

Effects of Pain and Audiovisual Stimulation on the Opioid-induced Depression of the Hypoxic Ventilatory Response

Suzanne Karan, M.D.,* William Voter, M.A.,† Linda Palmer, R.N.,‡ Denham S. Ward, M.D., Ph.D.§

Background: Normoxic and hypoxic ventilation are influenced by chemoreceptor and nonchemoreceptor drives. Although inhalational anesthetics blunt hypoxic ventilation, this effect is reversed by audiovisual stimulation but not by pain. Opioids reduce both normoxic and hypoxic ventilation, but their interaction with pain and audiovisual stimulation has not been fully reported.

Methods: Isocapnic, acute hypoxic ventilatory responses (AHRs) were measured in 11 volunteers. AHR and normoxic ventilation were measured under the following conditions: (1) eyes closed, no audio stimulation (low wakefulness); (2) low wakefulness conditions plus painful thermal stimulation; and (3) playing a computer game (high wakefulness), each with and without remifentanyl infusion.

Results: The average (\pm SD) remifentanyl dose was $0.035 \pm 0.012 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Both normoxic and hypoxic ventilation were significantly reduced by the remifentanyl infusion under all three conditions. The AHR values under low wakefulness conditions were 0.33 ± 0.19 and $0.89 \pm 0.49 \text{ l} \cdot \text{min}^{-1} \cdot \text{sat}^{-1}$ with and without remifentanyl, respectively ($P < 0.05$). High wakefulness significantly increased AHR with and without remifentanyl, whereas low wakefulness with pain did not. However, high wakefulness with remifentanyl did not increase the AHR back to what was observed during low wakefulness without remifentanyl.

Conclusions: The computer game was a more potent stimulus than pain in countering the depressant effect of remifentanyl on AHR. Although the effect of high wakefulness was more attenuated than was previously observed with respect to inhalational anesthetics, the significance of these findings is underlined by the more clinically relevant scenario of what is experienced in the face of opioid administration.

UPON noting the absence of posthyperventilation apnea in awake subjects, in contrast to its presence in anesthetized patients, Fink¹ hypothesized that a “wakefulness drive” plays an important role in maintaining ventilation. The wakefulness drive to breathe has also been referred to as the behavioral, cortical, or volitional drive. However, these terms may refer to distinct aspects of the nonchemoreflex drive to breathe, and the literature is ambiguous in defining this terminology.² Ventilation is established by an array of demands other than just the hypercapnic and hypoxic chemoreceptor reflexes. Although the metabolic influence is the primary determi-

nant of ventilation in those exposed to deep anesthesia or nonrapid eye movement sleep, these other “arousal drives” play an important role in the perioperative period. The variability in experimental outcomes related to the interaction between inhalational anesthesia-depressed hypoxic ventilation and arousal has been attributed to the differences in state of “wakefulness” or arousal.³ Understanding this wakefulness drive is integral in our care of patients recovering from anesthesia or undergoing moderate or deep sedation.

In this article, wakefulness is described in terms of the central nervous system state of “arousal or awareness.”⁴ The influence of the state of wakefulness on ventilation can alter respiratory variability (tidal volume and frequency), normoxic ventilation, and chemoreflex driven ventilation.^{2,5,6} However, the relation between wakefulness and ventilation is not altogether understood. For example, although common clinical observation indicates that pain is a respiratory stimulant in patients with a relative overdose of respiratory depressants^{7,8} or in those under the influence of general anesthesia,⁹ it is not clear by which pathways pain increases ventilatory drive. Audiovisual stimulation (AVS) can also have a pronounced effect on ventilation⁵ and is used clinically to help “wake up” a patient.

The interactions of pain and AVS on anesthetic drug-induced ventilatory depression have been extensively studied, although the results have been inconsistent. The depression of the isocapnic acute hypoxic ventilatory response (AHR) by low doses of volatile anesthetics has been shown to be reversed by AVS (for isoflurane) and not by pain (for sevoflurane),^{10,11} although a meta-analysis by Pandit¹² indicated that there may be differences in the pharmacodynamics among the various agents. Recently, Pandit *et al.*¹³ studied the interaction of pain and AVS on the effects of halothane in a single protocol and did not find a specific reversal effect of either AVS or pain.

