Effects of subanaesthetic sevoflurane on ventilation. 2: Response to acute and sustained hypoxia in humans

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We have determined the influence of 0.1 minimum alveolar concentration (MAC) of sevoflurane on the acute ventilatory response to hypoxia (AHVR), hypoxic ventilatory decline (HVD) and the magnitude of the rapid decline in ventilation on relief of sustained hypoxia (the off-response) in eight healthy adult volunteers. The following design was used with and without 0.1 MAC of sevoflurane: end-tidal \( P_{O_2} \) was maintained at 13.3 kPa for 5 min, at 7.9 kPa for 20 min and at 13.3 kPa for 5 min. End-tidal \( P_{CO_2} \) was held constant throughout at 1.3 kPa above the subject’s normal value. A dynamic end-tidal forcing system was used to generate these gas changes. Sevoflurane reduced AHVR from 14.5 (SEM 1.2) to 11.6 (1.6) litre min\(^{-1}\), and the off-response at cessation of hypoxia from 7.1 (1.1) to 6.3 (1.4) litre min\(^{-1}\). The magnitude of HVD was slightly increased by sevoflurane from 8.2 (1.1) to 10.6 (2.8) litre min\(^{-1}\). None of these changes was significant (ANOVA). These results suggest that 0.1 MAC of sevoflurane had very little effect on the AHVR, and that it did not markedly alter the processes underlying HVD during sustained hypoxia.

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Challenging the conventional wisdom of the time,1 Knill and colleagues found that several anaesthetics at low dose profoundly depressed the acute hypoxic ventilatory response in humans.2–5 Their observations have been broadly confirmed by recent studies. Enflurane 0.07–0.2 MAC depressed the response to hypoxia by 30–50%6 7 and 0.1–0.2 MAC of halothane by 50–75%.8 9 There has been less consistency in findings with respect to isoflurane: Knill, Kieraszewicz and Dodgson found that 0.1 MAC of isoflurane depressed the hypoxic response by 50%,4 but Temp, Henson and Ward found no effect of isoflurane on the hypoxic response.10 Reasons for this difference may lie in the nature of the ventilatory response to hypoxia and the methods used to test it.

It is now known that sustained isocapnic hypoxia causes a biphasic ventilatory response. Initially, there is a rapid increase in ventilation (the acute hypoxic ventilatory response, AHVR) and then a slower decrease over 20–30 min (the hypoxic ventilatory decline, HVD).11 In anaesthetized cats, the underlying mechanism appears to be a depressant effect of hypoxia on the central nervous system.12 In awake cats and awake humans, the mechanism underlying HVD may be a time-dependent decline in peripheral chemoreflex activity.13

To assess ventilatory responses, Knill, Kieraszewicz and Dodgson used a ‘ramp’ test in which hypoxia was induced slowly over 8–10 min.4 It is likely that within this time, the effects of HVD led to underestimation of the true magnitude of AHVR. Temp, Henson and Ward assessed this possibility by comparing AHVR measured using the slow ‘ramp’ and rapid ‘step’ tests in the same subjects, and confirmed that measured ventilatory responses were lower using the ‘ramp’ test.14 However, they failed to reproduce the findings of Knill and colleagues with isoflurane using either test. This led van den Elsen and colleagues to suggest that the state of arousal of subjects may explain the controversy.15 When external stimuli to subjects were absent (as in Knill’s experiments), a depressant effect of isoflurane was observed. When extraneous audiovisual stimuli were used (as in Temp’s studies), no such effect was seen. However, it remains unclear why these differences have been observed only with isoflurane and why there is more agreement for halothane and enflurane. van den Elsen and colleagues found that isoflurane depressed AHVR by 50%.15

In contrast to their depressant effects on AHVR, volatile agents do not appear to affect the absolute magnitude of HVD such that the ratio HVD/AHVR compared with controls is increased.7 10 14 16 17 This is surprising because
other interventions that affect AHVR also affect HVD in parallel, and the HVD/AHVR ratio is constant. First, in humans, the magnitude of HVD correlates with AHVR across individuals; second, drugs which alter the magnitude of AHVR such as almitrine and somatostatin also alter HVD proportionately; and third, in chemodenervated humans, HVD is abolished together with AHVR. It would appear that HVD and AHVR are functionally correlated and both determined by the sensitivity of the peripheral chemoreflex. It seems difficult to explain the differential effects of anaesthetics on AHVR and HVD. However, it is important to emphasize that HVD represents only the decline in total ventilation with sustained hypoxia and of itself provides no information on what causes the decline. What is needed is a measure of decline in peripheral chemoreflex sensitivity with sustained hypoxia.

