

Effect of Pain and Audiovisual Stimulation on the Depression of Acute Hypoxic Ventilatory Response by Low-dose Halothane in Humans

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Background: The effects of different low-dose volatile agents in blunting the acute hypoxic ventilatory response (AHVR) are variable. Arousal (due to audiovisual stimulation) may prevent isoflurane-induced blunting of AHVR. The purpose of this study was to assess whether this was also the case for halothane. The authors also assessed the effects of pain on the interaction of halothane and AHVR.

Methods: Step decreases in end-tidal partial pressure of oxygen using dynamic end-tidal forcing were performed from normoxia to hypoxia (50 mmHg) in 10 healthy volunteers, with end-tidal partial pressure of carbon dioxide held 1–2 mmHg above normal, in six protocols: (1) control conditions (darkened, quiet room, eyes closed) without halothane and (2) with 0.1 minimum alveolar concentration (MAC) halothane; (3) audiovisual stimulation (bright room, loud television) without halothane and (4) with 0.1 MAC halothane; (5) pain (electrical stimulation of skin over the tibia to produce a visual analog pain score of 5–6 out of 10) without halothane and (6) with 0.1 MAC halothane. The Bispectral Index of the electroencephalogram was also monitored.

Results: Halothane did not affect normoxic minute ventilation in any arousal state but significantly reduced the magnitude of AHVR by 50% regardless of the background arousal state ($P < 0.001$). Bispectral Index values were reduced by halothane only in the absence of arousal ($P < 0.003$). Both pain and audiovisual stimulation modestly increased normoxic minute ventilation ($P < 0.002$) and AHVR ($P < 0.003$).

Conclusions: Audiovisual stimulation does not prevent the blunting of AHVR by low-dose halothane. This result with halothane differs from previous results with isoflurane. Therefore, different anesthetics interact in different ways with arousal states. This finding raises the possibility that different anesthetics might differentially affect the hypoxic chemoreflex loop or that they might act in the brain at sites separate from the chemoreflex loop, differently to influence the wakefulness drive to ventilation.

It is long established that volatile anesthetic agents at doses of less than 0.2 minimum alveolar concentration (MAC) depress the acute hypoxic ventilatory response (AHVR) by approximately 50–70%.^{1–4} However, the effect of anesthetic agents can be very variable. In contrast to the earlier results of Knill *et al.*, Temp *et al.*^{5,6} were unable to demonstrate that 0.1 MAC isoflurane de-

pressed AHVR. Pandit *et al.*⁷ found that the anesthetic agent sevoflurane depressed AHVR much less than reported for other agents.

The source of this variability of effect was unclear, but van den Elsen *et al.*⁸ suggested that the state of arousal of subjects (and especially the effect of audiovisual stimulation in the form of watching television or music videos) might be important. When audiovisual stimulation was absent, isoflurane blunted AHVR; when audiovisual stimulation was present, isoflurane had no effect.⁸

In addition (and perhaps surprisingly), Sarton *et al.*^{9,10} found that acute pain (electrical stimulation over the tibial bone, which might seem at first to be more arousing than audiovisual stimulation) did not reverse the depression of AHVR by sevoflurane. They therefore concluded that audiovisual stimulation was a “specific” stimulus that interacted with the hypoxic chemoreflex in a unique manner to prevent anesthetic-induced blunting of AHVR. Pain, they argued, was a “nonspecific” stimulus that, while arousing the central nervous system in general, did not do so in a manner that specifically interacted with the hypoxic chemoreflex. In summary, the hypothesis was that the background study condition of arousal explained the variability of results seen in different studies for the effect of anesthetics on AHVR.¹¹

Pandit¹² has offered an alternative hypothesis. Many studies have demonstrated a greatly blunted AHVR by halothane^{13,14} and enflurane¹⁵ while subjects were audiovisually stimulated. Pandit explored this observation in a systematic review and concluded that the largest source of variability in published, pooled results was not due to the presence of an arousing stimulus but simply due to the type of anesthetic agent used.¹² The suggestion was that different anesthetic agents have intrinsically different effects on the hypoxic chemoreflex, regardless of background arousal state, perhaps because of different mechanisms of action at the cellular/molecular level.

