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ORIGINAL ARTICLE

Pharmacokinetics of sevoflurane elimination from respiratory gas and blood after coronary artery bypass grafting surgery

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Abstract
Purpose Sevoflurane, with a relative low blood-gas partition coefficient, is an ideal anesthetic to achieve rapid offset and recovery from general anesthesia. This study will determine the profiles of four concentration–time curves to characterize the pharmacokinetics of sevoflurane elimination.
Methods Eight patients (aged 54–76 years) undergoing coronary arterial bypass grafting surgery were enrolled in this study. At the end of surgery, anesthetic gas and blood were sampled 20 min before and after stopping sevoflurane administration, with prior maintenance of a fixed 5 % inspired sevoflurane (CIsev) in 6 L/min oxygen flow for 60 min before the cessation of sevoflurane administration for the subsequent 20 min elimination. An infrared analyzer was used to determine both CIsev and end-tidal sevoflurane (CEsev). The sevoflurane concentrations in the internal jugular-bulb (Jsev), arterial (Asev) and pulmonary arterial blood (PAsev) were analyzed by gas chromatography, and cardiac output was measured using an Opti-Q pulmonary artery catheter.
Results A bi-exponential decay function was the best fit for the CEsev,Jsev, Asev, and PAsev time curves. There were two distinct components, the initial 5-min fast or distribution phase and the subsequent 15-min slow or elimination phase. Before cessation of the sevoflurane supplement, the step-down concentration of sevoflurane was listed in the following order: CIsev > CEsev > Asev $\geqq$ Jsev > PAsev. During the elimination phase, the fastest decay occurred in CEsev, followed by Jsev, Asev and PAsev. Therefore, a reverse step-down pattern was observed (PAsev > Asev $\geqq$ Jsev > CEsev) after 20 min. The ratio of Asev to CEsev was 89 % at baseline before stopping sevoflurane administration, but the ratio of Asev to CEsev increased to 128 % at the twentieth min of the sevoflurane elimination phase.
Conclusions During elimination, the initial washout of sevoflurane from the functional residual capacity of the lungs was reflected in the fast component of the CEsev, Jsev, Asev, and PAsev time curves. In contrast, the slow component was dominated by the tangible effects of the physiological membrane barriers, such as the alveoli-pulmonary capillary and blood–brain barriers.

Keywords Anesthetic · Sevoflurane · Pharmacokinetics · Elimination

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Introduction

Sevoflurane is widely used in clinical anesthesia because of its relative lack of airway irritation or myocardial suppression effects. It has rapid induction and emergence characteristics compared with other available inhaled anesthetics [1]. Since sevoflurane has a low blood/gas solubility coefficient, it has been thought to have rapid elimination pharmacokinetics in human volunteers [2]. Moreover, precise information about the sevoflurane-elimination profile provides useful information with respect to patients' recovery from anesthesia [3–5]. The previous studies demonstrated the end-tidal or predicted cerebral concentrations of sevoflurane during elimination [4, 6], but not to describe the washout of actual blood concentrations in human. Thus, we try to examine the arterial and jugular venous blood concentrations of sevoflurane during the washout period and provide clinically useful pharmacokinetic data to predict emergence from sevoflurane anesthesia.

It is generally accepted that sevoflurane washout from well-perfused brain is more rapid than from the rest of body during the elimination phase. Sevoflurane elimination from the brain is reflected in the decreasing sevoflurane concentration–time curve of the jugular-bulb venous blood (Jsev). Likewise, elimination from the body is indicated by the analogous decrease in the sevoflurane concentration–time curve in the mixed venous blood (pulmonary arterial blood; PAsev). Determination of blood sevoflurane concentrations (partial pressures) using gas chromatography has made in vivo pharmacokinetic study possible [7, 8]. Therefore, in this study, we attempted to elucidate the pharmacokinetics of sevoflurane elimination from the human body and brain by measuring four different sevoflurane concentrations in both circulating blood and respiratory gas.

Methods

After approval was obtained from our institutional committee on human research and informed consent was received from each subject, eight American Society of Anesthesiologists (ASA) physical status II or III patients of both sexes were enrolled and underwent general anesthesia for elective coronary arterial bypass grafting surgery. Premedications consisted of intravenous fentanyl (2 μg/kg) and midazolam (40 μg/kg). Under local anesthesia (2 % xylocaine), a 20-gauge catheter was inserted into the left radial artery for blood sampling and monitoring of blood pressure.

