Anesthesiology
1996; 85:755-60
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Effects of Sevoflurane with and without Nitrous Oxide on Human Cerebral Circulation

Transcranial Doppler Study

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Background: **This study was designed to evaluate the effects of sevoflurane with and without nitrous oxide on human middle cerebral artery (MCA) flow velocity, cerebrovascular carbon dioxide reactivity, and autoregulation compared with the awake state using transcranial Doppler ultrasonography.**

Methods: **In 14 patients, the time-mean middle cerebral artery flow velocity (Vmca) was measured when the end-tidal carbon dioxide level was approximately 30, 40, and 50 mmHg under the following conditions: (1) awake; (2) with 2% (1.2 MAC) sevoflurane; and (3) with 1.2 MAC sevoflurane–60% nitrous oxide. In six other patients, the cerebrovascular autoregulation during anesthesia was determined using intravenous phenylephrine to increase blood pressure.**

Results: **Sevoflurane (1.2 MAC) significantly decreased Vmca compared with the awake value at each level of end-tidal carbon dioxide, whereas 1.2 MAC sevoflurane–60% nitrous oxide did not exert significant influence. The Vmca in normocapnic patients decreased from 69 cm/s to 55 cm/s with 1.2 MAC sevoflurane and then increased to 70 cm/s when nitrous oxide was added. Sevoflurane (1.2 MAC) with and without 60% nitrous oxide had a negligible effect on cerebrovascular carbon dioxide reactivity. A phenylephrine-induced increase of mean arterial pressure did not influence Vmca during anesthesia.**

Conclusions: **Sevoflurane (1.2 MAC) reduced Vmca compared with the awake condition, whereas the addition of nitrous oxide caused Vmca to increase toward the values obtained in the awake condition. The cerebrovascular carbon dioxide reactivity and autoregulation were well maintained during 1.2 MAC sevoflurane with and without 60% nitrous oxide. (Key words: Anesthetics, volatile: sevoflurane; nitrous oxide. Brain: blood flow velocity; carbon dioxide reactivity; autoregulation. Equipment: transcranial Doppler ultrasonography. Pharmacology: phenylephrine).**

SEVOFLURANE is a new volatile anesthetic recently introduced into clinical practice in the United States. In animal experiments, sevoflurane decreased both cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRo_2$) in pigs,[1] whereas it decreased $CMRo_2$ but not CBF in rabbits[2] and dogs.[3] Kitaguchi and associates[4] studied the effects of sevoflurane on the cerebral circulation of patients with ischemic cerebrovascular disease and reported that carbon dioxide reactivity of CBF was well maintained during 1.5% (0.88 MAC) sevoflurane–33% nitrous oxide anesthesia. However, in their study, CBF in the awake state was not measured and the influence of nitrous oxide was not examined in patients without cerebrovascular disease.

Transcranial Doppler ultrasonography can measure the middle cerebral artery flow velocity continuously and noninvasively. Although the middle cerebral artery (MCA) flow velocity does not reflect the absolute CBF, the change in the MCA flow velocity is directly proportional to the change in the CBF.[5,6] The present study was designed to evaluate the effects of sevoflurane with and without nitrous oxide on human MCA flow velocity, cerebrovascular carbon dioxide reactivity, and autoregulation.

Patients and Methods

The study was approved by the Ethics Committee for Human Study of Nagasaki University School of Medicine, and informed consent was obtained from each patient. Twenty patients scheduled for minor nonneu-

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Received from the Department of Anesthesiology, Nagasaki University School of Medicine, Nagasaki, Japan. Submitted for publication January 23, 1996. Accepted for publication June 16, 1996. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 15-19, 1994.

