Effects of subanaesthetic sevoflurane on ventilation. 1: Response to acute and sustained hypercapnia in humans

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We have determined the influence of 0.1 minimum alveolar concentration (MAC) of sevoflurane on ventilation, the acute ventilatory response to a step change in end-tidal carbon dioxide and the ventilatory response to sustained hypercapnia in 10 healthy adult volunteers. Subjects undertook a preliminary 10-min period of breathing air without sevoflurane to determine their normal ventilation and natural end-tidal $P_{CO_2}$. This 10-min period was repeated while breathing 0.1 MAC of sevoflurane. Subjects then undertook two procedures: end-tidal $P_{O_2}$ was maintained at 13.3 kPa and end-tidal $P_{CO_2}$ at 1.3 kPa above the subject’s normal value for 30 min of data collection, first with and then without 0.1 MAC of sevoflurane. A dynamic end-tidal forcing system was used to generate these gas profiles. Sevoflurane did not significantly change ventilation: 10.1 (SEM 1.0) litre min$^{-1}$ without sevoflurane, 9.6 (0.9) litre min$^{-1}$ with sevoflurane. The response to acute hypercapnia was also unchanged: mean carbon dioxide response slopes were 20.2 (2.7) litre min$^{-1}$ kPa$^{-1}$ without sevoflurane and 18.8 (2.7) litre min$^{-1}$ kPa$^{-1}$ with sevoflurane. Sustained hypercapnia caused a significant gradual increase in ventilation and tidal volume over time and significant gradual reduction in inspiratory and expiratory times. Sevoflurane did not affect these trends during sustained hypercapnia. These results suggest that 0.1 MAC of sevoflurane does not significantly affect the acute ventilatory response to hypercapnia and does not modify the progressive changes in ventilation and pattern of breathing that occur with sustained hypercapnia.

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Knill and colleagues1–4 investigated the effects of several anaesthetic agents on the hypercapnic ventilatory response in humans. They found that at doses of 0.1 MAC, nitrous oxide,1 enflurane2 and isoflurane3 reduced the slope of the ventilation–carbon dioxide response line (by 45%, 23% and 27%, respectively). Ether,1 methoxyflurane1 and halothane4 did not affect the response to carbon dioxide. However, Knill and colleagues assessed ventilatory responsiveness to carbon dioxide using the rebreathing method of Read (and, in the case of isoflurane, a single-breath test for carbon dioxide). It was suggested subsequently by Berkenbosch and colleagues that Read’s method gave misleading results which were difficult to interpret, especially when considering the effects of drugs on the ventilatory control system. They argued in favour of the use of the steady-state method to study ventilatory responses to carbon dioxide5–7.

More recently, halothane,8 nitrous oxide9 and desflurane10 have been investigated using the steady-state method. In contrast to the results of Knill and colleagues, Dahan and colleagues found that 0.1 MAC of halothane reduced the total slope of the ventilation–carbon dioxide response line by approximately 30%,8 while 0.17 MAC of nitrous oxide did not affect the response to carbon dioxide.9 These conflicting results were presumably caused in part by differences in the methods of measuring the response to carbon dioxide. Desflurane (0.1 MAC) could not be shown to affect the response to carbon dioxide.10

This article is accompanied by Editorial I.
In addition to the debate regarding rebreathing and steady-state methods of measurement, more is now known about the nature of the ventilatory response to sustained hypercapnia. If inspired carbon dioxide is increased such that end-tidal $P_{CO_2}$ ($P_{E'}CO_2$) is more than 0.26–0.39 kPa above the normal value, a progressive increase in ventilation (or ventilatory ‘drift’) occurs over the period of the hypercapnic exposure. $^{11}$ Only after 2–3 h is a true steady-state response achieved. $^{12}$

Sevoflurane is a newer anaesthetic agent, the properties of which, with respect to the ventilatory response to carbon dioxide in humans at subanaesthetic levels, have rarely been reported. Doid and Ikeda examined the effect of sevoflurane at anaesthetic concentrations of 1.1–1.4 MAC and found that it depressed the ventilatory carbon dioxide response slope (measured by a pseudo-rebreathing technique) by 65–90%. $^{13}$ van den Elsen and colleagues have recently reported that 0.1 MAC of sevoflurane reduced the acute peripheral but not central carbon dioxide sensitivity by approximately 27%. $^{14}$