Anesthesia was induced with thiopentone (3–4 μg/kg), and intubation was facilitated with pretreated pancuronium (0.015 μg/kg) and succinylcholine (1.25 mg/kg). A 5 % inspired concentration of sevoflurane in 6 L/min oxygen flow was administered to wash in functional residual capacity for 5 min, after which the oxygen flow rate was reduced to 1000 mL/min for maintenance of low-flow anesthesia. Then, 3.5–5.5 % inspired sevoflurane concentrations were adjusted with the change of hemodynamic status. After intubation, a single-lumen central venous catheter and a pulmonary arterial catheter were inserted into the right internal jugular-bulb and pulmonary artery, respectively, for blood sampling, as described previously [7]. The cardiopulmonary bypass (CPB) was set up for all patients with a crystalloid prime, a Medtronic membrane oxygenator, moderate hypothermia (28 °C), hemodilution to a hematocrit of 20–25 %, and alpha stat pH management. A perfusionist performed administration of 3.5–5.5 % sevoflurane into the bypass circuit for maintenance of the anesthesia. After weaning from the CPB circuit, the patient was ventilated again, and the fresh gas oxygen flow rate was kept at 1,000 mL/min to provide 3.5–5.5 % inspired sevoflurane before the study of sevoflurane elimination (Fig. 1).

An Ohmeda–Datex anesthetic machine was used with soda lime as a CO_2 absorber in the breathing circuit. System leakage was determined using constant-pressure ventilation with a test lung. All results were corrected for the leakage specific to the given anesthetic machine. Anesthetic gas concentrations were monitored on a multigas analyzer (Datex AS/4 Anesthesia system; Datex, Helsinki, Finland), which had been calibrated according to the manufacturer's recommendations. Sampled gases (approximately 210 mL/min) were redirected into the breathing circuit. The fixed 5 % inspired sevoflurane (CIsev), end-tidal sevoflurane (CEsev),, end-tidal CO_2, blood pressure, and heart rate were recorded every 30 s, and $PaCO_2$ was maintained at 36–42 mm Hg (4.8–5.6 kPa) during the study. A nasopharyngeal thermistor was used to measure body temperature, which was kept at 35.5–37.5 °C during the study. Cardiac output was measured using an Opti-Q catheter (Abbott Critical Care System, Mountain View, CA, USA) and connected with a Q-Vue continuous cardiac output computer (Abbott Critical Care System) during surgery [7, 9]. Hypotension, defined as a 25 % decrease in blood pressure from baseline, was treated with intravenous fluid administration and/or intravenous ephedrine (5 mg bolus).

The study was designed to maintain a 6,000 mL/min oxygen flow during the 60-min research period, including a 40-min maintenance phase before cessation of surgery and a 20-min elimination phase. According to our previous study [7], it takes 38.5 min to reach equilibrium between sevoflurane concentrations in arterial blood (Asev) and Jsev, and to demonstrate that the sevoflurane concentrations in gas (CEsev) and blood (Asev, Jsev, PAsev) reach a

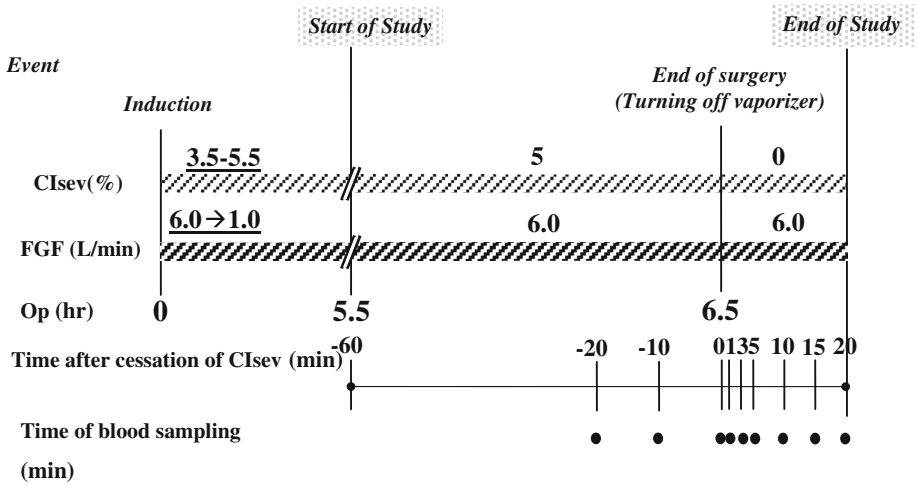

Fig. 1 Schematic representation of time frame for coronary arterial bypass grafting surgery with cardiopulmonary bypass under sevoflurane anesthesia. The sampling times for blood and gas phase sevoflurane concentrations were at −20, −10, 0 and 1, 3, 5, 10, 15 and 20 min after the cessation of sevoflurane administration. *CIsev* inspired sevoflurane concentration, *FGF* fresh gas flow. *Induction* start of anesthesia. *Filled circle* indicates the time point of blood sampling