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rologic elective surgery were studied in either experiment 1 or 2. In experiment 1, 14 healthy patients (five men and nine women) with a mean age of 33 ± 7 years (SD) and a mean weight of 55 ± 11 kg were studied; in experiment 2, six healthy patients (three men and three women) with a mean age of 29 ± 4 years and a mean weight of 59 ± 9 kg were studied. No preanesthetic medication was administered. Monitoring equipment included a radial artery catheter for direct arterial blood pressure measurement, a pulse oximeter, and an electrocardiograph. End-tidal carbon dioxide ($ETCO_2$) tension and nitrous oxide and sevoflurane concentrations were measured using a CAPNOMAC multigas analyzer (Datex, Helsinki, Finland) that was calibrated before the study. A rectal thermistor probe was placed after anesthesia was induced. Body temperature was maintained between 36 and 37°C using a warming blanket.

Middle Cerebral Artery Flow Velocity Measurements

Methods have been reported previously.[7] Briefly, the MCA flow velocity was measured continuously using a pulsed 2-MHz transcranial Doppler ultrasound (TC2-64B; EME, Uberlingen, Germany), which operates with a maximum of 100 mW/cm^2 ultrasonic intensity and pulse repetition frequencies between 4.96 and 20.52 kHz. Bidirectional signals were recorded with a 10-kHz low-pass filter and a 150-Hz high-pass filter. The Doppler probe was positioned at the right temporal scalp surface and was fixed at the site of best insonation. Transcranial Doppler ultrasound signals of the MCA were identified at a depth of 45 to 50 mm. The time-mean MCA flow velocity (Vmca) was computed by the instrument using a fast-four real-time frequency analysis. The Vmca values were obtained only during end-expiration to avoid respiratory fluctuations.

Experiment 1: Vmca and Carbon Dioxide Reactivity

Flow velocity of MCA in response to changes in $ETCO_2$ was determined in 14 patients under the following three states: (1) when patients were awake; (2) with 2% (1.2 MAC) sevoflurane; and (3) with 1.2 MAC sevoflurane–60% nitrous oxide. Measurements during the awake state were taken before anesthesia was induced, and the measurements during anesthetic state were done after the tracheal intubation but before surgery to avoid the influence of surgical stimulation.

Awake control carbon dioxide reactivity was obtained in the patients breathing through a mouthpiece and wearing a nose clip using a Mapleson D breathing system. End-tidal carbon dioxide tension was monitored in the expiratory limb of the breathing circuit close to the patient's mouth. All patients breathed 100% oxygen during normocapnic and hypocapnic states. After the patients were acclimated to the breathing system for 10 to 15 min, Vmca in normocapnia was measured. The fresh gas flow then was increased and intentional hyperventilation was maintained for 5 min. At least three Vmca values in hypocapnia were measured. Five minutes after recovery of normocapnia under spontaneous ventilation, hypercapnia was induced by having the patients breathe a mixture of 95% oxygen–5% carbon dioxide, which was maintained for 5 min to measure the minimum of three Vmca in hypercapnia. Determinations of Vmca were always made after a steady $ETCO_2$ was obtained for at least five respiratory cycles.

Five minutes after recovery of normocapnia under spontaneous ventilation, anesthesia was induced with inhalation of a mixture of sevoflurane–nitrous oxide–oxygen through a face mask using an F breathing system, and tracheal intubation was facilitated with 0.15 mg/kg intravenous vecuronium bromide. During anesthetic induction, approximately 500 ml lactated Ringer's solution was infused to avoid hypotension; after induction, lactated Ringer's solution was infused at a rate of 3 $ml \cdot kg^{-1} \cdot h^{-1}$ until all the measurements were made.

After tracheal intubation, measurements were taken while the patients were under anesthesia. Patients were randomly allocated to one of two groups. In group A (n = 7), measurements during 1.2 MAC sevoflurane and then 1.2 MAC sevoflurane–60% nitrous oxide were made. In group B (n = 7), measurements were made during 1.2 MAC sevoflurane–60% nitrous oxide followed by 1.2 MAC sevoflurane.

