCD) ultrasonography to measure time-averaged mean velocity in the middle cerebral artery (Vmax).

Methods: Twenty-four surgical patients were randomly assigned to three groups to receive halothane, isoflurane, or sevoflurane (eight patients, each). End-tidal concentration of the selected volatile anesthetic was maintained at 0.5, 1.0, and 1.5 MAC before surgery and then at 1.5 MAC during surgery, which lasted more than 3 h. Normothermia and normocapnia were maintained. Mean arterial blood pressure was kept above 70 mmHg, using phenylephrine infusion, if necessary. TCD recordings of the Vmax were performed continuously.

Results: Vmax at 0.5 MAC of halothane, isoflurane, and sevoflurane was 49 ± 19, 57 ± 8, and 48 ± 13 cm/s, respectively. Halothane significantly (P < 0.01) increased Vmax in a dose-dependent manner (0.5, 1.0, 1.5 MAC), whereas isoflurane and sevoflurane produced no significant dose-related changes. At 1.5 MAC for 3 h, Vmax changed significantly (P < 0.05) for the time trends, but it did not exhibit decay over time with all drugs. During burst suppression, observed electroencephalographically (EEG) on patients during isoflurane and sevoflurane anesthesia, the onset of a burst increased Vmax (approximately 5–30 cm/s), which was maintained for the duration of the burst.

Conclusions: The results indicate that there was no decay in Vmax over time during prolonged (3 h) inhalation of volatile anesthetics at 1.5 MAC in humans. The fluctuation of Vmax during burst suppression on EEG at 1.5 MAC indicates that the flow–metabolism coupling occurred. (Key words: Anesthetics, volatile: halothane; isoflurane; sevoflurane. Brain: blood flow velocity. Electroencephalograph: burst suppression. Surgical stimulation: anesthetic interaction with time.)

In general, most volatile anesthetics are considered to be cerebral vasodilators, although it is controversial whether the increase; if any, of cerebral blood flow (CBF) by volatile anesthetics is maintained for a prolonged period of anesthesia. In animals, cerebral hyperemia induced by isoflurane and halothane spontaneously decreases over time.7–10 Some reports have failed to observe the gradual decrease in CBF over time.7–10

In the previous human study, we found that the elevated CBF equivalent, an index of flow–metabolism relationship, was preserved during prolonged anesthesia with volatile anesthetics,11 while surgery is ongoing. However, one may have to consider that the CBF equivalent does not provide real CBF values.

Transcranial Doppler (TCD) ultrasonography provides a rapid, noninvasive, and continuous assessment of blood flow velocity of basal cerebral artery of interest. Although flow velocity is not equivalent to CBF, changes in flow velocity reflect corresponding relative changes in CBF12,13 and there is excellent validation. Recent human studies suggested that flow velocity in the middle cerebral artery (MCA) can be affected by a functional fluctuation induced by anesthetic itself14 and also can be affected by arousal response (increase of cerebral metabolism) induced by nociceptive stimulation,15 even if other physiologic variables are maintained.
within the normal range. To estimate the response of flow velocity to three different volatile anesthetics used, we measured time-averaged mean velocity in the MCA (V_{mca}) during induction, prolonged surgery, and emergence of anesthesia.

**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 (American Society of Anesthesiologist's [ASA] physical status I or II patients (15 men, 9 women) were randomly assigned to three groups (8 for each) receiving either halothane, isoflurane, or sevoflurane during elective surgery. Ages of the patients ranged from 20 to 73 yr. Surgical procedures included orthopedic and abdominal surgery, which lasted more than 3 h. Atropine sulfate, 0.5 mg, and midazolam, 3–5 mg, were given intramuscularly 30 min before induction. Anesthesia was induced with the selected volatile anesthetic in an air-oxygen mixture adjusted to obtain FiO\textsubscript{2} of 0.55, 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 level of 0.5 MAC, then increased to 1.0 MAC, 1.5 MAC before surgery, and maintained at 1.5 MAC for the period of surgical procedure. After the end of surgery, the concentration of volatile anesthetics was stepwise decreased (1.5, 1.0, and 0.5 MAC).

