

# End-tidal Sevoflurane and Halothane Concentrations during Simulated Airway Occlusion in Healthy Humans

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**Background:** In a patient whose airway is likely to become obstructed upon loss of consciousness, anesthesia may be induced using an inhaled vapor. If the airway occludes during such an inhalational induction, the speed of patient awakening is related to the rate at which anesthetic gas redistributes away from lung and brain to other body compartments. To determine whether redistribution occurs more rapidly with a more blood-soluble or a less blood-soluble agent, the authors used subanesthetic concentrations of halothane and sevoflurane to simulate inhalational induction and airway obstruction in eight healthy human volunteers.

**Methods:** Inhalational induction was simulated using stepwise increases in inspired halothane or sevoflurane concentration, sufficient to reach an end-tidal concentration of approximately 0.1 minimal alveolar concentration. Airway occlusion was then simulated by initiating a 90-s period of rebreathing from a 1-l bag. During rebreathing, end-tidal halothane or sevoflurane concentration was measured continuously by mass spectrometry, and a time constant for the decline in concentration was calculated using a monoexponential model.

**Results:** At the onset of rebreathing, end-tidal concentrations of halothane and sevoflurane were  $0.10 \pm 0.03$  and  $0.11 \pm 0.03$  minimal alveolar concentration, respectively (mean  $\pm$  SD;  $P > 0.1$ , Student  $t$  test). During rebreathing, the time constants for the decline in end-tidal halothane and sevoflurane concentration were  $22 \pm 9$  and  $62 \pm 16$  s, respectively ( $P < 0.0001$ ).

**Conclusions:** During simulated airway occlusion in healthy volunteers, the end-tidal concentration of halothane falls more rapidly than that of sevoflurane. Halothane may therefore lead to more rapid awakening, compared with sevoflurane, should the airway obstruct during an inhalational induction of anesthesia.

IN a patient whose airway is likely to become obstructed during anesthesia (e.g. in the presence of an upper airway mass), anesthesia may be induced by using an inhaled vapor, rather than a more conventional intravenous agent. This technique is useful because, should the airway become completely obstructed, inhalation of the vapor would cease and the patient should wake relatively quickly to restore his or her own airway, avoiding the need for urgent surgical intervention.

For many years, the anesthetic of choice for inhalational induction in patients with such a difficult airway was halothane. More recently, there have been numerous case reports suggesting that the newer agent sevoflurane is the more appropriate choice.<sup>1-5</sup> Although it also causes less hemodynamic depression and airway irritation than halothane,<sup>6,7</sup> the major advantage of sevoflurane is commonly reported to be its 3- to 4-fold lower blood-gas solubility coefficient (0.65 and 2.4 for sevoflurane and halothane, respectively).<sup>8</sup> This relatively low solubility of sevoflurane in the blood allows the alveolar and arterial partial pressure to rise more quickly during induction, and it is reported by some authors that a more rapid loss of consciousness can therefore be achieved, compared with the use of a more soluble agent such as halothane.<sup>9,10</sup>

In contrast to the substantial literature relating to induction characteristics of sevoflurane and halothane, there are few reports relating to the effect of the blood or tissue solubility on the speed of awakening from anesthesia when the airway obstructs during inhalational induction. In such a circumstance, any decrease in the alveolar and arterial partial pressure of the anesthetic agent will be primarily the result of redistribution from the lung to the body tissues. The greater solubility of halothane in the blood (i.e., greater blood-gas coefficient) would provide a larger conduit to the tissues, and the greater tissue-gas coefficient of halothane, compared with sevoflurane, would also provide a greater reservoir into which the agent may be distributed. On the basis of these theoretical considerations, it has been argued that halothane would be removed from the lung more rapidly than sevoflurane during airway obstruction, resulting in a more rapid decrease of alveolar and arterial partial pressure.<sup>11</sup> However, this view is not universal<sup>1,4,12</sup>; in a recent clinical study in two groups of patients undergoing simulated inhalational anesthesia with halothane or sevoflurane before surgery, the end-tidal concentration of sevoflurane was found to be lower than that of halothane after 3 min of airway obstruction.<sup>13</sup>