nearly steady status. Blood samples were collected at 20, 10, and 0 min just before and at 1, 3, 5, 10, 15, and 20 min after cessation of the sevoflurane administration. The duration of the elimination phase was limited to 20 min, because the respiratory patterns of the patients became poorly controlled with a ventilator after that. In addition, we found that the arterial blood pressure of the patients increased after the 20-min sevoflurane elimination phase. Thus, the sevoflurane-elimination data have been collected for 20 min in the study. Arterial, jugular-bulb, and pulmonary-artery blood samples were drawn simultaneously from the respective indwelling catheters into individual 1-mL heparinized syringes. Each blood sample of precisely 1.0 mL was then placed immediately in a 10-mL glass vial and tightly sealed. The blood sample was stored in a refrigerator at 4 °C for measurement within 24 h. All blood samples were analyzed for sevoflurane concentration using a gas chromatograph with a head-space sampler and a flame ionization detector according to the method used in our previous study [7]. All of the patients were interviewed 24 h after surgery to determine awareness during the sevoflurane elimination phase.

Sevoflurane elimination from the brain and body

The jugular bulb and pulmonary arterial blood provides drainage from the brain and body, respectively. Therefore, the decay of the Jsev-time and PAsev-time curves represent sevoflurane elimination from the brain and body, respectively.

Determination of blood sevoflurane concentration

Before determining the sevoflurane concentration in the blood, each patient's blood was used to determine the blood/gas partition coefficient (λ) of sevoflurane. Then we applied the λ and the known amounts of sevoflurane to construct each patient's sevoflurane calibration curve [10].

Gas chromatography (GC) conditions

The HP 6890 series GC system (Hewlett-Packard, Wilmington, DE, USA) consisted of a headspace sampler (HP 7694 E), an oven, a flame-ionization detector and an integrator. The oven temperature was set at 40 °C, increased at a rate of 15 °C per min to 200 °C, and maintained at this level for 4.33 min. Both the injection and detection temperatures were set at 250 °C. The inlet pressure was set at 345 kPa. Injection was performed in the splitless mode, and the purge off time was 5.0 min. The carrier gas (nitrogen) flow was 25.0 mL/min. Separation was achieved with a capillary column (HP-5, 30 m × 0.32 mm I.D. × 0.25 μm film thickness) (Restek, Bellefonte, PA, USA). An integrator and a data acquisition system were provided by HP CHEMOSTATION software.

Calibration curve for measuring blood sevoflurane concentration

A standard of liquid sevoflurane was incubated in a water bath at 4 °C for 1 h before use. Five known amounts of sevoflurane liquid were taken up using a microsyringe (Hamilton 0.5 μl syringe; No. 86259) and injected into five 10-mL glass vials (containing 1-mL of the patient's blank blood) at 4 °C. Blood samples were analyzed with a gas chromatograph, a headspace sampler, and a flame-ionization detector. A linear relationship between the signals for the peak height of sevoflurane (y-axis) and sevoflurane concentration (x-axis) was obtained and revealed an excellent correlation between the signal and sevoflurane concentration, with a range between 0.9958 and 0.9957. The analytical range of the sevoflurane concentration was

0.47–11.8 %. The concentration of sevoflurane in the blood phase was calculated from the calibration curve of a known amount of sevoflurane. The concentration of sevoflurane in the gas phase was obtained by directly comparing to that in the blood phase. The coefficients of variation of the intraday accuracy and precision of sevoflurane detection were 3.7 and 6.2 %, respectively.

Pharmacokinetics

The pharmacokinetic parameters were obtained using a pharmacokinetic program "WinNonlin" (Pharsight Corporation, Mountain View, CA, USA) to fit data to a mono-exponential or bi-exponential model [11]. For sevoflurane elimination, the pharmacokinetic parameters, including elimination rate and elimination half-life (t1/2), were estimated from the model interpretation. Sevoflurane concentrations and the estimated pharmacokinetic parameters were reported as mean (SD).

