

Increased lung clearance of isoflurane shortens emergence in obesity: a prospective randomized-controlled trial

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Background: There is a concern that obesity may play a role in prolonging emergence from fat-soluble inhalational anaesthetics. We hypothesized that increased pulmonary clearance of isoflurane will shorten immediate recovery from anaesthesia and post-anaesthesia care unit (PACU) stay in obese patients.

Methods: After Ethics Review Board approval, 44 ASA I–III patients with BMI > 30 kg/m² undergoing elective gynaecological or urological surgery were randomized after completion of surgery to either an isocapnic hyperpnoea (IH) or a conventional recovery (C) group. The anaesthesia protocol included propofol, fentanyl, morphine, rocuronium and isoflurane in air/O₂. Groups were compared using unpaired *t*-test and ANOVA.

Results: Minute ventilation in the IH group before extubation was 22.6 ± 2.7 vs. 6.3 ± 1.81/min in the C group. Compared

with C, the IH group had a shorter time to extubation (5.4 ± 2.7 vs. 15.8 ± 2.7 min, *P* < 0.01), initiation of spontaneous ventilation (2.7 ± 2.3 vs. 6.5 ± 4.5 min, *P* < 0.01), BIS recovery > 75 (3.2 ± 2.3 vs. 8.9 ± 5.8 min, *P* < 0.01), eye opening (4.6 ± 2.9 vs. 13.6 ± 7.1 min, *P* < 0.01) and eligibility for leaving the operating room (7.1 ± 2.9 vs. 19.9 ± 11.9 min, *P* < 0.01). There was no difference in time for eligibility for PACU discharge.

Conclusion: Increasing alveolar ventilation enhances anaesthetic elimination and accelerates short-term recovery in obese patients.

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OBESITY (BMI 30–35 kg/m²) presents specific related challenges in providing secure airway access¹ and adequate ventilation during surgery and weaning. The patient's ventilatory vulnerability is also increased during emergence. The safest approach is to promote a rapid restoration of consciousness and ventilatory self-sufficiency.² Traditionally, anaesthetics with low blood/gas solubility^{3–5} have been preferred for their greater pulmonary clearance for a given minute ventilation. Alveolar ventilation, has also been shown to be an independent determinant of anaesthetic clearance^{6–8} but its efficacy in obesity is unknown.

We hypothesized that in obese patients, increases in pulmonary clearance of isoflurane would accelerate the short-term recovery from anaesthesia such as time to extubation. As the initial phase of gas elimination accounts for the greater part of the reduction in body content of the anaesthetic,⁹ we also hypothesized that the early greater anaesthetic clearance would reduce the time from the end of anaesthesia (turning isoflurane vaporizer

off) to the readiness for post-anaesthesia care unit (PACU) discharge.

Methods

This is a prospective randomized-controlled trial that was registered at ClinicalTrials.gov on 22 July 2008 (the clinical Trials.gov Identifier is NCT00752492). After Institutional Ethics Review Board approval, recruitment was started in August 2008 and finished in May 2010. Figure 1 depicts the study flow diagram. Signed informed consent was obtained from 44 ASA I–III patients with BMI > 30 kg/m² undergoing elective gynaecological or urological surgery. Exclusion criteria were contra-indications to any part of the study anaesthetic protocol, a history of coronary artery disease, pulmonary hypertension, chronic obstructive lung disease, New York Heart Association class > 3, alcohol consumption of more than two standard drinks a day, a history of psychiatric illness such as dementia, schizophrenia and bipolar