If it is accepted that the magnitude of the abrupt increase in ventilation at the introduction of hypoxia (i.e. AHVR or ‘on-response’) provides information on peripheral chemoreflex activity at a certain time, then it should also be the case that the magnitude of the abrupt decrease in ventilation on relief of hypoxia (the ‘off-response’) provides information on peripheral chemoreflex activity at that time. The relative magnitude of the on- and off-responses is therefore an index of the underlying decline in peripheral chemoreflex activity with time. Bascom and colleagues used this measure to assess peripheral chemoreflex decline at different levels of sustained hypoxia, and found on- and off-responses to be unequal (further supporting the notion that HVD was caused by decline in peripheral chemoreflex sensitivity). One potential problem with measuring the off-response is that the true magnitude of the off-response may be limited by the need to maintain a basal level of ventilation. If this were the case then whenever total ventilation declined, the off-response would be smaller than the on-response because ventilation could not fall below a certain baseline. Cunningham, Robbins and Wolff have discussed the problem of a need to maintain basal ventilation with respect to ventilation at the eucapnic threshold. One way of avoiding this problem is to investigate the hypoxic chemoreflex against a background of steady hypercapnia. This raises baseline ventilation and so ventilation should be able to fall below this raised value on relief of hypoxia. Thus comparison of the AHVR and off-response in hypercapnia may provide more information on the degree to which peripheral chemoreflex activity has declined.

Our study had the following aims. First, we wished to assess the effect of low-dose sevoflurane on acute and sustained ventilatory responses to hypoxia. If sevoflurane resembled other volatile anaesthetics, we predicted that it would greatly reduce AHVR but have no effect on HVD. Second, we wished to estimate the effects of sevoflurane on peripheral chemoreflex decline by analysing its effects on the relative magnitudes of on- and off-responses. Therefore, we conducted our studies against a background of hypercapnia. Sustained hypercapnia itself causes a time-dependent increase in ventilation which can lead to underestimation of HVD. Therefore, we used data from a contemporaneous study in which no hypoxia was administered to help control for this effect.

Subjects and methods
We studied eight healthy volunteers (three men; mean age 20.8 (range 19–22.5) yr, height 1.68 (1.5–1.88) m and weight 63.4 kg (51.7–82) 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
During experiments, subjects were seated in a chair, wore a noseclip and breathed through a mouthpiece. 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 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 $P_{CO2}$ and $P_{O2}$. Volumes, flows, and $P_{CO2}$ and $P_{O2}$ at the mouth were recorded in real time with a 50-Hz sampling frequency by a computer. In addition, end-tidal gases were controlled by dynamic end-tidal forcing to maintain desired end-tidal values independent of changes in ventilation. Details of this technique and gas-mixing system have been described in detail elsewhere.

The mass spectrometer was calibrated for sevoflurane, as described previously.

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%. We took the MAC of sevoflurane to be 2.5% (Summary of Product Characteristics, Abbott Laboratories Ltd, Queenborough, Kent).

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

Procedures
Subjects had participated in a study described previously in which their normal values for $P_{E_{CO2}}$ were recorded when breathing air and 0.1 MAC of sevoflurane. They then undertook the following two procedures for this study in random order.

The control procedure consisted of 10 min during which the subject’s $P_{E_{CO2}}$ was held at 13.3 kPa, it was then reduced abruptly to 7.9 kPa for 20 min, and finally returned to 13.3 kPa for 5 min. $P_{E_{CO2}}$ was held at 1.3 kPa above the subject’s normal value throughout. The sevoflurane procedure was a repeat of the control procedure, but this time against a background of 0.1 MAC of sevoflurane.

It was planned that each subject should undertake each
of the procedures twice. Unfortunately, after recruitment, three subjects were able to complete each procedure only once, while five subjects completed each procedure twice. A total of 26 experimental periods was thus obtained.

Data analysis

Data were averaged into 1-min periods. The first 5 min of each of the control and sevoflurane exposures were excluded from data analysis, leaving 30 min for analysis.