In the current study, we chose to examine the opioid-induced depression of normoxic ventilation and the AHR due to its relevance in the clinical environment. Although the effects of the volatile anesthesia-induced depression of the AHR are pertinent to the immediate postoperative period, the consequences of the opioid-induced AHR depression are relevant throughout the postoperative period and applicable to much broader clinical situations. Our hypothesis was that the opioid-induced depression of the AHR would be attenuated by AVS but not by pain. If the effects of pain are separate from wakefulness on the opioid-induced depression of

* Assistant Professor, Departments of Anesthesiology and Psychiatry, † Senior Technical Associate, ‡ Clinical Research Associate, § Professor, Departments of Anesthesiology and Biomedical Engineering, School of Medicine and Dentistry, University of Rochester.

Received from the Department of Anesthesiology, University of Rochester, Rochester, New York. Submitted for publication January 20, 2005. Accepted for publication April 13, 2005. Supported by a Research Fellowship Grant (to Dr. Karan and the Department of Anesthesiology) from the Foundation for Education, Anesthesia, and Research, Rochester, Minnesota.

Address reprint requests to Dr. Karan: Department of Anesthesiology, 601 Elmwood Avenue, Box 604, Rochester, New York 14642. Address electronic mail to: suzanne_karan@urmc.rochester.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

the AHR, this would suggest different patient care strategies during recovery from anesthesia and during sedation.

Materials and Methods

The study was completed at the University of Rochester Medical Center (Rochester, New York) and approved by its human subjects protection committee. Written, informed consent was obtained from all subjects. Subjects were asked to fast from midnight before the experiment and to refrain from alcohol- and caffeine-containing beverages for 24 h before the experiments. Most of the subjects were experienced from other experiments in our laboratory and were familiar with the laboratory environment.

At the time of arrival at the laboratory, all subjects had an intravenous catheter inserted for administration of remifentanyl. A pulse oximeter was placed on a finger of the nondominant hand because the dominant hand was used for the game controller. A three-lead electrocardiogram was placed on the chest wall for heart rate and rhythm monitoring, and blood pressure was measured using an automated cuff. The subjects were then allowed to relax before the first experimental intervention.

The techniques of the respiratory measurements have been described in detail previously.¹⁴ Briefly, subjects were semirecumbent, with electrocardiography and pulse oximetry (Siemens Medical Electronics, Danvers, MA) monitored continuously for subject safety. Blood pressure was measured on arrival, before and after each run, every 5 min during the remifentanyl infusion (but not during measurement of the AHR), and before discharge. Subjects breathed from a gas-mixing chamber *via* a facemask (Vital Signs, Totawa, NJ). Inhaled and exhaled volumes were measured with a bidirectional impeller flow meter (VMM 110; Sensor Medics, Laguna Hills, CA). Airway gases were sampled continuously by a mass spectrometer (MGA 110; Perkin-Elmer, Pomona, CA). Computer-driven (Intel PC class) high-flow (total flow of 60 l/min) stepper-motor valves provided nitrogen, carbon dioxide, and oxygen to the gas-mixing chamber at desired concentrations on a breath-by-breath basis. Ventilation (\dot{V}_E , l/min), tidal volume (V_T , liters), breathing frequency (f , breaths/min), end-tidal gas concentrations (end-tidal pressure of oxygen [P_{ETO_2}] and end-tidal pressure of carbon dioxide [P_{ETCO_2}], mmHg), and hemoglobin oxygen saturation by pulse oximetry (SpO_2 , %) were determined and collected using the TIDAL software package.¹⁵

To study the ventilatory response to isocapnic hypoxia, a computer-driven dynamic end-tidal forcing tech-

