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Effects of sevoflurane and isoflurane on the ratio of cerebral blood flow/metabolic rate for oxygen in neurosurgery

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Abstract
Purpose. To examine the changes in cerebral blood flow (CBF) equivalent (CBF divided by cerebral metabolic rate for oxygen) during craniotomy under isoflurane and sevoflurane anesthesia in patients with intracranial disorders.
Method. In 16 neurosurgical patients (8 anesthetized with isoflurane and 8 with sevoflurane), the CBF equivalent was measured while the end-tidal concentration of the selected volatile anesthetic was maintained at 0.5 and 1.0 minimum alveolar concentration (MAC) before surgery, and then 1.0 MAC during surgery, which lasted more than 4 h.
Results. There was no significant difference in CBF equivalent at 0.5 MAC between the isoflurane (20 ± 4 ml blood/ml oxygen) and the sevoflurane (19 ± 4 ml blood/ml oxygen) groups. With increasing anesthetic depth from 0.5 to 1.0 MAC, the CBF equivalent significantly ($P < 0.05$) increased in both groups (22 ± 7 and 21 ± 5, respectively). At 1.0 MAC during operation, the CBF equivalent with both anesthetics was maintained with minimal fluctuation for 4 h. There were no significant differences in the average value of the CBF equivalent during a 4-h period at 1.0 MAC between the isoflurane (23 ± 5) and the sevoflurane (20 ± 4) groups.
Conclusion. Deepening anesthesia from 0.5 to 1.0 MAC with isoflurane and sevoflurane produced a slight increase in the CBF equivalent. The CBF equivalent at 1.0 MAC was maintained with no difference between the two agents during 4 h of neurosurgery.

Key words Volatile anesthetics · Sevoflurane · Isoflurane · Cerebral blood flow · Cerebral oxygen consumption · Craniotomy

Isoflurane has been widely used in neuroanesthesia because of its relatively small effect on cerebral blood flow (CBF), its profound reduction in brain metabolism, and its possible neuroprotective effect. Sevoflurane, which has recently become available for clinical use, may be an attractive drug for use during neurosurgery, because induction of and emergence from anesthesia is rapid. The effect of sevoflurane on cerebral circulation has recently been studied in humans. In patients with ischemic cerebrovascular disease, low values of CBF and cerebral metabolic rate for oxygen (CMR_{o2}) were reported under 1.5% sevoflurane and 33% nitrous oxide anesthesia [1]. In patients not undergoing neurosurgery, the mean flow velocity in the middle cerebral artery (V_{mca}) was decreased under 1.2 MAC sevoflurane [2]. In our previous study [3], performed in non-neurosurgical patients under sevoflurane and isoflurane, we found that the CBF equivalent (CBF divided by CMR_{o2}) significantly increased in a dose-dependent manner (0.5, 1.0, and 1.5 MAC), and that the increase in CBF equivalent was maintained with minimal fluctuation for 3 h at 1.5 MAC. In that study at 1.5 MAC, the CBF equivalent in the sevoflurane group was significantly smaller than that in the isoflurane group. In our subsequent study [4], again in non-neurosurgical patients, we found that V_{mca} changed significantly ($P < 0.05$) for the time trends, but did not decay over time. In that study, there were no significant differences in V_{mca} between sevoflurane and isoflurane at 1.5 MAC. Our concern now is what sort of CBF equivalent changes will be observed in patients with intracranial disorders, where neurosurgery is ongoing under anesthesia. We examined this issue by measuring the CBF equivalent in neurosurgical patients undergoing craniotomy anesthetized with constant end-tidal concentrations of sevoflurane or isoflurane.

