Isocapnic Hyperpnoea Shortens Postanesthetic Care Unit Stay After Isoflurane Anesthesia

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BACKGROUND: We conducted a prospective controlled clinical trial of the effect of isocapnic hyperpnoea (IH) on the times-to-recovery milestones in the operating room (OR) and postanesthetic care unit (PACU) after 1.5 to 3 hours of isoflurane anesthesia.

METHODS: Thirty ASA grade I–III patients undergoing elective gynecological surgery were randomized at the end of surgery to either IH or the conventional recovery (control). Six patients with duration of anesthesia of <90 minutes were excluded from the analysis. The anesthesia protocol included propofol, fentanyl, morphine, rocuronium, and isoflurane in air/O2. Unpaired t tests and analyses of variance were used to test for differences in times-to-recovery indicators between the two groups.

RESULTS: The durations of anesthesia in IH and control groups were 140.8 ± 32.7 and 142 ± 55.6 minutes, respectively (P = 0.99). The time to extubation was much shorter in the IH group than in the control group (6.6 ± 1.6 (SD) vs. 13.6 ± 3.9 minutes, respectively; P < 0.01). The IH group also had shorter times to eye opening (5.8 ± 1.3 vs. 13.7 ± 4.5 minutes; P < 0.01), eligibility for leaving the OR (8.0 ± 1.7 vs. 17.4 ± 6.1 minutes; P < 0.01), and eligibility for PACU discharge (74.0 ± 16.5 vs. 94.5 ± 14.7 minutes; P < 0.01). There were no differences in other indicators of recovery.

CONCLUSION: IH accelerates recovery after 1.5 to 3 hours of isoflurane anesthesia and shortens OR and PACU stay. (Anesth Analg 2010;111:403–8)

In principle, the time to recovery from inhalation anesthetics will depend on the anesthetic vapor, the degree of saturation of tissue stores before initiating emergence (i.e., drug exposure history), and postanesthetic alveolar ventilation. It has long been recognized that hyperventilation would increase the clearance of anesthetic from the blood via the lung, but concern about hypocapnia reducing cerebral bloodflow (CBF) and delaying the recovery of spontaneous ventilation made this approach impractical. The advantage of increased anesthetic clearance from the blood on the recovery of consciousness would be offset by the reduction in clearance of anesthetic from the brain caused by the lower CBF. However, alveolar ventilation and anesthetic clearance can be increased without hypocapnia. In the method of isocapnic hyperpnoea (IH), isocapnia is maintained despite large increases in alveolar ventilation by passively providing CO2 into the circuit in exact proportion to any increases in ventilation. A second method of preventing hypocapnia is to interpose a breathing circuit between the anesthetic circuit and endotracheal tube that allows rebreathing of exhaled gases from which anesthetic, but not CO2, is scrubbed. End-tidal PCO2 (PETCO2) is not tightly controlled with this system, which can result in hypercarbia, but time to arousal is nevertheless shortened in comparison with that of simple hyperventilation.

The first studies of IH and, later, hypercapnic hyperpnoea focused on very early outcome variables from the operating room (OR), such as time to eye opening, time to tracheal extubation, and a more quantifiable measure, time to recovery of the Bispectral Index (BIS). These variables predominantly reflect changes in anesthetic concentration in such fast compartments as the blood and the brain but may miss any delayed effects resulting from equilibration of the anesthetic between blood and slower tissue compartments such as muscle and fat. Consequently, our laboratory previously examined the effect of IH on recovery from sevoflurane anesthesia through to the end of the patient’s stay in the postanesthesia care unit (PACU). We found that patients who received IH at the termination of anesthesia reached their readiness for discharge earlier than did those who received standard recovery care. Such extended observations in the PACU may better reflect the lingering roles of anesthetic in tissue compartments and better address the clinical and economic impacts of interventions used to accelerate emergence.

