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In Reply:

We would like to thank Dr. Nathan L. Pace for his commentary and additional analysis of our study.¹ We agree that entire dose-response curve analysis does permit a more robust statistical comparison than ED₅₀ and ED₉₅ single-point comparisons. Dr. Pace's reanalysis found ED₅₀ and ED₉₅ values similar to our original calculations. We concur with the differences Dr. Pace found in the dose-response curves, noting higher dose requirements in this morbidly obese population compared with a nonobese population studied previously. Despite evidence of different dose-responses and higher ED₅₀ values in morbidly obese patients, we are hesitant to firmly conclude that obese patients require larger intrathecal doses of local anesthetics compared with nonobese patients for a number of reasons:

The primary objective of our study was to determine the ED₅₀ and ED₉₅ in our morbidly obese population. Comparisons of ED₅₀ and ED₉₅ values of these morbidly obese patients with those of a nonobese population previously studied by our group were only a secondary analysis and study endpoint. In addition, using historical controls from a number of years ago presents important limitations, as we mentioned in our manuscript. Historical controls are associated with many confounders and biases that may affect group comparisons. Both studies contained small study populations (42 morbidly obese and 42 nonobese patients); therefore, a few individuals can have a greater influence on the overall population dose-response curve than preferable. In addition, although we followed a methodology similar to that of the previous study, it was not identical (*e.g.*, 5–11 mg doses administered in the obese population were compared with 6–12 mg doses in nonobese patients).

While we acknowledge Dr. Pace's analysis of a rightward shift in the dose-response curves of the morbidly obese pop-

ulation compared with a nonobese population, the limitations noted above remain. We therefore do not want to go as far as recommending increasing the intrathecal local anesthetic dose in the morbidly obese patients undergoing cesarean delivery. It is worth noting that no patient in our study received the calculated ED₉₅ of 14.3 ± 0.9 mg, and we can therefore not comment on its safety. In contrast to expert advice, our study does suggest that the intrathecal bupivacaine dose should not be reduced for obese patients. Our findings also imply that morbidly obese patients are not well-suited to a single-shot spinal technique. More variable responses to intrathecal dosing and longer surgical times indicate that catheter-based techniques are more appropriate. Our study also highlights that initial satisfactory sensory block to pinprick following small intrathecal doses does not ensure adequate intraoperative anesthesia for the duration of the surgical procedure.

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Observations on the Study of Second Gas Effects

To the Editor:

This recent excellent study on the second gas effect was extremely interesting.¹ I would like to ask several questions to further appreciation of the findings presented. Which ventilator type, mode, inspiratory/expiratory time settings, and fresh gas flows intraoperatively (*vs.* 9 l/m during emergence) were used? Some ventilator models self-correct to end expiratory volumes, whereas others (*i.e.*, volume-controlled Narcomed II [Draeger Medical Inc., Telford, PA]) deliver fixed inspiratory volumes, which further affect expired volumes by changes in fresh gas flow as well as the additional significant N₂O egress volumes. Increasing fresh gas flow from 3 l/m to 9 l/m to fixed ventilator inspiratory volumes using 1:2 inspiratory/expiratory ratios can affect up to 200 *versus* 2,000 ml tidal *versus* minute volume changes, respectively. Although reported minute volumes are described as nonsignificantly different in N₂O *versus* air/oxygen control group *via* ml × min × kg (ml/Kg/min???) in your table 1, the calculated respective 6,605 *versus* 5,749 absolute ml/min is 15% difference (was this significant statistically?), which would be even

greater if ventilator delivered *versus* exhaled volumes were actually reported.

Severinghaus showed that N₂O volumes of 20–29 l accumulate in the body using 80% N₂O within 1–2 h and this volume is recovered and added to expiratory volumes during emergence, contributing to second gas removal. This occurs predominantly in the first 5–10 min and as much as 1 l/m N₂O alveolar-arterial mass flow were described with maximum changes in the fraction of inspired N₂O.² Diffusion hypoxia results, when during emergence, the combination of low tidal (ca 200 ml and just above dead space volumes *via* endotracheal tube)/min volumes, airway occlusion and mass flow of nitrous oxide from the body in the face of respiration of air (79% nitrogen and 21% oxygen) does not provide adequate oxygen transfer to meet demands. Hypoxemia is not obligate with adequately maintained minute volumes using high fresh gas flows and air, however.

