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Isocapnic hyperpnoea accelerates recovery from isoflurane anaesthesia

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Background. Hyperventilation should speed up elimination of volatile anaesthetic agents from the body, but hyperventilation usually results in hypocapnia. We compared recovery from isoflurane anaesthesia in patients allowed to recover with assisted spontaneous ventilation (control) and those treated with isocapnic hyperpnoea.

Methods. Fourteen patients were studied after approximately 1 h of anaesthesia with isoflurane. Control patients were allowed to recover in the routine way. Isocapnic hyperpnoea patients received 2–3 times their intraoperative ventilation using a system to maintain end tidal P_{CO_2} at 45–50 mm Hg. We measured time to removal of the airway and rate of change of bispectral index (BIS) during recovery.

Results. With isocapnic hyperpnoea, the time to removal of the airway was markedly less (median and interquartile range values of 3.6 (2.7–3.7) *vs* 12.1 (6.8–17.2) min, $P<0.001$); mean (SD) BIS slopes during recovery were 11.8 (4.4) *vs* 4.3 (2.7) min^{-1} ($P<0.01$) for isocapnic hyperpnoea and control groups, respectively. Isocapnic hyperpnoea was easily applied in the operating room.

Conclusions. Isocapnic hyperpnoea at the end of surgery results in shorter and less variable time to removal of the airway after anaesthesia with isoflurane and nitrous oxide.

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Hyperventilation increases the rate of elimination of volatile anaesthetics from the blood[1 2] but it also decreases arterial P_{CO_2}. This can cause post-hyperventilation apnoea,[3] and decrease cerebral blood flow,[4] thereby prolonging washout of anaesthetic from the brain. Hyperventilation could facilitate recovery from volatile anaesthetics if the disadvantages of hypocapnia could be prevented. We will refer to increased ventilation without a change in P_{CO_2} as 'hyperpnoea'.

Sasano and colleagues[5] demonstrated in dogs that isocapnic hyperpnoea speeded recovery from isoflurane-maintained anaesthesia. These results may not be applicable clinically if $\dot{V}_E$ cannot be increased mechanically in patients whose airways are controlled with laryngeal masks or tracheal tubes as they recover from anaesthesia. Recovery in humans and dogs may differ because of differences in proportion of muscle and fat, distribution of blood flow to the brain, and sensitivity of the brain to anaesthetics.[6] Post-surgical pain, which was absent in the dogs, may also affect arousal.[7]

In this study, we compared emergence from anaesthesia with isoflurane-nitrous oxide in patients who were allowed to recover under assisted spontaneous ventilation (control group) with those who were treated with isocapnic

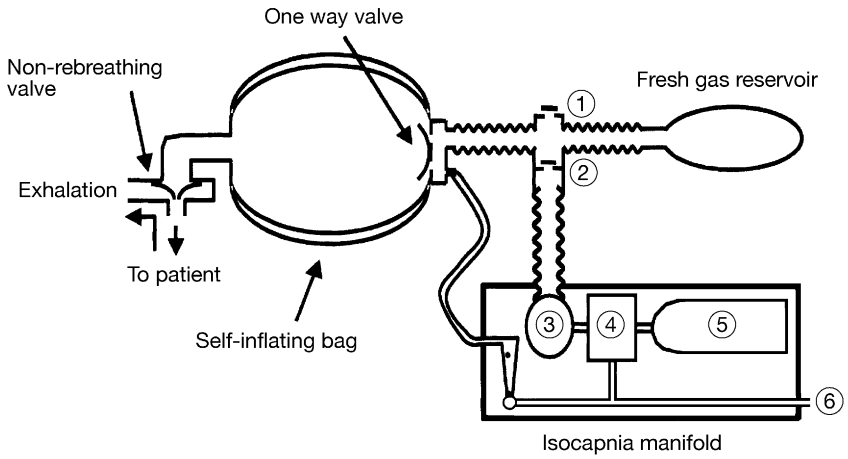

Fig 1 Isocapnic hyperpnoea apparatus composed of a standard resuscitation bag that includes a high-pressure relief valve (1) and a low-pressure relief valve (2) with the compact manifold attached. The manifold delivers oxygen 100% from an oxygen source (6) via a flowmeter, and contains a blender (4), which combines oxygen and carbon dioxide (5) to provide reserve gas to the low-pressure relief valve via a demand regulator (3).

hyperpnoea after surgery. We measured time to removal of the airway and the rate of change of bispectral index (BIS) during recovery.

