ANESTHESIOLOGY

Non–steady State Modeling of the Ventilatory Depressant Effect of Remifentanil in Awake Patients Experiencing Moderate-to-severe Obstructive Sleep Apnea

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ABSTRACT

Background: Evidence suggests that obstructive sleep apnea promotes postoperative pulmonary complications by enhancing vulnerability to opioid-induced ventilatory depression. We hypothesized that patients with moderate-to-severe obstructive sleep apnea are more sensitive to remifentanil-induced ventilatory depression than controls.

Methods: After institutional approval and written informed consent, patients received a brief remifentanil infusion during continuous monitoring of ventilation. We compared minute ventilation in 30 patients with moderate-to-severe obstructive sleep apnea diagnosed by polysomnography and 20 controls with no to mild obstructive sleep apnea per polysomnography. Effect site concentrations were estimated by a published pharmacologic model. We modeled minute ventilation as a function of effect site concentration and the estimated carbon dioxide. Obstructive sleep apnea status, body mass index, sex, age, use of continuous positive airway pressure, apnea/hypopnea events per hour of sleep, and minimum nocturnal oxygen saturation measured by pulse oximetry in polysomnography were tested as covariates for remifentanil effect site concentration at half-maximal depression of minute ventilation (Ce_{50}) and included in the model if a threshold of 6.63 ($P < 0.01$) in the reduction of objective function was reached and improved model fit.

Results: Our model described the observed minute ventilation with reasonable accuracy (22% median absolute error). We estimated a remifentanil Ce_{50} of 2.20 ng · ml^{-1} (95% CI, 2.09 to 2.33). The estimated value for Ce_{50} was 2.1 ng · ml^{-1} (95% CI, 1.9 to 2.3) in patients without obstructive sleep apnea and 2.3 ng · ml^{-1} (95% CI, 2.2 to 2.5) in patients with obstructive sleep apnea, a statistically nonsignificant difference ($P = 0.081$). None of the tested covariates demonstrated a significant effect on Ce_{50}. Likelihood profiling with the model including obstructive sleep apnea suggested that the effect of obstructive sleep apnea on remifentanil Ce_{50} was less than 5%.

Conclusions: Obstructive sleep apnea status, apnea/hypopnea events per hour of sleep, or minimum nocturnal oxygen saturation measured by pulse oximetry did not influence the sensitivity to remifentanil-induced ventilatory depression in awake patients receiving a remifentanil infusion of 0.2 μg · kg^{-1} of ideal body weight per minute.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients with obstructive sleep apnea are often said to have increased sensitivity to opioid-induced ventilatory depression

What This Article Tells Us That Is New

- The hypothesis that patients with moderate-to-severe obstructive sleep apnea are more sensitive to remifentanil-induced ventilatory depression was tested in 20 control patients with mild or no obstructive sleep apnea and 30 patients with moderate-to-severe obstructive sleep apnea, defined as an apnea/hypopnea index of 15 or more episodes per hour of sleep
- The predicted remifentanil effect site concentration at which half-maximal depression of minute ventilation occurred in awake patients receiving a remifentanil infusion of 0.2 μg · kg^{-1} of ideal body weight per minute did not differ between control patients and patients with moderate-to-severe obstructive sleep apnea
- This does not support the notion that adults with moderate-to-severe obstructive sleep apnea have increased sensitivity to opioid-induced ventilatory depression

Preoperative diagnosis of obstructive sleep apnea has been associated with an at least twofold increase in the risk for pulmonary complications in the first 24 h after surgery.[1,2] One proposed mechanism for this increased risk of complications is that obstructive sleep apnea increases patient's sensitivity to opioid-induced ventilatory depression.[3,4]

Experimental and clinical evidence demonstrate that intermittent hypoxia, a hallmark phenotype of obstructive sleep apnea, enhances sensitivity to the analgesic and ventilatory effects of opioids.[5–7] Retrospective analyses of life-threatening opioid-induced ventilatory events in the context of postoperative analgesia have shown obesity, somnolence, and a high risk for obstructive sleep apnea to be common among afflicted patients,[8–10] whereas opioids, when administered postoperatively, seem to aggravate sleep-disordered breathing in patients experiencing obstructive sleep apnea.[11] In spite of this evidence, studies that have formally assessed opioid-induced ventilatory depression in obstructive sleep apnea patients in comparison with controls are lacking. This knowledge gap has been recently identified by the assembly on Sleep and Respiratory Neurobiology in an official American Thoracic Society workshop.[12]

The aim of this prospective investigation was to compare the ventilatory depressant effect of remifentanil, a short-acting

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μ-opioid receptor agonist, when administered as a brief infusion, between awake patients with moderate-to-severe obstructive sleep apnea and control patients who did not have moderate-to-severe obstructive sleep apnea. We hypothesized that patients with moderate-to-severe obstructive sleep apnea are more sensitive to remifentanil-induced ventilatory depression.

Materials and Methods

The study was approved by the Stanford Research Compliance Office, Stanford, California (Human Subjects Research and Institutional Review Board (IRB): humansubjects.stanford.edu; Protocol No.: IRB-29762, Primary Investigator: A. G. Doufas, M.D., Ph.D.). After written informed consent, we evaluated surgical patients at Stanford Medical Center in this prospective, observational cohort.

Subjects

We recruited 50 patients between 18 and 70 yr old who were scheduled for head and neck surgery. Thirty patients had moderate-to-severe obstructive sleep apnea (obstructive sleep apnea group). These patients were scheduled for nasal, pharyngeal, or facial skeleton surgery for their obstructive sleep apnea, having failed, having refused, or wishing to discontinue continuous positive airway pressure treatment. Patients in the moderate-to-severe obstructive sleep apnea group had an apnea/hypopnea index of 15 or more episodes per hour of sleep during an in-laboratory or home-based polysomnography study. Twenty patients without obstructive sleep apnea, as indicated by a STOP-Bang (snoring, tiredness, observed apnea, blood pressure, BMI, age, neck circumference, gender as a screening tool for OSA)[13] score ≤ 2, or mild obstructive sleep apnea (apnea/hypopnea index less than 15) served as the control group. These patients were undergoing similar surgery (*e.g.*, tonsillectomy or sinus surgery).

We excluded patients who were morbidly obese (body mass index greater than or equal to 35 kg/m^2) and patients with severe neurologic, cardiopulmonary, or psychiatric disease, as well as patients with chronic pain treated with opioids. Patients who were compliant with continuous positive airway pressure (*i.e.*, used continuous positive airway pressure more than 4.5 h per night[14]) were also excluded from participating in the study. Finally, we excluded patients who were scheduled to undergo drug-induced sleep endoscopy before surgery.

Study Design

Study participants did not receive premedication before coming into the operating room. The study was conducted in the operating room before induction to general anesthesia.

In the operating room, patients lie supine on a regular operating table with their head and neck in a neutral position. After placement of standard American Society of Anesthesiologists anesthesia monitors (*i.e.*, electrocardiography, noninvasive blood pressure, and pulse oximetry), patients were connected to the anesthetic circuit through a tightly but comfortably fitting anesthesia pillow mask and breathed oxygen-enriched air (fraction of inspired oxygen: 0.5) throughout of the experiment. Extra care was taken to make sure that there was an adequate sealing of the anesthesia mask around the patient's mouth and nose.