Before the 1.2 MAC sevoflurane measurements, 1.2 MAC sevoflurane–100% oxygen was maintained for at least 15 min during normocapnia. Before the 1.2 MAC sevoflurane–60% nitrous oxide measurements, a mixture of 1.2 MAC sevoflurane, 60% nitrous oxide, and 40% oxygen was maintained for at least 15 min during normocapnia. After the measurements during normocapnia, hypocapnia was induced. After the measurements during hypocapnia, 5 min of normocapnia was maintained before hypercapnia was induced. Hypocapnia and hypercapnia were induced by changing the respiratory rate under a constant tidal volume, and at

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Table 1. Experimental Sequence in Experiment 1

	Measurement		
Group	First	Second	Third
A (n = 7)	Awake	Sevo	Sevo + N_2O
B (n = 7)	Awake	Sevo + N_2O	Sevo

Awake = awake state; Sevo = 1.2 MAC sevoflurane state; Sevo + N_2O = 1.2 MAC sevoflurane–60% N_2O state.

least three Vmca values were measured during hypocapnia and hypercapnia. The protocol was identical in groups A and B except that the order of 1.2 MAC sevoflurane and 1.2 MAC sevoflurane–60% nitrous oxide was reversed (table 1).

Experiment 2: Vmca and Autoregulation

In six other patients, Vmca in response to changes in mean arterial blood pressure (MAP) was determined during normocapnia under the following three conditions: (1) while patients were awake; (2) with 1.2 MAC sevoflurane; and (3) with 1.2 MAC sevoflurane–60% nitrous oxide. As in experiment 1, measurements during the awake state were performed before anesthesia was induced, and the measurements during anesthesia were done after tracheal intubation but before surgery.

Awake control data were obtained with the patients breathing 100% oxygen through a mouthpiece and wearing a nose clip using a Mapleson D breathing system. End-tidal carbon dioxide tension was monitored in the expiratory limb of the breathing circuit close to the patient's mouth. After the patients were acclimated to the breathing system for 10 to 15 min, Vmca in normocapnia was measured. Mean arterial blood pressure was increased by approximately 20 mmHg for 3 to 5 min by the intravenous infusion of phenylephrine, and then Vmca was measured in each patient.

Ten minutes after recovery, anesthesia was induced with inhalation of a mixture of sevoflurane, nitrous oxide, and oxygen through a face mask using an F breathing system. After tracheal intubation, the Vmca response to changes in MAP was determined during 1.2 MAC sevoflurane and 1.2 MAC sevoflurane–60% nitrous oxide in the same manner as when patients were awake.

Data Analysis

Data are expressed as mean ± SD. All variables of patients in groups A and B were compared using Student's *t* test. In experiments 1 and 2, all variables were analyzed using a repeated-measure analysis of variance. When significance was found, Tukey's test was used. The paired Vmca-$ETCO_2$ determinations were fitted to both exponential and linear regression analysis to determine the best fit for the relationship. A probability value of less than 0.05 was regarded as significant.

Results

Experiment 1

There were no significant differences between groups A and B concerning any of the measured variables, and thus mean and SD values represent the pooled data from each group. The mean hematocrit concentration in arterial blood measured just before the awake state measurements, during the anesthetic state measurements, and at the end of the measurements were 41 ± 5% (SD), 38 ± 3%, and 37 ± 2%, respectively, with no significant differences among them. The body temperature of the patients was maintained between 36 ± 1°C. The differences between Pa_{CO_2} and $ETCO_2$ values just before and after the awake state measurements and anesthetic state measurements were within 1.5 mmHg. Table 2 shows the MAP and heart rate during the experiments. There were no significant differences among the three experimental states. Because the MAP decreased to less than 60 mmHg under anesthesia with 1.2 MAC sevoflurane–60% nitrous oxide in one patient in group A and in two patients in group B, they required continuous intravenous administration of phenylephrine.

