

Obstructive Sleep Apnea Predicts Adverse Perioperative Outcome

Evidence for an Association between Obstructive Sleep Apnea and Delirium



This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

OBSTRUCTIVE sleep apnea (OSA) is a common disorder affecting up to 25% of the general population depending on sex, age, and definition; its incidence is even higher (up to 80%) in obese patients. It is an important risk factor for cardiovascular diseases including hypertension, myocardial infarction, and stroke. In this issue of ANESTHESIOLOGY, Flink *et al.* report in a prospective observational study that OSA is associated with postoperative delirium (POD),¹ a novel finding. If confirmed in subsequent studies, this association may have major implications for anesthesiology and critical care medicine.

Postoperative Delirium

Delirium is an acute, fluctuating impairment in attention and cognition. POD affects up to 70% of patients older than 65 yr undergoing surgery, with rates varying by the type of patients, surgery and diagnostic instrument.² A particularly high incidence of POD has been reported following hip surgery and cardiac surgery, where it is a strong independent predictor of mortality up to 10 yr postoperatively.³ Consequently, it is critical to identify potentially reversible causes of POD and to further elucidate the mechanisms that underlie it.

Illustration: ©istockphoto.com.

Accepted for publication January 9, 2012. Dr. Bateman is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article. Dr. Eikermann received research grants from Merck (Whitehouse Station, New Jersey) (nos. IISP 39442 and P 07981) and ResMed (San Diego, California) (no. P219406). Figure 1 was created by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

Copyright © 2012, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2012; 116:753-5



“... Flink et al. report ... that [obstructive sleep apnea] is associated with postoperative delirium, a novel finding.”

OSA and Perioperative Implications

Although obesity has clearly been linked with an increased incidence of perioperative complications, including wound infections and breakdown, venous thromboembolism, adverse cardiac events, and respiratory complications, some (but not all) data support the view that OSA, independent of obesity, increases perioperative risks. Potential mechanism underlying the increased risk of perioperative complications in OSA include, but are not limited to, drug effects, inflammation, and hypercoagulability, as well as perioperative changes in sleep architecture.⁴

Association between OSA and Delirium, and Pathophysiologic Considerations

The mechanism of the potential link between OSA and POD cannot be directly addressed in the present study, but it is tempting to speculate on possible pathways (fig. 1). Frequent episodes of airway collapse in OSA lead to hypoxia, disrupted sleep, sleep inertia, daytime sleepiness, and increased arousal threshold from sleep, all of which may be considered as potential precipitating and/or augmenting factors of delirium.^{2,5} Indeed, it is intriguing to note that OSA patients appear to be most vulnerable to hypoxia on postoperative night 2 or 3, the time interval during which postoperative delirium most typically presents.

◆ This Editorial View accompanies the following article: Flink BJ, Rivelli SK, Cox EA, White WD, Falcone G, Vail TP, Young OC, Bolognesi MP, Krystal AD, Trzepacz PT, Moon RE, Kwatra MM: Obstructive sleep apnea and incidence of postoperative delirium after elective knee replacement in the nondemented elderly. ANESTHESIOLOGY 2012; 116:788-96.

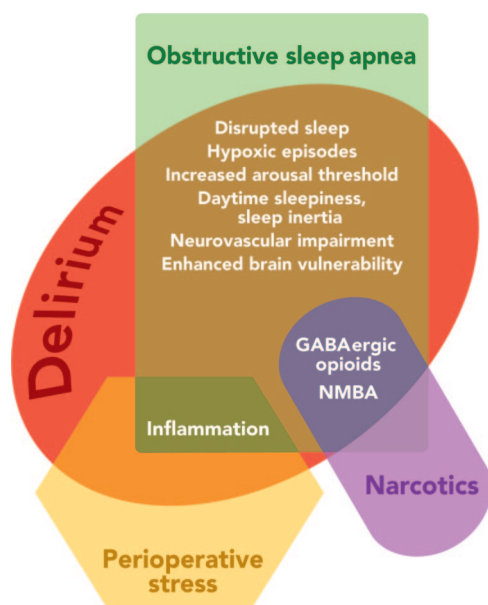


Fig. 1. Association between obstructive sleep apnea and postoperative delirium: Pathophysiologic considerations. The pathophysiology of both obstructive sleep apnea (green) and postoperative delirium (red) are multifactorial. Some signs and symptoms of obstructive sleep apnea represent possible precipitants of delirium. Both perioperative narcotics and stress may increase the severity of perioperative sleep disordered breathing and lower the threshold for delirium, potentially contributing to the observed association of obstructive sleep apnea and postoperative delirium. GABAergic = γ -aminobutyric acid-mediated; NMBA = neuromuscular blocking agent.

OSA is also, in part, an inflammatory disorder.⁶ Evidence suggests that chronic intermittent hypoxia and, possibly, sleep loss and fragmentation associated with OSA, increase the levels of various markers of inflammation and oxidative stress.⁶ Inflammation has been implicated in the pathophysiology of delirium, based on increased levels of proinflammatory cytokines and increased levels of C-reactive protein.⁷ Accordingly, it is possible that perioperative inflammation in combination with the baseline hyperinflammatory state associated with OSA may lead to delirium.