Isoflurane is an older but still very popular anesthetic with greater blood solubility than has sevoflurane. Although the efficacy of IH on short-term recovery from isoflurane has been demonstrated, the effect on intermediate recovery is unknown and difficult to predict. Isoflurane’s relatively high blood solubility tends to reduce its blood clearance in the lung. Nevertheless, at high minute ventilations, increased blood solubility allows for increased total body elimination because of better maintenance of the partial pressure gradient between the pulmonary capillary blood and the alveoli. We hypothesized that the increased total body elimination of the relatively highly soluble
anesthetic isoflurane with IH will offset the effect of reduced clearance at the lung and shorten the time to intermediate recovery in PACU. We compared the effect of IH to standard recovery in the OR on short and intermediate recovery profiles of patients after approximately 2 hours of exposure to isoflurane.

**METHODS**

The study was approved by the hospital IRB, and all patients gave verbal and signed informed consent. Thirty ASA grade I–III patients undergoing elective gynecological surgery volunteered for the study. Exclusion criteria were history of smoking, asthma, chronic obstructive pulmonary disease, alcoholism, psychiatric disorders, and chronic opiate or benzodiazepine use. No premedication with sedative drugs was given.

On arrival at the OR, standard anesthetic monitors were applied: electrocardiogram, noninvasive arterial blood pressure, pulse oximetry, temperature probe, and spirometer (Datex-Ohmeda S/5, Helsinki, Finland). After 2 minutes of oxygen administration, anesthesia was induced with fentanyl 0.1 μg/kg, propofol 2 to 2.5 mg/kg, and rocuronium bromide 0.6 mg/kg. The patient’s lungs were mechanically ventilated via a circle breathing circuit with an in-line CO2 absorber and fresh gas flow of 1 to 2 L/min. Minute ventilation was adjusted to maintain PETCO2 between 35 and 45 mm Hg. Anesthesia was maintained with isoflurane in O2 and air (inspired O2 concentration of 40%), titrated to provide an adequate depth of anesthesia as judged by heart rate, arterial blood pressure, and end-tidal isoflurane concentration (≥0.7 minimum alveolar concentration [MAC] as read from the anesthetic monitor). Supplementary doses of fentanyl or morphine were given as clinically indicated up to 20 minutes before the expected completion of the surgery. Rocuronium was used without restriction, as clinically indicated. We monitored PETCO2, end-tidal Po2 and isoflurane concentration, exhaled tidal volume, and minute ventilation (Datex-Ohmeda AS/5, Helsinki, Finland). All monitored analog data were digitized at 60 samples/s using a DI-720 analog-to-digital converter and recorded continuously using customized software (LabView VII, National Instruments, Austin, Texas).

After skin closure, patients were randomized into control or IH groups by using sealed envelopes containing equal numbers of marked papers. Isoflurane was turned off and residual neuromuscular block was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 m/kg (time = 0). For patients randomized into the control group, the O2 flow on the anesthetic machine was set at 15 L/min, gentle assisted ventilation was provided until spontaneous ventilation commenced, at which time the patient was allowed to breathe spontaneously. Patients randomized to the IH group were disconnected from the anesthetic circuit, leaving the pneumotachometer and gas sampling ports in situ and connected to the self-inflating bag attached to an IH manifold (ClearmateTM, Thornhill Research Inc., Toronto, Ontario, Canada) (Fig. 1). Manual ventilation was initiated with the self-inflating bag and, if not resisted by the patient, gradually increased to 20 to 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 to 25 L/min. The O2 flow was adjusted as necessary to maintain PETCO2 in the range of 35 to 45 mm Hg. Patients randomized to IH continued to breathe via the self-inflating bag attached to the Clearmate™ until tracheal extubation. All physiologic variables were continuously monitored and recorded in both groups during emergence. Patients were asked to open their eyes approximately every 30 seconds, and more frequently when they appeared to be on the verge of arousal. The endotracheal tube was removed when patients were able to breathe spontaneously, lift their heads, and follow commands.