The purpose of the current study was to test the hypothesis that the end-tidal concentration of halothane would decline 3-4 times more quickly than that of sevoflurane during simulated airway occlusion, reflecting the difference in their respective blood-gas and tissue-gas partition coefficients.<sup>8</sup> The relationship between blood or tissue content and gas partial pressure is widely recognized to be linear for inhalational anesthetics; therefore, we were able to achieve this aim in a laboratory setting by using anesthetic concentrations of ap-

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Received from the Department of Physiology, Anatomy and Genetics, University of Oxford, and Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headington, Oxford, United Kingdom. Submitted for publication October 9, 2008. Accepted for publication March 31, 2009. Supported by a Fellowship from the Foulkes Foundation, London, United Kingdom (to Dr. Talbot).

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proximately one tenth of the partial pressure commonly encountered clinically. Healthy volunteers were exposed to a stepwise increase in the inspired sevoflurane or halothane concentration, sufficient to reach an end-tidal concentration equivalent to approximately 0.1 minimal alveolar concentration (MAC). Airway obstruction was then simulated by sudden initiation of a 90-s period of closed-circuit rebreathing, during which end-tidal anesthetic concentration was measured breath-by-breath using a mass spectrometer.

## Materials and Methods

### *General Study Design*

The study was approved by the Oxfordshire Clinical Research Ethics Committee (OxREC, Oxford, United Kingdom), and volunteers gave written, informed consent on each day of participation. Eight healthy volunteers (six men, two women) each visited the laboratory twice. The mean ( $\pm$  SD) age was  $33 \pm 11$  yr (median 29 yr). During one visit, a standard simulated induction/rebreathing protocol (see Simulated Inhalational Induction and Simulated Airway Obstruction sections) was performed twice using halothane. During the other visit, the same protocol was performed twice using sevoflurane. Within each day, the two repeats of the protocol were separated by at least 60 min of breathing room air. Four volunteers were exposed to halothane during their first visit and sevoflurane during their second visit, and four volunteers *vice versa*. In accordance with standard anesthetic practice, volunteers ate no food for 6 h and drank no fluids for 2 h before taking part; as a result of the small risk of hepatotoxicity, they had not been exposed to halothane within 6 months of commencing the study.

### *Gas Delivery System*

During experiments, each volunteer sat in a comfortable chair and breathed through a mouthpiece with his or her nose occluded. A T-piece was positioned close to this mouthpiece, to which 100% oxygen was delivered *via* two routes: (1) a constant bias flow of 100% oxygen was delivered to the T-piece *via* a mass flow controller (MKS Instruments Ltd, Altrincham, Cheshire, United Kingdom) at a rate of at least 40 l/min and (2) a constant flow of 10 l/min of 100% oxygen was also delivered to the T-piece *via* a sevoflurane or halothane vaporizer, according to protocol.

Throughout all phases of the study, inspired and expired gas were sampled continuously (at a rate of 20 ml/min) by using a capillary tube positioned close to the mouth and analyzed by using a mass spectrometer (Airspec QP900; CASE Scientific, Biggin Hill, Kent, United Kingdom). Sevoflurane and halothane were detected at relative molecular masses of 79 and 118, respectively. Before each experiment, the mass spectrometer was

calibrated by using a gas cylinder containing a known concentration of halothane (0.208%) or sevoflurane (0.695%). Ventilatory volumes and timings were measured using a combination of a turbine and a pneumotachograph, connected in series. Data were acquired and recorded at 100 Hz using a desktop computer. A three-lead electrocardiogram and arterial oxygen saturation were monitored throughout all experiments.

To simulate airway obstruction, a two-way tap was included in the system, which could be turned to interrupt gas delivery and initiate rebreathing from an initially empty 1-l bag. This arrangement mimics airway occlusion by producing a closed ventilatory system in which any decrease in lung anesthetic concentration must represent redistribution to other body compartments. In addition, it has the advantage of preserving tidal gas flow, and it thereby facilitates breath-by-breath measurement of end-tidal anesthetic concentration.