Methods

With Institutional Research Board approval and after obtaining written informed consent, 14 ASA class I or II patients undergoing procedures estimated to be 1–2 h in duration were anaesthetized in a standard way. No premedication was used. Induction of anaesthesia was with propofol 2–2.5 mg kg^{-1}. The airway was maintained with a laryngeal mask or tracheal tube, according to the preference of the anaesthetist. Tracheal intubation was assisted with fentanyl 1–2 μg kg^{-1} and succinylcholine 1–2 mg kg^{-1}. Patients breathed spontaneously and anaesthesia was maintained with isoflurane and nitrous oxide. Fentanyl was given in increments of 25 μg i.v. at the discretion of the anaesthetist, but withheld in the 20 min before the expected completion of surgery. After the application of the wound dressing, patients were randomized to isocapnic hyperpnoea or control groups using sealed envelopes containing equal numbers of papers marked with either 'isocapnic hyperpnoea' or 'control'.

To begin the recovery period, isoflurane and nitrous oxide were turned off (time=0). In the control group, patients continued to breathe via the circle anaesthetic circuit. Oxygen flow was set greater than 10 litre min^{-1}, and the anaesthetist was instructed to assist ventilation as clinically indicated to prevent hypoxia, treat excess hypercarbia, and provide for the elimination of volatile anaesthetics. In the isocapnic hyperpnoea group, the anaesthetic circuit was disconnected from the patient's airway. The patient's lungs were then manually ventilated with the isocapnic hyperpnoea apparatus to maintain end-tidal P_{CO_2} ($P_{E'_{CO_2}}$) at 45–50 mm Hg independent of $\dot{V}_E$ and without re-breathing. The target ventilation was 15 litre min^{-1} measured using the ventilation monitor (Datex AS/3, Helsinki, Finland). The airway was removed (and timing stopped) when patients responded to the command to open their eyes. We monitored vital signs, tidal gas, and vapour concentrations, exhaled minute volume (Datex AS/3, Helsinki, Finland), and the BIS (Aspect Medical Systems, Newton, MA, USA). Data from the AS/3 were digitized at 60 Hz using a DI-720 analogue-to-digital converter (Dataq, Akron, OH, USA) and recorded continuously. Times from turning off the vaporizer to removal of the airway were recorded.

Isocapnic hyperpnoea apparatus

The isocapnic hyperpnoea apparatus (Fig. 1) was configured for the operating room as a modified self-inflating bag (Pulmanex, SensorMedics, Yorba Linda, CA, USA) supplied by gases from a compact manifold (SensorMedics) on a stand beside the anaesthetic machine. The manifold was supplied with pure carbon dioxide from an 'E-size' cylinder; oxygen was supplied via a T-piece to the manifold from the anaesthetic machine supply. The manifold had a flowmeter that supplied the self-inflating bag with the basal oxygen flow calculated to be equal to that alveolar ventilation resulting in P_{CO_2} of 50 mm Hg. The manifold also contained a gas blender that blended the pure carbon dioxide and oxygen to provide a mixture of carbon dioxide 6%:oxygen 94% ('reserve gas') and a demand regulator that supplied the reserve gas to the low-pressure relief valve of the self-inflating bag. With this system, when $\dot{V}_E$ is equal to or less than the basal oxygen flow, the resuscitation bag functions normally, providing oxygen 100%. When however, $\dot{V}_E$ is increased above the oxygen flow, the balance of the inspired gas consists of reserve gas drawn through the low-pressure relief valve. The volume of fresh gas entering the alveoli determines the alveolar P_{CO_2} ($P_{A_{CO_2}}$) and allows the