Specifically, Pandit¹² noted that although the interaction of audiovisual stimulation on AHVR had been examined in the presence of one agent (isoflurane)⁸ and the interaction of pain on AHVR had been examined in the presence of another agent (sevoflurane),⁹ both audiovisual stimulation and pain had not been explored together in the presence of the same agent. Pandit predicted that if this were done for halothane, neither audiovisual stimulation nor pain would prevent the blunting of AHVR.¹²

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The purpose of this study was to test this prediction. We planned to assess whether audiovisual stimulation would prevent the depression of AHVR by halothane (in the manner predicted by Dahan *et al.*⁹⁻¹¹) or whether audiovisual stimulation would have no effect (as predicted by Pandit¹²). We also wished to investigate the effects of acute pain. Both Dahan *et al.*⁹⁻¹¹ and Pandit¹² predict that pain would not prevent depression of AHVR by halothane. We accepted from the outset that, although our study was designed to test this specific prediction, direct replication of the study conditions of all previous investigations would be difficult or impossible. Finally, we planned to measure the Bispectral Index (BIS) score during our experiments to obtain some objective index of the level of central nervous system arousal in each study condition.¹¹

Materials and Methods

Subjects

This study was approved by the Oxford Research Ethics Committee, Oxford, United Kingdom. We studied 10 healthy volunteers (9 men and 1 woman), all of whom gave written informed consent.

Control of End-tidal Gases

During experiments, subjects were seated in a chair, wore a nose clip, and breathed through a mouthpiece. Respiratory volumes were measured by a turbine volume-measuring device, and flows were measured 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, United Kingdom) and analyzed for partial pressure of carbon dioxide (P_{CO_2}) and partial pressure of oxygen (P_{O_2}). The volumes and 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 locate end-tidal P_{CO_2} (P_{ETCO_2}) and end-tidal P_{O_2} (P_{ETO_2}). End-tidal gases were controlled by dynamic end-tidal forcing to maintain desired end-tidal values independently of changes in ventilation. Details of this technique and gas-mixing system have been described in detail elsewhere.^{16,17}

Halothane was administered using a Dräger vaporizer (Drägerwerk, Lübeck, Germany), and expired concentrations were detected using the mass spectrometer calibrated for halothane using a standard gas mixture of halothane (British Oxygen Company, Ltd., London, United Kingdom). During experiments, the vaporizer setting was adjusted manually to achieve an end-tidal breath-by-breath halothane concentration of at least 0.07% and no more than 0.09% (approximately 0.1 MAC). We took the MAC of halothane to be 0.8%.¹⁴

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

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Protocols

Before each experimental period, subjects underwent a period of quiet breathing to establish their ambient P_{ETCO_2} . In those experimental periods involving administration of halothane, this time interval (at least 8 min) was also used to reach the target end-tidal value (0.1 MAC) of halothane. Dynamic end-tidal forcing was then used to hold the P_{ETCO_2} 1-2 mmHg above this ambient value throughout each protocol. The P_{ETO_2} was controlled in the following manner: an initial 4-min period of 100 mmHg, followed by three steps of hypoxia (P_{ETO_2} 50 mmHg), each of 4 min duration and each separated by 4 min of normoxia (P_{ETO_2} 100 mmHg).

These end-tidal gas profiles were undertaken in six protocols (in random order on different days), with each protocol characterized by a distinct background arousal state (separately with and without 0.1 MAC halothane):

1. control: subjects were in a darkened, quiet room, with their eyes closed;
2. audiovisual stimulation: subjects watched television with sound in a bright, noisy room;
3. pain: subjects were exposed to experimentally induced acute pain in a darkened, quiet room, with their eyes closed.

Each subject was exposed to one control protocol with and one without halothane; one audiovisual stimulation protocol with and one without halothane; and one pain protocol with and one without halothane. Therefore, there were a total of 60 separate experimental periods for analysis. Each experimental period consisted of three steps of hypoxia, so there were a total of 180 separate hypoxic responses available for analysis.

Administration of Arousal Stimuli

Audiovisual Stimulation Protocols. Because it has been suggested that the choice of video (drama or comedy) might affect respiratory pattern,¹⁸ in the audiovisual stimulation protocols, subjects were free to choose the television programs or video of their choice. Some of these videos were documentaries or music videos unknown to the subjects. We ensured that a mixture of these types of audiovisual stimulus was used continuously throughout the protocol. The sound was turned high (but not so high that it was painful), the room was brightly lit, and experimenters talked freely.

Control and Pain Protocols. In the control and pain protocols, the room was darkened by window blinds, all noise was reduced to the bare minimum, the experimenters talked quietly or whispered only when necessary, the subjects' eyes were closed, and the subjects wore headphones to further eliminate noise.

