EDITORIAL

The multiple challenges of obstructive sleep apnea in children: morbidity and treatment

David Gozal and Leila Kheirandish-Gozal

Division of Pediatric Sleep Medicine, Department of Pediatrics, and Kosair Children's Hospital Research Institute, University of Louisville, Louisville, Kentucky, USA

Correspondence to David Gozal, MD, University of Louisville, Department of Pediatrics, KCHRI, 570 S. Preston Street, Suite 204, Louisville, KY 40202, USA
Tel: +1 502 852 2323; fax: +1 502 852 2215;
e-mail: david.gozal@louisville.edu

Current Opinion in Pediatrics 2008, 20:654–658

Purpose of review

To delineate some of the major morbid phenotypes that have emerged in pediatric obstructive sleep apnea (OSA), address new concepts in our understanding of OSA-associated morbidities, and elaborate on innovative therapeutic schemes that may improve outcomes for this condition. In addition, the conceptual framework whereby a childhood condition such as OSA can be linked to specific adult diseases will be presented.

Recent findings

OSA in children is a frequent condition that affects up to 3% of nonobese, otherwise healthy children. In recent years, increased awareness of OSA and changes in obesity rates in children have contributed to significant changes in disease prevalence and clinical presentation, such that distinct morbidity-related phenotypes have become apparent. Furthermore, oxidative stress and systemic inflammatory pathways are mechanistically involved in the pathophysiology of OSA-associated morbidity. Adenotonsillectomy, the treatment of choice for pediatric OSA, may not be as efficacious as previously thought. Alternative nonsurgical therapies have started to emerge and may become an essential component of treatment.

Summary

Pediatric OSA, particularly when obesity is concurrently present, is associated with substantial end-organ morbidities that primarily but not exclusively affect central nervous and cardiovascular systems. These morbidities are pathophysiologically mediated by inflammatory and free radical mediators. Although adenotonsillectomy remains the first line of treatment, more critical assessment of its role is needed, and incorporation of nonsurgical approaches to pediatric OSA seems warranted.

Keywords

adenotonsillectomy, corticosteroids, endothelial function, hypertension, inflammation, learning, obesity, obstructive sleep apnea

Curr Opin Pediatr 20:654–658

1040-8703

Introduction

Habitual snoring, a reliable indicator of increased upper airway resistance during sleep, is a frequent symptom during childhood, being reported in 10% of 2–8-year-old children [1–8], with decreases in this frequency after 9–10 years of age [9]. The polysomnographic criteria that allow for differentiation between innocent snoring (i.e., habitual snoring that does not lead to gas exchange abnormalities, sleep disruption, and/or to any morbid consequences) and snoring that leads to adverse consequences have yet to be defined (see pp. 000–000). Nevertheless, based on a consensus statement published in 2002 [10], it is estimated that the ratio between symptomatic habitual snoring and obstructive sleep apnea (OSA) revolves around 3 : 1–5 : 1 [11].

The prevalence and severity of overweight and obesity in children and adolescents have markedly increased worldwide in the last decades [12,13]. In the United States, the prevalence of childhood overweight doubled among children 6–11 years of age and tripled among 12–17-year-old children between 1980 and 2000 [14,15]. The presence of overweight or obesity has been repeatedly associated with an increased risk for OSA [16–22]. Indeed, whereas in the early years following description of the initial cases of pediatric OSA only 10% or even fewer of those who were diagnosed with OSA were obese, Mallory *et al*. [18] later showed the presence of polysomnographic abnormalities in 24% of 41 obese children. Similarly, Silvestri *et al*. [19] found evidence for partial airway obstruction in 66% and complete airway obstruction in 59% of the 32 obese children. In a case–control study design,

Redline *et al.* [16] examined risk factors for sleep-disordered breathing in children aged 2–18 years and found that the risk among obese children was increased by 4–5-fold. In fact, for every increment in BMI of 1 kg/m^2 beyond the mean BMI for age and sex, the risk of OSA increased by 12% [16]. Similar trends demonstrating an increased risk of OSA among obese and overweight children have been reported from all over the world. In this context, we have recently reported that the presence of obesity appears to modify the end-organ susceptibility to OSA and alters important aspects of the clinical syndrome, such that two distinct conditions can readily be identified [23•,24]. Notwithstanding the importance of such considerations, a detailed review of the differences between obese and nonobese children with OSA is beyond the scope of this article. Here, we will, therefore, examine some of the more salient aspects of end-organ morbidity associated with OSA in children and also critically assess the efficacy of current standard treatment approaches for this disease.

