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Effects of Alfentanil on the Ventilatory Response to Sustained Hypoxia

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Background: **The ventilatory response to acute hypoxia is biphasic, with an initial rapid increase followed by a slower decline. In humans, there is evidence that the magnitude of the decline in ventilation is proportional to the size of the initial increase. This study was done to define the role of exogenous opioids in the ventilatory decline seen with prolonged hypoxia.**

Methods: **Ten healthy persons were exposed to isocapnic hypoxia for 25 min, followed by 5 min of isocapnic normoxia and 5 min of isocapnic hypoxia. These conditions were repeated during a computer-controlled alfentanil infusion.**

Results: **Serum alfentanil levels were constant among the volunteers (38 ± 12 ng/ml). Alfentanil decreased both the initial and second acute hypoxic responses (from 1.27 ± 0.73 to 0.99 ± 0.39 $l \cdot min^{-1} \cdot \%^{-1}$, $P < 0.05$; and from 0.99 ± 0.70 to 0.41 ± 0.29 $l \cdot min^{-1} \cdot \%^{-1}$, $P < 0.05$, respectively). The magnitude of the decrease in ventilation during the 25 min of hypoxia was not changed (10 ± 3.3 l/min for control; 12.3 ± 7.5 l/min for alfentanil).**

Conclusions: **Alfentanil reduced the acute ventilatory response to hypoxia. The absolute value of hypoxic ventilatory decline was not increased, but a measure of residual hypoxic ventilatory decline (the ratio of ventilation between the second and first steps into hypoxia) was decreased, which supports the hypothesis that opioids potentiate centrally mediated ventilatory decline. (Key words: Acute hypoxic response; control of breathing; hypoxic ventilatory decline; opioids.)**

THE human ventilatory response to the sudden imposition of isocapnic hypoxia is biphasic. Initially there is a rapid increase in ventilation, known as the acute hypoxic response (AHR), which peaks approximately 3–5 min after the hypoxic stimulus is applied. The AHR is followed by a slow decrease in ventilation over 15–20 min, which has been called the hypoxic ventilatory decline (HVD). The biphasic nature of the ventilatory response to hypoxia has been well described in cats[1] and humans,[2,3] although the mechanisms are still controversial.

Although the AHR arises primarily from increased carotid body activity with hypoxia,[1] the mechanisms for the HVD are less obvious and may be multiple. The HVD may be the result of peripheral chemoreceptor adaptation, cerebral alkalosis caused by the hypoxia-induced increase in cerebral blood flow, direct depression of respiratory-related neurons from hypoxia, or changes in the balance of central inhibitor and excitatory neurotransmitters (see Bisgard and Neubauer[4] for a recent review). In humans subjected to mild to moderate hypoxia, the HVD seems to develop from central accumulation of inhibitory neurotransmitters (evidence from both human and animal studies would indicate that gamma-aminobutyric acid and adenosine are the likely candidates).[5,6] Interestingly in humans,[7] but not as clearly in cats,[8,9] this accumulation seems to depend on peripheral chemoreceptor input. Once the causative factors for the HVD have accumulated, apparently they dissipate slowly. A subsequent exposure to hypoxia after a brief return to normoxia does not elicit a full AHR, but rather the response remains depressed.[3] These characteristics of HVD may make it an important clinical effect, because postoperative hypoxemia, particularly during sleep, is common and episodic.

Exogenous opioids are commonly associated with depressed ventilation, primarily through a decrease in ventilatory responses to hypercapnia[10,11] and hypoxia.[12,13] Opioid receptors have been identified in proximity to respiratory control centers in the medulla, and this has led to the speculation of endogenous opioid involvement in ventilatory control. The availability of a specific

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opioid antagonist, naloxone, has resulted in multiple experiments that have addressed the role of endogenous opioids in ventilatory control. However, endogenous opioids do not appear to play a major role in ventilatory control in awake adults,[14] and only perhaps in some animals, human neonates, and certain diseases[15–17] do they seem to be involved in respiratory control. Of particular relevance to this study, Kagawa *et al.*[18] found that naloxone given during the development of HVD did not change the time course of the ventilatory decline. The role of exogenous opioids in the development of HVD has not been well studied.

