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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 distinct measures. We continuously observed the thoracic and abdominal movement of subjects and monitored pulse transit time. Pulse transit time is a noninvasive measure that gives an indication of respiratory effort.[2] The low values of end-tidal P_{CO_2} observed close to apnea are not the result of airway obstruction, but rather very low tidal volumes with open airways.

Overdyk and Hillmann's comments suggest that some aspects of our model deserve additional explanation. First, they state that end-tidal carbon dioxide (ET_{CO_2}) is an input for the model. This supposition is incorrect. Instead, ET_{CO_2} and measured minute ventilation are bivariate model outputs. We refer readers to equations 3 and 4 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 CO_2 kinetics into account and, consequently, P_{CO_2} 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 ET_{CO_2} values, they closely followed patterns observed for end-tidal P_{CO_2}. We refer readers to the first equation and figure 2 of our original article.[1] Our model was based on end-tidal P_{CO_2} 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.[3] In addition, using arterial P_{CO_2} 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 ET_{CO_2} data points increases the reliability of model parameter estimates. Our model enables realistic simulations of the ventilatory effects of opioids and sedatives with ET_{CO_2} 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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Multiples of Minimal Alveolar Concentration of Volatile Agents Are Not Necessarily Equipotent

To the Editor:

I read with interest the article titled, "Isoflurane Causes Greater Neurodegeneration Than an Equivalent Exposure of Sevoflurane in the Developing Brain of Neonatal Mice," in the June 2010 issue of ANESTHESIOLOGY by Liang *et al.*[1] The entire premise of the article is based on the assumption that 0.5 MAC of isoflurane is equipotent to 0.5 MAC of sevoflurane. Furthermore, the authors not only assume that these partial MAC values are equipotent for motion on surgical stimulation (the original comparative endpoint for MAC in humans), but that they are also equipotent for neurodegeneration in the developing mouse brain. I would submit that neither assumption is valid.

As early as 1970, Waud and Waud[2] published an editorial in ANESTHESIOLOGY explaining that MAC is only one point on an entire dose–response curve. This editorial inspired follow-up letters to the editor in support.[3–5] I can find no evidence in the literature that, to date, the shape of the entire dose–response curve for percentages of patients showing motion on stimulation *versus* end-tidal concentration for any volatile agent has been established. For example, the percentage of patients who will move on surgical stimulation under 0.5 MAC *versus* 1.5 MAC, etc., remains unknown. There is certainly no assurance that the dose–response curve for any volatile agent will parallel any other dose–response curve for the volatile agents. Moreover, MAC is really a median minimal alveolar concentration, and there is no assurance that any specific MAC value holds true for any given patient or mouse.

In addition to the unverified assumption that partial MAC values are equipotent, even for percentages of patients moving with surgical stimulation, the authors go on to make the assumption that partial MAC values are also equipotent for an entirely different dose–response curve (neurodegeneration in the developing mouse brain *vs.* alveolar concentration). Even full MAC values for motion cannot be assumed to be equipotent between agents for a totally different dose–response curve. Likewise, if the equipotency of partial MAC values cannot be assumed for the original dose–response

curve, it is at least equally invalid to assume equipotency of those partial MAC values when they are transferred to a totally different dose–response curve. The authors have not yet established a valid full MAC value for neurodegeneration in their study population. However, even if they did, there is no validity in assuming that partial MAC values for that dose–response curve would be equipotent, unless the authors determined the shape of the entire dose–response curve for each agent tested.

The authors only can assert with validity that, when given 0.5 MAC of isoflurane and 0.5 MAC of sevoflurane, there seems to be greater neurodegeneration in the developing mouse brain with isoflurane. The assertion that the mice have been administered equipotent doses of the two volatile agents can be supported by neither the definition of MAC nor the medical literature to date.

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In Reply:

We thank Dr. Cross for his insightful comments concerning our recent article.[1] Dr. Cross makes several excellent points in regard to the nonlinear dose-response curves and the validity of partial minimum alveolar concentration (MAC) values.

In 1963, Merkel and Eger[2] originated the term MAC, describing it as an "index of comparison" for different anesthetic agents. They defined 1 MAC as the end-tidal concentration of anesthetic that prevents movement in 50% of animals in response to a supramaximal painful stimulus.[2] Subsequently, the use of MAC, to represent "a unifying concept of inhaled anesthetic potency" has grown to incorporate other clinical endpoints, such as MAC awake, MAC intubation, and MAC-BAR (blunt autonomic reflexes).[3,4]