SLEEP DISORDERED BREATHING

Some Aspects of
RISK FACTORS, DIAGNOSIS AND THERAPY

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1  ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHI</td>
<td>Apnea and Hypopnea Index</td>
</tr>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<td>ASDA</td>
<td>American Sleep Disorders Association</td>
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<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
<tr>
<td>NB</td>
<td>Nose-breather</td>
</tr>
<tr>
<td>MB</td>
<td>Mouth-breather</td>
</tr>
<tr>
<td>ODI₄</td>
<td>Oxygen Desaturation (4%) Index</td>
</tr>
<tr>
<td>OI</td>
<td>Esophageal Index</td>
</tr>
<tr>
<td>ORO</td>
<td>Esophageal pressure, Respiratory flow and movement and Oximetry</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnea</td>
</tr>
<tr>
<td>OSAHS</td>
<td>Obstructive Sleep Apnea-Hypopnea Syndrome</td>
</tr>
<tr>
<td>OSLER</td>
<td>Oxford Sleep Resistance Test</td>
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<tr>
<td>Pes</td>
<td>Esophageal Pressure</td>
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<tr>
<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>RA</td>
<td>Respiratory Arousal</td>
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<tr>
<td>RDI</td>
<td>Respiratory Disturbance Index</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
</tr>
<tr>
<td>RERA</td>
<td>Respiratory Effort-Related Arousal</td>
</tr>
<tr>
<td>SDB</td>
<td>Sleep Disordered Breathing</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow Wave Sleep = Delta sleep</td>
</tr>
<tr>
<td>TIB</td>
<td>Time In Bed</td>
</tr>
<tr>
<td>TST</td>
<td>Total Sleep Time</td>
</tr>
<tr>
<td>UPPP</td>
<td>Uvulopalatopharyngoplasty</td>
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Abstract

2 ABSTRACT

The aim of Study I was to evaluate the effect of obesity on sleep disordered breathing (SDB) during pregnancy. In Study II, we tried to find a cost-effective system for the diagnosis of mild SDB by selecting polysomnography (PSG) parameters in a system that we called ORO [esophageal pressure (Pes), respiratory movements and airflow, and oximetry]. We compared ORO results with those of PSG. In Study III, we examined the effect of using a mouth-closing device (chinstrap) on mouth-leak with CPAP in SDB patients. In Study IV we evaluated the hypothesis that SDB patients who breathe mainly through their mouth during sleep would have more mouth-leak during CPAP, and therefore lower adherence to CPAP therapy, than those who breathe occasionally through their mouth.

Patients and Methods: I- We performed PSG studies in early and late pregnancy in 11 obese pregnant women and 11 non-obese pregnant controls. II- We also analysed ORO and PSG results in 88 subjects referred for evaluation of possible mild SDB who underwent PSG with Pes. III- Thereafter we conducted two PSG studies, one with the chinstrap in a random way on 15 consecutive patients with symptoms of mouth dryness and nasal obstruction and observed mouth-leak with CPAP. IV- Finally, we evaluated mouth breathing in CPAP-naive patients referred for snoring and daytime hypersomnolence. We included 30 patients with mouth breathing > 70% of total sleep time (mouth-breathers, MBs) and 21 with mouth breathing < 30% (nose-breathers, NBs). PSGs were performed with a computerized 24-channel polygraph. Pes was monitored by a piezoresistor pressure sensor. Sleep was manually scored in epochs of 30 seconds. Mouth breathing was calculated as percentage of total sleep time, with and without chinstrap, at baseline, at CPAP initiation and at 3-month CPAP therapy. Adherence (mean daily CPAP use in hours) was evaluated for 1 year.

Results: I- During early and late pregnancy, respiratory disturbance index, 4% oxygen desaturation and snoring times differed significantly between obese and non-obese women. II- The use of ORO for screening prior to PSG would have saved 5400 € per 100 patients compared to initial PSG, with sensitivity 64% and specificity 78%. III- With the chinstrap, both mouth-leak and the arousal index decreased significantly. However, snoring time showed a concomitant increase. Meanwhile, changes in the arousal index correlated positively with changes in mouth-leak. IV- Finally, we found that the adherence to CPAP therapy in NBs was better than in MBs, with 71% of NBs, but only 30% of MBs using CPAP daily for > 4 hours at 1 year follow-up.
We conclude that:

1 - Obesity is a significant risk factor for SDB during pregnancy.

2 - Use of the ORO system is not cost-effective for diagnosis of mild SDB.

3 - Mouth-leak during CPAP could be reduced by the chinstrap, nevertheless, the arousal index and mouth-leak remained unacceptably high.

4 - SDB patients with a high percentage of mouth breathing during sleep would be less adherent to nasal CPAP therapy than would patients exhibiting a low percentage of mouth breathing.
List of Original Publications

3 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals.