Materials and methods

The study protocol was approved by the Ethical Committee for Human Study of the Yamaguchi Rosai

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Table 1. Patient profiles

Anesthetic/patient no.	Age (yr)/sex	Diagnosis	Glasgow Coma Scale Score
Isoflurane			
1	44/F	Ruptured ACA aneurysm	11 (E3, V3, M5)
2	52/F	Ruptured rt ICA-PCA aneurysm	13 (E3, V4, M6)
3	41/F	Unruptured rt ICA-PCA aneurysm	15 (E4, V5, M6)
4	53/M	Unruptured ICA aneurysm	15 (E4, V5, M6)
5	76/M	lt MCA occlusion, infarction (lt)	14 (E4, V4, M6)
6	63/M	rt ICA stenosis, infarction	15 (E4, V5, M6)
7	70/M	lt ICA stenosis, infarction	11 (E4, V1, M6)
8	51/F	bl ICA stenosis	15 (E4, V5, M6)
Sevoflurane			
1	78/M	Intracerebral hematoma (traumatic)	13 (E3, V4, M6)
2	72/M	Acute subdural hematoma, contusion (bl)	15 (E4, V5, M6)
3	24/M	Acute epidural hematoma (rt frontotemporal)	7 (E2, V1, M4)
4	68/F	Ruptured lt ACA and MCA aneurysm	15 (E4, V5, M6)
5	69/F	Intracerebral hemorrhage (lt), infarction (bl)	14 (E4, V4, M6)
6	64/M	Metastatic brain tumor (rt)	15 (E4, V5, M6)
7	55/F	Multiple meningioma (lt)	15 (E4, V5, M6)
8	73/M	Brain abscess (rt occipital)	15 (E4, V5, M6)

rt, right; lt, left; bl, bilateral. Glasgow Coma Scale (E, eye opening; V, verbal response; M, best motor response). ACA, anterior communicating artery; ICA, internal carotid artery; PCA, posterior cerebral artery; MCA, middle cerebral artery.

Hospital, and informed consent was obtained from each patient or family. Sixteen patients of ASA physical status 1–3 (E) (9 men and 7 women) were randomly assigned to receive either isoflurane or sevoflurane during craniotomy. The patients' profiles are summarized in Table 1. All patients had a Glasgow Coma Scale (GCS) score greater than 11. Nine patients had focal neurologic signs such as aphasia, hemiplegia, and cranial nerve palsy. Despite the randomization of the study group, the surgical procedures performed appeared to deviate between the groups. All surgical procedures lasted more than 4 h. Atropine sulfate, 0.5 mg, and midazolam, 0–3 mg, were given intramuscularly 30 min before induction. Anesthesia was induced with thiopental (4–5 mg·kg^{-1}), fentanyl (2–4 μg·kg^{-1}), and the selected volatile anesthetic in an air–oxygen mixture adjusted to obtain an F_{IO_2} of 0.35. The inspired concentration of volatile anesthetic was increased to 2–3% over a 3- to 4-min period. Endotracheal intubation was facilitated with intravenous administration of 8 mg vecuronium bromide. After intubation, the end-tidal concentration of the selected volatile anesthetic was adjusted to an age-appropriate level [5–7] of 0.5 MAC, then increased to 1.0 MAC before surgery and maintained at 1.0 MAC for the period of the surgical procedure.

The patients were mechanically ventilated to maintain normocapnia, and F_{IO_2} 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). Lidocaine 200 mg was infiltrated into the skin incision area before surgery. Anesthesia was supplemented with small doses of fentanyl and vecuronium during the surgical procedure. Mannitol (0.5–1 g·kg^{-1}) was infused before opening the dura in all patients, and steroids were not used. Lactated Ringer's solution without glucose was infused continuously (7 ± 3 ml·kg^{-1}·h^{-1}). The nasopharyngeal temperature was monitored by a calibrated thermistor probe and was kept at 35.5–37.0°C by a cooling-warming water mattress. Bilateral unipolar (with the ear-lobe as a reference electrode), frontal (or prefrontal), and parietal (or occipital) electroencephalograms (EEG) were monitored and recorded continuously (Neuropack 8, Nihon Kohden, Tokyo, Japan). The electrocardiogram also was monitored. A 22-gauge Teflon indwelling catheter was placed in the radial artery, and an 18-gauge Medicut catheter (Nippon Sherwood, Tokyo, Japan) 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, Japan). The difference between mean arterial blood pressure and mean jugular venous pressure was defined as the cerebral perfusion pressure (CPP). The CPP was maintained above 60 mmHg with a continuous infusion of phenylephrine (0.1–1.0 μg·kg^{-1}·min^{-1}), if necessary. Arterial and internal jugular venous blood samples were obtained at 0.5 and 1.0 MAC during the induction of anesthesia (the equilibration time at each end-tidal con-

