Effect of increased body mass index and anaesthetic duration on recovery of protective airway reflexes after sevoflurane vs desflurane†

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Background. Increased BMI may increase the body's capacity to store potent inhaled anaesthetics, more so with more soluble agents. Accordingly, we asked whether increased BMI and longer anaesthesia prolonged airway reflex recovery.

Methods. We measured time from anaesthetic discontinuation until first response to command (T1); from response to command until ability to swallow (T2); and from anaesthetic discontinuation to recovery of ability to swallow (T3) in 120 patients within three BMI ranges (18–24, 25–29, and ≥30 kg m⁻²). All received sevoflurane or desflurane, delivered via an LMA.

Results. T1 and T3 after sevoflurane exceeded T1 and T3 after desflurane: 6.6 (SD 4.2) vs 4.0 (1.9) min (P<0.001), and 14.1 (± 8.3) vs 6.1 (2.0) min (P<0.001). T3 correlated more strongly with BMI after sevoflurane (28 s per kg m⁻², P=0.02) than desflurane (7 s per kg m⁻², P=0.03). Regarding T2, patients receiving sevoflurane with BMI ≥30 kg m⁻² were less often able to swallow 2 min after response to command than were those with BMI 18–24 or 25–29 kg m⁻² (3/20 vs 10/20 or 9/20, P=0.05). Each sevoflurane MAC-hour delayed T3 by 4.5 min (268 s) (R=0.46, P<0.001) whereas each desflurane MAC-hour delayed T3 by 0.2 min (16 s) (R=0.10, P=0.44).

Conclusions. Prolonged sevoflurane administration and greater BMI delay airway reflex recovery. The contribution of BMI to this delay is more pronounced after sevoflurane than desflurane.

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Volunteers1 and patients2–4 awaken more rapidly after desflurane than sevoflurane anaesthesia, in part at least because of the lesser solubility of desflurane. Does a more rapid awakening translate into greater patient safety, particularly into a faster recovery of protective airway reflexes? At 25% of MACawake, sevoflurane, isoflurane, and propofol significantly decrease the coordination of pharyngeal muscles,5 and patients anaesthetized with desflurane recover protective airway reflexes faster than those anaesthetized with sevoflurane.6

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*Declaration of interest. R.E.M. has received research support in the past from Baxter Healthcare for other studies, but did not receive support for this study. She has also received honoraria for speaking from Baxter Healthcare. Baxter manufactures sevoflurane and desflurane. R.E.M. is a member of the Speakers Bureau for Baxter Healthcare, manufacturer of sevoflurane and desflurane. In addition, Baxter Healthcare has provided research support to the University of California for some of R.E.M.’s investigator-initiated projects in the past.
Might body habitus affect recovery? Large differences in body mass (e.g., 350 g rats vs. a 6300 kg whale) correlate with rate of anaesthetic uptake, and obesity modestly increases uptake of isoflurane—but does not appear to concurrently slow rate of recovery.

The faster awakening from sevoflurane than isoflurane, and from desflurane than sevoflurane, reflects progressively smaller blood and tissue solubilities. Lean tissues, such as the vessel-rich group (heart, kidney, and viscera), and muscles receive most of the cardiac output, but have much smaller affinities for anaesthetics than does fat; thus anaesthetic equilibration with these tissues, respectively, takes minutes vs. hours. Both high anaesthetic capacity and low blood flow prolong time to equilibration of potent inhaled anaesthetics with the bulk fat compartment, and result in relatively low partial pressures of anaesthetic in that tissue. Anaesthetic partial pressure in bulk fat increases so slowly that bulk fat continues to take up anaesthetic after administration has been discontinued, and this process could accelerate recovery.

As opposed to bulk fat, fat immediately adjacent to viscera (e.g., omental and perirenal fat) and muscle (dermis and s.c. fat) may take up anaesthetic by intertissue diffusion, possibly accounting for 30% of anaesthetic uptake. In contrast to bulk fat, anaesthetic content in fat receiving anaesthetic by intertissue diffusion is much greater and may release anaesthetic earlier in recovery. Sevoflurane fat/gas and muscle/gas partition coefficients are 2.8 and 2.2 times greater than those of desflurane, suggesting greater distribution of sevoflurane vs. desflurane to fat. Furthermore, if an increased BMI increases the interface area between fatty tissues, viscera and muscle, an increased BMI might delay awakening and recovery of protective reflexes more after anaesthesia with sevoflurane compared with desflurane. Accordingly, we hypothesized that overweight (BMI ≥ 30 kg/m²) and obese (BMI ≥ 30) patients would (i) respond to command and experience recovery of protective airway reflexes more slowly after anaesthesia, and that (ii) this relationship would be more pronounced after sevoflurane, given its greater fat solubility, than after desflurane. We also postulated that increasing duration of anaesthesia would delay recovery of protective reflexes less after anaesthesia with desflurane.