After 3 min of stable breathing with no drug exposure, the study participants received a 10-min remifentanil infusion at 0.2 $\mu g \cdot kg^{-1}$ of ideal body weight per minute, through an antecubital intravenous catheter, using an electronic syringe pump (Alaris; CareFusion, USA). The infusion rate was selected to reach a remifentanil effect site concentration of approximately 4 $ng \cdot ml^{-1}$ by the end of the 10-min infusion, based on pharmacokinetic/pharmacodynamic simulations[15,16] using ideal body weight.[17,18]

The experiment was terminated prematurely if remifentanil-induced hypoventilation resulted in an oxygen saturation measured by pulse oximetry (Spo_2) less than 85% for more than 10 s or apnea periods greater than 60 s. At that point ventilation was supported by the anesthesiologist.

Measurements

All study participants were admitted to the sleep surgery division of the Department of Otolaryngology, Head & Neck Surgery at Stanford University, Stanford, California. Detailed information regarding their diagnoses and procedure indication were recorded, including their habitual daytime sleepiness using the Epworth sleepiness scale.[19] Demographic characteristics, including height, weight, age, sex, and race, were recorded on the day of the experiment. Ideal body weight was calculated from the height of the participants, based on the equations proposed by Devine[20] (*i.e.*, for men: ideal body weight = 49.9 + 0.89

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[Ht − 152.4]; for women: ideal body weight = 45.4 + 0.89 [Ht − 152.4]).

The values for polysomnography parameters related to breathing (*i.e.*, the number of apneas or hypopneas per hour of sleep) and peripheral oxygenation (*i.e.*, the number of desaturation episodes by at least 3% [oxygen desaturation index], minimum nocturnal Spo_2, and percentage of sleep time spent with an Spo_2 less than 90%) were collected from patients' electronic charts. Also, data on sleep efficiency (*i.e.*, the ratio of time spent asleep divided by the total recording time), use of continuous positive airway pressure, the type (laboratory- or home-based) and date of polysomnography, were also documented. All polysomnography studies were scored and evaluated in accordance with the 2012 update on the rules for scoring sleep-related respiratory events by the American Academy of Sleep Medicine.[21]

Before and during the remifentanil infusion ventilatory parameters of interest (minute ventilation [$\dot{V}_E$], expired tidal volume, ventilatory rate, and the partial pressure of end-tidal carbon dioxide) were measured through the anesthesia mask, using the standard flow sensor and monitors of an anesthesia workstation (Apollo; Dräger Medical GmbH, Germany). Data were captured directly from the anesthesia machine through a video camera that was focused on the monitor screen (displayed values are calculated over a 60-s moving window) and documented offline at 5-s intervals. This method of data collection was validated against proprietary software (Proto_service, Dräger Medical GmbH, Germany), which downloads data directly from the anesthesia machine to a laptop computer at 5-s intervals, and found to be accurate (*i.e.*, the time courses of the ventilatory parameters between the two methods were extremely close).

Alertness of the study participants was evaluated at the beginning of the experiment and at the end of remifentanil infusion using an 11-point verbal numerical rating scale (0: wide awake; 10: cannot keep my eyes open) and the 5-point responsiveness component of the observer's assessment alertness/sedation score (*i.e.*, 5: responds readily to name spoken in normal tone; 4: lethargic response to name spoken in normal tone; 3: responds only after name is spoken loudly and/or repeatedly; 2: responds only after mild prodding or shaking; 1: does not respond to mild prodding or shaking).[22]

Data Analysis

Individual demographic and morphometric parameters are presented as number of patients, means ± SDs, or medians (interquartile range). Friedman's supersmoother, a running-line smoother calculated using the R Language,[23] was used to compute the typical time course of all the collected ventilatory variables in each individual patient, thus facilitating visual exploration of measures of ventilatory response. Compared with end-tidal carbon dioxide, tidal volume, or ventilatory rate, $\dot{V}_E$ was the least noisy ventilatory response. We therefore selected $\dot{V}_E$ as the high-resolution measure of remifentanil-induced ventilatory depression.

Pharmacologic Model. Because this study was not performed at steady-state, we modeled drug effect as a function of predicted remifentanil effect site concentration rather than as a function of remifentanil infusion rate. We calculated remifentanil plasma and effect site concentrations for each subject throughout remifentanil infusion using a previously published three-compartment pharmacokinetic model[15,16] with an age-adjusted plasma effect site equilibration coefficient (k_{e0}).[15] We used a previously developed inhibitory sigmoid pharmacodynamic model to describe the relationship between remifentanil effect site concentration, and $\dot{V}_E$[24]:

$$\dot{V}_E(Ce) = \dot{V}_{E_0} - \left(\dot{V}_{E_0} - \dot{V}_{E_{min}}\right)\frac{Ce^{\gamma}}{Ce_{50}^{\gamma} + Ce^{\gamma}} \quad (1)$$

The parameters of the model are the baseline ventilation ($\dot{V}_{E_0}$), the minimum minute ventilation during remifentanil infusion ($\dot{V}_{E_{min}}$, expected to be 0 if the maximum effect or remifentanil on ventilation is apnea), the remifentanil concentration in the effect site associated with 50% of maximum effect (Ce_{50}), and the exponent reflecting the steepness of the concentration *versus* effect relationship, γ.

Inspection of the raw data showed that ventilation usually increased toward the end of the remifentanil infusion. We interpreted this as the stimulatory effect of accumulating carbon dioxide, similar to the observations by Bouillon *et al.* on the ventilatory effects of remifentanil.[25] Bouillon *et al.* modeled the influence of carbon dioxide rise on ventilation as a hyperbolic function relating increasing carbon dioxide to increasing ventilatory drive,

$$\dot{V}_E\left(P_{EC}CO_2\right) = \dot{V}_{E_0} \cdot \left[\frac{P_{EC}CO_2(t)}{P_{EC}CO_2(0)}\right]^F \quad (2)$$

where $P_{EC}CO_2$ is the carbon dioxide (CO_2) concentration at the hypothetical site of CO_2 effect on ventilation and F is the gain determining the change in $\dot{V}_E$ for a given change in $P_{EC}CO_2$ from time = 0 to time = t. $P_{EC}CO_2$ was calculated using the model published by Bouillon *et al.* (Bouillon's tables 2 and 4, and equations 3 and 6).[25] We combined equations 1 and 2 to describe the net effect for any given remifentanil effect site concentration and $P_{EC}CO_2$, on $\dot{V}_E$ as the product of the sigmoid inhibitory model for the maximum drug effect (E_{max}) and the nonlinear term for the CO_2 response:

$$\dot{V}_E\left(Ce, PecCO_2\right) = \left[V_{E_0} - \left(\dot{V}_{E_0} - \dot{V}_{E_{min}}\right)\frac{Ce^{\gamma}}{Ce_{50}^{\gamma} + Ce^{\gamma}}\right] \cdot \left[\frac{PecCO_2(t)}{PecCO_2(0)}\right]^{F} \quad (3)$$

The calculations were performed in the R Language[23] (Supplemental Digital Content, http://links.lww.com/ALN/B7821, which lists the R code used to estimate the nonlinear term for the CO_2 response, based on Bouillon's model[25]), and was then input to the NONMEM code.

