EFFECT OF A SUB-ANAESTHETIC CONCENTRATION OF HALOTHANE ON THE VENTILATORY RESPONSE TO SUSTAINED HYPOXIA IN HEALTHY HUMANS

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SUMMARY

We selected nine normal subjects (8M, 1F; aged 25–43 yr) with brisk hypoxic ventilatory responses, and studied their ventilatory response to sustained isocapnic hypoxia (SatO₂ 82 (SEM 0.1) % for 25 min) in the presence and absence of 0.1 % inspired halothane. Halothane had no significant effect on baseline ventilation or gas exchange. In the absence of halothane, ventilation increased initially from mean 7.57 (0.35) litre min⁻¹ to 14.54 (0.91) litre min⁻¹, and decreased subsequently to 10.74 (0.32) litre min⁻¹ during hypoxia (both P < 0.05). In the presence of 0.1 % inspired halothane, ventilation increased initially from 7.19 (0.47) litre min⁻¹ to 12.08 (0.99) litre min⁻¹ (P < 0.05), then decreased to 10.12 (0.28) litre min⁻¹ during sustained hypoxia (ns compared with baseline normoxic ventilation). Halothane reduced significantly the initial increase in ventilation (P < 0.05), but did not enhance the subsequent decrease. These results confirm that a sub-anaesthetic concentration of halothane depresses the initial hypoxic ventilatory response: the response during prolonged periods of hypoxia is, however, less than the initial response and is reduced in the presence or absence of a sub-anaesthetic concentration of halothane. (Br. J. Anaesth. 1993; 71: 642–647)

KEY WORDS


Halothane, given in anaesthetic concentrations of 1 MAC to humans, depresses resting ventilation under normoxic conditions and abolishes the hypoxic ventilatory response [1, 2]. These effects, although clinically important, are present when the patient is supervised during anaesthesia. Knill and Gelb [1], however, have shown that even a sub-anaesthetic concentration of halothane (0.1 MAC), which does not alter resting ventilation, suppresses the ventilatory response to hypoxia, possibly by a direct action on the carotid body chemoreceptors [3–6]. This effect has important clinical consequences, as sub-anaesthetic concentrations are present after operation when patients are relatively unsupervised. Suppression of the hypoxic ventilatory response would therefore be hazardous in patients after operation, as large clinical studies have reported frequent hypoxaemia in recovery room patients [7, 8]. Evidence that sub-anaesthetic concentrations of halothane suppress the ventilatory response to hypoxia in humans comes exclusively from one group of investigators [1, 2, 6]. Studies in animals [9–11] have not displayed this effect, showing only about a 50 % reduction in the hypoxic ventilatory response with anaesthetic concentrations of halothane. Although these discrepancies may arise from species differences, the effect of sub-anaesthetic doses in humans warranted verification because of the clinical implications for postoperative patient care.

The effect of sub-anaesthetic concentrations of halothane on the ventilatory response to sustained hypoxia is also of interest. It is now well documented [12–14] that the ventilatory response to a sustained isocapnic hypoxic stimulus which lasts longer than about 10 min is biphasic, with an initial increase followed by a subsequent decrease towards the normoxic baseline value. The secondary reduction in ventilation is not caused by changes in cerebral blood flow, and hence brain PCO₂, resulting from the hypoxia [15]. The exact mechanism is uncertain, but may be a reduction in peripheral chemosensitivity [14]. Because halothane may act at this site [6], hypoaxemic episodes which develop after anaesthesia may be more severe when halothane is present and the response to hypoxia is attenuated.

We have studied, therefore, the effect of approximately 0.1 MAC halothane on the ventilatory response to sustained hypoxia in normal subjects to see if a sub-anaesthetic concentration of halothane suppresses the initial increase and enhances the subsequent decrease in ventilation.