Morbidity of obstructive sleep apnea in children

As in adults afflicted with the disease, OSA in children is associated with an extensive array of morbidities, primarily affecting neurobehavioral and cardiovascular systems [25•,26••,27••]. However, although a dose-dependent relationship between the severity of OSA and the magnitude of end-organ dysfunction has emerged, there is significant variability in the presence of clinically meaningful deficits [28–31]. Furthermore, despite the traditional view that habitual snoring is essentially a benign condition, we have recently shown that such children display a higher risk for neurobehavioral deficits, albeit less severe than the deficits found in children with OSA [30,31]. For example, higher snore-induced arousal indices in young infants will be associated with reduced scores on standardized mental developmental assessments, thereby consolidating the concept that snoring is not just an innocent noise during sleep, and that, in fact, habitual snoring may represent the mildest component of the disease spectrum [32]. Thus, at any given level of OSA severity, there will be children with a spectrum of cognitive or cardiovascular function ranging from normal range to severe alterations even in the low range of severity of sleep-disordered breathing. The obvious question for such variable findings is 'why?' and this will be addressed after some of the proposed mechanisms mediating OSA-induced morbidity are reviewed.

Potential mechanisms of end-organ injury in pediatric obstructive sleep apnea

Obviously, the consequences of OSA can be ascribed to the interactions between the nocturnal episodic hypoxemia, hypercapnia, and sleep fragmentation that characterize the disease. It is important to emphasize here that delayed treatment or no treatment of OSA may result in irreversible morbidity [33].

On the basis of rodent models of OSA, we and others have identified oxidative stress and inflammatory processes as major mediators of increased neuronal cell loss in brain regions underlying learning, behavior, executive function, and memory [34–42]. Furthermore, the intrinsic activity of proteins such as apolipoprotein E and the ability to promote the activation of signaling cascades underlying cell survival or those mediating neuronal cell repair or neuronal progenitors appear to modify the susceptibility to OSA [43–46]. Similar mechanisms have thus far been identified in regard to the cardiovascular complications that may arise from OSA [47–50,51•,52•,53].

The findings derived from animal models raise the possibility that the variance in OSA-associated central nervous system (CNS) or cardiovascular susceptibility may be explained, at least in part, by specific gene polymorphisms. Indeed, the presence of apolipoprotein E epsilon 4 allele was associated with an increased probability of abnormalities in cognitive function in children with OSA [54••]. Similarly, children who developed more prominent inflammatory responses [i.e., increased morning plasma C reactive protein (CRP) levels] were more likely to display altered neurobehavioral results when compared with children with a similar degree of respiratory disturbance but with normal CRP levels [55••]. Conversely, the higher the serum insulin growth factor 1 responses to OSA, the less likely was the presence of cognitive dysfunction [56]. As a corollary to such findings, particular gene polymorphisms are being identified to explain the variance in hypertension among patients with OSA [57].

As is the case for many diseases, extrinsic factors such as environment and lifestyle may markedly alter the susceptibility to end-organ injury. For example, overall intellectually enriched daily activities may be protective [58], and food and micronutrient intake and physical activity patterns may also play a role [59,60]. Thus, in addition to OSA disease severity, the extent of end-organ morbidity may be accounted for by genetic variance in defense and injury-related pathways, as well as by lifestyle and environmental conditions.

Obstructive sleep apnea as a childhood antecedent of adult disease

An important aspect that has recently emerged regarding OSA in children is the possibility that this disease may interact with other disorders to accelerate or modify their temporal and severity trajectories. This is not a novel concept [61••] and, indeed, fetal and early childhood

environments have been recognized as important determinants of the prevalence and clinical severity of several frequent diseases such as hypertension, diabetes, and ischemic heart disease [62–65]. We have recently found in a rodent model that exposure to intermittent hypoxia during sleep that mimics the deoxygenation–reoxygenation patterns of OSA in developing rats leads to marked and lifelong alterations in some of the primary mechanisms underlying regulation of blood pressure [66,67], and that, when such alterations occur in rats genetically predisposed to develop hypertension, the severity of blood pressure elevations is markedly augmented [68••]. Interestingly, endothelial dysfunction is present in nonobese children with OSA and is not reversed by treatment of OSA in a subset of children who presented with strong family history of premature cardiovascular disease [69••]. Taken together, we propose that OSA-induced mechanisms of morbidity may launch the activation of existing disease-related genes in a subset of genetically predisposed children, and, therefore, initiate and propagate the disease processes that mediate such adult-onset disorders, thus leading to their clinical manifestations and enhanced severity at much earlier stages of the lifespan.