Table 1 Patient characteristics

	Age	Sex	Height (cm)	Weight (kg)	ASA score	Surgery
Isocapnic hyperpnoea group						
	66	F	165	77	2	Total knee replacement
	69	M	167	92	2	Trans-urethral prostatectomy
	36	F	160	60	2	Shoulder arthroscopy
	53	M	179	88	1	Knee arthroscopy
	68	M	175	84	2	Bilateral knee arthroscopy
	19	F	160	54	1	Knee arthroscopy
	51	M	179	80	1	Knee arthroscopy
Mean (SD)	52 (7)		169 (8)	76 (14)		
Control group						
	19	M	169	65	1	Bilateral knee ACL repair
	12	M	160	50	1	Bilateral knee ACL repair
	73	M	175	80	2	Hydrocelectomy
	31	F	170	67	1	Knee ACL repair
	64	F	150	47	2	Trans-urethral bladder resection
	41	M	168	75	1	Elbow arthroscopy
	58	F	155	65	2	Knee arthroscopy
Mean (SD)	43 (23)		164 (9)	64 (12)		

elimination of the volatile anaesthetic. The reserve gas does not affect the $P_{A_{CO_2}}$ (because its P_{CO_2} is approximately equal to that in the alveoli), but does increase the gas flow allowing washout of the volatile anaesthetic.

Statistical analysis

Analysis was performed using SigmaStat for Windows version 2.0 (Jandel Corporation), on an IBM Thinkpad T23 computer with a Pentium processor and Microsoft WindowsXP operating system. Parametric data were compared using two-tailed *t*-test with results expressed as means (SD); *P*-values <0.05 were judged significant. Non-parametric data were analysed using the Mann–Whitney *U*-test and expressed as medians with inter-quartile values.

Power analysis

We assumed that the average time to emergence in the control group would be about 10 min with an SD of 5 min. Assuming an alpha of 0.05 and a probability of accepting the null hypothesis of 0.8, power analysis predicted a sample size of 13 to identify a reduction of the recovery time by 50%.

Results

Seven patients were assigned to each group (see Table 1). Patients in the two groups were comparable with respect to anaesthesia (see Table 2). Patients tolerated isocapnic hyperpnoea without gagging, coughing, or cardiovascular instability. The anaesthetist was able to take over the ventilation of most patients; for those who continued to make ventilatory efforts, the anaesthetist assisted the patient's inspiratory efforts, increasing their tidal volume.

Table 2 Comparison of isocapnic hyperpnoea and control groups. Values are expressed as mean (SD), except fentanyl and propofol doses, which are expressed as median (interquartile range). End-tidal isoflurane concentration during last 3 min of anaesthesia

	Isocapnic hyperpnoea	Control
Duration of surgery (h)	1.1 (0.7)	1.0 (0.7)
Airway management		
Laryngeal mask	5	5
Tracheal tube	2	2
Total dose of propofol (mg)	200 (170–200)	250 (185–272)
Total dose of fentanyl (μg)	100 (81–138)	100 (56–100)
End-tidal isoflurane concentration (%)	1.1 (0.3)	1.3 (0.5)
Mean $P_{E'_{CO_2}}$ during emergence (mm Hg)	46.9 (2.7)	46.8 (3.5)

Results are shown in Figure 2. Patients in the isocapnic hyperpnoea and control groups had similar values of $P_{E'_{CO_2}}$ (46.9 (2.7) and 46.8 (3.5) mm Hg, respectively) despite greater $\dot{V}_E$ in the former (17.0 (3.8) *vs* 5.9 (1.2) litre min^{-1}, $P<0.05$). In the isocapnic hyperpnoea group, time to removal of the airway was less (median and interquartile values of 3.6 (2.7–3.7) *vs* 12.1 (6.8–17.2) min, $P<0.001$). BIS scores during emergence for all subjects are shown in Figure 3. The mean (SD) rate of change of BIS between the end of surgery and removal of the airway was 11.8 (4.4) *vs* 4.3 (2.7) unit min^{-1} ($P<0.01$) for isocapnic hyperpnoea and control groups, respectively. We did not observe any increase of anaesthetic depth after extubation. Clinical recovery in the post-anaesthetic care unit (PACU), as assessed from the nursing record, was uneventful in both groups. Our assessment was not sufficiently detailed to detect differences in fine motor skills, higher cognitive function, and incidence of post-operative nausea and vomiting.

