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# *Effects of Sevoflurane on Cerebral Circulation and Metabolism in Patients with Ischemic Cerebrovascular Disease*

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***Background:*** **Sevoflurane is a newly developed volatile anesthetic that has a low blood-gas partition coefficient. The effects of sevoflurane on the cerebral circulation or metabolism in humans have not been studied. The authors examined the cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMR_{O_2}$) during sevoflurane anesthesia. The carbon dioxide response and autoregulation of cerebral circulation were also examined.**

***Methods:*** **Ten patients with ischemic cerebrovascular disease undergoing extraintracranial artery anastomosis were studied. Cerebral blood flow and $CMR_{O_2}$ were determined by the Kety-Schmidt method using argon. These procedures were performed during the inhalation of 33% $N_2O$, 33% argon, and oxygen with 1.5% sevoflurane (0.88 minimum alveolar concentration). To examine the relationship of CBF to a change in $Pa_{CO_2}$, CBF was measured repeatedly at steady state $Pa_{CO_2}$, of 40, 35, and 45 mmHg. Furthermore, CBF was measured before and after an increase in mean arterial pressure (MAP) caused by intravenous infusion of methoxamine to determine the relationship between CBF and MAP.**

***Results:*** **Cerebral blood flow and $CMR_{O_2}$ were 28 ± 4 ml · 100 $g^{-1}$ · $min^{-1}$ and 1.34 ± 0.23 ml · 100 $g^{-1}$ · $min^{-1}$, respectively. Cerebral blood flow was found to vary directly with $Pa_{CO_2}$ alteration. The slope of the regression line between $Pa_{CO_2}$ and CBF was 1.29 ml · 100 $g^{-1}$ · $min^{-1}$ · $mmHg^{-1}$. On the other hand, CBF was constant throughout the elevation of MAP with vasopressor.**

***Conclusions:*** **Both carbon dioxide response and cerebral autoregulation were well maintained under 0.88 MAC sevoflurane anesthesia in patients with ischemic cerebrovascular disease. (Key words: Anesthetics, volatile: sevoflurane. Brain: autoregulation; blood flow; carbon dioxide reactivity; oxygen consumption.)**

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SEVOFLURANE is a nonflammable volatile anesthetic. Because of its blood-gas partition coefficient of 0.63, which is lower than that of other volatile anesthetics, induction of anesthesia and recovery should be faster with sevoflurane than with halothane or isoflurane.[1] Because rapid induction and recovery are desirable goals in neurosurgical anesthesia, sevoflurane may be an attractive agent for use during neurosurgery. In animal experiments, sevoflurane was found to decrease both CBF and $CMR_{O_2}$ in pigs,[2,3] whereas it decreased $CMR_{O_2}$, but not CBF, in rabbits[4] and dogs.[5] However, there has been no report on the effects of sevoflurane on the cerebral circulation or metabolism in humans.

In this study, we measured the CBF and $CMR_{O_2}$ during sevoflurane anesthesia in patients with ischemic cerebrovascular disease. Cerebral blood flow was determined by argon desaturation with the Kety-Schmidt method using a mass spectrometer. The effects of sevoflurane on CBF reactivity to $Pa_{CO_2}$ and on autoregulation of CBF were also studied.

## Materials and Methods

The study protocol was approved by the Ethical Committee for Human Study of the National Cardiovascular Center, and informed consent was obtained from each patient. Ten patients who suffered from ischemic cerebrovascular disease were selected for the study. Seven men and three women (mean age 51 ± 9 yr and weight 57 ± 10 kg) were studied. The patients underwent extracranial-intracranial (EC-IC) arterial anastomosis (superficial temporal artery-middle cerebral artery anastomosis) to correct surgically unilateral internal carotid artery stenosis. A small low-density area had been detected at the brain computed tomography examination in three of the ten patients. Using the grading system described by Sundt *et al.*,[6] all the patients were categorized into grade 1 or 2 (low risk).

Atropine sulfate (0.5 mg) and hydroxyzine (50 mg) were given intramuscularly 30 min before induction of anesthesia. Anesthesia was induced with thiopental (4 mg·kg$^{-1}$, intravenous bolus), and either vecuronium bromide or pancuronium bromide (8–10 mg, intravenous bolus) was administered as a muscle relaxant. The trachea of each patient was intubated and the lungs were mechanically ventilated to adjust $Pa_{CO_2}$ at approximately 40 mmHg. A radial artery was cannulated for continuous monitoring of blood pressure and for blood gas analysis. The bladder temperature was monitored and maintained at 36.8 ± 0.2° C. Anesthesia was maintained with sevoflurane in the presence of 33% $N_2O$ (0.33 minimum alveolar concentration [MAC]), 33% $N_2$, and oxygen during the surgery.

