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The effect of isocapnic hyperventilation on early recovery after remifentanil/sevoflurane anesthesia in O_2/air: A randomized trial

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Background: Isocapnic hyperventilation (ICHV) may hasten emergence from general anesthesia but remains inadequately studied. We prospectively determined emergence time after sevoflurane anesthesia of variable duration with and without ICHV.
Methods: In 25 ASA I-II patients, general anesthesia was maintained with one age-adjusted MAC sevoflurane in O_2/air and target-controlled remifentanil delivery. At the start of skin closure, the remifentanil effect-site concentration was reduced to 1.5 ng/mL, any residual neuromuscular block reversed, and once the remifentanil effect-site concentration had decreased to 1.5 ng/mL, remifentanil and sevoflurane administration was stopped, and the fresh gas flow increased above minute ventilation. Patients randomly received either normoventilation (n = 13) or ICHV (doubling minute ventilation while titrating CO_2 into the inspiratory limb to maintain isocapnia [n = 12]). Three early recovery end points were determined: time to proper response to verbal command; time to extubation; and time to stating one's name.
Results: Demographics were the same in both groups. Recovery end points were reached faster in the ICHV group compared to the normoventilation group: time to proper response to verbal command was 7.6 ± 2.2 vs 9.9 ± 2.9 min (P = 0.03); time to extubation was 7.6 ± 2.6 vs 11.0 ± 2.4 min (P = 0.002); and time to stating one's name was 8.9 ± 2.8 vs 12.5 ± 2.6 min (P = 0.003). Within each group, duration of anesthesia only marginally affected the times to reach these recovery end points.
Conclusion: Isocapnic hyperventilation only had a small effect on emergence times after anesthesia, suggesting that isocapnic hyperventilation may have limited clinical benefits with modern potent inhaled anesthetics.

1 | INTRODUCTION

At the end of a general anesthetic, the effect of the inhaled anesthetic drug is terminated by washout via the lungs. Hyperventilation may hasten emergence by maximizing the gradient across the alveolocapillary membrane.[1] However, the accompanying hypocapnia will decrease cerebral blood flow (CBF) and thus also the elimination of inhaled agents from the central nervous system (CNS),[2,3] potentially obfuscating the beneficial effects of hyperventilation. To prevent this decrease in CBF, carbon dioxide (CO_2) has been added to the inspired gas to maintain isocapnia, a technique called isocapnic hyperventilation (ICHV).[3] Some also advocate the use of hypercapnic hyperventilation to increase CNS blood flow to hasten CNS washout even more.[4-7]

The use of ICHV has been explored, but previous studies have several limitations, including unreported end-expired agent concentrations (F_A), nonstandardized opioid administration, and inconsistent

management of ventilation (the use of "gentle assisted ventilation" in the control group could have allowed hypoventilation during emergence).[3,8-10] A number of studies pertain to isoflurane,[3,9,10] which may favor the effect of ICHV because isoflurane is more soluble than sevoflurane and desflurane.[11]

We therefore examined the effect of ICHV on emergence after anesthesia maintained with well-defined sevoflurane and remifentanil concentrations. We devoted particular care to maintained normoventilation (NV) in the control group, which may have been suboptimal in previous studies. We hypothesized that ICHV hastens early recovery after general anesthesia with one age-adjusted MAC of sevoflurane, and that the duration of administration prolongs emergence. Three specific early recovery end points were determined.

Editorial Comment

Isocapnic hyperventilation through insufflating carbon monoxide into inspired gas at the end of an inhalational anesthetic has been considered over many years as a means to try to reduce emergence time and operating room time. This trial found measurable but only small effects to this end when tested in a controlled anesthetic which included a commonly used, highly insoluble potent inhalational anesthetic agent as well as a potent opioid.

