Effects of surgical stimulation on the apnoeic thresholds for carbon dioxide during anaesthesia with sevoflurane

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Summary
Mechanical hyperventilation may produce hypocapnic apnoea below the carbon dioxide off-switch threshold whereas an increase in arterial PCO₂ after post-hyperventilation apnoea causes reappearance of respiratory effort above the carbon dioxide on-switch threshold. To study the effects of surgical stimulation on these two thresholds, we have measured end-tidal PCO₂ (PE'CO₂) at the two thresholds, before and during surgical stimulation, in 14 patients undergoing mastectomy, anaesthetized with sevoflurane (1.2 MAC). Based on the reproducibility of the results, data from 11 patients were analysed and data from the three other patients were discarded. Before surgical stimulation, mean resting PE'CO₂, off-switch threshold and on-switch threshold were 5.7 (SEM 0.2), 5.2 (0.2) and 6.1 (0.2) kPa, respectively. The off-switch threshold was significantly less than resting PE'CO₂ (P < 0.01) but the on-switch threshold was significantly greater than resting PE'CO₂ (P < 0.01). During surgical stimulation, resting PE'CO₂, off-switch threshold and on-switch threshold were 4.8 (0.2), 4.1 (0.2) and 4.7 (0.2) kPa, respectively. Although the off-switch threshold was significantly less than resting PE'CO₂ (P < 0.01), there were no significant differences between resting PE'CO₂ and on-switch threshold. These results indicate that surgical stimulation does not affect equally the carbon dioxide on- and off-switch thresholds. (Br. J. Anaesth. 1994; 73: 583-586)

Key words
Anaesthetics volatile, sevoflurane. Ventilation, carbon dioxide response.

Ventilatory activity is particularly responsive to changes in carbon dioxide. In anaesthetized subjects, mechanical hyperventilation may easily produce hypocapnic apnoea. The apnoeic threshold for carbon dioxide, at which respiration ceases and apnoea begins, provides an index of respiratory activity [1-3]. Indeed, Hickey and co-workers [3] showed that deepening of anaesthesia is usually associated not only with a decrease in ventilatory response to inhaled carbon dioxide but also with an increase in the apnoeic threshold for carbon dioxide. Similarly, Hanks, Ngai and Fink [1] determined the apnoeic threshold for carbon dioxide in subjects anaesthetized with halothane and showed that an increase in halothane concentration shifted the carbon dioxide response curve in the hypocapnic range to the right with a decrease in the slope.

Lam, Clement and Knill [4] showed that in subjects anaesthetized with enfurane there was a parallel leftward shift of the ventilatory carbon dioxide response curve in response to surgical stimulation. However, they did not study the effect of surgical stimulation on the apnoeic threshold for carbon dioxide and the effects of this stimulation on the apnoeic threshold for carbon dioxide remain unknown.

Although theoretically the apnoeic threshold for carbon dioxide at which ventilation becomes zero is a single point on the ventilatory carbon dioxide response curve, it is not easy to determine the exact value of the apnoeic threshold because of technical difficulties. It is easier to obtain two different thresholds for carbon dioxide in anaesthetized subjects: (1) carbon dioxide off-switch threshold, at which respiration ceases and apnoea begins, during mechanical hyperventilation; (2) carbon dioxide on-switch threshold, at which post-hyperventilation apnoea ceases and respiration begins. Determination of the on- and off-thresholds may have an important practical bearing on restoration of spontaneous respiration in anaesthetized patients who have been subjected to a period of artificial ventilation. For example, knowing the influence of surgical stimulation on the two thresholds, we could predict not only the time required to resume spontaneous respiration at the end of surgery but also the eupnoic PACO₂ during spontaneous breathing.

To test the hypothesis that surgical stimulation affects these two thresholds equally, we measured end-tidal PCO₂ (PE'CO₂) at the two thresholds, before and during surgical stimulation, in patients anaesthetized with sevoflurane.

Patients and methods
After approval of the Ethics Committee of the National Cancer Centre Institution, informed consent was obtained from 14 female patients aged...
ventilation was commenced at a tidal volume of 10–15 ml kg⁻¹ and a frequency of 4 b.p.m. When the initial ventilator settings did not cause a sufficient decrease in $P_{\text{CO}_2}$ (0.13–0.15 kPa min⁻¹), ventilator frequency was increased by 2 b.p.m. every 2 min until objective evidence of spontaneous respiratory efforts decreasing with a parallel reduction in $P_{\text{CO}_2}$.