We estimated the model parameters using nonlinear mixed-effects modeling (NONMEM 7.3, ICON Development Solutions, Dublin, Ireland) with first-order conditional estimation.[26] NONMEM was deployed within the PLT Tools environment (PLTsoft, USA). We estimated the interindividual variability, ω^2, for $\dot{V}_{E_0}$ and Ce_{50} using additive and log-normal models, respectively. For the additive variance model, the coefficient of variation is ω / P_{TV}, whereas for the exponential variance model, the coefficient of variation is approximately ω, when ω is small (*e.g.*, $\omega < 0.3$).

Residual intraindividual error, ε, was modeled with both additive and proportional error terms,

$$O_{i,j} = P_{i,j}\,(1 + \varepsilon_{1_i}) + \varepsilon_{2_i} \quad (4)$$

where $O_{i,j}$ is the jth observed value in the ith subject, $P_{i,j}$ is the jth predicted value in the ith patient, and ε_1 and ε_2 are random variables with a mean of 0 and variance of σ_1^2 and σ_2^2, respectively.

Model Building. We first modeled the effect of remifentanil on ventilation using a sigmoidal model (equation 1) with interindividual variability on Ce_{50} and $\dot{V}_{E_0}$. Additional interindividual variance parameters introduced bias and model misspecification and were therefore excluded. The model consistently predicted more ventilatory depression than observed at the end of the infusion. This bias was removed by accounting for the stimulatory effects of accumulated carbon dioxide, as described above (equation 2). Models were evaluated based on the reduction in the NONMEM objective function (−2 log-likelihood) *and* a reduction in the median absolute error (measured / predicted ventilation). The latter step was incorporated into the model building process because some parameters, including additional intersubject variance parameters, reduced the objective function but increased the absolute error and bias to the model, resulting in models that visually described the data appreciably less well than models with higher log-likelihoods.

Model Evaluation. Model fit was assessed by the NONMEM objective function, visual inspection of plots of the observed ($\dot{V}_{E_{obs}}$) *versus* predicted $\dot{V}_E$ ($\dot{V}_{E_{pred}}$), linear regression, and calculation of the median prediction error and median absolute prediction error.[27] Prediction error was estimated for each observation ($\dot{V}_{E_{obs}}$) as percentage of the predicted $\dot{V}_{E_{pred}}$:

$$\text{Prediction Error} = \frac{\dot{V}_{E_{obs}} - \dot{V}_{E_{pred}}}{\dot{V}_{E_{pred}}} \times 100 \quad (5)$$

Prediction error, median prediction error, and median absolute prediction error were calculated for both the population and the *post hoc* individual model estimates.

Confidence in each pharmacodynamic parameter was assessed by using log-likelihood profiling and bootstrap analysis, as implemented within PLT Tools. The log-likelihood profile was calculated by plotting the objective function estimated for parameters near the final parameter estimate. Bootstrap analysis was used to estimate 95% CI for each parameter, by randomly sampling a new set from the patients' data, with replacement, and then repeating NONMEM estimation of the final model 1,000 times. According to the percentile method, the values between the 2.5 and the 97.5% rank of the distribution defined the 95% CI for each parameter. The log-likelihood profile addresses the confidence in the parameter relative to the overall model. The bootstrap analysis addresses the confidence in the parameter relative to the data.

To examine for a possible systematic bias in subjects with obstructive sleep apnea, the relationship between the predicted remifentanil effect site concentration and the fractional decrease in $\dot{V}_{E_0}$ measured (1-min average) at end-infusion was described and graphically presented by linear regression analysis, for the obstructive sleep apnea and control participants separately. Linear regression analysis was also used to describe the relationship between the total body weight of the participants and the cumulative dose of remifentanil they received during the infusion. Regression slopes were compared between the obstructive sleep apnea and control participants.

Covariate Analysis. The effects of obstructive sleep apnea on remifentanil-induced ventilatory depression were examined by testing prespecified covariates against Ce_{50}. Prespecified covariates of remifentanil-induced ventilatory depression were study group (obstructive sleep apnea *vs.* controls, the primary hypothesis), body mass index, sex, age, apnea/hypopnea index, and minimum nocturnal Spo_2. For the six control (non–obstructive sleep apnea) participants for whom polysomnography studies were not available, we imputed for apnea/hypopnea index and minimum nocturnal Spo_2 the values of 3 and 94, respectively. We also tested inadequate continuous positive airway pressure use, defined as more than 4.5 h per night, as a covariate of Ce_{50}. Covariates were included as additive effects on the Ce_{50}. Statistical significance was assessed by a decrease in objective function greater than 6.63 (χ^2 distribution for $P < 0.01$ with one degree of freedom) with the introduction of a new covariate.

We directly tested our primary hypothesis that obstructive sleep apnea affected remifentanil-induced ventilatory depression by calculating the log-likelihood profile of an additional parameter representing the effect of obstructive sleep apnea on the Ce_{50} for remifentanil-induced ventilatory depression,

$$Ce_{50} = \theta_2 \cdot \left(1 + \theta_5 \cdot OSA\right) \quad (6)$$

where θ_2 is the population estimate of Ce_{50} in the absence of obstructive sleep apnea, $\theta_2 \cdot (1 + \theta_5)$ is the population estimate of Ce_{50} in the presence of obstructive sleep apnea, and OSA is a binary 0 or 1 for the presence or absence, respectively, of obstructive sleep apnea. The log-likelihood profile provided an estimate of the sensitivity of the model to an effect of obstructive sleep apnea on remifentanil-induced ventilatory depression.

We also conducted an unplanned exploratory analysis on the effects of the above covariate on $\dot{V}_{E_0}$ and γ. All data processing, graphs, and statistical analyses other than that performed with NONMEM were performed using the R Language,[23] RStudio (Version 1.0.143, USA), and Prism 7.0c (GraphPad Software, Inc., USA).