The main purpose of this study was to assess whether 0.1 MAC of sevoflurane depressed spontaneous ventilation and the acute ventilatory response to hypercapnia. We wished to use the steady-state ‘dynamic end-tidal forcing technique’ to effect a square-wave change in $P_{E'}CO_2$ and to maintain $P_{E'}CO_2$ constant at a value of 1.3 kPa greater than each subject’s normal value. This relatively marked hypercapnia was chosen for two reasons: first, it is similar to that used by previous workers in studies assessing the response to hypercapnia $^{8–10}$; and second, ventilatory drift occurs readily if $P_{E'}CO_2$ is held at 1.3 kPa greater than normal. $^{11,12}$ A subsidiary aim of the study was to examine the interaction of sevoflurane with ventilatory drift.

**Subjects and methods**

We studied 10 healthy adult volunteers (five males; aged 19–21 yr; height 1.58–1.93 m; weight 51.7–89.5 kg). Subjects were asked to refrain from food for at least 6 h, and from drink for at least 4 h before each study. This study was approved by the Central Oxford Research Ethics Committee.

**Experimental technique**

Subjects were seated in a chair and breathed through a mouthpiece and wore a noseclip during the experiments. They watched television or read a book and held an alarm which, if they fell asleep and it fell from their hands would trigger a noise to alert the experimenter. Respiratory volumes were measured by a turbine volume measuring device $^{15}$ and flows by a pneumotachograph in series with the mouthpiece. Expired gas at the mouth was sampled continuously by a mass spectrometer (Airspec 3000, Airspec Ltd, Biggin Hill, Kent, UK) and analysed for $P_{CO_2}$ and $P_{O_2}$. Volumes, flows, and $P_{CO_2}$ and $P_{O_2}$ at the mouth were recorded in real time with a 50-Hz sampling frequency by a computer which also executed a peak-picking program to determine end-tidal $P_{CO_2}$ ($P_{E'}CO_2$), end-tidal $P_{O_2}$ ($P_{E'}O_2$), inspired and expired volumes, and duration of inspiration and expiration. Breath-by-breath end-tidal values were sent to a second computer which compared actual end-tidal values with desired values and adjusted the composition of the inspired gas by controlling a fast gas-mixing system to maintain the desired end-tidal values independent of changes in ventilation. Details of this dynamic end-tidal forcing technique and gas-mixing system have been described in detail elsewhere. $^{16,17}$

The mass spectrometer was zeroed with helium and calibrated for sevoflurane using the vaporizer with the output set at 3%. The accuracy of the vaporizer output was checked periodically using an infrared sevoflurane analyser (Datex Vitalert 3300, Drager, Telford, PA, USA) which had been calibrated independently with a standard concentration of sevoflurane. The readings of the vaporizer, mass spectrometer and infrared analyser were found to agree over a range of sevoflurane concentrations from 0.25% to 6%, and to be constant over a sustained period of use.

During experiments, the vaporizer setting was adjusted manually to achieve an end-tidal sevoflurane concentration of at least 0.25% and no more than 0.3% throughout the experiment. We took the MAC of sevoflurane to be 2.5% (Summary of Product Characteristics, Abbott Laboratories Ltd, Queenborough, Kent, UK).

A pulse oximeter was used to monitor oxygen saturation and an ECG to monitor heart rate.

**Procedures**

Subjects undertook a preliminary procedure consisting of a 10-min period of quiet air breathing. This was repeated while breathing 0.1 MAC of sevoflurane. Subjects then undertook the following two procedures in random order on separate days (if a control procedure was performed first, we allowed the subject to undergo a sevoflurane procedure on the same day, but not vice versa).

The control procedure consisted of 35 min during which the subject’s $P_{E'}CO_2$ was held constant at 1.3 kPa greater than the normal value. $P_{E'}O_2$ was maintained at 13.3 kPa throughout. The sevoflurane procedure was a repeat of the control procedure, but this time with 0.1 MAC of sevoflurane.

It was planned that each subject should undertake each of the above procedures twice. Unfortunately, after recruitment, two subjects were able to undertake each procedure only once.Seven subjects undertook each procedure twice. In one subject, an additional repeat of each procedure was undertaken. In total, 19 separate control experimental periods were obtained for the controls and 19 for the sevoflurane procedures.