Treatment of obstructive sleep apnea in children

OSA in children is most commonly associated with adenotonsillar hypertrophy, even when obesity is present, such that the currently recommended initial treatment consists of surgical removal of the adenoids and tonsils (T&A). In recent years, however, it has become apparent that the putatively favorable outcomes of T&A [70] may not be as favorable after all [71–73,74•,75•], particularly when OSA is severe preoperatively or when obesity is present. Indeed, the frequency of residual mild OSA after T&A is estimated at 45–50% with an additional 20–25% displaying moderate-to-severe OSA after surgery.

These findings have prompted a heated debate as to whether overnight sleep studies should routinely be conducted after T&A [76•,77•]. Additional unresolved issues include the choice of the surgical technique (e.g., cold surgery, coblation, and harmonic laser), the need for tonsillectomy and adenoidectomy vs. nonsurgical approaches [78,79], the use of one of these two surgical procedures alone, or whether tonsillotomy is preferable to tonsillectomy [80–82].

When residual OSA after T&A is moderate-to-severe, administration of nasal continuous positive airway pressure (CPAP) is usually preferred [83••]. However, the cost–benefit ratio of CPAP in milder cases of residual OSA probably does not justify its use, such that other approaches are being advocated. For example, anti-inflammatory therapy is increasingly being recognized as an alternative to surgery or as an effective intervention in residual mild OSA after T&A [83••,84–89]. For the sake of completeness, we should also mention that favorable experience with oral appliances and orthodontic approaches for treatment of OSA in children has been recently reported, even if the specific patient selection criteria for such interventions are yet to be delineated [90,91•,92•].

Conclusion

OSA in children is associated with substantial morbidities particularly affecting the central nervous and cardiovascular systems. The occurrence and magnitude of such end-organ dysfunction appear to be regulated not only by the severity of the underlying OSA, but also by specific gene variants and environmental and lifestyle patterns. Furthermore, it is possible that OSA in childhood may trigger the earlier onset and progression of diseases that usually become symptomatic during late adulthood. The conventional wisdom that T&A is all that is needed to effectively treat pediatric OSA needs to be urgently revisited, and the role of nonsurgical alternatives such as CPAP, anti-inflammatory agents, and oral appliances will need to be better defined through appropriate multicenter randomized trials.

Acknowledgements

D.G. is supported by National Institutes of Health grant HL65270, the Commonwealth of Kentucky Research Challenge for Excellence Trust Fund, and the Children's Foundation Endowment for Sleep Research. L.K.G. is supported by an investigator-initiated grant from Merck Company.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 752–753).

1 Ferreira AM, Clemente V, Gozal D, *et al.* Snoring in Portuguese primary school children. Pediatrics 2000; 106:E64.

2 O'Brien LM, Holbrook CR, Mervis CB, *et al.* Sleep and neurobehavioral characteristics in 5-7-year-old hyperactive children. Pediatrics 2003; 111:554–563.

3 Urschitz MS, Guenther A, Eitner S, *et al.* Risk factors and natural history of habitual snoring. Chest 2004; 126:790–800.

4 Ersu R, Arman AR, Save D, *et al.* Prevalence of snoring and symptoms of sleep-disordered breathing in primary school children in Istanbul. Chest 2004; 126:19–24.

5 Kaditis AG, Finder J, Alexopoulos EI, *et al.* Sleep-disordered breathing in 3680 Greek children. Pediatr Pulmonol 2004; 37:499–509.

6 Rosen CL, Larkin EK, Kirchner HL, *et al.* Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003; 142:383–389.

7 Montgomery-Downs HE, O'Brien LM, Holbrook CR, Gozal D. Snoring and sleep-disordered breathing in young children: subjective and objective correlates. Sleep 2004; 27:87–94.

8 Montgomery-Downs HE, Gozal D. Sleep habits and risk factors for sleep-disordered breathing in infants and young toddlers in Louisville, Kentucky. Sleep Med 2006; 7:211–219.