2 | MATERIALS AND METHODS

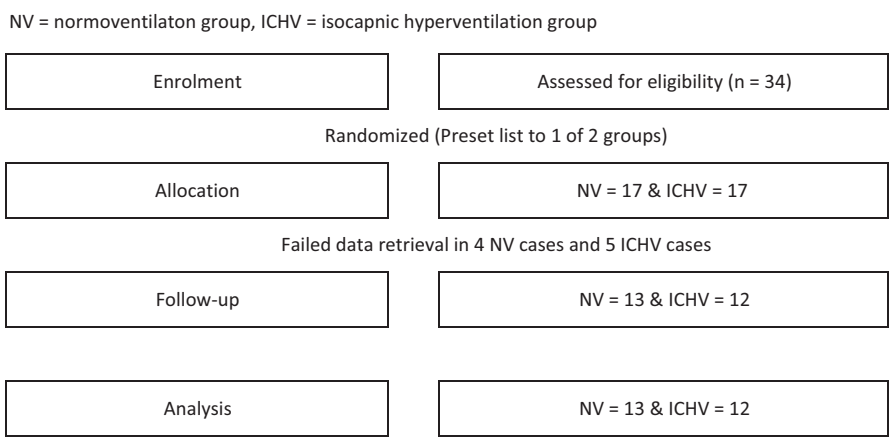
After obtaining IRB approval (IRB record number 2014/074 [April 30, 2014], and EUDRACT 2014-000678-20) and written patient informed consent, 34 ASA I-II patients undergoing plastic or ear-nose-throat surgery requiring tracheal intubation were enrolled (Table 1). Patients were randomly allocated to either NV or ICHV by blindly taking an envelope with a card with the study group from a closed box. Exclusion criteria included a history of cardiopulmonary disease; systemic hypertension requiring medical therapy; psychiatric disease; use of benzodiazepines, opioids, and psychogenic drugs; pregnancy and breastfeeding; and laparoscopic procedures. Patients were not premedicated. *Patient enrollment lasted from March 2014 until December 2017.*

After applying routine monitoring and establishing intravenous access, patients were pre-oxygenated (80% O_2 in 6 L/min O_2/air by facemask), and a target-controlled remifentanil infusion (Alaris® PK Carefusion, Switzerland, Rolle, Minto Model) was started with the target effect-site concentration (C_e) set at 3 ng/mL. After 3 minutes, anesthesia was induced with propofol (2 mg/kg). Following tracheal intubation, facilitated with rocuronium 0.6 mg/kg, the lungs were recruited and controlled mechanical ventilation was started, including 5 cm H_2O PEEP (Aisys® Anesthesia Machine, GE, Madison, WI, USA). Minute ventilation (MV) was adjusted to maintain the end-expired CO_2 partial pressure (F_ACO_2) between 35 and 40 mm Hg.

Anesthesia was maintained using the target control function of the Aisys®, with a target end-expired sevoflurane partial pressure ($F_A$sevo) of one age-adjusted MAC and a target inspired O_2 partial pressure (F_IO_2) of 40% in O_2/air. The MAC was age-adjusted according to Nickalls.[12] Gases were sampled at the Y-piece and analyzed by the multigas analyzer of the anesthesia machine (Datex-Ohmeda S/N APGR00751). If heart rate or blood pressure increased 20% above baseline values (immediate pre-induction values) or systolic blood pressure increased above 140 mm Hg, C_e remifentanil was increased. Hypotension (systolic blood pressure ≤80 mm Hg) was treated by decreasing the C_e remifentanil (with a 1.5 ng/mL lower limit), additional fluid administration, and by intravenous phenylephrine or ephedrine, depending on the prevailing heart rate.

Thirty minutes before the anticipated end of surgery, acetaminophen (1 g), diclofenac (75 mg), and ondansetron (4 mg) were administered intravenously. At the start of skin closure, C_e remifentanil

TABLE 1 CONSORT guideline flow chart diagram



ICHV, isocapnic hyperventilation group; NV, normoventilaton group.

was reduced to 1.5 ng/mL, and any residual muscle paralysis was reversed with neostigmine (0.06 mg/kg) and glycopyrrolate (0.012 mg/kg). Once C_e remifentanil had decreased to 1.5 ng/mL and the procedure completed, sevoflurane and remifentanil administration was discontinued. In both groups, F_IO_2 was increased to 100%, and fresh gas flow (FGF) increased to 20% above MV to avoid rebreathing. Ventilation was then managed according to the study group the patient had been assigned to. In the NV group, ventilation was left unchanged. In the ICHV group, respiratory rate was doubled, tidal volume left unchanged, and the I:E ratio set to 1:1 to keep peak inspiratory pressures as low as possible. A calibrated CO_2 rotameter (MEDEC, Aalst, Belgium) was used to titrate the CO_2 inflow into the sampling port of an HME filter placed between the machine outlet and the inspiratory limb of the breathing system to maintain F_ACO_2 between 35 and 40 mm Hg.

