

Accelerated Recovery from Sevoflurane Anesthesia with Isocapnic Hyperpnoea

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BACKGROUND: Isocapnic hyperpnoea (IH) reduces recovery time from isoflurane anesthesia in animals and humans. We studied the effect of IH on the emergence profile of sevoflurane-anesthetized patients by comparing postoperative recovery variables in patients administered IH (IH group) to those recovered in the customary fashion (control group).

METHODS: We enrolled 30 ASA I-III patients undergoing elective gynecological surgery. Induction and maintenance of anesthesia were standardized with a protocol consisting of fentanyl, propofol, rocuronium, and sevoflurane in air/O₂. Patients were randomly assigned to control (C) or IH groups at the end of the surgery. We recorded time intervals from discontinuing sevoflurane to recovery milestones.

RESULTS: Time to tracheal extubation was much shorter in the IH group compared with group C (6.2 ± 2.1 vs 12.3 ± 3.8 min, respectively, $P < 0.01$). The IH group also had shorter times to initiation of spontaneous ventilation (4.2 ± 1.7 vs 6.5 ± 3.8 min, $P = 0.047$), eye opening (5.5 ± 1.4 vs 13.3 ± 4.4 min, $P < 0.01$), bispectral index value >75 (3.9 ± 1.1 vs 8.8 ± 3.7 min, $P < 0.01$), leaving operating room (7.7 ± 2.0 vs 15.3 ± 3.4 min, $P < 0.01$), and eligibility for postanesthetic care unit discharge (67.2 ± 19.3 vs 90.6 ± 20.0 min, $P < 0.01$).

CONCLUSION: IH accelerates recovery from sevoflurane anesthesia and shortens operating room and postanesthetic care unit stay.

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The rate of elimination of vapor anesthetics is a complex function of alveolar ventilation (\dot{V}_A), solubility of the anesthetic in plasma and tissues, tissue perfusion, and cardiac output. For all practical purposes, anesthetic drug solubility and \dot{V}_A are the only variables amenable to manipulation. In the past, the extent of ventilation imposed on a patient at the termination of surgery was limited by the need to maintain end-tidal PCO₂ (PETCO₂) sufficiently high to stimulate return of spontaneous ventilation and to prevent reduction in cerebral blood flow. More recently, isocapnic hyperpnoea (IH) has been introduced as a method of increasing \dot{V}_A while preventing hypocapnia.¹ IH is a practical method of shortening recovery time from isoflurane anesthesia in animals² and humans.³

Sevoflurane is a newer inhaled anesthetic, which is much less soluble in plasma than isoflurane.⁴ It is

difficult to predict how much IH would accelerate patient recovery from sevoflurane anesthesia for three reasons. First, sevoflurane's lower solubility already provides rapid clearance from the blood at ordinary levels of ventilation; it is questionable how much additional benefit would result from increasing ventilation. Second, sevoflurane's lower blood solubility implies that a much smaller mass of anesthetic needs to be redistributed from the tissues (vessel rich group) to the blood to restore the partial pressure equilibrium with the tissues,⁴ thus raising the risk of rebound of somnolence after cessation of IH.⁵ Third, the effect of IH on patient recovery in the postanesthetic care unit (PACU) cannot be anticipated.

Our aim was to study the effect of IH on the recovery profile from anesthesia with sevoflurane. We hypothesized that (a) applying IH to sevoflurane-anesthetized patients would, at best, moderately (compared with that reported for isoflurane) accelerate the time of emergence, (b) cessation of IH would be followed by a transient rebound deepening of anesthesia, and (c) IH would not result in a clinically important difference in the PACU recovery profile compared with standard recovery after turning off the sevoflurane vaporizer and turning up the fresh gas flow.

METHODS

After IRB approval and obtaining signed informed consent, 30 ASA I-III patients scheduled to

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Dr. Joseph A. Fisher and Dr. Ludwik Fedorko are part of a group that developed the Clearmate™. The technology has been licensed to Viasys Healthcare Inc., Yorba Linda, California.