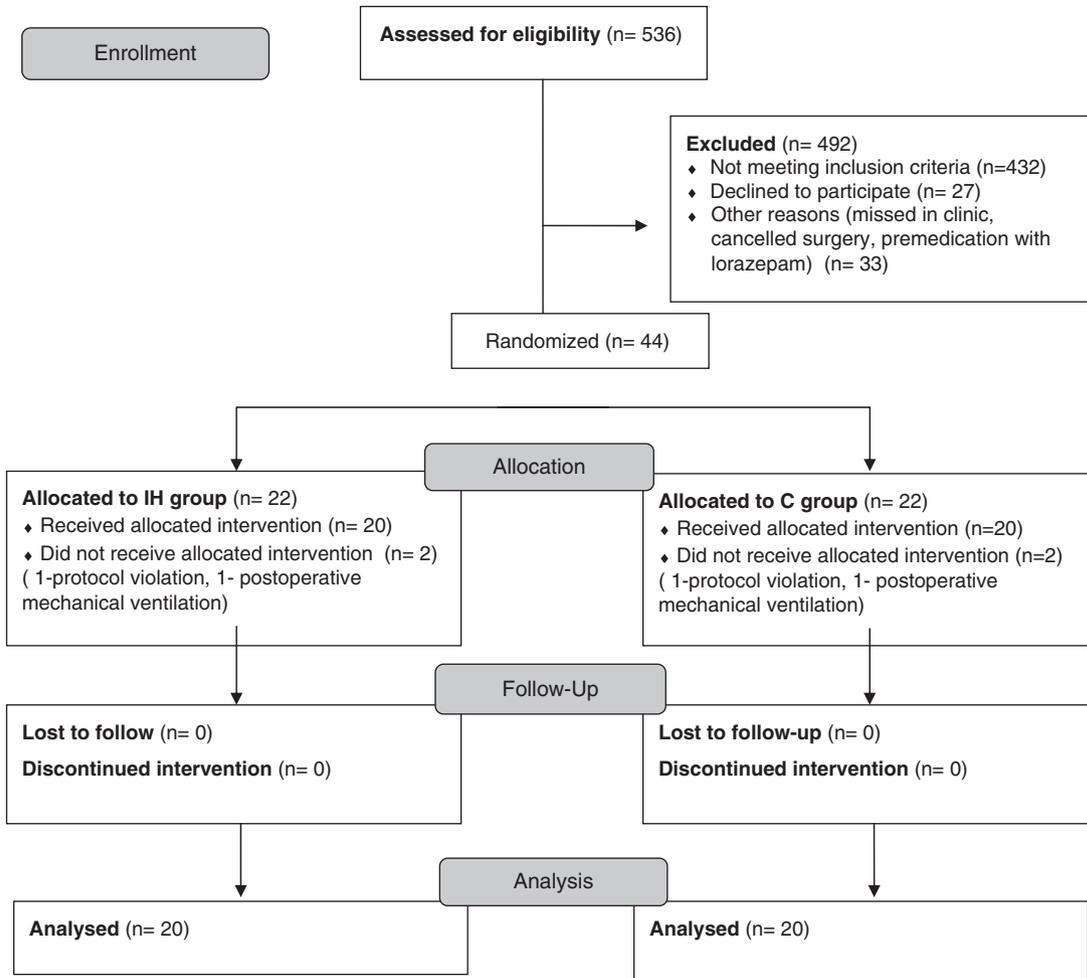


Fig.1. Protocol flow diagram.

disorder, and daily consumption of benzodiazepines, opiate narcotics or other psychoactive drugs.

Patients arrived in the operating room without premedication with sedatives. Standard operating room monitors consisting of 5-lead ECG, a blood pressure cuff and a pulse oximeter were applied, as well as BIS (Aspect Medical Systems, Newton, MA). Additional monitors during maintenance included spirometry, oesophageal temperature, end-tidal and inspired gas and anaesthetic vapour concentrations, tidal volume, airway pressures (Datex A/S 3, GE Healthcare, Madison, Wisconsin, USA) and a peripheral nerve stimulator. Data from the Datex AS/3 were digitalized at 60 Hz using a DI-720 analog-to-digital converter (Dataq, Akron, OH) and recorded continuously.

After pre-oxygenation, anaesthesia was induced with propofol 2–3 mg/kg, fentanyl 1–2 µg/kg and rocuronium 0.6–0.8 mg/kg. All drug doses and ventilation regimens were calculated based on the estimation of the ideal body weight.¹⁰ After

endotracheal intubation, patients’ lungs were ventilated via a circle anaesthetic circuit with a CO₂ absorber at initial settings of tidal volume 7 ml/kg ideal weight, respiratory rate 10 and PEEP 5 cmH₂O. Ventilator settings (AS-3 Datex, GE Healthcare) and fresh gas flows were adjusted to maintain end-tidal PCO₂ (PETCO₂) values at 40 ± 3 mmHg and SaO₂ >97%. Fresh gas flow consisted of a mixture of air and O₂ at <21/min during maintenance. The end-tidal isoflurane concentration was maintained above 0.7 MAC and titrated according to clinical signs of depth of anaesthesia and to maintain BIS values in the range of 40–50. Supplemental doses of fentanyl (50–100 µg) and morphine ((2–4 mg) were administered as clinically indicated. Supplemental doses of rocuronium (20–30 mg) were added if the train-of-four stimulation demonstrated two or more visible twitches or as required to provide for adequate surgical relaxation. Fifteen minutes before the anticipated end of surgery, the isoflurane