Table 2 and figure 1 show Vmca and $ETCO_2$ during hypocapnia, normocapnia, and hypercapnia under the three experimental conditions. Compared with the awake value at each level of $ETCO_2$, 1.2 MAC sevoflurane significantly reduced Vmca, but there was no significant difference in Vmca between 1.2 MAC sevoflurane–60% nitrous oxide and awake values.

Linear regression analysis demonstrated a close relationship between $ETCO_2$ and Vmca, with correlation coefficients of more than 0.95, and was used for subsequent comparisons. The carbon dioxide reactivity slopes derived by linear regression analysis for the awake, 1.2 MAC sevoflurane, and 1.2 MAC sevoflurane–60% nitrous oxide conditions were 2.5 ± 0.5 (SD), 2.2 ± 0.4, and 2.5 ± 0.3 ($cm \cdot s^{-1} \cdot mmHg^{-1}$). There were no significant differences among them.

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Table 2. Mean Arterial Blood Pressure (MAP), Heart Rate (HR), End-Tidal CO_2 (ET_{CO_2}), and Time-Mean Middle Cerebral Artery Flow Velocity (V_{mca}) during Hypocapnia, Normocapnia, and Hypercapnia under the Three Experimental Conditions

	Awake			1.2 MAC Sevo			1.2 MAC Sevo + N_2O		
	Hypocapnia	Normocapnia	Hypercapnia	Hypocapnia	Normocapnia	Hypercapnia	Hypocapnia	Normocapnia	Hypercapnia
MAP (mmHg)	82 ± 13	83 ± 12	82 ± 11	73 ± 8	76 ± 10	78 ± 10	72 ± 10	72 ± 11	73 ± 11
HR (beats/min)	77 ± 8	74 ± 14	71 ± 6	67 ± 11	66 ± 10	67 ± 10	67 ± 11	67 ± 10	69 ± 9
ET_{CO_2} (mmHg)	31 ± 2	41 ± 3	51 ± 2	31 ± 1	40 ± 1	50 ± 2	30 ± 1	39 ± 3	51 ± 1
V_{mca} (cm/s)	52 ± 9	69 ± 9	97 ± 11	33 ± 6*	55 ± 8*	78 ± 10*	45 ± 10†	70 ± 9†	93 ± 10†

Values are mean ± SD. Awake = awake state; 1.2 MAC Sevo = 1.2 MAC sevoflurane state; 1.2 MAC Sevo + N_2O = 1.2 MAC sevoflurane–60% N_2O state. V_{mca} values in hypercapnia > normocapnia > hypocapnia for all study conditions ($P < 0.05$).

* Significantly different from awake values ($P < 0.05$).

† Significantly different 1.2 MAC Sevo values *versus* 1.2 MAC Sevo + N_2O.

Experiment 2

The mean hematocrit concentration in arterial blood determined just before the awake state and anesthetic state measurements and at the end of the measurements were 42 ± 4% (SD), 38 ± 4%, and 37 ± 2%, respectively, with no significant differences among them. The body temperature of the patients was maintained between 36 ± 0.8°C. The differences between Pa_{CO_2} and $ETCO_2$ values just before and after the awake measurements and anesthetic condition measurements were within 1.5 mmHg. The MAP before phenylephrine treatment was more than 60 mmHg in all patients. As shown in table 3, intravenous infusion of phenylephrine increased MAP by approximately 20 mmHg and decreased heart rate by approximately 15 bpm in each experimental state. There was no significant change in Vmca or $ETCO_2$ during phenylephrine infusion.