Pain Protocols. In the pain protocols, two electrodes were placed on the skin overlying the tibial bone. The electrodes were attached to an electrostimulator (Microstim DB; Viomed Ltd., North Hollywood, CA), which delivered noxious electrical stimuli of 0.2 ms duration at 1 Hz. The current strength could vary from 0 to 80 mA and was adjusted to achieve a target visual analog pain scale (VAS) score of no less than 5 out of 10 and no higher than 6 out of 10 (scale: 0 = no pain, 10 = worst pain possible). The painful stimulus was administered for fixed durations of 6 min, spanning the hypoxic step and the 2 min of normoxia before hypoxia. The absence of pain for 2 min during normoxic periods was designed to minimize the possibility of adaptation to the pain. The VAS score was measured at the end of each protocol to assess stability of the stimulus.

Monitoring of Central Nervous System Arousal State

First, subjects were observed clinically. Their state was described by the Observer's Assessment of Alertness/Sedation score, which is a scale from 0 (unarousable subject) to 5 (normal, awake subject).⁸

Second, subjects in all protocols rested one arm passively upright (with the elbow resting on the armrest), holding an alarm constructed in our laboratory. If the arm fell or the hold on the alarm was released, a noise would sound, alerting the experimenters to the possibility of oversedation. This was particularly useful in the control protocols when the room was darkened. We have used this method previously.⁷

Finally, a Bispectral Index[®] monitor (BIS[®], A-2000 with XP upgrade; Aspect Medical Systems Inc., Newton, MA) was used. The BIS[®] electrodes (XP) were placed on the forehead in accordance with the manufacturer's instructions. The machine performed its own impedance test, and also, it took into account the signal quality index, yielding a BIS value only when this quality was acceptable. The monitor also gives an indication of electromyographic activity, which was very low in this study. The BIS[®] was programmed to yield values averaged over 5-min periods, and these readings of acceptable BIS values were recorded by hand.

Data Analysis

Data were averaged into 1-min periods. The ventilation in the last minute of normoxia, before any hypoxia was administered, was used as the baseline, normoxic ventilation for each study condition. The AHVR for each hypoxic step was then calculated as the difference between the peak ventilation reached in the 4 min of hypoxia and the ventilation in the last minute before the hypoxic exposure. Therefore, for each experimental period, there were three values of AHVR obtained, and these were averaged to yield the average value of AHVR

for the protocol. These individual subject values were then averaged to obtain the mean for the group.

Statistical Analysis

The values for baseline normoxic ventilation, AHVR, and BIS were first subjected to analysis of variance (ANOVA; SPSS version 10.0.5 for Windows; SPSS, Chicago, IL). The "response" was ventilation or AHVR, and there were three "factors": arousal (fixed factor, 3 levels); halothane (fixed factor, 2 levels); and subject (random factor, 10 levels). If ANOVA indicated a statistically significant effect, a *post hoc* paired Student *t* test was undertaken to locate the precise source of the significant effect. A value of $P < 0.05$ was taken as statistically significant. For those comparisons involving multiple *post hoc* tests, the Bonferroni correction was applied, and statistical significance was taken at a value of $P < 0.05/n$, where *n* was the number of comparisons made for the hypothesis tested.

Results

The mean age of subjects was 20.6 yr (range, 20–22 yr), their mean height was 1.78 m (1.65–1.85 m), and their mean weight was 72.1 kg (55–84 kg). The subjects were asked to refrain from food for at least 6 h and from drink for at least 4 h before each study.

Figure 1 (top) shows the gas input for one example subject (1,326) for one experimental period. Gas control by dynamic end-tidal forcing was good, with rapid steps into hypoxia, and reasonably steady $P_{ET}O_2$ during the hypoxic step. $P_{ET}CO_2$ was steady throughout, with slight imperfections at the steps into and out of hypoxia.

Figure 1 (bottom) shows the resulting ventilatory response during the gas input profile for two example experimental periods, one with and one without halothane. Ventilation increased rapidly and peaked within the 4-min period of hypoxia, returning to original baseline prehypoxic levels during the periods of normoxia. Halothane blunted the increase in ventilation with each hypoxic step but did not seem to change the normoxic baseline ventilation. For clarity, figure 1 (bottom) shows only the two experimental periods for the control protocol, but the same general pattern of response was seen for the other protocols (audiovisual stimulation and pain).