*Cerebral Blood Flow Measurement*

We measured CBF according to the Kety-Schmidt technique[7] with 33% argon (Ar) inhalation.[8,9] After anesthesia was induced, nonthrombogenic Teflon catheters (Physio Probe, Research Medical, UT) were inserted into the jugular bulb *via* the internal jugular vein, and also into the femoral artery to record the partial pressure of Ar in the blood. The catheters were then connected to the vacuum system of a medical mass spectrometer (Medspect II, Allied Healthcare Products, St. Louis, MO; Chemetron). First, 33% Ar gas was given instead of nitrogen, and the saturation curve was recorded until the arterial and venous Ar levels reached equilibrium. Next, the desaturation curve was recorded for 15–20 min as Ar was replaced by nitrogen. Cerebral blood flow was calculated from the desaturation curves according to the Fick principle. Femoral artery oxygen content ($Ca_{O_2}$) and internal jugular vein oxygen content ($Cj_{O_2}$) were also calculated from the oxyhemoglobin saturations (ABL II, Radiometer, Copenhagen, Denmark). Cerebral metabolic rate for oxygen was calculated by multiplying the arterial-jugular bulb oxygen content difference by the CBF.

*The Timing of Cerebral Blood Flow Measurement*

About 2 h after induction of anesthesia, during the preparation of donor superficial temporal artery, we measured CBF at the following five conditions; 1) normocapnea-normotension, 2) hypocapnea-normotension, 3) hypercapnea-normotension, 4) normocapnea-normotension, and 5) normocapnea-hypertension. Cerebral blood flow was measured during 1.5% of sevoflurane (end-tidal concentration, 0.88 MAC[10]). The administered concentration of sevoflurane was determined in a preliminary study of more than 50 patients undergoing EC-IC artery anastomosis. The concentration of sevoflurane was chosen to maintain blood pressure at the patients' resting level according to the criteria of anesthetic management for patients with ischemic cerebrovascular disease in our institution.

*Cerebral Blood Flow Reactivity to $Pa_{CO_2}$*

To characterize the reactivity of CBF to $Pa_{CO_2}$ alteration during sevoflurane anesthesia, the relationship between CBF and $Pa_{CO_2}$ was examined. The $Pa_{CO_2}$ levels of 40, 35, and 45 mmHg, respectively, were selected by changing the ventilatory rate on a guide with end-tidal carbon dioxide (CAPNOMAC; Datex, Helsinki, Finland). The target end-tidal carbon dioxide level was maintained for at least 15 min before CBF measurement, with the interval between measurements being more than 30 min. Each $Pa_{CO_2}$ level was then confirmed by arterial gas analysis. Cerebral blood flow was measured once at each $Pa_{CO_2}$ level in all patients.

*Cerebral Blood Flow Autoregulation*

To determine the relationship between CBF and mean arterial pressure (MAP) in sevoflurane anesthesia, MAP was increased by about 20–25 mmHg by intravenous infusion of methoxamine, and CBF was repeatedly measured by the Ar inhalation method.

*Data Analysis*

Data were expressed as mean ± SD. To define the carbon dioxide reactivity and CBF autoregulation during sevoflurane anesthesia, one-way ANOVA, followed by Tukey's test, was used to determine which values of $Pa_{CO_2}$, MAP, and CBF differed significantly. A $P$ value $< 0.05$ was regarded as significant.

## Results

There was no significant change in bladder temperature during the course of study. During CBF measurement, the MAP was maintained around the resting level with 1.5% sevoflurane in all patients.

*Cerebral Blood Flow and $CMR_{O_2}$*

Cerebral blood flow and $CMR_{O_2}$ were 28 ± 4 ml·100 g$^{-1}$·min$^{-1}$ and 1.34 ± 0.23 ml·100 g$^{-1}$·min$^{-1}$, respectively, when $Pa_{CO_2}$ was 40 ± 1 mmHg and MAP was

