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ORIGINAL ARTICLE

Pharmacokinetics of desflurane elimination from respiratory gas and blood during the 20 minutes after cardiac surgery

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Background/Purpose: Desflurane, with a low blood–gas partition coefficient, is an ideal anesthetic to achieve rapid offset and recovery from general anesthesia. Investigation of desflurane elimination from blood and respiratory gas should provide useful information with respect to a patient's recovery from anesthesia. Therefore, this study is designed to characterize the pharmacokinetics of desflurane elimination after cardiac surgery.
Methods: Sixteen patients undergoing coronary artery bypass graft surgery were enrolled. At the end of surgery, multiple gas and blood samples were taken in the 20 minutes before and after stopping desflurane administration, with prior maintenance of a fixed 7% inspired desflurane in 6 L/minute oxygen flow for 60 minutes before the cessation. The blood desflurane concentrations, including internal jugular-bulb blood (J_{des}), arterial blood (A_{des}) and pulmonary arterial blood (PA_{des}) were analyzed using gas chromatography. The inspiratory desflurane concentration (CI_{des}) and end-tidal desflurane (CE_{des}) were measured with an infrared analyzer, and cardiac output was measured using an Opti-Q pulmonary artery catheter.
Results: Before cessation of desflurane administration, the inspiratory desflurane concentration (CI_{des}) was relatively higher than end-tidal (CE_{des}), arterial (A_{des}), internal jugular-bulb blood (J_{des}), and pulmonary (PA_{des}) concentrations in sequence ($CI_{des} > CE_{des} > A_{des} \cong J_{des} > PA_{des}$). During the elimination phase, rapid decay occurred in CE_{des}, followed by J_{des},

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A_{des} and PA_{des}. Twenty minutes after stopping desflurane administration, the desflurane concentrations were: $PA_{des} > A_{des} \cong J_{des} > CE_{des}$. The decay curves of desflurane concentrations demonstrated two distinct elimination components: an initial, fast 5-minute component followed by a slow 15-minute component.

Conclusion: Desflurane is eliminated fastest from the lungs, as indicated by CE_{des}, compared to elimination from circulating blood. The initial, rapid 5-minute desflurane washout reflected the diluting effect of functional residual capacity of the lungs.

Introduction

Desflurane has a lower rate of metabolism (0.02%), a lowerblood—gas partition coefficient (0.42) and a lower brain—blood partition coefficient (1.29) compared with other inhalational agents. These physical characteristics make desflurane an ideal agent to achieve a rapid onset and offset and hence faster induction and recovery from general anesthesia.[1] In clinical practice, inspired and end-tidal concentrations are conventionally monitored by a rapid gas analyzer during general anesthesia. Previous studies found that the volatile anesthetic concentration (or partial pressure) in end-tidal gas differs widely from that in arterial blood,[2-7] which has been considered to reflect more accurately the concentration perfusing the brain and other organs.[8]

Previous studies on the pharmacokinetics of isoflurane elimination have reported different patterns of isoflurane elimination from alveoli and blood, including arterial, jugular venous and pulmonary arterial blood. However, still no attempt has been made to quantify the pharmacokinetics of desflurane elimination between blood and respiratory gas. Therefore we have investigated the pharmacokinetics of desflurane elimination during patient recovery from desflurane anesthesia.

Using gas chromatography (GC), the determination of desflurane concentration in different circulating blood has made possible the *in vivo* pharmacokinetic study of desflurane elimination from the brain and body.[7] This study was designed to characterize the eliminating kinetic pattern of desflurane by simultaneous measurement of circulating blood and respiratory gas in patients who had undergone coronary artery bypass graft surgery.

Methods

Anesthetic procedure

The protocol was approved by the Institutional Review Board (Tri-Service General Hospital, Taipei, Taiwan) and all patients included in the study provided written informed consent. Sixteen American Society of Anesthesiologists (ASA) classification II or III patients for elective coronary arterial bypass graft surgery under general anesthesia were enrolled in this study.Premedications consisted of intravenous fentanyl (2 μg/kg) and midazolam (40 μg/kg). Prior to induction of anesthesia, a 20-gauge catheter was inserted into the left radial artery for blood sampling under local anesthesia. Blood pressure was continuously monitored.