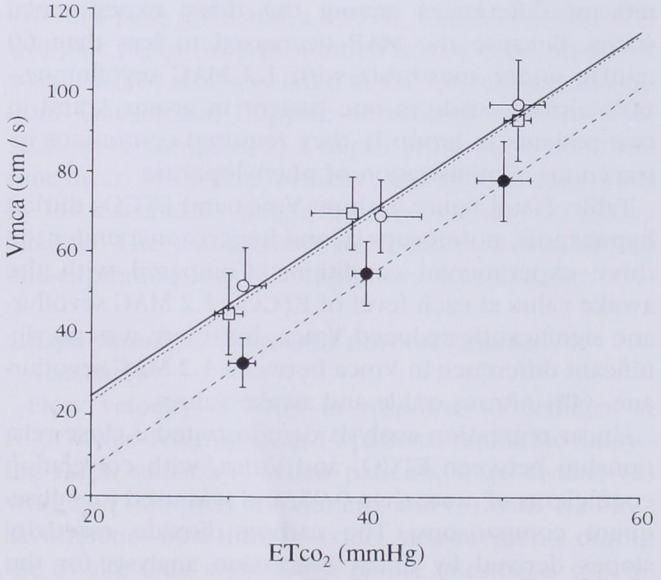

Fig. 1. Middle cerebral artery flow velocity and end-tidal carbon dioxide tension during hypocapnia, normocapnia, and hypercapnia under three experimental conditions. ○ Awake. ● 1.2 MAC sevoflurane. □ 1.2 MAC sevoflurane–60% nitrous oxide.

Discussion

The effects of halothane, enflurane, and isoflurane on cerebral circulation have been studied extensively in animals[8–10] and in humans.[11] Researchers report that these anesthetics have cerebral vasodilator properties that are dose dependent, and that isoflurane is a less-potent cerebral vasodilator.[8,9] The present results show that 1.2 MAC sevoflurane reduces Vmca compared with the awake value at each level of $ETCO_2$. Our data also show that cerebrovascular carbon dioxide reactivity is well maintained during 1.2 MAC sevoflurane anesthesia.

Manohar[1] reported that 1 MAC sevoflurane decreased CBF and $CMRO_2$ compared with an awake, nonanesthetized control state by approximately 30% and 50% in pigs, respectively. Scheller and associates[2] observed that CBF remained unchanged but that $CMRO_2$ was reduced significantly in rabbits under 1.0 MAC sevoflurane during morphine–nitrous oxide anesthesia. They also found that 0.5 to 2.14 MAC sevoflurane had minimal effects on CBF but significantly reduced $CMRO_2$ in dogs.[3] Takahashi and colleagues[12] reported that 0.5 to 1.5 MAC sevoflurane with 70% nitrous oxide did not increase intracranial pressure during established hypocapnia in dogs, in contrast with halothane and enflurane. Crawford and associates[13] demonstrated

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Table 3. Mean Arterial Blood Pressure, Heart Rate, ET_{CO_2}, and V_{mca} under the Three Experimental Conditions

	Prephenylephrine				Postphenylephrine			
	MAP	HR	ET_{CO_2}	V_{mca}	MAP	HR	ET_{CO_2}	V_{mca}
Awake	87 ± 4	73 ± 7	38 ± 3	62 ± 12	111 ± 13*	58 ± 5*	38 ± 4	60 ± 12
1.2 MAC sevoflurane	73 ± 11	62 ± 6†	38 ± 3	41 ± 12†	98 ± 13*†	48 ± 4*†	37 ± 3	42 ± 12†
1.2 MAC sevoflurane–60% N_2O	70 ± 10†	62 ± 5†	38 ± 3	55 ± 10	89 ± 10*†	53 ± 6*	37 ± 3	55 ± 9

Values are mean ± SD. MAP = mean arterial pressure (mmHg); HR = heart rate (beats/min).

* Significantly different from prephenylephrine values ($P < 0.05$).

† Significantly different from awake values ($P < 0.05$).

that in rats, compared with an awake, nonanesthetized control state, CBF remained unchanged under 0.5 and 1.0 MAC sevoflurane but increased by 61% and 120%, respectively, under 1.2 and 1.5 MAC sevoflurane. However, the influence of hypercapnia on the CBF could not be excluded in their study because the rats were spontaneously ventilated.