**Table 1. Arterial $CO_2$ Tension, Mean Arterial Pressure, and Cerebral Blood Flow during Sevoflurane Anesthesia**

| | Hypocapnia | | | Normocapnia | | | Hypercapnia | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | $Pa_{CO_2}$ | MAP | CBF | $Pa_{CO_2}$ | MAP | CBF | $Pa_{CO_2}$ | MAP | CBF |
| 1 | 37 | 82 | 19 | 42 | 92 | 25 | 47 | 92 | 30 |
| 2 | 37 | 73 | 20 | 40 | 81 | 23 | 47 | 115 | 35 |
| 3 | 36 | 99 | 23 | 41 | 78 | 25 | 45 | 85 | 37 |
| 4 | 36 | 98 | 20 | 41 | 100 | 26 | 45 | 103 | 37 |
| 5 | 37 | 75 | 23 | 39 | 82 | 32 | 47 | 95 | 38 |
| 6 | 36 | 95 | 21 | 40 | 94 | 26 | 44 | 93 | 36 |
| 7 | 33 | 99 | 22 | 39 | 96 | 32 | 47 | 93 | 37 |
| 8 | 36 | 92 | 26 | 42 | 95 | 32 | 45 | 100 | 37 |
| 9 | 34 | 92 | 24 | 39 | 90 | 33 | 45 | 87 | 43 |
| 10 | 36 | 76 | 18 | 42 | 85 | 24 | 46 | 87 | 36 |
| Mean ± SD | 36 ± 1* | 88 ± 11 | 22 ± 3† | 41 ± 1* | 89 ± 7 | 28 ± 4† | 46 ± 1* | 95 ± 9 | 37 ± 3† |

$Pa_{CO_2}$ = arterial carbon dioxide tension (mmHg); MAP = mean arterial pressure (mmHg); CBF = cerebral blood flow (ml · 100 $g^{-1}$ · $min^{-1}$).

* $P < 0.05$ compared to the other two states.

† $P < 0.01$ compared to the other two states.

93 ± 11 mmHg. At this time, heart rate was 80 ± 15 · $min^{-1}$, and hemoglobin was 10.9 ± 1.2 g%.

*Cerebral Blood Flow Reactivity to Changes in $Pa_{CO_2}$*

Cerebral blood flow was 28 ± 4 ml · 100 g−1 · $min^{-1}$ when $Pa_{CO_2}$ was 41 ± 1 mmHg (normocapnea), and decreased to 22 ± 3 ml · 100 $g^{-1}$ · $min^{-1}$ in response to a decrease in $Pa_{CO_2}$ to 36 ± 1 mmHg (hypocapnea). Cerebral blood flow increased to 37 ± 3 ml · 100 $g^{-1}$ · $min^{-1}$ when $Pa_{CO_2}$ was increased to 46 ± 1 mmHg (hypercapnea). Both the $Pa_{CO_2}$ and CBF values were significantly different from those in the other two states. The slope of the regression line between $Pa_{CO_2}$ and CBF was 1.29 ml · 100 $g^{-1}$ · $min^{-1}$ · $mmHg^{-1}$. Table 1 shows the relationship between $Pa_{CO_2}$ and CBF in each patient. The reactivity of CBF to changes in $Pa_{CO_2}$ was well maintained during sevoflurane anesthesia (fig. 1).

*Cerebral Blood Flow Autoregulation*

Cerebral blood flow was 31 ± 4 ml · 100 $g^{-1}$ · $min^{-1}$ when MAP was 89 ± 6 mmHg. When MAP was increased by methoxamine infusion to 113 ± 6 mmHg, CBF was 30 ± 4 ml · 100 $g^{-1}$ · $min^{-1}$ (table 2; fig. 2). There were no significant changes in CBF during the course of the deliberate hypertension. The slope of the regression line between MAP and CBF was 0.02 ml · 100 $g^{-1}$ · $min^{-1}$ · $mmHg^{-1}$.

## Discussion

Measurements of CBF and $CMR_{O_2}$ during sevoflurane anesthesia in humans have not been reported. In this study, we investigated the cerebral circulation of the patients with ischemic cerebrovascular disease using the Kety-Schmidt technique with argon. Cerebral blood flow and $CMR_{O_2}$ in sevoflurane anesthesia were 28 ± 4 ml · 100 $g^{-1}$ · $min^{-1}$ and 1.34 ± 0.23 ml · 100 $g^{-1}$ · $min^{-1}$, respectively. Our data also show that the reactivity of CBF to change in $Pa_{CO_2}$ was well maintained, and CBF was not affected by MAP changes from 89 ± 6 to 113 ± 6 mmHg.

