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Propofol Depresses the Hypoxic Ventilatory Response during Conscious Sedation and Isohypercarnia

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Background: Propofol infusion at subanesthetic doses provides reliable conscious sedation. However, the ventilatory effects of sedative doses of propofol have not been established. The current study was conducted to determine the effects of propofol sedation on the hypoxic ventilatory response.

Methods: Eight healthy, male volunteers received 1 mg · kg⁻¹ propofol followed by a propofol infusion adjusted to maintain a constant, subanesthetic level of sedation. Hypoxic ventilatory response was measured using an isocapnic rebreathing technique: while keeping P_{ET}CO₂ constant (≈6 mmHg above prestudy baseline), the authors continuously recorded minute ventilation and tidal volume, as oxygen saturation (Sp_{O₂}) decreased from 98 to 70%. Hypoxic response determinations were performed before and during propofol infusion, as well as 30 and 60 min after termination of the propofol infusion.

Results: The slope of the hypoxic ventilatory response curve (V_E vs. Sp_{O₂}) decreased from 0.88 ± 0.15 to 0.17 ± 0.03 l · min⁻¹ · %Sp_{O₂}⁻¹ during propofol sedation (X̄ ± SE). Thirty minutes after discontinuation of the propofol infusion, slope returned to its prepropofol value. In addition, minute ventilation at Sp_{O₂} = 90% decreased during propofol sedation, from 16.1 ± 0.8 to 8.7 ± 0.4 l · min⁻¹, accompanied by a similar decrease in tidal volume at Sp_{O₂} = 90%, from 1,099 ± 87 to 523 ± 21 ml. Thirty minutes after discontinuation of the propofol infusion, these variables also returned to their prepropofol values.

Conclusions: The authors concluded that propofol infusion for conscious sedation significantly decreases the slope and causes a downward shift of the hypoxic ventilatory response curve measured during isohypercapnia. (Key words: Anesthetics, intravenous: propofol. Complications: hypoventilation. Conscious sedation. Hypoxia: ventilatory response.)

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RAPID metabolism and prompt patient recovery have made propofol an attractive choice for "conscious sedation." Clinical situations in which propofol-induced sedation has been used include outpatient oral surgery,¹ gastrointestinal endoscopy,² and as a supplement to regional anesthesia.³ Although some investigators have found significant respiratory depression during propofol-induced sedation, others suggest that this does not occur with subanesthetic doses.^{2,3} We designed the current study to determine the effect of sedation with subanesthetic doses of propofol on the hypoxic ventilatory response.

Materials and Methods

Eight healthy, male volunteers who were nonsmokers, and who ranged in age from 25 to 32 yr, participated in this study, which was approved by our Institutional Review Board. After obtaining written informed consent from each subject, we conducted a prestudy history and physical examination. Exclusion criteria included clinical evidence of cardiac, pulmonary, or CNS disease, allergy to egg or soy products, use of centrally acting medications within the previous week, and a history of drug or alcohol abuse. Subjects refrained from oral intake for 8 h, and from alcohol and caffeine for 24 h before the study.

We inserted 20-G intravenous catheters into both arms of each subject, one for the administration of propofol, the other for blood sampling. We then affixed pulse oximeter (Ohmeda 3700, Boulder, CO, ear probe), ECG, and noninvasive blood pressure (Propaq 104, Beaverton, OR) monitors. Subjects listened to soft symphonic music through stereo headphones to minimize external auditory stimulation during respiratory measurements. Between ventilatory response determinations, subjects breathed room air.

After performing a "baseline" hypoxic ventilatory response (HVR) determination (see below), we ad-

Table 1. Definition of Somnolence Scores

Score	Definition
4	Awake and alert
3	Relaxed; lethargic response to name
2	Spontaneous eye closure; responds to loud voice
1	Responds only to prodding or shaking
0	Unresponsive

ministered $1 \text{ mg} \cdot \text{kg}^{-1}$ intravenous propofol, followed by a continuous infusion *via* a Bard InfusO.R. (North Reading, MA) pump at an initial rate of $75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Every 2 min, we assessed the level of somnolence⁴ (table 1) by asking the subjects to repeat a standard phrase. Based on this assessment, we adjusted the propofol infusion to maintain a level of somnolence at which subjects exhibited spontaneous eye closure and slurred speech, yet responded to verbal stimuli (somnolence score of 2). A minimum of 30 min after the start of the propofol infusion, and following at least 10 min of unchanged level of somnolence with a constant rate of propofol infusion, we obtained a blood sample for propofol analysis. We then performed a "during propofol" HVR determination.