Most previous descriptions of the effects of opioids on the hypoxic ventilatory response in humans have addressed the AHR but not the HVD. The first study of the effects of opioids on the hypoxic ventilatory response (by Weil *et al.*[12]) used a slow ramp (9 or 10 min) into hypoxia, which results in a ventilatory response that is a mixture of AHR and HVD. Given the presence of opioid receptors in close association with both peripheral[19] and central chemoreceptors,[20] and the close relation between AHR and HVD, we hypothesized that alfentanil would decrease hypoxic ventilatory responses through a combination of effects on the AHR and HVD. Gross *et al.*[21] studied the effects of alfentanil only on the AHR. van den Elson *et al.*[22] studied the effects of morphine on HVD and found no change even though the acute response was reduced.

Materials and Methods

Eleven healthy volunteers, 8 men and 3 women (aged 19–32 yr) were enrolled in this study. All were nonsmokers, took no medications other than birth control pills, and gave informed consent before the study began. The study was completed at the University of Rochester Medical Center and was approved by its human subjects protection committee.

When they arrived at the laboratory, all the volunteers had two catheters inserted in opposite arms, one for venous blood sampling and one for administration of alfentanil. The volunteers were allowed to relax for 30–45 min. The techniques of respiratory measurements have been described in detail before.[23] Briefly, the volunteers were seated in a comfortable chair with electric activity of the heart and pulse oximetry (Siemens Medical Electronics, Danvers, MA) monitored continuously for safety. The room was kept well lighted, with quiet music in the background and a travel video playing on a television monitor. The volunteers breathed from a gas mixing chamber *via* a face mask (Vital Signs, Totawa, NJ). Inhaled and exhaled volumes were measured with a bidirectional impeller flow meter (model VMM 110; Sensor Medics, Laguna Hills, CA). Airway gases were sampled continuously using a mass spectrometer (model MGA 110; Perkin-Elmer, Pomona, CA). Computer-driven (IBM-XT), high-flow, stepper-motor valves provided nitrogen, carbon dioxide, and oxygen to the gas mixing chamber at desired concentrations. The total flow of this system was 60 l/min. Ventilation ($\dot{V}_E$, l/min), tidal volume (V_T, l), breathing frequency (f, breaths/min), end-tidal gas concentrations ($P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$, mmHg), and hemoglobin oxygen saturation by pulse oximetry (%) were determined and collected using the TIDAL software package.[24]

To study the ventilatory response to isocapnic hypoxia we used the computer-driven "dynamic end-tidal forcing technique".[23] With this technique, we forced the $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ dynamically to follow a prescribed pattern in time by manipulating the inspired gas concentrations independent of the ventilatory response. In this study, we performed transitions in $P_{ET_{O_2}}$ at a background of constant $P_{ET_{CO_2}}$.

The volunteers first breathed room air for 10 min to determine their resting normoxic $P_{ET_{CO_2}}$ and acclimate them to the setup. The $P_{ET_{CO_2}}$ was elevated 5 mmHg above individual resting values so that both the control and alfentanil experiments could be performed at the same constant end-tidal carbon dioxide level.

The end-tidal oxygen tension was forced according to the following pattern (see also fig. 1): 8 min at 100 mmHg; a rapid decrease to 45 mmHg within three or four breaths; 25 min of sustained hypoxia at 45 mmHg; a rapid increase back to 100 mmHg, which was sustained for 5 min; a rapid decrease to 45 mmHg within three or four breaths; 5 min at 45 mmHg; and finally 2 min at an inspired oxygen concentration of >50%. The same pattern was repeated during the alfentanil infusion.

