Comparison of isoflurane with propofol on respiratory cilia

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Summary
We have investigated the effects of two techniques of clinical anaesthesia on human respiratory cilia by measuring cilia beat frequency of nasal tissue. In a randomized, controlled study, 13 patients undergoing either inhalation anaesthesia with isoflurane or total i.v. anaesthesia with propofol and alfentanil had nasal ciliated epithelial samples removed at the beginning and after 1 h of anaesthesia. Mean cilia beat frequency in the group anaesthetized with isoflurane changed significantly from 11.5 (95% confidence interval (CI) 10.7–12.2 Hz to 9.1 (8.1–10.1) Hz after anaesthesia whereas in the group anaesthetized with propofol and alfentanil there was a change from 11.5 (10.7–12.2) Hz to 11.0 (10.2–11.8) Hz (ns). The difference between the anaesthetic agents on cilia beat frequency was significant (MANOVA, \( P < 0.01 \)). These data suggest that different anaesthetic agents may impair respiratory defence mechanisms to differing extents. (Br. J. Anaesth. 1997; 79: 473–475).

Key words

Advances in anaesthesia over the past few decades have produced a very low level of mortality associated with anaesthesia; a recent report found that only three deaths out of almost 0.5 million procedures resulted from anaesthesia alone.1 Consequently, greater attention has focused on morbidity associated with anaesthesia, especially on serious forms of morbidity. An important and common type of morbidity is that caused by pulmonary infection. Prospective studies have described an incidence of 6–21%.2–5

The causes of postoperative pulmonary infections are multifactorial but depend on clearance of lung secretions. This requires effective coughing and ciliary transport of respiratory mucus. Most attention has been directed at improving coughing after its impairment by the effects of both anaesthesia and surgery. However, although it has been known for some time that anaesthetic agents can impair mucus transport rates,6,7 there have been few investigations.

It is most likely that impairment of mucus transport is caused by effects of the anaesthetic agents on the cilia.8 The most important determinant of ciliary transport of mucus is ciliary beat frequency9 and we have demonstrated previously, in vitro, differential effects of anaesthetic agents on cilia with a depressant effect after inhalation agents but no effect with propofol.10,11 This raises the possibility of a difference in clinical practice between the two techniques of inhalation anaesthesia and total i.v. anaesthesia (TIVA).

To investigate this possibility further, we have conducted a double-blind, randomized, controlled study of the effects of these two anaesthetic techniques on human respiratory cilia beat frequency.

Patients and methods
After obtaining Ethics Committee approval and informed patient consent, we studied 13 patients (nine males, four females, aged 27–71 yr) undergoing elective peripheral body surgery under general anaesthesia. Anaesthesia was induced with fentanyl 50–125 µg and propofol 160–320 mg, and a sample of ciliated nasal epithelial cells was obtained by passing a bronchoscopy brush over the inferior nasal turbinates as described previously.12 The brush was agitated in M199 medium to remove the cells.

Patients were allocated randomly to maintenance of anaesthesia with either an inhalation anaesthetic agent or TIVA as follows. Anaesthesia was maintained by face mask anaesthesia with 30–45% oxygen in air flowing via a circle system at 3 litre min\(^{-1}\) with the addition of either isoflurane or an i.v. infusion of propofol and alfentanil. Propofol and alfentanil were mixed together in a 60-ml syringe containing propofol 60 ml and alfentanil 2 mg. The concentration of isoflurane and the rate of propofol–alfentanil infusion were determined by clinical response to surgery. All patients received ketorolac 15 mg i.m. and local anaesthetic infiltration or regional nerve block of the surgical field before commencement of surgery.

The following variables were monitored and recorded: fractional inspired oxygen concentration, end-tidal carbon dioxide concentration, oesophageal temperature, non-invasive arterial pressure, ECG, arterial oxygen saturation and end-tidal isoflurane concentration.

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After 1 h of anaesthesia a second sample of nasal ciliated epithelium was obtained in the same manner as before.

Measurement of cilia beat frequency was undertaken as described and validated previously.13 Within 5 min of removal from the patient, the ciliated samples were transferred to a heated chamber for viewing by differential interference contrast microscopy (Nikon Diaphot 200, Nikon UK). The image of the cilia was transmitted to a video monitor (Sony KX-14CPI) via a video camera (Panasonic VW-CL 1 0-AK) to provide a magnified image of the moving cilia of 3000×. A pinhead photodiode with a diameter of 1 mm² was attached to the monitoring screen to detect interference in light caused by the moving cilia. The voltage across the diode was amplified to provide a signal to an oscilloscope greater than 0.2 V and low pass filtered with a cut-off above 25 Hz. The changing voltage signals were sampled by an analogue-to-digital converter. The voltage signals were collected over a period of 15 s and divided into three sequential 5-s intervals for analysis. Data were analysed by software written in Mathematica 2.2 to provide a power spectrum using fast Fourier transforms. The peak of the power spectrum was taken to represent cilia beat frequency. Baseline cilia beat frequency was similar in each group and is in close agreement with that reported previously in awake volunteers.16

### Results

Six patients were allocated randomly to receive isoflurane and seven to receive TIVA. Patients underwent lower limb varicose vein operations or day-case limb orthopaedic procedures. The groups were similar in age, sex distribution, oxygen saturation, carbon dioxide tension and core temperature (table 1). The reduction in beat frequency after 1 h of anaesthesia was 2.4 Hz. This reduction of more than 20% is significant in terms of its effects on mucus transport. This is based on the logarithmic relationship between cilia beat frequency and mucus transport rate such that modest reductions in beat frequency of the cilia are accompanied by greater reductions in mucus transport rate, and represents approximately a 50% reduction in mucus transport rate.