Table 1 shows the numerical values for the baseline normoxic ventilation in each of the six protocols. ANOVA did not show any significant effect of halothane, but the interactive term of halothane and arousal was significant ($P < 0.04$), indicating that halothane might influence baseline ventilation depending on the prevailing arousal state. However, *post hoc t* tests did not confirm this suggestion, and within each of the arousal states, there was no significant effect of halothane. There

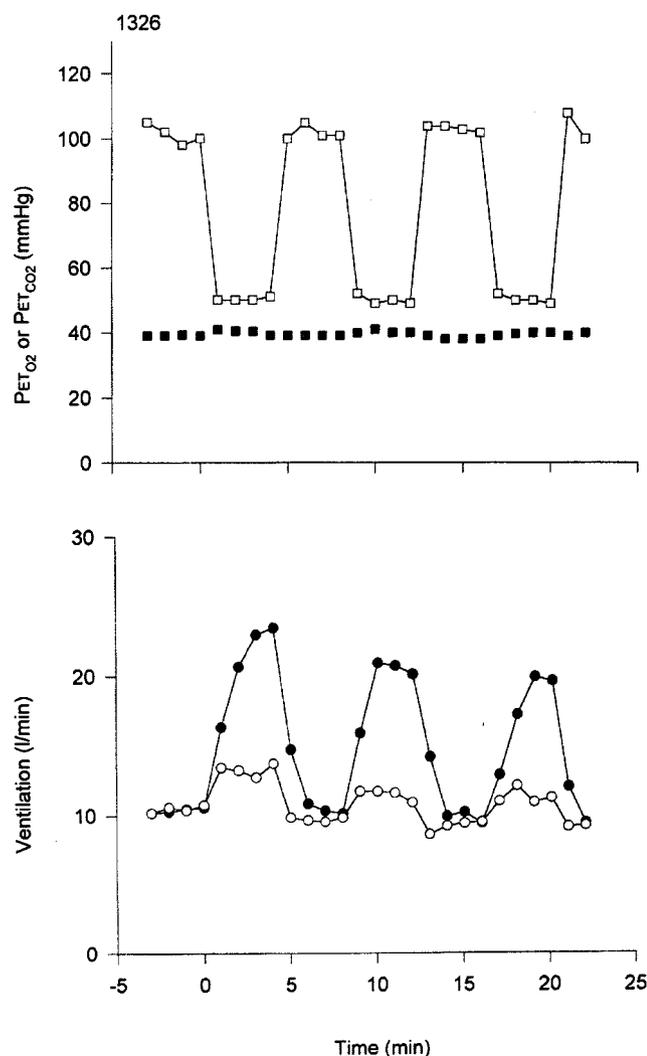


Fig. 1. (Top) End-tidal partial pressures for oxygen and carbon dioxide ($PE_{T_{O_2}}$ [□] and $PE_{T_{CO_2}}$ [■], respectively) gas input profiles during one control experimental period for one subject (1,326). This trace is shown to illustrate the generic gas input for each of the protocols. (Bottom) Minute ventilation during one control experimental period without halothane (●) and one period with halothane (○). Points are minute averages. Time = 0 is arbitrarily taken at the start of the first hypoxic step.

was a significant influence of arousal alone ($P < 0.008$, ANOVA). *Post hoc t* tests showed that the mean normoxic ventilation in the control protocol differed from ventilation in both audiovisual and pain protocols ($P < 0.002$ and $P < 0.001$, respectively). The mean ventilations in audiovisual and pain protocols were not different. Therefore, both types of arousal significantly and modestly increased baseline normoxic ventilation as compared with control, and this effect was not influenced by halothane.

Table 2 shows the values for AHVR in each of the six protocols. ANOVA showed significant effects of halothane ($P < 0.001$) but not of the interactive term of halothane and arousal, which suggested that halothane significantly reduced AHVR regardless of the back-

ground arousal state. The degree of depression of AHVR by halothane was 49% in the control protocol, 51% in the audiovisual stimulation protocol, and 53% in the pain protocol (fig. 2). ANOVA also indicated that arousal alone had a significant influence on AHVR ($P < 0.004$). *Post hoc t* tests showed that AHVR in the control protocol differed from AHVR in both audiovisual and pain protocols ($P < 0.003$ and $P < 0.001$, respectively), but AHVR did not differ between pain and audiovisual protocols. Therefore, both types of arousal increased AHVR modestly as compared with control.

Figure 3 shows the BIS values for the six protocols. ANOVA showed significant effects of halothane ($P < 0.009$), which suggested that halothane reduced BIS, and of arousal ($P < 0.018$), suggesting that BIS values differed between arousal states. The interactive term of halothane and arousal was significant ($P < 0.007$), which suggested that this effect of halothane on BIS varied with arousal state: *Post hoc t* tests showed that the effect of halothane was significant only in the control protocol ($P < 0.003$) and not in the audiovisual and pain protocols. Therefore, the ability of halothane to reduce BIS was antagonized by both types of arousal.

