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Effects of four volatile anesthesics on postanesthetic ventilation: a comparison of halothane, enflurane, isoflurane, and sevoflurane

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Abstract: To investigate the effects of four volatile anesthetics (halothane, enflurane, isoflurane, and sevoflurane) on postanesthetic ventilation and levels of consciousness, we enrolled 24 patients undergoing tympanoplasty in this study. Anesthesia was maintained with 67% nitrous oxide and one of four volatile anesthetics. We measured end-tidal carbon dioxide concentration ($C_{ET}CO_2$), minute volume ($\dot{V}_E$), and respiratory rate (RR), and determined the volatile anesthetic concentration in whole arterial blood (C_BAnesth) and arterial carbon dioxide tension ($Paco_2$) at 20 min and 2 h after tracheal extubation. We also observed the level of consciousness (awake, drowsy, and asleep) before the measurement. Ventilatory variables were similar among the four groups at 20 min, although the ratio of volatile anesthetic concentration in the alveoli to the minimum alveolar concentration (MAC) (C_AAnesth/MAC ratio) calculated from C_BAnesth in the halothane group was twice those in the other groups. In the halothane group, $Paco_2$ was significantly higher, and $\dot{V}_E$ and RR were significantly lower compared with the isoflurane and sevoflurane groups at 2 h. Halothane tended to prolong the recovery of levels of consciousness. We conclude that isoflurane and sevoflurane provide clinical advantages over halothane on postanesthetic ventilation and recovery of levels of consciousness.

Key words: Halothane, Enflurane, Isoflurane, Sevoflurane, Ventilatory depression

Introduction

Respiratory depression is a major complication encountered in postanesthetic management. When it is due to volatile anesthetics, respiratory depression facilitates intraoperative respiratory management during administration of neuromuscular blocking agents and tracheal intubation. Volatile anesthetics remaining in the blood or tissue, however, may cause postanesthetic respiratory depression. Isoflurane and sevoflurane have small blood/gas partition coefficients [1,2]. Therefore, they rapidly reach an equilibrium between alveolar and arterial blood tensions and are also rapidly excreted from the blood. Because they minimize postanesthetic respiratory depression caused by volatile anesthetics, isoflurane and sevoflurane, which have recently come into wide spread clinical use, are expected to be preferable to halothane, which has a larger blood/gas partition coefficient [1]. Doi and Ikeda studied the effects of halothane, isoflurane, and sevoflurane on postanesthetic respiratory depression and reported that the respiratory effects of halothane persisted for 20 min or more, which was longer than those of isoflurane and sevoflurane [3]. However, the effects of volatile anesthetics on postanesthetic ventilatory function beyond 20 min remain unknown.

We therefore conducted a randomized prospective study to evaluate the effects of four volatile anesthetics—halothane, enflurane, isoflurane, and sevoflurane—on postanesthetic ventilatory function 20 min and 2 h after cessation of anesthesia and to assess the level of consciousness thereafter.

Materials and methods

After obtaining informed consent from each patient and approval from our institutional ethics committee on human research, we enrolled 24 patients, ASA physical status I and undergoing elective tympanoplasty, in this study. The patients were randomly assigned to one of four anesthesia groups (6 patients each): halothane, enflurane, isoflurane, and sevoflurane. All patients received 0.5 mg atropine sulfate i.m. 30 min before induction of anesthesia. The right radial artery was cannulated under local anesthesia for the direct

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measurement of arterial blood pressure and for blood sampling. An intravenous catheter was inserted on the dorsum of the left hand, and we infused lactated Ringer's solution at a rate of $10 ml \cdot kg^{-1} \cdot h^{-1}$. Standard monitoring included bladder temperature, electrocardiogram (ECG), oscillometric blood pressure, hemoglobin oxygen saturation (Spo_2) determined by pulse oximetry, and end-tidal carbon dioxide tension ($P_{ET}co_2$). Anesthesia was induced with $4 mg \cdot kg^{-1}$ thiamylal i.v., and the trachea was intubated following i.v. administration of $1 mg \cdot kg^{-1}$ succinylcholine chloride. We maintained anesthesia with one of four volatile anesthetics and 67% nitrous oxide in oxygen. The concentration of volatile anesthetic was adjusted to maintain a sufficient depth of anesthesia to carry out the surgical procedure: 1.5 times the published minimum alveolar concentration (MAC) of each volatile anesthetic between skin incision and opening of the tympanum, and 1 MAC during the microsurgical procedure. No muscle relaxants were administered during anesthesia after tracheal intubation.