Anesthesia was induced with thiopental (3—4 mg/kg), and intubation was facilitated with pretreatment with pancuronium (0.015 mg/kg) and succinylcholine (1.25 mg/kg). A 7% inspired concentration of desflurane in 6 L/minute oxygen flow was administered for 5 minutes to fill the anesthetic circuit and functional residual capacity, after which the oxygen flow rate was reduced to 0.3 L/minute for maintenance of minimal low-flow anesthesia.[9,10] Then, 5.5—7.5% inspired desflurane was adjusted to maintain a hemodynamic range within 25% of baseline. 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.[4-7,11] 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 administered 3.5—5.5% desflurane into the bypass circuit for maintenance of anesthesia. After weaning from the CPB circuit, the patient was ventilated again and the fresh gas oxygen flow rate was kept at 0.3 L/minute, with 5.5—7.5% inspired desflurane before the study of desflurane elimination was commenced (Fig. 1).

A Datex Aestiva/4 anesthetic machine (Datex, Helsinki, Finland) was used with soda lime as 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 multi-gas analyzer (Datex AS/4 Anesthesia system; Datex, Helsinki, Finland) which had been calibrated according to the manufacturer's recommendations. Sampled gases (approximately 0.21 L/minute) were redirected into the breathing circuit. The inspiratory desflurane concentration (CI_{des}), end-tidal desflurane concentration (CE_{des}), end-tidal CO_2, blood pressure, and heart rate were recorded every 30 seconds, and $PaCO_2$ was maintained at 36—42 mmHg (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 except for during the period of CPB. 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 during surgery.[6,7,11] Hypotension, defined as a 25% decrease in blood pressure from baseline, was treated with intravenous fluid administration and/or intravenous ephedrine (5 mg bolus). As reported in our previous study,[7] it takes 25 minutes to achieve equilibrium between the arterial blood desflurane concentration (A_{des}) and the internal jugular bulb desflurane concentration

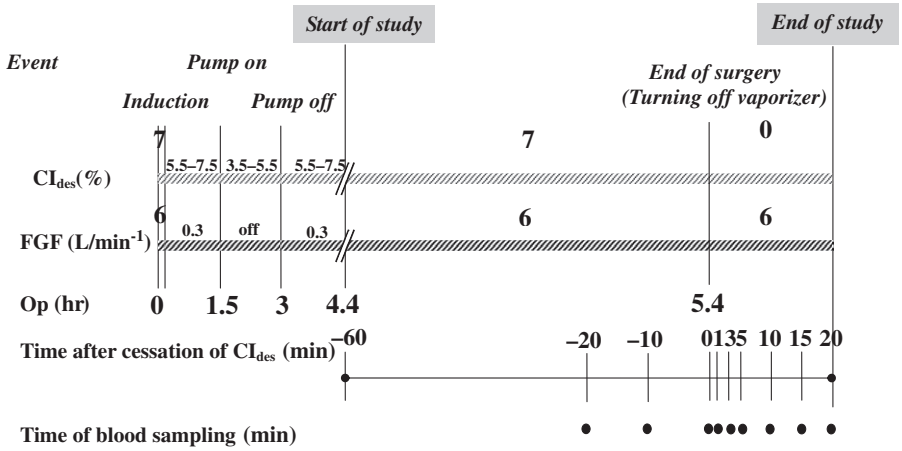

Figure 1 Schematic representation of time frame for coronary arterial bypass grafting surgery with cardiopulmonary bypass under desflurane anesthesia. The sampling times for blood and gas phase desflurane concentrations were at −20, −10, 0 and 1, 3, 5, 10, 15 and 20 minutes after the cessation of desflurane administration. CI_{des} = inspired desflurane concentration; CPB = cardiopulmonary bypass; FGF = fresh gas flow; Induction = start of anesthesia; ● = time point of blood sampling.

(J_{des}). Therefore, a 6 L/minute constant oxygen flow was maintained during the entire study (80 minutes), including a 60-minute maintenance phase with a fixed 7% inspired desflurane concentration prior to the completion of skin closure and a 20-minute elimination phase after the vaporizer was turned off (Fig. 1).