**Data analysis**

Data were averaged over 1-min periods. The first 5 min of each control and sevoflurane procedure were excluded from
Effects of sevoflurane on ventilatory response to carbon dioxide

Table 1 Mean values for ventilation ($V˙E$) and $P_{E\text{CO}_2}$ during quiet, resting breathing (carbon dioxide unclamped) with and without sevoflurane. Sevoflurane had no significant effect on either variable (paired t test)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Control $V˙E$ (litre min$^{-1}$)</th>
<th>Sevoflurane $V˙E$ (litre min$^{-1}$)</th>
<th>Control $P_{E\text{CO}_2}$ (kPa)</th>
<th>Sevoflurane $P_{E\text{CO}_2}$ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>030</td>
<td>8.1</td>
<td>7.5</td>
<td>4.45</td>
<td>4.83</td>
</tr>
<tr>
<td>031</td>
<td>9.0</td>
<td>6.9</td>
<td>3.61</td>
<td>4.74</td>
</tr>
<tr>
<td>032</td>
<td>9.0</td>
<td>8.6</td>
<td>4.10</td>
<td>4.66</td>
</tr>
<tr>
<td>033</td>
<td>8.7</td>
<td>9.1</td>
<td>5.05</td>
<td>5.04</td>
</tr>
<tr>
<td>034</td>
<td>18.6</td>
<td>16.7</td>
<td>3.62</td>
<td>3.93</td>
</tr>
<tr>
<td>035</td>
<td>10.9</td>
<td>11.1</td>
<td>4.72</td>
<td>4.43</td>
</tr>
<tr>
<td>036</td>
<td>8.8</td>
<td>9.3</td>
<td>5.25</td>
<td>5.24</td>
</tr>
<tr>
<td>037</td>
<td>7.6</td>
<td>7.1</td>
<td>4.71</td>
<td>4.66</td>
</tr>
<tr>
<td>039</td>
<td>10.7</td>
<td>9.9</td>
<td>5.41</td>
<td>4.95</td>
</tr>
<tr>
<td>040</td>
<td>9.1</td>
<td>9.6</td>
<td>5.47</td>
<td>5.67</td>
</tr>
<tr>
<td>Mean</td>
<td>10.1</td>
<td>9.6</td>
<td>4.64</td>
<td>4.82</td>
</tr>
<tr>
<td>SEM</td>
<td>1.0</td>
<td>0.9</td>
<td>0.22</td>
<td>0.14</td>
</tr>
</tbody>
</table>

data analysis, leaving 30 min of data for analysis. The last 1 min of the preliminary procedure was used to assess each subject’s normal $P_{E\text{CO}_2}$ and ventilation with and without sevoflurane.

To assess the acute ventilatory response to hypercapnia, ventilation values at the fifth minute of each procedure (i.e. 10 min after introduction of hypercapnia) were used, and compared with values from the last 1 min of the preliminary procedure. This was done for both the control and sevoflurane procedures.

To assess trends or drifts in respiratory variables during sustained hypercapnia, the mean of the values over the first 5 min of each procedure (i.e. the mean of minutes 5–10 after induction of hypercapnia) and the mean of values over the last 5 min of hypercapnia were used. This was done for both the control and sevoflurane procedures. The following variables were measured: ventilation ($V˙E$), tidal volume ($VT$), and expired and inspired times ($TE$ and $TI$).

**Statistical analysis**

For comparisons involving single values with and without sevoflurane, paired t tests were used. For comparisons where there may have been an effect over time, analysis of variance (ANOVA) was used with sevoflurane/no sevoflurane and the first 5 min/last 5 min as fixed factors. Subject number was treated as a random factor. Significance was accepted at $P<0.05$. The Minitab version 12 statistical software package for Windows 95 was used.

**Results**

None of the subjects released the hand-held alarm and none needed stimulation to keep them awake: verbal commands were used at intervals only as a further check that subjects were co-operative and not anaesthetized.

Table 1 shows the values for ventilation and $P_{E\text{CO}_2}$ from the preliminary procedure for each of the subjects and for the group as a whole. Resting ventilation was particularly high in subject 034 (and $P_{E\text{CO}_2}$ in this subject was correspondingly low), suggesting a degree of voluntary hyperventilation in response to the mouthpiece. Sevoflurane reduced ventilation by approximately 5%, and increased $P_{E\text{CO}_2}$ by 4%, but these changes were not statistically significant (paired t test).