Patients' lungs were mechanically ventilated to maintain normocapnia, and FiO\textsubscript{2} was kept at 0.35. The end-tidal concentrations of carbon dioxide (ETCO\textsubscript{2}) 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, which was used to maintain mean arterial blood pressure (MABP, see below). The nasopharyngeal temperature was monitored by a calibrated thermometer probe and was kept at 35.5–37.0°C using a cooling-warming water mattress. Bilateral unipolar (carlode as a reference electrode), frontal, and parietal electroencephalographs (EEGs) were monitored and recorded continuously (Neuropack 8, Nihon Kohden, Tokyo, Japan). The electrocardiograph (ECG) also was monitored. A 22-gauge Teflon indwelling catheter was placed in the radial artery for blood sampling and pressure measurement. The arterial pressure was measured by strain gauge transducers with the zero point at the mastoid process and was recorded on a polygraph (LifeScope 14, Nihon Kohden, Tokyo). The MABP was maintained above 70 mmHg with a continuous infusion of phenylephrine (0.1–1.0 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}), if necessary. Arterial blood samples were obtained every 60 min and analyzed for oxygen tension (P_{O2}) and carbon dioxide tension (P_{CO2}) with a blood gas analyzer (ABL505, Radiometer, Copenhagen, Denmark) at 37.0°C. Hemoglobin concentration was measured spectrophotometrically (OSM3, Radiometer).

**Doppler Measurements**

A 2-MHz pulsed Doppler ultrasound device (Transcan, EME, Überlingen, Germany) was used for transcranial measurements of blood flow velocity of the right MCA. TCD ultrasound signals were identified at a depth of 42–60 mm. Meticulous care was taken to ensure a constant position of the ultrasound probe by use of a suitable holder attached to the patient's head (IMP-2 monitoring probe holder, EME). Measurement of flow velocity was started shortly after induction of anesthesia. Flow velocity and blood pressure were displayed simultaneously on a video screen and continuously recorded on a microcomputer by use of the long-term monitoring option of the Doppler device. V_{mca} was derived from on-line integration of the recordings of envelope curves of maximal intravascular velocity. During induction or emergence of anesthesia, equilibration time at each end-tidal concentration is 5–10 min. During operation at 1.5 MAC, V_{mca} represents an average value of those recorded for approximately 1 min at each time point (every 15 min). When EEG shows burst suppression pattern, we calculated averaged value from both V_{mca} values during burst period and suppression period.

**Data Analysis**

Data are expressed as mean ± SD. Between-group comparisons of demographic data were made by one-way analysis of variance (ANOVA). Gender distribution between groups was compared by chi-square analysis. For the statistical analysis on physiologic variables and V_{mca}, the data were separated into three parts: the initial dose-response data (induction period, 0.5, 1.0, 1.5 MAC), the time course data at 1.5 MAC, and the final dose-response data (emergence period, 1.5, 1.0, 0.5 MAC). Two-way ANOVA for repeated measures was ap-
Table 1. Demographic Data

<table>
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<tr>
<th></th>
<th>Halothane (n = 8)</th>
<th>Isoflurane (n = 8)</th>
<th>Sevoflurane (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66 ± 5</td>
<td>53 ± 10</td>
<td>52 ± 17</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52 ± 7</td>
<td>63 ± 12</td>
<td>60 ± 7</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/3</td>
<td>3/5</td>
<td>7/1</td>
</tr>
</tbody>
</table>

Values are mean ± SD. There were no significant differences among three groups.

