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The comparative effects of sevoflurane versus isoflurane on cerebrovascular carbon dioxide reactivity in patients with previous stroke

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Abstract
Purpose. The use of volatile anesthetics is reportedly related to altered cerebrovascular carbon dioxide (CO_2) reactivity. We examined the comparative effects of sevoflurane versus isoflurane on cerebrovascular CO_2 reactivity in patients with previous stroke.
Methods. Twenty-four patients with previous stroke and 20 patients without previous stroke (serving as controls) were studied. Anesthesia was maintained with either end-tidal 1.0 minimum alveolar concentration (MAC) sevoflurane or 1.0 MAC isoflurane in 33% oxygen and 67% nitrous oxide. A 2.5-MHz pulsed transcranial Doppler (TCD) probe was attached to the patient's head at the right or left temporal window for continuous measurement of mean blood flow velocity in the middle cerebral artery (Vmca). After establishing baseline values of Vmca and cardiovascular hemodynamics, we increased end-tidal CO_2 by decreasing the ventilatory frequency by 2–5 breaths·min^{-1}.
Results. We found that values for absolute and relative CO_2 reactivity in the sevoflurane groups were lower than those in the isoflurane groups (absolute CO_2 reactivity in the sevoflurane groups: control, 3.3 ± 0.4*; previous stroke, 3.4 ± 0.4*; absolute CO_2 reactivity in the isoflurane groups: control, 4.2 ± 0.3; previous stroke, 4.5 ± 0.4, cm·s^{-1}·mmHg^{-1}; *$P < 0.05$ compared with isoflurane group). There were no significant differences in the values for absolute and relative CO_2 reactivity between the controls and the previous-stroke patients within each of the sevoflurane and isoflurane groups.
Conclusion. Our findings suggest that, in patients with previous stroke, cerebrovascular CO_2 reactivity under sevoflurane anesthesia was lower than that under isoflurane anesthesia.

Key words Cerebrovascular CO_2 reactivity · Previous stroke · Transcranial Doppler sonography · Sevoflurane · Isoflurane

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Introduction

Some data have been published showing that the use of volatile anesthetics is related to altered cerebrovascular carbon dioxide (CO_2) reactivity under general anesthesia [1–3]. Kitaguchi et al. [1] reported that CO_2 reactivity was well maintained under 0.88 minimum alveolar concentration (MAC) sevoflurane anesthesia. McPherson et al. [2] showed a difference in cerebrovascular CO_2 reactivity between 1.4% and 2.8% isoflurane anesthesia. Nishiyama et al. [3] reported that cerebrovascular CO_2 reactivity was greater under isoflurane anesthesia than under sevoflurane anesthesia in subjects without previous stroke or diabetes mellitus. This report implies that different volatile anesthetics may have differential effects on cerebrovascular CO_2 reactivity, because, as reported by Summors et al. [4], each volatile anesthetic has different effects on the cerebral vasculature at the same MAC.

There have been some reports showing cerebrovascular CO_2 reactivity in patients with previous stroke in the awake condition [5–7]. Maeda et al. [5] showed that CO_2 reactivity in patients with previous stroke was significantly lower than that seen in normal subjects. Meguro et al. [7] reported similar findings. In a previous study, we found that CO_2 reactivity under sevoflurane anesthesia was lower than that under isoflurane anesthesia in diabetic patients [8]. Hence, we hypothesized that cerebrovascular CO_2 reactivity in patients with previous stroke would also probably be lower under sevoflurane as compared with isoflurane anesthesia, as was previously found in normal and diabetic patients. No data, however, exist describing the comparative effects of sevoflurane and isoflurane on cerebrovascular CO_2 reactivity in patients with previous stroke.

The purpose of this study was to examine the comparative effects of sevoflurane versus isoflurane on cerebrovascular CO_2 reactivity in patients with previous stroke.