The $P_{\text{CO}_2}$ value at which spontaneous respiratory activity ceased was defined as the carbon dioxide off-switch threshold. After 2 min at the apnoea inducing degree of ventilation, a mechanical deadspace of 450 ml was added to the breathing circuit so that $P_{\text{CO}_2}$ was slowly increased by 0.2–0.25 kPa min⁻¹ without changing the ventilator settings. $P_{\text{CO}_2}$ at which phasic respiratory activity reappeared was defined as the carbon dioxide on-switch threshold. Mechanical ventilation was then discontinued and spontaneous respiration without the mechanical deadspace was re-established. These measurements of apnoea thresholds were performed in duplicate. Approximately 60 min after the start of surgery, the series of measurements was repeated twice with an interval of 10 min.

Data are expressed as mean (SEM). Statistical analysis was performed using analysis of variance (two-way) followed by Sheffe’s test and paired t test with Bonferroni correction where appropriate. $P < 0.05$ was considered to be significant.

**Results**

In 11 of 14 patients, duplicate measurements of the on- and off-switch $P_{\text{CO}_2}$ thresholds during surgery were almost identical and the difference in values was < 0.13 kPa. However, in three patients the differences were relatively large (0.4–0.53 kPa). Much of the intra-subject variation could be attributed to surgical stimulation during measurements of the off-switch threshold. Typically, surgical stimulation, such as retraction of the muscles, nerves, or both, induced sudden appearance of spontaneous respiratory activity immediately after apnoea had been produced by mechanical hyperventilation and therefore a further decrease in $P_{\text{CO}_2}$ was needed to determine the off-switch threshold. Data from these patients were not included in the results.

Figures 1 and 2 illustrate changes in airway pressure, oesophageal pressure and $P_{\text{CO}_2}$ for one of the patients. The data were collected before, during, and after mechanical ventilation.
Surgical stimulation and apnoeic thresholds

Discussion

The most difficult problem in studying the effects of surgical stimulation on regulation of respiration is that quantification of surgical stimulation is nearly impossible as the intensity varies from moment to moment. The intensity may also depend on the type and site of surgery. To minimize these problems, in the present study we elected to investigate patients undergoing modified radical mastectomy performed by the same surgical team. We limited our measurements to the dissection phase of surgery when strong surgical stimuli such as skin incision or strong retraction of the muscles were not present. Furthermore, measurements were made in duplicate and rejected if not reproducible. However, it should be noted that all the patients were women undergoing radical mastectomy, and our findings may not be applicable to males or children undergoing different types of surgery.

Determination of apnoeic thresholds, particularly the on-switch threshold, may depend on the method used to produce changes in $P^e$CO$_2$. A reduction in mechanical ventilation may cause haemodynamic changes through its effects on venous return, which in turn may affect the on-switch threshold. Also, given the importance of lung or chest wall mechanoreceptors in the control of respiration, non-chemical factors related to the magnitude and frequency of thoracic displacement during mechanical ventilation may influence the on-switch threshold. In order to minimize the possible effects of these influences, we investigated the on-switch threshold by using mechanical deadspace to reduce alveolar ventilation while maintaining total lung ventilation constant.

We have confirmed previous findings [4, 6] that surgical stimulation acts as a ventilatory stimulant, inducing increases in ventilation and thereby reducing $P^e$CO$_2$. Surgical stimulation reduced mean $P^e$CO$_2$ by 0.89 kPa from values observed during sevoflurane anaesthesia alone. A similar reduction in carbon dioxide during surgical stimulation has been reported in patients anaesthetized with equipotent doses of enflurane [4] and isoflurane [6].

Mean $P^e$CO$_2$ at the off-switch threshold before surgical stimulation was 0.52 kPa less than resting $P^e$CO$_2$. This reduction in carbon dioxide needed to

Table 1  Mean (SEM [range]) changes in resting $P^e$CO$_2$, off-switch threshold and on-switch threshold before and during surgery. Significant differences ($P < 0.01$) compared with:

<table>
<thead>
<tr>
<th></th>
<th>Before surgery (kPa)</th>
<th>During surgery (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting $P^e$CO$_2$</td>
<td>5.68 (0.15)</td>
<td>4.79 (0.17)$^+$</td>
</tr>
<tr>
<td>Off-switch threshold</td>
<td>5.16 (0.15)$^{**}$</td>
<td>4.12 (0.15)$^{**+}$</td>
</tr>
<tr>
<td>On-switch threshold</td>
<td>6.05 (0.16)$^{**}$</td>
<td>4.74 (0.15)$^+$</td>
</tr>
</tbody>
</table>

The patients, before and during surgery. During quiet breathing before surgery (fig. 1A), $P^e$CO$_2$ was 5.6 kPa. Mechanical ventilation progressively decreased spontaneous respiratory activity with a parallel reduction in $P^e$CO$_2$ and spontaneous respiratory activity disappeared at a $P^e$CO$_2$ value of 5.1 kPa (fig. 1B, off-switch carbon dioxide threshold). With the addition of mechanical deadspace, $P^e$CO$_2$ started to increase and spontaneous respiratory activity resumed when $P^e$CO$_2$ was 6.0 kPa (fig. 1C, on-switch carbon dioxide threshold).