Some unpublished data have been included. The publishers of the original articles have kindly granted their permission to reprint the papers in this thesis.
4 INTRODUCTION

The history of snoring and sleep research can be divided into three major periods. First, there was a prehistoric phase during which everything was ignored; the French call this "le repos du guerrier" (Peyre JM, Schweiz Rundsch Med Prax 1996). Sleep was regarded mainly as a phase of recovery. A second period began around the beginning of last century: scientists still did not know anything, but it was felt that something needed to be done. Modern times began in the middle of last century with the first serious work by medical scientists who discovered and defined the obstructive sleep apnea syndrome (OSAS) (Peyre JM, Schweiz Rundsch Med Prax. 1996).

It is generally believed that the first description of OSAS was made by Charles Dickens in the Pickwick Papers and that the first medical description was published in 1956. In fact, some of the features of OSAS were described in antiquity and brief medical reports were published prior to the Pickwick Papers (Kryger MH, Arch Intern Med 1983).

Later, scientists used the term sleep disordered breathing (SDB), which includes breathing disturbances during sleep, i.e., snoring, hypopnea, apnea, and also partial upper airway obstruction without apnea or hypopnea (AASM Task Force, Sleep 1999). OSA is a common disorder characterized by repetitive pharyngeal collapse during sleep that causing snoring, hypopnea and apnea, and is associated with repetitive drops in blood oxygen saturation (Flemons WW, Chest 2003). When daytime hypersomnolence is manifests in these patients we talk about OSA syndrome = OSAS (Flemons WW, Chest 2003). To effectively restore pharyngeal patency, individuals have recurrent arousals from sleep, which lead to fragmentation of sleep. OSAS patients are usually male, obese and suffer from excessive daytime hypersomnolence (Flemons WW, Chest 2003).
Review of the Literature

5  Review of the Literature

5.1  Epidemiology of Sleep Disordered Breathing

5.1.1  Prevalence

5.1.1.1  Snoring

Snoring is very common in the general population; 35–45% of men and 15–28% of women report habitual snoring (Young T, N Engl J Med 1993).

5.1.1.2  Sleep Apnea

The prevalence of sleep apnea, based on an apnea and hypopnea index (AHI) (number of apneas plus hypopneas per hour of sleep) of 5 or higher, is 24% in males and 9% in females aged 30 to 60 years. In the same age group, the prevalence of moderate sleep apnea (AHI > 15) is 9% and 4% in males and females, respectively (Young T, N Engl J Med 1993).

The prevalence of sleep apnea syndrome, based on an AHI > 5/h and a self-reported hypsomolence, is 4% in males and 2% in females aged 30 to 60 years (Young T, N Engl J Med 1993).

5.1.2  Incidence

Estimating the incidence of sleep apnea (i.e., the occurrence of new cases over a given time interval) is susceptible to all the problems that plague attempts to measure OSA prevalence. In addition, there are special problems in identifying representative disease-free cohorts in which to measure new occurrences of OSA (Young T, Am J Respir Crit Care Med 2002).

5.1.3  Risk Factors

5.1.3.1  Obesity

Obesity is an increasingly significant health problem (McTigue KM, Ann Intern Med 2003). Over the last 4 decades, the prevalence of obesity (body mass index [BMI] > 30 kg/m²) has increased from 13% to 31% in adults and the prevalence of overweight (a BMI of 25 to 29.9 kg/m²) has increased from 31% to 34% (National Center for Health Statistics, US, 2002). Obesity is more common in
women, and being overweight is more common in men (National Center for Health Statistics, US, 2001). Obesity is also a risk factor for major causes of death, including cardiovascular disease, numerous types of cancer, and diabetes (U.S. Preventive Services Task Force, 1996), and is linked with markedly diminished life expectancy (Fontaine KR, JAMA 2003; Peeters A, Ann Intern Med 2003). In addition, osteoarthritis, gall bladder disease, sleep apnea, respiratory impairment, diminished mobility, and social stigmatization are associated with obesity (Roe DA, J Am Med Womens Assoc, 1976). Health risks are better established for obese persons than for overweight persons (McTigue KM, Ann Intern Med 2003). However, overweight status also carries risk (NHLBI, 1998). Even mild to moderate overweight in young adults predicts subsequent obesity (McTigue KM, Ann Intern Med 2002), and weight gain is associated with adverse outcomes (Juhaeri, Int J Obes Relat Metab Disord 2002). Estimated direct obesity costs are 5.7% of total US health expenditures (Wolf AM, Obes Res 1998).