### *Simulated Inhalational Induction*

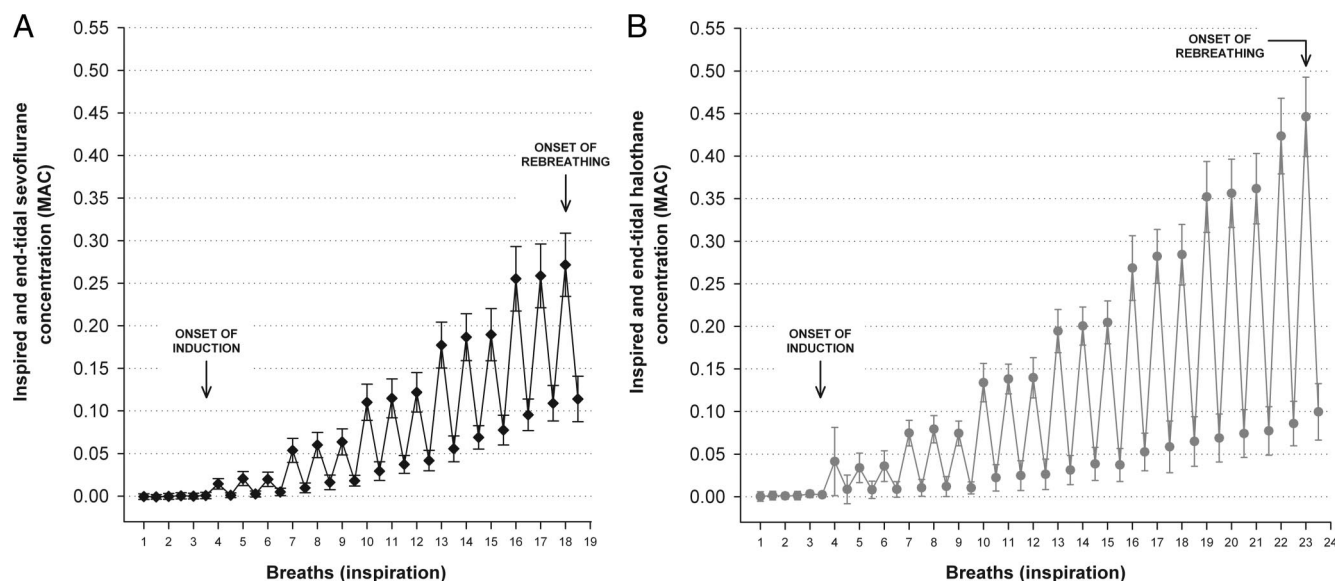
Volunteers initially breathed 100% oxygen for several minutes. Induction of anesthesia was then simulated by increasing the inspired anesthetic concentration by 0.05 MAC every third breath. Owing to its higher blood solubility compared with sevoflurane, a higher inspired concentration of halothane is required to produce a given end-tidal concentration. Therefore, induction was continued for 20 breaths in the case of halothane (maximum inspired concentration, approximately 0.35 MAC) and for 15 breaths in the case of sevoflurane (maximum inspired concentration, approximately 0.25 MAC). This difference was predicted to produce an end-tidal concentration of approximately 0.1 MAC for both agents on the basis of our own preliminary observations and on previously published data.<sup>13</sup> MAC was taken to be 2.6% for sevoflurane<sup>14</sup> and 0.7% for halothane.<sup>15</sup>

### *Simulated Airway Obstruction*

Airway obstruction was simulated in each protocol by repositioning the two-way tap immediately before the final expiration in the induction protocol, *i.e.*, following the 15th inspiration in the case of sevoflurane and the 20th inspiration in the case of halothane. Volunteers then rebreathed from the 1-l bag for 90 s, throughout which the mass spectrometer trace was carefully inspected for evidence of entrainment of air around the mouthpiece. Such entrainment would be visible as brief changes in gas composition towards that of air, namely very low carbon dioxide and vapor concentration and a reduction in the oxygen concentration, compared with alveolar gas. No such episodes were detected, demonstrating that the protocol was successful in modeling airway obstruction.