9 Corbo GM, Forastiere F, Agabiti N, *et al.* Snoring in 9- to 15-year-old children: risk factors and clinical relevance. Pediatrics 2001; 108:1149–1154.

10 Schechter MS; Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002; 109:e69.

11 Tang JP, Rosen CL, Larkin EK, *et al.* Identification of sleep-disordered breathing in children: variation with event definition. Sleep 2002; 25:72–79.

12 Magarey AM, Daniels LA, Boulton TJ. Prevalence of overweight and obesity in Australian children and adolescents: reassessment of 1985 and 1995 data against new standard international definitions. Med J Aust 2001; 174:561–564.

13 Lobstein T, Baur L, Uauy R, IASO International Obesity TaskForce. Obesity in children and young people: a crisis in public health. Obes Rev 2004; 5 (Suppl 1):4–104.

14 Ogden CL, Kuczmarski RJ, Flegal KM, *et al.* Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002; 109:45–60.

15 Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 2002; 288:1728–1732.

16 Redline S, Tishler PV, Schluchter M, *et al.* Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 1999; 159:1527–1532.

17 Marcus CL, Curtis S, Koerner CB, *et al.* Evaluation of pulmonary function and polysomnography in obese children and adolescents. Pediatr Pulmonol 1996; 21:176–183.

18 Mallory GB Jr, Fiser DH, Jackson R. Sleep-associated breathing disorders in morbidly obese children and adolescents. J Pediatr 1989; 115:892–897.

19 Silvestri JM, Weese-Mayer DE, Bass MT, *et al.* Polysomnography in obese children with a history of sleep-associated breathing disorders. Pediatr Pulmonol 1993; 16:124–129.

20 Sogut A, Altin R, Uzun L, *et al.* Prevalence of obstructive sleep apnea syndrome and associated symptoms in 3-11-year-old Turkish children. Pediatr Pulmonol 2005; 39:251–256.

21 Sulit LG, Storfer-Isser A, Rosen CL, *et al.* Associations of obesity, sleep-disordered breathing, and wheezing in children. Am J Respir Crit Care Med 2005; 171:659–664.

22 Chay OM, Goh A, Abisheganaden J, *et al.* Obstructive sleep apnea syndrome in obese Singapore children. Pediatr Pulmonol 2000; 29:284–290.

23 • Dayyat E, Kheirandish-Gozal L, Gozal D. Childhood OSA: one or two distinct disease entities? Clin Sleep Med 2007; 2:433–444.
Initial description of more than one phenotype for pediatric OSA.

24 Sans Capdevila O, Kheirandish-Gozal L, Dayyat E, Gozal D. Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. Proc Am Thorac Soc 2008; 5:274–282.

25 • Gozal D. Obstructive sleep apnea in children: implications for the developing central nervous system. Semin Pediatr Neurol 2008; 15:100–106.
Excellent insights into interactions between sleep disorders and CNS.

26 •• Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. Am J Respir Crit Care Med 2008; 177:369–375.
Thorough coverage of mechanisms underlying cardiovascular dysfunction in OSA.

27 •• Somers VK, White DP, Amin R, *et al.* Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Circulation 2008 ; 118:1080–1111.
Important statement on cumulative knowledge and future directions in the cardiovascular implication of OSA.

28 Amin RS, Kimball TR, Kalra M, *et al.* Left ventricular function in children with sleep-disordered breathing. Am J Cardiol 2005; 95:801–804.

29 Amin R, Somers VK, McConnell K, *et al.* Activity-adjusted 24-h ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. Hypertension 2008; 51:84–91.

30 O'Brien LM, Mervis CB, Holbrook CR, *et al.* Neurobehavioral implications of habitual snoring in children. Pediatrics 2004; 114:44–49.

31 O'Brien LM, Mervis CB, Holbrook CR, *et al.* Neurobehavioral correlates of sleep-disordered breathing in children. J Sleep Res 2004; 13:165–172.

32 Montgomery-Downs HE, Gozal D. Snore-associated sleep fragmentation in infancy: mental development effects and contribution of secondhand cigarette smoke exposure. Pediatrics 2006; 117:e496–e502.

33 Gozal D, Pope DW Jr. Snoring during early childhood and academic performance at ages thirteen to fourteen years. Pediatrics 2001; 107:1394–1399.