Statistical analysis

One-way analysis of variances (ANOVA) was conducted to examine differences between half-lives of four eliminations with respect to parametric variables. The post hoc Duncan test was conducted to test the significance of parametric values. Data were expressed as mean (SD). A P value of < 0.05 was regarded as statistically significant. A t test was used to compare any of two sevoflurane concentrations between PAsev and Asev (or Jsev) at the twentieth min after cessation of sevoflurane administration.

Results

Patients' general data consisted of the number of patients, age, weight, height, and duration of surgery, as shown in Table 1. There was no cognitive or memory impairment reported from eight study patients. Their average duration of surgery was 390 min. The mean arterial pressure, heart rate, cardiac index, and end-tidal CO_2 are shown in Table 2. The fluctuations of mean arterial blood pressure during the 20-min elimination phase were less than 20 % of the values at time zero. Neither additional intravenous fluid nor inotropic agent was needed during the study period. There were no significant differences in heart rate, cardiac indices and ventilatory variables during the 20-min elimination phase.

Figure 2 depicts the CIsev, arterial (Asev), jugular-bulb (Jsev), and pulmonary arterial sevoflurane (PAsev), and the end-tidal sevoflurane concentrations (CEsev) during the 20 min before and after the cessation of inspired sevoflurane. The CIsev was relatively higher than CEsev, Asev, Jsev and PAsev (in sequence). It shows that there were near-constant sevoflurane concentrations including CEsev, Asev, Jsev and PAsev during the 20 min period before the cessation of sevoflurane administration.

At time zero (just prior to the cessation of sevoflurane), different sevoflurane concentrations were observed in the following order: CIsev > CEsev > Asev $\cong$ Jsev > PAsev. After cessation of sevoflurane administration, the decay of sevoflurane concentration was rapid in CEsev, follow by the Asev (or Jsev) and then the PAsev. Arterial sevoflurane concentration was relatively lower than CEsev at time zero (prior to cessation of sevoflurane) and the ratio of Asev: CEsev was 0.89 on average. At time points of the tenth, fifteenth and twentieth min of the slow elimination component, different ratios of Asev: CEsev with respect to different time points of elimination were listed as 1.30, 1.26, and 1.28, respectively (Table 3).

We obtained the two-compartment model best fitted to concentration–time curves of CEsev, Asev, PAsev and

Table 1 Characteristics of patients

Number of patients	8
Age, year	65.6 (9.3)
Gender, M/F	7:1
Weight, kg	71.2 (15.2)
Height, cm	159.9 (12.5)
Duration of anesthesia, min	390.0 (50.7)
Consumption of fentanyl, μg	225 (66)

Values are mean (SD)

Table 2 Hemodynamic and ventilatory variables, including the 20 min (−20 to 0 min) before cessation of sevoflurane under 5 % inspired sevoflurane, and the next 20 min (1–20 min) during the sevoflurane elimination phase ($n = 8$)

Time (min)	MAP (mm Hg)	HR (beats/min)	CI (l min/m^2)	$ETCO_2$ (mm Hg)
−20	72.9 (13.8)	93.1 (12.3)	3.41 (0.73)	37.63 (2.13)
−10	66.3 (29.2)	95.5 (15.5)	3.46 (0.67)	39.13 (3.14)
0	69.3 (14.5)	95.6 (17.4)	3.43 (0.61)	39.75 (3.01)
1	74.3 (18.1)	93.0 (12.9)	3.41 (0.61)	40.6 (2.9)
3	82.9 (19.2)	91.0 (12.8)	3.46 (0.57)	41.5 (2.7)
5	84.5 (14.9)	90.6 (12.3)	3.56 (0.49)	41.9 (2.9)
10	92.9 (27.0)	89.5 (11.3)	3.77 (0.59)	42.4 (2.0)
15	80.5 (17.0)	94.3 (16.3)	4.05 (0.81)	42.6 (2.5)
20	85.0 (15.9)	89.8 (10.8)	3.99 (0.61)	43.4 (3.2)

Values are mean (SD)

MAP mean arterial pressure, *HR* heart rate, *CI* cardiac index, *$ETCO_2$* end-tidal CO_2

Jsev, using the least squares method and Akaike's information criteria. At the fifth min of elimination, the average sevoflurane concentrations for CEsev, Asev, Jsev and PAsev were 23, 32, 35 and 39 % of their maximal concentration at time zero. Those distribution half-lives represent the average time to allow the sevoflurane concentration to reach 50 % of their maximal concentrations; for CEsev, Asev, Jsev and PAsev, they were 0.8 (0.3), 0.8 (0.6), 1.2 (0.9), and 0.8 (0.6) min, respectively. There were no significant differences in Alpha, Beta, distribution and elimination half-lives among CEsev, Asev, Jsev and PAsev (Table 4).

