Obstructive Sleep Apnea—An Overview of the Disorder and Its Consequences

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Sleep apnea, and particularly obstructive sleep apnea, is a common disorder that is characterized by repetitive partial or complete cessation of air flow, associated with oxyhemoglobin desaturation and increased effort to breath. Middle-aged obese men are at particular risk but the disorder is also present in women and young children. Because individuals with narrow airways and/or craniofacial anomalies may have increased risk for obstructive sleep apnea/hypopnea syndrome, dentistry can play a pivotal role in the identification and possible treatment of patients with this syndrome. This article reviews some of the basic aspects of this sleep-related disorder, its diagnosis, treatment, and consequences in both adults and children. (Semin Orthod 2004;10:63-72.)

Over the past two decades, medicine and dentistry have increasingly focused on breathing disorders during sleep. Although a number of disorders can be included under the term "sleep disordered breathing," this review will focus specifically on obstructive sleep-disordered breathing, or obstructive sleep apnea. The characteristics of obstructive apnea have been described in the medical and classical literature for decades, as in a 19th century paper by Broadbent in an 1877 issue of *The Lancet*: "There will be perfect silence through two, three, or four respiratory periods in which there are ineffectual chest movements; finally air enters with a loud snort, after which there are several compensatory deep inspirations."[1]

Apnea is characterized by a cessation of airflow for 10 seconds or longer. Hypopnea, in contrast, is characterized by a reduction, without complete cessation, in airflow or respiratory effort.[2] Obstructive sleep apnea/hypopnea syndrome (OSAHS) is known to be a frequent clinical condition in the general population. A prevalence of 2% in the adult female population and 4% in the adult male population has been reported by Young and coworkers.[3] More recent figures up to 4%[4,5] established OSAHS as second only to asthma in the prevalence of chronic respiratory disorders, depending on the diagnostic criteria used.[6]

The morbidity of OSAHS relates principally to the cardiovascular system.[7] Rigorous epidemiologic studies have shown that sleep apnea is a risk factor for the development of arterial hypertension, independent of associated obesity, alcohol intake, sex, and age.[8-11] Animal studies have shown that apnea causes arterial hypertension, which is reversible with treatment.[12] OSAHS patients have significantly more hypertension, ischemic heart disease, and cerebrovascular disease than individuals without OSAHS.[7,8-11,13,14] However, OSAHS patients have a high incidence of other coexisting cardiovascular risk factors such as obesity, hyperlipidemia, increased age, smoking history, and excessive alcohol intake, which potentially confounds the identification of an independent association of OSAHS with cardiovascular disease.[15]

The relationship between obstructive sleep apnea/hypopnea syndrome (OSAHS) and stroke is still under discussion, but increasing evidence demonstrates that OSAHS is an inde-

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pendent risk factor for stroke.[16] The contribution of repeated apnea-related hypoxic events to atherogenesis through initiation of oxidative stress is currently being investigated, hypothesizing a molecular biological association between the hypoxia/reoxygenation episodes of OSAHS and cardiovascular disease.[17] However, in rare cases, OSAHS could be a consequence of stroke, especially if the strokes are located in the brainstem.[16]

Among other consequences of sleep apnea, excessive daytime sleepiness (EDS), cognitive impairment,[18,19] impaired ability to operate a motor vehicle,[20] and an increased automobile accident rate[20,21] have been recently documented. The patients' relative risk to have an accident lies between 2.3 and 7.3 times that of nonapneic individuals.

A series of recent studies agreed that patients with OSAHS have a reduced quality of life.[22-27] There is a clear association between headache and sleep disturbances, especially headaches occurring during the night or early morning. However, the cause and effect of this relation is not clear.[28] Patients with headache also report more daytime symptoms like fatigue, tiredness, or sleepiness.[29] These symptoms contribute to their reduced quality of life. Identifying respiratory-related sleep disorders in chronic headache patients is worthwhile, as improvement of the headache may follow treatment of sleep disorders in this group.[29]

OSAHS affects mainly middle-aged individuals, resulting in increasing health costs and loss of working days. The medical cost of undiagnosed sleep apnea has been evaluated in a case-control study group of 358 obese patients with moderate OSAHS.[30] In the year before the diagnosis, mean annual medical costs were $2720 per patient, compared with $1384 for controls. The severity of sleep-disordered breathing was correlated with the magnitude of medical costs. The additional cost estimation for the entire USA was calculated at $3.4 billion each year.