TABLE 2 Patient demographics and anesthetic characteristics in the normoventilation (NV) and isocapnic hyperventilation (ICHV) groups

	NV	ICHV	*P*
Height (cm)	166 ± 10	170 ± 8	0.54
Weight (kg)	73 ± 13	74 ± 14	0.92
Lean body mass (kg)	51 ± 8	52 ± 7	0.42
BMI	26 ± 4	26 ± 5	0.99
Age (y)	56 ± 18	47 ± 21	0.49
Patients per group (n)	13	12	
Procedures			
Rhinoseptoplasty	2	4	
Tumorectomy (Breast)	5	1	
Mastectomy	4	0	
Breast prosthesis	1	1	
Lipofilling	0	3	
Abdominoplasty	0	3	
Deep inferior epigastric artery plasty	1	0	
Maintenance $F_A$sevo (%)	1.60 ± 0.02	1.70 ± 0.05	0.84
Maintenance $F_A$sevo (age-adjusted MAC)	1.00 ± 0.01	1.02 ± 0.04	0.86
Maintenance F_ACO_2 (mm Hg)	35 ± 3	38 ± 2	0.02
Emergence F_ACO_2 (mm Hg)	37 ± 2	39 ± 1	0.01
Duration anesthetic agent administration (min)	128 ± 84	150 ± 63	0.14
Duration anesthesia (min)	133 ± 88	157 ± 60	0.13
Duration remifentanil infusion (min)	125 ± 85	153 ± 64	0.36
MV during maintenance (L/min)	4.2 ± 0.5	5.3 ± 1.4	0.02
MV during emergence (L/min)	4.2 ± 0.6	10.7 ± 2.7	<0.001
Tidal volume (mL)	429 ± 43	478 ± 73	0.06
RR during maintenance (1/min)	10 ± 1	10 ± 2	0.62
RR during emergence (1/min)	10 ± 1	20 ± 4	<0.001

MV, minute ventilation; RR, respiratory rate.

The beginning of emergence, time zero, T_0, was defined as the moment FGF was increased and the vaporizer turned off. During the study period, the patient was not touched or moved. We determined the time to proper response to verbal command (T_{EYE}); time to ETT removal (T_{ETT}); and time to name stating (T_{NAME}). The study ended after T_{NAME} was determined. Extubation was performed after the patient had regained consciousness (proper response to a verbal command to blink eyes) and had regular spontaneous breathing. At each of these recovery end points, $F_A$sevo and F_ACO_2 were recorded; after extubation, these were obtained by maintaining a tight mask fit. MV, $F_A$sevo, and F_ACO_2 data during maintenance were automatically downloaded from the anesthesia workstation to an Excel spreadsheet every minute. During emergence, these three parameters were manually recorded every 10 seconds. From $F_A$sevo, the time sequence of age-adjusted effect-site MAC (MAC_e) values for each patient was calculated using an effect-site half time of 3.2 minutes.[13] From these data, we calculated the time to reach 0.3 age-adjusted MAC_e in both groups. While 0.35 MAC is often used to denote a 50% probability of return of consciousness, we use 0.3 MAC to take the effect of opioids on MAC_{awake} into account.[14]

ANOVA followed by a significant parameter *t*-test was used to compare the following parameters between the two groups: demographic data; duration of anesthetic agent administration (defined as the time between propofol administration and turning off the sevoflurane vaporizer); duration of anesthesia (defined as the time between propofol administration and T_{EYE}); duration of remifentanil administration; time to reach recovery parameters (T_{EYE}, T_{ETT}, and T_{NAME}), and $F_A$sevo and F_ACO_2 at each recovery threshold. Linear regression analysis was arbitrarily chosen to examine the relationship between duration of anesthetic agent administration and T_{EYE}, T_{ETT}, and T_{NAME}. Results are presented as mean ± SD, with $P < 0.05$ considered statistically significant.