SUBJECTS AND METHODS

We studied 18 subjects: nine (eight male, one female; aged 25–43 yr) had an initial increase in ventilation of 20 % or more on the first visit (see Study plan) and...
were studied further. All had normal values for ventilatory capacity (FEV\textsubscript{1}, 93–122 % predicted; FVC 85–127 % predicted) and none had a history of cardiorespiratory disease. None was taking any medication at the time of study or had received halothane for anaesthesia previously. Local Ethics Committee permission was obtained and all subjects gave written informed consent. The subjects breathed through a low-resistance valve with a deadspace of 90 ml. The inspiratory port was connected to a five-way valve (Hans Rudolf 5-way Gatlins Valve Series 2430) which allowed the inspired gas mixtures to be changed abruptly without the subject’s knowledge. Expiratory gas passed via a heated pneumotachograph (Fleisch No. 2) through mixing and drying chambers to a Parkinson Cowan CD4 dry gas meter modified to give a digital output. The integrated expiratory flow signal, which gave breath-by-breath tidal volume, was calibrated against the output of the CD4 gas meter every 10 litre to correct for drift of the flow signal. Inspiratory and end-tidal oxygen (P\textsubscript{i,O\textsubscript{2}}, P\textsubscript{ET,O\textsubscript{2}}) and carbon dioxide (P\textsubscript{i,CO\textsubscript{2}}, P\textsubscript{ET,CO\textsubscript{2}}) partial pressures were measured at the lips with a mass spectrometer (VG Spectralab-M) calibrated previously with five gas mixtures of known concentrations of oxygen, carbon dioxide, nitrogen and argon. Ear arterial oxygen saturation (S\textsubscript{ao2}) was recorded continuously using a Hewlett-Packard 47201A ear oximeter adapted to give a fast response time of 1.6 s [16]. The electrocardiogram was also monitored throughout. Analog signals were digitized using a DEC PDP 11/23 computer and custom written programs provided breath-by-breath values for ventilatory frequency (f), tidal volume (V\textsubscript{T}), instantaneous ventilation (V\textsubscript{E} = f × V\textsubscript{T}), inspiratory time: total breath time ratio (T\textsubscript{i}:T\textsubscript{f}), mean inspiratory flow (V\textsubscript{T}:T\textsubscript{i}), inspiratory output (V\textsubscript{CO\textsubscript{2}}), and P\textsubscript{ET,CO\textsubscript{2}}. Data were recorded on disk and analysed off-line using a DEC PDP 11/73 computer.

Oxygen consumption (V\textsubscript{O\textsubscript{2}}) and carbon dioxide output (V\textsubscript{CO\textsubscript{2}}), both expressed as litre min\textsuperscript{-1} STPD, were measured over a 2-min period using a digital output from the dry gas meter and the oxygen and carbon dioxide concentrations of mixed expired gas sampled simultaneously from the mixing chamber. Oxygen concentration was measured using a Servomex O\textsubscript{2} analyser (model 570A) calibrated previously with air and 100 % nitrogen, and carbon dioxide was measured with a Gould capnograph (mark III) calibrated with four gas mixtures of known carbon dioxide concentration.

Ventilatory response to sustained hypoxia Measurements were made with the subject seated at rest. Initially, they breathed room air for 15 min with duplicate measurements of V\textsubscript{O\textsubscript{2}} and V\textsubscript{CO\textsubscript{2}} made between 10 and 14 min. S\textsubscript{ao2} was then reduced to 80–85 % for 25 min. A rapid onset of hypoxia was achieved by giving the subject three breaths of 100 % nitrogen followed by an inspired oxygen concentration of approximately 10 %. Similarly, at the end of hypoxia, a rapid return to normoxia was produced by taking two breaths of 100 % oxygen before returning to room air. All changes in inspired gas concentrations were made during expiration. Carbon dioxide was added manually to the inspired gas to keep P\textsubscript{ET,CO\textsubscript{2}} as close as possible to the baseline normoxic value.

Administration of halothane Halothane was administered using a Cyprane Fluotec Mark 3 vaporizer. The inspired concentration was adjusted as necessary to maintain an inspired concentration of 0.1 % throughout. Concentrations were measured at the lips with a Bruel and Kjaer halothane analyser (model 1304). Mean values were recorded for each 1 min using a custom-written program on a BBC microcomputer.

Study plan The subjects attended the laboratory on two occasions. The first visit constituted a familiarization and screening study. A medical history was taken and FEV\textsubscript{1} and FVC were measured to confirm normal lung function. The ventilatory response to sustained hypoxia was then measured. Subjects were recruited for the definitive study only if the initial increase in ventilation in response to hypoxia was 20 % or more.

On the second visit, the ventilatory response was measured in duplicate. On one occasion, halothane was added to the inspired gas for the entire measurement period, and on the other no halothane was used. The order of the studies was randomized, and the two measurements separated by at least 60 min of breathing room air to ensure that the halothane was fully excreted and there was full recovery of the hypoxic ventilatory response [13].

Analysis and statistics Group data are given as mean (SEM). In each subject, mean values were calculated for baseline normoxia (A1: 4 min immediately before onset of hypoxia); early hypoxia (H1: 3–6 of hypoxia); late hypoxia (H2: minutes 14–17 of hypoxia); and normoxic recovery phase (A2: minutes 2–5 after the return to breathing room air).