After the control experiment (approximately 45 min), the alfentanil infusion was started using a computer-controlled infusion pump (MiniMed, San Fernando, CA). An initial target level of 20 ng/ml was selected. The program used to control the infusion pump applied the pharmacokinetic data from Maitre *et al.*[25] Thirty minutes after the alfentanil infusion was started, the volunteers breathed room air for 5 min to determine normoxic $P_{ET_{CO_2}}$. If any of the volunteers had a normoxic $P_{ET_{CO_2}}$ level greater than the $P_{ET_{CO_2}}$ concentration employed

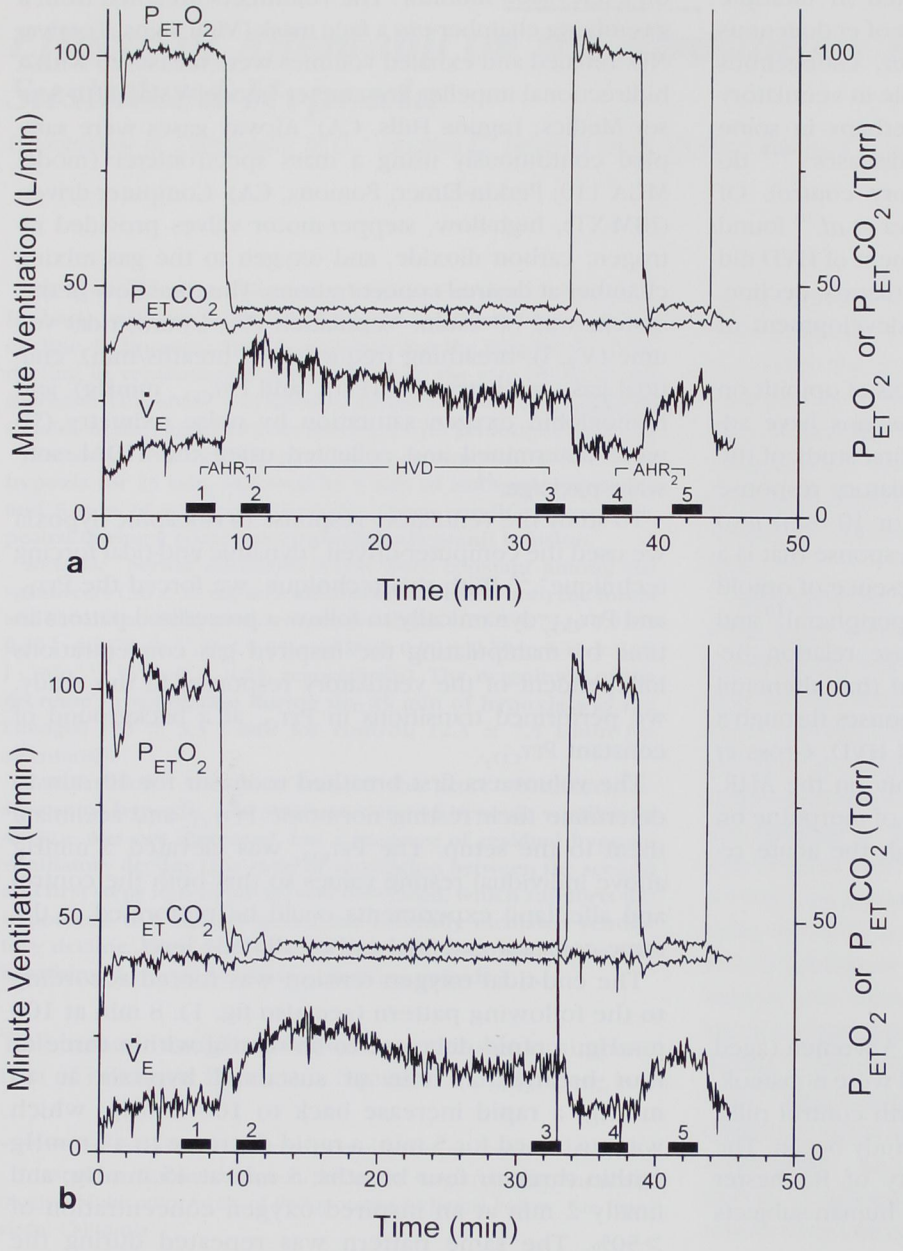

Fig. 1. Typical breath-to-breath data for a single volunteer during the control experiment (*A*) and alfentanil experiment (*B*). The bars on the x axis represent the 2-min time periods (1–5) for which ventilation was averaged (see also fig. 3 and table 1).

during the control protocol, the alfentanil infusion would be decreased (but this was never required). Venous samples were drawn to analyze the alfentanil level at the start of the experiment (time = 0 min), after the sustained hypoxic period (time = 35 min), and after the final hypoxic period (time = 45 min). Analysis of serum alfentanil level was performed by an outside laboratory (University of North Carolina) using a radioimmunoassay.