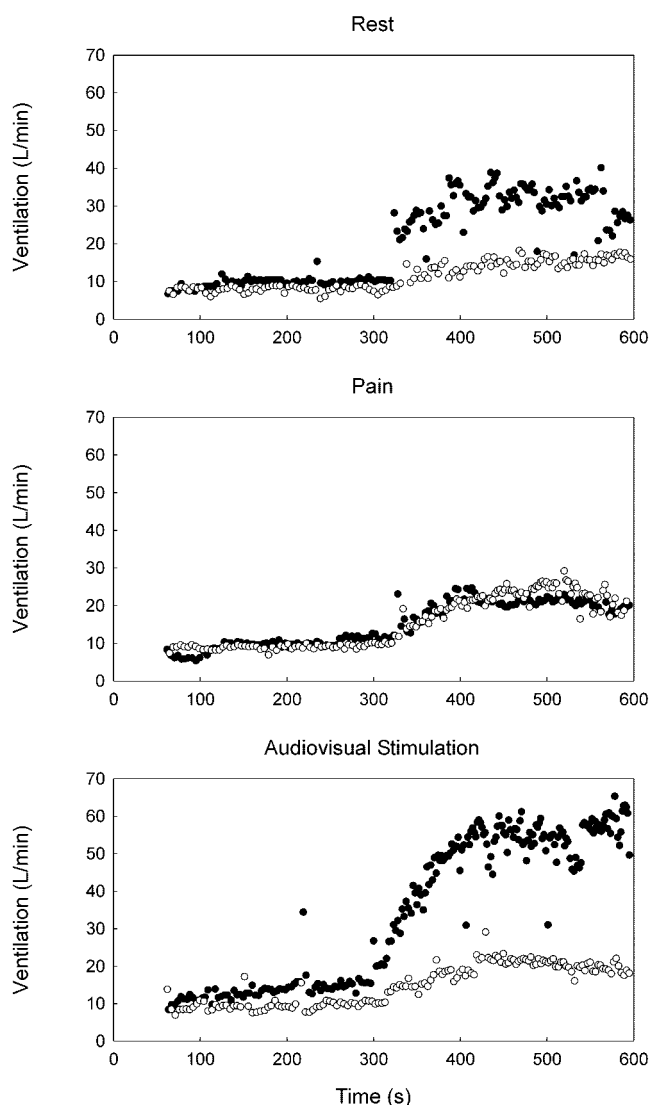


Fig. 1. Ventilatory responses to hypoxia under all six conditions for a single subject. Breath-to-breath data are plotted, and the hypoxic step starts at time 300 s. *Closed circles* are the control experiments, and *open circles* are with remifentanyl. The *top panel* is under low wakefulness, the *middle panel* is during low wakefulness with pain, and the *bottom panel* is during high wakefulness.

nique was used. With this technique, P_{ETO_2} and P_{ETCO_2} are dynamically forced to follow a prescribed pattern in time by manipulation of the inspired gas concentrations independent of the ventilatory response. In this study, step transitions in P_{ETO_2} were used with a background of constant P_{ETCO_2} that was individually determined for each subject. The 10-min breathing period started with 5 min of normoxia (P_{ETO_2} = 100 mmHg) and then a rapid decrease to P_{ETO_2} of 45 mmHg within two to three breaths; it was then sustained for 5 min.

The hypoxic response was repeated for each subject under six conditions (fig. 1): low wakefulness (LW), high wakefulness (HW), and low wakefulness with pain (LWP), with and without (control) a continuous infusion of remifentanyl.

¹⁵ TIDAL software package. Available at: <http://sourceforge.net/projects/tidal/>. Accessed March 17, 2005.

The LW experiments were performed under the conditions of “resting wakefulness,” which is similar to that described by others as the subject having closed eyes and headphones on to prevent auditory stimulation.^{4,6} Electroencephalographic monitoring was not applied, but subjects were asked to remain awake and were queried if they fell asleep at the end of the run. The laboratory was kept quiet, and any movement by laboratory personnel was out of sight of the subjects.