Subjects reported that with halothane, they were sleepy or "felt drunk." Clinically, they appeared sedated, and none lost consciousness or dropped the handheld alarm (although we noticed that in some subjects, the arm holding the alarm tended to sway considerably during halothane experiments). The subjects' state as described by the Observer's Assessment of Alertness/Sedation score was 5 for all protocols without halothane and for both pain protocols (with or without halothane) and was either 4 or 5 for all other protocols with halothane. The VAS scores remained between 5 and 6 out of 10 at the end of all experiments involving induced pain. There was no difference in the current needed to achieve the target VAS score between the protocols with and without halothane, and the currents were in the range of 45–80 mA.

Discussion

The striking result of this study is that audiovisual stimulation does not prevent the blunting of AHVR by 0.1 MAC halothane. Previous reports that audiovisual stimulation prevents the blunting of AHVR by 0.1 MAC isoflurane⁸ might lead to the prediction that the same is true for all agents, but this is not the case. A second result is that pain does not prevent the blunting of AHVR by 0.1 MAC halothane. A third result is that, regardless of the effect of halothane, arousal (both audiovisual and pain) can modestly augment normoxic ventilation and AHVR.

Table 1. Baseline Ventilation in Normoxia, with End-tidal Pco₂ Kept 1–2 mmHg above Normal

Subject	Control		Audiovisual Stimulation		Pain	
	No Halothane	Halothane	No Halothane	Halothane	No Halothane	Halothane
1,316	12.3	8.6	13.1	10.9	15.5	8.8
1,317	11.3	22.4	9.2	13.1	18.5	14.5
1,318	10.1	7.4	14.6	10.5	15.2	8.4
1,319	9.9	10.9	9.3	13.1	9.0	8.8
1,320	10.6	9.6	16.3	13.1	15.0	10.9
1,321	12.7	15.9	15.6	19.7	15.1	20.4
1,322	10.9	10.9	9.5	17.0	16.2	14.1
1,323	7.2	9.2	16.4	15.8	17.6	14.1
1,325	8.6	8.1	9.8	15.2	11.7	12.1
1,326	10.7	10.8	14.3	12.0	15.7	15.6
Mean	10.4 ± 1.6	11.4 ± 4.5	12.8 ± 3.1	14.0 ± 2.9	14.9 ± 2.8	12.8 ± 3.8

Values are presented as mean ± SD in l/min. Analysis of variance and *post hoc t* tests show that within each arousal state, halothane has no effect and that both audiovisual stimulation and pain increase baseline ventilation vs. control ($P < 0.002$ and $P < 0.001$, respectively).

Pco₂ = partial pressure of carbon dioxide.

Comments on Experimental Protocols

Before we consider the physiologic interpretation of our findings, it is important to examine in detail some aspects of the experimental protocol that might have contributed to our result. First, if the effect of halothane in our control protocol was very different in magnitude from that which might be expected, this might explain a difference between our results and those reported for isoflurane. However, this was not the case. Pandit,¹² pooling 16 published results, found that halothane at a dose of less than 0.2 MAC reduces AHVR by an average of 58% of control value (95% confidence interval, 48–68%). This value is not different from our value of approximately 50%.

A second possibility is that our audiovisual input was insufficiently stimulating to the subjects, and this might explain its failure to antagonize the effect of halothane. However, this seems unlikely. We have used background audiovisual stimulation in a previous study using sevoflurane.⁷ It was later suggested¹¹ that this was the reason we found no effect of sevoflurane on AHVR. The degree of audiovisual stimulation in our current study (in terms of television sound and laboratory noise) was intentionally higher than in our previous study. The BIS data also suggest that audiovisual stimulation sufficiently aroused the central nervous system in that it prevented the decrease in BIS with halothane (fig. 3).