Nitrous oxide was discontinued at the end of the microsurgical procedure, and the inspiratory concentration of the volatile anesthetics was thereafter maintained at 1.5 MAC each. The volatile anesthetic was discontinued at the completion of surgery, and a mass spectrometer (MGA-1100, Perkin-Elmer, Norwalk, CT, USA) was used to confirm that no nitrous oxide was present in the expiratory gas. The lungs were mechanically ventilated during surgery to maintain $P_{ET}co_2$ between 30 and 40 mmHg. The patients were extubated after confirming their ability to open their eyes and grasp a hand in response to verbal commands. An anesthetic mask was immediately fitted tightly to supply pure oxygen ($8 l \cdot min^{-1}$) via a nonrebreathing anesthetic circuit in the supine position.

After 15-min inhalation of pure oxygen, we collected 3 ml of arterial blood to determine the concentration of volatile anesthetic in whole blood. The blood sample was immediately packed in a plastic tube sealed with a rubber cap, and it was frozen and stored at −40°C until analysis of the blood concentration. Then we installed the adapter of an infrared gas analyzer (Capnomac Ultima SV, Datex, Helsinki, Finland) between the anesthetic mask and the nonrebreathing anesthetic circuit. End-tidal carbon dioxide and volatile anesthetic concentrations ($C_{ET}co_2$ and C_{ET}Anesth), minute volume ($\dot{V}_E$), and respiratory rate (RR) were measured continuously and recorded every 30 s for 5 min under inhalation of pure oxygen. We collected 1 ml of arterial blood for analyzing blood gases with a blood gas analyzer (ABL2, Radiometer, Copenhagen, Denmark) after completion of the measurements. With the exception of C_{ET}Anesth, respiratory variables were represented as mean values for 5 min, and C_{ET}Anesth was represented as a value in the first minute. We calibrated a capnograph with a standard gas before each measurement. The limitation of determination of each volatile anesthetic in the infrared gas analyzer was 0.01%.

We measured the respiratory variables described above by the same method in the recovery room 2 h after tracheal extubation. The blood samples were also collected before measurement by a capnograph, and analyzed and frozen as described above. We calculated minute carbon dioxide elimination ($\dot{V}co_2$) from $\dot{V}_E$ and $C_{ET}co_2$, and the slope of the ventilatory response curve to carbon dioxide from $\dot{V}_E$ and arterial carbon dioxide tension ($Paco_2$), in each anesthetic group.

Furthermore, until the commencement of measurements in the recovery room, the patients' level of consciousness was observed every 30 min by a trained nurse, who remained blinded to the identity of the volatile anesthetic used. The level of consciousness was divided into three grades: awake = 3, drowsy but responsive to verbal commands = 2, and asleep = 1. No sedatives or analgesics were given prior to the completion of measurements in the recovery room.

The concentrations of volatile anesthetics in whole blood were determined using a gas chromatography method reported by Miwa et al. [4]. This technique was based on the method developed by Yokota et al. [5] and improved by Yamada et al. [6]. The measuring equipment consisted of a gas chromatograph (GC-4CM, Shimadzu, Kyoto, Japan) equipped with both a hydrogen flame ionization detector (H_2-FID) and a thermal conductivity detector and blood gas sampler (BGS-1-A, Shimadzu). The conditions of the blood gas sampler were as follows: sample space heated at 100°C for 60 s, sampling volume of 20 µl, and sampling time of 25 s. Coiled glass columns (2 m × 3 mm I.D.) packed with 15% DEGS on Chromosorb W (GC-4CM, Shimadzu) were used. The column temperature was 130°C for gas chromatography and 130°C for the H_2-FID. Nitrogen was used as the carrier gas at a flow rate of $60 ml \cdot min^{-1}$. Intra- and interassay variations were less than 5% for each volatile anesthetic agent. To determine intraassay variations of the gas chromatography equipment, we used blood samples stored at −40°C for 4 days that we collected from other patients in the preliminary study.