Data Analysis

The studies were evaluated by calculating mean values of the breath-to-breath data over identical time segments (see fig. 1) as follows: period 1, initial normoxia = last 2 min of normoxia before sustained hypoxia; period 2, initial peak hypoxia = min 3 and 4 of sustained hypoxia; period 3, final hypoxia = final 2 min of sustained hypoxia before normoxia; period 4, second normoxia = last 2 min of normoxia before

Table 1. Ventilatory Variables with Control and Alfentanil over the Different Time Periods

		Time Period				
		1	2	3	4	5
$P_{ET_{CO_2}}$ (mmHg)	Control	41.8 ± 1.6	42.0 ± 1.5	42.0 ± 1.5	42.0 ± 1.5	42.0 ± 1.6
	Alfentanil	41.6 ± 1.9	41.9 ± 1.5	41.9 ± 1.5	42.1 ± 1.4	41.9 ± 1.6
$P_{ET_{O_2}}$ (mmHg)	Control	100.7 ± 0.6	44.9 ± 0.4†	45.3 ± 0.2†	100.6 ± 0.7‡	44.9 ± 0.8†
	Alfentanil	101.4 ± 1.3	45.5 ± 0.6†	45.5 ± 0.7†	101.2 ± 1.6‡	45.1 ± 0.5†
Saturation	Control	96.12 ± 0.75	78.07 ± 1.82†	78.62 ± 1.93†	96.77 ± 0.86‡	78.66 ± 2.83†
Sp_{O_2} (%)	Alfentanil	95.54 ± 0.58	79.01 ± 1.48†	77.41 ± 2.79†	95.93 ± 0.75‡	77.1 ± 2.03†
$\dot{V}_E$ (L/min)	Control	14.7 ± 3.9	36.9 ± 13.4†	26.9 ± 12.0†‡	15.6 ± 5.8‡	33.0 ± 15.1†
	Alfentanil	10.7 ± 2.9*	27.1 ± 8.8*†	14.8 ± 5.3*†‡	10.0 ± 2.4*‡	17.6 ± 7.0*†‡
V_T (L)	Control	0.92 ± 0.30	1.85 ± 0.69†	1.32 ± 0.50†‡	0.87 ± 0.29‡	1.55 ± 0.59†‡
	Alfentanil	0.71 ± 0.16*	1.42 ± 0.50*†	0.91 ± 0.32*†‡	0.68 ± 0.19*‡	1.03 ± 0.38*†‡
f (min^{-1})	Control	16.9 ± 2.9	20.6 ± 2.2†	20.5 ± 2.7†	18.3 ± 2.2	21.3 ± 3.1†
	Alfentanil	15.4 ± 2.5	19.9 ± 3.2†	16.6 ± 1.9*‡	15.6 ± 2.1*‡	17.3 ± 2.4*‡

Values are mean ± SD.

Period 1 = initial normoxia; Period 2 = initial peak hypoxia; Period 3 = final hypoxia; Period 4 = second normoxia; Period 5 = second peak hypoxia.

* $P < 0.05$ *versus* control at corresponding time period.

† $P < 0.05$ *versus* Period 1 within control or alfentanil experiments.

‡ $P < 0.05$ *versus* Period 2 within control or alfentanil experiments.

reintroduction of hypoxia; and period 5, second peak hypoxia = min 3 and 4 of the second bout of hypoxia.

We defined the difference in $\dot{V}_E$ between the initial peak hypoxia (period 2) and the initial normoxia (period 1) as the first acute hypoxic response (AHR_1); between the initial peak hypoxia (period 2) and the final hypoxia (period 3) as the hypoxic ventilatory decline (HVD); and between the second peak hypoxia (period 5) and the second normoxia (period 4) as the second acute hypoxic response (AHR_2).