Measurements were made between 14 and 17 min of hypoxia because, in two subjects, the breathing pattern after 18 min of hypoxia became too irregular for accurate analysis. For technical reasons, data also were not available for the end of hypoxia and recovery periods in a further one subject. Longitudinal comparisons were therefore made using data from eight subjects, using Analysis of Variance with the Sheffé test for comparison of all possible pairs. Comparisons between control and halothane were made using Student’s paired t test.

RESULTS The mean (SEM) inspired halothane concentration measured throughout the nine studies was 0.10 (0.01) %; mean end-tidal halothane concentration was 0.05 (0.003) %. Before hypoxia was induced, halothane had no significant effect on gas exchange, ventilatory pattern, oxygen saturation or P\textsubscript{ET,CO\textsubscript{2}} (table 1).

In both the control and the halothane studies, a reduction in S\textsubscript{ao2} to approximately 80 % (fig. 1)
caused an initial increase, followed by a subsequent decrease, in $V_{\text{E}}^{\text{instant}}$ (fig. 1). $P_{\text{E}_2}^{\text{CO}_2}$ was maintained within 0.3 kPa on average (fig. 1).

There were no significant differences in $V_{\text{E}}^{\text{instant}}$, $V_{T}$, $f$ or $V_{T}:T_{1}$ ratio recorded during the normoxic periods before and after hypoxia in either the control or halothane studies (table II). In both control and halothane studies, hypoxia caused an initial increase in $V_{\text{E}}^{\text{instant}}$ which was significantly different from both the baseline and recovery normoxic periods ($P < 0.05$) (table II). In the control study, $V_{\text{E}}^{\text{instant}}$ was significantly greater ($P < 0.05$) during early than during late hypoxia (table II). However, the decline was not significantly different in the halothane study, although the consecutive mean values showed a similar trend (fig. 1).

The changes in $V_{\text{E}}^{\text{instant}}$ in both the control and halothane studies were largely caused by changes in $V_{T}$, with no significant changes in $f$ (table II). In both studies, there was a significant increase ($P < 0.05$) in $V_{T}:T_{1}$ during early hypoxia. In the control study, $V_{T}:T_{1}$ during early hypoxia was also significantly greater ($P < 0.05$) than that during the recovery normoxic period (table II). In the halothane study, $V_{\text{E}}^{\text{instant}}$ was significantly less ($P < 0.05$) than control during early hypoxia, but not during late hypoxia (fig. 2); similar results were obtained for $V_{T}:T_{1}$. There were no significant differences in $V_{T}$ or $f$ between the two studies at any time.

$S_{\text{A}_0}$ and $P_{\text{E}_2}^{\text{CO}_2}$ were similar in the two studies at each of the four times of measurement (table II). $P_{\text{E}_2}^{\text{CO}_2}$ did not change significantly during either the control or halothane studies (table II), but $P_{\text{E}_2}^{\text{CO}_2}$ was slightly but significantly ($P < 0.05$) smaller in the control than the halothane study during early hypoxia. There was no significant difference in heart rate between the control and halothane studies at any of the four times (table II).

**DISCUSSION**

In normal subjects, we have shown that a sedative concentration of halothane reduced significantly the stimulation of ventilation which occurs within the first 10 min of exposure to hypoxia. These results confirm the findings of Knill and Gelb [1], who showed that sedation with halothane reduced significantly the hypoxic ventilatory response in humans using the progressive isocapnic method. This method imposes a gradual reduction in $F_{\text{I}_2}$ over a period of 8–10 min. The smaller effect of halothane seen in the present study (an approximately 30% reduction in response compared with 70% reported by Knill and Gelb [1]) may have been caused partly by the inadvertent hypocapnia at the start of hypoxia in the control study, which would reduce the response and thus lead to an underestimation of the ventilatory response to hypoxia without halothane during this initial period. However, the absolute level of ventilation after exposure to hypoxia for more than 15 min was not affected significantly by halothane.