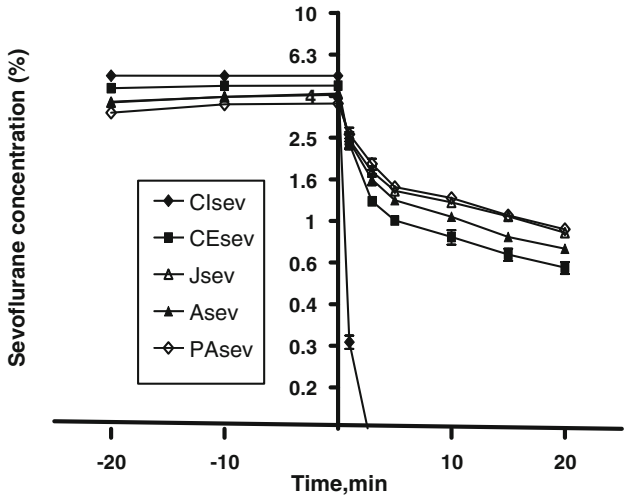

Fig. 2 Sevoflurane concentration–time curves over 20 min before and after stopping inspired sevoflurane supplement. The sampling times for blood and gas-phase sevoflurane concentrations were −20, −10, 0 (just before), and 1, 3, 5, 10, 15, and 20 min after the cessation of sevoflurane administration. Sevoflurane concentrations for inspired (CIsev; *Filled diamond*), and end-tidal (CEsev; *Filled square*) gases, and arterial (Asev; *Filled triangle*), jugular-bulb (Jsev; *Open triangle*), and pulmonary arterial bloods (PAsev; *Open diamond*) were plotted, respectively. Data are presented as mean (SD)

Discussion

This study produced four main findings. Firstly, there were two distinct components of sevoflurane elimination: the initial 5-min fast (distribution) and the subsequent 15-min slow (elimination) components for the CEsev, Jsev, Asev, and PAsev time curves. Secondly, the decay of sevoflurane concentration was rapid in end tidal gas (CEsev), followed by Jsev, Asev and PAsev. Secondly, under a fixed 5 % inspired sevoflurane concentration, the relationship between different sevoflurane concentrations is listed as follows: CIsev > CEsev > Jsev ≅ Asev > PAsev. Twenty min after cessation of sevoflurane administration, the sevoflurane concentrations were listed as the following order: PAsev > Asev ≅ Jsev > CEsev. Thirdly, the averaged Asev:CEsev ratio was 2.4 at the twentieth min elimination phase. The PAsev was relatively higher than both Jsev and Asev at the twentieth min of the elimination phase. Fourthly, the Asev was persistently higher than the CEsev at the tenth, fifteenth and twentieth min during the slow component, with similar average ratios of Asev to CEsev of 1.30, 1.26, and 1.28, respectively.

In an ordinary pharmacokinetic study, the sevoflurane blood concentration should be measured until it is minimal (or near zero), and those measurements could be used to determine the best fit for the concentration–time curve. The reason for stopping the study immediately following the 20-min cessation of sevoflurane administration was that the anesthetic depth becomes lighter and the respiratory pattern appears irregular. We do not know what happens to the sevoflurane concentrations after the 20-min sevoflurane elimination because we only studied the concentration–time curves for the 20-min sevoflurane elimination with the pharmacokinetic model. In addition, the total body uptake of sevoflurane was not estimated before turning off the vaporizer, because the inspired sevoflurane concentration had been adjusted according to the arterial blood pressure

Table 3 The CEsev, Asev, Jsev, PAsev, and Asev/CEsev ratio under 5 % inspired sevoflurane anesthesia at 0 min (just before cessation of sevoflurane as the basal level of the sevoflurane maintenance phase), and at 1, 3, 5, 10, 15, and 20 min after sevoflurane discontinuation ($n = 8$)