3 | RESULTS

After excluding patients because of protocol violations and incomplete data, 13 patients remained in the NV and 12 in the ICHV group. Patient demographics, duration of anesthetic agent

TABLE 3 Immediate outcome parameters in the normoventilation (NV) and isocapnic hyperventilation (ICHV) groups

	NV	ICHV	*P*
Time to T_{EYE} (min)	9.9 ± 2.9	7.6 ± 2.2	0.03
Time to T_{ETT} (min)	11.0 ± 2.4	7.6 ± 2.6	0.002
Time to T_{NAME} (min)	12.5 ± 2.6	8.9 ± 2.8	0.003
$F_A$sevo at T_{EYE} (%)	0.25 ± 0.16	0.12 ± 0.12	0.03
$F_A$sevo at T_{ETT} (%)	0.23 ± 0.15	0.12 ± 0.12	0.04
$F_A$sevo at T_{NAME} (%)	0.19 ± 0.10	0.11 ± 0.11	0.08
F_ACO_2 at T_{EYE} (mm Hg)	38 ± 2	39 ± 2	0.20
F_ACO_2 at T_{ETT} (mm Hg)	39 ± 4	39 ± 2	0.47
F_ACO_2 at T_{NAME} (mm Hg)	38 ± 3	39 ± 3	0.69

administration, duration of anesthesia, and duration of remifentanil infusion did not differ (Table 2). Blood loss during surgery was less than 100 mL in all patients, and there was no need for vasoactive agents during surgery.

During maintenance, $F_A$sevo, age-adjusted MAC, and F_ACO_2 were the same in both groups; however, MV was higher in the ICHV group (Table 2). During the T_0-T_{EYE} interval, MV was higher in the ICHV group (10.7 ± 2.7 vs 4.2 ± 0.6 L/min). F_ACO_2 was higher in the ICHV group but always remained within the isocapnic range (35–45 mm Hg) in individual patients. Recovery times were shorter in the IHCV group: 7.6 ± 2.2 vs 9.9 ± 2.9 min for T_{EYE}; 7.6 ± 2.6 vs 11.0 ± 2.4 min for T_{ETT}; and 8.9 ± 2.8 vs 12.5 ± 2.6 min for T_{NAME} (Table 3). In the ICHV group, extubation occurred immediately after regaining consciousness in all patients; thus, T_{EYE} and T_{EXT} are the same in this group.

During emergence, the $F_A$sevo (expressed as fraction of age-adjusted MAC) declined faster in the ICHV group (Figure 1), as did the corresponding effect-site age-adjusted MAC_e values (0.3 after