During surgical stimulation, resting $P^e$CO$_2$ was 5.1 kPa (fig. 2A) and the carbon dioxide on-switch and off-switch thresholds were 4.1 and 5.0 kPa, respectively (fig. 2B, C). These values were less than those before surgery.

Table 1 summarizes the changes in mean $P^e$CO$_2$, during resting breathing and at the apnoeic thresholds in 11 subjects before and during surgery. Before surgical stimulation, the off-switch threshold was significantly less than resting $P^e$CO$_2$ but the on-switch threshold was significantly greater. Surgical stimulation decreased significantly resting $P^e$CO$_2$, off-switch threshold and on-switch threshold. During surgical stimulation, the off-switch threshold was significantly less than resting $P^e$CO$_2$. However, there was no significant difference between the values of resting $P^e$CO$_2$ and on-switch threshold. Furthermore, the reduction in on-switch threshold produced by surgical stimulation (1.31 (0.11) kPa) was significantly larger ($P < 0.05$) than that for the off-switch threshold (1.04 (0.11) kPa).
produce apnoea was similar to that found by Hickey and colleagues [3] in subjects anaesthetized with halothane but was much less than that reported by Fink, Hanks and Holaday [7] who showed that in subjects anaesthetized with thiopentone and nitrous oxide, the off-switch threshold $P_{\text{ET}}^2\text{CO}_2$ was 1.33 kPa less than resting $P_{\text{ET}}^2\text{CO}_2$. Furthermore, the on-switch threshold $P_{\text{ET}}^2\text{CO}_2$ was 0.67 kPa less than resting $P_{\text{ET}}^2\text{CO}_2$ whereas in our study $P_{\text{ET}}^2\text{CO}_2$ at the on-switch threshold before surgical stimulation was 0.37 kPa greater than that of resting breathing. The differences between our results and those of Fink, Hanks and Holaday [7] could be attributed to the different anaesthetic agents or different levels of anaesthesia. Also, some of the data of Fink, Hanks and Holaday were obtained after minor surgery, and it is possible that even such minor surgery might have influenced the thresholds. In addition, there were differences between the two studies in the determination of the on-switch threshold. Fink, Hanks and Holaday increased carbon dioxide by reducing active ventilation whereas we increased carbon dioxide by addition of mechanical deadspace while maintaining the same ventilation. This difference may influence the on-switch threshold through mechanical ventilation-induced feedback. In this context, there is evidence that in human subjects, neuromechanical feedback related to mechanical ventilation causes inhibition of inspiratory muscle recruitment, causing an increase in the on-switch carbon dioxide threshold [8, 9].

The differences between on-switch and off-switch thresholds may in part be caused by the slow equilibration of $P_{\text{CO}_2}$ between the alveoli and central nervous system [7]. In this study, surgical stimulation reduced both the carbon dioxide on- and off-switch thresholds. However, the effects of surgical stimulation on the two thresholds were by no means equal as the reduction in the on-switch threshold during surgical stimulation was greater than that of the off-switch threshold. A possible explanation for the more marked reduction in the on-switch threshold during surgery is that by increasing cardiac output, surgical stimulation may facilitate equilibration of carbon dioxide tension between the alveoli and the respiratory neurones. However, we made no systematic examination of the effect of haemodynamic changes on the equilibration time in this study.

Another possible explanation is that surgical stimulation may counteract the neuromechanical inhibitory effect on respiratory muscle activity during mechanical ventilation, causing a marked reduction in the on-switch threshold.

Our results may have clinical implications in the restoration of spontaneous respiration in anaesthetized patients who have been subjected to a period of artificial hyperventilation. For example, when a surgical patient is allowed to resume spontaneous respiration after mechanical hyperventilation, spontaneous breathing may occur immediately after cessation of mechanical ventilation whereas in a non-surgical patient there may be a considerable delay in restoring spontaneous breathing after the same procedure.

References