Results

A summary of demographic data is shown in table 1. There were no significant differences among three groups. Figure 1 showed MABP and heart rate during the study. There were no significant differences among three groups except MABP during induction: MABP in

the sevoflurane group was significantly (P < 0.05) lower than those in the halothane and isoflurane groups during induction. The total number of patients given phenylephrine was eight, three, and four in the halothane, isoflurane, and sevoflurane groups, respectively. Hemoglobin concentration (9.4–14.6 g/dl), PaO₂ (99–250 mmHg), PaCO₂ (37–45 mmHg), ETCO₂ (35–48 mmHg), and nasopharyngeal temperature (35.7–37.5°C) were stable in each patient. No statistical significant differences were observed in these data among three groups.

Figure 2 shows the time course of the changes of Vₘca. Vₘca at 0.5 MAC of halothane, isoflurane, and sevoflurane was 49 ± 19, 57 ± 8, and 48 ± 13 cm/s, respectively, with no significant difference among the anesthetics. Halothane significantly (P < 0.01) increased Vₘca in a dose-dependent manner (0.5, 1.0, 1.5 MAC) during induction, whereas other two anesthetics produced no dose-related increase. During 3h anesthesia period at 1.5 MAC, ANOVA for repeated measures showed significance (P < 0.05) for the time trends for Vₘca data in all groups, but there was no decay in Vₘca over time (fig. 2). No significant differences of Vₘca.
were obtained among three groups at 1.5 MAC during operation. During emergence of anesthesia, \( V_{\text{mca}} \) significantly \((P < 0.01)\) decreased in a dose-dependent manner (1.5, 1.0, 0.5 MAC) in the halothane group, whereas no significant dose-related decrease was observed in the isoflurane and sevoflurane groups.

At 1.5 MAC, EEG recordings showed frequent burst (sharp or spike wave, 50–200 \( \mu \)V) and suppression in the isoflurane group, whereas in the halothane and sevoflurane groups, 12–15 Hz activities (50–90 \( \mu \)V) and 9–13 Hz activities (70–100 \( \mu \)V) were predominant, respectively. In the sevoflurane group, burst suppression was observed in a short time in 2 patients.

Figure 3 depicts representative recordings of MABP, \( V_{\text{mca}} \), and EEG in a patient anesthetized with 1.5 MAC isoflurane. During burst and suppression in EEG, the onset of a burst resulted in a substantial increase (approximately 5–30 cm/s) in \( V_{\text{mca}} \), which was maintained for the duration of the burst in all patients.

**Discussion**

This study demonstrated in humans that \( V_{\text{mca}} \) significantly \((P < 0.01)\) increased during induction or decreased during emergence in a dose-dependent manner in halothane anesthesia, whereas isoflurane and sevoflurane produced no significant dose-dependent change. Changes of \( V_{\text{mca}} \) during 3-h period at 1.5 MAC were significant \((P < 0.05)\) for the time trends for all anesthetics, but there was no decay in \( V_{\text{mca}} \) over time. It was also shown that \( V_{\text{mca}} \) fluctuated during burst suppression in EEG at 1.5 MAC of isoflurane (and sevoflurane), \( V_{\text{mca}} \) being increased during burst activity and decreased during suppression.

Dose-related increase in \( V_{\text{mca}} \) observed in the halothane group is in good agreement with that reported by Thiel \textit{et al.} \( ^{20} \) With isoflurane, Bissonnette \( ^{21} \) showed no difference of \( V_{\text{mca}} \) between 0.5 and 1.5 MAC, and Thiel \( ^{20} \) showed no difference between 2 MAC and awake values. There have been many studies describing that the increase in CBF in isoflurane anesthesia, if present at all, is smaller than the changes observed with halothane. \( ^{22} \) Although the studies for sevoflurane are limited in number, either decreased \( ^{23,24} \) or unchanged \( ^{25,26} \) CBF was reported in animals. Low CBF values were reported in patients with ischemic cerebrovascular disease who were anesthetized with 1.5% sevoflurane and 33% nitrous oxide. \( ^{27} \) Recent study in healthy patients showed that \( V_{\text{mca}} \) was decreased under 1.2 MAC sevoflurane anesthesia when compared with the awake value. \( ^{28} \) Although we have no awake value of \( V_{\text{mca}} \); considering these previously mentioned results, no dose-related increase in the current study may be the case for isoflurane and sevoflurane.