We calculated the alveolar concentration of each volatile anesthetic (C_AAnesth) from the blood concentration obtained by gas chromatography using the following modified formula described by Yokota et al. [5]:

$$C_A\text{Anesth} = C_B\text{Anesth} \cdot 22.4 \cdot (273 + 37)/(MW \cdot P \cdot 273)$$

where C_BAnesth is the volatile anesthetic concentration in whole blood, and MW and P are the molecular weight and blood/gas partition coefficient of each volatile anesthetic, respectively. The blood/gas partition coefficients of halothane, enflurane, isoflurane, and sevoflurane

were 2.3, 1.9, 1.4 [1], and 0.63 [personal communication, Central Institute of Maruishi Pharmaceutical], respectively. We then calculated a C_AAnesth/MAC ratio in each volatile anesthetic from its C_AAnesth. MACs for halothane, enflurane, isoflurane and sevoflurane were adopted: 0.74% [7], 1.68% [8], 1.15% [9], and 2.05% [10], respectively.

Parametric data were analyzed by one-way or two-way analysis of variance (ANOVA), and the results were assessed by Scheffe's F-test or paired *t*-test. Non-parametric data were assessed by the Kruskal-Wallis test. A *P* values less than 0.05 was considered statistically significant.

Results

Two patients, one in the enflurane group and one in the isoflurane group, were excluded because they received additional muscle relaxants during microsurgery. There were no significant differences among the four anesthesia groups in sex, age, and weight, or in operation and anesthesia times, or in duration between discontinuation of inhalation of volatile anesthetic and tracheal extubation (Table 1).

Mean arterial pressure (MAP) and heart rate (HR) at 2h after tracheal extubation were approximately 10% lower ($P < 0.01$) than those at 20min in all anesthesia groups. Bladder temperature at 2h was similar to that at 20min in each group. There were no significant differences in MAP, HR, and bladder temperature among the four groups at corresponding time points (Table 2).

The pH, base excess, and Pao_2 of arterial blood gas were maintained within normal limits throughout the study in the four groups at each measurement point. $Paco_2$ was higher ($P < 0.05$) in the halothane group than in the sevoflurane group at 20min and was also higher ($P < 0.05$) in the halothane group than in the other groups at 2h. $Paco_2$ was significantly lower ($P < 0.05$) at 2h than at 20min in all anesthesia groups. $\dot{V}_E$ in the halothane group at 2h was significantly lower ($P < 0.05$) than those in the isoflurane and sevoflurane groups, but was similar to that in the enflurane group. RR in the halothane and enflurane groups decreased significantly ($P < 0.05$) with time, while RR in the isoflurane and sevoflurane groups did not show significant alterations resulting in a significant increase in RR at 2h in comparison with the halothane group. The ratios of $\dot{V}_E$ to $Paco_2$ were significantly higher ($P < 0.05$) in the isoflurane and sevoflurane groups than in the halothane group 2h after extubation, while they were similar among the four anesthesia groups 20min after extubation. $\dot{V}co_2$ was similar among the four groups at each measurement point. However, except in the sevoflurane group, $\dot{V}co_2$ levels were significantly lower at 2h than those at 20min (Table 3).

Table 1. Profiles of 22 patients anesthetized with one of four volatile anesthetics

	Halothane	Enflurane	Isoflurane	Sevoflurane
n (M/F)	6 (4/2)	5 (3/2)	5 (3/2)	6 (4/2)
Age (yr)	36 ± 17	37 ± 18	41 ± 12	37 ± 18
Weight (kg)	61.9 ± 13.4	57.4 ± 11.0	56.3 ± 6.4	59.1 ± 10.0
Operation time (min)	147 ± 69	144 ± 44	133 ± 71	160 ± 73
Anesthesia time (min)	210 ± 66	213 ± 33	201 ± 64	220 ± 71
Duration until extubation (min)	17 ± 4	14 ± 3	13 ± 3	13 ± 4

Values are expressed as mean ± SD.
Duration until extubation, time between discontinuation of volatile anesthetic and tracheal extubation.