Third, if the electrical stimulus we used was insuffi-

Table 2. Acute Hypoxic Ventilatory Response

Subject	Control		Audiovisual Stimulation		Pain	
	No Halothane	Halothane	No Halothane	Halothane	No Halothane	Halothane
1,316	8.7 (6.2–13.4)	2.9 (2.1–4.6)	7.6 (6.0–9.5)	5.5 (3.5–7.7)	12.4 (11.2–13.7)	5.3 (4.4–6.9)
1,317	9.0 (8.1–10.0)	7.3 (5.2–9.8)	9.3 (9.0–9.6)	8.2 (6.7–10.9)	13.0 (11.3–14.2)	10.8 (9.4–12.2)
1,318	3.4 (2.9–3.8)	1.6 (0.6–2.2)	9.5 (8.1–10.4)	2.2 (1.5–3.0)	8.1 (5.9–10.6)	2.3 (1.7–3.2)
1,319	5.9 (2.3–8.0)	3.0 (2.5–3.7)	7.8 (6.8–9.5)	4.5 (2.8–5.4)	8.0 (7.4–8.4)	4.2 (2.7–5.2)
1,320	9.5 (6.5–12.8)	5.1 (4.1–6.9)	22.8 (21.0–26.1)	6.6 (2.6–10.2)	16.6 (12.8–20.1)	6.2 (4.3–8.7)
1,321	9.1 (8.1–9.9)	6.8 (3.8–9.8)	8.5 (6.8–10.1)	5.1 (5.0–5.2)	6.1 (4.7–8.7)	6.8 (4.2–9.9)
1,322	9.6 (8.6–10.4)	3.9 (2.1–4.8)	6.6 (4.3–10.1)	5.9 (5.4–6.3)	10.9 (9.7–11.8)	5.9 (4.9–6.7)
1,323	6.0 (5.6–7.8)	2.7 (2.4–3.3)	12.0 (8.8–16.2)	4.8 (2.8–4.9)	8.9 (7.7–10.5)	4.6 (4.2–5.0)
1,325	5.0 (2.5–7.4)	2.0 (1.3–2.3)	6.0 (3.8–9.7)	3.1 (1.9–5.7)	8.5 (7.5–9.1)	3.5 (2.6–4.8)
1,326	11.0 (9.8–12.8)	2.5 (1.9–3.0)	12.7 (10.8–15.5)	6.7 (5.2–10.3)	16.1 (12.1–19.3)	8.3 (5.4–11.5)
Mean	7.7 ± 2.5	3.8 ± 1.9	10.3 ± 4.9	5.3 ± 1.8	10.9 ± 3.6	5.8 ± 2.5

Values are presented as mean ± SD (range) in l/min. Analysis of variance and *post hoc t* tests show that within each arousal state, the effect of halothane is significant ($P < 0.001$) and that both audiovisual stimulation and pain increase acute hypoxic ventilatory response vs. control ($P < 0.003$ and $P < 0.001$, respectively).

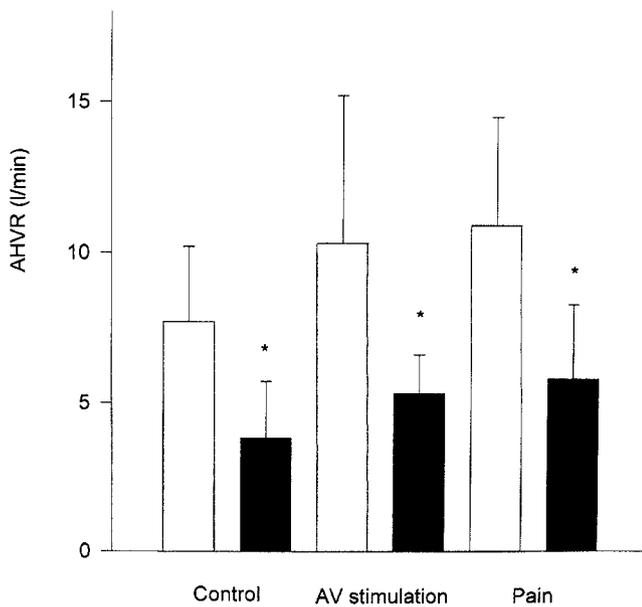


Fig. 2. Mean values (\pm SD) of acute hypoxic ventilatory response (AHVR) from table 1 for the protocols without halothane (hollow bars) and with halothane (filled bars). * Effect of halothane significant regardless of prevailing arousal state ($P < 0.001$, analysis of variance). AV = audiovisual.

ciently painful, this might have failed to prevent blunting of AHVR by halothane. This seems unlikely. We chose electrically induced pain because this was also the method used by Sarton *et al.*^{9,19} in previous studies. Subjects clearly found our stimulus painful; they did not like it and reported it as unpleasant: A VAS score of 5–6

