risk of cerebral hypoperfusion in these patients. However, some studies have failed to find a difference in mean arterial pressure (MAP) at the lower limit of cerebral autoregulation in patients with these comorbidities and have generally found predicting the MAP to target during cardiopulmonary bypass (CPB) difficult based on clinical history and preoperative blood pressure.[2] While it is generally believed that intraoperative MAP goals should be individualized to the patient's physiology, how to monitor and target cerebral perfusion remains difficult without specialized equipment for real-time cerebral autoregulation monitoring. Near-infrared spectroscopy-based methods may provide an acceptable alternative for monitoring cerebral autoregulation during cardiac surgery, yet studies demonstrating the ability of this and similar monitoring techniques to improve neurocognitive outcomes after cardiac surgery remain limited by small cohort size, short duration of follow-up, and mixed results.[2,3] Furthermore, cardiac surgical patients are at risk of hemodynamic instability beyond the intraoperative period; thus, cerebral hypoperfusion may occur outside of the monitored intraoperative environment and remains difficult to detect and preempt postoperatively. Given that blood pressure was not the focus of our current study, we did not employ specialized monitoring of cerebral autoregulation.

Drs. Cao and Zhu further correctly identify other factors that may influence postoperative neurocognitive outcomes, including anesthetic depth and duration, rewarming during CPB, and cerebrovascular events. CPB times, and thus presumably anesthetic duration, were not different between the groups in our study. While we did not specifically record and report anesthetic depth, the literature again lacks convincing evidence that the use of routinely employed anesthetic depth monitors (*i.e.,* processed electroencephalography monitors) can prevent postoperative delirium or cognitive decline.[3] Electroencephalography-based anesthetic titration shows greater promise in reducing postoperative cognitive decline in older adults,[3] but was not used in our study. Based on our previous findings,[4] standard institutional practice is to warm patients at a slower rate, maintaining no more than 2° C difference between nasopharyngeal and CPB perfusate temperature. Rate of rewarming was therefore unlikely to have had a significant effect in our study. Finally, cerebrovascular events, regardless of etiology, are certainly influential with regard to cognitive outcomes after cardiac surgery. We did report on the rate of stroke in our study cohort, which was overall quite low, occurring in two patients in the lidocaine group and six patients in the placebo group (not statistically different). Furthermore, we included these stroke patients in our sensitivity analysis, assigning them to worst cognitive performance, and still failed to find a difference in postoperative cognitive dysfunction between treatment groups. This suggests that the few patients who suffered early postoperative stroke did not skew the findings of our study.

Competing Interests

The authors declare no competing interests.

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Opioid-induced Miosis Is Unaltered by Obstructive Sleep Apnea: Comment

To the Editor:

We read with interest the article by Montana *et al.*[1] "Opioid Sensitivity in Children with and without Obstructive Sleep Apnea." The authors are to be commended on their measurement of *in vivo* remifentanil

concentrations—which interestingly were higher and more variable in their patient group with presumed obstructive sleep apnea—instead of pharmacologic extrapolation. This article provides evidence that serum remifentanil concentrations may not be constant independent of age or weight.

However, from the points of view of a pediatric anesthesiologist and a sleep apnea researcher, we have concerns regarding the presentation of the study findings. The study, while adding to our fund of knowledge regarding opioid effect on the pupillary sphincter in awake patients, was unable to draw any conclusions regarding the two groups' sensitivity to opioid-induced respiratory depression. Although addressed in the discussion, this fact is not exactly highlighted in the abstract or in the Editor's Perspective and is open to unintentional misinterpretation. We fear it may provide a false sense of security to those administering or prescribing opioids to children with obstructive sleep apnea and/or obesity.

The authors hypothesize that children with sleep apnea have an increased sensitivity to the miotic and respiratory depressant effects of remifentanil, and the study did not support this conclusion. It is not clear whether the method used to test the hypothesis, pupillary constriction, is appropriately sensitive to the clinical opioid effect we all seek to best understand, respiratory depression. The terms opioid sensitivity and opioid effect are used interchangeably and do not necessarily imply a linkage from pupil size to respiratory vulnerability. Thus, the summative statement, "this study questions the notion that all children with a clinical diagnosis of sleep apnea are more sensitive to opioids" is particularly concerning to us when the test itself lacked specificity for the clinically concerning effect in question. The actual conclusion is that the relationship between opioid effect and pupillary miosis as it relates to respiratory depression or analgesia remains unaddressed.