Results

To recruit 50 study participants, we screened 101 patients between December 2015 and April 2017. According to the protocol, 30 participants had moderate-to-severe obstructive sleep apnea (apnea/hypopnea index exceeding 15 episodes per hour of sleep) and 20 had no (N = 9) to mild (N = 11) obstructive sleep apnea. Among the nine non–obstructive sleep apnea participants, six did not have a polysomnography study available and were recruited based on a STOP-Bang score of 2 or lower (one participant with 2, two with 1, and three with 0 score). Table 1 lists the demographic and morphometric characteristics of study participants, as well as baseline obstructive sleep apnea–related information and ventilation parameters. Figure 1 presents data on apnea/hypopnea index

Table 1. Demographics, Morphometrics, Polysomnography Descriptors, and Baseline Ventilation

	OSA (AHI ≥ 15, N = 30)	Controls (AHI < 15, N = 20)
Demographics and morphometrics		
Age, yr	43 ± 13	34 ± 10
Female, n (%)	4 (13)	6 (30)
White race, n (%)	18 (60)	11 (55)
Height, cm	178 (170–183)	178 (164–181)
Total body weight, kg	87 (80–101)	78 (73–95)
Ideal body weight, kg	72 (64–78)	73 (57–76)
BMI, kg/m^2	29 (26–33)	28 (23–32)
BMI ≥ 30, n (%)	12 (40)	7 (35)
ESS (0–24)	10 (5–15)	10 (6–13)
ESS > 10, n (%)	15 (50)	8 (40)
Sleep study breathing and oxygenation variables		
Time interval between PSG and surgery, months	10 (6–18)	3 (2–17)
Overnight attended (Level I) PSG, n (%)	21 (70)	10 (71)
Sleep efficiency, %	87 (75–92)	93 (86–95)
Apnea/hypopnea index, events per hour of sleep	38 (24–51)	6 (5–12)
Fraction of hypopnea events during sleep ($F_{hypopneas}$)	0.78 (0.50–0.94)	0.97 (0.87–0.99)
Oxygen desaturation index, events per hour of sleep*	23 (12–42)	3 (2–5)
Minimum nocturnal Spo_2, %	83 (80–86)	91 (86–92)
Time spent at Spo_2 < 90%, % of total sleep time†	1.12 (0.04–6.59)	0 (0–0.08)
Ever used CPAP treatment (noncompliant), n (%)	12 (40)	4 (29)
Ventilation at baseline (3-min average)		
Minute ventilation ($\dot{V}_E$), l · min^{-1}	6.5 (5.4–7.5)	7.1 (5.6–8.9)
Breathing tidal volume (V_T), ml	590 (420–780)	580 (400–790)
End-tidal pressure of carbon dioxide ($PETCO_2$), mmHg	38 (36–40)	38 (36–39)
Respiratory rate (RR), breaths · min^{-1}	10 (8–13)	11 (8–16)

Continuous variables are reported as mean ± SD, or median (interquartile range).

*This variable indicates the number of breathing episodes where Spo_2 decreased by at least 3%. Only 25 from the 30 OSA and 9 from the 20 control participants had information on this PSG variable. †Only 25 from the 30 OSA and 12 from the 20 control participants had information on this PSG variable.

AHI, apnea/hypopnea index (events per hour of sleep); BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; PSG, polysomnography; Spo_2, oxyhemoglobin saturation by pulse oximetry.

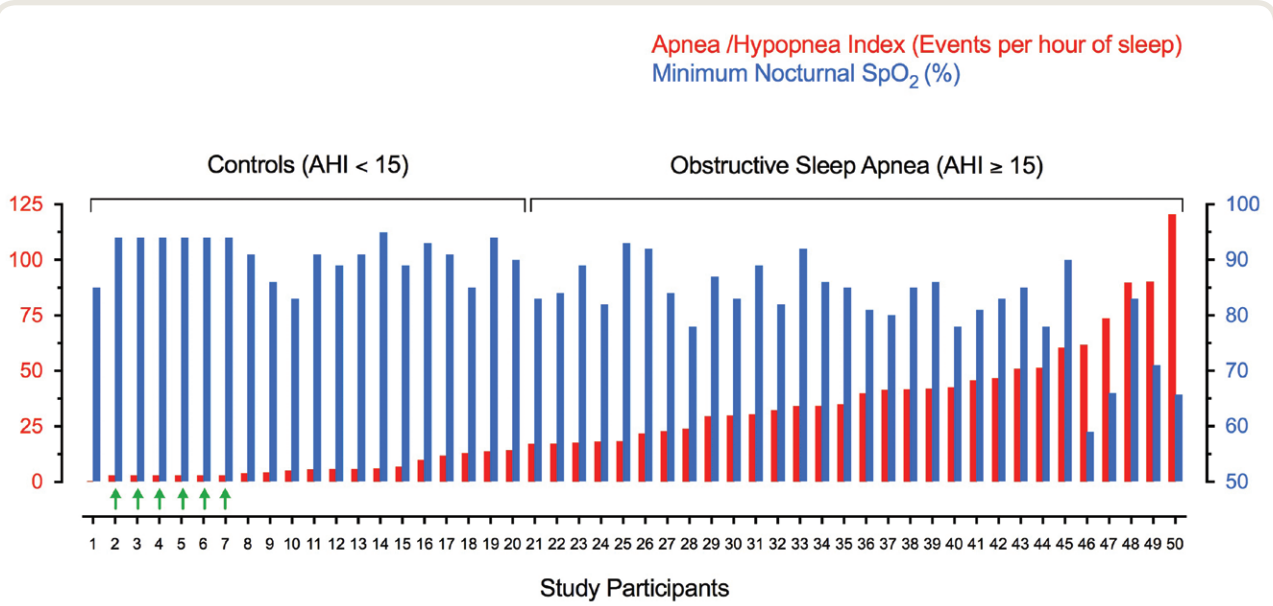

Fig. 1. Individual study participants, each depicted as a *double column*, one representing apnea/hypopnea index (AHI, *red, left y axis*) and the other minimum nocturnal oxygen saturation measured by pulse oximetry (Spo_2, *blue, right y axis*), ordered by AHI. *Green vertical arrows* indicate the six control participants with missing data for whom an AHI of 3 and Spo_2 of 94 were imputed.

and minimum nocturnal Spo_2 for individual study participants ordered by increasing apnea/hypopnea index.

Figure 2 depicts the time course of recorded ventilatory parameters, including $\dot{V}_E$, expired tidal volume, ventilatory rate, and the partial pressure of end-tidal carbon dioxide, during the baseline and remifentanil infusion phases of the experiment. The total median doses of remifentanil administered in obstructive sleep apnea and control participants were 144 μg (interquartile range: 128 to 156) and 146 μg (113 to 156), respectively. During drug infusion, study participants experienced moderate-to-increased sleepiness (*i.e.*, up to 9 on a 0 to 10 scale), but none presented with an observer's assessment alertness/sedation score less than 4 (*i.e.*, lethargic response to name spoken in normal tone). None of the participants presented with an Spo_2 less than 92% as a result of remifentanil-induced ventilatory depression.

Among the patient covariates, only age significantly affected the Ce_{50} for remifentanil-induced ventilatory depression, reducing the NONMEM objective function by eight points. Age was not included in the final model because its incorporation worsened rather than improved the population fit of the model to the data and did not appreciably change the parameter estimates.

Table 2 presents the parameters of the final model for remifentanil-induced ventilatory depression estimated by NONMEM. The estimated typical value for Ce_{50} was 2.20 ng · ml^{-1} (95% CI, 2.09 to 2.33; estimated by bootstrap resampling). The estimated value for Ce_{50} was 2.1 ng · ml^{-1} (95% CI, 1.9 to 2.3) in patients without obstructive sleep apnea, and 2.3 ng · ml^{-1} (95% CI, 2.2 to 2.5) in patients with obstructive sleep apnea, a statistically nonsignificant difference (unpaired *t* test, $P = 0.081$). The population model (fig. 3) estimated the observed $\dot{V}_E$ with reasonable accuracy (median prediction error of −3%, median absolute prediction error of 22%; fig. 3, A and C). The individual *post hoc* model did not show evidence of model misspecification (median prediction error of 0%, median absolute prediction error of 8%; fig. 3, B and D).