centration is 20 min) and every 30 min during the operation at 1.0 MAC. Blood samples were analyzed for oxygen tension (Po_2), carbon dioxide tension (Pco_2), 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). The oxygen content (Co_2) was calculated from the hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen (estimated from Po_2 and oxygen solubility). The CBF equivalent (CBF/$CMRo_2$) was calculated as the reciprocal of the arterial − jugular venous oxygen content difference [$=1/(Cao_2 - Cjvo_2)$].

Data analysis

Data are expressed as means ± SD. Between-group comparisons of demographic data and intraoperative fluid balances were made by the unpaired *t*-test. The sex distribution between groups was compared by chi-square analysis. Physiological variables were compared by two-way analysis of variance (ANOVA) for repeated measures. Spearman's rank correlation analysis was used between the CBF equivalent at 0.5 MAC during induction and the preanesthetic GCS score. The Kruskall-Wallis test was applied for the comparison of CBF equivalent at 0.5 MAC during induction among the different types of intracranial disorder. For the statistical analysis of Cao_2, $Cjvo_2$, and CBF equivalent, the data were separated into two parts: the initial dose–response data (induction period; 0.5 and 1.0 MAC) and the time-course data at 1.0 MAC. Two-way ANOVA for repeated measures was applied to each part. Bonferroni's post hoc test was applied for between-group comparisons as indicated. Differences were considered statistically significant when $P < 0.05$.

Results

A summary of demographic and intraoperative data is shown in Table 2. There were no significant differences between the two groups in demographic data or intraoperative fluid balances. Table 3 lists physiologic variables at each time point during the study. There were no significant differences in physiologic variables between the two groups, and these were maintained within physiologic range. The total number of patients given phenylephrine was six in the isoflurane group and eight in the sevoflurane group. The dose of phenylephrine in these patients was $0.4 \pm 0.2\,\mu g \cdot kg^{-1} \cdot min^{-1}$. Fentanyl (2–$4\,\mu g \cdot kg^{-1}$) was added during the operation in three patients in the isoflurane group and two in the sevoflurane group.

Figure 1 shows the correlation between the CBF equivalent at 0.5 MAC during induction and the preanesthetic GCS score or the type of intracranial disorder. The CBF equivalent at 0.5 MAC during induction correlated neither with the preanesthetic GCS score nor with the type of intracranial disorder. Figure 2 plots all values of CBF equivalent at 0.5 and 1.0 MAC during induction. Table 4 shows the time course of the changes

Table 2. Demographic and intraoperative data

Value	Isoflurane ($n = 8$)	Sevoflurane ($n = 8$)
Age (yr)	56 ± 12	63 ± 17
Weight (kg)	55 ± 11	56 ± 11
Male/female	4/4	5/3
Fluid infusion volume (ml)	2338 ± 663	2663 ± 823
Urine volume (ml)	1194 ± 599	1091 ± 757
Blood loss (g)	239 ± 104	454 ± 294

Values are expressed as means ± SD. There were no significant differences between the two groups.