concentration was adjusted to maintain BIS values in the range 55–60. Patients were randomly allocated to either an isocapnic hyperpnoea (IH) or a Control (C) group according to a computer-generated randomization code in predetermined size blocks of four. The randomization sequence was prepared and kept by a research coordinator. A sealed envelope containing the designation of the cohort was released to the anaesthesiologist in the OR during the skin closure. After the last stitch, train-of-four stimulation was performed and in the presence of at least one visible twitch the residual neuro-muscular block was reversed by administering neostigmine in doses up to 0.05 mg/kg and glycopyrrolate 0.01 mg/kg lean body weight. Then, the isoflurane vaporizer was turned off.

In the C group, air flow was turned off and the O₂ flow was set at 15 l/min to prevent any rebreathing of anaesthetic vapour. Ventilatory assistance was provided intermittently to maintain SaO₂ > 97% and PETCO₂ at 40–50 mmHg to hasten the return of spontaneous ventilation. Patients randomized to the IH group were disconnected from the circle circuit and connected to the self-inflating bag attached to the IH system^{7,11} (Clear-Mate™, Thornhill Research Inc., Toronto, ON, Canada). Ventilation was assisted to maintain a tidal volume of 8–10 ml/kg and a respiratory rate of 20–25 breaths/min, with minute ventilation of 15–20 l/min. PETCO₂ was maintained in the range of 40–50 mmHg by adjusting the O₂ flow to the self-inflating bag. The minimum criteria for extubation for both groups was spontaneous ventilation with tidal volumes of 6–7 ml/kg of lean body weight, following commands and ability to lift the head off the pillow. The following OR events were recorded: duration of anaesthesia (beginning of induction to turning off the vaporizer), duration of surgery (skin incision to skin closure), time of resumption of spontaneous ventilation, arousal (opening eyes in response to verbal command), BIS value exceeding 75, extubation, time to fulfilment of criteria for leaving the OR (stable vital signs, adequate ventilation and following simple commands) and time to eligibility for PACU discharge.

On arrival in the PACU, the patients were placed in a semi-recumbent position with the back of the stretcher tilted at 30°. O₂ was administered via a face mask at 6 l/min. Post-operative analgesia was provided in the same manner in both groups of patients, according to standard practice: ketorolac 15–30 mg i.v., morphine 2 mg i.v. or fentanyl 50–100 mcg i.v. q 5 min prn for breakthrough

pain. Patient-controlled analgesia was used if clinically indicated. Patients were assessed at 10-min intervals during the first hour after PACU admission by the PACU nurse who was blinded to the patient's group allocation. This assessment included a Richmond Agitation Sedation Score,¹² a pain score from a standardized 10 cm visual analogue score (0 – no pain, 10 – worst, unbearable pain) and Aldrete score¹³ (assessing activity, consciousness and vital signs). Patients were considered ready for discharge when the Aldrete score was 10 and the pain score was < 5.

Any occurrences of nausea and vomiting, shivering or respiratory complications, and unexpected prolonged PACU stay were documented. All time intervals were measured from the end of anaesthesia defined as a turning isoflurane vaporizer off till the event.

Data analysis

Continuous measures were compared through a series of independent-samples *t*-test. Categorical measures were tested through chi-square tests. Any tests resulting in a *P*-value of < 0.05 were considered statistically significant at an α -level of 0.05. Categorical values are presented as *N* (%), while continuous measures are summarized as the mean \pm SD unless otherwise specified. A series of non-parametric Mann–Whitney *U*-test was performed to determine whether pain/sedation/Aldrete scores differed significantly between the groups.

Power analysis

In a previous study,⁷ IH reduced the time from the end of anaesthesia until readiness for discharge from PACU by 20 \pm 19 min. With β set at 0.2 (power = 0.8) and α = 0.05, 20 patients in each group were sufficient to test this hypothesis. Therefore, considering an attrition rate of 10%, we proposed to test a total of 44 patients.