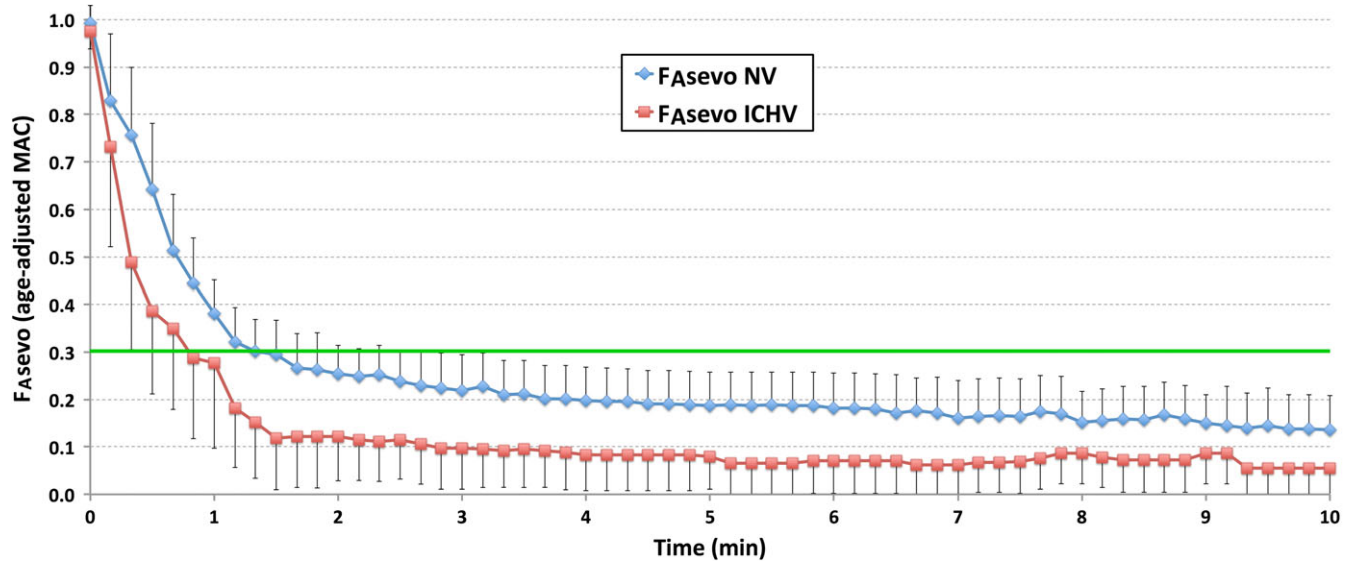


FIGURE 1 End-expired sevoflurane partial pressure ($F_A$sevo, expressed as fraction of age-adjusted MAC) over time during emergence in the normoventilation (NV) and isocapnic hyperventilation (ICHV) groups. The horizontal green line = 0.3 MAC [Colour figure can be viewed at wileyonlinelibrary.com]