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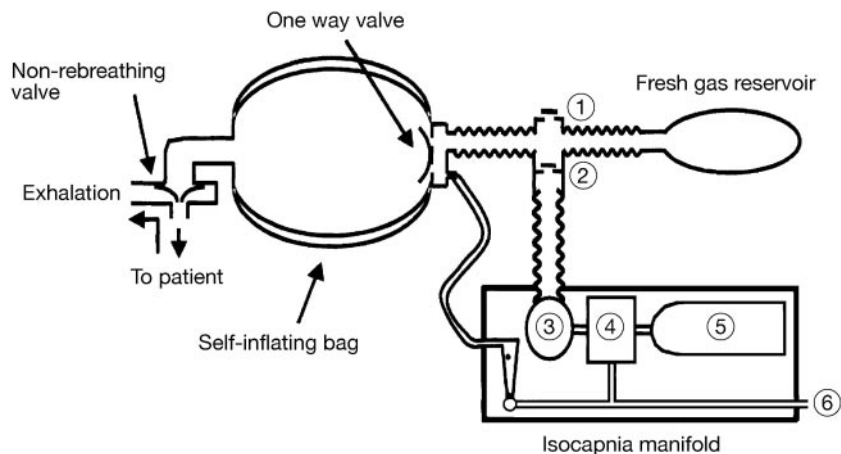


Figure 1. Schematic of isocapnic system (reproduced from Vesely et al.,³ with permission from Oxford University Press). The isocapnic system is composed of a standard self-inflating bag connected to the isocapnic manifold (ClearMate™). The isocapnic manifold provides O₂ (6) to the self-inflating bag. The target PETCO₂ during isocapnic hypernoea (IH) is set by adjusting the O₂ flow equal to the corresponding \dot{V}_A according to the relation $PETCO_2 = V_{CO_2}/\dot{V}_A$, where V_{CO_2} is the estimated CO₂ production. When minute ventilation exceeds the O₂ flow, the balance of the minute ventilation is composed of 6% CO₂ in O₂ produced by a gas blender (4) mixing CO₂ (5) and O₂ and delivered to the inspiratory relief valve (2) by a demand regulator (3). The pressure relief valve (1) releases O₂ if O₂ flow exceeds minute ventilation.

undergo elective gynecological surgery were enrolled in the study. Exclusion criteria were history of smoking, asthma, chronic obstructive pulmonary disease, alcoholism, and chronic opiate or benzodiazepine use.

Patients arrived in the operating room (OR) without premedication by sedatives. Standard anesthetic monitors were applied: electrocardiogram, noninvasive arterial blood pressure, pulse oximetry, temperature probe (Datex-Ohmeda S/5, Helsinki Finland) and bispectral index (BIS) electrodes (Aspect Medical Systems, Newton, MA). Patients were administered oxygen, and anesthesia was induced with fentanyl 0.001 mg/kg and propofol 2–2.5 mg/kg. Muscle relaxation to facilitate endotracheal intubation and prevent abdominal muscle tone was obtained with rocuronium bromide 0.6 mg/kg. Patients were mechanically ventilated via a breathing circuit with CO₂ absorber and fresh gas flow at 2 L/min. Minute ventilation was adjusted to maintain PETCO₂ between 35 and 45 mm Hg. Anesthesia was maintained with sevoflurane in O₂ and air, titrated to provide an adequate depth of anesthesia as judged by heart rate, arterial blood pressure, and BIS readings between 40 and 55. Supplementary doses of fentanyl were given, as clinically indicated, in increments of 0.001 mg/kg up to 20 min before the expected completion of the surgery. Rocuronium was used without restriction, as clinically indicated.

We monitored end-tidal concentrations of CO₂, O₂, and sevoflurane, minute ventilation (Datex-Ohmeda AS/5, Helsinki Finland), neuromuscular blockade (Fisher & Paykel Electronics Ltd., Auckland N.Z.), and BIS number. All monitored analog data were digitized at 60 samples per second using a DI-720 analog-to-digital converter and recorded continuously using customizable software (LabView VII, National Instruments, Austin, TX). After the surgical dressing was

applied, patients were randomized into control (C) or IH groups using sealed envelopes containing equal numbers of marked papers. Sevoflurane was turned off and residual neuromuscular blockade was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.005 mg/kg (time = 0). For patients randomized into the C arm, the O₂ flow on the anesthetic machine was set at 15 L/min, the patient received gentle assisted ventilation until spontaneous ventilation commenced, and was then allowed to breathe spontaneously. Patients randomized to the IH arm were disconnected from the anesthetic circuit and connected to the self-inflating bag attached to a Clearmate™ (both provided by Viasys Healthcare, Yorba Linda, CA) (Fig. 1). Manual ventilation was commenced with the self-inflating bag and, if not resisted by the patient, gradually increased to 20–25 L/min. If the patient exhibited any spontaneous ventilatory efforts, these were assisted by synchronizing assisted breaths with the patient's inspiratory efforts, depending on the patient's tolerance, up to 20–25 L/min. The O₂ flow was adjusted if necessary to maintain PETCO₂ in the range of 45–50 mm Hg.