Collection of blood samples for desflurane measurement

The sampling times for blood were at −20, −10, 0 (just before), 1, 3, 5, 10, 15 and 20 minutes from the cessation of the desflurane administration (Fig. 1). Arterial, jugular-bulb and pulmonary artery blood samples were drawn simultaneously from the respective indwelling catheters into individual 1-mL heparinized syringes. The blood samples from the internal jugular bulb were withdrawn slowly at approximately 2 mL/minute to avoid contamination of internal jugular venous blood samples by blood drainage from tissues other than the brain.[12] Each 1-mL blood sample was immediately injected into a 10-mL tightly sealed glass vial, and stored in a refrigerator at 4°C for measurement within 24 hours. All blood samples were analyzed for desflurane concentration using a HP 6890 series GC system (Hewlett-Packard, Wilmington, DE, USA) consisted of a headspace sampler, an oven, a flame-ionization detector according to the method used in our previous study.[7] Twenty-four hours after surgery all of the patients were interviewed to determine the presence of awareness during the desflurane elimination phase.

Determination of blood desflurane concentration

Before determining the desflurane concentration in the blood, 10 mL blood was obtained from each patient prior to anesthesia as blank blood for determining the individual blood−gas partition coefficient (λ) of desflurane (Appendix 1). Desflurane in each blood sample was converted to the corresponding concentration, based on gas chromatographic measurements and individual blood−gas partition coefficient of desflurane (λ) measured (Appendix 2).

Desflurane uptake and elimination

Under a fixed 7% inspired desflurane concentration, blood desflurane concentration including A_{des}, J_{des} and PA_{des} were determined at −20, −10 and 0 minutes prior to the cessation of desflurane. Twenty minutes prior to stopping desflurane administration, the rate of desflurane body uptake (mL of vapor per minute) was defined as follows: (A_{des} − PA_{des})×Cardiac Output×10. During the elimination phase, the jugular bulb and pulmonary arterial blood provide drainage from the brain and body, respectively. Therefore, the decay of the J_{des} time curve and PA_{des} time curve might represent the desflurane elimination phases from the brain and body, respectively. Desflurane concentration and pharmacokinetic parameters were reported as mean ± standard deviation (SD).

Pharmacokinetic analysis

Pharmacokinetic analyses were performed for CE_{des}, A_{des}, PA_{des} and PA_{des} time curves by using noncompartmental methods with WinNonlin Professional version 5.2 (Pharsight Corporation, Mountain View, CA, USA). The selection of the best model was made by the Akaike information criterion (AIC).[13] The model that gives the lowest AIC value is considered the best fit. The pharmacokinetic parameters, including elimination half-life ($t_{½}$), area under the concentration time curve (AUC), and mean residence time (MRT), were estimated from the model interpretation.

Statistical analysis

One-way analysis of variances (ANOVA) was conducted to examine differences between the 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 <0.05 was regarded as statistically significant. A t test was used to compare any of two desflurane concentrations between PA_{des} and A_{des} (or J_{des}) 20 minutes after the cessation of desflurane administration.

Results

Demographic data for the study patients are shown in Table 1. Patient hemodynamic and ventilatory parameters, including mean arterial blood pressure, heart rate, cardiac index and end-tidal CO_2, are summarized in Table 2. They remained stable throughout both the uptake and elimination phases of the study. None of the patients reported awareness. The mean (SD) of blood/gas partition coefficient of desflurane (λ) was 0.42 (0.02).

