http://dx.doi.org/10.5665/sleep.2094

Restoration of Autonomic Dysfunction in Children with Obstructive Sleep Apnea after Adenotonsillectomy

Commentary on Crisalli et al. Baroreflex sensitivity after adenotonsillectomy in children with obstructive sleep apnea during wakefulness and sleep. SLEEP 2012;35:1335-1343.

Hiren Muzumdar, MD; Raanan Arens, MD

Children's Hospital at Montefiore and Albert Einstein College of Medicine, Bronx, NY

Obstructive sleep apnea syndrome (OSAS) is associated with significant adverse neurobehavioural, cardiovascular, and metabolic outcomes. In recent years, studies of autonomic nervous system (ANS) function have demonstrated autonomic dysregulation in both children[1-3] and adults with OSAS.[4-7] Studies on ANS function and OSAS are important because they can potentially provide mechanistic pathways to explain some of the important morbidities associated with OSAS, such as hypertension, cardiovascular disease and insulin resistance,[8,9] and provide a better understanding of how treatment modalities can mediate outcomes of OSAS via the ANS.

Several methods have been used to study ANS responses in children with OSAS. Pulse arterial tonometry is a noninvasive technique for detecting sympathetic vasomotor tone in peripheral vessels using a finger plethysmograph. Increased sympathetic activity resulting in vasoconstriction corresponds to attenuation of the tonometry signal on the plethysmograph.[2] Heart rate variability estimates sympathetic to parasympathetic balance by calculating the ratio of low-frequency to high-frequency band power extracted from electrocardiographic recordings.[10] In general, the above methods have demonstrated sympathetic predominance in children with OSAS.[1,2,11] This sympathetic predominance may be mediated by the stimulation of peripheral arterial chemoreceptors by hypoxemia that results in increased sympathetic efferent traffic during hypoxemic episodes. In addition, respiratory events during sleep such as apnea/hypopnea may interrupt physiologic sympathetic inhibition during inhalation by vagal circuits.[12,13] Finally, arousals resulting from OSAS may also induce increased sympathetic output.[14]

Baroreflex sensitivity (BRS), in contrast, evaluates the baroreflex function of the ANS. Baroreceptors in the carotid sinus and aortic arch relay changes in arterial wall stretch to control centers in the brainstem from where autonomic outflow is modulated, producing changes in cardiovascular variables—heart rate (HR), heart contractility and vasoconstriction. The change in HR in response to changes in arterial blood pressure (ABP) provides a measure of BRS. It can be assessed in the time domain for ascending and descending sequences by the slope of regression of HR interval versus ABP and in the frequency domain by calculating the α index from spectral analysis of variability in HR interval and ABP. The α index is the square root of the integration of the ABP and HR interval power spectra where the coherence (a measure of correlation) between the HR and ABP changes is greater than 0.5. The α index is estimated at the low frequency band (0.04 to 0.15 Hz) and also the high-frequency band (0.15 to 0.5 Hz), which corresponds to the respiratory frequency. Changes in BRS are associated with an increased risk of developing hypertension and cardiovascular disease.[15,16]

In this issue of *SLEEP*, Crisalli and colleagues report on the extent of restoration of BRS changes in children with OSAS after adenotonsillectomy.[17] Their study follows a cross-sectional study by the authors[3] demonstrating altered BRS in young children with severe OSAS (obstructive apnea-hypopnea index > 5/hour) in the form of absence of the normal monotonic overnight increase in BRS in the ascending and descending sequences and high-frequency α index. Severe OSAS was also associated with lower temporal and spectral BRS indices compared to children with mild OSAS and matched controls who were healthy non-snoring children. Also, children with mild OSA had lower high-frequency α than control children. In the current study Crisalli and colleagues used an interventional model to test if ANS changes associated with OSAS are reversible by tracking BRS in these children with OSAS six months after tonsillectomy along with their matched controls. This is a convenient model since adenotonsillectomy usually resolves or significantly mitigates OSAS in children, as was the case in this cohort. The authors report increases in all BRS parameters in children with severe OSAS following adenotonsillectomy except the low-frequency α index, in addition to a restoration of the normal pattern of rising baroreflex gain during the night. BRS remained mostly unchanged in controls for the duration of the study. Of note, the magnitude of improvement in baroreflex gain correlated with the change in the apnea-hypopnea index and change in arousal index, but not the oxygen desaturation index. Thus BRS impairment correlated with severity of OSAS, but the data did not have sufficient resolution to discriminate between the effects of oxygen desaturation and arousals. Significantly, the temporal indices of BRS and the high-frequency (respiratory frequency associated) α index in children with severe OSAS remained lower than that of control subjects even after 6 months; this may be related to residual mild OSAS or a slow restoration of autonomic function. The low-frequency α index was not different in the children with severe OSAS from controls at six months, but this may be due to power issues

Submitted for publication August, 2012
Accepted for publication August, 2012
Address correspondence to: Raanan Arens, MD, FAASM, Children's Hospital at Montefiore, Pediatric Respiratory and Sleep Medicine; 3415 Bainbridge Avenue, Bronx, NY; Tel: (718) 515-2330; Fax: (718) 515-2608; Email: rarens@montefiore.org

from loss of some subjects to follow-up. The authors speculate that baroreflex suppression with OSAS leads to reduction in the direct inhibition of sympathetic discharge by the baroreceptor stimulation, in turn leading to sympathetic predominance, particularly at the respiratory frequency from disruption of the coordination of the respiratory drive, baroreflex sensitivity and sympathetic discharge.

