Opioid Modeling of Central Respiratory Drive Must Take Upper Airway Obstruction into Account

To the Editor:
The elegant modeling of the dynamic effects of remifentanil on respiratory depression by Olofsen et al. is a useful contribution to our understanding of opioid effects on respiratory control. The authors’ incorporation of non–steady state changes in opioid concentration and the addition of propofol to induce apnea help in their goal to reproduce real-life conditions in patients receiving opioids and sedatives. This is particularly relevant when considering morbidity and mortality incurred by patients in general care ward settings who receive opioids and sedatives. However, we believe that the model neglects important considerations that simulate real-life clinical situations relating to predisposed patients whose depth of sedation is sufficient to induce loss of consciousness and upper airway obstruction.

Olofsen et al. used end-tidal carbon dioxide (ETCO₂) and remifentanil concentrations as inputs to the model and measured ventilation as an output. The study’s stated objective is to build a model that predicts apnea at finite opioid and hypnotic concentrations under dynamic conditions. Our concern is that at concentrations of sedation commensurate with loss of responsiveness, as occurred in this study, partial or complete airway collapse could preclude sampled ETCO₂ from being an accurate reflection of the arterial carbon dioxide, and thereby a valid input to the model. As it stands, the model assumes a patent upper airway. The authors acknowledge that, close to apnea, the ETCO₂, used by the model to set the ventilation gain G (equation 6), is likely to be falsely low. The authors account for the inaccuracy of this model input by assigning a residual error to the ETCO₂ and modeling it as a probability density function, in addition to ignoring values less than 37.5 torr. Low and unpredictable ETCO₂ values are common in the periapneic period, as shown during the 15-min breathing after the period of apnea in 8 of 10 study subjects receiving remifentanil and propofol (fig. 3, original article). It is feasible that an upper airway obstructive component could contribute to these events. Consequently, the model could break down in obstruction-prone subjects for both the ETCO₂ input (fig. 5F, original article) and minute ventilation (fig. 5E, original article) output during the periapneic period, the precise time for which the model is designed to provide insights.

Hillman et al. have shown that an abrupt increase in the tendency of the upper airway to collapse at the point of loss of consciousness with propofol in healthy volunteers can be attributed to a precipitate decrease in tone of the primary upper airway dilator, the genioglossus muscle. Hajja et al. recently demonstrated that opioids cause a dose-related suppression of tonic brainstem stimulatory input to the genioglossus in rats. Thus, apart from their suppression of central respiratory drive, opioids and other sedatives can also precipitate upper airway obstruction. The authors use the term apnea (cessation of airflow) throughout the article as synonymous with suppression central respiratory drive (a central apnea), without considering obstruction (an obstructive apnea). This is an important omission, and the distinction is critical in understanding the time course and relative contributions of upper airway collapse and reduced central respiratory drive to ventilatory failure. It has important implications for our ability to monitor, diagnose, and prevent respiratory decompensation. Thus, ambiguity in the models’ critical inputs during the periapneic periods and failure to account for airway obstruction in modeling respiratory responses to opioid/propofol infusion detract from its use.

We believe the model would be improved by including components that account for the complex interactions between the respiratory control mechanisms and airway patency, as eloquently described by Younes. Consistent with standard control theory, we would divide the overall (closed-loop) gain of the system into a controller gain and a plant gain. White describes controller gain as the ventilatory responsiveness to hypercapnia or hypoxia, whereas plant gain reflects the effectiveness of any given concentration of ventilatory drive in eliminating carbon dioxide. As obstructive hypopneas and apneas develop, a ramped-up controller gain from accumulating PaCO₂ may be attenuated by a negative plant gain from an obstructed airway. In these patients, the ability to rescue themselves from a fatal decompensation, either through a central nervous system arousal or sufficient chemical drive, to cause reflex opening of their airway is a tenuous dynamic that only can be simulated by a model that includes all these components. A metric relating to propensity for upper airway obstruction, perhaps related to critical closing pressure, should be among these. We also commend the approach of Bouillon et al., who uses PaCO₂ as the dependent variable in modeling remifentanil-induced ventilatory depression, with a method that takes carbon dioxide kinetics into account.