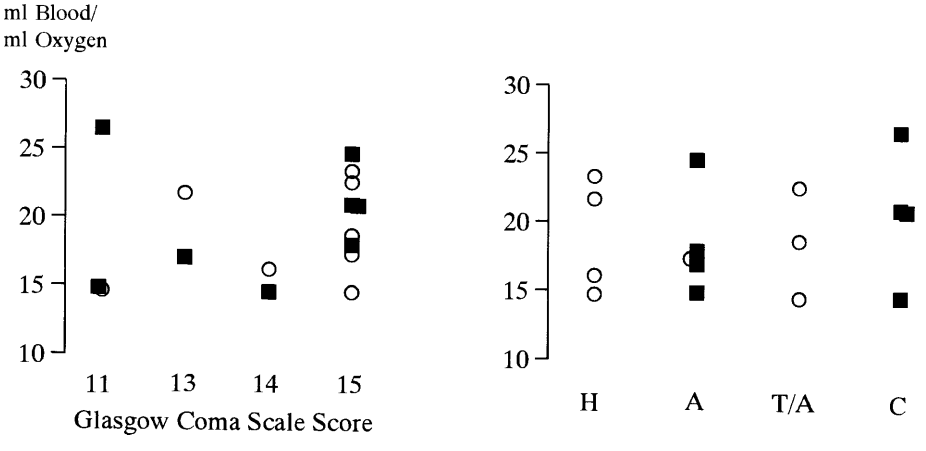

Fig. 1. CBF equivalent at 0.5 MAC during induction and preanesthetic Glasgow Coma Scale (GCS) score or the type of intracranial disorder. CBF equivalent at 0.5 MAC during induction was not significantly correlated with preanesthetic GCS score or type of intracranial disorder. H, hematoma/hemorrhage; A, aneurysm; T/A, tumor/abscess; C, cerebral artery stenosis/occlusion; ■, isoflurane; ○, sevoflurane

Table 3. Physiologic variables

Time	MAC	CPP (mmHg)		HR (min^{-1})		Hb ($g \cdot dl^{-1}$)		Pao_2 (mmHg)		$Paco_2$ (mmHg)		Nasopharyngeal temperature (°C)	
		I	S	I	S	I	S	I	S	I	S	I	S
Induction	0.5	81 ± 30	89 ± 30	79 ± 15	89 ± 15	11.8 ± 1.1	10.9 ± 2.1	171 ± 37	174 ± 45	41 ± 2	39 ± 5	35.8 ± 0.6	36.5 ± 1.0
After induction (h)													
1	1.0	77 ± 21	77 ± 15	78 ± 11	92 ± 18	11.4 ± 0.5	10.5 ± 1.7	179 ± 31	176 ± 42	41 ± 3	39 ± 4	35.8 ± 0.6	36.3 ± 1.1
2	1.0	76 ± 15	77 ± 14	81 ± 13	90 ± 18	10.9 ± 0.8	10.4 ± 2.1	171 ± 28	171 ± 45	41 ± 3	38 ± 4	35.6 ± 0.5	36.2 ± 0.9
3	1.0	71 ± 18	80 ± 11	76 ± 14	94 ± 27	11.1 ± 0.9	10.4 ± 1.6	168 ± 31	178 ± 42	41 ± 3	38 ± 4	35.7 ± 0.8	36.1 ± 0.8
4	1.0	72 ± 12	78 ± 22	73 ± 9	86 ± 12	10.9 ± 1.0	10.4 ± 1.6	172 ± 29	177 ± 41	40 ± 3	38 ± 2	35.8 ± 1.0	36.1 ± 0.8
5	1.0	74 ± 14	83 ± 18	74 ± 12	90 ± 11	10.8 ± 0.9	10.3 ± 1.4	170 ± 34	174 ± 37	41 ± 2	38 ± 2	36.0 ± 1.0	36.2 ± 0.9

Values are means ± SD. At 1.0 MAC, only values at 1, 2, 3, 4, and 5 h after induction are tabulated. There were no significant differences between the two groups. I, isoflurane; S, sevoflurane; CPP, cerebral perfusion pressure; HR, heart rate; Hb, hemoglobin concentration; Pao_2, arterial oxygen tension; $Paco_2$, arterial carbon dioxide tension.