Fig. 2 depicts 7% inspired desflurane concentration (CI_{des}), arterial (A_{des}), jugular-bulb (J_{des}) and pulmonary arterial desflurane (PA_{des}), and end-tidal desflurane concentration (CE_{des}) in the 20 minutes prior to and after the cessation of inspired desflurane. During the 20 minutes prior to stopping desflurane administration,the CI_{des} was relatively higher than CE_{des}, A_{des}, J_{des} and PA_{des} (in sequence). It shows that the concentrations of desflurane (including CE_{des}, A_{des}, J_{des} and PA_{des}) were nearly constant during the 20-minute period before stopping desflurane administration. At time 0 (just prior to the cessation of desflurane), differentdesflurane concentrations were observed in the following order: $CI_{des} > CE_{des} > A_{des} \cong J_{des} > PA_{des}$. After stopping desflurane administration, desflurane concentrationdecayed rapidly in CE_{des}, followed by A_{des} (or J_{des}) and then PA_{des}. The arterial desflurane concentration was relatively lower than CE_{des} at time 0 (prior to cessation of desflurane) and the average ratio of A_{des}:CE_{des} was 0.87. After 10, 15 and 20 minutes of the slow elimination component, different ratios of A_{des}:CE_{des} were listed as 2.32, 2.40 and 2.46, respectively. After 20 minutes of desflurane elimination,PA_{des} was significantly higher than A_{des} ($p = 0.02$) and J_{des} ($p = 0.03$) (Tables 3 and 4).

We obtained the two-compartment model best fitted to the concentration time curves of CE_{des}, A_{des}, PA_{des} and J_{des}, using the least squares method and Akaike's information criteria. After 5 minutes of elimination, the average desflurane concentrations of CE_{des}, A_{des}, J_{des} and PA_{des} were 27%, 61%, 63% and 66% of their maximal concentration at time 0. The distribution half-lives (i.e., the average time for the desflurane concentration to reach 50% of its maximal concentration) for CE_{des}, A_{des}, J_{des} and PA_{des} were 0.5 (0.2), 2.4 (3.2), 3.8 (4.9) and 2.7 (3.3) minutes, respectively.

There were no significant differences in alpha, beta, distribution and elimination half-lives among CE_{des}, A_{des}, J_{des} and PA_{des} (Table 4). During the elimination phase, the AUC (% min) for CE_{des}, A_{des}, J_{des} and PA_{des} was 55.6 (10.6), 128.6 (32.3), 156.8 (71.8) and 165.8 (85.4), respectively. The mean residence time (MRT) for CE_{des}, A_{des}, J_{des} and PA_{des} was 23.8 (6.8), 34.0 (13.6), 45.1 (32.9) and 45.9 (37.8) minutes, respectively. There were no significant differences in AUC or MRT among CE_{des}, A_{des}, J_{des} and PA_{des}.

Table 1 Patients' demographic characteristics ($n = 16$).

Age (y)	66 (12)
Weight (kg)	68 (12)
Height (cm)	163 (10)
Gender (M:F)	12:4
Duration of operation (min)	325 (42)
Duration of CPB (min)	113 (19)
Pancuronium consumption (mg)	10.4 (2.0)
Fentanyl consumption (μg)	255 (33)

Values are presented as mean (SD).
CPB = cardiopulmonary bypass.

Table 2 Hemodynamic and ventilatory variables during the 20 minutes before and after cessation of 7% inspired desflurane ($n = 16$).

Time (min)	MABP (mmHg)	HR (beats/min)	CI (L/min/m^2)	$ETCO_2$ (mmHg)
−20	80.7 (13.9)	99.8 (10.6)	3.58 (1.10)	38.6 (2.8)
−10	76.2 (12.6)	99.5 (12.7)	3.49 (1.07)	38.8 (3.3)
0	78.6 (10.2)	100.2 (11.9)	3.76 (1.30)	38.7 (3.2)
1	76.9 (12.2)	99.3 (13.2)	3.69 (1.20)	39.0 (3.1)
3	79.0 (10.3)	100.3 (12.3)	3.56 (1.28)	39.4 (3.3)
5	90.1 (11.6)	101.5 (13.6)	3.48 (1.15)	39.7 (3.0)
10	93.8 (12.2)	104.2 (13.8)	3.45 (1.21)	40.1 (3.0)
15	95.9 (12.5)	102.3 (13.7)	3.77 (1.37)	39.9 (3.3)
20	91.8 (13.7)	102.1 (13.7)	3.93 (1.54)	40.1 (3.0)

Values are presented as mean (SD).
CI = cardiac index; $ETCO_2$ = end-tidal CO_2; HR = heart rate; MABP = mean arterial blood pressure.