Table 2. Physical status of patients 20min and 2h after inhaled anesthesia

		Halothane ($n = 6$)	Enflurane ($n = 5$)	Isoflurane ($n = 5$)	Sevoflurane ($n = 6$)
MAP (mmHg)	20min	97 ± 7	98 ± 5	101 ± 7	100 ± 6
	2h	87 ± 8*	90 ± 6*	89 ± 10*	91 ± 8*
Heart rate (beats·min^{-1})	20min	90 ± 9	94 ± 9	87 ± 8	93 ± 10
	2h	83 ± 8*	79 ± 9*	77 ± 10*	80 ± 8*
Bladder temperature (°C)	20min	37.0 ± 0.3	37.1 ± 0.2	37.2 ± 0.3	37.1 ± 0.3
	2h	36.9 ± 0.2	37.1 ± 0.3	37.1 ± 0.2	37.0 ± 0.2

Values are expressed as mean ± SD.
*$P < 0.01$ *vs* value at 20min.
MAP, mean arterial pressure.

Table 3. Ventilatory variables and minute carbon dioxide elimination at 20 min and 2 h after inhaled anesthesia

Ventilatory variables	Period	Halothane ($n = 6$)	Enflurane ($n = 5$)	Isoflurane ($n = 5$)	Sevoflurane ($n = 6$)
$Paco_2$ (mmHg)	20 min	45.6 ± 2.3	44.6 ± 1.6	44.0 ± 2.6	42.6 ± 2.3[c]
	2 h	43.2 ± 1.8	40.5 ± 2.5[b,c]	40.5 ± 1.6[b,c]	40.8 ± 1.1[a,c]
$\dot{V}_E$ ($l \cdot min^{-1}$)	20 min	8.3 ± 1.6	9.9 ± 1.5	9.2 ± 1.4	10.3 ± 3.8
	2 h	6.8 ± 1.0[a]	8.3 ± 1.9	8.2 ± 0.4[c]	9.2 ± 1.6[d]
RR	20 min	20 ± 5	22 ± 4	19 ± 3	21 ± 5
($breaths \cdot min^{-1}$)	2 h	15 ± 3[a]	17 ± 3[a]	20 ± 3[c]	21 ± 5[d]
$\dot{V}_E/Paco_2$ ratio	20 min	0.18 ± 0.04	0.22 ± 0.04	0.21 ± 0.04	0.25 ± 0.10
($l \cdot mmHg^{-1}$)	2 h	0.16 ± 0.03	0.21 ± 0.06	0.20 ± 0.02[c]	0.23 ± 0.04[c]
$\dot{V}co_2$ ($l \cdot min^{-1}$)	20 min	0.49 ± 0.08	0.58 ± 0.07	0.52 ± 0.05	0.57 ± 0.17
	2 h	0.42 ± 0.07[a]	0.44 ± 0.07[b]	0.44 ± 0.01[a]	0.49 ± 0.08

Values are expressed as mean ± SD. [a] $P < 0.05$ *vs* value at 20 min. [b] $P < 0.01$ *vs* value at 20 min. [c] $P < 0.05$ *vs* halothane group. [d] $P < 0.05$ *vs* halothane group.
$Paco_2$, arterial carbon dioxide tension; $\dot{V}_E$, minute volume; RR, respiratory rate; $\dot{V}co_2$, minute carbon dioxide elimination.