It should be mentioned that there was no matching on body weight between patients and controls, so that the cost differences could be due to obesity and not to OSAHS. In addition, these cost estimations did not account for medical consequences of apnea-related traffic accidents.[31]

Physiology and Pathophysiology

Negative airway pressure is generated by the activity of the diaphragm and intercostal muscles during inhalation. To a large extent, the patency of the upper airway is dependent on the action of oropharyngeal muscles. These dilator and abductor muscles are normally activated in a rhythmic mode in coordination with each inspiration. When the negative pressure exceeds the force produced by these muscles, the pharynx will collapse, occluding the airway.[32]

Frequently, sleep apnea patients have constricted upper airways that increase the pharyngeal resistance during inspiration. This, in turn, necessitates an increase in pharyngeal dilator muscle contraction to maintain airway patency. Such an increase has been shown in OSAHS patients during wakefulness,[33] but was also shown to decrease in contraction during sleep, thus contributing to the development of obstructive apnea.[34] Interestingly, when compared with normals, OSAHS patients show greater pharyngeal dilator muscle contraction during sleep, suggesting that an imbalance between negative airway pressure and dilator muscle contraction is responsible for the obstruction, rather than a primary deficiency in muscle contraction.[6] A sustained increase in dilator muscle contraction in OSAHS could predispose these muscles to fatigue,[35] possibly aggravating the tendency to pharyngeal occlusion.[6]

Although this model explaining OSAHS pathophysiology needs to be studied much further, the role of negative intrapharyngeal pressure as a stimulus to dilator muscle contraction is reinforced by studies of the impact of nasal continuous positive air pressure (CPAP) on pharyngeal muscle function.[6] Nasal CPAP results in a marked decrease in both tonic and phasic contraction of the genioglossus muscle.[36]

A clear understanding of the pathophysiology of the disorder is essential to implementing the optimal treatment, as well as developing future therapeutic modalities. Our current treatment approaches have been based, to a large extent, on the principle of counteracting the factors that contribute to OSAHS pathophysiology.[6] CPAP therapy is based on counteracting the negative airway pressure during inspiration, and hypoglossal nerve stimulation was suggested to enhance pharyngeal dilator muscle contraction.[37]

Other procedures such as uvulopalatopharyngoplasty (UPPP) and mandibular advancement (either surgical or with a mandibular advancement oral appliance) are based on the principle of pharyngeal enlargement to reduce the degree of negative intrapharyngeal pressure during inspiration.[38,39] The translation of these basic concepts into realized therapeutic benefits does not occur consistently, especially in the arena of surgical management.[40] These difficulties with remediation emphasize the complex nature of the disorder.[6]

Diagnosis

Originally, sleep medicine began in academic research environments to investigate the physiology and psychophysiology of sleep and dreaming. Sleep research was largely the domain of psychiatry and psychology. During the past 2 decades, the mounting evidence of the significance of sleep disorders to health, and thus the clinical relevance of sleep, spurred growth in the field of sleep medicine aimed at diagnosis and treatment of sleep disorders. The historically research-based laboratory studies are still considered the primary standard for the diagnosis of sleep apnea.[41] The laboratory recording technique is called polysomnography (PSG), and was proposed by Holland and colleagues[42] in 1974 to describe the recording, analysis, and interpretation of multiple, simultaneous physiologic parameters. As a tool, PSG has been essential in the diagnosis for sleep-disordered patients and in the enhancement of our understanding of both normal sleep and its disorders.[43]

Polysomnography is a complex procedure that should be performed by a trained technologist. Using electrodes and other sensors, a routine clinical polysomnogram includes the monitoring of brain electrical activity (electroencephalogram, EEG), electro-oculography, electromyography, effort to breath (generally from both thoracic and abdominal sensors), nasal and oral airflow, oxygen saturation (oximetry), electrocardiography, and body position. Other more specialized studies may include additional measures, such as endoesophageal pressure.[44]

The major polysomnographic measurement used to determine if a patient is clinically diagnosed with sleep-disordered breathing has been the frequency of the respiratory events per hour of sleep. This measure provides the major index of severity of the disorder and generally is a combination of the number of apneas and hypopneas per hour of sleep. The apnea-hypopnea index (AHI), or more recently the respiratory disturbance index (RDI), has been shown to be a reproducible measure within a patient as well as a predictor of associated cardiovascular disease.[45] The severity of the accompanying oxygen desaturation and sleep fragmentation during polysomnography are combined with the clinical symptoms to assess the immediate consequences to the individual from the sleep-disordered breathing.[45]

While the definition of apnea is generally agreed on, the definition of hypopnea has been inconsistent. A duration of at least 10 seconds in adults was generally agreed on for both apnea and hypopnea. However, the inconsistency in the definition of hypopnea has been due to the inclusion or exclusion of different parameters, and the different methods used to measure them, eg, the degree of airflow or respiratory effort reduction, degree of oxyhemoglobin desaturation, and arousal from sleep.[2,41] An important recent development in the definition of various sleep apnea syndromes has been the report of a working group of the American Academy of Sleep Medicine,[46] which laid out the clinical criteria necessary for the diagnosis of a clinically significant sleep apnea syndrome and also proposed a grading of severity.[6]

