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 $PCO_2$ 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 but it also decreases arterial $PCO_2$. This can cause post-hyperventilation apnoea, and decrease cerebral blood flow, 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 $PCO_2$ as ‘hyperpnoea’.

Sasano and colleagues demonstrated in dogs that isocapnic hyperpnoea speeded recovery from isoflurane-maintained anaesthesia. These results may not be applicable clinically if $Ve$ 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. Post-surgical pain, which was absent in the dogs, may also affect arousal.

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
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 pre-
medication 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 main-
tained 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 hyper-
pnoea apparatus to maintain end-tidal PCO₂ (PECO₂) at 45–
50 mm Hg independent of VE 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
anologue-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) sup-
plied 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;
oxxygen was supplied via a T-piece to the manifold from the
anaesthetic machine supply. The manifold had a flowmeter
that supplied the basal oxygen flow calculated to be equal to that
at the alveolar ventilation resulting in PCO₂ 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 VE is equal to or less
than the basal oxygen flow, the resuscitation bag functions
normally, providing oxygen 100%. When however, VE 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 PCO₂ (PACO₂) and allows the

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).
elimination of the volatile anaesthetic. The reserve gas does not affect the $P_{ACO_2}$ (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.

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**Table 1** Patient characteristics

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

**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

<table>
<thead>
<tr>
<th>Isocapnic hyperpnoea</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (h)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td>Airway management</td>
<td></td>
</tr>
<tr>
<td>Laryngeal mask</td>
<td>5</td>
</tr>
<tr>
<td>Tracheal tube</td>
<td>2</td>
</tr>
<tr>
<td>Total dose of propofol (mg)</td>
<td>200 (170–200)</td>
</tr>
<tr>
<td>Total dose of fentanyl (µg)</td>
<td>100 (81–138)</td>
</tr>
<tr>
<td>End-tidal isoflurane concentration (%)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Mean $P_{E CO_2}$ during emergence (mm Hg)</td>
<td>46.9 (2.7)</td>
</tr>
</tbody>
</table>

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 $V_{E}$ 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.
Discussion

We describe the first application of isocapnic hyperpnoea to patients to reduce the time of emergence from anaesthesia. In our patients, tripling $V_E$ gave a reduced and less variable recovery time. The apparatus described by Sasano and colleagues 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 $P_{\text{ET}}CO_2$ values were obtained in all patients regardless of $V_E$ 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

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.
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 VE. 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:

\[ \text{Clearance} = \frac{1}{1 + \lambda \frac{Q}{VE}} \]  

(1)

where \( \lambda \) is the solubility of the vapour in blood, \( Q \) is cardiac output, and \( VE \) is alveolar ventilation.\(^1\)

Figure 4 illustrates that with only an approximately 3.5-fold increase in \( VE \), the clearance of isoflurane (\( \lambda=1.38 \))\(^8\) becomes equal to that of desflurane (\( \lambda=0.42 \)).\(^8\) 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 \( VE \) 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.

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 \( VE \) and, when \( VE \) is increased, adds carbon dioxide in the form of carbon dioxide 6% in oxygen, in direct proportion to the increase in \( VE \) in order to maintain isocapnia.\(^13\) The separate circuit, in contrast to using carbogen (carbon dioxide 5%, oxygen 95%), maintains isocapnia independent of \( VE \) without increasing the rate of consumption of the carbon dioxide absorbent.

The isocapnic hyperpnoea circuit has an additional failsafe 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 \( PCO_2 \) 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 \( P'CO_2 \) might not have time to reach that equilibrium value.

Increased \( VE \) 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 $P_{aCO_2}$ 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 recovery time to recovery.

A further consideration is the effect of hyperpnoea on cardiovascular stability. Henderson and Haggard increased $V_e$ 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 $V_e$ 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 $PCO_2$ 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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