Table 4. Whole blood concentrations and alveolar concentrations for four volatile anesthetics at 15 min and 2 h after extubation

	Period	Halothane ($n = 6$)	Enflurane ($n = 5$)	Isoflurane ($n = 5$)	Sevoflurane ($n = 6$)
C_BAnesth ($mg \cdot dl^{-1}$)	15 min	2.81 ± 0.90	1.83 ± 0.67	1.22 ± 0.53	1.12 ± 0.58
	2 h	0.98 ± 0.78	0.71 ± 0.43	0.53 ± 0.15	0.46 ± 0.34
C_AAnesth (%)	15 min	0.16 ± 0.05	0.13 ± 0.05	0.12 ± 0.05	0.23 ± 0.02
	2 h	0.09 ± 0.05	0.05 ± 0.03	0.05 ± 0.04	0.09 ± 0.05
C_AAnesth/MAC ratio	15 min	0.21 ± 0.07	0.08 ± 0.03*	0.10 ± 0.04*	0.11 ± 0.01*
	2 h	0.07 ± 0.05	0.03 ± 0.02	0.05 ± 0.03	0.05 ± 0.03
C_{ET}Anesth (%)	15 min	0.19 ± 0.04	0.16 ± 0.04	0.14 ± 0.04	0.22 ± 0.05
	2 h	0.13 ± 0.03 (4)	0.1 (2)	0.1 (1)	0.1 (1)

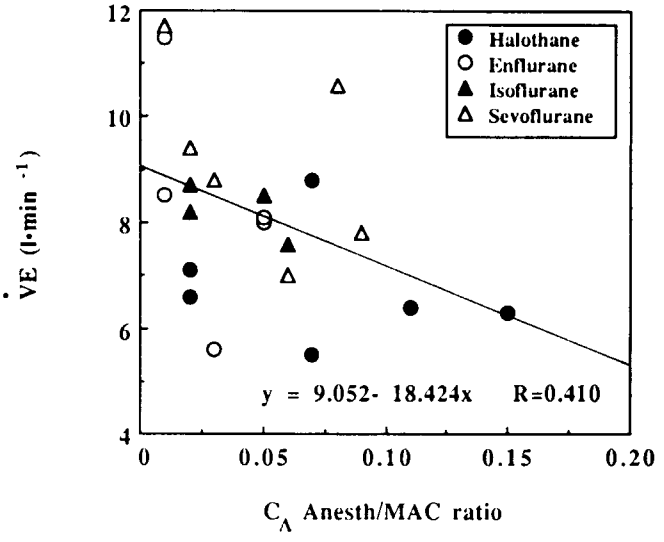
Values are expressed as mean ± SD.
* $P < 0.01$ *vs* halothane group.
C_BAnesth, volatile anesthetic concentration in whole blood; C_AAnesth, volatile anesthetic concentration in alveoli; C_{ET}Anesth, end-tidal concentration of volatile anesthetic.
Numbers in parentheses are numbers of patients in whom the end-tidal concentration of volatile anesthetic could be detected.

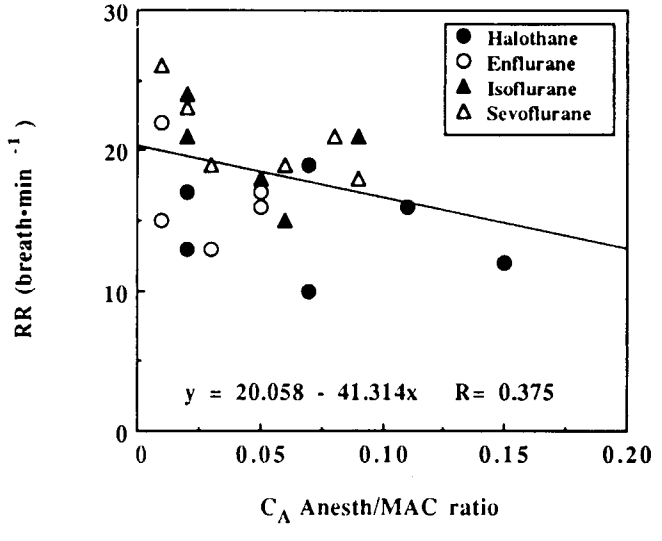
Table 5. Recovery of levels of consciousness after inhaled anesthesia in the recovery room