In clinical studies, Kitaguchi and associates[4] investigated the effects of sevoflurane on cerebral circulation in patients with ischemic cerebrovascular disease using the Kety-Schmidt technique with argon. They reported that CBF and $CMRO_2$ in sevoflurane anesthesia were 28 ml · 100 mg^{-1} · min^{-1} and 1.34 ml · 100 mg^{-1} · min^{-1}, respectively, and that carbon dioxide reactivity of CBF was well maintained. In their separate study,[14] CBF and $CMRO_2$ in awake patients with ischemic cerebrovascular disease were 42.3 ml · 100 mg^{-1} · min^{-1} and 2.81 ml · 100 mg^{-1} · min^{-1}, respectively. Thus CBF and $CMRO_2$ during sevoflurane anesthesia were 34% and 52% less, respectively, than those in awake patients.

Researchers report that nitrous oxide dilates cerebral vasculature in combination with inhaled anesthetics.[15–17] We examined the effects of the addition of nitrous oxide to sevoflurane. Our results show that 1.2 MAC sevoflurane–60% nitrous oxide has little effect on MCA flow velocity and that cerebrovascular carbon dioxide reactivity and autoregulation are well maintained during 1.2 MAC sevoflurane–60% nitrous oxide anesthesia. The present results correlate with those of Manohar and Parks,[16] who found that sevoflurane reduced CBF relative to the awake situation, whereas the addition of nitrous oxide caused CBF values to return toward those in the awake condition in pigs.

Autoregulation of CBF refers to alterations in cerebral vascular resistance in response to perfusion pressure. If autoregulation of CBF works well, CBF does not change when the cerebral perfusion pressure increases or decreases within a certain range. Miletich and associates[10] reported that because halothane and enflurane increased CBF by dilatation of cerebral vasculature, autoregulation of CBF was absent during anesthesia with these agents. Isoflurane was reported to have a weaker cerebral vasodilating action than halothane.[8] Todd and Drummond[9] observed the cerebrovascular and metabolic effects of halothane and isoflurane in cats and concluded that isoflurane had a smaller effect on autoregulation of CBF compared with halothane. The present results show that cerebrovascular autoregulation is well maintained during anesthesia with 1.2 MAC sevoflurane or a mixture of 1.2 MAC sevoflurane and 60% nitrous oxide.

The patients were divided into two groups in experiment 1 to avoid the time effect of volatile anesthesia. The results showed that the experimental sequence of sevoflurane and sevoflurane–nitrous oxide states had no influence on the measured parameters. Thus we considered that the order of the experimental states did not introduce significant bias and did not use the reversed order in experiment 2.

The MAP decreased to less than 60 mmHg during 1.2 MAC sevoflurane–60% nitrous oxide anesthesia, and continuous intravenous administration of phenylephrine was required in three patients in experiment 1. It does not seem possible that phenylephrine infusion might have influenced the measured Vmca, because the dose of phenylephrine was the minimum necessary to maintain MAP at levels greater than 60 mmHg; furthermore, the phenylephrine-induced increased MAP did not influence Vmca during 1.2 MAC sevoflurane or 1.2 MAC sevoflurane–60% nitrous oxide anesthesia in experiment 2.

It is unlikely that preoperative anxiety might have spuriously increased the baseline Vmca in the present study because no preanesthetic medication was used. The normal Vmca during the awake resting state varies from 35 to 90, with an average value of 60 cm · s^{-1},[18]

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and our results are consistent with these values as the Vmca in normocapnia under awake state in experiments 1 and 2 were 69 ± 9 and 62 ± 12 $cm \cdot s^{-1}$.

Sevoflurane reduced Vmca compared with the awake condition, whereas the addition of nitrous oxide caused Vmca to increase toward the awake condition. The cerebrovascular carbon dioxide reactivity and autoregulation were well maintained during sevoflurane with and without nitrous oxide anesthesia.

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