Figure 4 shows the contribution of remifentanil (equation 1) and carbon dioxide (equation 2) on the predicted $\dot{V}_E$ (dotted lines). The predicted $\dot{V}_E$ closely follows the median observed $\dot{V}_E$ (solid lines). Figure 5A shows the linear regression between the remifentanil effect site concentration and the fractional decrease in $\dot{V}_{E_0}$ at end-infusion, separately for the obstructive sleep apnea and control participants. The graph does not reveal any systematic bias regarding the obstructive sleep apnea subjects (*i.e.*, slope of the regression line was not statistically different from 0 for both study groups). Figure 5B shows the significant linear relationship between the cumulative dose of remifentanil and total body weight in obstructive sleep apnea and control participants, separately. Comparison of the regression slopes did not reveal any statistically significant difference between the two groups.

Figure 6 shows the effect of obstructive sleep apnea on Ce_{50}, determined by the log-likelihood profile of an additional parameter for the fractional effect of obstructive sleep apnea on Ce_{50}. The estimated typical value for the effect of obstructive sleep apnea on Ce_{50} was a 7% increase in C_{50} in obstructive sleep apnea patients (*i.e.*, 7% *decrease* in

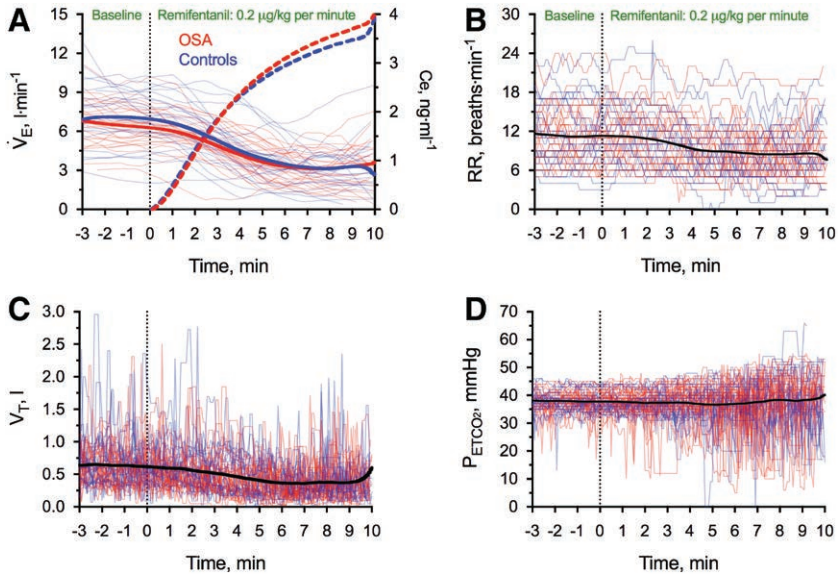

Fig. 2. Time course of the remifentanil effect on minute ventilation ($\dot{V}_E$; *A*), respiratory rate (RR; *B*), tidal volume (V_T; *C*), and end-tidal pressure of carbon dioxide (P_{ETCO_2}; *D*), during the 3-min baseline (no drug exposure) and the 10-min-long drug infusion. For each parameter, *graphs* present individual curves for obstructive sleep apnea (OSA; *red*) and control (*blue*) participants, separately, whereas in graph *A*, a *heavier line* of the same color, summarizing the effect of individual observations in the two groups, is also depicted. In the same graph (*A*), the summarized remifentanil effect site concentration (Ce, *right y axis*) curve, is also presented as a *heavier dotted line*, separately for the two study groups, using the same color coding as above.

Table 2. Typical Parameter Values and Basic Statistics of the Pharmacodynamic Model Describing Remifentanil-induced Ventilatory Depression

Parameter	P_{TV}	ω^2	CV (%)	1,000 Bootstraps (median, 95% CI)	σ_1^2, σ_2^2
$\dot{V}_{E_0}$, l · min^{-1}	6.58	3.32	27.7	6.59 (6.08–7.11)	0.004, 0.37
Ce_{50}, ng · ml^{-1}	2.20	0.03	7.9	2.20 (2.09–2.33)	
$\dot{V}_{E_{min}}$, l · min^{-1}	0*	—	—	—	
γ	3.55	—	—	3.55 (3.17–4.00)	

*Nonlinear mixed-effects modeling estimated a typical value of 0.001 for $\dot{V}_{E_{min}}$; therefore, this parameter was fixed to zero in the final model.

Ce_{50}, effect site concentration at half-maximal depression of minute ventilation; CV, coefficient of variation ($=\sqrt{\omega^2} / P_{TV}$); P_{TV}, typical parameter value; $\dot{V}_{E_{min}}$, baseline minute ventilation; $\dot{V}_{E_{min}}$ minimum minute ventilation; γ, shape of the sigmoid relationship between effect site concentration and minute ventilation; σ_2, variance of the intraindividual random effects (ε), modeled as both a proportional (σ_1^2) and an additive (σ_2^2) term; ω^2, variance of the interindividual random effects.

remifentanil sensitivity in obstructive sleep apnea patients). The 99% CI ranged from −5% to +21%. The log-likelihood profile includes 0, precluding a statistically significant effect. Additionally, the 99% CI suggests that the effect, if any, is not greater than a 5% reduction in Ce_{50}.

Exploratory covariate testing on $\dot{V}_{E_0}$ and γ revealed a significant effect of obstructive sleep apnea on γ, reducing the objective function by 100 points. Despite the statistical significance, the effect was clinically insignificant (γ of 3.36 for obstructive sleep apnea *vs.* 3.81 for controls) and not pursued further.

Figure 7 presents the log-likelihood profiles for all estimated model parameters, together with the associated 95% CI for their typical values, based on a 3.84-point reduction in the objective function.