It is now accepted that a diagnosis of clinically significant OSAHS should be accompanied by compatible signs and symptoms, and not based simply on an arbitrary AHI/RDI threshold.[3,47,48] The syndrome should be defined when an index of abnormal obstructed breathing events, or arousals caused by them, exceeds a threshold in a patient with clinical features or symptoms related to the abnormal respiratory pattern during sleep.[41] A recent suggestion by Kryger[41] stated that patients with daytime sleepiness who have more than 5 abnormal respiratory events per hour of sleep should be treated, or at the very least receive a clinical trial of nasal CPAP, is in agreement with the previously published consensus statement in 1999.[49]

The formulation of clear-cut guidelines for the assessment, management, and follow-up of OSAHS patients is essential.[50] In the near future,

the assessment of these patients will likely involve clinicians outside major sleep centers. The high prevalence of OSAHS, and the increasing availability of new simplified limited diagnostic systems, suggest this likelihood.[6] An expert consensus is required to establish the ideal combination of variables to be recorded by the new limited diagnostic systems; the oxygen saturation is still the only consistent variable common to such devices. The efficacy of home-based sleep studies has been recently reviewed. While offering improved sleep quality and cost savings, the risk of technically unsatisfactory results is still high due to the lack of technician supervision.[51] The benefits and limitations of these approaches need further evaluation.

Positive Airway Pressure Therapy

The first reported use of nasal continuous airway pressure (nCPAP or CPAP) for OSAHS in adults was by Sullivan and colleagues[52] in 1981. Their device consisted of intranasal tubes attached to a blower unit. In 1983, the nasal mask delivery system, similar to contemporary systems, was introduced.[53] Fundamentally, the application of a therapeutic level of CPAP results in immediate relief in the upper airway obstruction.

This benefit has been attributed to the CPAP functioning as a "pneumatic splint" for the upper airway.[54] Additional physiologic benefits of CPAP application have been shown to include improvement in the function of pharyngeal dilator muscles,[55] ventilator drive,[56] and upper airway morphology.[57] CPAP rarely results in serious side effects. However, about 25% of patients may develop nasal congestion with chronic use.[58]

The benefit of CPAP in treating the sleepiness associated with OSAHS has been well established.[59-63] The patient's perceived quality of life showed a significant increase after treatment.[59-63] Interestingly, the spouses of OSAHS patients also gained from CPAP therapy, as it eliminated the impairment of their own sleep due to the snoring and sleep disruption caused by bed partners.[64] Furthermore, data from a large uncontrolled study suggested a strong benefit from CPAP in reducing the frequency of driving accidents.[65] The reduced sleepiness, and the improved ability to steer a motor vehicle, were positive outcomes of CPAP therapy as shown in a recent prospective randomized placebo-controlled clinical trial (controlled with subtherapeutic CPAP administration).[63,66]

The usefulness of CPAP in reducing the cardiovascular consequences of OSAHS is still being determined.[67,68] However, the posttreatment improvement of potential surrogate markers for cardiovascular mortality such as blood pressure, endogenous catecolamine levels, and muscle sympathetic neural activity has been shown.[69,70] There is now convincing evidence of an independent association of OSAHS with hypertension,[7,9,11] and this association has been reinforced by recent randomized placebo-controlled studies demonstrating a reduction in blood pressure levels with CPAP therapy.[71,72] More recently, emerging evidence suggests that CPAP therapy reduces long-term morbidity and mortality from cardiovascular causes.[73,74]

While current effective management of moderate to severe sleep apnea is largely dependent on nasal CPAP, the process is still cumbersome. Study data demonstrate only moderately satisfactory patient compliance.[75,76] The recent review by Engleman and Wild[77] addressed the issue of compliance and stressed the importance of a multidisciplinary approach to the initiation and maintenance of CPAP therapy involving educational, behavioral, technological, and medical components. The authors advocated "high intervention" support for certain at-risk patients, as well as those where poor CPAP compliance is documented.

The introduction of automatically adjusting CPAP devices (auto-CPAP) over the past several years represents a significant advancement in CPAP technology since its inception in 1981. The device continuously adjusts the applied airway pressure to an "optimum" level throughout the night and appears to improve compliance. Upper airway resistance is influenced by many dynamic factors that may change, such as body position, sleep stages, sleep deprivation, body weight, and fluctuations of nasal congestion. Some of these factors may change within a single night.[32] Alcohol intake can also depress the tone and contractility of the pharyngeal muscles, resulting in higher pressure requirements to maintain pharyngeal patency.[78] Therefore, a single pressure level, as with standard CPAP, could result in a situation in which the pressure is excessive for parts of the night, but may be

insufficient at other times, particularly after alcohol consumption.[6]

After having been shown to improve compliance in comparison to standard CPAP,[79] auto-CPAP is expected to become more popular in the future as it facilitates the initiation and follow-up of the treatment, especially the process of optimal initial pressure titration, and the elimination of repeated titrations over prolonged years of therapy.[6]