Figure 1 shows the acute carbon dioxide response lines for the group as a whole with and without sevoflurane. Sevoflurane may have shifted the line to the right although, as noted above, changes in ventilation and $P_{E\text{CO}_2}$ were not significant. Little change in overall slope or sensitivity to carbon dioxide was apparent: mean decrease in carbon dioxide sensitivity with sevoflurane was 1.4 (SEM 3.0) litre min$^{-1}$ kPa$^{-1}$ (ns, paired t test).

Figure 2 shows the trends in $V˙E$, $VT$, $TE$ and $TI$ during hypercapnic exposure. Table 2 shows the means for the first 5 min and last 5 min for these variables for each procedure, upon which statistical analysis was conducted. Figure 2 suggests a generalized increase over time in $V˙E$ and $VT$, and a generalized decrease over time in $TE$ and $TI$. 

Fig 1 Ventilation ($V˙E$) vs end-tidal $PCO_2$ ($P_{E\text{CO}_2}$) for acute exposure to hypercapnia under control conditions (no sevoflurane) and breathing 0.1 MAC of sevoflurane. Each point represents the mean (SEM) of 10 subjects. The points for eucapnia were obtained from the preliminary procedure; the points for hypercapnia were obtained from the fifth minute of the hypercapnic procedures.
Fig 2 Ventilation ($V_E$) (A), tidal volume ($V_T$) (B), inspired time ($T_I$) (C) and expired time ($T_E$) (D) vs time under control conditions (no sevoflurane, ○) and breathing 0.1 MAC of sevoflurane (●). Points represent minute averages from the 10 subjects. In all four panels, unidirectional error bars (SEM) are shown as examples for data points at minute 3 and minute 28.

Table 2 Trends in respiratory variables during hypercapnia in the absence (control) and presence of 0.1 MAC of sevoflurane. Mean group values for the first and last 5 min for $V_E$, $V_T$, $T_E$ and $T_I$ are shown. For each variable, the difference between the first 5 min and last 5 min was significant (ANOVA). There were no significant differences between control and sevoflurane procedures for any variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Mean (SEM) of first 5 min</th>
<th>Sevoflurane Mean (SEM) of first 5 min</th>
<th>Control Mean (SEM) of last 5 min</th>
<th>Sevoflurane Mean (SEM) of last 5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_E$ (litre min$^{-1}$)</td>
<td>36.1 (3.1)</td>
<td>34.2 (3.6)</td>
<td>1.60 (0.09)</td>
<td>1.45 (0.11)</td>
</tr>
<tr>
<td>$V_T$ (litre)</td>
<td>1565 (189)</td>
<td>1495 (98)</td>
<td>1349 (121)</td>
<td>1200 (45)</td>
</tr>
<tr>
<td>$T_E$ (ms)</td>
<td>1431 (217)</td>
<td>1251 (122)</td>
<td>1211 (123)</td>
<td>1054 (59)</td>
</tr>
<tr>
<td>$T_I$ (ms)</td>
<td>1349 (121)</td>
<td>1200 (45)</td>
<td>1211 (123)</td>
<td>1054 (59)</td>
</tr>
</tbody>
</table>

These effects were significant ($P<0.05$, ANOVA). Sevoflurane did not significantly affect the trends over time (ANOVA). Figure 2 also suggests that while sevoflurane may not have had an effect on $V_E$ or $V_T$, there is a suggestion that it may have decreased $T_E$ and $T_I$. However, none of these apparent effects of sevoflurane was statistically significant (ANOVA).

Discussion

The main finding of this study was that 0.1 MAC of sevoflurane did not significantly affect overall ventilatory sensitivity to carbon dioxide. Furthermore, subanaesthetic concentrations of sevoflurane did not markedly alter the progressive increase in ventilation (or drift) which occurs with sustained hypercapnia.