After the "propofol" HVR determination, we obtained a second blood sample for propofol analysis and terminated the propofol infusion. Thirty minutes later, we obtained a third blood sample and determined the first of two "recovery" HVRs; 60 min after discontinuing the propofol infusion, we performed the final HVR determination. Subjects remained in the laboratory until fully awake, and then were escorted home.

Hypoxic ventilatory response determinations were performed in the following manner. Subjects breathed a mixture of O₂ (21%) and N₂ through a face mask incorporated in a closed, to-and-fro circuit with variable CO₂ absorption.⁵ The measured resistance of the circuit is approximately $0.03 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{min}$ at a flow rate of 100 l/min; the volume of the circuit and rebreathing bag is about 5.5 l. An Instrumentation Laboratories (Lexington, MA) IL200 CO₂ analyzer, calibrated with three reference mixtures of 3, 6, and 9% CO₂ in O₂ (Linde, North Haven, CT, primary standard grade $\pm 0.01\%$) continuously measured CO₂ tensions at the mask. A Hans Rudolph (Kansas City, MO) #3700 heated pneumotachograph, along with a Validyne (Northridge, CA) DP45 differential pressure transducer and electronic integrator, determined ventilatory volumes at BTPS. Before each set of measurements, we

performed a three-point volume calibration and linearity check with a Collins (Braintree, MA) #3200 "supersyringe." An AIMT Medspect (St. Louis, MO) mass spectrometer monitored circuit O₂ concentration, and a computer recorded breath-by-breath values for Sp_O₂, P_{ET}CO₂, tidal volume (TV), and minute ventilation (\dot{V}_E) *via* an analog-to-digital converter.

For each subject, all HVR determinations were performed at the same CO₂ tension. The target P_{ET}CO₂ (46–48 mmHg) was 6 mmHg above each subject's resting P_{ET}CO₂ before propofol administration. To ensure equilibration of CNS medullary centers, subjects breathed 21% O₂ in N₂, with P_{ET}CO₂ held constant, for 8 min before each HVR determination. During equilibration, we adjusted O₂ and N₂ delivery to maintain an F_IO₂ of 21% and constant volume of the rebreathing bag. At the end of the equilibration period, we stopped the O₂ inflow and began data collection, allowing subjects' metabolism to decrease the circuit O₂ concentration (fig. 1). We adjusted N₂ inflow to maintain constant rebreathing bag volume and varied CO₂ absorber flow to keep P_{ET}CO₂ constant ± 1 mmHg despite changes in ventilation. When O₂ saturation reached 70%, usually within 4 to 5 min after discontinuation of O₂ inflow, we terminated data collection and allowed the subjects to breathe 100% O₂ until Sp_O₂ increased to baseline.

For each HVR determination, the computer generated five-breath averages⁶ of \dot{V}_E , TV, and Sp_O₂, and computed the least squares regressions of \dot{V}_E and TV *versus* Sp_O₂. From the regressions, we computed \dot{V}_E90 and TV90 (\dot{V}_E and TV at 90% O₂ saturation) as indices of the position of the ventilatory response curve. To de-

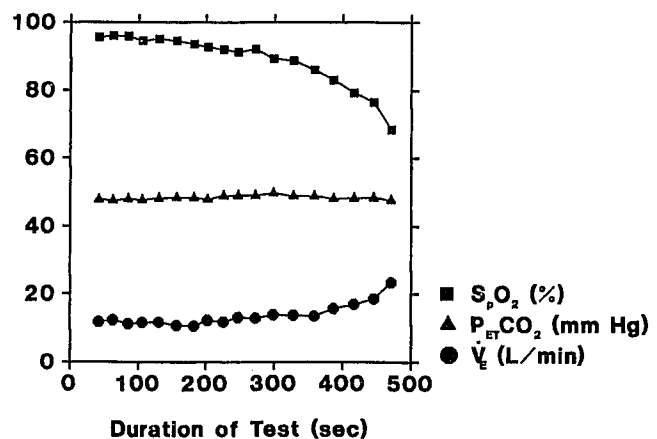


Fig. 1. Data from a typical determination of hypoxic ventilatory response, showing five-breath averages of Sp_O₂, P_{ET}CO₂, and \dot{V}_E .