There is a strong association between BMI and the severity and prevalence of OSA (Young T, J Respir Crit Care Med 2002). Studies in awake subjects failed to demonstrate a BMI effect on pharyngeal size (Mohsenin V, Chest 2001; Huang J, Respiration 1998). However, several studies reported that obesity increases upper airway collapsibility in awake (Ryan CF, Am J Respir Crit Care Med 1996; Suratt PM, Chest 1987; Rubinstein I, Am Rev Respir Dis 1988) and in sleeping subjects (Schwartz AR, Am Rev Respir Dis 1991). It is not known, however, whether increased collapsibility is the only relevant mechanism (Younes M, Am J Respir Crit Care Med. 2003). Most patients display a mix of periods of stable breathing and periods in which breathing is cyclic (repetitive obstructive hypopneas and apneas) (Younes M, Am J Respir Crit Care Med 2003). Lower functional residual capacity, higher metabolic rate, and lower arterial partial oxygen pressure (PO2) are characteristic of obesity. These factors would increase periods of unstable breathing (Younes M, Am J Respir Crit Care Med 2003).

Obese subjects suffer from social bias, prejudice and discrimination, on the part not only of the general public but also of health professionals, and this may make them reluctant to seek medical assistance (WHO report, Obesity 2000).

In summary, the effect of obesity on SDB is related to three factors: increased passive collapsibility, increased flow demand, and increased periods of unstable breathing. There is no evidence of impairment of compensatory mechanisms (Younes M, Am J Respir Crit Care Med 2003). Moreover, SDB may itself predispose individuals to worsening obesity because of sleep deprivation, daytime somnolence, and disrupted metabolism (Gami AS, Endocrinol Metab Clin North Am 2003).

5.1.3.2  Weight Gain

Any weight gain in adulthood is usually a result of an increase in fat stores, and
the risk of ill-health from increasing weight actually begins at a quite low BMI (Gill T, Asia Pac J Clin Nutr 2002). Unfortunately, this weight gain can be difficult to slow or reverse in the middle years because of physiological and behavioral changes that occur at this time of life (Gill T, Asia Pac J Clin Nutr 2002).

Relative to stable weight, a 10% weight gain predicts an approximate 32% increase in the AHI and a 6-fold increase in the odds of developing moderate-to-severe SDB (Peppard PE, JAMA 2000). Patients on long-term neuroleptic treatment have high rates of obstructive sleep apnea mediated via the weight gain produced by such medications (Winkelman JW, J Clin Psychiatry 2001). In addition, weight gain after heart transplantation is associated with an increased prevalence of sleep apnea (Javaheri S, Eur Heart J 2004).

A 10% weight loss predicts a 26% decrease in the AHI, therefore, modest weight control is likely to be effective in managing SDB and reducing new occurrence of SDB (Peppard PE, JAMA 2000). Moreover, OSA can be cured with sufficient lifestyle-mediated or surgical weight loss; however, in the absence of long-term weight maintenance, OSA returns with weight gain (Gami AS, Endocrinol Metab Clin North Am 2003).

5.1.3.3 Neck Circumference

Several investigators have emphasized the importance of obesity in SDB, both generalized obesity as reflected by weight or BMI, as well as regional obesity as reflected by parapharyngeal fat deposits (Shelton KE, Am J Respir Dis 1993) or neck circumference (Davies RJ, Eur Respir J 1990; Davies RJ, Thorax 1992; Hoffstein V, Eur Respir J 1992). Patients with sleep apnea have higher parapharyngeal tissue volume (either due to fatty deposits or tissue swelling) than nonapneic control subjects (Dancey DR, Chest. 2003). A short and fat neck in patients with sleep apnea is a very characteristic sign for SDB. Neck/height ratio is reported to be a significant predictor of AHI (Dancey DR, Chest. 2003). Moreover, the regional distribution of body fat is a more significant determinant of AHI than generalized obesity measured by BMI (Dancey DR, Chest 2003). Measurement of neck circumference has become a standard part of the physical examination of patients suspected of having sleep apnea (Schellenberg JB, Am J Respir Crit Care Med 2000; Strohl KP, Am J Respir Crit Care Med 1996).

5.1.3.4 Pregnancy

During pregnancy there is a decrease in pharyngeal dimensions (Pilkington S, Br J Anaesth 1995), in nasal patency (with 42% of women at 36 weeks gestation reporting nasal congestion and rhinitis) (Bende M, Laryngoscope 1999), and a 20% reduction in functional residual capacity (FRC) arising from elevation of the diaphragm to accommodate the enlarging uterus (Weinberger SE, Am Rev Respir Dis 1980). Sleep itself is also associated with a fall in FRC, therefore, maternal
oxygenation is decreased (Edwards N, Thorax. 2002). Increased airway closure may occur during tidal ventilation resulting in increased ventilation/perfusion mismatch (Holdcroft A, Anaesthesia 1977). However, the right-shift of the oxyhemoglobin desaturation curve in normal pregnancy facilitates the delivery of oxygen to the placenta and maternal tissue (Edwards N, Thorax 2002).