### *Data Analysis and Statistics*

Ventilatory timings were used to identify accurate inspired and end-tidal concentrations of halothane and



**Fig. 1.** End-tidal and inspired concentrations of sevoflurane (A) and halothane (B) during simulated inhalational induction. In each panel, the *upper* set of data points represent inspired concentrations, and the *lower* set of data points represent end-tidal concentrations. Inspired anesthetic concentration was increased by approximately 0.05 minimal alveolar concentration (MAC) every three breaths. The greater number of breaths in the halothane protocol was required to reach an equivalent end-tidal MAC by the end of induction. Data points represent mean  $\pm$  SD of sixteen experiments in eight participants.

sevoflurane. Values represent the average of 50 data points (*i.e.*, 500 ms). To estimate the time course of the decline in halothane or sevoflurane levels during rebreathing, end-tidal measurements were modeled using a simple monoexponential function in the form  $y = ae^{-t/\tau}$ , and a time constant ( $\tau$ ) was calculated for each experiment. Unless otherwise stated, data are presented as mean  $\pm$  SD and statistical comparisons were performed using a paired Student *t* test.  $P < 0.05$  were considered statistically significant.

## Results

All volunteers remained awake and alert at all times. Most reported a degree of light-headedness for a few moments after the end of the protocol and a degree of dyspnoea during rebreathing, but these symptoms resolved within minutes. No adverse events occurred during the study, and no volunteer withdrew at any stage.

### Simulated Inhalational Induction

Mean inspired and end-tidal anesthetic concentrations during the induction phase of the study are shown in figure 1. Data for individual participants are shown in table 1. At the onset of rebreathing, there was no difference between the end-tidal concentration of halothane ( $0.10 \pm 0.03$  MAC) and sevoflurane ( $0.11 \pm 0.03$  MAC,  $P > 0.1$ ).

The duration of induction was significantly longer in the halothane protocol ( $96.1 \pm 25.3$  s) compared with the sevoflurane protocol ( $77.8 \pm 22.3$  s,  $P < 0.0001$ ).

This difference reflects the greater number of breaths during induction in the halothane protocol.

### Simulated Airway Occlusion

The major finding of this study is that the end-tidal sevoflurane concentration during the rebreathing phase of the experiment fell with a significantly slower time course than that of halothane. The monoexponential time constants ( $\tau$ ) for the decline of end-tidal halothane and sevoflurane concentration were  $22.1 \pm 8.6$  and  $62.1 \pm 15.7$  s, respectively ( $P < 0.0001$ ). Example data and model fits for one participant are shown in figure 2, which demonstrates the very close matching of the monoexponential model to our experimental data. Model fits for all experiments are shown in figure 3, and parameters for individual participants are given in table 1.

## Discussion

The main finding of this study is that the end-tidal concentration of halothane declines around three times more rapidly than the end-tidal concentration of sevoflurane after simulated inhalational induction and acute airway obstruction in healthy volunteers. If the rate at which the partial pressure of anesthetic decreases in the lung is assumed to reflect the rate at which it declines at the site of anesthetic action, this result suggests that a patient with an obstructed airway may wake more rapidly after induction with a more soluble agent such as halothane, compared with a less soluble agent such as sevoflurane.



**Table 1. Data from Each Individual Participant for Each Individual Experiment**

Volunteer ID	Duration of Induction, s		Final End-tidal Concentration (MAC)		Time Constant ( $\tau$ ) for Decline during Rebreathing, s	
	Sevoflurane	Halothane	Sevoflurane	Halothane	Sevoflurane	Halothane
1096, run 1	80.1	101.5	0.10	0.12	54.5	32.5
1096, run 2	93.6	112.0	0.07	0.11	82.3	35.8
9998, run 1	66.7	92.9	0.09	0.12	37.7	19.5
9998, run 2	71.4	88.8	0.14	0.14	57.9	26.8
1638, run 1	60.1	83.7	0.12	0.12	63.7	21.4
1638, run 2	67.3	77.3	0.13	0.09	56.6	16.0
1640, run 1	78.6	106.6	0.16	0.12	60.9	23.1
1640, run 2	98.3	133.5	0.12	0.13	58.1	30.0
1637, run 1	44.1	46.5	0.10	0.08	70.6	27.3
1637, run 2	34.3	57.2	0.07	0.13	50.5	30.1
8887, run 1	89.7	87.3	0.11	0.05	68.4	9.2
8887, run 2	98.0	92.9	0.10	0.02	85.9	22.0
8888, run 1	56.9	93.7	0.10	0.11	40.0	7.2
8888, run 2	85.6	92.4	0.16	0.08	45.9	8.4
1641, run 1	104.2	129.9	0.13	0.07	68.4	18.9
1641, run 2	115.8	140.8	0.12	0.09	92.9	25.8
Mean $\pm$ SD	77.8 $\pm$ 22.3	96.1 $\pm$ 25.3*	0.11 $\pm$ 0.03	0.10 $\pm$ 0.03	62.1 $\pm$ 15.7	22.1 $\pm$ 8.6*