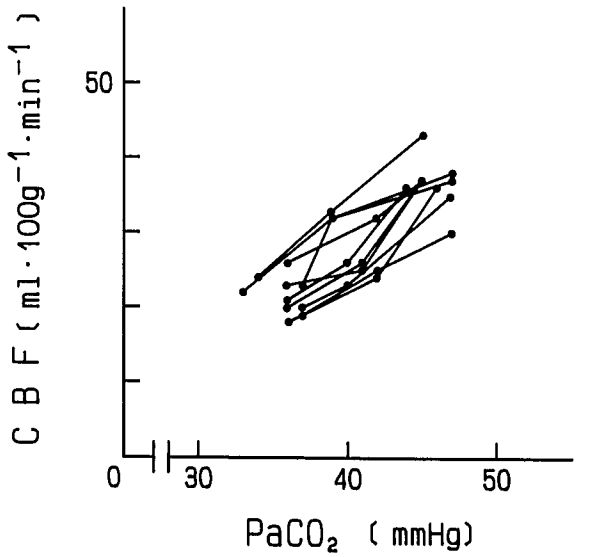


**Fig. 1. The relationship between cerebral blood flow (CBF) and $Pa_{CO_2}$ during sevoflurane anesthesia in each patient.**

**Table 2. Mean Arterial Pressure, Arterial Carbon Dioxide Tension, and Cerebral Blood Flow during Sevoflurane Anesthesia**

| | Pre-MTX | | | Post-MTX | | |
|---|---|---|---|---|---|---|
| Patient | MAP | $Pa_{CO_2}$ | CBF | MAP | $Pa_{CO_2}$ | CBF |
| 1 | 92 | 42 | 25 | 112 | 41 | 26 |
| 2 | 89 | 46 | 30 | 115 | 47 | 30 |
| 3 | 85 | 41 | 32 | 110 | 41 | 31 |
| 4 | 98 | 41 | 36 | 120 | 41 | 39 |
| 5 | 90 | 43 | 22 | 121 | 43 | 26 |
| 6 | 87 | 37 | 32 | 104 | 39 | 30 |
| 7 | 96 | 39 | 32 | 121 | 38 | 30 |
| 8 | 79 | 39 | 32 | 112 | 39 | 35 |
| 9 | 90 | 39 | 33 | 110 | 41 | 34 |
| 10 | 85 | 42 | 34 | 105 | 39 | 33 |
| Mean ± SD | 89 ± 6 | 41 ± 3 | 31 ± 4 | 113 ± 6* | 41 ± 3 | 30 ± 4 |

MTX = methoxamine infusion; MAP = mean arterial pressure (mmHg); $Pa_{CO_2}$ = arterial carbon dioxide tension (mmHg); CBF = cerebral blood flow (ml·100 $g^{-1} \cdot min^{-1}$).

* $P < 0.01$ compared to pre-MTX values.

Effects of sevoflurane on cerebral circulation have been investigated only in experimental animals. Manohar *et al.*,[2,3] who examined the effect of sevoflurane on the regional brain blood flow in pigs with the radionuclide-labeled microsphere method, reported that the cerebral and brainstem blood flow were decreased significantly during 1.0 and 1.5 MAC of sevoflurane anesthesia as compared with the awake state.[2] By contrast, Scheller *et al.*[4] found that 1 MAC of sevoflurane caused no significant change in CBF, but decreased $CMR_{O_2}$ by about 50% relative to levels during morphine/nitrous oxide anesthesia in rabbits. Furthermore, they[5] reported that, in dogs, using the venous outflow technique, even 2.14 MAC sevoflurane did not significantly affect CBF, and $CMR_{O_2}$ was attenuated by 30% when the sevoflurane concentration was increased from 0.5 to 2.14 MAC. In animal experiments, sevoflurane decreased $CMR_{O_2}$, although a species difference was recognized on the influences of sevoflurane on CBF. In our study, we did not measure the control values of CBF and $CMR_{O_2}$ in the awake state. In a separate study, we[11] measured CBF and $CMR_{O_2}$ in awake patients with ischemic cerebrovascular diseases by the same technique as that employed in the current study, and found that CBF and $CMR_{O_2}$ were 42.3 ± 7.5 ml·100 $g^{-1} \cdot min^{-1}$ and 2.81 ± 0.65 ml·100 $g^{-1} \cdot min^{-1}$, respectively. Comparison between the two measurements indicates that both CBF and $CMR_{O_2}$, during sevoflurane anesthesia, were lower than those values in awake patients by 34% and 52%, respectively.