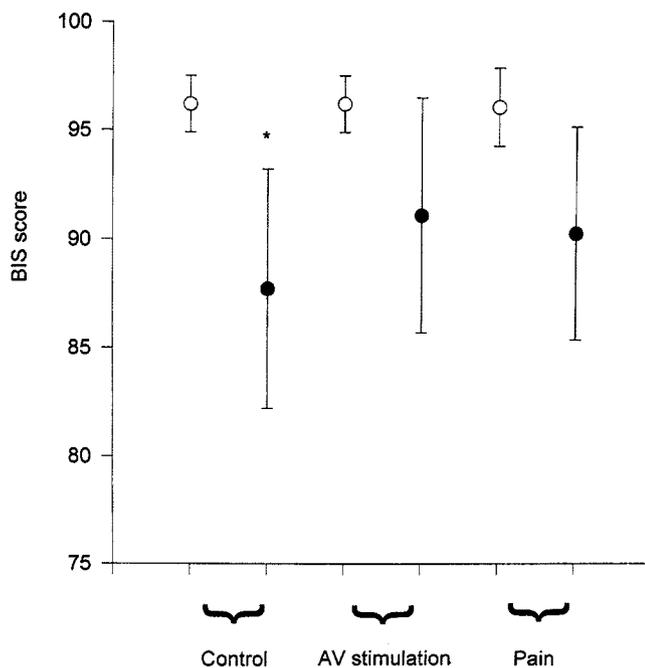


Fig. 3. Mean (\pm 95% confidence intervals) for Bispectral Index (BIS) for the protocols without halothane (hollow circles) and with halothane (filled circles). * $P < 0.003$ for comparison with control protocol without halothane (Student *t* test). AV = audiovisual.

out of 10 is quite high. Furthermore, we were careful to ensure that this VAS score was unchanged at the end of the study period, excluding the possibility of any “adaptation” or “drift” in the painful stimulus. Again, the BIS data suggest that pain sufficiently aroused the central nervous system in that it prevented the decrease in BIS with halothane (fig. 3).

Fourth, our subjects wore a mouthpiece and nose clip; some (but not all) previous studies have instead used a tight-fitting facemask. It has been suggested that the mouthpiece and nose clip modestly stimulate breathing as compared with a facemask.²⁰ However, the nose clip/mouthpiece is suggested to augment arousal; nonetheless, we found that this putative “extra” arousal had no effect on the extent to which halothane blunted AHVR.

Finally, there is the remote possibility that although the end-tidal partial pressures of halothane were steady in our study, the brain partial pressures were not equilibrated with end-tidal values. This putative effect is less likely with isoflurane, which is relatively less soluble. However, both Knill and Clement² and van den Elsen *et al.*²¹ have modeled the relations and concluded that, in the steady state, the end-tidal and brain partial pressures are similar for both halothane and isoflurane. This is supported by direct experimental data of Zbinden *et al.*,²² who found that, when the end-tidal partial pressures of halothane and isoflurane are steady, so too are the brain partial pressures for both agents.

Effects of Halothane on Normoxic Ventilation

We did not observe any effects of 0.1 MAC halothane on normoxic baseline ventilation. This result is consistent with previous results for low-dose halothane,^{13,14} isoflurane,^{5,6,8,22} and sevoflurane.^{7,9,10,23} This observation further supports the notion that volatile anesthetics have a more profound effect on the hypoxic chemoreflex than they do on the mechanisms controlling basal ventilation.

Effects of Pain on Ventilatory Variables

Normoxic Ventilation. Like Sarton *et al.*,^{9,19} we also found that pain *per se* increased baseline ventilation, suggesting a degree of interaction between pain and the neural factors that control basal ventilation.

AHVR. In addition, we found that pain increased AHVR modestly as compared with control. This result differs from some previous work, which suggests that pain does not augment the peripheral hypoxic chemoreflex.^{9,19,24,25} One possible explanation is that we used a slightly higher stimulus level, titrating the pain to a VAS score of 5–6 out of 10, rather than 4–5 out of 10 as used in previous studies. Different intensities of pain may differentially stimulate A δ fibers and C fibers, and this might conceivably result in different effects on respiratory responses.²⁴ Another possible explanation is that at

least a small part of the increase in AHVR we observed was due to a "startle" response in ventilation at the onset of acute pain. However, previous work suggests that this startle response is complete and ventilation reaches a steady state within 60 s after the onset of pain,^{19,26} whereas in our study, AHVR was measured at least 3 min after the start of pain. Finally, it is possible that our result of augmented AHVR is specific to the quality (and not just intensity) of pain stimulus we used: Other groups have reported different patterns of ventilatory response with heat,²⁵ pressure-induced pain,²⁶ and surgical stimulation.²⁷

Interaction of Pain and Halothane. Halothane did not influence the degree to which pain increased baseline ventilation. Halothane blunted AHVR by 50% with or without pain.

Effect of Audiovisual Stimulation on Ventilatory Variables

Normoxic Ventilation. We found that the effect of audiovisual stimulation on baseline ventilation was significant (mean increase, 2.4 l/min in the control protocol; table 1). Although Karan *et al.*²⁵ used a different method of audiovisual stimulation (playing a computer game), they reported similar results. Previously, van den Elsen *et al.*⁸ reported a larger increase of 3.9 l/min with audiovisual stimulation, but this did not reach statistical significance in their study.

AHVR. We found that audiovisual stimulation increased AHVR significantly (by 2.6 l/min in the control protocol; table 2). This result is similar to that of Karan *et al.*,²⁵ but van den Elsen *et al.*⁸ previously observed an increase of only 0.4 l/min (not significant).