Pediatric Aspects

Children can develop a sleep apnea syndrome similar to that seen in adults. Epidemiological reports suggest a relatively high prevalence of up to 2% of all children.[80,81] The frequency of snoring in the general pediatric population ranges from 8% to 27%.[82-85] Snoring is considered the hallmark of OSAHS in children. The definition of what constitutes pathology in a snoring child still needs to be clearly defined in terms of the clinical significance of a given index (AHI/RDI).[86] However, the decision to treat OSAHS is dependent on a thorough understanding of the morbidity associated with this problem. The prevention or cessation of morbidities constitutes the primary rationale for the treatment. In the pediatric patient, 3 major categories of morbidity can be defined: neurobehavioral, cardiovascular, and somatic growth.[87]

Neurobehavioral Aspects

Sleep fragmentation is considered to be relatively unusual in OSAHS pediatric patients.[88] Parental observations and objective sleep latency testing do not report excessive daytime sleepiness as a major symptom; thus it cannot be considered a predominant feature, in contrast with adult patients.[89,90] The major concern is the association of the OSAHS, and even snoring, with significant and at least partially reversible behavioral and learning deficits.[91-100] Gozal and colleagues[87,100] found higher OSAHS rates in a failing group of first graders, and that their school performance was improved significantly 1 year after surgical treatment of adenotonsillar hypertrophy. They also found that children who snore loudly and frequently during sleep are at a higher risk for lower grades in school years after the sleep-disordered breathing had resolved. They suggested that OSAHS imposes adverse and sustained neurocognitive deficits and diminished academic achievement, especially when it occurs during critical phases of brain growth and development. Early recognition and effective treatment of the disorder is thus very important.

Cardiovascular Aspects

Despite the paucity of studies addressing this area in children, the current evidence suggests children with OSAHS have elevated diastolic blood pressure that persists during wakefulness,[101] in addition to changes in left ventricular wall thickness, indicating elevated afterload and systemic blood pressure elevations.[102] Additional studies are needed to assess the implications of recurrent upper airway obstruction in children on autonomic regulatory mechanisms, and the possible development of more severe hypertension.[87]

Somatic Growth

Children with OSAHS have a higher risk for failure to thrive. The incidence of this consequence has not been systematically assessed; however, increased awareness and early diagnosis have reduced this problem in recent years.[91] The mechanisms underlying the process of growth retardation in OSAHS are not fully understood. Dysphagia and loss of appetite are possible reasons in a minority of cases. Marcus and coworkers[103] postulated that the increased respiratory effort during sleep leads to increased metabolic expenditure and slower weight gain in these children. OSAHS treatment has been associated with decreases in energy expenditure and weight gain. A hormonal mechanism has been recently suggested to explain this effect. Decreased insulin growth factor-1 may account for the slower growth in some OSAHS children.[104] Weight gain has been reported after treatment, even in obese subjects.[105]

Intervention

Although the full extent of the morbidity of OSAHS in children has not been determined, our current knowledge of the adverse consequences necessitates early and effective intervention to treat this condition. It is widely accepted

that once the diagnosis of OSAHS has been established, the first line of treatment is the surgical removal of the enlarged tonsils and/or adenoids. However, the effectiveness of this treatment needs to be further established.[87] The exact influence of preoperative severity on the effectiveness of the surgical procedure still needs clarification. One study suggested that children from certain ethnic minorities, obese children, and those with a family history of sleep-disordered breathing were at a higher risk for having residual OSAHS after tonsillectomy and adenoidectomy.[106] The establishment of pediatric criteria such as the RDI threshold at which tonsillectomy and adenoidectomy are indicated, and the identification of patient groups in need of postsurgical polysomnographic evaluation, are important clinical goals.

As for nonsurgical approaches, steroids do not appear to have a significant role in the management of pediatric OSAHS. On the other hand, noninvasive mask ventilation emerges as a viable secondary line of treatment. CPAP intervention in children appears to be safe but requires extensive behavioral training to achieve reasonable compliance. It is usually reserved for children with OSAHS in association with other medical conditions, and also for a few otherwise normal children, in whom a failed tonsillectomy and adenoidectomy procedure had culminated in residual postoperative severe OSAHS.[91]

A variety of conditions involving children have been associated with OSAHS: Down syndrome, Crouzon and Apert syndromes, Treacher-Collins syndrome, Pierre-Robin syndrome, cerebral palsy, and multiple other rare craniofacial disorders are included. The degree of obstruction in many of these conditions could be so severe as to warrant tracheotomy. The approach to the treatment of these patients is usually a highly individualized surgical approach to correct the craniofacial abnormalities and relieve the airway obstruction to prevent the need for tracheotomy. A variety of surgical techniques have been implemented to achieve these goals; they include maxillomandibular advancement, distraction osteogenesis, septoplasty, and turbinectomy. In addition to tonsillectomy and adenoidectomy, soft tissue procedures could include uvulopalatopharyngoplasty, uvulectomy, epiglottoplasty, and tongue reduction.