Discussion

This is the first human study to simultaneously measure desflurane concentrations in arterial blood, jugular-bulb

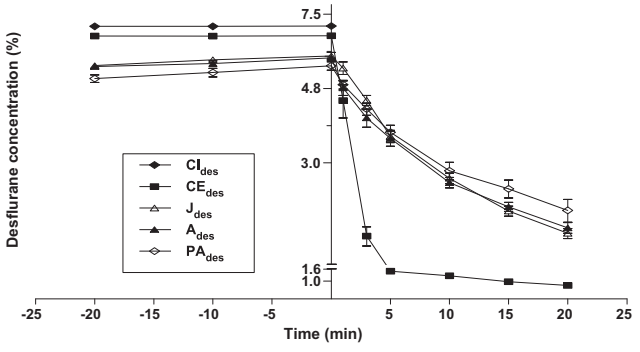

Figure 2 Desflurane concentration time curves during the 20 minutes before and after cessation of inspired desflurane administration. The sampling times for blood and gas phase desflurane concentrations were at −20, −10, 0 (before) and 1, 3, 5, 10, 15 and 20 minutes after the cessation of desflurane administration. Desflurane concentrations of inspired (CI_{des}; -◆-), and end-tidal (CE_{des}; -■-) gases, and arterial (A_{des}; -▲-), jugular-bulb (J_{des}; -△-), and pulmonary arterial blood (PA_{des}; -◇-) are shown. Data are presented as mean (SD).

Table 3 CE_{des}, A_{des}, J_{des}, PA_{des} and A_{des}:CE_{des} ratio under 7% inspired desflurane anesthesia at 0 minutes (just prior to cessation of desflurane; as basal level of desflurane maintenance phase), and at 1, 3, 5, 10, 15 and 20 minutes after desflurane discontinuation ($n = 16$).

Time (min)	0	1	3	5	10	15	20
CE_{des} (%)	6.60 (0.18)	4.14 (1.81)	1.90 (0.45)	1.46 (0.31)	1.23 (0.20)	0.98 (0.16)	0.84 (0.14)
A_{des} (%)	5.75 (0.27)	4.77 (0.86)	3.97 (0.89)	3.49 (0.65)	2.72 (0.35)	2.29 (0.25) **	2.01 (0.27) *
J_{des} (%)	5.70 (0.53)	5.42 (0.84)	4.42 (0.55)	3.54 (0.54)	2.73 (0.35)	2.22 (0.27) **	1.94 (0.24) *
PA_{des} (%)	5.47 (0.57)	4.87 (0.52)	4.19 (0.63)	3.63 (0.64)	2.86 (0.62)	2.55 (0.57)	2.23 (0.63)
A_{des}:CE_{des}	0.87 (0.05)	1.19 (0.63)	2.23 (0.81)	2.46 (0.53)	2.32 (0.42)	2.40 (0.51)	2.46 (0.60)

Values are mean (SD).
A_{des} = desflurane concentration in arterial blood; CE_{des} = end-tidal desflurane concentration; J_{des} = jugular-bulb blood desflurane concentration; PA_{des} = desflurane concentration in pulmonary arterial blood.
* $p < 0.05$.
** $p < 0.01$ vs. PA_{des}.

blood, pulmonary arterial blood and end-tidal gas during the elimination phase. The study produced three main findings. Firstly, there were two distinct components: an initial 5-minute fast component and a subsequent 15-minute slow elimination component for the above four concentrationtime curves during desflurane elimination. The decay of desflurane was rapid in end-tidal gas (CE_{des}), followed by J_{des}, A_{des} and PA_{des}. Secondly, under a fixed 7% inspired desflurane concentration, the relationships between different desflurane concentrations were: $CI_{des} > CE_{des} > J_{des} \cong A_{des} > PA_{des}$. Twenty minutes after stopping desflurane administration, the desflurane concentrations were: $PA_{des} > A_{des} \cong J_{des} > CE_{des}$. Thirdly, the average A_{des}:CE_{des} ratio was 2.4 after 20 minutes of elimination. The PA_{des} was relatively higher than both J_{des} and A_{des} after 20 minutes of elimination.