Progesterone is known to markedly up-regulate ventilatory drive at the level of the central chemoreceptors (Lyons HA, Pharmacol Ther 1976). As a result, there is a reduction in PaCO₂ and an increase in mean arterial pH, 7.44 compared with 7.40 in the non-pregnant women, with a tendency to central apnea during non-rapid eye movement sleep (N-REM) (Edwards N, Thorax 2002). In addition, upregulation of the central respiratory drive increases diaphragmatic effort, with greater negative inspiratory pressures that may increase the tendency for the upper airway to collapse during sleep (Edwards N, Thorax 2002).

The incidence of self-reported chronic snoring is markedly increased during pregnancy (14 to 23% compared to 4% in non-pregnants) (Loube MDI, Chest 1996; Franklin KA, Chest 2000). In addition, intermittent snoring was reported more often at the 6-month pregnancy visit (41%) than at the 6-week visit (18%) (Guilleminault C, Sleep Med 2000).

Weight gain during pregnancy was significantly higher in pregnant women reporting chronic snoring than in those reporting occasional snoring (Franklin KA, Chest 2000). Nevertheless, Guilleminault et al., (Sleep Med 2000) found no relation between mean weight gain at 6-months and snoring.

The frequency of OSAS during pregnancy is unknown due to the lack of longitudinal epidemiologic data (Meurice JC, Rev Neurol 2003). Meanwhile, pre-eclampsia is reported to be associated with increased incidence of snoring (Franklin KA, Chest 2000), and with an increased upper airway resistance during sleep (Connolly G, Eur Respir J 2001). In addition, upper airway dimensions were markedly reduced in pre-eclampsia compared to normal pregnancy or non-pregnant woman (Izci B, Am J Respir Crit Care Med 2003).

5.1.3.5 Age

The effects of age on the severity of apnea are unknown (Bixler E, Am J Respir Crit Care Med 1998). Epidemiological studies have shown that 15% of men and 5% of women between the ages of 30 and 60 years have SDB, defined as a respiratory disturbance index (RDI) > 10 (Young T, Arch Intern Med 1997). Using this definition adults over the age of 65 had considerably higher prevalence rates, reaching 70% for men and 56% for women (Ancoli-Israel S, Sleep 1991). Meanwhile, ten years later, the same author reported in a larger cohort studied over an 18-year period, that RDI did not consistently change with age and that any changes were not a function of age, but rather a function of changes in BMI (Ancoli-Israel S, Sleep Med 2001).
Review of the Literature

5.1.3.6 Gender

SDB is more common in men than in women despite the fact that women with SDB tend to be more obese and have smaller upper airway size than men (Young T, N Engl J Med 1993; Young T, Sleep 1997a; Bradley T, N Engl J Med 1986; Isono, J Appl Physiol 1997). The male dominance regarding the prevalence and severity of OSA disappears over the age of 55 years (Resta O, Eur J Clin Invest 2003). Moreover, the prevalence of OSA is higher in postmenopausal than in premenopausal women (Resta O, Eur J Clin Invest 2003).

The discrepancy between the lower prevalence of SDB, greater frequency of obesity and the smaller airway size in women compared to men suggests that a true gender difference underlies this condition. This gender difference has not been adequately explained on the basis of obesity, upper airway size and neural control of upper airway muscles (Brown, J Appl Physiol 1986; Martin, Eur Respir J 1997; Huang J, Respiration 1998). Nevertheless, men demonstrated more collapsibility of the upper airway during sleep than women when exposed to an external inspiratory load (Pillar G, Am J Respir Crit Care Med 2000). No gender difference was found in genioglossal or tensor palatini muscle activation in response to inspiratory resistive loading during sleep however, suggesting differences in upper airway anatomy and mechanics rather than neural control of upper airway muscles. Men tend to have a larger but more collapsible airway during mandibular movement than women and this, in part, may play a role in the positional dependency and severity of SDB in men (Mohsenin, Sleep Med 2003).

5.1.3.7 Smoking

Smoking is a major risk factor for respiratory diseases and the frequency of snoring increases with cigarette smoking (Shin C, Chest 2003). Nevertheless, smoking does not seem to be associated with increased apneic activity during sleep but rather with a decrease in nocturnal oxygen saturation (Hoffstein V, Sleep 2002; Casasola GG, Sleep Breath 2002). There may be several mechanisms by which smoking may affect OSA:

- Sleep instability may be increased by overnight reductions in nicotine blood levels (Young T, Am J Respir Crit Care Med 2002).
- A "rebound effect" may occur in which the acute effects of nicotine that favor increased upper airway tone are reversed during overnight nicotine withdrawal (Wetter DW, Arch Intern Med 1994).
- Smoking-related airway inflammation and disease may increase vulnerability to OSA (Young T, Am J Respir Crit Care Med 2002).
5.1.3.8 Alcohol

Nocturnal alcohol ingestion has been demonstrated to increase SDB (Issa FG, J Neurol Neurosurg Psychiatry 1982) as well as the RDI in snoring and non-snoring healthy men (Herzog M, Eur Arch Otorhinolaryngol 2003). Furthermore, patients with obstructive pulmonary disease showed an increase in SDB under the influence of alcohol (Dolly FR, Chest 1983; Easton PA, Sleep 1987). Moreover, alcohol may reduce the affinity of hemoglobin for oxygen (Van de Borne P, Hypertension 1997).