Results

Comparison of the primary endpoint

The patients in the IH group had significantly shorter times to initiation of spontaneous breathing, eye opening, extubation and readiness to leave OR (Table 1). Five patients (two in IH group and three in the C group) demonstrated a decrease in the level of consciousness after extubation. Three of these patients (one in the IH group and two in the

Table 1

Immediate and intermediate outcome parameters of obese patients undergoing gynaecological and urological surgery.

Outcome in minutes from turning off vaporizer to	IH (N= 20)	Control (N= 20)	P-value
Initiation of spontaneous ventilation	2.7 ± 2.3	6.5 ± 4.5	0.002
BIS > 75	3.2 ± 2.3	8.9 ± 5.8	<0.01
Eyes opening	4.6 ± 2.9	13.6 ± 7.1	<0.01
Extubation	5.4 ± 2.7	15.8 ± 8.7	<0.01
Eligibility to leave OR	7.1 ± 2.9	19.9 ± 11.9	<0.01
First pain medication in the PACU	38.5 ± 14.2	48.9 ± 24.5	0.15
Eligibility for discharge from PACU	91.9 ± 16.5	107.8 ± 40.9	0.15
Re-hypnotization after extubation, n (%)	2 (10%)	3 (15%)	1.0
Incidence of nausea or vomiting, n (%)	3 (15%)	1 (5%)	0.34
Incidence of shivering, n (%)	1 (5%)	1 (5%)	1
Incidence of postoperative hypoxaemia, n (%)	0	1 (5%)	1.0

IH, isocapnic hyperpnoea; PACU, post-anaesthesia care unit.

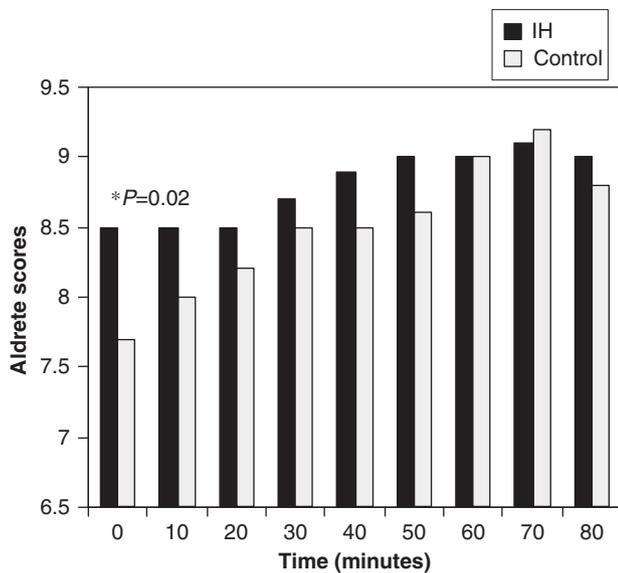


Fig. 2. Aldrete Scores in post-anaesthesia care unit (PACU).

C group) required the insertion of an oral airway to maintain upper airway patency. One patient (in the C group) had to be re-intubated in the OR.

On arrival in the PACU, patients in the IH group had higher Aldrete scores than the patients in the C group (Fig. 2). Otherwise, there were no clinically significant differences between the groups in readiness to discharge to the floor and incidences of nausea, vomiting and shivering (Table 1). The total post-operative administered dose of analgesic and antiemetic medications in the PACU and the average RASS and pain scores were similar.

Comparison of experimental conditions between groups

Twenty-two patients were randomized to each group. Four patients (two in each group) were

Table 2

Demographic and surgical characteristics of obese patients undergoing gynaecological and urological surgery.

Characteristic	IH (n= 20)	Control (n= 20)
Age (years)	55.6 ± 7.7	58.5 ± 9.8
Males/female	7/13	10/10
BMI (kg/m ²)	35.1 ± 3.3	36.7 ± 8.9
Laparotomy/laparoscopy	6/14	5/17
Length of surgery (min)	182.5 ± 52.4	162.1 ± 65.4
Duration of anaesthesia (min)	210.7 ± 52.8	192.9 ± 64.0

IH, isocapnic hyperpnoea.