in Cao_2, $Cjvo_2$, and CBF equivalent. No significant differences in Cao_2 or $Cjvo_2$ were observed between the two groups or for the time trends. There were no significant differences in CBF equivalent at 0.5 MAC between the isoflurane (20 ± 4 ml blood/ml oxygen) and the sevoflurane (19 ± 4 ml blood/ml oxygen) groups. With increasing anesthetic depth from 0.5 to 1.0 MAC, both volatile anesthetics significantly ($P < 0.05$) increased CBF equivalent (22 ± 7 and 21 ± 5, respectively) (Fig. 2). At 1.0 MAC from 1 to 5 h after induction, including the period of surgery, ANOVA for repeated measures showed no significant differences in the time trends for CBF equivalent in both groups. There were no significant differences in the average value of CBF equivalent (calculated from all values obtained during the 4-h period) at 1.0 MAC between the isoflurane (23 ± 5) and the sevoflurane (20 ± 4) groups.

Figure 3 shows representative EEGs after 1 and 5 h of anesthesia at 1.0 MAC. At 1.0 MAC, 9–14 Hz activities (70–150 μV) and 9–13 Hz activities (70–100 μV) were predominant in the isoflurane and sevoflurane groups, respectively. In three patients, bursts (sharp or spike wave, 50–100 μV) and suppressions were observed for a short period of time in both groups (not shown in Fig. 3). These EEG patterns, examined without knowledge of the sequence of each recording, proved to be relatively unchanged with time during the observation period at 1.0 MAC.

Discussion

The principal findings of the study are that the CBF equivalent increased with increasing depth of anesthesia with isoflurane and sevoflurane from 0.5 to 1.0 MAC, and that the CBF equivalent was maintained during prolonged (4 h) anesthesia at 1.0 MAC during craniotomy, with no obvious difference between the two agents.

We calculated the CBF equivalent by sampling blood from the right internal jugular bulb, irrespective of the laterality of the intracranial disorder, for three reasons: the CBF equivalent represents the global ratio between CBF and $CMRo_2$; the blood flow in the right internal jugular vein has been reported to be dominant to that on the left side; and the degree of intracranial disorder in the patients was relatively mild (GCS score greater than 11), even though focal neurologic signs were observed in nine patients. It is unfortunate that there was some deviation between the two groups in the surgical procedures performed. However, the CBF equivalent at 0.5 MAC after induction correlated neither with the preanesthetic GCS score nor with the type of intracranial disorder. During surgery, physiologic variables could be preserved within the normal range to maintain