We did not wish to expose more subjects to the combination of hypoxia and halothane than was necessary, because of the known, albeit unlikely, risk of liver damage. Subjects who responded to hypoxia were therefore selected deliberately so that the total number studied could be minimized. We cannot exclude the possibility that individuals with a low initial ventilatory response to hypoxia may respond to a combination of hypoxia and halothane in a different manner, thus limiting the relevance of these findings to the general population. The fact that the mean initial increase in ventilation in our study is greater than that reported by Easton, Slykerman and Anthonisen [12] would suggest also that we have studied an atypical population. However, only four
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TABLE II. Ventilatory variables, ear oxygen saturation and end-tidal gas tensions (mean (SEM)) during the control and halothane studies. * Significant difference (P < 0.05) compared with early hypoxia value

<table>
<thead>
<tr>
<th></th>
<th>Normoxia Baseline</th>
<th>Hypoxia Early</th>
<th>Hypoxia Late</th>
<th>Normoxia Recovery</th>
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</thead>
<tbody>
<tr>
<td>( V_{\text{Em}} ) (litre min(^{-1}))</td>
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<tr>
<td>Control</td>
<td>7.57 (0.35)*</td>
<td>14.54 (0.90)</td>
<td>10.74 (0.32)*</td>
<td>7.58 (0.18)*</td>
</tr>
<tr>
<td>Halothane</td>
<td>7.19 (0.47)*</td>
<td>12.08 (0.99)</td>
<td>10.12 (0.28)</td>
<td>7.86 (0.28)*</td>
</tr>
<tr>
<td>( V_T ) (litre)</td>
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</tr>
<tr>
<td>Control</td>
<td>0.59 (0.04)*</td>
<td>0.99 (0.07)</td>
<td>0.75 (0.06)*</td>
<td>0.60 (0.05)*</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.57 (0.04)*</td>
<td>0.89 (0.10)</td>
<td>0.72 (0.08)</td>
<td>0.62 (0.06)</td>
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<tr>
<td>( f ) (b.p.m.)</td>
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<td></td>
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<tr>
<td>Control</td>
<td>13.4 (0.9)</td>
<td>15.1 (0.7)</td>
<td>14.4 (0.7)</td>
<td>13.3 (1.2)</td>
</tr>
<tr>
<td>Halothane</td>
<td>13.3 (1.0)</td>
<td>14.3 (1.0)</td>
<td>14.6 (0.9)</td>
<td>13.1 (1.0)</td>
</tr>
<tr>
<td>( V_T \cdot T ) (litres(^{-1}))</td>
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<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>20.9 (1.2)*</td>
<td>36.5 (2.1)</td>
<td>28.2 (2.6)</td>
<td>21.8 (1.9)*</td>
</tr>
<tr>
<td>Halothane</td>
<td>20.1 (1.8)*</td>
<td>31.6 (2.7)</td>
<td>28.2 (2.7)</td>
<td>23.5 (2.9)</td>
</tr>
<tr>
<td>( S_{\text{ao}} ) (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>96 (0.5)*</td>
<td>83 (2.9)</td>
<td>82 (1.1)</td>
<td>95 (1.5)*</td>
</tr>
<tr>
<td>Halothane</td>
<td>96 (0.5)*</td>
<td>83 (3.0)</td>
<td>82 (1.4)</td>
<td>96 (1.4)*</td>
</tr>
<tr>
<td>( P_{\text{CO}_2} ) (kPa)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>5.21 (0.12)</td>
<td>5.03 (0.38)</td>
<td>5.23 (0.37)</td>
<td>5.35 (0.32)</td>
</tr>
<tr>
<td>Halothane</td>
<td>5.31 (0.08)</td>
<td>5.22 (0.24)</td>
<td>5.37 (0.20)</td>
<td>5.36 (0.36)</td>
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<tr>
<td>( P_{\text{O}_2} ) (kPa)</td>
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<tr>
<td>Control</td>
<td>13.81 (0.20)*</td>
<td>6.80 (0.17)</td>
<td>6.81 (0.19)</td>
<td>12.85 (0.61)*</td>
</tr>
<tr>
<td>Halothane</td>
<td>13.79 (0.28)*</td>
<td>6.83 (0.16)</td>
<td>6.84 (0.19)</td>
<td>13.47 (0.46)*</td>
</tr>
<tr>
<td>HR (beat min(^{-1}))</td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>63 (4)</td>
<td>76 (4)</td>
<td>69 (4)</td>
<td>60 (4)</td>
</tr>
<tr>
<td>Halothane</td>
<td>62 (3)</td>
<td>74 (4)</td>
<td>69 (4)</td>
<td>60 (3)</td>
</tr>
</tbody>
</table>

We chose to administer 0.1% halothane and monitor the end-tidal concentration rather than attempt to adjust the inspired concentration in order to maintain a constant end-tidal concentration. This was primarily because the resolution of the digital output from the analyser was limited at this concentration, and secondly because fluctuations in end-tidal halothane concentrations over short periods would not necessarily reflect cerebral concentrations. In addition, previous evidence suggested that after about 15 min of 0.1% inspired halothane, the end-tidal concentration was likely to be in the desired range of 0.05-0.07% [18].