In previous work we have shown that a bolus dose of propofol has no effect on nasal cilia beat frequency measured 1 h later13 and in another investigation we showed there were no opioid receptors on the nasal cilia. Therefore, a bolus of propofol and fentanyl would not be expected to have an effect on cilia beat frequency. Baseline cilia beat frequency was similar in the two groups and is in close agreement with that reported previously in awake volunteers.16

### End-tidal isoflurane concentration

End-tidal isoflurane concentration were 1.5–2.5% and the range of concentrations measured was 1.5–2.5% and the range of propofol delivered was 500–600 mg. Mean cilia beat frequency in the group anaesthetized with isoflurane changed from 11.5 (95% confidence interval (CI) 10.7–12.2) Hz to 9.1 (8.1–10.1) Hz after anaesthesia and in the group anaesthetized with propofol and alfentanil from 11.5 (10.7–12.2) Hz to 11.0 (10.2–11.8) Hz (fig. 1). The difference between the anaesthetic agents on cilia beat frequency was significant (MANOVA, P<0.01).

### Discussion

We have found a difference in the beat frequency of nasal cilia exposed to inhalation agent anaesthesia with isoflurane compared with TIVA with propofol and alfentanil.

Figure 1  Effects of inhalation anaesthesia (IA) and total i.v. anaesthesia (TIVA) on human nasal cilia beat frequency (CBF) (mean (95% CI)).

**Table 1**  Patient data and variables measured during anaesthesia (mean (95% CI)) in the group who received inhalation anaesthesia (IA) compared with the total i.v. anaesthesia (TIVA) group

<table>
<thead>
<tr>
<th></th>
<th>Group IA</th>
<th>Group TIVA</th>
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<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/2</td>
<td>5/5</td>
</tr>
<tr>
<td>Age (range) (yr)</td>
<td>29–38</td>
<td>27–71</td>
</tr>
<tr>
<td>End-tidal isoflurane concn (%)</td>
<td>1.5–2.5%</td>
<td>—</td>
</tr>
<tr>
<td>Propofol delivered (mg)</td>
<td>—</td>
<td>500–600</td>
</tr>
<tr>
<td>(P_{\text{0.02}}) (%)</td>
<td>0.35–0.40</td>
<td>0.36–0.45</td>
</tr>
<tr>
<td>(S_{\text{0.02}}) (%)</td>
<td>96–98</td>
<td>96–98</td>
</tr>
<tr>
<td>End-tidal CO₂ (kPa)</td>
<td>4.5–6.8</td>
<td>5.0–7.0</td>
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<tr>
<td>Core temperature °C,</td>
<td></td>
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<tr>
<td>30 min</td>
<td>34.9–36.8</td>
<td>35.4–36.8</td>
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<tr>
<td>60 min</td>
<td>34.7–36.5</td>
<td>35.1–36.5</td>
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Comparison of isoflurane with propofol on respiratory cilia beat frequency.11 Thus our in vitro investigations concur with the findings from this clinical study.

We undertook a comparative study of patients under anaesthesia because there were several limitations to our earlier in vitro investigations. It is likely that the concentrations of drugs in the cilia are different when drugs are delivered to tissue samples in the laboratory compared with delivery by anaesthetic equipment to patients. Indeed the difference between these two agents on the cilia may be the result of different methods of delivery in clinical practice, with gas phase drug delivery possibly being more harmful than delivery to the cilia via the bloodstream. Furthermore, previous in vitro work did not include a controlled investigation comparing these two agents.

Various methods have been described for measurement of cilia beat frequency but are limited to in vitro techniques. Laser light scattering spectroscopy is a recent and sophisticated light technique that is not restricted to in vitro use;18 however, this technique is invasive and its use has been restricted by its expense which has limited its validation. The in vitro transmitted light technique is the most widely used and reliable technique for measurement of cilia beat frequency. It is reproducible, convenient and requires minimal subjective assessment; however, it is subject to the effects of extraneous vibrations and it cannot detect individual cilia. We have overcome the problem of vibration by setting the imaging system on an anti-vibration concrete base.13 Using an in vitro method for determination of cilia beat frequency introduces possible effects on the cilia by removal from their natural environment; however, the experiment was conducted in a controlled manner to take account of this.

It has been demonstrated by other workers that cilia beat frequency measured from nasal brushings is the same as that from samples taken from further down the respiratory tract19 and therefore nasal samples are likely to be representative of cilia from more distal parts of the lungs. Therefore, we elected to use nasal tissue for analysis as this is a less invasive sampling technique and modified the anaesthetic technique accordingly. By using a face mask, the inhalation anaesthetic agents passed over these ciliated cells in a similar manner to effects on bronchial cilia when using other airway devices.

The effects of a reduction in cilia beat frequency on respiratory defences and the subsequent development of pulmonary infections is not known. Retrospective comparisons of inhalation anaesthesia and TIVA have not demonstrated a difference in this regard.20 A controlled prospective study is required including groups at risk of postoperative pulmonary infections to determine if the choice of anaesthetic technique is important in this regard.

References