Patients and methods

After obtaining the approval of the ethics committee of our institution, written, informed consent was obtained from all patients. We studied 24 consecutive patients with a previous history of stroke (Table 3) who were scheduled for elective orthopedic, cardiac, or thoracic surgery, and we compared data from these patients with data from 20 consecutive age-matched control patients who were similarly scheduled for elective orthopedic, cardiac, or thoracic surgery. Patients with previous stroke were defined as having a history of ischemic cerebrovascular disease and symptoms of a neurological disorder. This was confirmed by preoperative brain computed tomography (CT scan) or magnetic resonance imaging (MRI). Patients with a history of psychiatric illness and those with active liver disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase >50 $U \cdot dl^{-1}$) were excluded from the study. All patients were examined for the presence of carotid artery stenosis by the performing of ultrasonography and MRI preoperatively. The presence of carotid artery stenosis was defined as luminal narrowing of more than 50% [9]. None of the patients selected for the study had carotid artery stenosis.

The 24 patients with previous stroke were prospectively randomized into two groups, a sevoflurane group and an isoflurane group. The 20 patients without previous stroke (controls) that we selected had no history of ischemic cerebrovascular disease or symptoms suggestive of a neurological disorder. The sevoflurane and isoflurane groups were determined by a random number table. Anesthesia was induced with 2 $mg \cdot kg^{-1}$ propofol, 2 $\mu g \cdot kg^{-1}$ fentanyl, and 0.1 $mg \cdot kg^{-1}$ vecuronium, followed by endotracheal intubation. Muscular relaxation was achieved by the intermittent administration of vecuronium. All patients were ventilated with 33% oxygen and 67% nitrous oxide, with the continuous monitoring of end-tidal carbon dioxide (Pet_{CO_2}) (Ultima; Datex, Helsinki, Finland). The tympanic membrane temperature was continuously monitored with Mon-a-Therm (Mallinckrodt, St. Louis, MO, USA). Anesthesia was maintained with either end-tidal 1.0 minimum alveolar concentration (MAC) sevoflurane or 1.0 MAC isoflurane in 33% oxygen and 67% nitrous oxide (1 MAC = 1.71% for sevoflurane and 1.15% for isoflurane). A bispectral index (BIS) monitor (ASPECT Medical Systems, Natick, MA, USA) was used to assess the effects of equipotent doses of isoflurane and sevoflurane in each group.

The study was performed after the induction of anesthesia and before the start of surgery, during a stable hemodynamic period (approximately 20–30 min after the induction of anesthesia) under 1.0 MAC sevoflurane or isoflurane anesthesia. A 2.5-MHz pulsed transcranial Doppler (TCD) probe was attached to the patient's head at the right or left temporal window and mean blood flow velocity in the middle cerebral artery (Vmca) was measured continuously (2.5-MHz transducer; SONOS 5500; Hewlett Packard, Andover, MA, USA). After the signals were identified at a depth of 45–60 mm, the probe was fixed using a probe folder, so as not to change the insonation angle. The Vmca value at end-expiration was recorded. The measurement of Vmca was performed at the same site as that of the former stroke. After the measurement of baseline Vmca and cardiovascular hemodynamic values, Pet_{CO_2} was increased by reducing the ventilatory frequency by 2–5 $breaths \cdot min^{-1}$. This resulted in an increase in the Pet_{CO_2} by approximately 6–9 mmHg, within several minutes. All measurements were repeated when Pet_{CO_2} increased and remained stable for 5–10 min.

To confirm the accuracy of Pet_{CO_2} as an indicator of arterial CO_2, arterial CO_2 and Pet_{CO_2} were simultaneously measured in several patients, and an excellent correlation was found between Pet_{CO_2} and arterial CO_2 in these patients (data not shown).

The cerebral vasodilatory response to hypercapnia in each patient was calculated as both the absolute change in Vmca ($cm \cdot s^{-1} \cdot mmHg^{-1}$) and the percentage change in Vmca (percentage of baseline $Vmca \cdot mmHg^{-1}$) per millimeter of mercury change in Pa_{CO_2}, using the following formulae [10–12]:

$$\text{Absolute } CO_2 \text{ reactivity} = \Delta \text{ Vmca}/\Delta \, Pa_{CO_2}$$
$$\text{Relative } CO_2 \text{ reactivity} = (\text{absolute } CO_2 \text{ reactivity}/\text{baseline Vmca}) \times 100,$$

where Δ Vmca is the difference between the flow velocity after Pa_{CO_2} elevation and the baseline flow velocity, and $\Delta \, Pa_{CO_2}$ is the difference between the final and baseline Pa_{CO_2}.