34 Kheirandish L, Gozal D, Pequignot JM, *et al.* Intermittent hypoxia during development induces long-term alterations in spatial working memory, monoamines, and dendritic branching in rat frontal cortex. Pediatr Res 2005; 58:594–599.

35 Row BW, Liu R, Xu W, *et al.* Intermittent hypoxia is associated with oxidant stress and spatial learning deficits in the rat. Am J Respir Crit Care Med 2003; 167:1548–1553.

36 Gozal E, Gozal D, Pierce WM, *et al.* Proteomic analysis of CA1 and CA3 regions of rat hippocampus and differential susceptibility to intermittent hypoxia. J Neurochem 2002; 83:331–345.

37 Xu W, Chi L, Row BW, *et al.* Increased oxidative stress is associated with chronic intermittent hypoxia-mediated brain cortical neuronal cell apoptosis in a mouse model of sleep apnea. Neuroscience 2004; 126:313–323.

38 Ramanathan L, Gozal D, Siegel JM. Chronic hypoxia leads to oxidative stress in the rat cerebellum and pons. J Neurochem 2005; 93:47–52.

39 Shan X, Chi L, Ke Y, *et al.* Manganese superoxide dismutase protects mouse cortical neurons from chronic intermittent hypoxia-mediated oxidative damage. Neurobiol Dis 2007; 28:206–215.

40 Li RC, Row BW, Gozal E, *et al.* Role of cyclooxygenase 2 in intermittent hypoxia-induced learning deficits in the rat. Am J Respir Crit Care Med 2003; 168:469–475.

41 Row BW, Kheirandish L, Li RC, *et al.* Platelet-activating factor receptor deficient mice are protected from experimental sleep apnea-induced spatial learning deficits. J Neurochem 2004; 89:189–196.

42 Li RC, Row BW, Kheirandish L, *et al.* Nitric oxide synthase and intermittent hypoxia-induced spatial learning deficits in the rat. Neurobiol Dis 2004; 17:44–53.

43 Kheirandish L, Row BW, Li RC, *et al.* Apolipoprotein E deficient mice exhibit increased vulnerability to intermittent hypoxia-induced spatial learning deficits. Sleep 2005; 28:1412–1417.

44 Goldbart A, Row BW, Kheirandish L, *et al.* Intermittent hypoxic exposure during sleep induces changes in CREB activity in the rat CA1 hippocampal region: water maze performance correlates. Neuroscience 2003; 122:585–590.

45 Goldbart A, Cheng Z, Brittian KR, Gozal D. Intermittent hypoxia induces time-dependent changes in Akt signaling pathway in the hippocampal CA1 region of the rat. Neurobiol Dis 2003; 14:440–446.

46 Gozal D, Row BW, Gozal E, *et al.* Temporal aspects of spatial task performance during intermittent hypoxia in the rat: evidence for neurogenesis. Eur J Neurosci 2003; 18:2335–2342.

47 Ryan S, Taylor CT, McNicholas WT. Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2006; 174:824–830.

48 Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 2005; 112:2660–2667.

49 Allahdadi KJ, Cherng TW, Pai H, *et al.* Endothelin type A receptor antagonist normalizes blood pressure in rats exposed to eucapnic intermittent hypoxia. Am J Physiol Heart Circ Physiol 2008; 295:H434–H440.

50 de Frutos S, Duling L, Alò D, *et al.* NFATc3 is required for intermittent hypoxia-induced hypertension. Am J Physiol Heart Circ Physiol 2008; 294:H2382–H2390.

51 • Dyugovskaya L, Polyakov A, Lavie P, Lavie L. Delayed neutrophil apoptosis in patients with sleep apnea. Am J Respir Crit Care Med 2008; 177:544–554.
Evidence of activation of neutrophils and increased inflammation in patients with OSA.

52 • Troncoso Brindeiro CM, da Silva AQ, Allahdadi KJ, *et al.* Reactive oxygen species contribute to sleep apnea-induced hypertension in rats. Am J Physiol Heart Circ Physiol 2007; 293:H2971–H2976.
More evidence on the role of reactive oxygen species in OSA-induced cardiovascular morbidity.

53 Lavie L, Dyugovskaya L, Lavie P. Sleep-apnea-related intermittent hypoxia and atherogenesis: adhesion molecules and monocytes/endothelial cells interactions. Atherosclerosis 2005; 183:183–184.