Alterations in chemoreflex sensitivity are unlikely to explain the effects of alcohol on sleep apnea. Nevertheless, after alcohol uptake there is an increase in inspiratory resistance and inspiratory effort. Both would increase the tendency of an unstable upper airway to collapse, and could account for the aggravation of OSA by alcohol (Dawson A, Alcohol Clin Exp Res 1997).

5.1.3.9 Hypnotics

The conventional approach is that benzodiazepines, particularly long-acting ones, should not be given to patients with OSA (Guilleminault C, J. Gerontol. 1984). These are sedative hypnotic drugs, i.e., central nervous system depressant drugs, that may adversely affect the control of ventilation during sleep (Guilleminault C, J. Gerontol 1984). Prescription of these drugs may worsen SDB, especially in patients with chronic obstructive pulmonary disease or cardiac failure (Guilleminault C, J. Gerontol 1984). Although benzodiazepines may reduce sleep fragmentation, their long-term use may also cause health problems, such as complete OSA in heavy snorers or short repetitive central sleep apneas in patients with recent myocardial infarction (Guilleminault C, Am J Med 1990). Meanwhile, a number of reports appear to support the use of short-acting benzodiazepines in the management of patients with central sleep apnea (Bonnet, Sleep 1990). A cyclopyrrolole hypnotic drug (zopiclone) at a dose of 7.5 mg has had no adverse effects on sleep architecture, respiratory parameters during sleep, or daytime sleepiness in patients with increased upper airway resistance (Loftso F, Eur Respir J 1997).

5.1.3.10 Nasal Obstruction

Nasal airway resistance is responsible for approximately 70% of the total airway resistance (Ferris B, J Appl Physiol 1964). Symptoms of nasal obstruction often correlate poorly with actual resistance to airflow. For example, patients who have atrophic rhinitis following extensive turbinate resection may perceive nasal obstruction despite objective evidence of excellent nasal patency (Rappai M, Chest 2003). Moreover, some patients may have significant nasal mucosal edema or nasal polyps but report no symptoms of nasal obstruction (Hollingsworth, Diagnosis and Treatment of Symptoms of the Respiratory Tract. Armonk, NY:
Review of the Literature

Futura 1997). In addition, nasal congestion measured subjectively by symptom score or by direct visualization is imprecise (Rappai M, Chest 2003).

Few studies have examined the relationship between increased nasal airway resistance and SDB (Rappai M, Chest 2003; Virkkula P, Acta Otolaryngol 2003). The nasal administration of lidocaine increased nasal and pharyngeal obstruction and was associated with a 4-fold increase in SDB events (White D, Am Rev Respir Dis 1985). There is, therefore, evidence to suggest that receptors in the nasopharynx may have an effect on muscle tone in the oropharynx (White D, Am Rev Respir Dis 1985). Several studies have investigated the effects of experimental nasal occlusion on sleep in normal subjects. Nasal occlusion was associated with disturbed sleep as manifested by increased arousals and/or awakenings, frequent sleep stage changes, less delta sleep and increased apneas and/or hypopneas associated with EEG arousals (Zwillich C, Am Rev Respir Dis 1981; Olsen K, Otolaryngol Head Neck Surg 1981; Lavie P, Acta Otolaryngol 1983; Taasan V, Laryngoscope 1981).

An epidemiologic study of middle-aged adults has shown that complaints of nasal congestion, particularly nocturnal nasal congestion, are a strong independent risk factor for habitual snoring (Young T, J Allergy Clin Immunol 1997). Similarly, patients with complaints of nasal congestion due to allergy have been reported to be 1.8 times (odds ratio) more likely to have moderate-to-severe SDB than are those without symptomatic nasal congestion (Young T, Arch Intern Med 2001). Moreover, Rappai et al., (Chest 2003) suggested that SDB can both result from, and be worsened by, nasal obstruction.

5.1.3.11 Genetics

OSA is considered as a complex genetic disorder. Descriptive studies from several countries have consistently shown familial aggregation of the AHI and symptoms of OSA (Gaultier C, Rev Neurol 2003). The genetics of OSA may differ among racial groups. Phenotypic markers of OSA have been identified, such as obesity, upper airway anomalies, and abnormal breathing control through which genes might act to increase susceptibility. These data suggest a common causal pathway regulating both OSA and obesity in Caucasian families (Gaultier C, Rev Neurol 2003).