excluded from the analysis: one patient in each arm of the study underwent elective post-operative mechanical ventilation because of the extent of the surgical procedure. Two other patients were excluded due to protocol violation: one patient in the C group received midazolam intraoperatively and one patient in the IH group received propofol in the last 10 min before the skin closure. Data from the remaining 40 patients (20 in each group) were analysed. The demographic and surgical characteristics are presented in Table 2. Anaesthetic management was comparable in the two groups (Table 3). Minute ventilation in the IH group before extubation was 22.6 ± 2.7 vs. 6.3 ± 1.8 l/min in the C group but there were no differences in exhaled isoflurane concentration [0.08 ± 0.08% (IH) vs. 0.13 ± 0.1% (C), P = 0.17] or PETCO₂s [43 ± 4.2 mmHg (IH) vs. 40.4 ± 4.5 mmHg (C), P = 0.07] immediately before extubation. All patients in the IH group tolerated IH without haemodynamic or respiratory instability.

Discussion

Traditionally, the differences in pulmonary clearance of anaesthetics are attributed to the effect of

Table 3

Intra-operative medications administered to obese patients undergoing gynaecological and urological surgery.			
Medication	IH (N=20)	Control (N=20)	P-value*
Propofol (mg) (median, min, max)	200.0 (150.0, 400.0)	250.0 (140.0, 400.0)	0.67
Fentanyl (µg) (median, min, max)	250.0 (150.0, 500.0)	250.0 (125.0, 550.0)	0.89
Rocuronium (mg) (median, min, max)	110.0 (50.0, 250.0)	95.0 (60.0, 280.0)	0.09
Ketorolac (mg) (median, min, max)	0.0 (0.0, 30.0)	0.0 (0.0, 30.0)	0.94
Morphine (mg) (median, min, max)	5.5 (2.0, 7.0)	4.5 (2.0, 6.0)	0.34
Granisetron (mg) (median, min, max)	1.0 (0, 1.0)	1.0 (0, 1.0)	0.97
Isoflurane (MAC-h) [†]	3.2 ± 0.9	2.9 ± 1.1	0.09

*Because of the distributional properties of the data, Mann–Whitney *U*-test were used instead of *t*-test for these group comparisons.

[†]MAC-h (MAC-hour) was calculated as average MAC × length of exposure.

IH, isocapnic hypernoea.

blood-gas solubility (λ).¹⁴ However, review of the determinants of fractional clearance of anaesthesia (*F*) [Equation (1)] indicates that in addition to cardiac output (\dot{Q}), alveolar ventilation ($\dot{V}A$) also affects anaesthetic clearance:

$$F = 100\% \frac{1}{1 + \lambda(\dot{Q} + \dot{V}A)} \quad (1)$$

In this study, we found that for isoflurane, increasing *F* alone via IH markedly shortened the time to extubation (as a milestone recovery) in obese patients by two-thirds (5.4 vs. 15.8 min). Whereas the time to extubation in the control cohort was similar to those previously reported in obese subjects anaesthetized with isoflurane (14,⁵ 27³ and 12.2 min²), IH shortened the time to extubation to that in obese patients anaesthetized with desflurane (6.7¹⁵ and 5.6 min²), as predicted previously.⁷ The time to extubation with IH in this study was also similar to that in our previous study where IH was applied after isoflurane anaesthesia in non-obese patients (6.6 min⁸).

On arrival to the PACU, patients who had received IH had more stable airway control and were more responsive as measured by the Aldrete scores, compared with patients in the control group. However, contrary to our hypothesis, there was no difference between the groups in any of the outcome measures. The anaesthesia duration in our study was 2–3 h. Although after 2 h the obese group had not been saturated to any significant degree, we had expected that greater body clearance from VRG and MG as well as the FG acting as a depot for anaesthetic would provide better intermediate recovery measures. That IH does not affect intermediate recovery is consistent with the lack of clinically important differences in intermediate recovery metrics when anaesthetics of different blood/gas partition coefficients are studied. In morbidly obese

patients anaesthetized with sevoflurane and isoflurane, Sollazzi et al.⁵ found faster time to extubation, but no significant difference in recovery parameters after the first 10 min. In morbidly obese patients, comparisons of recovery profiles from anaesthesia sevoflurane vs. isoflurane,³ desflurane vs. isoflurane² or sevoflurane vs. desflurane¹⁶ showed little difference in intermediate recovery. In a previous study in our institution where IH was applied to enhance recovery in non-obese patients anaesthetized with isoflurane, we noted only small differences between IH and control patients in the intermediate recovery period.⁸