There seems to be an agreement that sleep studies need to be an integral part of the pre/postoperative workup to measure the success of the OSAHS treatment. Although the literature has a plethora of case-series studies of various conditions,[107-122] only few offered critical postoperative outcome assessment with polysomnography. In a prospective study of 18 cerebral palsy and OSAHS patients, surgery decreased the RDI from 7 to1.4, increased the lowest recorded oxygen saturation from 73.7% to 88.2%, and required tracheotomies in only 17% of the cases.[110] More recently, Cohen and colleagues[108] also reported outcomes of a variety of individualized procedures in 70 children. The average RDI was decreased from 25.9 to 4.4 postoperatively. The lowest recorded oxygen saturation increased from an average of 61% to 92% after surgery, while the tracheotomy rate was lowered to 9.6%. A prospective analysis of a subgroup from this study has suggested that surgery is most effective at ages greater than 12 months.[109]

Summary

Obstructive sleep apnea is a disorder that has significant medical and psychosocial consequences. As discussed in this review, this is a common, underdiagnosed disorder that affects both adults and children. Although recognized for centuries, its importance for individuals and society has only recently been appreciated. Because individuals with narrow airways and/or craniofacial anomalies may have increased risk for obstructive sleep apnea/hypopnea syndrome, dentistry can play a pivotal role in the identification and possible treatment of patients with this syndrome.

References

1. Broadbent WH. On Cheyne-Stokes' respiration in cerebral haemorrhage. Lancet 1877;1:307-309.
2. Mozer NJ, Phillips B, Berry DTR, et al. What is hypopnea anyway? Chest 1994;105:426-428.
3. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-1235.
4. Young T, Peppard P. Epidemiology of obstructive sleep apnea. In: McNicholas WT, Phillipson EA (eds). Breathing Disorders in Sleep. London, UK: WB Saunders, 2001, pp 31-43.
5. Duran J, Esnaola S, Rubio R, et al. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 years. Am Respir Crit Care Med 2001;163:685-689.

6. McNicholas WT. Sleep apnoea syndrome today: Much done, more to do. Sleep Med Rev 2003;7:3-7.
7. Partinen M, McNicholas WT. Epidemiology, morbidity and mortality of the sleep apnoea syndrome. In: McNicholas WT (ed). Respiratory Disorders During Sleep. European Respiratory Monographs, Vol 3. Copenhagen, Denmark: Munksgard Press, 1998, pp 63-74.
8. Garcia Rio F, Racionero MA, Pino JM, et al. Sleep apnoea and hypertension. Chest 2000;117:1417-1425.
9. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-1384.
10. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnoea, and hypertension in a large community-based study: Sleep Heart Health Study. JAMA 2000;283:1829-1836.
11. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ 2000;320:479-482.
12. Brooks D, Horner RL, Kozar LF, et al. Obstructive sleep apnoea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997;99:106-109.
13. Shahar E, Whitney CW, Redline S, et al. for the Sleep Heart Health Study Research Group: Sleep-disordered breathing and cardiovascular disease cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19-25.
14. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: Final report on 128 patients. Sleep 1999;22:217-223.
15. Kiely JL, McNicholas WT. Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. Eur Respir J 2000;16:128-133.
16. Neau JP, Paquereau J, Meurice JC, et al. Stroke and sleep apnoea: Cause or consequence? Sleep Med Rev 2002;6:457-469.
17. Lavie L. Obstructive sleep apnoea syndrome—An oxidative stress disorder. Sleep Med Rev 2003;7:35-51.
18. Decary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnoea syndrome: A proposed neuropsychological test battery. Sleep 2000;23:369-381.
19. Lojander J, Kajaste S, Maasilta P, et al. Cognitive function and treatment of obstructive sleep apnoea syndrome. J Sleep Res 1999;8:71-76.
20. Juniper M, Hack MA, George CF, et al. Steering simulation performance in patients with obstructive sleep apnoea and matched control subjects. Eur Respir J 2000;1(suppl):590-595.
21. Young T, Blustein J, Finn L, et al. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep 1997;20:608-613.
22. Yang EH, Hla KM, McHorney CA, et al. Sleep apnoea and quality of life. Sleep 2000;23:535-541.
23. Hui DS, Chan JK, Choy DK, et al. Effects of augmented continuous positive airway pressure education and support on compliance and outcome in a Chinese population. Chest 2000;117:1410-1416.
24. Hoy CJ, Vennelle M, Kingshott RN, et al. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnoea/hypopnea syndrome? Am J Respir Crit Care Med 1999;159:1096-1100.
25. D'Ambrosio C, Bowman T, Mohsenin V. Quality of life in patients with obstructive sleep apnoea: Effect of nasal continuous positive airway pressure—a prospective study. Chest 1999;115:123-129.
26. Meslier N, Lebrun T, Grillier Lanoir V, et al. A French survey of 3, 225 patients treated with CPAP for obstructive sleep apnoea: Benefits, tolerance, compliance and quality of life. Eur Respir J 1998;12:185-192.
27. Bolitschek J, Schmeiser Rieder A, Schobersberger R, et al. Impact of nasal continuous positive airway pressure treatment on quality of life in patients with obstructive sleep apnoea. Eur Respir J 1998;II:890-894.
28. Jennum P, Jensen R. Sleep and headache. Sleep Med Rev 2002;6:471-479.
29. Paiva T, Farinha A, Martins A, et al. Chronic headaches and sleep disorders. Arch Intern Med 1997;157:1701-1705.
30. Kapur V, Blough DK, Sandblom RE, et al. The medical cost of undiagnosed sleep apnea. Sleep 1999;22:749-755.
31. Thierry Pieters T, Rodenstein DO. Therapeutic options in obstructive sleep apnoea: Have we made enough progress? Sleep Med Rev 2001;5:3-6.
32. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. Eur Respir J 1995;8:1161-1178 (review).
33. Mezzanotte WS, Tangel DJ, White OP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). Clin Invest 1992;89:1571-1579.
34. Mezzanotte WS, Tangel OJ, White OP. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. Am Respir Crit Care Med 1996;153:1880-1887.
35. Hers V, Liistro G, Oury M, et al. Residual effect of nCPAP applied for part of the night in patients with obstructive sleep apnoea. Eur Respir J 1997;10:973-976.
36. Deegan PC, Nolan P, Carey M, et al. Effects of positive airway pressure on upper airway dilator muscle activity and ventilatory timing. Appl Physiol 1996;81:476-479.
37. Schwartz AR, Eisele OW, Hari A, et al. Electrical stimu!ation of the lingual musculature in obstructive sleep apnea. Appl Physiol 1996;81:643-652.
38. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of upper airway in adults with obstructive sleep apnea syndrome. Sleep 1996;19:156-177.
39. Ferguson K, Ono T, Lowe A, et al. A short term controlled trial of an adjustable oral appliance versus nasal continuous positive airway pressure in the treatment of mild to moderate obstructive sleep apnea. Thorax 1997;52:362-368.
40. Sher AE. Upper airway surgery for obstructive sleep apnea. Sleep Med Rev 2002;6:195-212.
41. Kryger M. What data do we need to diagnose and treat obstructive sleep apnoea syndrome. Sleep Med Rev 2002;6:3-6.
42. Holland JV, Dement WG, Raynall DM. "Polysomnography": A response to a need for improved communication. Presented at the 14th Annual Meeting of the