In the HW state, AVS was provided by having the subjects play a computer game entitled “You Don’t Know Jack—The Ride” (Berkeley Systems, Jellyvision Inc., Chicago, IL, 1998) on a laptop computer positioned directly in front of them. The audio portion of the game was played through external sound-deadening headsets (Realistic NOVA 40; RadioShack, Fort Worth, TX) that were worn for all experiments (no sound for the pain and rest experiments). The subjects answered the trivia questions posed by the game by pressing a key on a game control pad (minimal movement required). Computer games have been used previously as a means to increase the state of wakefulness.^{4,16}

For LWP, painful stimulation by a thermode (PPS-3; Precision Pain Source, Cygnus, Paterson, NJ) was added to the LW state. The skin on the ventral surface of the arm, contralateral to the arm with the intravenous catheter, was preheated to a temperature of 40°C for 5 min and then sensitized with 0.075% capsaicin cream under an occlusive dressing for at least 30 min.^{17,18} The subjects reported their pain scores *via* an ordinal score that ranged from 0 (no pain) to 10 (intolerable pain). The pain score was the average of the two scores reported at the beginning and end of the experimental run. Subjects were instructed to notify personnel if their pain score was minimal (< 3) during the experimental run by raising a hand. In those cases ($n = 2$), the run was discontinued and repeated using a new thermal stimulation site on the forearm. During the remifentanyl infusion, the temperature of the thermode was increased to maintain the same pain score, but for safety reasons, the maximum temperature was limited to 47°C.

The remifentanyl was administered *via* a syringe infusion pump (Baxter Infusion Pump, model AS50; Baxter Healthcare Corp., Deerfield, IL). The sequence of the runs was randomized by the Latin square method,¹⁹ with the limitation that the control and remifentanyl experiments were always alternated to avoid a prolonged infusion and possible tolerance to the opioid.²⁰ To reach steady state, at least 30 min was allowed after turning off the remifentanyl before a control experiment, and the remifentanyl infusion was started at least 15 min before a hypoxic response.²¹

All subjects participated in preliminary experiments to determine their individual remifentanyl dose and appropriate carbon dioxide level for the subsequent hypoxic response. These experiments were either on a different

day ($n = 5$) or earlier in the same day ($n = 6$) as the main experiment. The selected dose of remifentanyl for these experiments was a dose of remifentanyl that required a significant increase in the thermode temperature to maintain the same pain score without exceeding the maximum of 47°C, and with an increase in $PETCO_2$ of approximately 5 mmHg. If the $PETCO_2$ increased too much with the remifentanyl, then the hypoxic response under control conditions with the same $PETCO_2$ may not have been tolerated well by the subjects. In these preliminary experiments, we used increasing doses of remifentanyl starting at $0.025 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and going to an expected maximum of $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and measured the pain score, ventilation, and $PETCO_2$. A dose of remifentanyl that adequately blunted the pain while increasing the $PETCO_2$ by approximately 5 mmHg was determined in all subjects. For each subject, this dose of remifentanyl was subsequently used for all of the experiments. The isocapnic AHR was performed at a $PETCO_2$ level 2–3 mmHg higher than that which was individually determined in these preliminary experiments.

Data and Statistical Analysis

The respiratory measurements were averaged over the 2 min before the hypoxic step and for 2 min between minutes 2 and 4 of the hypoxic period. The saturation was calculated with use of the measured $PETO_2$ using the equation suggested by Severinghaus.²² The acute hypoxic response was calculated as the change in ventilation divided by the change in saturation.

Data are reported as mean \pm SD. Statistical analysis was performed using the STATA software package (Stata Corp., College Station, TX). Initial analysis of variance was performed on the AHR and the other ventilatory variables using the following factors: sex, subject nested within sex, test condition (LW, LWP, or HW), drug (control or remifentanyl), test condition and sex interaction; and drug and sex interaction. Subsequent analysis of variance dropped nonsignificant terms. When a significant test effect was found, a *post hoc* Wald test was used to isolate the differences for pairwise comparisons. Overall significance for multiple comparisons was set at 0.05 using the false discovery rate procedure.²³ One-way analysis of variance was used to test for a drug effect within a test condition.