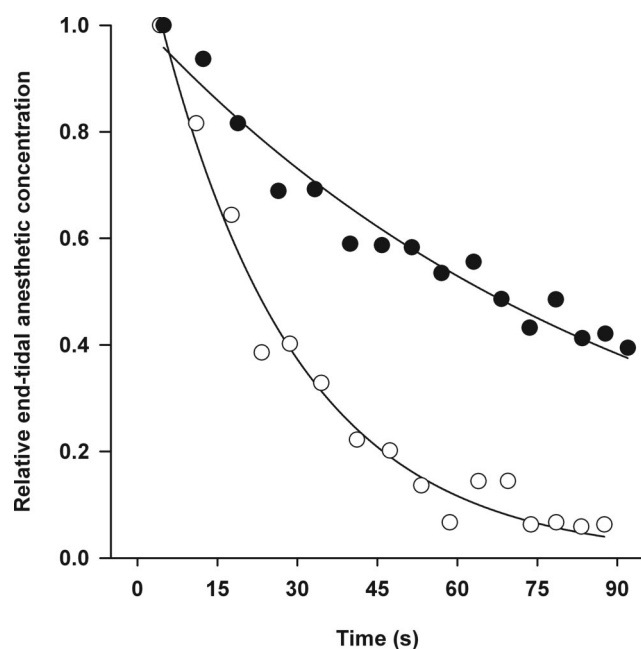
Each volunteer underwent the halothane protocol twice and the sevoflurane protocol twice. Duration of induction refers to the period between the first addition of anesthetic to the inspired gas and the onset of rebreathing. Final end-tidal concentration of anesthetic refers to the first end-tidal value after the onset of rebreathing. The time constant of decline ( $\tau$ ) was calculated by fitting a monoexponential model ( $y = ae^{-t/\tau}$ ) to the end-tidal concentrations of anesthetic for each volunteer during rebreathing.

\* Significant difference between halothane and sevoflurane protocols ( $P < 0.0001$ , paired Student  $t$  test).

ID = identification; MAC = minimum alveolar concentration.

### Comparison with Existing Literature

The findings of this study are in the line with a number of reports in the literature. Fenlon and Pearce, for example, predicted on the basis of blood and tissue solubility