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scribe the precision of CO₂ control during hypoxic re-breathing, we computed the standard deviation of PET_{CO₂} during each determination, as well as the regression of PET_{CO₂} versus SpO₂.

Blood samples for propofol determination were drawn into heparinized glass tubes from the venous catheter located in the arm contralateral to the propofol infusion. After centrifugation, the plasma was frozen at -10° C until analysis by high-performance liquid chromatography. The assay has a coefficient of variation of less than 5%, with bias of -1 to +4% in the range of 0.1–5 μg · ml⁻¹.

We analyzed parametric data using two-way ANOVA (subjects × condition) followed by Bonferroni-corrected paired *t* tests when overall significance was present. Data are expressed as mean ± SE, with *P* < 0.05 indicating statistical significance.

Results

None of the subjects suffered any sequelae as a result of participation in the study. However, while receiving propofol infusion, and breathing room air between HVR determinations, four subjects became transiently hypoxic (SpO₂ < 90%), despite their being responsive to verbal stimuli. We ensured that each subject's SpO₂ exceeded 95% before HVR determination began. All subjects reached the target level of somnolence during propofol infusion; somnolence scores remained stable during the propofol HVR determinations (level 2 before and after each "propofol" measurement for all subjects). Within 30 min after termination of the propofol infusion, all subjects were fully awake.

The rate of propofol infusion necessary to maintain a somnolence score of 2 was 85 ± 9 μg · kg⁻¹ · min⁻¹ (\bar{X} ± SE, range 46–127 μg · kg⁻¹ · min⁻¹). Mean plasma propofol concentrations were 2.0 ± 0.5 μg · ml⁻¹ immediately before, and 2.4 ± 0.7 μg · ml⁻¹ immediately after, the "propofol" HVR determination (*P* = NS). Propofol concentrations decreased to 0.7 ± 0.2 μg/ml 30 min after discontinuation of the propofol infusion.

Mean values of PET_{CO₂} did not differ significantly among pre-, during-, and two postpropofol measurements. The overall mean variability of PET_{CO₂} (as expressed by the standard deviation of PET_{CO₂} during each hypoxic challenge, *vide supra*) was 0.68 mmHg, with no significant difference among treatment conditions. The mean slope of the regression of PET_{CO₂} versus SpO₂ did not differ significantly from zero during pre-

and postpropofol determinations. There was a slight, but statistically significant, positive correlation between PET_{CO₂} and SpO₂ in the "during propofol" determinations (see below). It is most likely that this was related to a modest elevation of PET_{CO₂} at the beginning of these hypoxic challenges as a result of propofol-induced ventilatory depression (fig. 2).

During propofol infusion, the slope of the hypoxic ventilatory response decreased from 0.88 ± 0.15 to 0.17 ± 0.03 l · min⁻¹ · %SpO₂⁻¹ (*P* < 0.005). Thirty minutes after discontinuation of the propofol infusion, the slope recovered to 0.97 ± 0.15 l · min⁻¹ · %SpO₂⁻¹ (*P* < 0.05 *vs.* during propofol, *P* = NS *vs.* baseline; fig. 3). Figure 4 demonstrates the hypoxic ventilatory response curves obtained from one subject.

\dot{V}_{E90} decreased from a baseline of 16.1 ± 0.8 to 8.7 ± 0.4 l/min during propofol sedation (*P* < 0.005; fig. 5). Likewise, TV90 decreased from 1,099 ± 87 to 523 ± 21 ml (*P* < 0.005; fig. 6). Both \dot{V}_{E90} and TV90 recovered to baseline values 30 min after termination of the propofol infusion.