Results

Seventeen paid volunteers (nine men) who had an American Society of Anesthesiologists physical status of I, were aged 18–40 yr, were nonsmokers, and took no medications other than birth control pills were enrolled. Eleven subjects completed the protocol (six male and five female subjects). Six subjects did not complete the

Table 1. Effect of Remifentanyl on Ventilatory Variables and Heart Rate under Study Conditions

	Low Wakefulness		Low Wakefulness with Pain		High Wakefulness	
	Control	Remifentanyl	Control	Remifentanyl	Control	Remifentanyl
Ventilation, l/min						
Normoxia	11.5 ± 3.3	8.5 ± 2.8*	13.0 ± 3.3	8.4 ± 1.8*	19.1 ± 3.9†‡	12.8 ± 1.8*†‡
Hypoxia	27.5 ± 11.5	14.2 ± 5.2*	24.8 ± 7.3	14.0 ± 4.8*	41.2 ± 10.8†‡	22.5 ± 5.9*†‡
V _T , l						
Normoxia	0.86 ± 0.23	0.73 ± 0.16*	0.97 ± 0.25	0.72 ± 0.13*	1.10 ± 0.25†‡	0.79 ± 0.21*
Hypoxia	1.74 ± 0.51	1.07 ± 0.35*	1.74 ± 0.67	1.11 ± 0.33*	1.83 ± 0.5	1.21 ± 0.33*
f, min ⁻¹						
Normoxia	13.9 ± 3.4	12.1 ± 4.1	14.2 ± 4.4	12.0 ± 2.4	18.3 ± 3.9†‡	17.0 ± 3.3†‡
Hypoxia	15.9 ± 4.8	14.0 ± 4.1	15.4 ± 4.4	13.6 ± 4.5	23.3 ± 4.6†‡	19.2 ± 2.3*†‡
PETCO ₂ , mmHg						
Normoxia	43.3 ± 2.2	44.1 ± 2.8	43.3 ± 2.1	44.4 ± 2.8*	44.3 ± 2.9	43.3 ± 2.7†‡
Hypoxia	43.9 ± 2.7	43.6 ± 2.5*	43.8 ± 2.8	43.8 ± 2.6	43.8 ± 2.7†	43.9 ± 2.6†
Saturation, %						
Normoxia	97.9 ± 0.1	97.8 ± 0.1	97.8 ± 0.2	97.8 ± 0.2	97.8 ± 0.1	97.8 ± 0.1
Hypoxia	80.0 ± 1.1	80.3 ± 1.0	80.4 ± 1.1	80.0 ± 0.9	81.0 ± 0.8†‡	80.4 ± 0.6*
Heart rate, min ⁻¹						
Normoxia	65.5 ± 9.1	61.4 ± 7.9	67.3 ± 6.8	60.1 ± 9.3*	72.0 ± 7.6†‡	68.0 ± 10.8*†‡
Hypoxia	91.2 ± 12.6	79.5 ± 12.2*	89.2 ± 11.5	79.1 ± 14.9*	93.5 ± 13.0†	88.4 ± 12.7†‡
AHR, l · min ⁻¹ · % sat ⁻¹	0.89 ± 0.49	0.33 ± 0.19*	0.67 ± 0.28	0.32 ± 0.26*	1.38 ± 0.61†‡	0.55 ± 0.28*†‡

* $P \leq 0.05$ different from control within same state. † $P \leq 0.03$ different from low wakefulness within same treatment (remifentanyl or control). ‡ $P \leq 0.03$ different from low wakefulness with pain within same treatment (remifentanyl or control).

AHR = acute hypoxic ventilatory response; f = breathing frequency; PETCO₂ = end-tidal pressure of carbon dioxide; V_T = tidal volume.

study: Two subjects dropped out because of nausea and diaphoresis with the remifentanyl, one subject's experiment was aborted because of his vomiting, one subject elected not to return for unknown reasons, one subject experienced syncope during placement of the intravenous cannula, and the computer malfunctioned during the remaining subject's experiment. The average age was 21.2 ± 2.1 yr, and the average body mass index was 24.0 ± 2.7 kg/m². During the experiments with pain, the temperature was successfully adjusted to maintain similar pain scores, but in two subjects, it required using a new forearm site because of inability to stimulate these subjects to a high enough pain score. In two subjects, a blister subsequently developed at the thermode site, but this resolved without consequence. No subject reported any painful sensation from the capsaicin cream before the application of the thermode.