Patients randomized to IH continued to breathe via the self-inflating bag attached to the Clearmate™ until tracheal extubation. All physiologic variables including minute ventilation, PETCO₂, and BIS were continuously monitored and recorded in both groups during emergence. Patients were asked to open their eyes approximately every 30 s, when they appeared to be on the verge of arousal. The endotracheal tube was removed when patients were able to breathe spontaneously, lift the head, and follow commands. Patients were then taken to the PACU. Nurses caring for the patients were blinded to the type of emergence. On arrival in the PACU, the patient was placed in a semirecumbent position. Oxygen administered via a facemask at 6 L/min during transfer from the OR was

Table 1. Anthropomorphic Characteristics and Duration of Surgery (Mean \pm sd or Number of Patients)

Characteristic	IH (<i>n</i> = 15)	Control (<i>n</i> = 15)	Statistical significance
Age (y)	47.9 \pm 13.7	49.1 \pm 11.0	NS
Height (cm)	157 \pm 22	162 \pm 6	NS
BMI (kg/m ²)	27.4 \pm 5.3	27.3 \pm 5.6	NS
Duration of surgery (min)	130.1 \pm 53.5	130.0 \pm 66.5	NS
Duration of anesthesia (min)	155.5 \pm 57.4	153.1 \pm 66.0	NS
Laparotomy versus laparoscopy	10/5	8/7	NS

IH = isocapnic hyperpnoea; BMI = body mass index; NS = not significant.

continued throughout the stay in the PACU. Routine PACU monitoring included electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry. The tip of the sampling line of a calibrated gas analyzer (Datex AS/3, Helsinki, Finland) was taped close to the patient's nostril and expiratory gas was analyzed continuously for sevoflurane concentration. The position of the sampling line was considered optimal when PETCO₂ values were in the clinically expected range and the CO₂ concentration curve had a typical profile. The same monitor was used for all patients. Postoperative analgesia orders included ketorolac 15–30 mg IV and morphine 2–4 mg IV every 5 min as necessary to be administered by the nurse on clinical grounds, followed by patient-controlled analgesia with morphine when the nurse judged the patient had recovered sufficiently to use it.

We noted the following OR events: duration of anesthesia (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, and tracheal extubation. We also collected end-tidal concentrations of sevoflurane after extubation and time to fulfillment of criteria for leaving the OR (stable vital signs, adequate ventilation, and following simple commands). In the PACU, we monitored end-tidal sevoflurane concentrations at 5-min intervals for the first hour. The PACU nurse recorded Richmond Agitation Sedation Score (0 is calm and alert, –1 to –5 means sedated from drowsy to unarousable, +1 to +4 means agitated from restless to combative and violent),⁶ a 10-cm visual analog pain score (0—no pain, 10—worst, unbearable pain), and Aldrete score⁷ (readiness for discharge) every 10 min during the patient's PACU stay. Patients were considered ready to discharge when the Aldrete score was 10 and the pain score was <5.

We also reviewed the charts retrospectively to note any occurrences of nausea and vomiting, shivering, administration of pain medication (noting time and dose), cardiac or respiratory complications, and unexpected prolonged PACU stay.

Data Analysis

Continuous measures were compared through a series of independent samples *t*-tests. Categorical measures were tested through χ^2 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* (%), whereas continuous measures are summarized as the mean \pm sd unless otherwise specified. A series of nonparametric Mann-Whitney *U*-test was performed to determine whether pain/sedation scores differed significantly between the groups. Repeated measures ANCOVA was performed to test whether exhaled concentrations changed over time and whether they changed at different rates between the two treatment groups.

Power Analysis

We assumed that the expected difference in mean wakeup time would be 5 min with an expected standard deviation of 4 min. Assuming an α of 0.05 and power 0.91, we calculated the required sample size to be 15 in each of the C and IH groups.