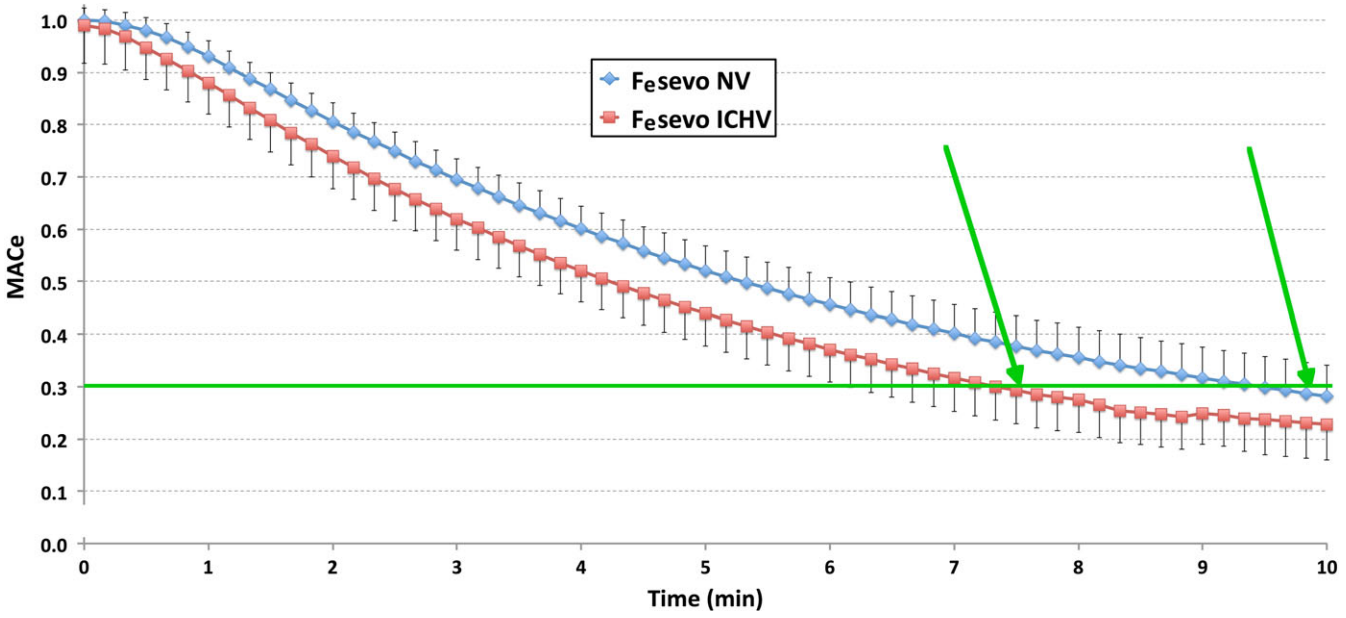


FIGURE 2 Calculated age-adjusted effect-site MAC (MAC_e) values during emergence the normoventilation (NV) and isocapnic hyperventilation (ICHV) groups. Horizontal green line = 0.3 MAC_e; green arrows = clinically observed T_{EYE} in each group (9.9 min in the NV group and 7.6 min in the ICHV group) [Colour figure can be viewed at wileyonlinelibrary.com]

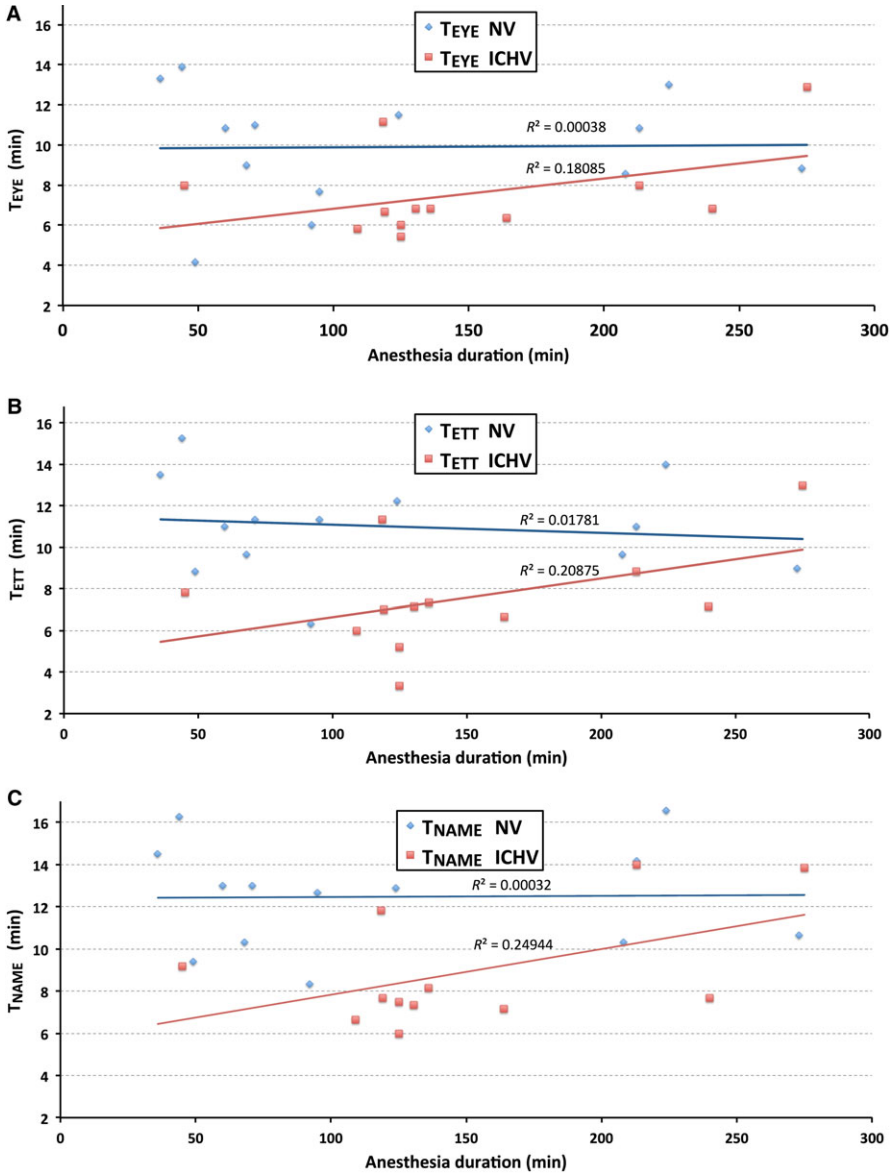


FIGURE 3 Linear regression analysis of anesthesia duration versus time to reach recovery end points (A: T_{EYE}; B: T_{ETT}; C: T_{NAME}) for NV and ICHV groups [Colour figure can be viewed at wileyonlinelibrary.com]