The average dose of remifentanyl, as determined by the preliminary experiments, was 0.035 ± 0.012 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and the dose was not significantly different between the male and female subjects. The remifentanyl infusion required a significantly higher temperature ($46.1 \pm 1.1^\circ$ vs. $44.0 \pm 2.0^\circ\text{C}$; $P < 0.05$), whereas the pain scores were not significantly different (3.8 ± 0.7 vs. 4.2 ± 0.8 for remifentanyl and control, respectively). All subjects reported remaining awake during the resting runs. During the remifentanyl infusion, the subjects consistently progressed through the computer game and never needed reminding to play the game.

The end-tidal carbon dioxide and saturation were well controlled across states and drug (table 1). The SD in PETCO₂ shown in table 1 reflects primarily the variation

across subjects, each having their own carbon dioxide set point. There were some small differences that achieved statistical significance because of the consistency of the gas control system we used. However, these differences were generally less than 1 mmHg in carbon dioxide or 1% saturation and did not significantly affect the results.

Figure 1 shows the superimposed breath-to-breath results of the six hypoxic steps in one subject. This subject had a pronounced increase in the ventilatory response to hypoxia during HW but a decrease during LWP. The hypoxic response was clearly depressed by the remifentanyl infusion in all states.

Overall analysis of variance on the AHR (fig. 2 and table 1) showed significant state and drug effects but no sex, state and sex interaction, or drug and sex interaction. Therefore, subsequent analysis did not include sex or its interactions, but the small number of subjects limits our ability to detect a sex effect if actually present. The drug and state interaction was not significant ($P = 0.06$), and the final statistical analysis was done within each treatment group (remifentanyl or control). The AHR during HW was significantly increased over low wakefulness with and without pain. Although the presence of pain caused a decrease in the AHR over LW without pain, this was not statistically significant. The remifentanyl infusion reduced the AHR in all three states, and the HW state was still significantly different from the others (table 1). The increase in AHR (either directly or as a percentage of the LW value) with HW from LW was not significantly different between control and remifentanyl.

The results for normoxic ventilation were similar to

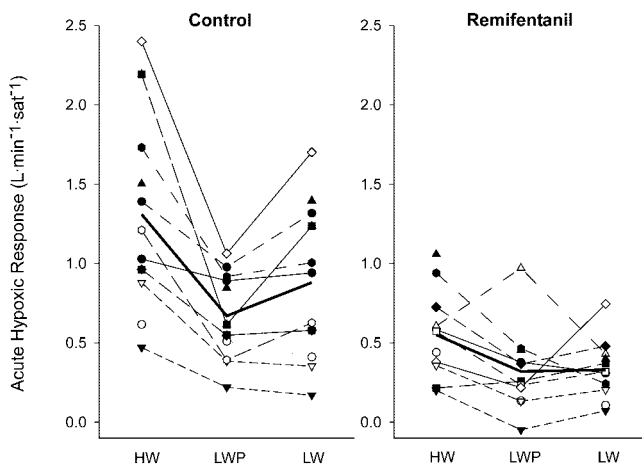


Fig. 2. Acute hypoxic response for all subjects. The left panel is for the three test conditions with no remifentanyl (control), and the right panel is with remifentanyl infusion. The same symbol is used for the same subject in both panels. The heavy line without any symbol is the mean. HW = high wakefulness; LW = low wakefulness; LWP = low wakefulness with pain.

the result for AHR (table 1). HW significantly increased both normoxic and hypoxic ventilation for both control and remifentanyl. Although pain slightly increased normoxic ventilation during control experiments, this was not statistically significant. Looking at the pattern of breathing, remifentanyl significantly decreased the tidal volume, with a decrease in breathing frequency that usually did not reach statistical significance. The effect of HW was seen in both tidal volume and breathing frequency during normoxia and primarily in breathing frequency during the remifentanyl infusion. Interestingly, comparing across drug conditions, the breathing frequency during remifentanyl and HW was significantly higher than control LW in both normoxia and hypoxia.

The heart rate response followed a similar pattern (table 1). Remifentanyl reduced the heart rate under all conditions, although not significantly during LW in normoxia and HW in hypoxia. Similar to ventilation, both with and without remifentanyl, HW caused an increase in heart rate over LW, whereas LWP did not.