Methods

With approval from the University of California Committee on Human Research, we recruited patients aged 18–75, in BMI ranges 18–24, 25–29, and ≥30 kg/m², undergoing surgery for which an LMA was the planned method of airway management, and randomly assigned these patients to receive sevoflurane or desflurane. Any patient with a history of neuromuscular disorder, stroke, dysphagia, dysphonia, impaired gastric emptying, or previous pharyngeal or upper gastrointestinal surgery or radiation was excluded. We determined that all could swallow 20 ml of water in an upright position. We judged swallowing to be adequate if no coughing or drooling occurred after the water passed into the mouth, and no water remained in the oropharynx upon subsequent visual inspection. Anaesthesia consisted of premedication with midazolam 2 mg, induction with lidocaine (0–1.5 mg kg⁻¹) and propofol (1–3 mg kg⁻¹), fentanyl as necessary, and maintenance of anaesthesia with sevoflurane or desflurane (randomly assigned) at a concentration judged to be appropriate by the clinician in oxygen 50% and nitrous oxide 50%. Neuramucosal blocking agent was avoided in all cases. Standard anti-emetic prophylaxis consisted of dexamethasone 4 mg, administered at induction, and ondansetron 4 mg, administered 15–45 min before the end of surgery.

An observer, blinded to anaesthetic assignment, noted the time from discontinuation of anaesthetic administration until the patient’s first appropriate response to commands ‘open your eyes’ and ‘squeeze my hand’. At 2, 6, 14, 22, and 30 min after first response to either command, the patient was placed in a 60° upright position and asked to swallow 20 ml of water. Swallowing was judged successful as described above.

Outcomes measured were: (i) time from anaesthetic discontinuation until first response to command (T1; recovery of consciousness); (ii) time from first response to command until first demonstrated ability to swallow (T2); and (iii) time from anaesthetic discontinuation until first demonstrated ability to swallow (T3).

Analysis of T1, T2, and T3 vs BMI and maintenance anaesthetic was conducted both separately and together in a multivariate analysis. Post hoc analyses were performed to distinguish whether lean body mass (calculated from a previously validated formula, noted in the Appendix) duration of anaesthesia (MAC-hours), age, or fentanyl administration contributed independently to pharyngeal recovery.

Regarding the impact of increasing fat, we also considered two opposing kinetic effects. As bulk fat and BMI increase, the area of interface between lean tissue and bulk fat increases, providing greater surface area for uptake of anaesthetic by intertissue diffusion, an effect that would be expected to delay recovery. On the other hand, the surface to volume ratio of bulk fat decreases with increasing volume, and bulk fat equilibrates very slowly and should continue to absorb anaesthetic well into the recovery period. Thus, the effect of increased interface surface of fat, while important, may asymptotically reach a limit. In contrast to fat served by intertissue diffusion, bulk fat itself might be expected to accelerate recovery, particularly during the time immediately after discontinuation of anaesthetic administration. Thus, beyond some point, further increase in BMI might actually counteract the kinetic effect of intertissue diffusion on recovery. Accordingly, we performed post hoc analysis to assess...
whether a stronger correlation between delayed recovery and BMI exists within a more restricted BMI range.

Statistical analysis

On the basis of previous recovery data, we calculated that a sample size of 120 (60 receiving sevoflurane and 60 receiving desflurane), with BMI ranging from 21 to 37, would produce an 80% chance of detecting a difference in slope of 13.4 s in awakening time vs BMI (kg m⁻²) for sevoflurane compared with desflurane.

Comparison of categorical outcomes was made by χ² analysis with Yates’ correction where indicated. Comparison of continuous variables was made by t-test, ANOVA, or linear regression. Statistical analysis was performed using STATA version 9.2 (College Station, TX, USA).