Association for the Psychophysiological Study of Sleep, Jackson Hole, Wyoming, June 1974.
43. Broughton RJ. Polysomnography: Principles and applications in sleep and arousal disorders. In: Niedemeyer E, Lopes da silva F (eds). Electroencephalography: Basic Principles. Clinical Applications and Related Fields (ed 2). Baltimore, MD: Urban & Schwarzenberg, 1987, 687-724.
44. Keenan S. Polysomnography: Technical aspects in adolescents and adults. J Clin Neurophysiol 1992;9:21-31.
45. Meoli AL, Casey KR, Clark RW, et al. Hypopnea in sleep-disordered breathing in adults. Sleep 2001;24: 469-470.
46. Task Force of the American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22: 667-689.
47. Deegan PC, McNicholas WT. Predictive value of clinical features for the obstructive sleep apnoea syndrome. Eur Respir J 1996;9:117-124.
48. Flemons WW, McNicholas WT. Clinical prediction of the sleep apnea syndrome. Sleep Med Rev 1997;1:19-32.
49. Loube DI, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnoea patients: A consensus statement. Chest 1999;115:863-866.
50. McNicholas WT. Follow-up and outcomes of nasal CPAP therapy in patients with obstructive sleep apnoea syndrome. Monaldi Arch Chest Dis 2001;56:535-539.
51. Douglas NJ. Home diagnosis of the obstructive sleep apnoea/hypopnoea syndrome. Sleep Med Rev 2003;7: 53-59.
52. Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862-865.
53. Sanders MH, Moore SE, Eveslage J. CPAP via nasal mask: A treatment for occlusive sleep apnea. Chest 1983;83:144-145.
54. Abbey NC, Cooper KR, Kwentus JA. Benefit of nasal CPAP in obstructive sleep apnea is due to positive pharyngeal pressure. Sleep 1989;12:420-422.
55. Mortimore IL, Douglas NJ. Palatal muscle EMG response to negative pressure in awake sleep apneic and control subjects. Am J Respir Crit Care Med 1997;156: 867-873.
56. Lin CC. Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnoea syndrome. Eur Respir J 1994;7:2005-2010.
57. Ryan CF, Lowe AA, Li D, et al. Magnetic resonance imaging of the upper airway in obstructive sleep apnea before and after chronic nasal continuous positive airway pressure therapy. Am Rev Respir Dis 1991;144:939-944.
58. Pepin JL, Leger P, Veale D, et al. Side effects of nasal continuous positive airway pressure in sleep apnea syndrome: study of 193 patients in two French sleep centers. Chest 1995;107:375-381.
59. Ballester E, Badia JR, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:495-501.
60. Redline S, Adams N, Strauss ME, et al. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. Am J Respir Crit Care Med 1998;157:858-865.
61. Engleman HM, Martin SE, Kingshott RN, et al. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. Thorax 1998;53:341-345.
62. Engleman HM, Kingshott RN, Wraith PK, et al. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999; 159:461-467.
63. Jenkinson C, Davies RJO, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised prospective parallel trial. Lancet 1999;353: 2100-2105.
64. Beninati W, Harris CD, Herold D, Shepard Jr JW. The effect of snoring and obstructive sleep apnea Ion the sleep quality of bed partners: The spousal arousal syndrome. Mayo Clin Proc 1999;74:955-958.
65. Krieger J, Meslier N, Lebrun T, et al. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: A prospective study. Chest 1997;112:1561-1566.
66. Hack M, Davies RJ, Mullins R, et al. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. Thorax 2000;55:224-231.
67. Beninati W, Sanders MH. Optimal continuous positive airway pressure for the treatment of obstructive sleep apnea/hypopnea. Sleep Med Rev 2001;5:7-23.
68. Hedner J, Darpo B, Ejnell H, et al. Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: Cardiovascular implications. Eur Respir J 1995;8:222-229.
69. Wilcox I, Grunstein RR, Hedner JA, et al. Effect of nasal continuous positive airway pressure during sleep on 24-hour blood pressure in obstructive sleep apnea. Sleep 1993;16:539-544.
70. Waradekar NV, Sinoway LI, Zwillich CW, et al. Influence of treatment on muscle sympathetic nerve activity in sleep apnea. Am J Respir Crit Care Med 1996;153: 1333-1338.
71. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. Lancet 2002;359:204-210.
72. Faccenda JF, Mackay TW, Boon NA, et al. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;163: 344-348.
73. Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with ob-