To calculate the components of the hypoxic response, four 1-min periods were used for data analysis (Fig. 1): ventilation in the last 1 min of euoxia before the step into hypoxia ($V_{E1}$, pre-hypoxic or baseline ventilation); peak ventilation reached during the first 5 min of the hypoxic period ($V_{E2}$, peak ventilation); ventilation during the last 1 min of the hypoxic period ($V_{E3}$, depressed ventilation); and minimum ventilation reached in the first 5 min on return to euoxia ($V_{E4}$, post-hypoxic ventilation).

AHVR was calculated as the difference between peak and pre-hypoxic ventilation ($V_{E2} - V_{E1}$). The magnitude of the off-response was calculated as the difference between depressed and post-hypoxic ventilation ($V_{E3} - V_{E4}$). It was evident that there was an increasing baseline ventilation so simply subtracting depressed ventilation from peak ventilation would have underestimated HVD. Therefore, we used data from a contemporaneous study investigating the effect of 0.1 MAC of sevoflurane on the ventilatory response to sustained euoxic hypercapnia (1.3 kPa above resting) to control for this effect.26 These euoxic studies were used as controls for the control and sevoflurane hypoxic procedures from this study. Figure 1 shows how this was done, using values for $V_{E2}$ and $V_{E3}$ as corresponding euoxic points for peak and depressed ventilation, respectively. We used the formula: $HVD = (V_{E2} - V_{E3}) + (V_{E3} - V_{E2})$. Values for AHVR (i.e. the on-response), HVD and off-response were obtained for each subject and from these, means for the group as a whole were obtained.

Statistical analysis

The significance of differences for AHVR, HVD and off-response for control and sevoflurane studies was assessed using paired t tests on the mean value for each subject.30 Comparisons between AHVR and the off-response were made using analysis of variance (ANOVA) with fixed factors of AHVR/off-response and sevoflurane/no sevoflurane, with subjects treated as a random factor. The Minitab version 12 for Windows 95 statistical software package was used. $P<0.05$ was taken as statistically significant.

Results

All subjects were lightly sedated during the sevoflurane procedures but none fell asleep or showed evidence of airway obstruction. None released the hand-held alarm and none needed stimulation to keep them awake: verbal

![Fig 1](image.png) Top: ventilation ($V_E$) vs time for one experimental period in one subject (032) for the hypoxic procedure without sevoflurane (●). Hypoxia is from time 0 to 20 min. Also shown are data for this subject from a procedure involving no hypoxia (without sevoflurane) but conducted at the same background level of $P_{CO_2}$ (○). Points $V_{E1}$–$V_{E4}$ and calculation of AHVR, HVD and off-response are explained in the text. Middle: values of end-tidal $P_{CO_2}$ for this subject for the hypoxic procedure without sevoflurane from the same experimental period (●). Bottom: values of end-tidal $P_{O_2}$ for this subject for the hypoxic procedure without sevoflurane from the same experimental period (●) and the control euoxic procedure for the same experimental period as shown in the top panel (○). (The euoxic control data have been presented in part in our accompanying article.26)
ventilation such that ventilation after relief of hypoxia did not decrease to pre-hypoxic levels. Although ventilation in the pre-hypoxic period (minutes –5 to 0; Fig. 2) was not very steady, it was very similar to the observations in the respective euoxic controls (Fig. 2). At the end of the hypoxic period on return to euoxia, within the first few minutes, ventilation decreased to a value lower that it would have been if there had been no hypoxia (i.e. there was an ‘undershoot’).

Table 1 shows the numerical values for individual subjects for AHVR, HVD and off-response, together with the group means. Sevoflurane had no significant effect on any of these values (paired t tests). The off-response was significantly smaller than AHVR (P<0.001, ANOVA) and this was not affected by sevoflurane (ns, ANOVA). The ratios of off-response/AHVR were similar between procedures (0.49 for control and 0.54 with sevoflurane).

Discussion

The striking finding of this study was that unlike other volatile agents, 0.1 MAC of sevoflurane had little depressant effect on the acute ventilatory response to hypoxia. In common with other agents, however, HVD was not affected. Furthermore, as the off-response was smaller than AHVR and similar between control and sevoflurane procedures, we can conclude that 0.1 MAC of sevoflurane did not affect the underlying decline in peripheral chemoreflex activity which occurs with sustained hypoxia.