We are keen to encourage such an approach because root-cause analysis of a case series of postoperative patients found dead in bed on the ward by one of us (F.O.) found serosanguinous pulmonary edema not to be an uncommon autopsy finding. Although nonspecific, a potential explanation for this finding is negative pressure pulmonary edema secondary to upper airway obstruction, with fatal consequences.


Accepted for publication September 14, 2010.
In Reply:

We thank Drs. Overdyk and Hillmann for their interest in our study on the dynamic modeling of the respiratory effects of remifentanil and propofol in humans.1

In their comments, they raise an important issue—incorporation of airway collapse in the pharmacodynamic model. Although we certainly considered obstructive apnea, we intentionally did not incorporate in our current model a component that accounts for airway patency. The reason for this decision was simply that airway collapse did not play a role in the respiratory responses observed in our cohort of young healthy volunteers. The subjects inhaled and exhaled through a mask placed over nose and mouth, held in position by one of the investigators, and aimed at keeping the airway open. Furthermore, we controlled for airway patency by two or three times per min) arterial carbon dioxide measurements is sometimes problematic. See, for example, reference 3, where we acknowledge the discussion we had with our ethics committee regarding placement of arterial lines in healthy volunteers.1 In addition, using arterial PCO2 as a model output requires frequent sampling, which has stimulatory effects on breathing.4 To the best of our knowledge, there are no studies with arterial sampling regimens that come close to the frequency of that used in our most recent study.1 We submit that, relative to sparse (e.g., two or three times per min) arterial carbon dioxide measurements, the use of frequent ETCO2 data points increases the reliability of model parameter estimates. Our model enables realistic simulations of the ventilatory effects of opioids and sedatives with ETCO2 as output.

As stated previously,4 breathing in the perioperative patient is under the influence of many factors, including respiratory drive, arousal state, and the functionality of pharyngeal dilating muscles. Opioids, anesthetics, and sedatives have an effect on all three elements. In our most recent study,1 we explored their effect on the ventilatory drive only. The effect of these agents on changes in arousal state and upper-airway patency requires further investigation.

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References


In our model.1 Remifentanil concentration and propofol are the model inputs.

Second, Overdyk and Hillmann state that our model does not incorporate a controller and a plant. In our second figure,1 we presented both elements; the controller is highlighted, and the top part (i.e., carbon dioxide kinetics) is the plant. Because we have a medical audience, we decided not to use wording specific to engineering when defining the plant part of our model. Interested readers may wish to refer to Lennart Ljung’s System Identification: Theory for the User (Englewood Cliffs, NJ, Prentice-Hall, 1987).

Third, we do take CO2 kinetics into account and, consequently, PCO2 is a dependent variable.

Finally, we measured arterial carbon concentrations at various time points during our experiments (data not shown). Although the values we observed were somewhat higher than ETCO2 values, they closely followed patterns observed for end-tidal PCO2. We refer readers to the first equation and figure 2 of our original article.1 Our model was based on end-tidal PCO2 for various reasons. It is an easily measured variable and, consequently, may be used clinically as well.

The use of arterial lines for repetitive arterial carbon dioxide measurements is sometimes problematic.3 See, for example, reference 3, where we acknowledge the discussion we had with our ethics committee regarding placement of arterial lines in healthy volunteers.1 In addition, using arterial PCO2 as a model output requires frequent sampling, which has stimulatory effects on breathing.4 To the best of our knowledge, there are no studies with arterial sampling regimens that come close to the frequency of that used in our most recent study.1 We submit that, relative to sparse (e.g., two or three times per min) arterial carbon dioxide measurements, the use of frequent ETCO2 data points increases the reliability of model parameter estimates. Our model enables realistic simulations of the ventilatory effects of opioids and sedatives with ETCO2 as output.

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