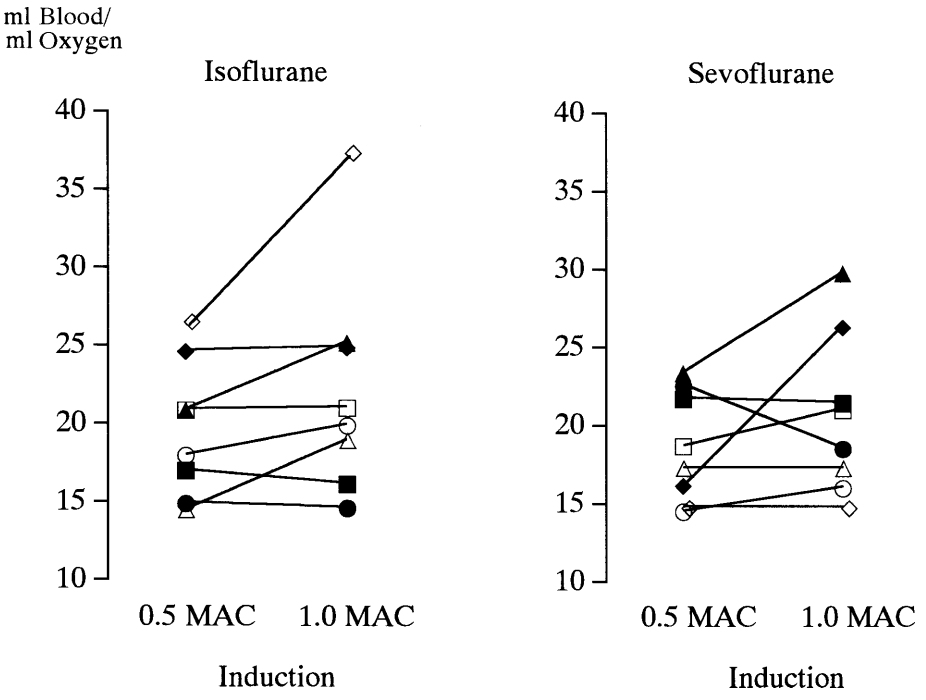

Fig. 2. All values of CBF equivalent (CBF divided by $CMRo_2$) at 0.5 and 1.0 MAC during induction. With increasing anesthetic depth from 0.5 to 1.0 MAC, both volatile anesthetics significantly ($P < 0.05$) increased CBF equivalent

Table 4. CBF equivalent related variables

		Cao_2 (ml·dl^{-1})		$Cjvo_2$ (ml·dl^{-1})		CBF equivalent (ml blood/ml oxygen)	
Time	MAC	I	S	I	S	I	S
Induction	0.5	16.5 ± 1.4	15.1 ± 2.7	11.2 ± 1.8	9.6 ± 2.5	20 ± 4	19 ± 4
After induction (h)							
1	1.0	16.1 ± 0.8	14.9 ± 2.6	11.3 ± 1.6	9.8 ± 2.7	22 ± 7	21 ± 5
1.5	1.0	15.7 ± 1.3	14.8 ± 2.3	10.9 ± 1.7	9.8 ± 2.6	22 ± 6	21 ± 2
2	1.0	15.6 ± 1.3	14.6 ± 2.9	11.4 ± 1.4	9.4 ± 2.8	25 ± 5	20 ± 4
2.5	1.0	15.4 ± 1.7	14.7 ± 2.8	11.3 ± 1.8	9.7 ± 2.7	25 ± 4	21 ± 3
3	1.0	15.5 ± 1.0	14.7 ± 2.3	11.0 ± 1.1	9.4 ± 2.4	23 ± 3	20 ± 4
3.5	1.0	15.6 ± 0.8	14.4 ± 2.2	11.1 ± 1.1	8.9 ± 2.4	23 ± 3	19 ± 3
4	1.0	15.3 ± 1.3	14.7 ± 2.2	10.8 ± 0.9	9.1 ± 2.9	23 ± 4	19 ± 3
4.5	1.0	15.3 ± 1.1	14.4 ± 2.0	10.7 ± 1.0	8.9 ± 2.3	22 ± 3	19 ± 3
5	1.0	15.2 ± 0.9	14.4 ± 1.9	10.9 ± 0.9	9.2 ± 2.2	24 ± 3	20 ± 3

Values are means ± SD. Cao_2, arterial oxygen content; $Cjvo_2$, jugular venous oxygen content; I, isoflurane; S, sevoflurane.
There were no significant differences between the two groups.
There were no significant differences for the time trends for Cao_2, $Cjvo_2$, and CBF equivalent in both groups.

adequate cerebral oxygen supply. ANOVA for repeated measures showed no significant differences in the time trends for CBF equivalent at 1.0 MAC during operation. The effect of mannitol was thought to be negligible because of the nonsignificant change in the CBF equivalent before and after its injection. Taken together, the intracranial pathology and surgical procedure, as examined in the present study, did not appear to affect the response of the CBF equivalent generally throughout the study.