5.1.3.12 Cranio-Facial Anomalies

The particular cranio-facial patterns observed in patients with OSAS are short craniospinal field, a retro-maxillary, a retro-mandibula, antero-inferior vertical excess of the face, and class II malocclusion (Sebille S, Rev Stomatol Chir Maxillofac 2003)
5.2 Respiratory Physiology during Sleep

5.2.1 Control of Breathing during Sleep

The major goal of the respiratory control system is a homeostatic one: to keep blood gases within such a range so that the metabolic functions of the body remain normal (Douglas NJ, Principles and Practice of Sleep Medicine, 2nd ed. Philadelphia: WB Saunders eds., 1994). The respiratory center receives and responds to three general types of information: chemical information (from chemoreceptors responding to PaO₂, PaCO₂, and pH), mechanical information (from receptors in the lung and chest wall), and behavioral information (from higher cortical centers) (Douglas NJ, Principles and Practice of Sleep Medicine, 2nd ed. Philadelphia: WB Saunders eds., 1994). Sleep alters both the breathing pattern and the respiratory responses to many external stimuli. The ventilatory response to hypoxia is decreased (Berthon-Jones M, Am Rev Respir Dis 1982) and the hypercapnic ventilatory response is depressed (Douglas NJ, Principles and Practice of Sleep Medicine, 2nd ed. Philadelphia: WB Saunders eds., 1994). The decrease in the slope of the ventilation-CO₂ response from wakefulness to non-rapid eye movement (NREM) sleep is approximately 50% (Douglas NJ, Am Rev Respir Dis 1982). Moreover, during rapid eye movement (REM) sleep, the ventilatory response to chemical stimuli is at its lowest (Douglas NG, Am Rev Respir Dis 1982).

5.2.2 Factors Affecting Upper Airway Patency during Sleep

5.2.2.1 Respiratory Muscles

The activity of the upper airway opening muscles decreases during NREM sleep, with a further marked reduction during REM sleep (Orem J, J Appl Physiol 1980). The diaphragm and accessory muscles of respiration are affected differently by sleep. Diaphragmatic function is largely preserved, which is essential for the maintenance of adequate ventilation during sleep. However, accessory muscle function is reduced, particularly during REM sleep, which may have adverse effects on lung mechanics (Douglas NJ, Principles and Practice of Sleep Medicine, 2nd ed. Philadelphia: WB Saunders eds., 1994). These changes contribute to hypoventilation and worsening ventilation-perfusion mismatching, particularly in patients with chronic lung disease such as chronic obstructive pulmonary disease (COPD), resulting in oxygen desaturation. (McNicholas WT, Monaldi Arch Chest Dis 2002). Furthermore, serotonin delivery is reduced to upper airway dilator...
motor neurons in sleep, and this contributes, at least in part, to sleep-related reductions in dilator muscle activity and upper airway obstruction (Veasey SC, Am J Respir Med 2003).

5.2.2.2 Body Position

Body position plays a significant role in the severity of SDB. The mandible tends to move inferiorly and posteriorly during sleep in the supine position (Miyamoto K, Arch Oral Biol 1999), a movement associated with decreased pharyngeal diameter and increased upper airway resistance (Kuna ST, Med Clin North Am 1985; Meurice JC, Am J Respir Crit Care Med 1996). Moreover, there is compelling evidence that pharyngeal collapsibility is increased in the supine position during sleep (Boudewyns A, Chest 2000; Neill AM, Am J Respir Crit Care Med 1997; Penzel T, Sleep 2001) as the pharyngeal airway is structurally surrounded by soft tissues such as the tongue and lateral soft tissue. Gravitational force is considered to be one significant determinant of the closing pressure of the airway (Watanabe T, Am J Respir Crit Care Med 2002). The number of obstructive events during sleep is much higher in the supine position than the lateral position in patients with SDB (Cartwright RD, Sleep 1984; Yildirim N, Am Rev Respir Dis 1991; Pevernage DA, Sleep 1992; Phillips BA, Chest 1986).

During sleep, neural inputs to pharyngeal dilator muscles are diminished, allowing anatomical forces to increase pharyngeal collapsibility. Whether increased collapsibility accounts for the entire positional effect on OSA severity is unknown (Younes M, Am J Respir Crit Care Med. 2003). The supine position probably impairs compensatory mechanisms by reducing the mechanical advantage of upper airway dilators. This could happen, for example, if the site of closure/flow limitation moves to a place where upper airway dilators are less effective or if upper airway muscle length is reduced in the supine position. This would reduce the muscle’s pressure-generating capacity (Isono S In: Principles and practice of sleep medicine, Kryger, 2nd ed. Philadelphia: WB Saunders; 1994). Alternatively, the reduced effectiveness may be related to changes in chemical control in the supine position through, for example, a lower FRC or lower PaO₂. Such changes would increase the chemical control loop gain, resulting in greater ventilatory instability (Younes M, Am J Respir Crit Care Med 2001).