Yasuda et al. demonstrated that duration of desflurane administration affects end-tidal desflurane (CE_{des}) elimination.[2,8] In the present study, the average desflurane exposure was 6.5 hours. CE_{des0} denotesthe desflurane concentration at time 0 (i.e., the last end-tidal desflurane concentration during desflurane administration). The gradient of the CE_{des}:CE_{des0}slope at 10–20 minutes of elimination was about −0.0013, which was between the values of 4 hours (−0.002) and 8 hours (−0.001) of desflurane exposure reported in previous study.[14] Our study of the rate of CE_{des} elimination was similar to the previous study of Yasuda et al. In particular, the current study illustrates pharmacokinetic analysis of blood desflurane concentrations and provides the kinetic profile of desflurane elimination from circulating blood with respect to patient recovery. These pharmacokinetic parameters of desflurane elimination may provide useful correlation data for future studies of pharmacodynamic responses during emergence.

As is well known, desflurane is inhaled and absorbed into body via alveoli.[7] After cessation of desflurane administration, the desflurane was washed out from the brain and body via circulating blood, delivering it into the alveolar space through the pulmonary arterial mixed venous blood, and then allowing lungs to ventilate with air. Simulating software was used to fit the time curves of CE_{des}, J_{des}, A_{des} and PA_{des} in a pharmacokinetic modelof desflurane elimination and demonstrated a bi-exponential curve. The average half-life during the fast elimination component of the CE_{des}, J_{des}, A_{des} and PA_{des}time curves ranged from 0.5 to 3.4 minutes. Therefore, bi-exponentially decaying functions were observed with different time constants: an initial fast (less than 5 minutes) period and a subsequent slower elimination component. This phenomenon suggested that the rapid washout of desflurane from the function residual capacity dominates the initial dilution of CE_{des}. With a characteristic lower blood–gas partition coefficient (0.42), the A_{des}, after alveolar exchange of desflurane, decreased rapidly, which was followed by J_{des} and PA_{des}. The effect of a large gradient between pulmonary capillary and alveolar concentration then disappeared after three time constants of washout within 5 minutes at 6 L/minute oxygen flow.[15] Desflurane elimination appeared to become

Table 4 The fitting of CE_{des}, J_{des}, PA_{des} and A_{des} time curves with bi-exponential equation ($n = 16$).

Parameter [a]	A	B	Alpha	Beta	Distribution half-life (min)	Elimination half-life (min)
CE_{des}	10.23 (6.90)	1.80 (0.40)	1.47 (0.57)	0.039 (0.010)	0.5 (0.2)	19.1 (5.1)
A_{des}	3.23 (2.39)	3.23 (0.98)	0.51 (0.32)	0.028 (0.017)	2.6 (3.2)	26.5 (11.0)
J_{des}	3.68 (1.80)	3.17 (0.83)	0.46 (0.54)	0.027 (0.013)	3.8 (4.9)	27.4 (16.1)
PA_{des}	1.83 (1.11)	3.84 (1.09)	0.42 (0.33)	0.028 (0.019)	2.7 (3.3)	32.8 (27.6)

Values are mean (SD).
A_{des} = desflurane concentration in arterial blood; CE_{des} = end-tidal desflurane concentration; J_{des} = jugular-bulb blood desflurane concentration; PA_{des} = desflurane concentration in pulmonary arterial blood.
[a] Parameters of pharmacokinetic analysis of desflurane concentration time curves were fitted from time 0 (just after cessation of desflurane) to 20 minutes. Bi-exponential equation: $Y = A \times \exp(-\text{alpha} \times T) + B \times \exp(-\text{beta} \times T)$, where Y is CE_{des}, A_{des}, J_{des} and PA_{des}.

slower during the subsequent elimination component, which might be explained by its relative higher tissue—blood than that of gas—blood partition coefficient.