structive sleep apnea: A 7-year follow-up. Am J Respir Crit Care Med 2002;166:159-165.
74. Doherty LS, Swan V, McNicholas WT. Long-term cardiovascular outcomes of patients with obstructive sleep apnoea not treated with nasal CPAP. Eur Resp J 2002; 20(suppl):294.
75. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993;147: 887-895.
76. McNicholas WT. Compliance with nasal CPAP in obstructive sleep apnoea: How much is enough. Eur Resp J 1997;10:969-970 (editorial).
77. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHs). Sleep Med Rev 2003;7:81-99.
78. Bonora M, Shields GI, Knuth SL, et al. Selective depression by ethanol of upper airway respiratory motor activity in cats. Am Rev Respir Dis 1984;130:156-161.
79. Meurice JC, Marc I, Series F. Efficacy of auto-CPAP in the treatment of obstructive sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1996;153:794-798.
80. Gislason T, Benediktsdottir B. Snoring, apneic episodes and nocturnal hypoxemia among children 6 months to 6 years old: An epidemiologic study of lower limit of prevalence. Chest 1995;107:963-966.
81. Ali NJ, Pitson D, Stradling JR. Snoring, sleep disturbance, and behaviour in 4-5 year olds. Arch Dis Child 1993;68:360-366.
82. Corbo GM, Fuciarelli F, Foresi A, et al. Snoring in children: Association with respiratory symptoms and passive smoking (published erratum appears in BMJ 1990;300:226). BMJ 1989;299:1491-1494.
83. Owen GO, Canter RJ, Robinson A. Snoring, apnoea and ENT symptoms in the paediatric community. Clin Otolaryngol 1996;21:130-134.
84. Hulcrantz E, Lofstrand TB, Ahlquist RJ. The epidemiology of sleep related breathing disorders in children. Int J Pediatr Otorhinolaryngol Suppl 1995;6:S63-S66.
85. Ferreira AM, Clemente V, Gozal D, et al. Snoring in Portuguese primary school children. Pediatrics 2000; 106(5):E64.
86. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. Am J Resp Crit Care Med 1996;153:866-878.
87. Lipton AJ, Gozal D. Treatment of obstructive sleep apnea in children: Do we really know how? Sleep Med Rev 2003;7:61-80.
88. Goh DY, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. Am J Respir Crit Care Med 2000;162:682-686.
89. Carroll JL, McColley SA, Marcus CL, et al. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest 1995;108:610-618.
90. Gozal D, Wang M, Pope DW. Objective sleepiness measures in pediatric obstructive sleep apnea. Pediatrics 2001;108:693-697.
91. Hill W. On some causes of backwardness and stupidity in children: And the relief of the symptoms in some instances by nasopharyngeal scarifications. BMJ 1889; 2:711-712.
92. Weissbluth M, Davis A, Poncher J, et al. Signs of airway obstruction during sleep and behavioral. Developmental and academic problems Dev Behav Pediatr 1983;4: 119-121.
93. Leach J, Olson J, Hermann J, et al. Polysomnographic and clinical findings in children with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 1992;118: 741-744.
94. Singer LP, Saenger P. Complications of pediatric obstructive sleep apnea. Otolaryngol Clin North Am 1990; 23:665-676.
95. Guilleminault C, Korobkin R, Winkle R. A review of 50 children with obstructive sleep apnea syndrome. Lung 1981;159:275-287.
96. Ali NJ, Pitson D, Stradling JR. Natural history of snoring and related behaviour problems between the ages of 4 and 7 years. Arch Dis Child 1994;71:74-76.
97. Chervin R, Dillon J, Bassetti C, et al. Symptoms of sleep disorders. Inattention and hyperactivity in children. Sleep 1997;20:1185-1192.
98. Owens J, Opipari L, Nobile C, et al. Sleep and daytime behavior in children with obstructive sleep apnea and behavioral sleep disorders. Pediatrics 1998;102:1178-1184.
99. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. Eur J Pediatr 1996;155:56-62.
100. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998;102:616-620.
101. Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998;157:1098-1103.
102. Amin RS, Daniels S, Kimball T, et al. Echocardiographic changes in children with obstructive sleep apnea. Sleep 2000;23:A99.
103. Marcus CL, Carroll JL, Koerner CB, et al. Determinants of growth in children with the obstructive sleep apnea syndrome. J Pediatr 1994;125:556-562.
104. Bar A, Tarasiuk A, Segev Y, et al. The effect of adenotonsillectomy on serum insulin-like growth factor-1 and growth in children with obstructive sleep apnea syndrome. J Pediatr 1999;135:76-80.
105. Soultan Z, Wadowski S, Rao M, et al. Effect of treating obstructive sleep apnea by tonsillectomy and/or adenoidectomy on obesity in children. Arch Pediatr Adolesc Med 1999;153:33-37.
106. Rosen CL, Morton S, Larkin E, et al. Persistence of sleep disordered breathing in children post-tonsillectomy. Am J Respir Crit Care Med 2001;163:A184.
107. Cohen SR, Ross DA, Burstein FD, et al. Skeletal expansion combined with soft-tissue reduction in the treatment of obstructive sleep apnea in children: Physiologic results. Otolaryngol Head Neck Surg 1998;119: 476-485.
108. Cohen SR, Simms C, Burstein FD, et al. Alternatives to tracheostomy in infants and children with obstructive sleep apnea. J Pediatr Surg 1999;34:182-186.
109. Januszkiewicz JS, Cohen SR, Burstein FD, et al. Age