5.3 Mouth Breathing

Healthy subjects with normal nasal resistance breathe almost exclusively through the nose during sleep (Fitzpatrick MF, Eur Respir J 2003).
5.3.1 Etiology

5.3.1.1 Nasal Obstruction

Oro-nasal breathing occurs in response to increased nasal obstruction, and the level of oro-nasal partitioning maintains an adequate level of respiratory resistance (Fitzpatrick MF, Eur Respir J 2003). When upper airway resistance is increased, limitation of flow occurs. Snoring indicates a mild degree of flow limitation, whereas apnea occurs when upstream pressure falls below a critical pressure (Goffart Y, Acta Otorhinolaryngol Belg 1993). Meanwhile, the distribution of ventilation between the mouth and nose in patients with allergic rhinitis may not correspond to the degree of nasal obstruction (Chowanetz W, Bull Eur Physiopathol Respir 1987). Furthermore, mouth breathing, particularly in children, does not always signify severe nasal obstruction (Chadha T, Chest 1987).

5.3.1.2 Other Causes of Mouth Breathing

Besides nose obstruction, other etiological factors can explain the development of mouth breathing (Limme M, Acta Otorhinolaryngol Belg 1993):

a - Facial malformation (Binder’s syndrome, Bimler’s microrhinodysplasia, Apert’s and Crouzon’s syndrome).

b - Alterations or deviations of the tongue (Robin’s syndrome, macroglossia, ankyloglossia).

c - Lip closure problems.

5.3.2 Consequences of Mouth Breathing

5.3.2.1 Impact on Craniofacial Growth

One school of thought holds that severely limited nasal breathing produces physiologic postural changes in the head and neck, which would have a direct effect on craniofacial growth, leading to the so-called Long Face Syndrome or Adenoid Facies (Toure L, Rev Belge Med Dent 1994). Moreover, oral breathing with nasal obstruction is associated with modifications in the shape of the palpebral fissure (“round eye”), by stretching of the facial mask, and with modifications of the orbital rims (“sad eye”) due to lack of naso-sinusal expansion (Gola R, J Fr Ophtalmol 2002).

Rappai et al. (Chest 2003) reported that oral breathing in children would lead to the development of facial structural abnormalities associated with SDB.
5.3.2.2 Impact on nasal CPAP Therapy

Interest in mouth breathing has increased recently as mouth-leak with nasal CPAP may compromise CPAP therapy (Berry RB, Sleep Med 2000). An attempt has been made to reduce nasal symptoms associated with mouth-leak by using heated humidification (Martins De Araújo MT, Chest 2000) or applying CPAP therapy through the mouth (Beecroft J, Chest 2003).

5.4 Classification of Sleep

Sleep consumes almost one-third of any human lifetime, yet its biological function remains unknown (Kadotani H, Genome Res 1998). Electrophysiological studies have shown that sleep is physiologically heterogeneous. Sleep onset is first characterized by light non-rapid eye movement (NREM) sleep (stage I and II) (Figure 1 and Figure 2), followed by deep NREM sleep or slow-wave sleep (delta sleep = stage III and IV) (Figure 3) and finally REM sleep (Figure 4). This sleep cycle is ~90 min long and is repeated multiple times during nocturnal sleep. REM sleep, also called paradoxical sleep, is characterized by low-voltage fast electroencephalogram activity, increased brain metabolism, skeletal muscle atonia, rapid eye movements, and dreaming (Kadotani H, Genome Res 1998). Sleep is usually represented by a hypnogram that shows sleep stages, movements and wake periods (Figure 5).

5.5 Definitions of Sleep Disordered Breathing

The polysomnographic spectrum of SDB includes: apnea, hypopnea, inspiratory flow limitation, REM sleep hypoventilation, periodic breathing, dysrhythmic breathing, and prolonged periods of sleep-onset respiratory instability (Thomas RJ, Sleep Med 2002; Meoli AL, Sleep 2001; AASM Task Force, Sleep 1999; Cracowski C, Am J Respir Crit Care Med 2001).

5.5.1 Apnea/Hypopnea

An apnea/hypopnea is an abnormal respiratory event (obstructive, central or mixed) (Figure 6) lasting > 10 seconds with a 50% decrease in baseline airflow amplitude, or an abnormal respiratory event lasting > 10 seconds with a smaller reduction in airflow amplitude, but with an associated desaturation/arousal (AASM Task Force, Sleep 1999).