54 •• Gozal D, Capdevila OS, Kheirandish-Gozal L, Crabtree VM. APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. Neurology 2007; 69:243–249.
Conclusive study implicating gene variants in the pathophysiology of OSA-induced cognitive deficits.

55 Gozal D, Crabtree VM, Sans Capdevila O, *et al.* C-reactive protein, obstructive •• sleep apnea, and cognitive dysfunction in school-aged children. Am J Respir Crit Care Med 2007; 176:188–193.
Important evidence linking systemic inflammation and end-organ CNS morbidity in children with OSA.

56 Gozal D, Sans Capdevila O, Crabtree VM, *et al.* Plasma IGF-1 levels and cognitive dysfunction in children with obstructive sleep apnea. Sleep Med 2008. [Epub ahead of print]

57 Patel SR, Larkin EK, Mignot E, *et al.* The association of angiotensin converting enzyme (ACE) polymorphisms with sleep apnea and hypertension. Sleep 2007; 30:531–533.

58 Row BW, Goldbart A, Gozal E, Gozal D. Spatial pretraining attenuates hippocampal impairments in rats exposed to intermittent hypoxia. Neurosci Lett 2003; 339:67–71.

59 Goldbart AD, Row BW, Kheirandish-Gozal L, *et al.* High fat/refined carbohydrate diet enhances the susceptibility to spatial learning deficits in rats exposed to intermittent hypoxia. Brain Res 2006; 1090:190–196.

60 Burckhardt IC, Gozal D, Dayyat E, *et al.* Green tea catechin polyphenols attenuate behavioral and oxidative responses to intermittent hypoxia. Am J Respir Crit Care Med 2008; 177:1135–1141.

61 Barker DJ. The origins of the developmental origins theory. J Intern Med 2007; •• 261:412–417.
Comprehensive review of the evidence linking fetal and early childhood environment to adult diseases.

62 Joseph KS, Kramer MS. Review of the evidence on fetal and early childhood antecedents of adult chronic disease. Epidemiol Rev 1996; 18:158–174.

63 Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents. Pediatrics 2006; 118:1683–1691.

64 Barker DJ, Bagby SP. Developmental antecedents of cardiovascular disease: a historical perspective. J Am Soc Nephrol 2005; 16:2537–2544.

65 Eriksson JG, Forsén TJ, Kajantie E, *et al.* Childhood growth and hypertension in later life. Hypertension 2007; 49:1415–1421.

66 Soukhova-O'Hare GK, Cheng ZJ, Roberts AM, Gozal D. Postnatal intermittent hypoxia alters baroreflex function in adult rats. Am J Physiol Heart Circ Physiol 2006; 290:H1157–H1164.

67 Soukhova-O'Hare GK, Roberts AM, Gozal D. Impaired control of renal sympathetic nerve activity following neonatal intermittent hypoxia in rats. Neurosci Lett 2006; 399:181–185.

68 Soukhova-O'Hare GK, Ortines RV, Gu Y, *et al.* Postnatal intermittent hypoxia •• and developmental programming of hypertension in spontaneously hypertensive rats: the role of reactive oxygen species and L-Ca2+ channels. Hypertension 2008; 52:156–162.
Conclusive evidence linking increased severity of hypertension in genetically predisposed individuals to OSA during childhood.

69 Gozal D, Kheirandish-Gozal L, Serpero LD, *et al.* Obstructive sleep apnea and •• endothelial function in school-aged nonobese children: effect of adenotonsillectomy. Circulation 2007; 116:2307–2314.
Endothelial dysfunction is consistently present in children with OSA and may not be reversible in genetically susceptible individuals.

70 Lipton AJ, Gozal D. Treatment of obstructive sleep apnea in children: do we really know how? Sleep Med Rev 2003; 7:61–80.

71 Mitchell RB, Kelly J. Outcome of adenotonsillectomy for severe obstructive sleep apnea in children. Int J Pediatr Otorhinolaryngol 2004; 68:1375–1379.

72 Tauman R, Gulliver TE, Krishna J, *et al.* Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 2006; 149:803–808.

73 Guilleminault C, Huang YS, Glamann C, *et al.* Adenotonsillectomy and obstructive sleep apnea in children: a prospective survey. Otolaryngol Head Neck Surg 2007; 136:169–175.