related outcomes of sleep apnea surgery in infants and children. Ann Plast Surg 1997;38:465-477.
110. Cohen SR, Lefaivre JF, Burstein FD. Plast Reconstr Surg 1997:99:638-646.
111. Hoeve HLJ, Joosten KFM, van den Berg S. Management of obstructive sleep apnea syndrome in children with craniofacial malformation. Int J Pediatr Otorhinolaryngol 1999;49(suppl 1):S59-S61.
112. Bull MJ, Givan DC, Sadove AM, et al. Improved outcome in Pierre-Robin sequence: Effect of multidisciplinary evaluation and management. Pediatrics 1990; 86:294-301.
113. Strome M. Obstructive sleep apnea in Down syndrome children. A surgical approach. Laryngoscope 1986; 1340-1342.
114. Bower CM, Richmond D. Tonsillectomy and adenoidectomy in patients with Down syndrome. Int J Pediatr Otorhinolaryngol 1995;33:141-148.
115. Donaldson JD, Redmond WM. Surgical management of obstructive sleep apnea in children with Down syndrome. J Otolaryngol 1988;17:398-403.
116. Kosko JR, Derkay CS. Uvulopalatopharyngoplasty: treatment of obstructive sleep apnea in neurologically impaired pediatric patients. Int J Pediatr Otorhinolaryngol 1995;32:241-246.
117. Magardino TM, Tom LWC. Surgical management of obstructive sleep apnea in children with cerebral palsy. Laryngoscope 1999;109:1611-1615.
118. Seid AB, Martin PJ, Pransky SM, et al. Surgical therapy of obstructive sleep apnea in children with severe mental insufficiency. Laryngoscope 1990;100:507-510.
119. Kirk VG, Morielli A, Gozal D, et al. Treatment of sleep-disordered breathing in children with myelomeningocele. Pediatr Pulmonol 2000;30:445-452.
120. James D, Ma L. Mandibular reconstruction in children with obstructive sleep apnea due to micrognathia. Plast Reconstr Surg 1997;100:1131-1137.
121. Bell RB, Turvey TA. Skeletal advancement for the treatment of obstructive sleep apnea in children. Cleft Palate Craniofac J 2001;38:147-154.
122. Uemara T, Hayashi T, Satoh K, et al. A case of improved obstructive sleep apnea by distraction osteogenesis midface hypoplasia of an infantile Crouzon's syndrome. Craniofacial Surg Au: Pls verify or fix year 2001;12:73-77.