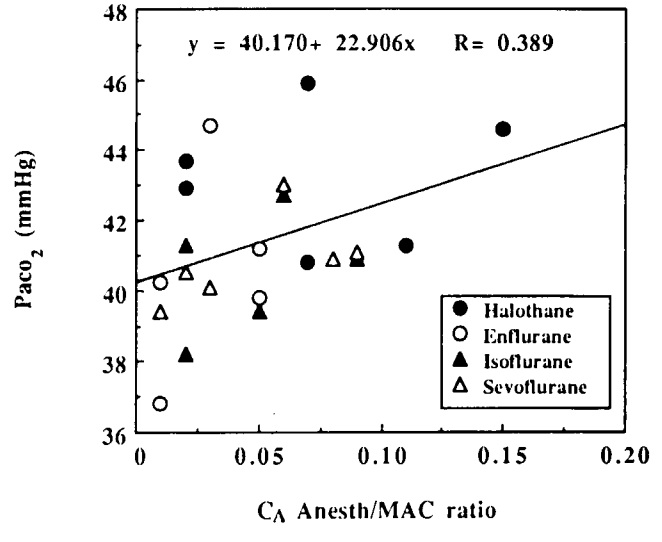
Period	Level of consciousness	Halothane ($n = 6$)		Enflurane ($n = 5$)		Isoflurane ($n = 5$)		Sevoflurane ($n = 6$)	
		n	Score	n	Score	n	Score	n	Score
30 min	Awake	0/6	1.3 ± 0.5	1/5	1.6 ± 0.9	1/5	1.8 ± 0.8	2/6	2.2 ± 0.8
	Drowsy	2/6		1/5		2/5		3/6	
	Asleep	4/6		3/5		2/5		1/6	
60 min	Awake	1/6	1.7 ± 0.8	2/5	2.2 ± 0.6	2/5	2.4 ± 0.6	4/6	2.7 ± 0.5
	Drowsy	2/6		2/5		3/5		2/6	
	Asleep	3/6		1/5		0/5		0/6	
90 min	Awake	2/6	1.8 ± 1.0	3/5	2.6 ± 0.6	4/5	2.8 ± 0.5	5/6	2.8 ± 0.4
	Drowsy	1/6		2/5		1/5		1/6	
	Asleep	3/6		0/5		0/5		0/6	

Values are expressed as mean ± SD.
Period, time after transfer from operating room to recovery room.
Scores: awake = 3; drowsy = 2; asleep = 1.

At both 15 min and 2 h after extubation, C_BAnesth was determined according to its blood/gas partition coefficient in all four groups in the following order: halothane, enflurane, isoflurane, and sevoflurane. The C_AAnesth/MAC ratio calculated from C_AAnesth was significantly ($P < 0.01$) higher in the halothane group than in the other groups at 15 min, while there were no significant differences among the four anesthesia groups in the C_AAnesth/MAC ratio at 2 h. C_{ET}Anesth determined by an infrared gas analyzer was similar to C_AAnesth calculated from C_BAnesth in each group at 15 min. However, C_{ET}Anesth either could not be de-







tected with an infrared gas analyzer or was close to the limitation of detection of an infrared gas analyzer at 2h (Table 4).

Figure 1 shows the relationships between C_AAnesth/MAC ratio and $\dot{V}_E$, RR, and $Paco_2$ in which significant differences were observed among the four anesthesia groups at 2h. No significant correlations were found in the three respiratory variables.

The recovery of levels of consciousness after extubation tended to be prolonged in the halothane group compared with the other anesthesia groups but did not show significant differences among the four groups (Table 5).

Discussion

Recent progress in medical engineering has enabled easy and convenient measurement of inspiratory and expiratory concentrations of volatile anesthetic agents. However, we adopted a method to obtain the alveolar concentrations of volatile anesthetics by calculation from whole blood concentrations, because we did not know whether an infrared gas analyzer could detect the very low expiratory concentrations of volatile anesthetics, such as those at 2h after extubation, and had concluded that it would be impossible. This conclusion appeared to be correct, since the infrared gas analyzer we used was unable to detect an anesthetic agent in the expiratory gas or showed unreliable and unstable values for the expiratory concentrations of anesthetic agents. Tympanoplasty is usually associated with minimal changes in body temperature and little effect of surgical invasion on respiratory function during anesthesia. The patients were therefore suitable for evaluating the effect of concentrations lower than the MAC-awake of volatile anesthetics [11,12] on postanesthetic respiratory function.