To detect the significance of differences among the different periods, a two-way analysis of variance was performed on $\dot{V}_E$, V_T, f, $P_{ET_{O_2}}$, and $P_{ET_{CO_2}}$. Comparisons between the control and alfentanil experiments ($P < 0.05$) were made using paired t tests; the Bonferroni method was used to correct the accepted level of significance for repeated t tests. All values are presented as mean ± SD unless otherwise stated.

Results

One volunteer did not complete the study because of a headache while breathing the hypoxic gas mixture, so data are reported on the remaining 10 volunteers. During the alfentanil infusion, all volunteers reported subjective feelings of "tiredness," although they all remained awake and no significant side effects were observed. Good control was maintained over the $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ levels (table 1). There were no statistically significant differences in the $P_{ET_{CO_2}}$ between control and alfentanil for any time period or across time periods. There were also no statistically significant differences between the $P_{ET_{O_2}}$ at the beginning or the end of the sustained hypoxic period or in the second hypoxic bout. Figure 1 shows a typical breath-to-breath ventilatory response for both control and alfentanil experiments in one volunteer.

Serum alfentanil levels were stable over time among the volunteers (37.6 ± 11.9 ng/ml, n = 9, fig. 2). Alfentanil samples were not suitable for analysis in one volunteer because of hemolysis. There was considerable variation among volunteers in the actual serum alfentanil level compared with the target level predicted by the computer-controlled infusion.

Alfentanil was associated with a decrease ($P < 0.05$) in average minute ventilation and tidal volume during each of the 5 measured time intervals (table 1 and fig. 3). During the control experiments, breathing frequency increased with initial exposure to hypoxia and remained elevated for the rest of the experiment. Breathing frequency was not affected by the alfentanil infusion during the initial normoxic or the peak hypoxic period (periods 1 and 2). However, by the end of the sustained hypoxia (period 3) the respiratory rate was significantly reduced

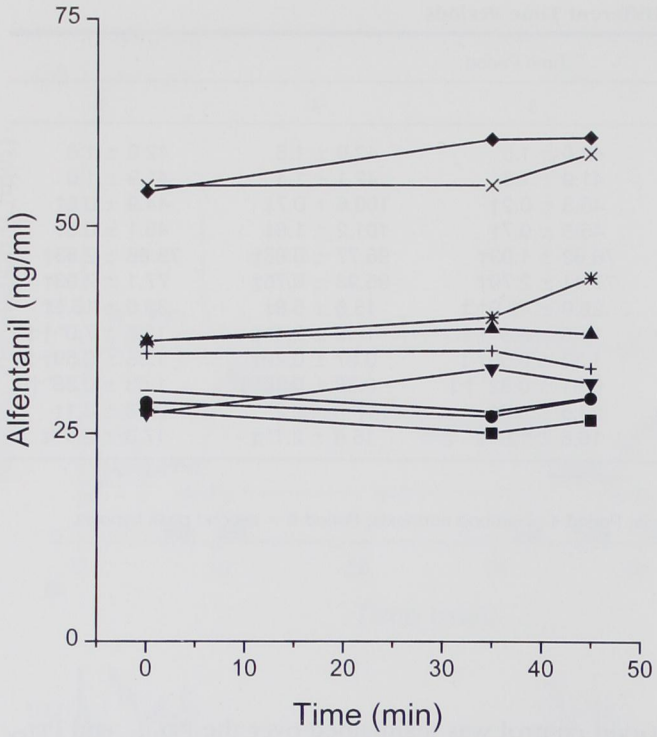

Fig. 2. Serum alfentanil levels for 9 of the 10 volunteers. Alfentanil was measured at the start of the experiment, after the sustained hypoxic period, and after the final hypoxic period (time = 0, 35, and 45 min).

and remained reduced for the rest of the alfentanil experiment.