Comments on methodology

The steps into and out of hypoxia were rapid and isocapnia was well maintained by dynamic end-tidal forcing (Fig. 1) so that the problems of a ‘ramp’ input of hypoxia were avoided.2–5

Our decision to study chemoreflexes at a $P_{O_2}$ of 1.3 kPa above resting was to some extent justified by the observation that on relief of hypoxia, ventilation decreased to a value below that which would have occurred had there been no hypoxic exposure. Ventilation at all times was above any level that might be considered ‘basal’, confirming that the degree of hypercapnia was sufficient to allow this undershoot to develop fully.

The magnitude of AHVR in some subjects (e.g. 040; Table 1) appeared to be rather low for a background $P_{O_2}$ of 1.3 kPa above resting. Mean AHVR in the study of Nagyova and colleagues, conducted at a $P_{O_2}$ value of 0.67 kPa above resting, was 20.1 litre min$^{-1}$. The reason for this may be that in our study, our hypoxic stimulus was a $P_{O_2}$ of 7.9 kPa rather than the value of 6.7 kPa used by Nagyova and colleagues.

The use of male and female subjects in our study raises the potential problem that the changing pattern of female hormones during the menstrual cycle may have influenced our results in an unpredictable manner. However, almost all studies on the effect of volatile anaesthetics on respiratory responses have used male and female subjects without specifying the time in the menstrual cycle at which the subjects were studied. Furthermore, it is reassuring that Dahan and colleagues found no difference in the chemoreflex responses of women between the follicular and luteal phases of their cycles and therefore it is unlikely that this would have profoundly influenced our results.

Some groups studied their subjects once on one day only, with the problems that procedures were not always repeated and not always randomized.15 Our approach retained the advantages of random exposure but raised the potential problem of day-to-day variability in responses. However, such variability is only a major problem if there are consistent effects, and one way of minimizing these effects in one direction is to perform repeated studies.

State of arousal of subjects

It has been suggested that the state of arousal of subjects may have a profound influence on measurement of
AHVR, and this may have influenced the different findings of various groups with respect to isoflurane, as discussed above. There is a genuine dilemma concerning the correct state in which to study subjects. If subjects are recumbent in a darkened room, there is a risk that they may fall asleep or become anaesthetized. As sleep itself is well established to influence chemoreflexes, this may affect the resulting measurements. The definition of ‘conscious sedation’ (as opposed to ‘anaesthesia’) is that verbal contact with the subject must be maintained and therefore if verbal contact is not used it is more difficult to be certain that the anaesthetic dose is not excessive. Anaesthesia and sleep can lead to airway obstruction which, even if it is partial, may interfere with measurement of expired ventilation.

On the other hand, a series of studies concluded that even modest audiovisual stimulation may change a 50% reduction in AHVR by isoflurane to a negligible effect. However, it is unlikely that audiovisual stimulation alone is responsible for such profound effects for the following reasons. First, it is unclear what constitutes ‘stimulation’. Temp, Henson and Ward actively spoke to or touched subjects (who were already watching television) and this was probably ‘active stimulation’. An auditory stimulus alone is not thought to increase AHVR. In our study, subjects kept their eyes open and watched television or read a book but we did not actively arouse them. This level of stimulus was probably somewhat more than simple auditory input, but somewhat less than in the study of Temp, Henson and Ward, although it is impossible to be certain as there is no objective measure of ‘stimulation’. Second, even when Sarton and colleagues gave subjects painful stimuli, they did not find attenuation of depression of AHVR by sevoflurane. This finding is at odds with the notion that arousal explains the attenuation of AHVR depression by isoflurane: it is unclear why simply watching television should ‘arouse’ the central nervous system more than painful electric shock. Third, different groups have produced results which broadly agree as to the extent of depression of AHVR by halothane, enflurane and isoflurane, even though the state of arousal and study conditions of the subjects were very different. It is unclear why the differences in results attributed to arousal have been confined to isoflurane alone. It appears that the greatest influence on the degree of depression of AHVR is the anaesthetic agent used, and not the state of arousal of the subject.