$Paco_2$ is determined by both alveolar ventilation and production of carbon dioxide. The higher $Paco_2$ at 2h in the halothane group may have resulted from the reduction of alveolar minute volume because there were significant differences in $\dot{V}_E$ and RR but not in $\dot{V}co_2$ among the four anesthesia groups. This was supported by the fact that the $\dot{V}_E/Paco_2$ ratio in the halothane group was

Fig. 1. Correlations between the ratio of volatile anesthetic concentration in the alveoli to the minimum alveolar concentration (MAC) (*C_AAnesth/MAC ratio*) and minute volume ($\dot{V}_E$), respiratory rate (*RR*), and arterial carbon dioxide tension ($Paco_2$) at 2h after extubation when there were significant differences in the above-described respiratory variables among the four anesthesia groups. No significant correlation was found between the C_AAnesth/MAC ratio and each respiratory variable

lower than those in the other anesthesia groups. However, the C_AAnesth/MAC ratios calculated from C_BAnesth at 2h were similar among the four anesthesia groups, and there was no significant correlation between the C_AAnesth/MAC ratio and $\dot{V}_E$, RR, or $Paco_2$. These findings suggest that the significant ventilatory depression in the halothane group at 2h was also not due to the proposed factors of C_BAnesth and C_AAnesth/MAC ratio.

What caused the significant ventilatory depression in the halothane anesthesia group? It is thought to have been the sedative effect of halothane on higher levels of the central nervous system (CNS), which control consciousness, rather than its direct depressive effect on the respiratory center in the brainstem. There are two possible findings which may help to explain this hypothesis. First, the recovery of levels of consciousness in the halothane group tended to be prolonged in comparison with the other anesthesia groups. Second, the expiratory concentration of volatile anesthetics is lower than the cerebral concentration in isoflurane and sevoflurane, which have smaller blood/gas partition coefficients than halothane [13]. Furthermore, halothane has a two- to fourfold larger oil/gas partition coefficient than isoflurane, enflurane, or sevoflurane, leading to its slow release from lipids of the CNS and resulting in accumulation of halothane in the CNS. Halothane also has a larger tissue/gas partition coefficient in both the brain and lipids compared with that of isoflurane or sevoflurane [14]. Therefore, halothane may take longer to reach an equilibrium between alveolar and arterial blood tensions or between arterial blood and brain tensions; there may also be a larger discrepancy between expiratory and cerebral concentrations, thus prolonging the recovery of levels of consciousness. Actually, C_BAnesth of halothane obtained at 2h in this study was higher than those of the other groups; furthermore, the ratio of $\dot{V}_E$ to $Paco_2$, indicating the response of the respiratory center to the increase of $Paco_2$, was significantly lower in the halothane group than in the isoflurane and sevoflurane groups.

On the other hand, the significantly higher $Paco_2$ at 20min than at 2h is considered to result from the increases of $\dot{V}co_2$ [15] and the ratio of dead space ventilation to tidal volume (V_D/V_T) immediately after tracheal extubation. The stability of the hemodynamic variables at 2h may be maintained by the decreased activity of the sympathetic nervous system, which is enhanced immediately after extubation or associated with awakening. In this early period, we did not find significant differences in respiratory variables among the four anesthesia groups as reported previously [3]. The C_AAnesth/MAC ratio was the only significant factor. This was consistent with the previous result [3].

In conclusion, halothane caused postanesthetic ventilatory depression more frequently than isoflurane and sevoflurane at 2h after extubation but was similar to enflurane, although there were no significant differences in respiratory variables among the four anesthetic agents at 20min. The significant ventilatory depression in halothane may be due to its sedative effect on the CNS. Isoflurane and sevoflurane, which have smaller blood/gas partition coefficients, provide clinical advantages over halothane on postanesthetic ventilatory function and recovery of levels of consciousness.

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