The second concern we have regarding the conclusion relates to the translation of opioid effects while awake to effects in the sleeping state. The authors distinctly note that although the aim was to achieve sleeping levels of sedation, this did not occur. Current evidence does not support the assumption that sensitivity to opioids while awake translates to risk of respiratory depression when asleep. Because most, if not all, pediatric posttonsillectomy deaths have been associated with opioids and sleep,[2] we hope that readers of this study would not erroneously feel secure in translating findings in awake pediatric patients to their own practices in the postoperative setting.

Finally, we are not reassured that the obstructive sleep apnea group was functionally dissimilar to the control group, especially in light of the fact that only 9 of 15 study patients had overnight polysomnography and were not stratified according to Apnea–Hypopnea Index severity. In contrast, the adults in the similar study group of Doufas *et al.*[3] all had polysomnography and were stratified according to severity. In fact, in the Doufas study, those with mild sleep apnea were sorted to the control/"no obstructive sleep apnea" group, and only the moderate or severe Apnea–Hypopnea Index diagnoses were considered the "obstructive sleep apnea" group. We wondered whether all nine of Montana's study patients had mild apnea or whether the other six had obstructive sleep apnea at all. There is also no robust evidence that 14 of 15 children in the control group did not have obstructive sleep apnea. Why should a study on pediatric patients be held to different standards, especially with such a small sample size? We appreciate that recruitment of pediatric patients for research is difficult. However, this tempers our confidence in translating the results.

There is still much to be discovered regarding opioid sensitivity in children with sleep apnea, as the article by Montana *et al.* demonstrates. The relationship of pupillary miosis to analgesia, respiration, or even sleep-associated miotic changes in children with and without sleep apnea are all exciting areas for further research—and this study can help to inform them.

Competing Interests

The authors declare no competing interests.

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Opioid-induced Miosis Is Unaltered by Obstructive Sleep Apnea: Reply

In Reply:

I appreciate the interest that Drs. Webber and Karan showed in our study of opioid sensitivity in children with sleep apnea[1]

and welcomed their comments. They note that opioid-induced miosis and opioid-induced respiratory depression are distinct effects. I agree and explicitly stated as much in the abstract, noting that although remifentanil administration resulted in miosis, "the administered dose of remifentanil did not affect respiratory rate or end-expired carbon dioxide in either group." Nowhere in the article do I make the claim that my study addresses the paramount concern of respiratory depression in children with or without obstructive sleep apnea. However, our study failed to find a difference in opioid-induced miosis between patients with and without a clinical diagnosis of obstructive sleep apnea. This was surprising and raises the need to assess other opioid-mediated effects in patients with and without obstructive sleep apnea, especially respiratory depression.

Regarding the concern that Drs. Webber and Karan raise about obstructive sleep apnea diagnosis, many patients do not have a formal sleep study before presenting to the operating room for tonsillectomy. We sought to replicate real-world diagnostic practices and used surgeon diagnosis to determine whether a patient carried an obstructive sleep apnea clinical diagnosis. We assessed sleep studies in patients where one was available, just as would be performed in a real-world environment. Of note, 60% of our obstructive sleep apnea patients did have a sleep study, and the remainder had at least two of the following symptoms: snoring, witnessed breathing pauses or gasping for breath, restless sleep, or daytime somnolence. The editorialists' concerns regarding a perceived failure to assess obstructive sleep apnea severity are addressed in table 1.[1] Only two of the patients who underwent polysomnography had mild obstructive sleep apnea; the others had either moderate or severe obstructive sleep apnea.

I agree that much remains to be discovered regarding opioid sensitivity in children with and without obstructive sleep apnea. As Drs. Webber and Karan point out, the relationship between pupillary miosis, ventilation, oxygenation, and obstructive sleep apnea status are all areas ripe for further research.

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Competing Interests

The author declares no competing interests.

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