AHVR: comparison with other studies

Our results confirm and extend the observations of Sarton and colleagues who examined the effect of pain and arousal on the ventilatory response to acute (but not sustained) hypoxia and the interaction with sevoflurane sedation (0.1 MAC). They found that sevoflurane reduced AHVR by 30% which was slightly greater than our value (20%) but which in their study was statistically significant. We tested AHVR against a background of hypercapnia which may have served to maintain ventilation and limit any attenuation of AHVR by sevoflurane. However, Nagyova and colleagues found that the reduction in AHVR by 0.2 MAC of enflurane was actually greater when measured against a background of hypercapnia than during eucapnia. Differences between the findings of Sarton and co-workers and ours are small, and a striking feature of both results is that the reduction in AHVR by sevoflurane (20–30%) was smaller than occurs with most other volatile agents.

In this respect, sevoflurane may resemble nitrous oxide and desflurane, which have been suggested not to depress AHVR. However, these agents appear to have been studied only once using dynamic end-tidal forcing, and previous reports showed nitrous oxide to depress AHVR by 40–65% at subanaesthetic doses. The desflurane study was complicated because AHVR was depressed (by 30%) against a background of modest hypercapnia but not at isocapnia; unusually, three subjects failed to complete the study because of nausea, vomiting and discomfort, and it is unclear to what extent the known effects of airway irritability caused by the agent influenced the result.

We are not aware of any studies on the effects of sevoflurane on the hypoxic response at concentrations greater than 0.1 MAC.

HVD and off-response: comparison with other anaesthetics and physiological significance of the results

We were unable to find a significant effect of 0.1 MAC of sevoflurane on HVD. This result is consistent with other studies of halothane, enflurane and isoflurane. The effect of sevoflurane on HVD has not been examined previously.

Two previous studies analysed the relative magnitudes of AHVR and off-responses to examine in more detail this (lack of) effect of anaesthetics on HVD. The attempt of Nagyova and colleagues was limited by the fact that 0.2 MAC of enflurane caused a progressive reduction in euoxic ventilation. Dahan’s group examined 0.15 MAC of halothane and found that while the magnitudes of AHVR and off-responses were unequal in controls (implying a decline in peripheral chemoreflex activity), they were equal during halothane sedation. They concluded that in contrast to the control state the HVD which occurs during halothane sedation was not caused by a decline in peripheral chemoreflex activity (and hence occurs by some other mechanism). Our results with sevoflurane suggest that AHVR and off-responses remain unequal, indicating that peripheral chemoreflex dynamics are not altered by this agent. This raises the possibility that individual anaesthetic agents may not act in the same way, but instead interact differently with the hypoxic chemoreflex. However, if it is true that each agent generates HVD by a different mechanism, it is intriguing that the absolute magnitude of HVD is constant for different agents.
Effects of sevoflurane on hypoxic ventilatory response

Clinical significance of the results

Clinically, knowledge of the subanaesthetic effect on the hypoxic response is probably of greater importance than knowing the effect at higher, anaesthetic doses. When patients are anaesthetized, the anaesthetist is always present to take corrective action and it does not matter whether or not the underlying hypoxic response is abolished. It is during recovery and on the general ward when subanaesthetic concentrations are present and the patient is less comprehensively supervised that failure to respond to hypoxia may be important.

In an editorial in the British Journal of Anaesthesia, Goodman argued that the effect of subanaesthetic doses of volatile anaesthetics on the hypoxic response was clinically unimportant: ‘...for most patients complete loss of the hypoxic response does not matter. For those patients in whom it might be important we would be negligent to believe that such patients could be left unsupervised...’52 We cannot agree with either statement. After exposure to 1 MAC of enflurane or isoflurane for a period of 1 h, brain concentrations of these agents may remain greater than 0.1 MAC for more than 60 min.53 By this time after operation, most patients would have returned to the ward to be left (relatively) unsupervised. There are numerous causes of postoperative hypoxaemia: isoflurane and enflurane approximately halve the hypoxic response and so this may matter a great deal. Furthermore, an important part of the defence mechanism of airway obstruction is arousal and this is mediated in part by the chemoreflex response to hypoxia.34 Other situations in which lack of a hypoxic response may matter is the use of volatile anaesthetics in sedation and for analgesia in labour. Low concentrations of isoflurane added to Entonox have been advocated,55 although it is known that women in labour are prone to hypoxia.56 In general terms, it may be prudent to use an agent which has a small effect, rather than a profound depressant effect on chemoreflexes. Figure 3 summarizes most of the results to date regarding volatile agents and AHVR. It would appear that sevoflurane has the least depressant effect on the hypoxic response.

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