Alfentanil caused a decrease in the AHR_1 (from 22.2 ± 11.8 to 16.4 ± 6.6 l/min, $P = 0.03$) and AHR_2 (from 17.4 ± 12 to 7.5 ± 5.2 l/min, $P = 0.006$). The AHR_1 was significantly larger than the AHR_2 for both control ($P = 0.015$) and alfentanil ($P = 0.0012$). The AHR_2, as a percentage of AHR_1, decreased from 77 ± 24% for the control experiments to 47 ± 23% for the alfentanil experiments ($P < 0.05$). However, alfentanil did not significantly change the magnitude of HVD (10 ± 3.3 l/min for control, and 12.3 ± 7.5 l/min for alfentanil).

The HVD:AHR_1 ratio trended upward (from 0.53 ± 0.24 to 0.73 ± 0.25) with the alfentanil infusion, but the increase was not significant ($P = 0.072$). The ventilatory responses can also be calculated as the ratio of the ventilatory change to the change in saturation—the hypoxic sensitivity. Alfentanil decreased the acute hypoxic sensitivity from 1.27 ± 0.73 to 0.99 ± 0.39 $l \cdot min^{-1} \cdot \%^{-1}$ ($P < 0.05$) for the initial response (AHR_1) and decreased the sensitivity of the second hypoxic bout (AHR_2) from 0.99 ± 0.70 to 0.41 ± 0.29 $l \cdot min^{-1} \cdot \%^{-1}$ ($P < 0.05$).

Discussion

We found a characteristic biphasic hypoxic ventilatory response in this study for the control experiments. The initial acute hypoxic sensitivity (1.27 $l \cdot min^{-1} \cdot \%^{-1}$) is typical,[26] as is the subsequent decrease in ventilation after 20 min to a level intermediate between the peak hypoxic ventilation and the previous normoxic ventilation.[2] We found that this reduction in ventilation occurred solely through a decrease in tidal volume without a change in breathing frequency. Previous studies have found that at least a portion of HVD seems to be accounted for by a reduction in breathing frequency.[2,3,27] The reduction in the ventilatory response to the second bout of hypoxia to 77% of the first response is also a well described characteristic of HVD.[3]

The amount of reduction in AHR with alfentanil was similar to that found by Gross *et al.*,[21] although their measured alfentanil levels were lower (approximately 10 ng/ml) than the levels attained in this study. Alfentanil reduced the normoxic ventilation (period 1, table 1) through a reduction in tidal volume without a change in breathing frequency. The effects of opioids on ventilatory rate and tidal volume have long been known, and often respiratory rate is used as an indicator of the

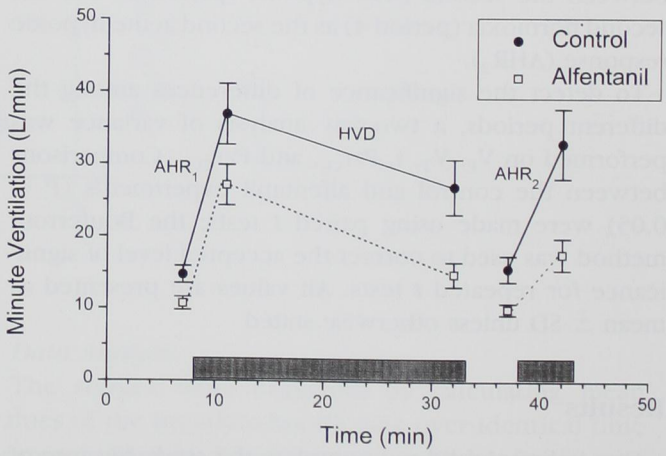

Fig. 3. Average minute ventilation for control and alfentanil for all volunteers. At all time points, minute ventilation was decreased with alfentanil ($P < 0.05$). Bars on the x axis represent the two hypoxic periods. The changes represented by the first acute hypoxic response (AHR_1), hypoxic ventilatory decline (HVD), and the second acute hypoxic response (AHR_2) are demarcated on the graph (see also table 1).

degree of narcosis. However, the reduction in rate is not a consistent finding, particularly at lower doses in awake persons.[13] This reduction in ventilatory frequency may depend on the level of other central neuromodulators, because after prolonged exposure to hypoxia, respiratory frequency was significantly less with alfentanil compared with control (periods 3, 4, and 5; table 1). Alfentanil reduced the hypoxic ventilatory response for both bouts of hypoxia.