Time (min)	0	1	3	5	10	15	20
CEsev, %	4.4 (0.21)	2.2 (0.13)	1.24 (0.40)	1.01 (0.10)	0.84 (0.12)	0.09 (0.19)	0.06 (0.11)
Asev, %	4.04 (0.21)	2.63 (0.17)	1.73 (0.11)	1.29 (0.64)	1.08 (0.35)	0.82 (0.11)	0.71 (0.07)
Jsev, %	4.09 (0.08)	2.46 (0.42)	1.73 (0.28)	1.42 (0.17)	1.23 (0.11)	1.05 (0.09)	0.9 (0.05)
PAsev, %	3.66 (0.26)	2.42 (0.23)	1.71 (0.36)	1.43 (0.15)	1.24 (0.14)	1.02 (0.11)	0.87 (0.09)
Asev/CEsev	0.90 (0.02)	1.07 (0.36)	1.27 (0.17)	1.27 (0.19)	1.30 (0.29)	1.26 (0.28)	1.28 (0.28)

Values are mean (SD)

CEsev end-tidal sevoflurane concentration, *Jsev* jugular-bulb blood sevoflurane concentration, *Asev* sevoflurane concentration in arterial blood, *PAsev* sevoflurane concentration in pulmonary arterial blood, *Asev/CEsev* ratio of sevoflurane concentration in arterial blood to end-tidal sevoflurane concentration

Table 4 The fitting of CEsev, Jsev, and PAsev, Asev versus time curves with a bi-exponential equation

Parameter	A	B	Alpha	Beta	Fast component half-life (min)	Slow component half-life (min)
CEsev, %	3.31 (0.17)	1.12 (0.26)	1.093 (0.506)	0.0309 (0.0138)	0.8 (0.3)	34.1 (34.0)
Jsev, %	2.55 (0.25)	1.56 (0.21)	1.311 (0.721)	0.0273 (0.0075)	0.8 (0.6)	27.8 (10.3)
Asev, %	2.71 (0.28)	1.41 (0.23)	1.22 (0.75)	0.0328 (0.0108)	0.8 (0.6)	23.7 (9.3)
PAsev, %	2.18 (0.41)	1.51 (0.33)	0.920 (0.573)	0.0265 (0.0094)	1.2 (0.9)	29.8 (12.5)

Value were mean (SD)

CEsev end-tidal sevoflurane concentration, *Jsev* jugular-bulb blood sevoflurane concentration, *Asev* sevoflurane concentration in arterial blood, *PAsev* sevoflurane concentration in pulmonary arterial blood

and heart rate. Because of the unknown dose of sevoflurane, the distribution volume and clearance of sevoflurane were not derived from the study.

After cessation of sevoflurane, washout commenced from the body and the circulating blood of the pulmonary artery delivered the sevoflurane into the alveolar space and finally allowed the lungs to ventilate it into the air. The CIsev decreased rapidly to zero within 3 min after the cessation of sevoflurane administration under high fresh gas flow. The pharmacokinetic software simulation model was only used for curve fitting of the CEsev, Asev, Jsev, and PAsev time curves in the study.

The pharmacokinetic software simulation model demonstrated a bi-exponential curve fitting for the CEsev, Jsev, Asev, and PAsev time curves. Two exponentially decaying functions were observed with different time constants: an initial 5-min fast and a subsequent 15-min slow component. We speculate that the phenomenon of the two distinct components of sevoflurane elimination can be explained by a rapid washout of sevoflurane from the function residual capacity (FRC) immediately after stopping sevoflurane administration, which dominates the initial elimination of sevoflurane (the rapidly decreasing alveolar concentration of sevoflurane during the respiratory phase caused the increased pulmonary artery-alveolar concentration gradient). After the effect of the FRC on sevoflurane elimination disappears (three time-constants occurred within 5 min because the minute ventilation is larger than the FRC in the study), the pulmonary capillary-alveolar membrane and tissue-blood interface would become the critical determinants in limiting the rate of sevoflurane elimination.