Many animal studies using dogs and goats revealed that cerebral hyperemia induced by isoflurane and halothane spontaneously decreased over time. \( ^{1,6} \) However, some reports \( ^{7,8} \) have failed to observe the gradual decrease in CBF over time. There is no clear explanation for the different results reported in animals, but it may be a result of the differences of species or the technique of CBF measurement. It has been our concern whether time-dependent decay of CBF takes place in humans. There has been limited human investigation on this matter, and reported results suggest that CBF does not decrease over time during anesthesia. \( ^{9,10} \) However, this lack of time decay was based on two determinations in the beginning and at the end of the study only (1- and 2-h, \( ^{9} \) and 3- and 6-h \( ^{10} \) periods after induction). In our previous study, \( ^{11} \) we found that the elevated CBF equivalent, calculated every 20 min, was preserved during prolonged anesthesia (3 h) with volatile anesthetics and suggested that the increase of CBF was maintained over time. However, this indirect method has limitations; real CBF cannot be obtained, and only the global ratio of CBF—metabolism for certain time period is obtained. In the present study, we incorporated TCD technique to measure \( V_{\text{mca}} \) continuously during prolonged anesthesia. Flow velocity is not equivalent to CBF, but
it is well accepted that the changes in flow velocity reflect corresponding relative changes in CBF. Because the flow velocity with isoflurane and sevoflurane did not increase in a dose-dependent manner, it is difficult to state that an "increase" in flow velocity is maintained during isoflurane and sevoflurane anesthesia. However, no decay in $V_{mc}$ over time in all groups in this study suggests that the gradual decrease in CBF over time do not take place in humans.

The statistical significance of the changes in $V_{mc}$ for the time trends during 3-h period at 1.5 MAC was interpreted as a reflection of the fluctuation of $V_{mc}$ possibly in association with functional changes. The changes of EEG activity reflects the functional changes of the brain and may be associated with the change of CBF. During burst suppression pattern in EEG observed at 1.5 MAC isoflurane (and sevoflurane) anesthesia, the onset of a burst activity was associated with an increase of $V_{mc}$, which was maintained for the duration of the burst, and $V_{mc}$ decreased during the suppression period (fig. 3). This observation coincides with that by Lam et al. The fluctuation of $V_{mc}$ at 1.5 MAC may partly be ascribed to the nociceptive stimulation. The change of flow velocity induced by surgical stimulus has been recently reported by von Knobelsdorff et al., showing that flow velocity significantly increases, lasting for 3 or 11 min after skin incision in 1 and 2 MAC isoflurane-anesthetized patients. These changes were possibly a result of the increased cerebral metabolism (i.e., arousal response) but not to the increase of MABP. Bissonnette et al. showed that $V_{mc}$ remained stable during 1.0 MAC isoflurane anesthesia, with concomitant use of epidural local anesthetic. The fluctuation of $V_{mc}$ at 1.5 MAC may also partly be ascribed to changes in CBF associated with MABP changes because of the possibility of impaired autoregulation. Taken together, the changes of $V_{mc}$ observed appear to be the net results of the vascular and metabolic action of anesthetics and the effect of nociceptive stimulation. Our previous observation that CBF equivalent was preserved is in agreement with the present one in view of existence of flow–metabolism coupling during 1.5 MAC volatile anesthesia.

In summary, the current study shows that no decay in CBF over time occurs in the patients during surgery under prolonged (3 h) inhalation of volatile anesthetics (1.5 MAC). The fluctuation of CBF observed during burst suppression in EEG at 1.5 MAC during isoflurane and sevoflurane anesthesia indicates the existence of flow–metabolism coupling.

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