Discussion

We found that awake patients receiving a remifentanil infusion of 0.2 μg · kg^{-1} of ideal body weight per minute with moderate-to-severe obstructive sleep apnea were not different from

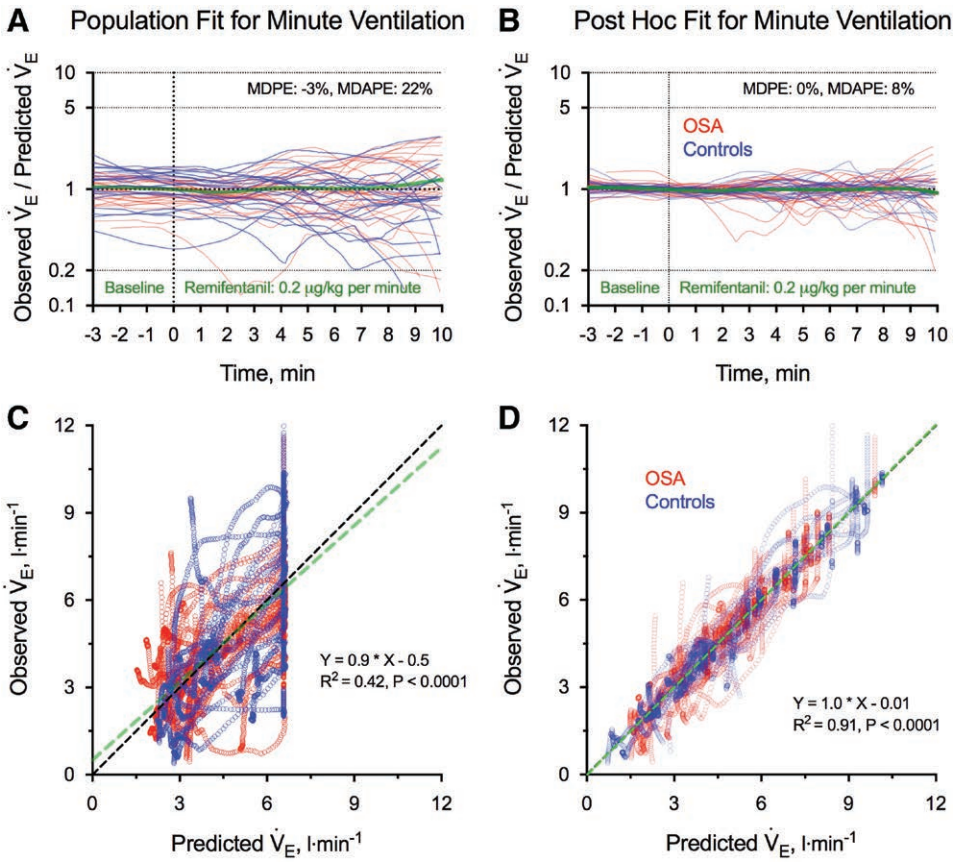

Fig. 3. *Panels A* and *B* present the ratio of the observed *versus* predicted minute ventilation ($\dot{V}_E$) for the population (*A*) and the individual *post hoc* (*B*) model fits, as a function of time. Performance metrics for the respective models (*i.e.*, median prediction error [MDPE] and median absolute prediction error [MDAPE]) are also indicated. *Panels C* and *D* show the goodness of fit (*green dotted line*) for the population prediction (*C*) and the prediction based on the individual *post hoc* estimates (*D*) *versus* the observed minute ventilation, using linear regression (line of identity is depicted in *black*). The color of lines or dots discriminates between the two different study groups, as indicated in graphs *B* and *D*. OSA, obstructive sleep apnea (study group assignment: yes /no).

controls or patients with mild obstructive sleep apnea, with regard to the predicted remifentanil Ce_{50}. Covariate analysis showed that neither apnea/hypopnea index nor minimum nocturnal Spo_2 during polysomnography was a significant modifier of remifentanil Ce_{50} for ventilatory depression.

It is important to emphasize what we did not find. We did not measure remifentanil concentrations. As a result, our data do not tell us whether moderate-to-severe obstructive sleep apnea influences remifentanil concentrations. For the same reason, our data do not tell us whether moderate-to-severe obstructive sleep apnea influences the ventilatory response to a given remifentanil concentration. All we can state with moderate confidence is that moderate-to-severe obstructive sleep apnea does not influence the relationship between remifentanil dose, reported as *predicted* remifentanil effect site concentration, and ventilation.

We used predicted remifentanil effect site concentration in our analysis, rather than dose, as recommended by Avram,[28] who noted that "simply reporting the infusion rate of an intravenous anesthetic is akin to reporting only the vaporizer dial setting of a volatile anesthetic without reporting the fresh gas flow, the alveolar ventilation, and the many other factors that influence uptake and distribution of volatile anesthetics."[28] Predicted effect site concentration is almost the only meaningful way, short of measuring plasma concentrations, to report the brain exposure for intravenous hypnotics and opioids. We could report the dose as micrograms per minute, but plasma remifentanil concentrations responsible for the drug effect will be higher in small individuals than in large individuals receiving identical remifentanil infusions (*i.e.*, same micrograms per minute). We could also report the dose as micrograms per kilogram per minute, but this will result in the opposite artifact: obese individuals will have higher plasma remifentanil concentrations than individuals of normal size when given identical micrograms of

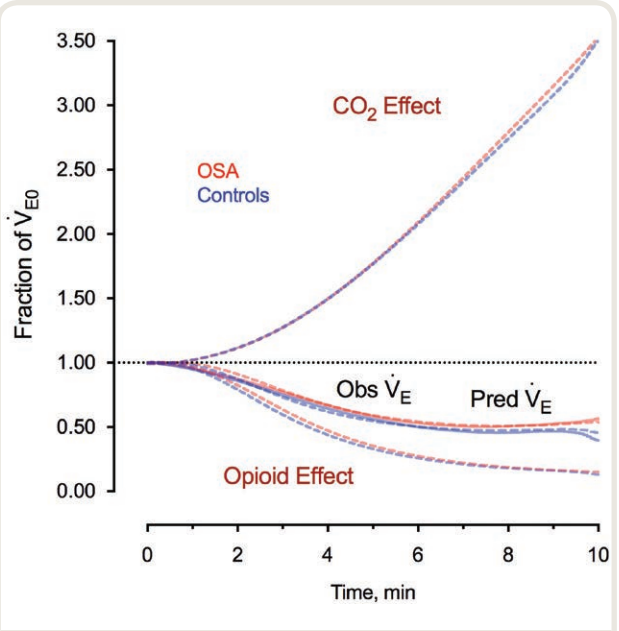

Fig. 4. This graph presents the separate contributions of the remifentanil inhibitory (opioid effect) and the carbon dioxide (CO_2) stimulatory effects on ventilation (fraction of $\dot{V}_{E_0}$), as these were combined in our final model, in relation to the predicted (Pred $\dot{V}_E$) and observed (Obs $\dot{V}_E$) ventilation. Predicted and observed parameters are depicted by *dotted* and *solid lines*, respectively. Color separates between obstructive sleep apnea (OSA; *red*) and controls (*blue*).

remifentanil per kilogram per minute. In our study, we infused remifentanil at 0.2 micrograms per kilogram of ideal body weight per minute. However, using this "dose" in the analysis would compromise the ensuing analysis of the dose *versus* response relationship, because it does not correct for the increase in remifentanil concentrations over time, nor does it incorporate the equilibration delay between the plasma concentration and the concentration at the site of drug effect (effect site concentration). Expressing dose as predicted effect site concentration, as recommended by Avram,[28] permits identifying the "dose" responsible for ventilatory depression in units independent of patient size, time, equilibration delay, and dose history.

Avram also recommended that predicted concentrations should not be used to develop pharmacokinetic and pharmacodynamic models.[28] We agree that models of underlying pharmacology should use measured concentrations. This study serves as an example. We cannot state whether moderate-to-severe obstructive sleep apnea affected the relationship between remifentanil infusion rate and plasma concentration, nor can we state whether moderate-to-severe obstructive sleep apnea affected the relationship between plasma remifentanil concentration and ventilation. However, that was not our goal. What we can state is that moderate-to-severe obstructive sleep apnea does not affect the relationship between remifentanil dose and ventilation during a brief infusion.