Our previous pharmacokinetic study of isoflurane elimination demonstrated two similar distinct components of elimination for end-tidal and arterial blood isoflurane, but there was only one component of isoflurane elimination for pulmonary artery blood and jugular-bulb blood.[11] This study demonstrated that blood desflurane decays more rapidly than isoflurane at the initial distribution component, because both PA_{des} and J_{des} were well fitted to the two-component model. To explain why there was bi-exponential decay of blood desflurane, but only mono-exponential isoflurane elimination from pulmonary arterial blood and jugular bulb blood, we suggest that desflurane has a lower rate of metabolism, a lower blood—gas partition coefficient and a lower brain—blood partition coefficient compared with isoflurane. Therefore, blood desflurane decreases more rapidly because it passes from circulating blood into the alveoli or tissue more rapidly than isoflurane. Our study finding is consistent with the lesser solubility of desflurane in blood and tissue,[16] indicating that recovery from anesthesia with desflurane will be more rapid than from isoflurane in clinical practice.

There were no significant differences in the fast and slow elimination half-lives of CE_{des}, A_{des}, J_{des} and PA_{des}. The decay rate of desflurane in gas (CE_{des}) was faster than those in the blood (A_{des}, J_{des} and PA_{des}) during the initial 5-minute rapid component. The end-tidal desflurane concentration (CE_{des}) descended rapidly and became the lowest concentration than the others (A_{des}, J_{des} and PA_{des}) during the subsequent slow elimination component. It is interesting that equations derived from the fitted curves ofA_{des}, J_{des} and PA_{des} might be used to estimate the desflurane concentration of different circulating blood at certain times during desflurane elimination. Perhaps, it will be feasible to provide indicators for monitoring anesthetic depth and also help theanesthesiologist predict more precisely when a patient will be awakened from desflurane anesthesia.[17]

There was a nearly constant relationship between different desflurane concentrations, which was similar to the previous study of desflurane uptake, in the following order: $CI_{des} > CE_{des} > A_{des} \cong J_{des} > PA_{des}$.[7] The current study also showed a similar pattern in desflurane concentrations just before the cessation of desflurane administration. After stopping desflurane administration, the decay of CE_{des} was rapid compared to blood desflurane. The decrementing rate of blood desflurane was first in A_{des}, second in J_{des}, and last in PA_{des}. Then, 20 minutes after stopping desflurane administration, the relationship between desflurane concentrations was: $PA_{des} > A_{des} \cong J_{des} > CE_{des}$. This phenomenon suggests that the elimination profile of desflurane in blood and gas could be considered as the inverse of its uptake profile.

Our present study showed that the average ratios of A_{des}:CE_{des} after 10, 15 and 20 minutes in the elimination phase were 2.32, 2.40 and 2.46, respectively. Evidently, CE_{des} does not always present the same ratio to A_{des}, because it underestimates A_{des} during elimination. However, the nearly constant A_{des}:CE_{des} ratios during the slow component would reflect a first-order elimination of desflurane from circulating blood into alveolar space. Perhaps, it would be possible to predict the desflurane concentration in arterial blood from the end-tidal desflurane concentration, which could be measured using noninvasive, rapid gas analyzers during emergence from anesthesia.

There were two limitations in this study. First, the blood sampling of desflurane was only achieved in a limited 20-minute period following the cessation of desflurane. In a typical elimination study, the samples of desflurane in blood are often measured for a longer period to determine the best fit for the concentration time curve. However we stopped blood sampling 20 minutes after cessation of desflurane administration, because the patients' anesthetic depth became lighter and their respiratory patterns started to become irregular. Second, the inspired desflurane concentration had been adjusted according to the changes of arterial blood pressure and heart rate during the pre-bypass, bypass and post-bypass period, so the total body uptake of desflurane could not be determined before turning off the vaporizer. As such we could not derive the volume distribution of desflurane during the elimination phase.

In conclusion, the bi-exponential curve of desflurane concentrations demonstrated two distinct components of desflurane elimination. An initial rapid desflurane washout caused by a functional residual capacity diluting effect dominates the distribution component of desflurane elimination. Desflurane elimination from the lungs is the fastest, indicated by CE_{des}, compared with the desflurane concentration in circulating blood.

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Appendix 1

Determination of blood—gas partition coefficient (λ) of desflurane for each patient's blood.

To obtain standard gas concentrations, five 550-mL glass bottles, each with a turnable stopcock and Teflon septum were used.[18] After flushing each bottle with nitrogen for 6 minutes, the septum was pierced with a syringe needle and 2, 5, 10, 20, or 50 μL of liquid desflurane was injected into the glass bottles at 4°C. The calibration curve relating counts to concentration was obtained by injecting different concentrations of desflurane in 225 μL gas into the gas chromatogram (GC) using a gas-tight Hamilton syringe (Hamilton 250 μL; PN81156). The calculated desflurane volume percentage was plotted against the measured GC counts.