Patients were then transported to the PACU. PACU nurses were blinded to the group allocation. On arrival in the PACU, the patients were placed in a semirecumbent position. Postoperative analgesia included ketorolac 15 to 30 mg IV and morphine 2 to 4 mg IV every 5 minutes to be administered by the nurse if clinically necessary, followed by patient-controlled analgesia with morphine when indicated and the patient judged sufficiently recovered to use it. We recorded the following OR events: duration of anesthesia (beginning of induction to turning off the isoflurane vaporizer), duration of surgery (skin incision to skin closure), time of resumption of spontaneous ventilation, arousal (opening eyes in response to verbal command), and extubation. We also recorded the time of first pain medication administration in the PACU and time to fulfillment
of criteria for leaving the OR (stable vital signs, adequate ventilation, and following simple commands). The PACU nurses recorded Richmond Agitation Sedation Score (RASS) (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), a 10-cm visual analog pain score (0 = no pain; 10 = worst, unbearable pain), and Aldrete score (readiness for discharge) every 10 minutes during the patient’s PACU stay. Patients were considered ready to discharge when the Aldrete score was 10 and the pain score was <5. Incidences of nausea and vomiting, shivering, and unexpected prolonged PACU stay were recorded.

**Data Analysis**

Continuous measures were compared through a series of independent-samples t tests. Categorical measures were evaluated using χ² 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 continuous measures are summarized as the mean (± standard deviation).

**Power Analysis**

We tested for a difference in mean wake-up time of 5 minutes with an expected SD of 4 minutes. Assuming an α of 0.05 and power of 0.90, we calculated the required sample size to be 15 in each group.

**RESULTS**

Of the initial 30 patients studied, 6 patients were excluded from the analysis because the duration of anesthesia was <90 minutes. Of the remainder, there were 12 patients randomized to each group. There were no differences in age, body mass index, type and length of surgery, and duration of anesthesia between groups (Table 1). Anesthetic management was comparable in both groups (Table 2). Intraoperative isoflurane concentrations in the IH and control patients are presented in Figure 2. The average minute ventilation and PetCO₂ during the last minute before closing the vaporizer, immediately after closing the vaporizer, and before extubation are presented in Table 3. IH duration was 5.5 ± 1.6 minutes. The exhaled isoflurane concentration and PetCO₂ immediately before extubation were 0.1 ± 0.1% [IH] versus 0.2 ± 0.1% [control], P < 0.001; and 39 ± 4 mm Hg [IH] versus 41 ± 6 mm Hg [control], P = 0.07. All patients in the IH group tolerated IH without hemodynamic or respiratory instability.

The patients in the IH group had significantly shorter times to eye opening, tracheal extubation, readiness to leave OR, and eligibility for PACU discharge (Table 4). There were no differences between the groups in time of initiation of spontaneous breathing in the OR and the time to the administration of pain medications in the PACU. Incidences of nausea and vomiting and shivering were similar between the two groups (Table 4). On arrival in the PACU, all patients had an Aldrete score >8 and SaO₂ >98%.

There were no differences between the groups in average RASS and pain scores in the PACU and no difference in the total postoperative administered dose of morphine (median [min,max]) (4.5 [2.7] mg for IH vs. 4.5 [2.6] mg for control, P = 0.65) (Tables 5, 6).

**DISCUSSION**

In this study we found that IH markedly reduced the times-to-recovery milestones from isoflurane in the OR (initiation of spontaneous ventilation, eye opening, extubation, and eligibility to leave the OR). Interestingly, these times differed by less than 1 minute from those our group found previously for sevoflurane. IH also reduced the time to intermediate recovery from isoflurane anesthesia in the form of time to eligibility for discharge from the PACU. Once again, the intermediate recovery measure from isoflurane anesthesia was nearly the same as that reported for sevoflurane (74 ± 17 in this study vs. 67 ± 19 for sevoflurane).