The number of studies examining the effect of sevoflurane on cerebral circulation in humans has been limited. In patients with ischemic cerebrovascular disease, low values of CBF (66% of the awake value) and $CMRo_2$ (48% of the awake value) were reported with 1.5% sevoflurane and 33% nitrous oxide anesthesia [1]. In non-neurosurgical patients, V_{mca} was reported to be decreased by 20% at 1.2 MAC sevoflurane anesthesia [2]. At 1.5 MAC, we previously found that sevoflurane had a significantly smaller CBF equivalent than

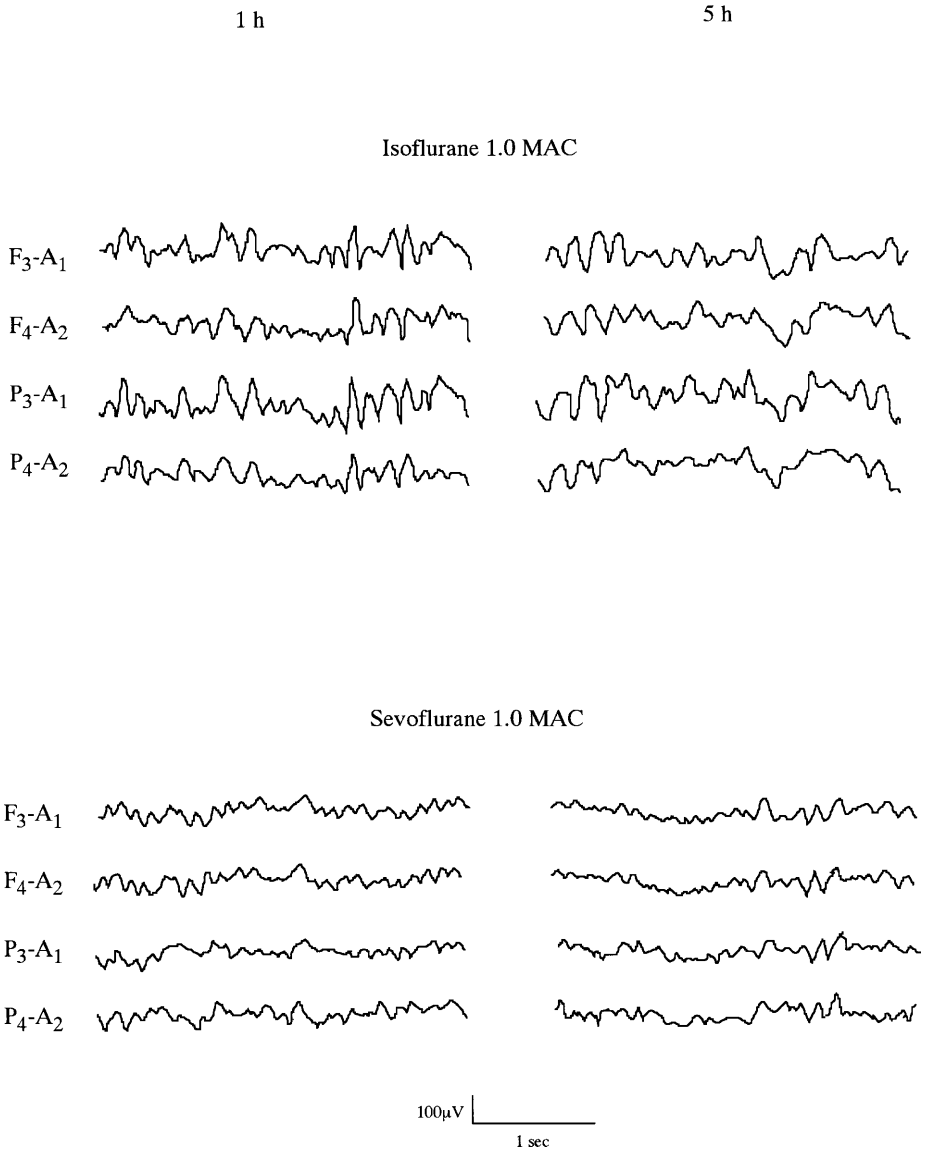

Fig. 3. Representative electroencephalograms (EEG) at 1 and 5 h of anesthesia at 1.0 MAC. 9–14 Hz activities (70–150 μV) and 9–13 Hz activities (70–100 μV) were predominant in the isoflurane and sevoflurane groups, respectively