Interaction of Audiovisual Stimulation and Halothane. Halothane did not influence the effect of audiovisual stimulation on baseline ventilation. Halothane reduced AHVR by 50%, with or without audiovisual stimulation. This is the main result of the study, and there seem to be no previous studies exploring the interaction of audiovisual stimulation and halothane.

BIS Responses with Halothane and Arousal

Both pain and audiovisual stimulation antagonized the depression of BIS by halothane. Therefore, there was a dichotomy between the BIS and AHVR responses: Halothane depressed AHVR but did not depress BIS in the presence of arousal (either audiovisual stimulation or pain).

Breathing (and AHVR) can be influenced by a wakefulness drive (which has been referred to as the *behavioral control system*) and separately by a chemoreflex drive (also known as the *metabolic control system*).⁸ Arousal augments the wakefulness drive to breathe, which in turn can augment AHVR (or can prevent blunting of AHVR by anesthetic).⁸ Because BIS is purported to measure wakefulness, the dichotomy we found suggests ei-

ther (1) that the primary mechanism by which halothane depressed AHVR in our two arousal protocols is not by reducing the wakefulness drive (and so occurs by some other mechanism; presumably by an effect on the chemoreflex) or (2) that the primary mechanism for halothane is indeed by reducing wakefulness drive but that wakefulness is not accurately measured by the BIS value. It is important to emphasize that all BIS data must be interpreted with caution. The limitations of BIS have been well documented elsewhere.²⁸ The data regarding low-dose volatile agents and BIS is sparse, but the large variability in BIS values we obtained (fig. 3) is consistent with the large variability found by Ibrahim *et al.*,²⁹ who examined sedative concentrations of sevoflurane.

Implications of the Results

Although the two agents have not been directly compared within a single study, our results here with halothane differ strikingly from previous results for isoflurane.⁸ Audiovisual stimulation prevents isoflurane-induced blunting of AHVR but does not prevent halothane-induced blunting of AHVR. Broadly, there are two possible interpretations.

One interpretation is that the actions of isoflurane and halothane are in reality similar, but methodologic differences between studies alone account for any differences. This seems, to us, very unlikely.

An alternative interpretation is that the two anesthetics (isoflurane and halothane) genuinely differ in their actions on the ventilatory control system. If this is so, there are a number of possible ways in which they might differ. Unfortunately, the results of this study itself do not help to determine conclusively which of the possibilities below is the most likely.

First, the anesthetics might differ in their action on the hypoxic chemoreflex, at any site along the reflex pathway, including differences in action on the carotid body itself. However, evidence in support of such differences is currently sparse. Previous studies of the dynamic effects of isoflurane and halothane on the hypoxic and hypercapnic reflexes suggest that the actions of the two agents were similar (and specifically located to a similar action at the carotid body).^{8,13,22,30} More recently, Teppema *et al.*³¹ have found that antioxidants prevented the blunting of AHVR by halothane. They hypothesized that the antioxidants were influencing the redox state (and hence opening) of the hypoxia-sensitive potassium channel in the carotid body glomus cell to produce this effect.³¹ It remains to be seen how antioxidants might affect the effect of isoflurane on AHVR (and its interaction with arousal).

The second possibility is that the two anesthetics might differ in their action more centrally, on the wakefulness drive of the behavioral control system. If halothane caused a greater degree of central nervous system sedation than isoflurane at the same dose, this might

explain the failure of audiovisual stimulation to prevent the blunting of AHVR with halothane. However, if we accept the BIS data as a proper reflection of the degree of central nervous system sedation, then our data suggest that halothane does not cause significant sedation in the presence of audiovisual stimulus (consistent with our clinical observation that subjects were not sleepy when watching television). This BIS data also seems consistent with the conclusion of Dahan and van den Elsen *et al.*,^{8,13,21,30} who concluded that halothane did not affect either the central chemoreflex loop or the integrating centers in the central nervous system. A technique more sophisticated than the BIS might be needed to detect any differential effects between halothane and isoflurane on the brain. One such technique might be functional magnetic resonance imaging. Heinke and Schwarzbauer³² have reported that isoflurane significantly reduces task-induced activation in only three specific brain areas and not homogeneously in the entire brain. Willis *et al.*³³ have found significant differences in visually induced functional magnetic resonance imaging signals between isoflurane and propofol anesthesia in dogs. These early findings suggest that some interactions between visual and task arousals and anesthetic effects in the brain can be highly specific and that these specific effects might differ between anesthetics. It would be important to extend such observations to the interaction of arousal and anesthetics with the ventilatory control system.

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