Discussion

The effect of low-dose propofol infusions on the hypoxic ventilatory response has not been described; however, previous investigations have demonstrated decreases in the hypoxic ventilatory response with other

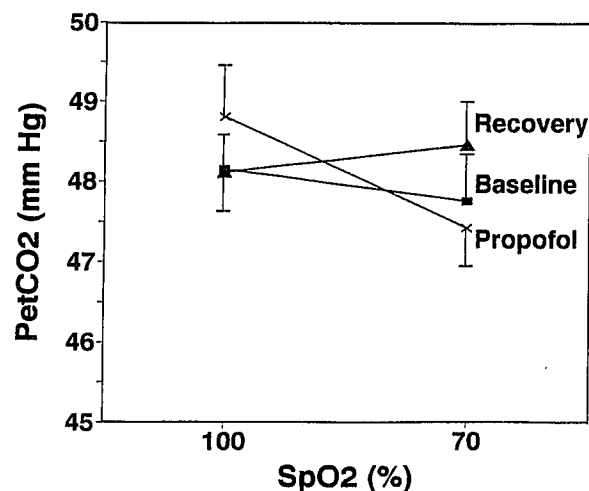


Fig. 2. Mean regression lines of PET_{CO₂} versus SpO₂ before ("baseline"), during ("propofol"), and 30 min after termination of propofol infusion ("recovery"). The 60-min post-infusion line is omitted for clarity; it is indistinguishable from "baseline."

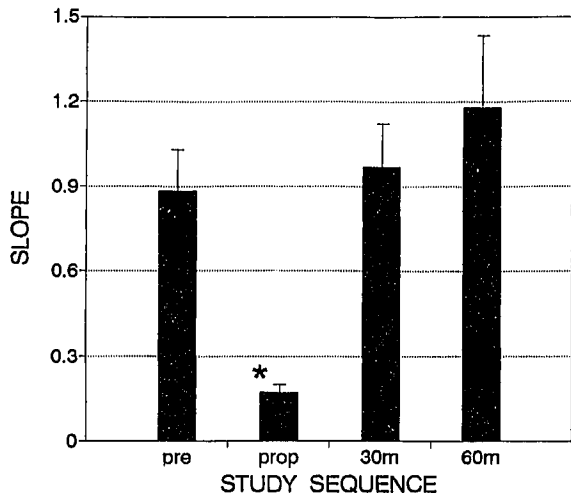


Fig. 3. Slope of hypoxic ventilatory response ($l \cdot \text{min}^{-1} \cdot \% \text{SpO}_2^{-1}$) before (pre), during (prop), and 30 and 60 min after propofol infusion. Values are mean \pm SEM. * $P < 0.005$ versus prepropofol value.

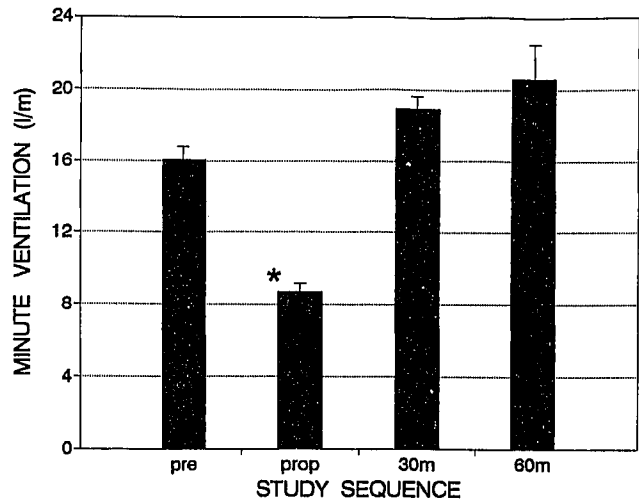


Fig. 5. Minute ventilation at $\text{SpO}_2 = 90\%$ (\dot{V}_{E90} , l/min). Observation times are the same as in figure 3. Values are mean \pm SEM. * $P < 0.005$ versus prepropofol (pre) value.

sedatives and anesthetic agents. Knill and Clement, for example, showed that subanesthetic doses of enflurane, halothane, diethyl ether, and nitrous oxide significantly decrease the ventilatory response to hypoxemia.⁷ Sim-

ilarly, depression of the hypoxic ventilatory response has been shown following midazolam⁸ and diazepam.⁹ The possibility of a common inhibitory mechanism of action is supported by the work of Concas *et al.*, who suggested that propofol, like other anesthetics and sedatives, may enhance inhibitory GABAergic transmission.¹⁰

Previous evaluations of the ventilatory depressant effects of propofol sedation used apnea and SpO_2 as out-