isoflurane in non-neurosurgical patients [3]. This could be because, in comparison with isoflurane, sevoflurane has a smaller metabolic depressive effect relative to vasodilating effect at 1.5 MAC. At 0.5 and 1.0 MAC, the present results demonstrated no significant differences in the global CBF relative to $CMRo_2$ between the two drugs. Although we did not compare the values of CBF equivalent with those in the awake condition in the present study, the values at 0.5 and 1.0 MAC with both anesthetics are greater than those of awake patients reported with the use of the same technique [8].

Because of the small sample size in each group (n = 8), the power of our negative findings on the difference in CBF equivalent between the two groups should be considered. The data have the potential for a type II error (β = 0.52). The sample size required to reach statistical significance with adequate power (β = 0.2) is 32 patients in each group if the means and variances remain largely unchanged. In addition, a nonsignificant, but slightly higher, $Paco_2$ in the isoflurane group compared with that in the sevoflurane group may have contributed to the slightly higher CBF equivalent values. Thus, the differences, if any, would not be clinically important.

Many animal studies have found that cerebral hyperemia induced by isoflurane and halothane spontaneously decreases over time [9–14], but others have not [15,16]. In humans [17,18], no time decay in CBF during anesthesia was reported. In the previous study [3], we found that the elevated CBF equivalent was preserved during prolonged anesthesia with halothane, isoflurane, and sevoflurane at 1.5 MAC in non-neurological surgery. In the present study, the absence of significant differences in the time trends in CBF equivalent in

both groups suggested that the CBF equivalent was maintained with minimal fluctuation irrespective of the surgical procedure, at 1.0 MAC from 1 to 5 h after induction. Although $CMRo_2$ was not measured, it is unlikely that global $CMRo_2$ consistently changed over time, because the EEG pattern was relatively stable except for the appearance of occasional burst suppression during operation. $CMRo_2$ has also been reported to be maintained during prolonged anesthesia if the anesthetic depth is maintained stable [9–12]. The relatively constant CBF equivalent observed in our study suggests that the direction and magnitude of the changes in global CBF relative to cerebral metabolism are well preserved during a prolonged period of volatile anesthesia during craniotomy in the type of patients examined.

Since our measurements of CBF equivalent were performed while surgery was ongoing, the possibility of a contribution of nociceptive stimulation to the results must be considered. In our previous studies to examine the prolonged (3 h) exposure to volatile anesthetics (1.5 MAC) during abdominal or orthopedic surgery, we found that the CBF equivalent was maintained [3] and that V_{mca} was maintained but was not perfectly stable over time [4]. Preservation of the CBF equivalent suggested that functional changes, presumably metabolic changes, coupled with flow changes had been occurring during surgery. In the present study, in which we infiltrated lidocaine on the skin incision area and added fentanyl, the CBF equivalent was also maintained as well as in the previous study [3], despite the use of a lower MAC (1.0 *vs* 1.5 MAC). This could be because there was less nociceptive stimulation with intracranial surgical procedures than with abdominal or orthopedic surgery. Moreover, scalp infiltration of a local anesthetic was reported to attenuate the changes in cerebral arteriovenous oxygen content difference and blood pressure by incision in neurosurgery [19]. Bisonnette et al. reported that V_{mca} was unchanged during isoflurane anesthesia for 1.5–6 h at 1.0 MAC in children with concomitant epidural local anesthetic [20]. We think that the anesthesia level of 1.0 MAC with the volatile agents lidocaine and fentanyl in this study may have substantially prevented changes in CBF equivalent resulting from nociceptive stimuli in neurosurgery.

In summary, this study demonstrated in humans that the CBF equivalent slightly increased with increasing depth of isoflurane and sevoflurane anesthesia from 0.5 to 1.0 MAC, and the CBF equivalent was maintained for 4 h with no obvious difference between the two agents in the clinical settings studied.

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