The effect of IH on the short-term milestones of recovery from isoflurane anesthesia has been reported. It is the
effect of IH on the intermediate milestones of recovery that were difficult to predict. On the one hand, because of its higher solubility, one would expect lower clearance of isoflurane for a given level of IH tending to prolong recovery. On the other hand, the rate of elimination of anesthetic from the body would be greater with IH because it is a function of minute ventilation and end-tidal anesthetic concentration. The latter would be better maintained during IH with a drug of greater solubility. The greater total body elimination of isoflurane would tend to
shorten intermediate recovery. An additional consideration is that the recovery rate is more closely tied to dose history for drugs of greater blood solubility. The actual half-time of elimination for an anesthetic is determined by the multieponential washout curves of the 5 main anesthetic tissue compartments, of which the muscle group (MG) has the greatest effect. Indeed, after rapid washout of anesthetic from the lung and vessel rich group with IH, it was possible that anesthetic would redistribute from the MG and increase the anesthetic concentration in the vessel rich group, resulting in rehypnotization. The duration of anesthesia had to be sufficient to allow substantial saturation of the MG to discern the effect of IH on intermediate recovery time from isoflurane anesthesia. Eger and Shafer reasoned that as MAC awake for isoflurane is 1/3 MAC, there should be little difference in 80% decrement for anesthesia after about 120 minutes of exposure. Our patients were exposed to isoflurane for about 2 hours (140 ± 33 minutes for IH and 142 ± 56 minutes for control). As was stated above, we noted shorter times to readiness for discharge and no signs of rehypnotization.

The rate of ventilation affects the rate of recovery from volatile anesthetics. Stoelting and Eger demonstrated that increases in ventilation enhanced the clearance of anesthesia from the blood in anesthetized ventilated dogs. They did not control PaCO₂ independently of ventilation and did not actually monitor recovery of consciousness. Sasano et al. were the first to examine the effect of ventilation on the rapidity of recovery. They used isoflurane anesthesia in an unpremedicated dog model and controlled for the effect of ventilation on CBF by maintaining PaCO₂ constant during hyperpnea (i.e., IH). They reported only the immediate effects on recovery, i.e., the interval between cessation of administration of isoflurane and the onset of responses to stimuli (tail pinch, touching the cornea) and time to extubation. This group reported a similar effect of IH on recovery in humans undergoing brief (approximately 1 hour) anesthesia maintained with isoflurane. Again, only immediate indices of anesthetic recovery were reported, including the first use of the BIS to assess recovery with hyperpnea. Gopalakrishnan et al. studied pigs anesthetized with isoflurane and sevoflurane. To reverse the anesthesia, they increased the animals’ minute ventilation with no CO₂ added (i.e., true “hyperventilation”) or with hypercapnia induced by the controlled flow of CO₂ into the circuit. They observed more rapid onset of spontaneous movements and normalization of BIS in the hypercapnic animals. Sakata et al. performed similar studies in humans anesthetized for about 3 hours. Again, hyperpnea with hypercapnia and scrubbing of anesthetic from inhaled gas accelerated short-term recovery from anesthesia with isoflurane, sevoflurane, and desflurane, but intermediate recovery variables in the PACU were not reported.

In our study, the reduction in time for discharge from the PACU, approximately 20 minutes, was accounted for by a 9-minute earlier discharge from the OR, leaving an 11-minute difference in PACU stay. Although the Aldrete score was >8 on arrival in the PACU for both IH and control groups, and the RASS and pain scores were similar in both groups, the combined data were used for the objective discharge criteria, and we were able to demonstrate a difference between groups. There are some limitations to our study. First, in the control group, minute ventilation was reduced after turning off the vaporizer, and the patients’ lungs gently ventilated by hand.
while allowing their P\textsubscript{CO}\textsubscript{2} to increase to the point at which they resumed spontaneous ventilation. This could have led to hypoventilation, which would have prolonged the time to recovery in comparison with maintaining normal ventilation during recovery. Our data indicate that, if at all, such “hypoventilation” was minimal (Table 2), and our control group has the advantage of following universal practice. Second, we excluded 6 patients from the analysis because their exposure to isoflurane was <90 minutes. However, recalculating our data with these patients included did not change the main findings. Third, we excluded patients with respiratory and cardiovascular disease from the study. Although we did not notice any hemodynamic or respiratory instability during IH, the results of the study could be applied cautiously to this patient population.

In conclusion, IH in the OR shortens both immediate and intermediate emergence from isoflurane anesthesia.

**DISCLOSURE**

Joseph A. Fisher and Ludwik Fedorko are part of a group that developed the technology for administering isocapnic hyperpnoea and have sought protection for related intellectual property in compliance with the Intellectual Property Policy of the University Health Network.

**REFERENCES**

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