Response to acute hypercapnia: comparison with other studies

It is difficult to compare our results with those from studies using non steady-state or rebreathing techniques to induce hypercapnia. Our result that 0.1 MAC of sevoflurane had no effect on the response to carbon dioxide supports the findings of Dahan and colleagues for 0.1–0.2 MAC of nitrous oxide and desflurane. van den Elsen and colleagues studied the effects of sedative levels of halogenated anaesthetics on the acute ventilatory response to hypercapnia. They did not present ventilation data but modelled the results they obtained in terms of a two-compartment model. They argued that 0.1 MAC of sevoflurane selectively depressed the peripheral chemoreflex because it reduced the gain term associated...
with the peripheral chemoreflex \( (G_P) \) by 27%, but the gain term associated with the central chemoreflex \( (G_C) \) was unaffected. This would seem to differ from our findings. However, the overall slope of the ventilation–carbon dioxide relationship (i.e. \( G_{TOT} \)) is given by the sum of \( G_P \) and \( G_C \). Calculating \( G_{TOT} \) from the data of van den Elsen and co-workers yields a value of 14.1 litre min\(^{-1}\) kPa\(^{-1}\) for controls and 12.6 litre min\(^{-1}\) kPa\(^{-1}\) for sevoflurane (a non-significant reduction of 10%). Our results showed slopes of 20.2 litre min\(^{-1}\) kPa\(^{-1}\) (control) and 18.8 litre min\(^{-1}\) kPa\(^{-1}\) (sevoflurane), a reduction of 7%. Therefore, the effect of sevoflurane in the two studies was very similar.

Comparing our result with those of Dahan and colleagues for halothane,\(^8\) it appears that at 0.1 MAC, sevoflurane had less effect on the response to carbon dioxide than halothane. However, Doi and Ikeda found that at 1.1–1.4 MAC, these effects appeared to be reversed and sevoflurane was the more profound depressant of the response.\(^13\) Doi and Ikeda did not use a steady-state technique to measure the ventilatory response but there is some evidence from animal studies that these comparative effects of sevoflurane and halothane may be dose-related. Masuda and co-workers found that at 0.5 MAC, phrenic nerve activity in decerebrate cats was more profoundly depressed by halothane than sevoflurane; at 1 MAC, depression by the two agents was equal.\(^19\)

**Responses to sustained hypercapnia**

Reynolds, Millhorn and Holloman observed that ventilation increased progressively over a 30-min period of breathing 5–7% inspired carbon dioxide\(^11\). Tansley and colleagues confirmed that this drift in ventilation continued for up to 2 h when \( P_{\text{ETCO}} \) was maintained at 0.86–0.92 kPa greater than normal levels.\(^12\) The mechanisms underlying this response are unclear. They may involve slow changes in the central or peripheral chemoreceptors, or progressive neural adaptation secondary to elevated ventilation. Whatever the underlying processes, it is apparent that the overall time course of the ventilatory response to carbon dioxide is much slower than assumed previously and that a true steady-state ventilatory response to hypercapnia is not achieved within 1–2 h.

Reynolds, Millhorn and Holloman\(^11\) observed that \( V_T \) reached a plateau and frequency increased progressively during sustained hypercapnia. Our control procedure was largely consistent with this finding, but we found that \( V_T \) also increased slightly during the hypercapnic period (Fig. 2). Overall, we did not find that sevoflurane had a significant effect on frequency or tidal volume, nor did it alter the overall trend of an increase in \( V_T \) and frequency with time. In some of our subjects, however, sevoflurane appeared to reduce \( V_T \), \( T_I \) and \( T_E \); the effect of this on the means of these variables is shown in Figure 2. This is interesting in the light of clinical observations that sevoflurane may produce tachypnoea in some individuals, especially when used during induction of anaesthesia.\(^20\)

The effects of anaesthetics on ventilatory drift have not been studied extensively. Nagyova and colleagues examined the effects of 0.2 MAC of enflurane on the ventilatory response to sustained hypercapnia (\( P_{\text{ETCO}} \) 0.67 kPa above normal values).\(^21\) Our findings differed considerably from their results for enflurane. In the absence of enflurane, ventilation increased progressively (i.e. hypercapnic drift occurred). In the presence of enflurane, this drift was reversed such that ventilation declined progressively throughout the period of hypercapnia despite constant end-tidal concentrations of enflurane.\(^21\) Therefore, it is possible that there is a difference between the effects of subanaesthetic concentrations of enflurane and sevoflurane on ventilation with sustained hypercapnia.

In summary, we have confirmed that 0.1 MAC of sevoflurane largely preserved the ventilatory response to hypercapnia. In view of the slow component of the ventilatory response to hypercapnia (ventilatory drift), it would seem important for future studies on the ventilatory effects of anaesthetics to examine also their effects on the response to sustained hypercapnia.


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