The pulsatile index (PI) and Vmca were calculated for all study participants, using the following formulae [10–12]:

$$PI = (\text{systolic velocity} - \text{diastolic velocity})/\text{mean velocity}$$
$$\text{Vmca} = (\text{systolic velocity} - \text{diastolic velocity})/3 + \text{diastolic velocity}$$

The examiners who measured the MCA flow velocity were unaware of the study group to which each patient belonged. The data obtained in this study were analyzed later by an independent researcher, who was also blind to the group to which each patient had been assigned.

Statistical analysis

All data values were expressed as means ± SD. Unpaired *t*-test was used for analysis between the sevoflurane and isoflurane groups. Following the confirmation of equal

variance among groups by the Bartlett test, one-way factorial measure analysis of variance was performed with multiple comparisons. When the F-value was significant, the Bonferroni method was used to make multiple comparisons. After the study was completed, we evaluated the sample size, which was calculated based on the hypothesis that absolute CO_2 reactivity in patients receiving sevoflurane would decrease by 0.5 $cm \cdot s^{-1} \cdot mmHg^{-1}$ compared with that in patients receiving isoflurane. The sample size provides 80% power to detect a 20% difference between groups with a 5% probability of an α-type error.

Statistical significance was set at $P < 0.05$. All calculations were performed on a Macintosh computer with SPSS (SPSS, Chicago, IL, USA) and Stat View 5.0 software packages (Abacus Concepts, Berkeley, CA, USA).

Results

Table 1 shows the demographic data in the groups. All patients in both the sevoflurane and the isoflurane groups had easily detectable MCA flow velocities. The groups were well matched for age, weight, and height. There were no significant differences between the awake blood pressure (BP) levels in the isoflurane and sevoflurane groups. Hypertensive patients in the sevoflurane and isoflurane groups were well matched for the anti-hypertensive drug therapy they were receiving.

Table 2 shows cerebrovascular CO_2 reactivity data in the sevoflurane and isoflurane groups. Values for BIS, baseline BP, baseline Pet_{CO_2}, Pet_{CO_2} at hypercapnia, PI, and Vmca were essentially identical in the four groups. The values for absolute and relative CO_2 reactivity in the sevoflurane groups were lower than those in the isoflurane groups ($P < 0.05$ compared with isoflurane group). There were no significant differences in the values for absolute and relative CO_2 reactivity between the control subjects and patients with previous stroke within each of the sevoflurane and isoflurane groups.

Discussion

The present study showed that, in patients with previous stroke, cerebrovascular CO_2 reactivity under sevoflurane anesthesia was lower than that under isoflurane anesthesia. No intragroup differences in cerebrovascu-

Table 1. Demographic data in each group

	Sevoflurane		Isoflurane	
	Control ($n = 10$)	Previous stroke ($n = 12$)	Control ($n = 10$)	Previous stroke ($n = 12$)
Age (years)	58 ± 5	60 ± 5	57 ± 7	61 ± 8
Height (cm)	162 ± 6	161 ± 6	161 ± 6	159 ± 7
Weight (kg)	59 ± 6	60 ± 5	58 ± 6	59 ± 6
ACE blocker (no.)	3	3	2	3
Ca. blocker (no.)	1	1	1	1
Awake mean BP (mmHg)	93 ± 10	95 ± 9	97 ± 11	94 ± 10

* $P < 0.05$ compared with other subgroups in the sevoflurane or isoflurane group; ** $P < 0.05$ compared with isoflurane group
Values are means ± SD
BP, Blood pressure; ACE, angiotensin-converting enzyme; Ca. blocker, calcium channel antagonist

Table 2. Comparative effects of sevoflurane and isoflurane on cerebrovascular CO_2 reactivity in each group