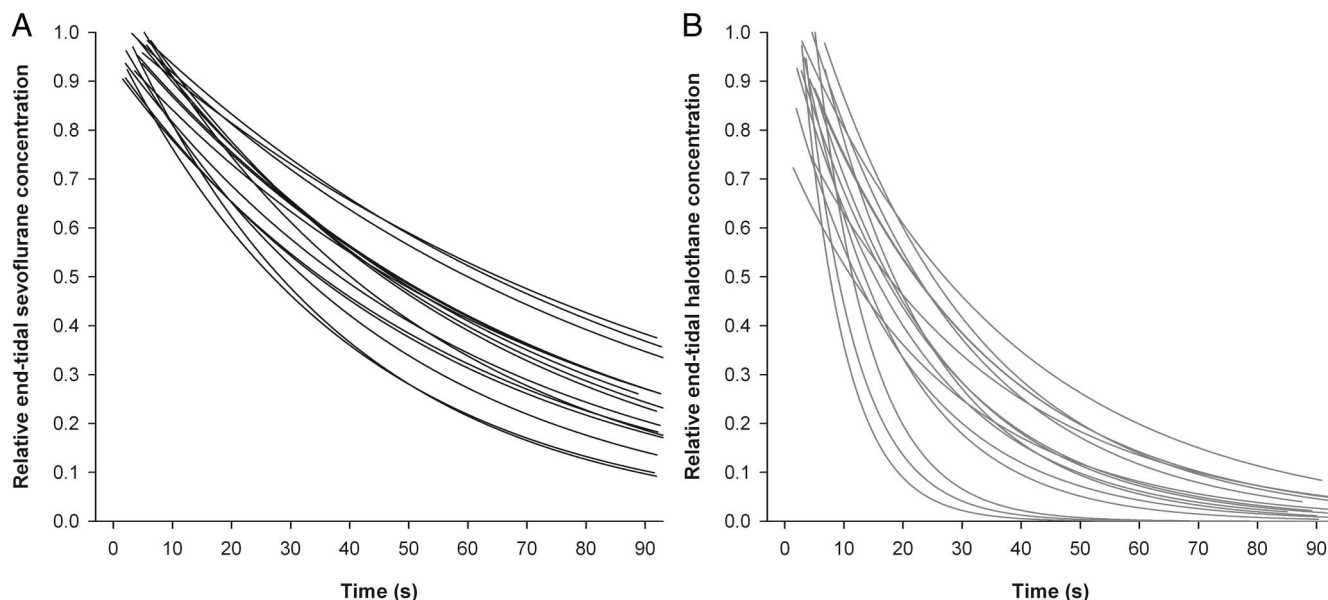


**Fig. 2.** Sample data from two experimental runs in one volunteer (ID number 1641) showing the decline in end-tidal sevoflurane and halothane concentration during 90 s of rebreathing from a 1-l bag. Symbols represent end-tidal sevoflurane (filled symbols) and halothane (open symbols) concentrations. Solid lines show monoexponential model fits ( $y = ae^{-t/\tau}$ ) for each set of data points. For ease of comparison, data are expressed relative to the first end-tidal value recorded during rebreathing.

characteristics that the partial pressure of halothane in the blood would decrease more rapidly than that of sevoflurane during airway obstruction, when the decrease would primarily result from redistribution of the agent from blood to tissues.<sup>11</sup> By using standard blood and tissue solubility data from the literature and a four-compartment mathematical model of the adult human, it can be calculated for a range of anesthetic depths that the partial pressure of halothane would not only decline faster than that of sevoflurane, but that it would also remain lower for at least 5 min after inhalational induction and airway obstruction (data from mathematical modeling provided by Andrew D. Farmery, D.M., F.R.C.A., Oxford, United Kingdom, 2009).

In contrast to these reports, some authors appear to suggest that the lower solubility of sevoflurane may in fact lead to a more rapid decline in arterial partial pressures during airway occlusion, compared with halothane.<sup>1,4</sup> However, although there is considerable experimental and clinical evidence for faster elimination of sevoflurane in the context of a patent airway, when low solubility may enhance elimination *via* the lung,<sup>16,17</sup> the rationale for suggesting a more rapid decline of alveolar sevoflurane concentration during airway obstruction is unclear.

One possibility supported by Girgis *et al.* is that redistribution of anesthetic during airway obstruction is related to the duration of induction.<sup>13</sup> In an experimental study on 40 patients before surgery, in whom anesthesia was initially induced using an intravenous agent, these authors mimicked inhalational induction using either halothane or sevoflurane. The inspired anesthetic con-



**Fig. 3.** Monoexponential model fits ( $y = ae^{-t/\tau}$ ) for the decline in end-tidal sevoflurane (**A**) and halothane (**B**) concentration during rebreathing for all participants. For ease of comparison, data are expressed relative to the first end-tidal value recorded for each individual during rebreathing. Each *line* represents 1 individual experimental run, and each *panel* presents a total of 16 experiment runs composed of 2 runs in each of 8 volunteers. The time constants ( $\tau$ ) for the decline in end-tidal sevoflurane and halothane concentrations were  $62.1 \pm 15.7$  and  $22.1 \pm 8.6$  s, respectively (mean  $\pm$  SD,  $P < 0.0001$ ).

centration was increased by 0.5 MAC every three breaths until an end-tidal concentration of 2 MAC was achieved. This required a mean of 36 breaths for halothane, compared with 27 breaths for sevoflurane. When the airway was subsequently occluded for 3 min and the end-tidal gas sampled immediately thereafter, it was found that the end-tidal sevoflurane concentration was significantly lower than the end-tidal halothane concentration. This result was interpreted as evidence of a more rapid redistribution of sevoflurane than halothane, and the authors suggested that the reason for this difference was the longer duration of induction when using halothane. Given the similar blood-tissue solubility coefficients for halothane and sevoflurane,<sup>8</sup> the longer induction may have allowed the concentration of halothane in body compartments other than brain and blood to rise higher than the corresponding concentrations of sevoflurane. When the airway was then acutely obstructed and the anesthetic redistributed away from the blood to other compartments, the concentration gradient for sevoflurane was suggested to be greater and redistribution more rapid.