Results

Patient characteristics

Age, per cent females, MAC-hours, and administered dose of fentanyl in patients anaesthetized with sevoflurane vs desflurane in BMI ranges 18–24, 25–29, and ≥30 are shown (Table 1). The average BMI value was 27.4 with a standard deviation of 5.1. Two patients (one receiving sevoflurane and the other desflurane) were excluded from linear regression analysis on the basis of outlying BMI values (52 and 64 kg m⁻², respectively, both more than 3 SD above the mean), although they were included in the other analyses. The BMI of the 118 subjects in the linear regression analysis ranged from 18.3 to 40.2 kg m⁻².

Recovery of consciousness

Time from anaesthetic discontinuation until first ability to swallow (T3) was shorter among patients receiving desflurane than those receiving sevoflurane [4.0 (SD 1.9) vs 6.6 (4.2) min, P<0.001]. T1 correlated significantly (linear regression) with lean body mass but not with BMI (Table 2).

Recovery of airway reflexes in the overall population and in patients given sevoflurane vs desflurane

Time from discontinuation of anaesthetic until first ability to swallow (T3) was shorter and more predictable among patients receiving desflurane compared with sevoflurane [6.1 (SD 2.0) vs 14.1 (8.3) min, P<0.001, Table 2].

In the combined (all patients) population, T3 correlated directly with increasing BMI [0.34 min (20 s) per kg m⁻²; R=0.24, P=0.01, linear regression]. Anaesthetic choice influenced this correlation. The slope for the correlation between T3 vs BMI was greater after sevoflurane anaesthesia [0.47 min (28 s) per kg m⁻²; R=0.30, P=0.02] than after desflurane [0.12 min (7 s) per kg m⁻²; R=0.28, P=0.03, linear regression, Fig. 1A]. The difference between these slopes did not reach statistical significance (ANOVA P=0.09). A longer time from anaesthetic

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics of populations, by BMI category. *P&lt;0.05, BMI ≥30 vs 18–24 kg m⁻²; **P&lt;0.01, sevoflurane vs desflurane</th>
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<tr>
<td>BMI range (kg m⁻²)</td>
<td>18–24</td>
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<tr>
<td>Number of subjects</td>
<td>Sevoflurane</td>
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<tr>
<td>Age</td>
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<tr>
<td>Sevoflurane</td>
<td>41 (13)</td>
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<td>Desflurane</td>
<td>39 (8)</td>
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<td>Female [n (%)]</td>
<td>Sevoflurane</td>
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<td>Desflurane</td>
<td>14 (70)</td>
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<tr>
<td>MAC-hours</td>
<td>Sevoflurane</td>
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<td>Desflurane</td>
<td>0.9 (0.7)</td>
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<td>Fentanyl (µg)</td>
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<td>Desflurane</td>
<td>127 (97)</td>
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<tr>
<td>Anaesthetic discontinuation to response to command (T1, min)</td>
<td>Sevoflurane</td>
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<tr>
<td>Desflurane</td>
<td>3.2 (1.6)</td>
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<tr>
<td>Anaesthetic discontinuation to first ability to swallow (T3, min)</td>
<td>Sevoflurane</td>
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<tr>
<td>Desflurane</td>
<td>5.2 (1.6)</td>
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<tr>
<td>Time after first response to command</td>
<td>Number of subjects able to swallow without coughing or drooling</td>
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<td>2 min</td>
<td>Sevoflurane</td>
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<td>Desflurane</td>
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<td>14 min</td>
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<td>22 min</td>
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<td>30 min</td>
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<td>Desflurane</td>
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Table 2 | Linear regression analysis was performed on recovery endpoints [anaesthetic discontinuation until first response to command (response to command, T1) and time from anaesthetic discontinuation until first ability to swallow (airway reflex recovery, T3)] vs BMI and lean body mass |
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<td>Endpoint</td>
<td>Population</td>
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<tr>
<td>Response to command (T1)</td>
<td>Sevoflurane</td>
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<td>Desflurane</td>
<td>5.23</td>
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<tr>
<td>Airway reflex recovery (T3)</td>
<td>Sevoflurane</td>
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<td>Desflurane</td>
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discontinuation to first response to command correlated with lean body mass but not BMI by linear regression (Table 2). Delay in T3 correlated (linear regression) with estimated lean body mass by 1.8 min per 10 kg after sevoflurane ($R^2 = 0.30$, $P = 0.02$) and 0.4 min per 10 kg after desflurane ($R^2 = 0.20$, $P = 0.06$).