7.3 ± 2.2 and 9.5 ± 2.8 min in the ICHV and NV group, respectively; Figure 2). The clinical recovery end points were reached at lower $F_A$sevo values in the IHCV group (except for T_{NAME}), but F_ACO_2 values upon reaching these clinical end points did not differ (Table 3).

While linear regression analysis indicated duration of anesthesia had no effect on recovery times in the NV group, duration had some influence on recovery times in the ICHV group. However, the effect of ICHV on emergence times decreased with increasing duration of anesthesia (Figure 3).

4 | DISCUSSION

Isocapnic hyperventilation (ICHV) hastens emergence after one age-adjusted MAC of sevoflurane anesthesia, a finding congruent with that of previous studies with isoflurane and sevoflurane.[3,8-10] However, the overall effect of ICHV was more modest than previously reported, which may be the result of the combination of tight control of normoventilation in the control group (instead of the "gentle assisted ventilation" in previous studies) and strict control of anesthetic depth (well-defined age-adjusted MAC and target-controlled infusion of remifentanil). The times for response to verbal command (T_{EYE}) and the calculated times for age-adjusted MAC_e to reach 0.3 are similar: T_{EYE} 7.6 ± 2.2 min vs 7.3 ± 2.2 min for MAC_e to reach 0.3 in the ICHV group, and T_{EYE} 9.9 ± 2.9 min vs 9.5 ± 2.8 min for MAC_e to reach 0.3 in the NV group. These results provide further support for our conclusions that, under well-controlled conditions, the reduction in emergence time with ICHV when used with modern inhaled anesthetics is only a few minutes, suggesting that ICHV may not have enough benefits to justify its routine use in clinical practice. A potential disadvantage of ICHV is that it may result in a slightly higher incidence of rehypnotization if hypoventilation occurs after emergence from anesthesia.[11,15]

Isocapnic hyperventilation results in a lower $F_A$sevo at emergence, confirming that $F_A$sevo reflects effect-site partial pressure less

when changes in $F_A$sevo are more rapid (hysteresis). The reverse has been shown as well: during slow alveolar washout on emergence, $F_A$sevo reflects depth of anesthesia very well.[13]

We also observed that duration of anesthesia has minimal effect on emergence times as predicted by simulation studies where 80% decrement times of sevoflurane and desflurane in the vessel rich group were apparently minimally affected by duration of anesthesia.[16] In addition, the effect of ICHV on emergence times decreases with increasing duration of anesthesia (Figure 3), which may be related to a higher saturation of the muscle tissue group with longer procedures.

Some study limitations exist. First, minute ventilation during maintenance was higher in the ICHV group, which indicates that either endogenous CO_2 production or dead space ventilation was higher than in the control group. Second, the study results should not be extrapolated beyond the boundaries of its methods. For example, the effect of ICHV after prolonged anesthesia in patients having received long-acting opioids may require further study, as does the use of N_2O in this setting.

Hypercapnic hyperventilation can further reduce emergence times by increasing cerebral blood flow, presumably by faster removal of the inhalational agent from the CNS.[4-7] Hypercapnia increases cerebral blood flow by 6% for every mm Hg the P_aCO_2 increases above 40 mm Hg.[17] However, it is unclear how well hypercapnia itself is tolerated during emergence. Therefore, it is difficult to justify the use of hypercapnia to achieve supposedly small additional reductions in emergence times.

To summarize, under well-controlled conditions, the clinical benefits of isocapnic hyperventilation to speed up emergence after remifentanil/sevoflurane anesthesia in O_2/air appear to be small, making the introduction of ICHV in our daily practice of questionable value.

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CONFLICT OF INTEREST

None.

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