The effects of halothane and isoflurane on the CBF reactivity to $Pa_{CO_2}$ have been extensively studied, and these agents have been demonstrated to preserve carbon dioxide reactivity.[12–14] However, the effect of sevoflurane on the CBF–carbon dioxide reactivity has not been previously documented. In the current study, we found that CBF remained responsive to changes in $Pa_{CO_2}$ in patients anesthetized with sevoflurane. Cerebral blood flow reactivity to $Pa_{CO_2}$ in patients with isch-

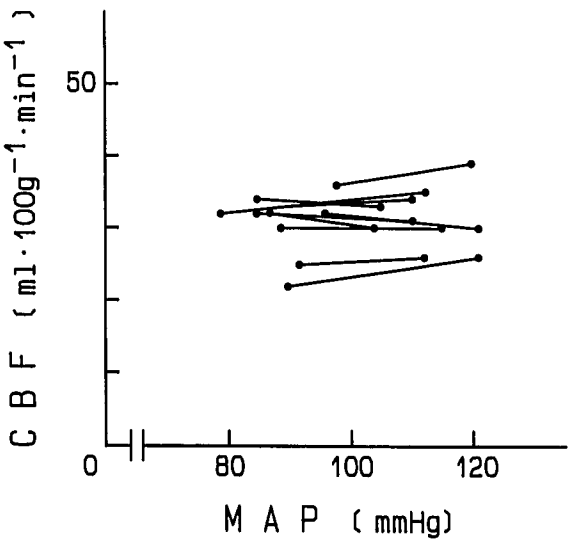


**Fig. 2. The relationship between cerebral blood flow (CBF) and mean arterial pressure (MAP) during sevoflurane anesthesia in each patient.**

emic cerebrovascular disease is influenced by their clinical status.[15,16] Young *et al.*,[17] using the intravenous method of $^{133}$Xe-CBF determination, reported that the mean CBF reactivity to changes in $Pa_{CO_2}$ (ml · 100 $g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$) was 1.78 for halothane and 1.74 for isoflurane during carotid endarterectomy. In their study, four out of seven patients in the halothane group, and five out of seven patients in the isoflurane group, were categorized into the high risk group (grade 3 and 4) using the grading system described by Sundt *et al.*[6] In our study, the carbon dioxide reactivity to changes in $Pa_{CO_2}$ for sevoflurane was 1.29 in patients categorized into the low risk group (grade 1 and 2). We could not compare the value of carbon dioxide reactivity in sevoflurane anesthesia to those in halothane or isoflurane anesthesia reported by Young *et al.*, because the risk grade of our patients was lower than those of patients in Young's study. However, the low carbon dioxide response may reflect the specific action of sevoflurane on cerebral circulation, because Bullock *et al.*[15] reported that the carbon dioxide response was diminished with an increasing clinical risk.

Cerebral autoregulation is a physiologic regulatory mechanism that maintains a CBF constant at the cerebral perfusion pressure in the range of 50 and 150 mmHg, which protects the brain against abrupt changes in arterial blood pressure. Some anesthetic agents affect cerebral autoregulation.[18,19] Halothane and enflurane have been reported to impair cerebral autoregulation[20] because they dilate cerebral resistance vessels and increase CBF. Isoflurane is known to disturb autoregulation to a lesser extent than halothane,[21] because of its lesser dilating effect on cerebral arteries than halothane,[22] which is, in part, attributed to its greater reduction of $CMR_{O_2}$. The current study demonstrated that sevoflurane did not impair cerebral autoregulation in the patients with ischemic cerebrovascular disease. The results of earlier studies indicated that sevoflurane reduced CBF and $CMR_{O_2}$ to the same extent as isoflurane (about 50%).[4] The properties of sevoflurane, preservation of carbon dioxide reactivity and cerebral autoregulation, make it suitable for use on patients undergoing neurosurgery.

Continuous *in vivo* measurement of partial pressures of blood gases was first used clinically by Brantigan *et al.*[23] The technique used in this study to measure CBF has already been used in some clinical settings. Dyken[8] compared this method with the $Kr^{85}$ desaturation technique, and found a close correlation between the findings obtained by the two methods. Hass *et al.*[9] also reported that the argon-washout technique gave results similar to those obtained by the nitrous oxide method. Soma *et al.*[24] measured CBF during extracorporeal circulation by the same method. The anesthetic action of Ar is far weaker than that of Xe or nitrous oxide.[25] It is unlikely that the 33% Ar gas inhalation has any significant effect on cerebral or systemic circulation.

In conclusion, during sevoflurane anesthesia in patients with ischemic cerebrovascular disease, CBF and $CMR_{O_2}$ were 28 ± 4 ml · 100 $g^{-1} \cdot min^{-1}$ and 1.34 ± 0.23 ml · 100 $g^{-1} \cdot min^{-1}$, respectively. Both carbon dioxide reactivity and cerebral autoregulation were well maintained.

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