RESULTS

Fifteen patients were randomized to the IH group and 15 to the C group. The groups were comparable with respect to anthropomorphic characteristics as well as length of anesthesia and surgery (Table 1). Doses of opiates, nonsteroidal antiinflammatory drugs, muscle relaxants, and intraoperative concentrations of sevoflurane were comparable (Table 2). The induction dose of propofol was slightly higher in the control group. Both IH and C groups had similar PETCO₂s (39 \pm 6 [IH] vs 36 \pm 5 mm Hg [C], *P* = 0.1) and exhaled sevoflurane concentrations (0.3 \pm 0.2 [IH] vs 0.3 \pm 0.2% [C], *P* = 0.1) immediately before tracheal extubation. The mean duration of IH was 4.8 \pm 1.4 min. Minute ventilation in the IH group was 23 \pm 2.3 vs 4.6 \pm 1.4 L/min in C. All patients in the IH group tolerated IH without hemodynamic instability. Time to tracheal extubation in the IH group was much shorter compared with group C (6.2 \pm 2.1 vs 12.3 \pm 3.8 min, respectively; *P* < 0.01). The IH group also had shorter times to initiation of spontaneous ventilation, eye opening, appropriate response to verbal command, BIS value >75, leaving OR and eligibility for PACU discharge (Table 3).

On arrival in the PACU, all patients had an Aldrete score >8 and SaO₂ of 99%. The average PETCO₂s in the PACU were 34.2 \pm 5.0 mm Hg in the IH group and 34.9 \pm 5.0 mm Hg in the C group (*P* = 0.9). Respiratory rate in the PACU was 14 \pm 4 per

Table 2. Intraoperative Medications [Median (Interquartile Range) or Mean \pm sd]

Drug	IH (<i>n</i> = 15)	Control (<i>n</i> = 15)	Statistical significance
Propofol ^a (mg)	150.0 (120.0–200.0)	200.0 (120.0–250.0)	0.02
Fentanyl ^a (μ g)	250.0 (250.0–350.0)	250.0 (250.0–300.0)	NS
Rocuronium ^a (mg)	70.0 (50.0–80.0)	60.0 (50.0–80.0)	NS
Sevoflurane (MAC-h) ^b	2.3 \pm 0.9	2.1 \pm 0.7	NS
Ketorolac ^a (mg)	0.0 (0.0–15.0)	15.0 (0.0–15.0)	NS

IH = isocapnic hyperpnoea; MAC = minimum alveolar concentration; NS = not significant.

^a Mann-Whitney *U* tests were used instead of *t*-tests for this comparison because of the distributional properties of the data.

^b MAC-h was calculated as average MAC \times length of exposure.

Table 3. Time from Turning Off Vaporizer until Event in Minutes (Mean \pm sd)

	IH (<i>n</i> = 15)	Control (<i>n</i> = 15)	Statistical significance
Initiation of spontaneous ventilation	4.2 \pm 1.7	6.5 \pm 3.8	0.047
Eye opening	5.5 \pm 1.4	13.3 \pm 4.4	<0.01
BIS >75%	3.9 \pm 1.1	8.8 \pm 3.7	<0.01
Extubation	6.2 \pm 2.1	12.3 \pm 3.8	<0.01
Leaving OR	7.7 \pm 2.0	15.3 \pm 3.4	<0.01
Awake	7.9 \pm 2.0	16.1 \pm 4.2	<0.01
Eligibility for PACU discharge	67.2 \pm 19.3	90.6 \pm 20.0	<0.01

IH = isocapnic hyperpnoea; BIS = bispectral index; OR = operating room; PACU = postanesthesia care unit.

Table 4. Post Anesthesia Care Unit (PACU) Medications

Drug	IH (<i>n</i> = 15)	Control (<i>n</i> = 15)	Statistical significance
Granisetron ^a (mg) (median, min, max)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	NS
PACU Morphine ^a (mg) (median, min, max)	5.0 (0.0–20.0)	3.0 (0.0–20.0)	NS
PACU Ketorolac ^b (mg) (median, min, max)	0.0 (0.0–30.0)	15.0 (0.0–30.0)	NS

^a Mann-Whitney *U* tests were used instead of *t*-tests for this comparison because of the distributional properties of the data.

^b Fisher's exact test was used instead of χ^2 test because of the paucity of events.

minute in the IH group and 15 \pm 3 per minute in the C group (*P* = 0.57).

There were no differences between groups in average Richmond Agitation Sedation Score and pain scores in the PACU. However, patients in the IH group required pain medication and started using patient-controlled analgesia earlier (25 \pm 7 min from time of turning off vaporizer) than patients in the C group (40 \pm 11 min, *P* < 0.01). There were no differences in total administered dose of morphine, antiemetic, and antiinflammatory drugs (Table 4). The incidence of nausea and vomiting was similar in both groups (20% vs 28.6%, *P* = 0.68). Two patients in the control group experienced shivering (13.3%), whereas none in the IH group did; this difference was not statistically significant (Fisher's exact test, *P* = 0.48). None of the patients in either group had cardiovascular or respiratory complications. The exhaled sevoflurane concentrations in the IH group were lower than those in the C group for 20 min after the initiation of emergence and showed no signs of "rebound" (Fig. 2).