Recovery of airway reflexes may be defined as the time from response to command (rather than time from discontinuation of anaesthetic administration) until recovery of ability to swallow (T2). This has the advantage of starting from the same level of behavioural recovery (awareness) with both inhaled anaesthetics. T2 showed virtually no variability among patients receiving desflurane; 59 of 60 subjects swallowed successfully at the earliest test interval (2 min), and all were able to do so at the second interval (6 min). In contrast, only 22 of 60 patients receiving sevoflurane could swallow without coughing or drooling at the 2 min test interval, 44 of 60 at the 6 min interval, and 56 of 60 at the 14 min interval (Fig. 2). Patients receiving sevoflurane with BMI $>30$ kg m$^{-2}$ were less likely to
swallow 2 min after following command than those subjects with BMI < 30 kg m\(^{-2}\); by 6 min, this relationship failed to show statistical significance (Table 1, Fig. 2). Two subjects receiving sevoflurane did not swallow adequately at any of the test intervals, still coughing or drooling 30 min after response to command.

**Exploratory post hoc analysis of factors influencing recovery of airway reflexes**

A multivariate post hoc analysis examined the influence of other factors on time to recovery of airway reflexes. The strongest factor influencing time from discontinuation of anaesthetic administration until return of ability to swallow water (T3) was the choice of anaesthetic (sevoflurane vs desflurane). Duration of anaesthesia (MAC-hours) was the next important factor but was influenced, in turn, by anaesthetic choice: for sevoflurane T3 increased by 4.47 min (268 s) per MAC-hour (\(R=0.46, P<0.001\)); in contrast, T3 did not correlate significantly with MAC-hours desflurane [0.25 min (16 s) per MAC-hour, \(R=0.10, P=0.44\), Fig. 3]. A smaller factor was patient age, with an increase of 1.7 min per decade after sevoflurane (\(P=0.018\)) and 0.6 min per decade after desflurane (\(P=0.001\)). Opioid administration did not significantly correlate with T2 or T3, in uni- or multivariate analysis.

**Exploratory post hoc analysis of a restricted BMI group**

In consideration of the expected opposing kinetic effects of increased lean surface interface with fat vs increased bulk fat, we assessed whether the delay in airway reflex recovery associated with greater BMI reached a ceiling at some large BMI. Post hoc examination of our data suggested this might occur at BMI exceeding 35 kg m\(^{-2}\). Accordingly, we performed post hoc analyses confined to BMI values of 35 or less, finding, as anticipated, significant differences between sevoflurane and desflurane anesthetized patients that were more clear-cut than the entire data set (i.e. containing BMI values >35) suggested (Fig. 1b). The T3 coefficients in this restricted group (\(n=109\)) were 0.76 min (46 s) per kg m\(^{-2}\) vs 0.47 min (28 s) per kg m\(^{-2}\) in the unrestricted group among patients receiving sevoflurane, and 0.10 min (6 s) vs 0.12 min (7 s) in the unrestricted group after desflurane. Therefore, these T3 coefficients among the restricted population were greater among patients receiving sevoflurane, and the slopes differed significantly (and to a greater extent than in the unrestricted population) between patients receiving sevoflurane vs desflurane (ANOVA \(P=0.01\)) (Table 3).

**Discussion**

Overall times from response to command (T2) or discontinuation of anaesthetic administration until airway reflex recovery (T3) both correlated significantly with increased BMI. Consistent with previous findings, those time intervals were significantly longer after sevoflurane than desflurane anaesthesia.\(^1\)\(^-\)\(^4\)

The anaesthetic chosen (sevoflurane vs desflurane) and MAC-hours of sevoflurane contributed most to delayed airway reflex recovery (T3), with lesser contributions of BMI and patient age. Airway reflex recovery correlated with BMI more strongly after sevoflurane compared with desflurane anaesthesia, possibly because of sevoflurane’s greater solubility in fat, particularly fat immediately adjacent to

**Fig 2** Airway reflex recovery was significantly less predictable after sevoflurane compared with desflurane until 14 min after response to command (**\(P<0.00001\) at 2 min; *\(P=0.0005\) at 6 min). After desflurane, airway reflex recovery was complete in 39 of 60 subjects by 2 min after following commands, and in all subjects at subsequent test periods. After sevoflurane, patients with BMI >30 kg m\(^{-2}\) were less likely able to swallow 2 min after following command compared with those with BMI 18–29 kg m\(^{-2}\) (\(P<0.05\)).
lean tissue. Our findings support the hypothesis that both blood flow and intertissue diffusion determine anaesthetic transferred to and from fat, even during anaesthetics lasting less than hours. Recovery of protective airway reflexes differs between sevoflurane and desflurane more than their blood/gas and tissue/blood solubilities alone would suggest: the slope for time to airway reflex recovery (T3) vs BMI for sevoflurane is four-fold larger than that of desflurane, a ratio more closely approximating their respective fat/gas than lean tissue/gas partition coefficients.