There are other limitations that need to be addressed. We used the model reported by Minto *et al.*[15,16] The Minto model is based on a pharmacokinetic and pharmacodynamic study of patients with normal weight. Kim *et al.*[29] recently published a remifentanil pharmacokinetic analysis incorporating obese patients. Because approximately 40% of our study participants were obese (body mass index greater than or equal to 30 kg/m^2), we repeated the analysis

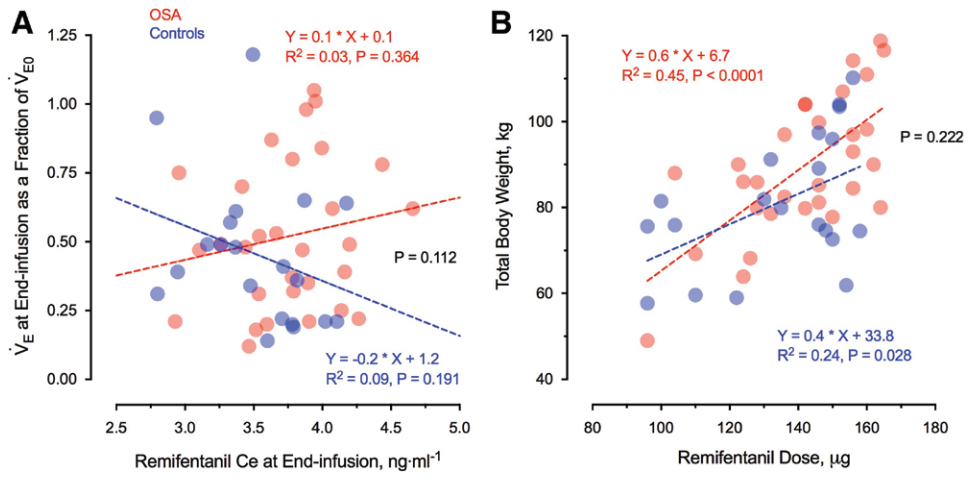

Fig. 5. Graph *A* depicts the relationship between the remifentanil effect site concentration (Ce) and the fractional decrease in baseline ventilation ($\dot{V}_{E0}$) measured (1-min average) at end-infusion. Linear regression analysis did not reveal any systematic bias of the obstructive sleep apnea (OSA) subjects (*i.e.*, for both study groups, the slope of the regression line was not different than 0). Graph *B* shows the significant linear relationship between the cumulative dose of remifentanil and total body weight in OSA and control participants, separately. Comparison of the regression slopes did not reveal any statistically significant difference between the two groups ($P = 0.222$).

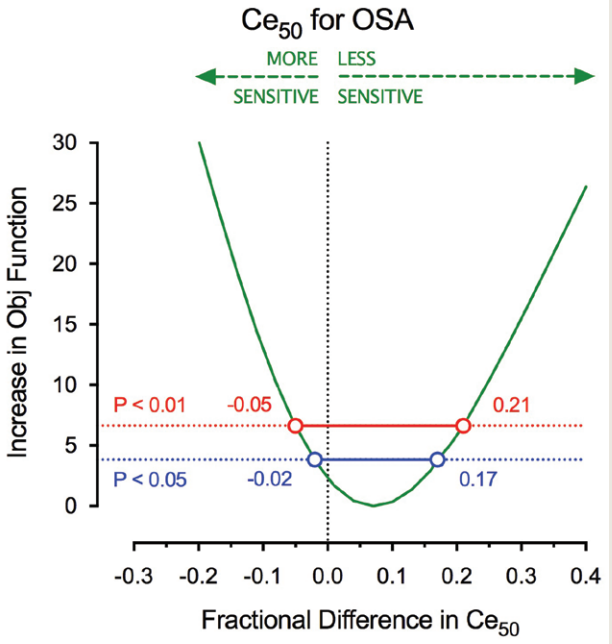

Fig. 6. Log-likelihood profile (*green curve*) of the parameter indicating the possible fractional difference between effect site concentration at half-maximal depression of minute ventilation (Ce_{50}) in obstructive sleep apnea (OSA) and control participants. *Black vertical dotted line* indicates 0, whereas *red* and *blue horizontal solid lines* represent the estimated 99% and 95% CIs, respectively. Based on the study observations, nonlinear mixed-effects modeling estimated with high confidence that Ce_{50} for remifentanil-induced ventilatory depression is greater in OSA than controls by approximately 7% (99% CI, −5 to 21). Obj, objective.

using remifentanil effect site concentration predicted by the Kim model.[29] The results were nearly identical to the results obtained with the Minto model. Therefore, we have retained the Minto model in the present study, because this is the model that has been incorporated in commercially available target controlled infusion devices.

There are several other limitations worth addressing. First, ventilation was measured using the flowmeters on the anesthesia machine, which could be less precise than using a laboratory-grade differential pressure spirometer. Second, no data were collected during remifentanil washout. The modeling exercise would have been more robust had data been collected during both washin and washout. Unfortunately, because the study was conducted in surgical patients, further delay in surgery to capture ventilation during washout was considered clinically impractical. Finally, although the use of STOP-Bang (snoring, tiredness, observed apnea, blood pressure, BMI, age, neck circumference, gender as a screening tool for OSA) score, instead of polysomnography, to rule out moderate-to-severe obstructive sleep apnea in 6 of 20 control participants might be a source of concern, studies have shown that a STOP-Bang score less than 3 demonstrates higher than 80% probability to correctly exclude moderate-to-severe obstructive sleep apnea (apnea/hypopnea index greater than or equal to 15) in surgical patients.[30]

The infusion scheme we used did not allow the estimation of ke0 for the $\dot{V}_E$ end point, and an encephalography-based (ke0 of 0.52 min^{-1})[15,16] rather than ventilation-derived ke0 was used to calculate remifentanil effect site concentration. However, human evidence supports a close pharmacodynamic link between the sedative, analgesic, and ventilatory depressant effects of opioids.[31,32] Furthermore, although ventilatory control is far more sensitive to the effect of opioids (C_{50} between 0.7 and 3.3 ng · ml^{-1}, depending on the study method),[33–36] compared with spectral edge frequency of the electroencephalogram (C_{50} of 11.2 ng · ml^{-1} in Minto *et al.*[15] and 19.9 ng · ml^{-1} in Egan *et al.*[37]), studies have estimated similar ke0 values for the electroencephalogram (ke0 of 0.43 min^{-1} in Egan