Previous work including studies using serum markers of neuronal damage also suggest that delirium may also be ischemically mediated. OSA patients show distinct reversible brain structural changes,⁸ and OSA is an independent risk factor for stroke.⁹ It may be that patients with OSA are more vulnerable to perioperative brain ischemia leading to POD. Also, along this line, sleep disorder breathing has recently been linked to the development of cognitive impairment. Patients with cognitive impairment have significantly higher rates of delirium, another possible pathway linking OSA and POD.¹⁰

Methodologic Considerations

All of this said, there are significant methodologic limitations to the present study, suggesting that the observed association between OSA and POD should be considered “hypothesis-generating” rather than “proven.” The association was not a

prespecified hypothesis, but rather arose in the setting of screening approximately 20 different patient characteristics/comorbidities for an association with POD. This approach increases the chance of making a type-1 error. Also, as the sample size is relatively small and the number of outcomes few, it is not possible for the authors to perform a rigorous multivariate regression analysis to fully account for the factors that might confound a causal relationship between OSA and POD. Further, there are important known risk factors for POD, including postoperative anemia, electrolyte abnormalities, renal dysfunction, infection, benzodiazepine and opiate use, and postoperative pain scores that were not collected in the present study and which therefore could not be analyzed as potential confounders.

Future Directions

The present study does, however, provide a strong rationale for adequately powered investigations specifically designed to test the hypothesis that OSA contributes to POD. Future studies will also need to establish whether strategies that mitigate the perioperative consequences of OSA, including titrating narcotics and neuromuscular blocking agents carefully to minimize residual effects on upper airway muscle strength, as well as promoting early mobilization, and utilizing continuous positive airway pressure,^{11–13} decrease the occurrence of POD. If it turns out that OSA does cause POD and that there are effective strategies to prevent it from doing so, then the paper by Flink *et al.* will be a landmark in the quest to address this most challenging perioperative complication.

Brian T. Bateman, M.D.,* Matthias Eikermann, M.D., Ph.D.† *Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. †Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, and Klinik fuer Anaesthesiologie und Intensivmedizin, Universitaetsklinikum Essen, Duisburg-Essen University, Essen, Germany. meikermann@partners.org.

References

1. Flink BJ, Rivelli SK, Cox EA, White WD, Falcone G, Vail TP, Young CC, Bolognesi MP, Krystal AD, Trzepacz PT, Moon RE, Kwatra MM: Obstructive sleep apnea and incidence of postoperative delirium after elective knee replacement in the nondemented elderly. *ANESTHESIOLOGY* 2012; 116:788–96
2. Steiner LA: Postoperative delirium. Part 1: Pathophysiology and risk factors. *Eur J Anaesthesiol* 2011; 28:628–36
3. Gottesman RF, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, Selnes OA, McKhann GM: Delirium after coronary artery bypass graft surgery and late mortality. *Ann Neurol* 2010; 67:338–44
4. Eikermann M: Respiratory concerns in the obese patient. In: Ortiz V, Wiener-Kronish J, eds. *Perioperative Anesthetic Care of the Obese Patient*. New York: Informa Healthcare, 2009, pp 12–20
5. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, Trzepacz PT: Phenomenology of delirium. Assessment of 100 adult cases using standardised measures. *Br J Psychiatry* 2007; 190:135–41
6. Lurie A: Inflammation, oxidative stress, and procoagulant and thrombotic activity in adults with obstructive sleep apnea. *Adv Cardiol* 2011; 46:43–66

7. Burkhart CS, Dell-Kuster S, Gamberini M, Moeckli A, Grapow M, Filipovic M, Seeberger MD, Monsch AU, Strebel SP, Steiner LA: Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2010; 24:555-9
8. Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, Alemanno F, Ferini-Strambi L: Obstructive sleep apnea: Brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011; 183: 1419-26
9. Drager LF, Polotsky VY, Lorenzi-Filho G: Obstructive sleep apnea: An emerging risk factor for atherosclerosis. *Chest* 2011; 140:534-42
10. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL: Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; 306:613-9
11. Hall JB, Schweickert W, Kress JP: Role of analgesics, sedatives, neuromuscular blockers, and delirium. *Crit Care Med* 2009; 37:S416-21
12. Alfille PH, Merritt C, Chamberlin NL, Eikermann M: Control of perioperative muscle strength during ambulatory surgery. *Curr Opin Anaesthesiol* 2009; 22:730-7
13. Kasotakis G, Schmidt U, Perry D, Grosse-Sundrup M, Benjamin J, Ryan C, Tully S, Hirschberg R, Waak K, Velmahos G, Bittner EA, Zafonte R, Cobb JP, Eikermann M: The surgical intensive care unit optimal mobility score predicts mortality and length of stay. *Crit Care Med* 2011; [E-pub ahead of print]

ANESTHESIOLOGY REFLECTIONS

Reversal of Fortune: Axis of Evil?



Invited as a curatorial consultant 25 years ago to the headquarters of the American Society of Anesthesiologists, I soon found myself wading through a basement room haplessly jammed full of old anesthesia machines. After resolving to inventory the larger machines by May of 1987 for the Wood Library-Museum, I shifted my focus to the adjoining small room. It was filled with map drawers and pharmaceutical cabinets. In a near corner of the room, a heavy 27-cubic-foot wooden crate was perched on top of something on wheels. Lifting the crate carefully, I was amazed to discover the prototype Cotton-Boothby Apparatus flipped upside down around the axis of its carrying handle (*right*). After dragging the crate down the hallway, I returned to the classic apparatus and flipped it respectfully upright around the axis of its carrying handle. Decades later, for display purposes, I would add compressed gas cylinders in colors contemporaneous with the apparatus (*left*), black cylinders for nitrous oxide and red ones for oxygen. (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.