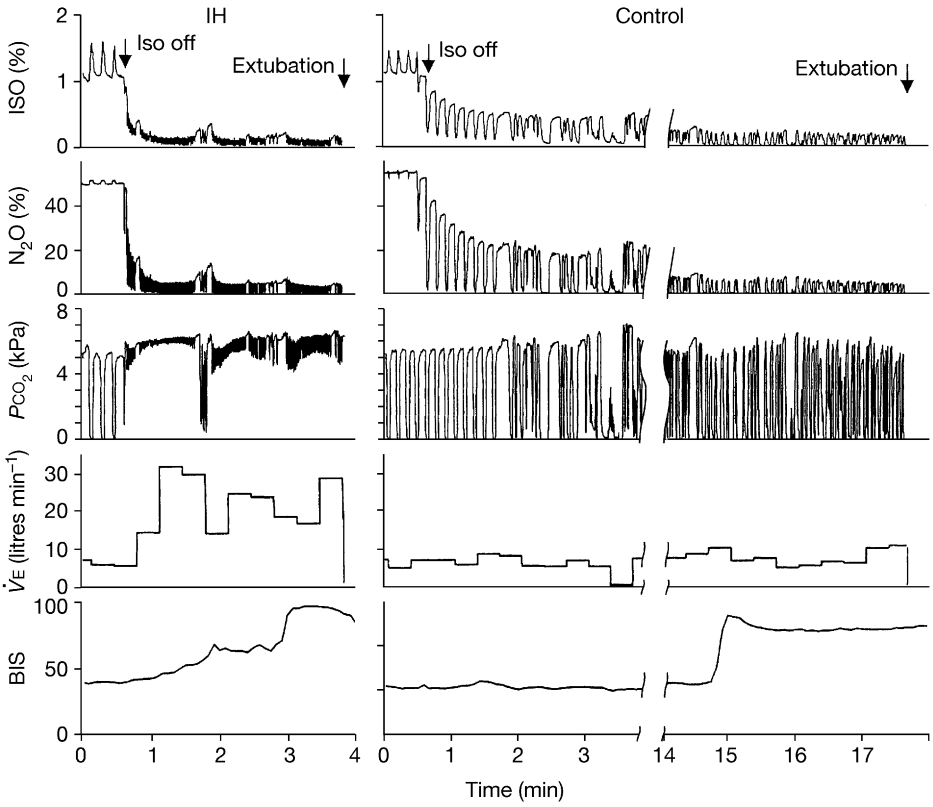

Fig 2 Comparison of recovery times of typical patients from isocapnic hyperpnoea (left panel) and control (right panel) recovery groups.

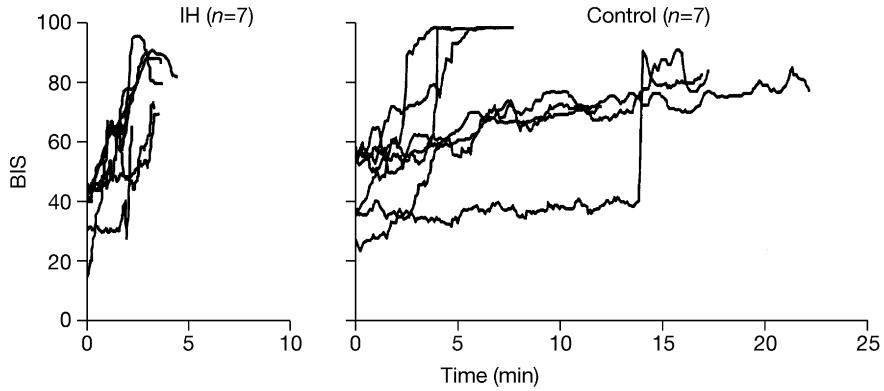

Fig 3 BIS scores from all subjects from beginning of emergence to removal of airway.

Discussion

We describe the first application of isocapnic hyperpnoea to patients to reduce the time of emergence from anaesthesia. In our patients, tripling $\dot{V}_E$ gave a reduced and less variable recovery time. The apparatus described by Sasano and colleagues[5] was convenient to use. It was easy to disconnect the anaesthetic circuit from the patient's airway, turn off the anaesthetic gas flow, and attach the self-inflating bag to the patient's airway. Stable $P_{E'CO_2}$ values were obtained in all patients regardless of $\dot{V}_E$ without specific attention to the pattern of breathing, and without the need for repeated adjustment of oxygen flow into the isocapnic hyperpnoea circuit.