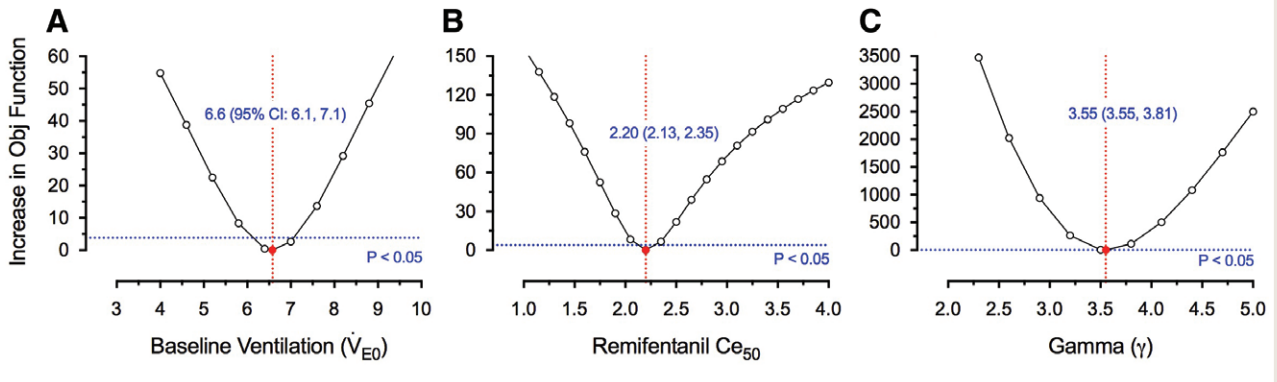

Fig. 7. Log-likelihood profiles of the model parameters, including baseline ventilation (V_{E0}; *A*), remifentanil effect site concentration at half-maximal depression of minute ventilation (Ce_{50}; *B*), and γ (*C*). Significance threshold at $P < 0.05$ is indicated by the *dotted blue line*, whereas 95% CIs for the typical values (indicated by the *dotted vertical red line*) of model parameters are also presented. Obj, objective.

et al.[37] and 0.52 min^{-1} in Minto *et al.*[15]) and ventilatory (*i.e.*, ke0 values between 0.34 and 1.30 min^{-1})[34–36] end points. As a consequence, our model produced an accurate fit of the observed $\dot{V}_E$ with a median prediction error of −3% and median absolute prediction error of 22% for the population, and median prediction error of 0% and median absolute prediction error of 8% for the *post hoc* individual estimates. The time course of drug effect, as well as the maximum ventilatory depressant effect of remifentanil, were comparable with those demonstrated previously in healthy subjects by simulating similar infusion schemes for remifentanil.[25,36,38]

The effect of opioids on ventilation is offset, in part, by the effect of $Paco_2$ on ventilatory drive. In poikilocapnic (free-floating carbon dioxide) study designs, the C_{50} of an opioid is therefore a function of $Paco_2$. When $Paco_2$ information is available through arterial sampling, non–steady-state modeling of the ventilatory depressant effects of opioids can incorporate the stimulating effect of carbon dioxide on ventilation in a *context-specific* potency (C_{50}) of the opioid.[25,36] We accounted for the ventilatory stimulatory effects of carbon dioxide using the model developed by Bouillon *et al.*[25] The basic assumption of our modeling, that the carbon dioxide responsiveness (represented by the gain *F* in equations 2 and 3) is similar between obstructive sleep apnea and control participants, is supported by literature evidence in awake humans.[39,40]

Our estimated Ce_{50} for remifentanil-induced ventilatory depression (2.20 ng · ml^{-1}) is consistent with values in studies incorporating the effect of carbon dioxide on remifentanil-induced ventilatory depression, either in non–steady-state conditions, as in Olofsen *et al.*[36] (C_{50} of 1.6 ng · ml^{-1}) and Bouillon *et al.*[25] (C_{50} of 0.92 ng · ml^{-1}), or in isohypercapnic experiments by Babenco *et al.*[34] (C_{50} of 1.4 ng · ml^{-1}) and Nieuwenhuijs *et al.*[33] (C_{50} of 0.7 ng · ml^{-1}). These C_{50} values are lower than those estimated by Nieuwenhuijs *et al.*[33] (C_{50} of 3.3 ng · ml^{-1}) and Dahan *et al.*[35] (C_{50} of 2.6 ng · ml^{-1}), using models that did not account for the stimulating effect of carbon dioxide on ventilation.

Obstructive sleep apnea is a common but highly heterogeneous disorder.[41] We based obstructive sleep apnea diagnosis on overnight polysomnography and clinical symptoms, but did not proceed to deep phenotyping[42,43] (*i.e.*, evaluating airway muscles responsiveness, ventilatory control loop gain, and arousal threshold) of our patients. Important obstructive sleep apnea phenotypes, like the loop gain of respiratory chemosensory controller (chemical loop gain: the ratio of the magnitude of the change in ventilation to the magnitude of the change in $Paco_2$ or Pao_2[44]) and arousal threshold (*i.e.*, the level of ventilatory effort during airway obstruction that is associated with arousal and termination of hypopnea), have major implications for the airway stability during sleep,[43,45] especially in obstructive sleep apnea patients with moderate anatomical impairment.[42] These more complex phenotypes appear responsible for the observed variability in the response to benzodiazepines,[46,47] opioids,[48,49] or oxygen administration.[50]

Our results may not apply to other obstructive sleep apnea populations, to patients in other clinical settings, and even to our study participants when sedated or asleep. Because of the arousal state dependency of central ventilatory control,[51] especially in obstructive sleep apnea,[52,53] the pharmacologic concept of *ventilatory sensitivity to opioids* may degenerate during sleep (either natural or pharmacologically induced sleep), when a dissociation between central ventilatory drive and airway function occurs. For example, sleeping/sedated patients with intact (or even heightened, as a result of hypercapnia) ventilatory drive may demonstrate heavily depressed ventilation attributable to severe upper airway obstruction, a phenomenon that commonly appears in obstructive sleep apnea. How an opioid (used in moderation) could affect such a scenario is not easy to predict and would depend on several factors, including those reported above. Although a recent systematic review of the actions of opioids and hypnotics on the severity of sleep-disordered breathing have overall demonstrated no effect,[54] we need to emphasize that our findings pertain to awake patients with obstructive sleep apnea and exercise caution when opioids are administered to patients with decreased state of arousal.

During the experiment, remifentanil increased subjective sleepiness by roughly 5 units (in a 0 to 10 verbal scale), independently of the obstructive sleep apnea status. An objective assessment, using the responsiveness component of observer's assessment alertness/sedation score,[22] revealed only mild drowsiness, as others have previously documented using both clinical[34] and encephalography-based[33,36] instruments, at similar drug concentrations. Thus, although we cannot exclude the possibility that the sedative effect of remifentanil might have influenced its effect on ventilation (a state-dependent function[51]) by causing a right shift in the ventilatory response to carbon dioxide,[55] it is rather unlikely that this effect was significant or modified by obstructive sleep apnea status.

In summary, we found that among surgical patients, those who experience moderate-to-severe obstructive sleep apnea are not more sensitive to the ventilatory depressant effect of remifentanil than non–obstructive sleep apnea patients or patients with mild obstructive sleep apnea. Neither the number of obstructed breathing events nor the minimum Spo_2 during sleep were found to have a significant indepedent influence on the sensitivity to remifentanil-induced ventilatory depression.

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Competing Interests

The authors declare no competing interests.

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