	Sevoflurane		Isoflurane	
	Control ($n = 10$)	Previous stroke ($n = 12$)	Control ($n = 10$)	Previous stroke ($n = 12$)
BIS value	50 ± 5	51 ± 3	49 ± 4	49 ± 3
Baseline mean BP	83 ± 9	85 ± 10	85 ± 11	88 ± 11
Baseline Pet_{CO_2}	35 ± 4	34 ± 3	35 ± 4	35 ± 3
Pet_{CO_2} at hypercapnia	43 ± 3	43 ± 3	44 ± 3	43 ± 4
Baseline Vmca ($cm \cdot s^{-1}$)	35.6 ± 4.4	36.1 ± 4.9	36.6 ± 4.8	37.7 ± 4.8
PI	1.07 ± 0.10	1.09 ± 0.14	1.08 ± 0.11	1.06 ± 0.14
Absolute CO_2 reactivity ($cm \cdot s^{-1} \cdot mmHg^{-1}$)	3.3 ± 0.4*	3.4 ± 0.4*	4.2 ± 0.3	4.5 ± 0.4
Relative CO_2 reactivity (%/mmHg)	6.0 ± 0.4*	6.0 ± 0.4*	7.7 ± 0.4	7.8 ± 0.4

* $P < 0.05$ compared with isoflurane group
Values are means ± SD
BIS, Bispectral index; Vmca, mean blood flow velocity in the middle cerebral artery; BP, blood pressure; PI, pulsatile index

lar CO_2 reactivity were found between the control subjects and the patients with previous stroke within either the sevoflurane or the isoflurane group.

Numerous studies exist describing the effects of volatile anesthetics on cerebrovascular CO_2 reactivity [1–4,8,13–16]. McPherson et al. [2] showed that cerebrovascular responsiveness to Pa_{CO_2} was retained during both 1 and 2 MAC isoflurane. In contrast, Olsen et al. [13] reported that cerebral blood flow (CBF) autoregulation was disrupted at 2 MAC isoflurane, but not during 1 MAC isoflurane anesthesia. Nishiyama et al. [3] examined the comparative effects of sevoflurane and isoflurane on cerebrovascular CO_2 reactivity in patients without known cerebral disease, and found that cerebrovascular CO_2 reactivity was greater in the isoflurane (0.6–0.7 MAC) anesthesia group than in the sevoflurane (0.6–0.7 MAC) anesthesia group. The differential effects of these two volatile anesthetics are probably due to the fact that sevoflurane reportedly has a less direct vasodilatory effect than isoflurane [3–4,8,15].

In contrast to reports on normal subjects, there are few reports regarding the effects of volatile anesthetics on cerebrovascular CO_2 reactivity in patients with cerebrovascular disease [1]. Kitaguchi et al. [1] reported that both CO_2 reactivity and cerebral autoregulation were well maintained during the inhalation of 33% nitrous oxide, 33% argon, and oxygen with 1.5% sevoflurane (0.88 MAC) in patients with ischemic cerebrovascular disease. The present study, which is the first of its kind to evaluate the differential effects of sevoflurane versus isoflurane on cerebrovascular CO_2 reactivity in patients with previous stroke, showed that cerebrovascular CO_2 reactivity was greater in the isoflurane (1.0 MAC) anesthesia group than in the sevoflurane (1.0 MAC) anesthesia group.

Numerous studies have been conducted examining cerebrovascular CO_2 reactivity in patients with previous stroke in the awake state. Maeda et al. [5] examined the reactivity of CBF to CO_2 in patients with various types of ischemic cerebrovascular disease, and found that CO_2 reactivity was significantly lower than that seen in normal control subjects. They later reported that CO_2 reactivity in hypertensive patients with cerebral infarction was impaired compared with that in normotensive controls. Meguro et al. [7] showed that CBF and CBF-cerebral blood volume (CBV) ratios were reduced in patients with severe periventricular hyperintensity, as determined by MRI. Our results were inconsistent with those of Meguro et al. [7], because we found no significant difference in cerebrovascular CO_2 reactivity between control patients and those with previous stroke under either sevoflurane or isoflurane anesthesia. The reason for this discrepancy is unclear, but the different results might be attributable to the presence of carotid artery disease in the patients with a previous history of stroke in the Meguro et al. [7] study. We excluded patients with carotid artery disease from the present study. Sugimori et al. [6] showed that the severity of carotid artery disease had a significant influence on cerebrovascular CO_2 reactivity. Our study indicated that, in patients with previous stroke, the degree of control of CBF in response to changes in Pa_{CO_2} was greater during isoflurane than during sevoflurane anesthesia. Hence, our clinical impression is that, in patients with previous stroke, the control of CBF or CBV obtained by altering Pa_{CO_2}, as is often required during neurosurgical anesthesia, can be better achieved under isoflurane as compared with sevoflurane anesthesia.