The experimental protocol required following a practice that may conflict with usual practice. Opioid administration (type and dose) was restricted in the later part of anaesthetic maintenance; the concentrations of nitrous oxide and isoflurane adjusted accordingly, and maintained without tapering, until the end of surgery. Nevertheless, the protocol provided comparable conditions to test the two strategies for recovery from anaesthesia. Patients were randomized only

at the end of surgery so anaesthetists were unable to bias their anaesthetic technique towards either group. In addition, BIS provided an objective measure of recovery.

How much isocapnic hyperpnoea will speed recovery from anaesthesia in practice will depend on the details of the anaesthetic (e.g. agent used, depth and duration of anaesthesia, changes in agent concentration towards the end of surgery, use of adjuvant drugs such as opioids and benzodiazepines, type of airway management), surgery, and patient characteristics (e.g., age, sex, body size, sensitivity to various anaesthetics). Nevertheless, for any given operation and anaesthetic that uses an anaesthetic vapour, there will be a range of recovery times, which could be reduced by increasing the rate of vapour elimination. Isocapnic hyperpnoea may allow this.

To reduce recovery from anaesthesia, much effort and expense has been devoted to developing anaesthetics with low blood solubility, (λ). In contrast, we have taken the approach of increasing anaesthetic clearance by increasing $\dot{V}_E$. The rationale for hyperpnoea to speed emergence from anaesthesia follows from the relation between the factors determining the clearance of volatile anaesthetic agent from the blood passing through the lung as expressed by:

$$\text{Clearance} = \frac{1}{1 + \lambda \frac{\dot{Q}}{\dot{V}_E}} \quad (1)$$

where λ is the solubility of the vapour in blood, $\dot{Q}$ is cardiac output, and $\dot{V}_E$ is alveolar ventilation.[1]

Figure 4 illustrates that with only an approximately 3.5-fold increase in $\dot{V}_E$, the clearance of isoflurane (λ=1.38)[8] becomes equal to that of desflurane (λ=0.42).[8] Times to removal of the airway in our control subjects were within those reported previously for isoflurane but those in our subjects treated with isocapnic hyperpnoea were within the 4–10 min range expected for desflurane and sevoflurane (see tables VI and VII in Patel and Goa[8]).

The efficacy of hyperpnoea in accelerating recovery from anaesthesia is not surprising.[9] In 1923, White[10] reported that the average time for recovery of consciousness from ether anaesthesia could be reduced from an average of 75 to 14 min by adding carbon dioxide to inhaled gas, thereby increasing $\dot{V}_E$ to 25–35 litre min^{-1}. The use of hyperpnoea and adding carbon dioxide to inspired gas continued to be popular. A random survey of 1528 anaesthetists in the UK published in 1989 indicated that 60% of the 1100 respondents routinely used carbon dioxide.[11] Since that time, the practice has been discouraged (Checklist For Anaesthetic Apparatus, 2, Association of Anaesthetists, 1997). In North America, adding carbon dioxide to the inspiratory limb of a circuit to stimulate breathing or to maintain isocapnia during imposed hyperpnoea is now seldom practised, mainly because it is technically awkward to perform, risks inadvertent hypercarbia,[12] and increases the consumption of carbon dioxide absorbent.