74 Mitchell RB, Kelly J. Outcome of adenotonsillectomy for obstructive sleep • apnea in obese and normal-weight children. Otolaryngol Head Neck Surg 2007; 137:43–48.
Obese children are at increased risk for residual OSA after tonsillectomy and adenoidectomy.

75 Amin R, Anthony L, Somers V, *et al.* Growth velocity predicts recurrence of • sleep-disordered breathing 1 year after adenotonsillectomy. Am J Respir Crit Care Med 2008; 177:654–659.
Obesity, African–American ethnicity, severe OSA, and rapid weight gain after T&A are all risk factors for recurrence of OSA in children after tonsillectomy and adenoidectomy.

76 Friedman NR. Polysomnography should not be required both before and after • adenotonsillectomy for childhood sleep disordered breathing. J Clin Sleep Med 2007; 3:678–680.
Arguments against sleep studies in pediatric OSA.

77 Hoban TF. Polysomnography should be required both before and after • adenotonsillectomy for childhood sleep disordered breathing. J Clin Sleep Med 2007; 3:675–677.
Arguments in favor of performing sleep studies in pediatric OSA.

78 Brouillette RT, Manoukian JJ, Ducharme FM, *et al.* Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr 2001; 138:838–844.

79 Alexopoulos EI, Kaditis AG, Kalampouka E, *et al.* Nasal corticosteroids for children with snoring. Pediatr Pulmonol 2004; 38:161–167.

80 Hultcrantz E, Linder A, Markstrom A. Tonsillectomy or tonsillotomy? – A randomized study comparing postoperative pain and long-term effects. Int J Pediatr Otorhinolaryngol 1999; 51:171–176.

81 Shapiro NL, Bhattacharyya N. Cold dissection versus coblation-assisted adenotonsillectomy in children. Laryngoscope 2007; 117:406–410.

82 Kay DJ, Bryson PC, Casselbrant M. Rates and risk factors for subsequent tonsillectomy after prior adenoidectomy: a regression analysis. Arch Otolaryngol Head Neck Surg 2005; 131:252–255.

83 Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children •• with mild obstructive sleep apnea syndrome. Pediatrics 2008; 122:e149–e155.
Randomized, double-blind trial with crossover design showing the beneficial effects of intranasal corticosteroids in mild pediatric OSA.

84 Goldbart AD, Veling MC, Goldman JL, *et al.* Glucocorticoid receptor subunit expression in adenotonsillar tissue of children with obstructive sleep apnea. Pediatr Res 2005; 57:232–236.

85 Berlucchi M, Salsi D, Valetti L, *et al.* The role of mometasone furoate aqueous nasal spray in the treatment of adenoidal hypertrophy in the pediatric age group: preliminary results of a prospective, randomized study. Pediatrics 2007; 119:e1392–e1397.

86 Goldbart AD, Goldman GL, Li RC, *et al.* Differential expression of cysteinyl leukotriene receptors 1 and 2 in tonsils of children with obstructive sleep apnea and recurrent infection. Chest 2004; 126:13–18.

87 Kaditis AG, Ioannou MG, Chaidas K, *et al.* Cysteinyl leukotriene receptors are expressed by tonsillar T cells of children with obstructive sleep apnea. Chest 2008; 134:324–331.

88 Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. Am J Respir Crit Care Med 2005; 172:364–370.

89 Kheirandish L, Goldbart AD, Gozal D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. Pediatrics 2006; 117:e61–e66.

90 Villa MP, Bernkopf E, Pagani J, *et al.* Randomized controlled study of an oral jaw-positioning appliance for the treatment of obstructive sleep apnea in children with malocclusion. Am J Respir Crit Care Med 2002; 165: 123–127.

91 Villa MP, Malagola C, Pagani J, *et al.* Rapid maxillary expansion in children with • obstructive sleep apnea syndrome: 12-month follow-up. Sleep Med 2007; 8:128–134.
Long-term follow-up of the beneficial effects of orthodontic approaches in pediatric OSA.

92 Guilleminault C, Quo S, Huynh NT, Li K. Orthodontic expansion treatment and • adenotonsillectomy in the treatment of obstructive sleep apnea in prepubertal children. Sleep 2008; 31:953–957.
Preliminary favorable outcomes using a combination of surgical and orthodontic approaches for pediatric OSA.