Discussion

In a single study, we compared the effects of pain and audiovisual stimulation on the opioid-depressed acute isocapnic hypoxic ventilatory drive. The most interesting finding in this study, and contrary to our hypothesis, is that although HW augmented the AHR in the presence of remifentanyl, the reversal of the depressed AHR was not complete and was less than the increase caused by HW without remifentanyl (fig. 2). Pain had little effect on the AHR, even in the presence of remifentanyl. However, HW during the remifentanyl infusion did restore normoxic ventilation to that found during LW without drug.

There are many factors in the design of this protocol

that could greatly influence the results and make comparisons with previous studies difficult. The study design is complex, and there are potential confounding effects in the sequence of runs for both the remifentanyl infusion and the stimulation.

A randomization sequence was selected that should have minimized these effects in the final data analysis. In particular, remifentanyl experiments were alternated with control (no drug) runs to avoid prolonged infusions that might cause acute tolerance, whereas the sequence of HW, LW, and LWP was randomized. The techniques we used to assess the hypoxic ventilatory response are standard^{24,25} and frequently used in our laboratory.¹⁴ The resting values for ventilation and the AHR, with and without remifentanyl, are comparable to values in the literature. Specific issues regarding the selection of the drug and stimuli will be addressed in the next sections.

Remifentanyl

Remifentanyl has been reported to cause persistent hyperalgesia and tolerance under certain conditions. The remifentanyl dose used was below the reported infusion rate that causes intense opioid receptor activation and possible persistent increase in pain sensitivity, or hyperalgesia.²⁶ In a study of 20 male volunteers receiving a 3-h infusion of remifentanyl at $0.08 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (above our average dose), there was no development of acute opioid tolerance.²⁰ Therefore, it is unlikely that the dose and sequence of remifentanyl infusions distorted subsequent experiments.

Pain

Although it may be assumed that the ascending pain pathways can influence both the metabolic and the behavioral control of breathing, there is little information regarding differences in type of painful stimulation. Many experimental pain models have been used in respiratory control studies, including electrical stimulation,^{7,10,13} pressure,²⁷ and limb ischemia^{7,8,28,29} in humans and thermal stimulation in animals.³⁰ Electrical pain may stimulate both cutaneous and muscle receptors, but remifentanyl causes more of an increase in muscle *versus* cutaneous pain thresholds.³¹ Interestingly, activation of muscle *versus* cutaneous pain receptors may have greater ventilatory effects.⁷ Cutaneous pain, whether electrical or thermal,³² may not be a reliable indicator of clinical and acute postoperative pain and is different from simulated visceral pain as well.³³ Because there is no consensus about the best model, the capsaicin-sensitized skin thermal model was selected because it has been well described as being sensitive to remifentanyl analgesia.¹⁸

The choice of a painful thermal stimulus may not have permitted a noxious enough stimulus to elicit the augmentation of ventilation. However, the reported pain scores were in the moderate range and similar to those

reported for other types of painful stimulation.¹⁰ The thermal stimulation was increased during the remifentanyl infusion to maintain the same reported pain level. This was done to maximize the effect of pain on breathing as has been previously shown by Waldrop *et al.*³⁰; presumably, if the thermal stimulation was not adjusted, the reported pain scores would have been lower during the remifentanyl infusion, and even less effect of pain on breathing would have been observed.

Although the type of painful stimulus was different than that of Sarton *et al.*,¹⁰ the results are similar in that the painful stimulus did not significantly alter either normoxic or hypoxic ventilation. This differs from the results of Pandit *et al.*,¹³ who found a small stimulation of both normoxic ventilation and the AHR with their painful stimulus. Both Sarton *et al.* and Pandit *et al.* used electrical stimulation to arrive at similar pain intensities.

The mechanism of action of pain on breathing is still enigmatic. The interaction of pain and breathing seems to be mediated primarily *via* the effect of pain on normoxic ventilation and not on the chemoreflexes.^{7,34-36} Pain has been noted to elicit a ventilatory response in the absence of a cardiovascular or somatic response, even while under 1 minimum alveolar concentration (MAC) of inhalational anesthesia, clearly indicating an effect independent of any volitional control.⁹ Interestingly, Lam *et al.*³⁶ found that pain in the form of surgical stimulation increased baseline ventilation but did not restore the AHR in the setting of 1 MAC enflurane anesthesia. However, we have found that even with volitional control still intact (LWP), the AHR remained depressed by remifentanyl.

