Respiratory response to skin incision during anaesthesia with infusions of propofol and alfentanil

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Background. The ventilatory response to skin incision during anaesthesia with enflurane is an increase in tidal volume without a change in frequency. As opioids affect respiratory frequency and also affect the processing of pain, we investigated if the breathing response to a painful stimulus could be different during anaesthesia using opioids.

Methods. We studied 12 patients during anaesthesia with target-controlled infusions of propofol (plasma target concentration 4–6 μg ml⁻¹) and alfentanil (plasma target concentration 40–60 ng ml⁻¹), having varicose vein surgery.

Results. After the initial skin incision, tidal volume increased promptly by 17 (4, 81)% (median, quartile values) (P<0.01). Respiratory frequency changed variably with no significant change overall [median change 2 (-8, +50)%]. The duration of inspiration was virtually unaltered, and the duration of expiration decreased gradually by 5 (-7, 32)%.

Patients who showed more response also showed more change in tidal volume, so that there was a significant relationship between increased inspiratory flow rate and reduced expiratory time (P<0.05).

Conclusions. During opioid anaesthesia, the mechanism of ventilatory increase after stimulation involves changes in both drive and timing of breathing. This pattern of response does not resemble the changes seen during anaesthesia with potent volatile agents.

Br J Anaesth 2002; 88: 649–52

Keywords: anaesthesia, general; anaesthetics i.v., propofol; analgesics opioid, alfentanil; ventilation, surgical stimulus

Accepted for publication: December 17, 2001
was recorded with a pneumotachograph (Mercury F10L, Mercury, Glasgow, UK) connected to a differential pressure transducer (Furness FC40) and a laptop computer with an analogue–digital converter (Amplicon PC30G) and a sampling rate of 20 Hz. This rate is approximately 200 times the fundamental frequency of the breathing we expected, and allows waveform reconstruction with good fidelity. The flow signal was subsequently integrated to obtain volume. From the flow and volume signals, we measured tidal volume and the durations of inspiration ($T_I$) and expiration ($T_E$) for each breath and calculated the mean inspiratory flow rate ($V_T/T_I$). Because of limits in the storage capacity of the software we used, the time available for recording was limited. After skin preparation and application of the surgical drapes, the patient received limited direct stimulation until the surgeon was ready to start the operation, but no other precautions were taken to standardize the stimulation of the patient during this time. Measurements were made of the three breaths before the first skin incision, and we calculated the average values for these breaths.

At the time of the first skin incision, we recorded the breaths taken during the next 20 s. No specific instructions

![Fig 1] Mean breathing pattern before and after surgical stimulation, with volume as a percentage of pre-incision tidal volume plotted against time.

![Fig 2] Changes in respiratory variables for the five breaths after incision, all expressed as fractions of the value before incision. The plots show the range, median and interquartile values.
were given to the surgical team about further manipulation. The tidal volume values from these breaths were expressed as fractions of the average of the three breaths before incision. We summarized these values and the timing of the breaths as median and quartile values. We compared the proportional changes in timing, tidal volume and drive using paired t-tests (Minitab version 12.1). Inspection of the changes suggested a relationship between the changes in drive and expiratory time which was confirmed by linear correlation.

**Results**

We studied five males and seven females, mean age 46 (range 25–77) yr, mean weight 75 (SD 9) kg. In one patient, the respiratory rate decreased to 4 b.p.m. in the period before the skin incision and data from this patient could not be analysed.

After surgical skin incision over the saphenous vein junction, minute ventilation increased, with considerable individual variation in the response (Fig. 1). Median tidal volume increased by the second breath by 17% (Fig. 2). However, the range of change was large (between 4 and 81%; quartile values). The duration of inspiration was virtually unaltered, and the duration of expiration decreased more gradually by 5 (–7 to 32)% (Fig. 2).

Patients with a greater increase in tidal volume also had a greater decrease in the duration of expiration. We found a significant relationship between the mean inspiratory flow rate and the decrease in expiratory time ($P<0.05$) (Fig. 3). The median respiratory rate after the initial painful stimulus was 8 (7–10) b.p.m. compared with a rate of 8 (6–9) b.p.m. before stimulation. However, the range of the respiratory rate varied widely, from 6 to 16 b.p.m. before stimulation and from 5 to 14 b.p.m. after stimulation.

**Discussion**

We found that the respiratory response to a painful stimulus during anaesthesia with infusions of propofol and alfentanil was a decrease in expiratory time, without a significant change in the duration of inspiration, and an increase in mean inspiratory flow rate. The responses were variable and the sample size limited. Nevertheless, the change in the duration of inspiration was very small and the variation less. Retrospectively, we estimate that the study had sufficient power to detect a clinically important change of 20%.

We found changes in both aspects of the control of breathing, often categorized as ‘drive’ and ‘timing’. These features, which are the rate of increase in central inspiratory neural activity (indicated by the mean inspiratory flow rate, $VT/VT_{total}$) and the duration of the inspiratory and expiratory phase of the respiratory cycle, are considered to be controlled separately. Mean inspiratory flow rate is a good indication of central neural ‘output’, and timing indicates features such as bulbopontine control and pulmonary and somatic afferent influences. Together, these measures provide a more fundamental indication of the control process than tidal volume and frequency.

We found changes that differed from the respiratory response to a painful stimulus in a conscious subject. This is both an increase in respiratory drive, leading to greater mean inspiratory flow and larger tidal volumes, and also a proportionate reduction in the duration of both phases of the respiratory cycle ($T_{I}$ and $T_{E}$), causing an increase in respiratory rate.

There is generally a linear relationship between $T_{I}$ and $T_{E}$, so that if $T_{I}$ is reduced, $T_{E}$ is reduced in proportion, and $VT/VT_{total}$ remains constant. A painful stimulus applied to patients anaesthetized with enflurane increases respiratory drive without a change in timing. However, other, less exact data report that a painful stimulus in patients anaesthetized with isoflurane increases minute ventilation by an increase in respiratory rate. The respiratory response to painful stimulation could differ according to the choice of anaesthetic.

In these studies, the anaesthetic was given by inhalation. The delivery of the anaesthetic and the depth of anaesthesia would be affected by the respiratory response to the initial painful stimulus. When using injected agents, as we did, the agents are delivered to the patient independently of the respiratory response. Our present study shows that, when a painful stimulus is applied to patients anaesthetized with propofol and alfentanil, in whom the duration of expiration is already increased, there is both an increase in respiratory drive and a reduction in expiratory duration. During anaesthesia, the effects of opioids are to reduce drive and increase duration of expiration, and both these effects are reduced by the stimulus. However, we did find great variation in the capacity of the stimulus to antagonize these effects, which may have been caused by different degrees of opioid activity in individual subjects.
Target-controlled infusion systems can generate blood concentrations greater than predicted and should be adjusted according to the clinical response. There may be a kinetic synergism between propofol and alfentanil, as propofol can inhibit the metabolism of alfentanil, and alfentanil can increase the plasma concentration of propofol. Propofol and alfentanil also interact pharmacodynamically. The opioid increases the effect of propofol, on consciousness and suppression of the lash reflex. Despite these potential effects, we established steady and generally acceptable anaesthesia with the agents before surgical stimulation. We conclude that, during opioid anaesthesia by propofol infusion, the mechanism of ventilatory increase after stimulation involves changes in both drive and timing of breathing.

Acknowledgement
Dr Elizabeth Lovie helped with the clinical management of the patients.

References