Overall, this study demonstrates that OSAS in children alters BRS and that BRS impairments are reversible to a large extent, but may persist for prolonged periods after resolution of OSAS. These findings are in concordance with other studies that note improvement in ANS function using HRV measure in children with OSAS after adenotonsillectomy,[11,18] but the current study has the advantages of a prospective design, larger numbers and a comparison group of healthy children who were followed for an equivalent interval.

One of the important issues in sleep medicine is establishing the thresholds of sleep indices that are associated with pathophysiologic changes. While normative data have been established for polysomnography indices in children,[19,20] the diverse morbidities of OSAS may be associated with disparate levels of various polysomnography indices. This study suggests that autonomic dysfunction is likely to be present with an obstructive apnea hypopnea index $\geq$ 5/hour.

Overall, this study provides compelling evidence of autonomic dysfunction caused by OSAS in children that is at least partially reversible with appropriate treatment. However, several additional questions are raised by these findings. How strongly is the biological effect of altered ANS function associated with clinical outcomes such as hypertension? Do children with significant persistent OSAS have a greater likelihood of complications in adult life because of prolonged exposure to OSAS? How effective are available treatments in preventing complications related to autonomic dysfunction? The answers to these interrelated questions will require carefully planned longitudinal studies and treatment trials powered by large numbers of subjects.

CITATION

Muzumdar H; Arens R. Restoration of autonomic dysfunction in children with obstructive sleep apnea after adenotonsillectomy. *SLEEP* 2012;35(10):1311-1312.

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

REFERENCES

1. Baharav A, Kotagal S, Rubin BK, Pratt J, Akselrod S. Autonomic cardiovascular control in children with obstructive sleep apnea. Clin Auton Res 1999;9:345-51.
2. O'Brien LM, Gozal D. Autonomic dysfunction in children with sleep-disordered breathing. Sleep 2005;28:747-52.
3. McConnell K, Somers VK, Kimball T, et al. Baroreflex gain in children with obstructive sleep apnea. Am J Respir Crit Care Med 2009;180:42-8.
4. Bonsignore MR, Parati G, Insalaco G, et al. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2002;166:279-86.
5. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. Circulation 1998;98:1071-7.
6. Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE, Somers VK. Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. Hypertension 1998;32:1039-43.
7. Parati G, Di Rienzo M, Bonsignore MR, et al. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. J Hypertens 1997;15:1621-6.
8. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002;165:670-6.
9. Selim B, Won C, Yaggi HK. Cardiovascular consequences of sleep apnea. Clin Chest Med 2010;31:203-20.
10. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.
11. Muzumdar HV, Sin S, Nikova M, Gates G, Kim D, Arens R. Changes in heart rate variability after adenotonsillectomy in children with obstructive sleep apnea. Chest 2011;139:1050-9.
12. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation 1998;97:943-5.
13. Smith ML, Niedermaier ON, Hardy SM, Decker MJ, Strohl KP. Role of hypoxemia in sleep apnea-induced sympathoexcitation. J Auton Nerv Syst 1996;56:184-90.
14. Morgan BJ, Crabtree DC, Puleo DS, Badr MS, Toiber F, Skatrud JB. Neurocirculatory consequences of abrupt change in sleep state in humans. J Appl Physiol 1996;80:1627-36.
15. Genovesi S, Pieruzzi F, Giussani M, et al. Analysis of heart period and arterial pressure variability in childhood hypertension: key role of baroreflex impairment. Hypertension 2008;51:1289-94.
16. Lucini D, Zuccotti G, Malacarne M, et al. Early progression of the autonomic dysfunction observed in pediatric type 1 diabetes mellitus. Hypertension 2009;54:987-94.
17. Crisalli JA, McConnell K, VanDyke RD, et al. Baroreflex sensitivity after adenotonsillectomy in children with obstructive sleep apnea during wakefulness and sleep. Sleep 2012;35:1335-43.
18. Kaditis AG, Chaidas K, Alexopoulos EI, Varlami V, Malakasioti G, Gourgoulianis K. Effects of adenotonsillectomy on R-R interval and brain natriuretic peptide levels in children with sleep apnea: a preliminary report. Sleep Med 2011;12:646-51.
19. Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. Pediatrics 2006;117:741-53.
20. Traeger N, Schultz B, Pollock AN, Mason T, Marcus CL, Arens R. Polysomnographic values in children 2-9 years old: additional data and review of the literature. Pediatr Pulmonol 2005;40:22-30.