Because the PAsev is the sevoflurane concentration in the mixed venous blood, its decay over time could represent the elimination rate of sevoflurane from body. Similarly, the decay of the Jsev, the sevoflurane in the jugular bulb blood, could indicate the elimination rate of sevoflurane from the brain. Our results demonstrated that the PAsev and Jsev were fitted best to a two-component model. It is concluded that the initial FRC washout of sevoflurane affected the decreasing rates of change over time of PAsev and Jsev during the initial 5 min of the sevoflurane elimination phase. Thereafter, the sevoflurane concentrations in the jugular and pulmonary arterial blood decayed almost constantly during the last 15-min sevoflurane elimination phase. The elimination half-life of Jsev was slightly shorter than that of PAsev, but there was no significant difference between the elimination half-lives of Jsev and PAsev. We had expected that because the brain is a vessel-rich organ, its uptake/elimination of sevoflurane should be faster than that of the body, which consists of organs with poor to rich vessel supplies. It is inferred that whenever the duration of the sevoflurane elimination phase is permitted to be longer than 20 min, it could be possible to observe the differences between the elimination half-lives of PAsev and Jsev.

In our previous study in humans, there was a step-down pattern of sevoflurane concentration during sevoflurane anesthesia [7, 8, 12]. The current study showed a similar step-down pattern in sevoflurane concentration before cessation of sevoflurane administration, as follows: CIsev > CEsev > Asev $\geqq$ Jsev > PAsev. After cessation of sevoflurane administration, the decay of CEsev was the most rapid of the four sevoflurane concentrations. The first decrease of blood sevoflurane was in Asev, and then in Jsev, and the last was in PAsev during the sevoflurane elimination. At the twentieth minute of the sevoflurane elimination phase, the step-down pattern of sevoflurane concentration was reversed in the following order: PAsev > Asev $\geqq$ Jsev > CEsev. This phenomenon suggests that the elimination profile of sevoflurane could be considered as the inverse of its uptake.

The Asev was persistently higher than the CEsev at the tenth, fifteenth and twentieth min during the slow component of the elimination phase, with similar average ratios of Asev to CEsev of 1.30, 1.26, and 1.28, respectively. Consequently, CEsev is not suitable to represent Asev because it underestimates Asev during the sevoflurane elimination phase. Yet, the similar ratios of Asev to CEsev during the slow phase reflect a first-order elimination of sevoflurane from the circulating blood into the alveolar space.

Yasuda et al. have demonstrated that the duration of sevoflurane administration affects end-tidal sevoflurane

(CEsev) elimination [2, 13]. This means that longer exposures to sevoflurane correspond to slower CEsev elimination curves. In this study, the sevoflurane exposure time was an average of 6.50 h. We analyzed the slope of the CEsev curve between 10 and 20 min and found that it was about −0.010 during the 20-min sevoflurane elimination phase and similar to the value under 6 h of sevoflurane exposure in Yasuda's study. In addition to determining the CEsev decay during the sevoflurane elimination phase, our results depicted the decay of blood sevoflurane concentration in the form of the Asev, Jsev, and PAsev elimination curves, illustrating the elimination of sevoflurane from the human body and brain.

There were three limitations of this study on sevoflurane elimination. One was that the blood samplings of Asev, Jsev, and PAsev were done only during the first 20 min of sevoflurane elimination. The second was that there was no way to estimate the total body uptake of sevoflurane before the cessation of administration. The third was that the hemodynamic conditions after coronary artery bypass grafting surgery might have influenced the pharmacokinetics of sevoflurane.

Our previous studies have demonstrated both isoflurane and desflurane elimination from the circulating blood [14, 15]. Thus, the present study focuses on the pharmacokinetics of blood sevoflurane elimination anesthesia. This is the first quantitative investigation of arterial and jugular venous blood concentrations of sevoflurane during elimination. By these blood data, we can clarify the actual washout of sevoflurane in human body and brain, and further verify the reality of the alveolar end-tidal or simulated concentrations during elimination in the previous studies. This might facilitate the pharmacodynamic study of the awakening blood sevoflurane concentration in a future study. The pharmacokinetic parameters of sevoflurane elimination determined by our study provide useful data to elucidate how sevoflurane is washed away from the human body and brain during the emergence period. Moreover, the blood sevoflurane concentrations during the elimination phase could be an indicator for predicting emergence from sevoflurane anesthesia in the future pharmacodynamic studies.

The elimination kinetics for CEsev, Jsev, Asev, and PAsev yielded the best fit in the form of a bi-exponential curve with fast and slow components. The initially rapid sevoflurane washout caused by the FRC diluting effect could reflect the fast component of sevoflurane elimination in CEsev, Asev, Jsev, and PAsev. However, the slow component is dominated by the tangible effects of physiological membrane barriers, such as the alveoli-pulmonary capillary and blood–brain barriers.

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