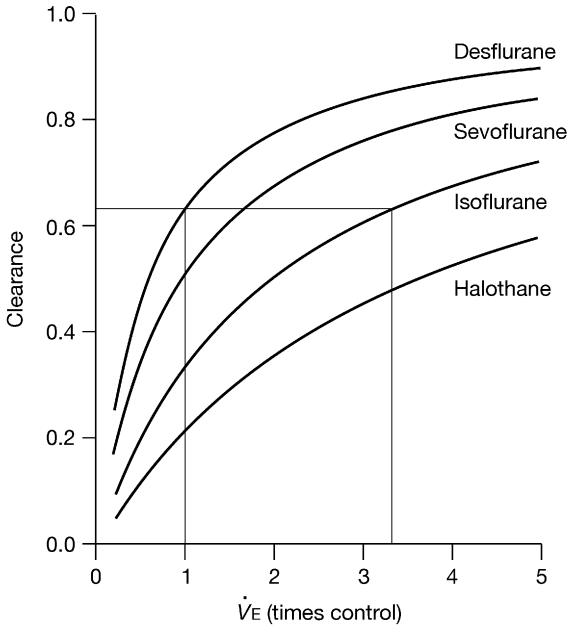

Fig 4 Calculated clearance of anaesthetic as a function of $\dot{V}_E$, using equation 1 with known values of λ, and assuming 'normal' $\dot{V}_E$ of 5 litre min^{-1}, $\dot{V}_E$=0.7 $\dot{V}_E$, and $\dot{Q}$=5 litre min^{-1} and independent of $\dot{V}_E$.

Sasano and colleagues[5] recently introduced a new method of non re-breathing isocapnic hyperpnoea, which avoids the risk of hypercarbia. Manual hyperventilation is applied using a separate circuit consisting of a modified standard self-inflating bag (Fig. 1). Patients can be monitored routinely with pulse oximeter and capnograph. The isocapnic hyperpnoea circuit provides oxygen at low $\dot{V}_E$ and, when $\dot{V}_E$ is increased, adds carbon dioxide in the form of carbon dioxide 6% in oxygen, in direct proportion to the increase in $\dot{V}_E$ in order to maintain isocapnia.[13] The separate circuit, in contrast to using carbogen (carbon dioxide 5%, oxygen 95%), maintains isocapnia independent of $\dot{V}_E$ without increasing the rate of consumption of the carbon dioxide absorbent.

The isocapnic hyperpnoea circuit has an additional fail-safe feature. Even with only mild hyperpnoea (10 litre min^{-1}) and with a complete failure of oxygen flow (oxygen flow=0), in a 70 kg male, the Pa_{CO_2} would equilibrate between 70 and 80 mm Hg, which is unlikely to be dangerous in most well-oxygenated patients. Moreover, hyperpnoea with reserve gas alone will still result in the patient waking within the same time as with the oxygen flow and therefore the $P_E'_{CO_2}$ might not have time to reach that equilibrium value.

Increased $\dot{V}_E$ affects the rate of elimination of isoflurane from the lungs.[2] As the equilibration of isoflurane in the blood with the tissues is very rapid,[14] the removal of isoflurane from the blood via the lungs will be followed closely by removal from the vessel rich group (VRG). The

clearance of anaesthetic from the various parts of the VRG will also depend on their respective blood flows. Conventional hyperventilation and reduction of Pa_{CO_2} at the end of surgery reduces blood flow to the brain, and may delay the clearance of anaesthetic from the brain relative to other tissues of the VRG. This would offset the effect of more rapid elimination from the blood on time to recovery. For an equivalent minute ventilation, maintaining normocapnia and higher brain blood flow should allow more rapid equilibration of partial pressures of anaesthetic between brain and arterial blood. However, further investigation is required to ascertain whether isocapnic hyperpnoea shortens or improves the quality of emergence compared with hyperventilation.

A further consideration is the effect of hyperpnoea on cardiovascular stability. Henderson and Haggard[9] increased $\dot{V}_E$ to 30–70 litre min^{-1} in their ether-anaesthetized patients and noted a decrease in arterial pressure of only 5–15 mm Hg. Deliberate hyperpnoea does not decrease stroke volume or arterial pressure in animals[15 16] or humans.[17] We observed no cardiovascular effects of increased $\dot{V}_E$ with isocapnic hyperpnoea to, at most, 20 litre min^{-1}. However, the isocapnic hyperpnoea was applied during recovery when arterial pressure and heart rate naturally increase and this may have obscured any such effects.

Isocapnic hyperpnoea may also speed up the elimination from the blood, via the lung, of other volatile agents such as carbon monoxide[18 19] and be useful as a research tool in studying the pharmacokinetics of such agents, or in other instances in which it is necessary to keep the patient's P_{CO_2} constant.

Conclusion

Isocapnic hyperpnoea was successfully applied in the operating room and, for our anaesthetic protocol, resulted in faster, less variable emergence time.

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