DISCUSSION

Ours is the first study to examine the effect of IH on recovery from sevoflurane anesthesia. As reported by Vesely et al.,³ in their isoflurane-anesthetized patients,

we found that IH was well tolerated by sevoflurane-anesthetized patients. Compared with the "standard" recovery routine for sevoflurane, IH reduced by 50% the time to eye opening in response to command, resulting in an average reduction recovery time in OR from 15 to 7.6 min. The IH group had a much shorter stay in the OR and PACU combined (67 min) compared with the C group (91 min) (*P* < 0.01). Patients in the IH group had earlier requirements for pain medication but there were no differences in pain and sedation scores, respiratory rate, PETCO₂, analgesic requirements, incidence of shivering, vomiting, or other complications.

We were not able to identify any anesthetic "rebound effect" as we had hypothesized. The rationale behind this hypothesis was that, with its low blood solubility and low anesthetic capacitance, even small amounts of sevoflurane diffusing back into the blood could markedly increase its partial pressure. The fact that we did not see rebound could also be explained by the complementary effect of sevoflurane's low blood solubility: efficient elimination of sevoflurane from the blood by ventilation. In other words, sevoflurane elimination through the lungs, even at the presumably low minute ventilations during early recovery, must at least have matched the rate of its mobilization from the slower compartments.

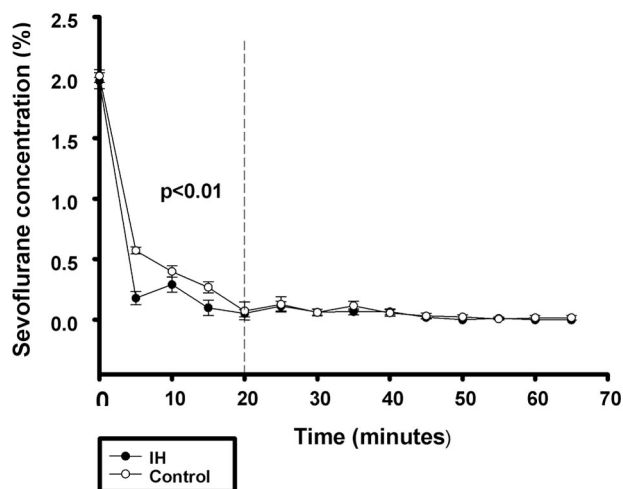


Figure 2. Time and treatment effects on exhaled sevoflurane concentration. Circles represent the mean exhaled concentration (percent) at each time point. Error bars are ± 1 SEM.

Also consistent with this explanation is our observation that low sevoflurane concentrations persisted for the first 20 min of the recovery period in the PACU in the IH group (Fig. 2). The observed earlier requirement for analgesics in these patients may have been related to their earlier recovery from anesthesia.

Increasing the rate of elimination of anesthetics by hyperventilation is not new.^{8,9} Anesthesiologists are restrained from hyperventilating their patients at the end of surgery by concerns related to the accompanying hypocapnia. Low partial pressures of CO₂ in the blood reduce cerebral blood flow and may delay the washout of anesthetic from the brain compartment. Furthermore, the contribution of hyperventilation to shortening the time to awakening is offset by the delay of return of spontaneous ventilation from the hypocapnia. Even relatively recently,¹⁰ anesthesiologists dealt with this dilemma by adding CO₂ into the anesthesia circuit at the end of surgery, thus stimulating ventilation while preventing reductions in arterial Pco₂. The main disadvantage of this maneuver is a lack of control of the patient's Pco₂, which may lead to acute and dangerous levels of hypercapnia.¹¹ In 1998, Sommer et al.¹ described a simple apparatus that automatically maintains isocapnia with increases in minute ventilation by passively adding a flow of CO₂ to the inspirate in proportion to increases in ventilation above a baseline ventilation. Sasano et al.² used this device to increase \dot{V}_A and accelerate off-gassing in isoflurane-anesthetized dogs. Vesely et al.³ demonstrated that the device can be applied to humans in the OR to shorten the time of waking. These authors reported an average reduction in time to tracheal extubation of 8 min (from 12 to 4 min). More recently, Sakata et al.¹² used a method of inducing hyperpnoea while attempting to prevent hypocapnia by rebreathing through a dead-space with a charcoal filter; they reported a 59% reduction in time to extubation (from