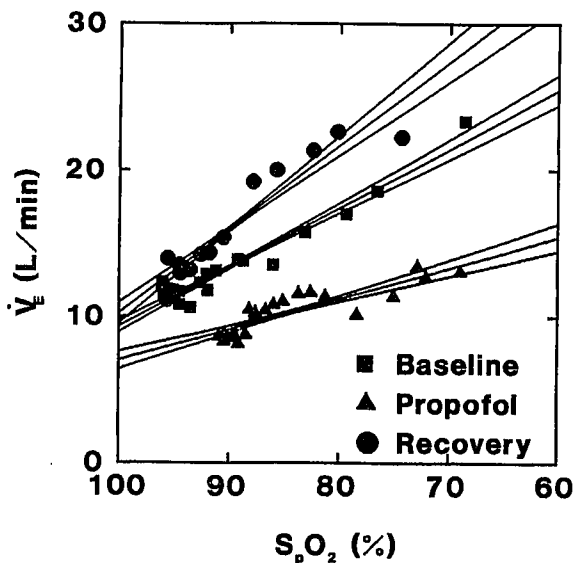


Fig. 4. Examples of hypoxic ventilatory response curves, along with their 99% confidence limits, obtained from the same subject as figure 1. Measurements were made before ("baseline"), during ("propofol"), and 30 min after termination of propofol infusion ("recovery"); the 60-min postpropofol curve is omitted for clarity.

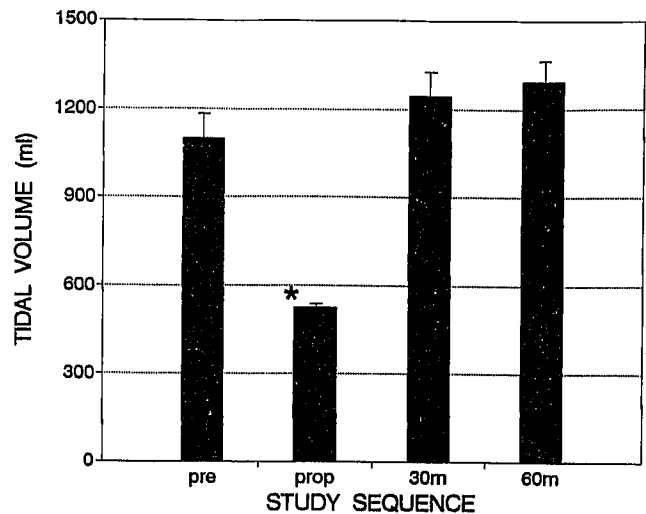


Fig. 6. Tidal volume at $\text{SpO}_2 = 90\%$ (TV₉₀, ml). Observation times are the same as in figure 3. Values are mean \pm SEM. * $P < 0.005$ versus prepropofol (pre) value.

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come variables. Patterson *et al.*, for example, compared propofol and midazolam as sedative agents for outpatient endoscopy, and found that significant oxygen desaturation ($Sp_{O_2} \leq 90\%$) occurred with both drugs.[#] Using sedation criteria similar to those in the current study, Church *et al.* described significant reductions in oxygen saturation (mean minimum of 88%) in patients sedated with propofol for upper gastrointestinal endoscopy.² Although these investigators did not evaluate the ventilatory response to hypoxia, their findings are consistent with ours: four of our eight subjects became hypoxic while breathing room air during propofol infusion. The fact that this resolved when we aroused the subjects indicates that the hypoxia resulted from hypoventilation, rather than from a persistent propofol-induced gas exchange abnormality.

Several investigators, on the other hand, have suggested that respiratory depression does *not* occur with propofol sedation. However, methodologic problems may limit the validity of their conclusions. For example, in patients undergoing molar extractions with local anesthesia and propofol sedation, Valtonen *et al.* described no significant perioperative decreases in arterial oxygen saturation, but failed to indicate whether or not patients received supplemental O_2 .¹ Also, two separate studies of patients sedated with propofol during spinal anesthesia concluded that subanesthetic doses of propofol had no respiratory depressant effects.^{3,11} However, in neither of the studies was Sp_{O_2} monitored; in fact, "respiratory depression" was simply defined as cough, airway obstruction, or apnea.

Decreases in \dot{V}_{E90} and TV90 indicate that, in addition to its effect on the slope, propofol sedation causes a downward displacement of the hypoxic response curve. However, because the current study was performed during isohypercapnic conditions, the effect of propofol on \dot{V}_{E90} and TV90 probably represent depression of a combination of hypoxic and hypercarbic ventilatory control. In studies of hypoxic ventilatory response, one cannot completely eliminate the contribution of hypercarbic ventilatory response, because elimination of the CO_2 drive causes apnea in sedated subjects,¹² making ventilatory measurements impossible.