We used a similar method to that described by Smith et al.[19] to determine the blood—gas partition coefficient of desflurane (λ) as follows:

1. A 2-mL blood sample from each patient with known desflurane concentration was added into the first 10-mL vial (with 2 mL of gas removed before injection), sealed with a Teflon septum at 10°C temperature room and then incubated at 37°C for 30 minutes.
2. The desflurane concentration in the headspace of the first vial (C1) was determined by GC.
3. 1 mL of the sample was withdrawn immediately from the first vial and transferred to a second 10-mL vial (with 1 mL of gas removed before injection), sealed with a Teflon septum and then incubated at 37°C for another 30 minutes.
4. The desflurane concentration in the headspace of the second vial (C2) was again determined by GC. Thus, λ can be calculated by the following equation:

$$\lambda = \frac{9 \times C2}{C1 - C2}$$

Appendix 2

Conversion of desflurane liquid to vapor by known λ of desflurane.

According to the physical properties of desflurane,

MW/D = volume for 1 mole of desflurane liquid;

MW = molecular weight (for desflurane, 168.04);

D = density of desflurane, 1.4892 at 10°C;

Standard blood–gas partition coefficient (desflurane) = 0.42

According to the ideal gas law, 1 mole desflurane (MW = 168.04 g) is equal to 22.4 L of desflurane vapor at 1 atm pressure and 0°C. Therefore, 1 mL desflurane vapor = 7.50 mg. As temperature is increased from 0 to 37°C, 1 mL desflurane vapor should be equal to 6.61 mg, according to the ideal gas law: $V_{37C} = 273K/273K + 37K \times 7.50mg$

The patient's blood–gas partition coefficient obtained in the above paragraph. For example, if $\lambda_{b/g}$ is assumed to be 0.42, an ideal equilibrated sample of 100 mL desflurane gas and 100 mL of blood (each at 1% concentration) would contain 6.61 mg and 2.8 mg of desflurane, respectively at 37°C (1 atm). Therefore, it can be calculated that 1 mL of 1% desflurane in blood would contain 0.0281 mg of desflurane. In other words, the gas chromatogram (GC) count measured from the headspace was registered as containing 1% of desflurane in blood, after 0.028 mg of desflurane was injected into a 10-mL vial and equilibrated with 1 mL of blank blood.

Gas chromatography 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 minute to 200°C, and maintained at this level for 4.33 minutes. Both the injection and detection temperature were set at 250°C. An integrator and a data acquisition system were provided by HP CHEMOSTATION software (Hewlett-Packard, Wilmington, DE, USA).

Calibration curve for measuring blood desflurane concentration

A standard of liquid desflurane was equilibrated in a cold bath at 10°C for 1 hour before use. Five known amounts of desflurane liquid were taken up using a microsyringe (Hamilton 0.5 μL syringe; PN: 86259) and then injected into five 10-mL glass vials (containing the patient's 1-mL blank blood). These vials were swirled in a cold bath at 10°C for 30 minutes, and then transferred to a water bath at 37°C for 30 minutes. A linear relationship between the signals for the peak height of desflurane (y-axis) and desflurane concentration (x-axis) was obtained and revealed an excellent correlation with a range of 0.9975 and 0.9998 between the signal and desflurane concentration. The analytical range of the desflurane concentration was 0.70–17.5%. The desflurane concentration represented as the % could be converted to the unit of partial pressure (mmHg) by the following equation: 1 kPa = 7.50 Torr (mmHg). Precision and accuracy were determined on spiked human samples at six concentrations (0.70–17.5%) with respect to a calibration graph prepared every day. The limit of detection (LOD) was 0.02% per mL gas based on a signal-to-noise ratio of 3. The limit of quantification (LOQ) of method for standard samples was 0.1% per mL blood. The precision of the method was expressed as the within-day and between-day coefficient of variation (%) less than 7.4%.

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