Effect of obesity on the rate of recovery

MAC_{awake} is not affected by obesity.¹⁷ Obesity may prolong emergence from anaesthesia because of a greater volume of distribution of anaesthetic. Lean body mass makes up 20–40% of excess weight in obesity¹⁰ and would contribute to the muscle group content of the anaesthetic. Similarly, the highly perfused organs such as the heart, kidneys, intestines and liver are surrounded by increased amount of pericardial, perinephric, mesenteric and omental fat that exchange the anaesthetic with these organs by intertissue diffusion,^{10,14} increasing the anaesthetic content of the VRG. All three of the currently available inhalational agents are highly fat soluble, isoflurane the most so. The greater the fat solubility of the anaesthetic, the lower its partial pressure for a given mass dissolved in the fat. During anaesthetics of 2–4 h, the partial pressure of anaesthetic in the bulk fat remains below MAC_{awake}, continuing the diffusion of anaesthetic from the blood to the fat, even after the patient wakes up.^{15,18} In obesity, the fat compartment receives a lower percentage of the cardiac output (2% vs. 5% in lean),¹⁰ resulting in

a prolongation of the time constant of exchange of the fat compartment with the blood. As a result, the functional fat mass^{10,19} is only a small proportion of the increased fat mass in obesity. Measured washout^{4,20} and recovery times for anaesthetics lasting 2–4 h are about the same for obese and non obese patients.^{19,21} The small effect of the total fat mass on blood concentrations of anaesthetic leaves the main determinants for times for emergence such as the body stores of anaesthetic in VRG and MG and the lung clearance, which is related to λ and $\dot{V}A$.

Five patients in our study demonstrated signs of re-hypnotization after extubation (two in the IH group and three in the C group). It is unlikely that the decrease in the level of consciousness was a result of the redistribution of anaesthetic from the fat. First, as discussed above, during emergence, the fat partial pressure is well below MAC_{awake} . Second, the time constants for the equilibration of inhalational agents with fat are very long (2110 min with isoflurane) compared with those in the lung and vessel-rich group (0.4 and 5.8 min, respectively),²² which reflect the times to extubation. Indeed, no differences have been found in the time of emergence between obese and non-obese patients with desflurane,¹⁹ sevoflurane,²⁰ isoflurane,⁴ enflurane and halothane.²³ When either sevoflurane or desflurane is used, the wake-up time does not show any correlation when regressed against BMI for BMI between 35 and 47 kg/m². A possible contributing effect to the rebound observed in both groups could be the cumulative effect of fentanyl and morphine, which can be relatively long acting in obese patients.²⁴ At the end of the anaesthetic, the presence of a tracheal tube often simulates coughing and respiration and maintains arousal. However, after extubation, the withdrawal of stimulation could lead to hypoventilation and a reduced lung clearance of residual anaesthetic from the blood and tissues, resulting in re-hypnotization.

IH

Hyperventilation is not commonly used to increase F as it also results in hypocapnia and has an undesirable effect on cerebral blood flow and delayed re-establishment of spontaneous ventilation. IH^{11,25} is a method developed to increase F by increasing VA without affecting $PaCO_2$. The method maintains $PaCO_2$ constant by providing a fixed gas flow while passively increasing the inspired concentration of CO_2 proportionally to increases in minute ventilation.^{26,27}

Study limitations

In previous studies of the effect of IH on anaesthetic recovery,^{7,8,11} the anaesthesia context was standardized by avoiding the variable effects of drug distribution caused by pre-recovery tapering of anaesthetic levels.²⁸ In the current study, anaesthetic depth was reduced 15 min before the end of surgery to allow BIS values to increase from 45–50 to 55–60 ranges, more in keeping with the common practice when using anaesthetics with a greater blood/gas partition coefficient.

Conclusion

This study demonstrates that increased pulmonary clearance of isoflurane at the termination of anaesthesia shortens short-term recovery even in the presence of obesity. It has no effect on readiness for PACU discharge.

Acknowledgements

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Conflict of interest: R. Katznelson, J. Duffin, L. Fedorko and J. Fisher are in the team that developed ClearMateTM and are shareholders in Thornhill Research Inc. (TRI), a for-profit company incorporated according to the guidelines of the University Health Network's (UHN) Technology Development and Commercialization Office.

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