Study limitations

We assumed that nitrous oxide was required for the maintenance of adequate anesthetic depth, and we administered nitrous oxide together with the inhalational agent. Hence, our results were probably affected by the effects of nitrous oxide on cerebrovascular CO_2 reactivity. It is reported that the combination of nitrous oxide and isoflurane has a more potent cerebral vasodilatory effect than an equipotent dose of isoflurane used alone [17]. Although we did not make allowances for the effects of nitrous oxide in our study, because nitrous oxide was administered at the same concentration in all groups, it is possible that nitrous oxide may have differential effects on cerebral circulation when used in combination with different volatile anesthetics.

In this study, we examined the cerebrovascular response to Pa_{CO_2} by using hypoventilation to increase Vmca, rather than by using hyperventilation to decrease Vmca. Hypercapnia may decrease blood flow to the ischemic area around the area of a stroke, by causing vasodilation of vessels in the nonischemic area of the brain and diverting blood away from the ischemic area of the brain, the vessels of which cannot be further dilated by hypercapnia (intracerebral steal phenomenon). It is possible that part of the explanation for the observed lack of difference in CO_2 reactivity between our control group and patients with previous stroke within both the sevoflurane and isoflurane groups is related to intracerebral steal. However, in this study, Vmca was measured at the same site as the location of the former stroke. It is possible that the observed CO_2 reactivity in our patients with stroke was a regional phenomenon, being indicative of CO_2 reactivity in the ischemic area rather than in the entire brain. To eliminate this possibility, we measured Vmca on the side opposite to that of the location of the previous stroke in some of the patients with previous stroke (data not shown), and found no difference in Vmca between the same side as the previous stroke and the side opposite the location of the previous stroke.

Table 3. Neurological diagnosis in patients with previous stroke

	Sevoflurane	Isoflurane
Multiple lacunar stroke	4	3
Small stroke lesion	7	8
Broad infarction	1	1

Patients with previous stroke together with carotid artery disease were excluded from our study, to eliminate the effects of carotid artery disease on cerebrovascular CO_2 reactivity. In addition, the degree of neurological dysfunction in our patients was not severe, as shown in Table 3. It is possible that our findings may not be reproducible in patients with more severe neurological disorders. Moreover, the absence of neurological disorders in the control patients was not confirmed by preoperative brain CT or MRI. Further studies are, therefore, necessary to clarify the exact effects of volatile agents such as sevoflurane or isoflurane on cerebrovascular CO_2 reactivity in patients with previous stroke.

Although the effects of propofol and fentanyl used for the induction of anesthesia were ignored in our study, because these drugs were administered at the same dosage in both the sevoflurane and isoflurane groups, it is possible that the different induction agents may have had different effects on our results.

There are no data regarding the effects of oral antihypertensive drugs on cerebrovascular CO_2 reactivity. One report, by Kawaguchi et al. [18], showed that cerebrovascular reactivity to hypocapnia was maintained during nicardipine-induced hypotension in fentanyl/diazepam/nitrous oxide anesthesia. Hence, we cannot rule out the possibility that the different oral antihypertensive drugs may have had some effects on cerebrovascular CO_2 reactivity in the patients with previous stroke.

In conclusion, in patients with previous stroke, cerebrovascular CO_2 reactivity is lower under sevoflurane anesthesia than under isoflurane anesthesia. Our findings suggest that, in patients with previous stroke, the degree of control of CBF in response to changes in Pa_{CO_2} is greater under 1.0 MAC isoflurane than under 1.0 MAC sevoflurane anesthesia.

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