Our results appear to contradict this hypothesis directly. In the current study, the time course of the decline in end-tidal halothane concentration was significantly more rapid than that of sevoflurane, despite a substantially longer period of induction. The reasons for this apparent discrepancy are not clear. One possibility relates to the lack of sampling of end-tidal gas by Girgis *et al.* during airway occlusion. It is possible, for example, that a relatively higher washout rate of sevoflurane in the first few breaths after airway restoration could have favored lower end-tidal values for sevoflurane, compared

with halothane, in their study. Alternatively, an early, rapid decline in halothane concentration could have occurred undetected. A second theoretical possibility relates to the hepatic metabolism of halothane. The longer duration of airway occlusion in the study of Girgis *et al.* (180 s), compared with the current study (90 s), would favor greater metabolism of halothane in the former study. In contrast, animal studies suggest that halothane metabolism is concentration-dependent, such that fractional removal of halothane is much greater at subanesthetic concentrations, such as those used in the current study.<sup>18</sup> In fact, we believe that metabolism of halothane is unlikely to contribute significantly to the findings in either study. Using published kinetics for halothane metabolism by human liver microsomes *in vitro*<sup>19</sup> and data relating total microsomal protein content to liver and body size in humans,<sup>20,21</sup> the rate of halothane metabolism *in vivo* can be estimated to be in the range 6–12  $\mu\text{mol/min}$ . At an end-tidal concentration of 0.1 MAC (the value at the onset of rebreathing in the halothane protocol), the blood halothane concentration would be expected to be approximately 70  $\mu\text{M}$  and total blood halothane content 350–420  $\mu\text{mol}$ . Hepatic metabolism would therefore have reduced blood halothane content by significantly less than 5% over the 90 or 180 s of airway occlusion. Sevoflurane is metabolized to a lesser extent than halothane, so metabolism is unlikely to be significant for either agent.<sup>22,23</sup>

#### Limitations of the Experimental Approach

As discussed above, one important interpretation of the findings of the current study is that the higher solu-

bility of halothane, compared with sevoflurane, favors redistribution from the lung to other body compartments during simulated airway occlusion. In turn, this result may be interpreted as evidence in favor of more rapid awakening from a halothane anesthetic, should the airway obstruct during induction. There are, however, a number of assumptions inherent in these interpretations.

First, as discussed above, it is assumed that differences in the metabolic elimination of anesthetic do not contribute to our findings. Second, we assume that the levels of halothane and sevoflurane in the brain closely follow those in the arterial blood and lung. This assumption is commonly made for the steady-state, but it may not be reasonable when anesthetic concentrations are changing. Furthermore, we assume that the rate of equilibration between the blood and brain is similar for the two agents. In support of this assumption, the reported brain-blood partition coefficients for halothane and sevoflurane are very similar<sup>8,24</sup>; in both cases, equilibration would be expected to proceed very rapidly, given the high blood flow to tissue volume ratio in the brain.<sup>8</sup> Finally, our approach was to model the measured decline in end-tidal anesthetic concentration as a monoexponential function of time. Clearly, this is a simplification of the known multicompartment nature of anesthetic distribution. However, although a multiexponential model would be required over a longer time period, we feel that our monoexponential approach provides a valid approximation during the brief 90-s period of rebreathing in this study.

In conclusion, although sevoflurane is reported to have a number of distinct advantages over halothane for inhalational induction of anesthesia, our results suggest that the alveolar partial pressure of halothane may fall more rapidly than that of sevoflurane after acute airway obstruction. Assuming that speed of awakening is proportional to alveolar partial pressure in this setting, the greater blood and tissue solubility of halothane, compared with sevoflurane, may lead to more rapid awakening in the event of airway obstruction during inhalational induction of anesthesia.

The authors thank Simon Goddard, B.Sc., B.M., B.Ch., Frenchay Hospital, Bristol, United Kingdom, for assistance with data analysis; Mr. David O'Connor, Chief Technician, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom, for technical assistance; and all volunteers for their participation.

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