One could postulate that pain would be expected to more directly counteract the depressive effect of the opioid remifentanyl on the AHR. Similar to previous studies, though, our painful stimulation did not affect the chemoreflex drive to breathe.

Audiovisual Stimulation

There is also no consensus on the best experimental model to assess the influence of the arousal state on ventilatory control. Passive forms of cortical activity (mental arithmetic or watching and listening to various videos) may not provide the same level of wakefulness, and it is difficult to assess in an individual subject. In this study, we used an interactive computer game to obtain our central nervous system HW state.⁴ The current choice of audiovisual stimulation is different from what has been commonly used when studying the effects of inhalational anesthetics, because our stimulus required a reaction from the subjects, and its effect on hypoxic breathing may be different as well. We did not define the wakefulness state by an observer's scale or by the electroencephalogram or Bispectral Index, as has been done previously.¹⁰ Instead, we sought to maximize the wakefulness state as has been described.^{4,16} The subjects in

our study were able to play the computer game during the remifentanyl infusion without any need for reminders to continue to progress.

Similar to previous studies,^{10,25} we found a significant increase in normoxic ventilation during HW. We formerly reported a significant augmentation of the AHR during HW compared with low wakefulness with and without pain, in a larger cohort of subjects, without infusion of drug.³⁷

Although ventilation during HW and hypoxia was generally increased over LW and LWP, the subjects subjectively reported less discomfort from the increased ventilation during HW than they did during the other states. This was noted especially when the drug was not being infused. Interestingly, pain has been found to intensify the sensation of dyspnea.²⁸

Comparison to Studies with Inhalational Anesthetics

The effects of inhalational anesthetics on the hypoxic ventilatory response and the effects of AVS and pain on this interaction have been previously extensively studied.^{10-12,38} A specific reversal effect of AVS on the depression of the AHR has been found for isoflurane¹¹ but not for halothane.¹³ In the latter study, though, the subjects did perform the exercise of holding an arm raised, which may have affected their experimental outcome. Pandit¹² has argued that there may be true differences between the effects on the AHR of the various inhalational agents and that the reported differences cannot be completely explained by the various experimental techniques used. However, even small differences in the study protocols may have greatly affected study outcomes.

In any case, there are obvious differences in mechanisms between the inhalational anesthetics and opioids, although both can achieve a similar reduction in the AHR. One relevant difference is the action of the inhalational anesthetics on the carotid bodies, whereas the depression of the AHR by opioids occurs by a central action because spinal opioids have been shown to depress the AHR.²⁷

Another difference between the drugs may be the level of sedation produced. Although our study can be criticized for not using the Bispectral Index[®] monitor (Aspect Medical Systems, Newton, MA) as a quantitative assessment,³⁹ the Bispectral Index[®] may not be a sensitive monitor for opioid sedation levels.⁴⁰ Our subjects were consistently able to maintain wakefulness while playing the computer game and did not report falling asleep during the LW or LWP experiments when they had their eyes closed.

This confirmation of what has been already found in the setting of inhalational anesthetics is even more clinically significant with opioids because the effects of

narcosis on patients is longer lasting and a more constant threat than the effects of inhalational anesthetics.

Conclusion

In this study of the remifentanyl-induced depression of the isocapnic AHR, an HW state (simulated by playing a computer game) did not restore the AHR to baseline, although it did augment it more than painful thermal stimulation. Clinically, these results could indicate that a specific audiovisual stimulation requiring a volitional patient reaction may be more effective than pain in restoring adequate ventilation in responsive narcotized patients.

In light of the conflicting data resulting from studies of inhalational anesthetic influence on the AHR, the opioid interaction, and the effects of different arousal states, it is clear that future studies are needed to clarify the mechanisms involved.

The authors thank James Robotham, M.D., F.R.C.A. (Chairman, Department of Anesthesiology, University of Rochester, Rochester, New York), for his thoughtful review and discussions during the preparation of this article.

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