Although hypoxic and hypercarbic drives act synergistically, the design of the current study does not allow

determination of the relative contribution of each mechanism to the decreases in \dot{V}_{E90} and TV90. Previous investigations indicate concomitant depression of hypercarbic ventilatory response by propofol. For example, we recently found that, after an induction dose of propofol (2.5 mg/kg), significant depression of the slope of the ventilatory response to CO_2 persists for 20 min, although subjects were awake and oriented by the end of that time.¹³ However, based on the short duration of hypoxic exposure, one could speculate that our findings resulted primarily from depression of the peripheral chemoreceptors, rather than from central ventilatory control mechanisms.

In the current study, subjects' levels of consciousness remained stable throughout the "propofol" hypoxic response determination. Consistent with this observation was the absence of a significant difference in plasma propofol concentrations measured immediately before and after the "propofol" hypoxic response determinations. Furthermore, our subjects' plasma propofol levels (about 2.2 $\mu\text{g/ml}$) were similar to those previously reported to provide a level of sedation similar to that of the current study. Beller *et al.*, for example, measured mean blood propofol concentration of 2.9 $\mu\text{g/ml}$ in 14 intensive care patients sedated with propofol infusions.¹⁴ Likewise, using a pharmacokinetic model in patients undergoing upper GI endoscopy, Church *et al.* predicted that a blood propofol concentration of 2.5 $\mu\text{g/ml}$ was necessary for endoscopy insertion.²

Our ability to maintain a narrow range of PET_{CO_2} during HVR determinations is reflected in the small standard deviations of measured PET_{CO_2} . Nonetheless, there was a positive correlation between PET_{CO_2} and Sp_{O_2} when HVR was measured during propofol infusion. The magnitude of this effect was such that PET_{CO_2} decreased by approximately 1.4 mmHg as Sp_{O_2} decreased from 100 to 70%. As shown in figure 2, this appears to have been related to a modest increase in normoxic PET_{CO_2} during propofol infusion; thus, even with $F_{ICO_2} = 0$, we were unable to achieve the target CO_2 tension until ventilation was stimulated by hypoxia.

While this effect may have artificially decreased the measured slope of the ventilatory response during propofol, it is unlikely that this affected the validity of our findings for the following reasons. First, the observed changes in \dot{V}_{E90} during the "propofol" HVR determinations did not result from the gradual decline in PET_{CO_2} ; because of the slight elevation of PET_{CO_2} at normoxia, the mean PET_{CO_2} at $Sp_{O_2} = 90\%$ was actually

Patterson KW, Casey PB, McEllistrem RF, O'Boyle CA, Cunningham AJ: Propofol sedation for out-patient endoscopy—A comparison with midazolam (abstract). *Anesth Analg* 68:S222, 1989.

higher during "propofol" determinations than during pre- or postpropofol determinations. Second, the magnitude of the change in P_{ETCO_2} was insufficient to significantly affect the hypoxic ventilatory response slopes measured during propofol infusion. Belleville *et al.*¹⁵ found that, during hypoxia, the total "gain" of the hypercarbic ventilatory control mechanism is approximately $3 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$. Thus, even with complete equilibration, a 1.4 mmHg change in P_{ETCO_2} as Sp_{O_2} decreased from 100 to 70% would be expected to decrease our measurement of \dot{V}_E at $Sp_{O_2} = 70\%$ by a maximum of 4.2 l/min. The maximum decrease in slope that can be accounted for by this mechanism, $(4.2/30) = 0.14 \text{ l} \cdot \text{min}^{-1} \cdot \%Sp_{O_2}^{-1}$, accounts for only 20% of the $0.70 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ decrease in HVR slope that we observed during propofol infusion. Even when the null hypothesis is altered to take this potential bias into account, the change in slope remains highly significant ($P < 0.005$).

In conclusion, we found that, under the conditions of this study, conscious sedation with a propofol infusion is associated with profound depression of the hypoxic ventilatory response, as measured during isohypercarbia. When combined with the known effect of propofol on the hypercarbic ventilatory response, this may further predispose patients to hypoxia during propofol sedation. These findings underscore the importance of appropriate monitoring and the ability to provide airway support when propofol is used for conscious sedation.

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