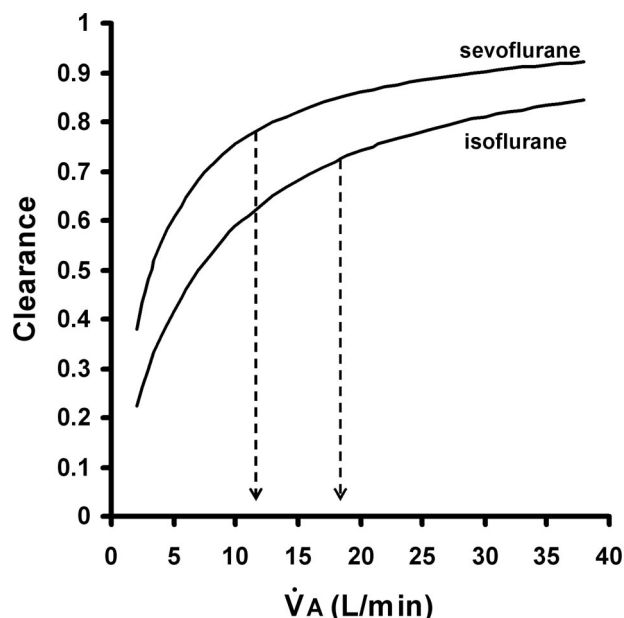


Figure 3. Predicted anesthetic clearance as a function of alveolar ventilation (\dot{V}_A) for sevoflurane and isoflurane. Calculations were made with Eq. (1) using λ of 0.65 for sevoflurane and 1.45 for isoflurane. It was assumed that cardiac output was 5 L/min and independent of minute ventilation. \dot{V}_A was assumed to be $0.7 \times$ minute ventilation.³ The dotted lines indicate the \dot{V}_A predicted to result in 85% of the clearance achievable with \dot{V}_A of 40 L/min.

18 to 7 min) in isoflurane-anesthetized patients. In contrast to these studies, our 50% reduction in time to eye opening in patients anesthetized with sevoflurane is more modest.

The differences in blood:gas solubility of sevoflurane (0.65) and isoflurane (1.45) account for the difference in the relationship between anesthetic clearance (C) and \dot{V}_A .⁵

$$C = \frac{1}{1 + \lambda \frac{\dot{Q}}{\dot{V}_A}} \quad (1)$$

where \dot{Q} is the cardiac output, and λ is the blood:gas solubility. Figure 3 illustrates that the lower blood:gas solubility of sevoflurane results in the optimization of the balance between ventilation and clearance at much lower ventilations (reaching 85% maximum clearance at \dot{V}_A of 12 L/min approximately) compared with those required for isoflurane (18 L/min), where "maximum clearance" is taken as the clearance at a maximum achievable \dot{V}_A of 40 L/min. This is because the elimination of poorly soluble anesthetics becomes perfusion-limited at lower minute ventilations than do more soluble anesthetics. An important implication of this analysis is that the advantages in recovery from sevoflurane would have been achievable at about half the minute ventilation of 20–25 L/min used in this study.

STUDY LIMITATIONS

All anesthetics were administered in a consistent manner outlined in the study protocol that may vary from the practice of some anesthesiologists. Our protocol compromised some clinical practices (such as reducing the concentrations of inhaled vapor towards the end of surgery) to provide a consistent anesthetic protocol to highlight differences in recovery profile from control patients attributable to IH. We allowed the C group to recover while breathing on the breathing circuit at maximal fresh gas flows to establish the best possible recovery time from sevoflurane anesthesia available with the anesthetic machine. The patients in the IH group were ventilated manually (as opposed to increasing their P_{ETCO_2} and allowing them to breathe spontaneously) as we aimed at maintaining their P_{ETCO_2} at 45–50 mm Hg yet required their minute ventilations to exceed those resulting from the respiratory drive.

In studies like these, the observer making measurements in the OR cannot be blinded to the treatment arm.^{2,3} However, most of the study was blinded, as neither the anesthesiologist nor observer knew the treatment arm until the lot was drawn at the end of surgery. In addition, as noted, the PACU staff were blinded to the intraoperative treatment arm.

In conclusion, IH reduced recovery times by 40%–50% in all sevoflurane-anesthetized patients in the IH group, resulting in an average reduction of OR and PACU stay of over 20 min. There was no evidence of rebound of somnolence after IH.

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