Surgeries and positions also were not defined (although one patient in the lateral position was excluded due to mucus plugs), whereas especially endoscopic/thoracic surgeries and nonsupine positions would expectantly significantly affect respiration parameters. The use of bispectral index delineation of anesthetic depth was an unusual distraction, resulting in two different fraction of inspired sevoflurane concentrations for emergence. This resulted in the development of a theoretic “normalized sevoflurane in N₂O” curve. The reported sevoflurane blood/gas partition coefficients (Pa₀-S/Pa₀-S) for Control *versus* N₂O groups are 0.76 and 0.83 (using data from table 1 and before changing from steady-state gas anesthesia at T₀), quite different from the known 0.65.³ To what do the authors attribute these differences? During emergence, were there significant pulmonary or methodologic problems/differences in the two groups that might compound Pa/Pa₀-S relationships over time emerging, or is this more likely due to increasing methodologic inaccuracies, as the inhaled and then measured sevoflurane concentrations decline? Emergence phenomena including reversal agent hemodynamic perturbations, coughing, straining, breath-holding, switching to and anesthetic depression of spontaneous ventilation, further complicate volatile elimination, occurring typically well before eye opening, extubation, and emergence. Was this evident? The authors speculated as to the source of differences in the arterial carbon dioxide concentrations at 2 and 5, *versus* 30 min during emergence, but with so many possible and undescribed factors, it is interesting yet difficult to clarify as a reader. The use of (unknown) intraoperative and postoperative narcotics in the postanesthesia care unit certainly may be another factor in these surgeries requiring arterial line insertion. Why were fentanyl and morphine at induction chosen and in which group and at what rates/intervals, with such different known durations of opioid effect?

I understand the authors wished to emulate clinical emergence, but emergence itself is a significant confounding issue in this study of gas pharmacokinetics. The many

confounding issues are important and remain of interest at this point. A self-subject crossover controlled study before surgery, using fixed high fresh gas flow greater than minute volumes (*i.e.*, 10–15 l/m), fixed inspiratory volumes using maintenance sevoflurane 1.4% and 66% nitrous oxide *versus* 1.4% sevoflurane in oxygen with propofol total intravenous anesthesia to ensure anesthetic depth in both groups (a true comparison test), switched to air (or oxygen) only during N₂O elimination (with sustained manual ventilation, anesthetic depth, and paralysis), would have effectively removed the multiple variables questioned previously, provided clearer information and obviated any need for extrapolation of a “normalized sevoflurane in N₂O curve.” There is no need to emerge from anesthesia, simply to document effects on elimination of the second gas sevoflurane at one concentration during the switch from 66% N₂O *versus* control to oxygen. Using bispectral index as a questionable index of anesthetic depth *versus* known minimum alveolar concentration constants, only complicated the issues here (also recognized by the authors).

Finally, it is not required to use N₂O to speed emergence *via* second gas effect. One can maintain carbon dioxide at permissively higher concentrations toward the end of surgery (and thus ensuring patient respiration) and once the sevoflurane is terminated and high fresh gas flow is instituted, a simple increase in minute volume by 1–2 l/min toward normocapnea will more than compensate any mass flow or second gas effect of N₂O egress on speeding emergence, as this effect is limited to the maximum 10–15 l N₂O flowing from the body in the first 10 min. We may not be able to provide an inspired concentration of less than zero on emergence, but we can increase manual ventilation, hyperventilating from permissive hypercapnia to normocapnic levels to remove gases. Similarly, switching from pure sevoflurane to N₂O monoanesthesia near surgical end (near or after peritoneum closure) can further speed emergence and avoid surgical disdain from bowel distention, as bowel is now hidden from view, inadequate time remains to accumulate significant intraabdominal volumes of nitrous oxide and emergence from N₂O alone is *the* most rapid emergence.

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