The magnitude of reduction in the AHR is similar to the reported opioid-induced reduction in the hyperoxic hypercapnic response.[12,13] Because the hyperoxic hypercapnic response is entirely mediated by central chemoreceptors, the similarity of effect suggests that opioids may mediate both hypoxic and hypercapnic responses through central mechanisms. Berkenbosch *et al.*[28] reached this same conclusion when they found that morphine affected the central and peripheral carbon dioxide sensitivities equally in cats. However, because opioid receptors have been described in the carotid bodies of cats[19] and carotid body firing rates decrease with local application of beta-endorphin[29] or morphine,[30] the reduction in the hypoxic response could also be mediated in part by a peripheral effect. The data from this study cannot provide information about the site of action for the reduction in the AHR.

Hypoxic ventilatory decline is a complex phenomenon that is generally thought to arise from central mechanisms. Specific support for this hypothesis comes from experiments in anesthetized cats, in which phrenic nerve firing decreased with prolonged hypoxia, whereas carotid sinus nerve firing did not.[1] When artificial perfusion of the brain stem was used to separate the peripheral and central circulation in anesthetized cats, central hypoxia caused a reversible decrease in ventilation regardless of the state of excitation of the peripheral chemoreceptors.[8] However, neither component of the usual biphasic ventilatory response was observed in carotid sinus-denervated awake cats,[31] suggesting that peripheral chemoreceptor input is necessary for HVD to develop.

Evidence in humans suggests that HVD depends on both peripheral input and central integration. Drugs that decrease peripheral chemoreceptor response (such as somatostatin[32] and dopamine[33]) are associated with decreased HVD. Conversely, increasing peripheral chemoreceptor response with almitrine leads to increased HVD.[27] In these pharmacologic experiments, and also when the hypoxic response is increased with hypercapnia,[34] the ratio of HVD to AHR tends to remain constant. Centrally acting drugs can also alter HVD independent of changes in the AHR. In anesthetized cats, the gamma-aminobutyric acid antagonist, bicuculline, can reverse HVD,[5] and pretreatment with aminophylline can decrease HVD.[9] In humans, aminophylline[35] reduces HVD and a decline in tidal volume persists, but an increase in breathing frequency results in less HVD, whereas midazolam seems to increase HVD.[36] These studies indicate that gamma-aminobutyric acid, adenosine, or both may play a role as neuromodulators in the development of HVD.[4]

Our experiments provide evidence that alfentanil increases HVD by a central mechanism that is independent of the reduction in AHR. First, if alfentanil only reduced the carotid body drive from hypoxia, it would be expected that HVD would also decrease and the ratio of HVD to AHR would remain constant. In our experiments, HVD did not decrease, and although it was not statistically significant, the HVD:AHR ratio increased with alfentanil. Second, the reduction in the magnitude of the second hypoxic response by alfentanil is evidence that the effect of HVD is increased. If HVD were not increased, the relation between AHR_1 and AHR_2 would not be changed.

Studying the effects of drugs (particularly the inhalational anesthetics) that influence levels of consciousness is complicated by the potential effects of alertness on the hypoxic response (see Ward[37] for a recent review). Although Dahan *et al.*[38] found that halothane increased the relative amount of HVD, Young *et al.*[39] did not. The Leiden laboratory studied the effects of morphine on HVD in cats[28] and humans.[22] In humans, their results were similar in that the acute response was reduced while the magnitude of the decline was not changed. Thus the amount of HVD, relative to the acute increase, was increased. In the cat, morphine did not decrease the hypoxic sensitivity (but only shifted the response to a lower ventilation in a parallel manner), but because the peripheral carbon dioxide sensitivity was reduced, they concluded that morphine lessened HVD.[28]

These findings may be of some clinical significance in the postoperative period. Postoperative opioid use has been associated with desaturation,[40,41] particularly episodically during sleep.[42] Opioid suppression of the protective acute hypoxic ventilatory response and potential enhancement of HVD may play a role in the occurrence of these events. However, these experiments were performed with isocapnia and precise

control of the end-tidal oxygen level in volunteers with a patent airway. These conditions are not likely to be replicated in the clinical situation and will modify the responses.

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