Ability to swallow at standard time intervals following response to command (T2) was more variable and delayed after sevoflurane in patients with increased BMI. In contrast, ability to swallow was consistently successful after desflurane, and therefore no relationship between T2 and BMI could be established.

Although our data suggest that increasing BMI delayed recovery of airway reflexes, particularly after sevoflurane (Fig. 1), delayed time from anaesthetic discontinuation until first response to command (T1) correlated more strongly with lean body mass (Table 2), specifically with sevoflurane but not desflurane (multivariate analysis not shown). These results support the finding by Wahrenbrock that the rate of increase (and presumably, the rate of decrease) of alveolar anaesthetic concentration, is inversely related to body size. The rationale behind this finding is that metabolism, ventilation, and perfusion per kilogram decrease with increasing body size. If heavier individuals have smaller perfusion per kilogram, their tissues should have longer time constants.

Our data suggest that increased BMI prolongs recovery of protective airway reflexes after administration of anaesthetic, and that this relationship is more pronounced after sevoflurane than desflurane anaesthesia. That is, small MAC fractions of anaesthetic can impair vital protective functions during early recovery, even in seemingly awake patients, and thus such patients can be vulnerable to airway obstruction or aspiration. Obesity compounds this problem. Patients with BMI >30 kg m⁻² are at a two- to three-fold greater risk of critical respiratory events (airway obstruction, hypventilation, and desaturation) during early recovery from anaesthesia compared with non-obese patients. Small MAC fractions of anaesthetic may add to these respiratory events by blunting hypoxic ventilatory responses, and such an effect has greater consequences for overweight and obese patients.
Our study has several limitations. First, our population was relatively healthy, had short to moderate length surgery, and was managed without tracheal intubation, neuromuscular blocking agent, or high-dose opioid, hindering generalization of our findings to a more complex surgical population. We would speculate, however, that airway reflex recovery and BMI might correlate more strongly in intubated patients undergoing major surgery requiring longer anaesthesia because these factors themselves are associated with untoward respiratory effects.21 22

Secondly, opioid administration failed to correlate with airway reflex recovery, contradicting evidence suggesting an association between opioid use and pharyngeal dys-function.23 Possible explanations for our negative finding are the relatively modest doses given to these patients (all breathed spontaneously during surgery), and the overshadowing contributions of MAC-hours of sevoflurane, BMI, and age.

Thirdly, possibly presence of the LMA may have impaired sensory input needed for initiation of swallowing efforts. It is unclear why that effect would preferentially influence patients as a function of BMI or chosen anaesthetic.24

Fourthly, possibly a lingering effect of anaesthetics (opioid, inhaled agents) contributed to suppression of cough, thereby making the swallowing test less sensitive than other established tests of pharyngeal function. However, this is an unlikely explanation, since previous investigations indicate that most intubated patients awakening from isoflurane begin to cough at concentrations of 0.5 MAC or greater, suggesting that inhaled anaesthetics in low concentration do not effectively obtund the cough reflex.25

Finally, our water swallowing test provides a yes–no result rather than quantitative (graded) data. And, although there is no visual confirmation of the misdirected bolus into the laryngeal inlet, water-swallowing tests correlate strongly with aspiration as confirmed by imaging.26 27

In summary, the overweight patient, with higher risk and poorer tolerance for postoperative physiological insults such as hypoventilation, airway obstruction, and aspiration, is likely to experience slower recovery of protective physiological function after sevoflurane compared with desflurane anaesthesia. And increasing duration of anaesthesia, again especially after sevoflurane, may further slow such recovery. Finally, patients who require either neuromuscular blocking drugs or tracheal intubation may be at still greater risk, since both of these interventions contribute independently to pharyngeal dysfunction and morbidity.21 22

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Appendix

### Lean body mass calculation

**Male:** \[\frac{9.27 \times 10^3 \times \text{body weight (kg)}}{6.68 \times 10^3 + 216 \times \text{BMI (kg m}^{-2}\text{)}}\]

**Female:** \[\frac{9.27 \times 10^3 \times \text{body weight (kg)}}{8.78 \times 10^3 + 244 \times \text{BMI (kg m}^{-2}\text{)}}\]

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