The extent to which halothane affects the initial ventilatory response to hypoxia appears to vary between species. Anaesthetic concentrations of halothane have been shown to cause a 50-70% reduction in the ventilatory or chemoreceptor response to hypoxia in cats [4], dogs [9] and goats [11], whereas our study, and that of Knill and Gelb [1] demonstrated 30% and 70% reductions, respectively, with sedative concentrations only. As species differences in carotid body histochemistry [19, 20] and pathophysiological responses to hypoxia [21, 22] are well documented, this finding is not surprising, and merely reinforces the fact that results obtained in animal models may not always predict the response in humans.

The mechanism of the secondary decline in ventilation during hypoxia remains unclear. It was suggested initially [12] that sustained hypoxia released a central neuro-inhibitory substance such as adenosine or gamma aminobutyric acid. However, Khamnei and Robbins [14] argued that, if central respiratory neurone activity was depressed in this way, ventilation should decrease to less than before the initial increase.
hypoxia on removal of the hypoxic stimulus. As they and others [12] were unable to demonstrate such an effect in adult humans, it was suggested that the secondary reduction in ventilation was the result of peripheral chemoreceptor attenuation. This study confirms the absence of an undershoot in ventilation on removal of the hypoxic stimulus in the presence or absence of halothane—an observation which merely suggests that hypoxia does not have a persistent direct depressant effect on central respiratory neurones. Although absence of an undershoot is compatible with the hypothesis that the secondary decline in ventilation is the result of peripheral chemoreceptor attenuation, it does not exclude the possibility that responses to chemoreceptor input are being modified centrally. Furthermore, direct measurements of carotid sinus nerve activity in animals do not support consistently the proposal of peripheral chemoreceptor attenuation. Whilst a decrease in carotid sinus nerve activity during sustained hypoxia has been demonstrated in rabbits [23, 24], this has not been observed in cats [25, 26] and goats [27]. Although this may again indicate a species difference, the hypoxia (Pao2 2.2–4.7 kPa) studied in the rabbits was more severe than that studied in cats, goats and humans [12, 14], in which Pao2 values of 5.3–6.6 kPa have been used. The decrease in chemoreceptor activity during sustained hypoxia seen in rabbits may therefore be a consequence of the degree of hypoxia studied, particularly as in rabbits, Ponte and Sadler [24] found that the adaptation in carotid sinus nerve discharge was more pronounced as the severity of hypoxia was increased.

Indirect estimates in humans [6] and direct neural recordings in cats [3, 4] suggest that halothane acts at the peripheral chemoreceptors. However, halothane has also been shown to act centrally, at least in cats [10, 28]. In this study, we cannot exclude the possibility that halothane was acting centrally, as the concentration used is known to produce other central effects such as sedation [29, 30]. The observation that halothane reduced the initial ventilatory response, but did not alter ventilation during sustained hypoxia, is consistent with the possibility that the peripheral chemoreceptor response is facilitated initially by a central mechanism [31] which wanes subsequently if exposure to hypoxia is continued. Such cortical facilitation may be susceptible to sedative drugs. This proposal is compatible with the findings of Chin and colleagues [32], who found an increased rate of offset of the secondary decline in ventilation during stage 2 sleep in humans which they attributed to the removal of a behavioural component of the biphasic hypoxic ventilatory response. The mathematical model of the ventilatory response to sustained hypoxia described by Khamnei and Robbins [14] is compatible with mechanisms other than peripheral attenuation and more work is needed to determine the exact processes involved in the biphasic hypoxic ventilatory response in humans.

After general anaesthesia, hypoxaemia is frequent and may be severe. Episodes of hypoxaemia are more common in smokers and the elderly and may occur despite routine oxygen therapy [7]. Usually, such episodes of hypoxaemia are short (median duration 1 min), but they occasionally last much longer. These episodes are probably caused by transient airway obstruction. Recovery appears to depend on arousal, presumably in part resulting from peripheral chemoreceptor stimulation [33]. The influences of residual anaesthetics, such as the modern volatile agents, are likely to persist for up to 2 h [18] and could thus contribute to many hypoxaemic episodes [7]. The present study suggests that, although residual volatile anaesthetic agents may increase the danger of transient episodes of hypoxaemia, the response to longer periods of hypoxia is reduced regardless of the presence or absence of residual anaesthetic agent.

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References

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