5.5.2 Inspiratory Flow Limitation

Narrowing of the upper airway with sleep onset is a normal phenomenon (Wieand L, J Appl Physiol 1989), nevertheless it is not “all or none” in nature, and thus...
Figure 1: Sleep Stage I
A 30 seconds polysomnography recording showing a low-voltage electroencephalogram with few slow eye movements.
Figure 2: Sleep Stage II

A 30 seconds polysomnography recording showing the absence of eye movements and the presence of spindles and K complex.
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Figure 2: Slow Wave Sleep
A 30 seconds polysonomography recording showing Delta waves and the absence of eye movements.
Figure 4: Rapid Eye Movement Sleep
A 30 seconds polysomnography recording showing rapid eye movements and a low muscle tonus in the chin channel.
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**Figure 5: Hypnogram**

Normal hypnogram with 4 sleep cycles and sleep duration of > 6 hours. Delta sleep (stage III, IV) is more predominant during the first half of sleep. Bars represent REM periods.

**Figure 6: Obstructive, Mixed and Central Apneas**

A 60 seconds polygraphy recording showing > 10 seconds obstructive, mixed and central apneas.

Upper airway narrowing is a continuously variable phenomenon. The points along this continuum at which inspiratory resistance rises, snoring develops, hypoventilation ensues, or full apneas occur are fairly arbitrary but relatively easily identifiable. The level of hypoventilation required to define a respiratory event is quite arbitrary, usually reduced by 50%, and could vary considerably with the transducers and actual analysis algorithms employed in a sleep study (Redline S, Sleep 1997, Tsai WH, Am J Respir Crit Care Med 1999). The addition of attendant hypoxic dipping was advocated to improve consistency, but again the threshold to define a dip was arbitrary and 2%, 3%, or 4% have been used resulting very different event rates (Redline S, Am J Respir Crit Care Med
Figure 7: Normal Airflow and Stable Flow Limitation

A 4 minutes polygraphy recording. On the left: a normal nasal pressure profile and absence of snoring. On the right: flattening of the inspiratory (upside) part of nasal pressure curves indicating a limitation in the inspiratory flow. Notice the appearance of snoring. Respiratory movements are monitored using respiratory inductive plethysmography (RIP) measurements that are based on the detection of changes in volume of the chest and abdomen over the breathing cycle. SCSB = static charge sensitive bed with a low sampling rate of 10 Hz.

2000). Inspiratory flow limitation may be stable and non-progressive (periods of continuous high effort) (Figure 7) or unstable and progressive (crescendos) (Figure 8) (Thomas RJ, Sleep Med 2002)

5.5.3 Dysrhythmic Breathing

Dysrhythmic breathing is an irregular breathing rhythm that can be seen in neurological disorders such as Parkinson’s disease and multiple system atrophy [a neurodegenerative disorder of unknown aetiology (Wullner U, J Neurol Neurosurg Psychiatry 2004)], or less frequently in neurologically normal individuals (Thomas RJ, Sleep Med 2002) (Figure 9)

5.5.4 Arousal

Arousal is any shift in the EEG frequency to alpha or theta for at least 3 seconds (ASDA 3-second definition) (Figure 10) or at least 1.5 seconds (ASDA 1.5-second definition) (Figure 11), irrespective of any change in submental EMG during NREM sleep, but accompanied by a concurrent increase in submental EMG amplitude during REM sleep (ASDA, Sleep 1992).
5.5.5  **Respiratory-Related EEG Arousal**

Respiratory-Related EEG Arousal (Respiratory Arousal) is an arousal associated with apnea, hypopnea or respiratory effort related to increases in esophageal pressure (Adachi H, Sleep Med 2003) (Figure 12).

5.5.6  **Respiratory Effort-Related Arousal (RERA) Event**

RERA event is a sequence of breaths characterized by increasing respiratory effort leading to arousal from sleep, but which does not meet the criteria for apnea/hypopnea. The event must last > 10 seconds and show a pattern of progressively more negative esophageal pressure, terminated by a sudden change in pressure to a less negative level and an arousal (AASM, Task Force, Sleep 1999) (Figure 13).

5.6  **Severity Criteria**

The severity of obstructive sleep apnea syndrome (OSAS) has two components: severity of daytime sleepiness and overnight monitoring. The rating of severity
for the syndrome should be based on the most severe component (AASM Task Force, Sleep 1999).

5.6.1 Sleep Related Obstructive Breathing Events

RDI = apnea + hypopnea + respiratory effort-related arousals

5.6.1.1 Mild

RDI 5–15 events/hour of sleep

5.6.1.2 Moderate

RDI > 15–30 events/hour of sleep

5.6.1.3 Severe

RDI > 30 events/hour of sleep
**Figure 10: A > 3 seconds Arousal**

A shift to alpha for more than 3 seconds from sleep stage II associated with an increase in chin muscle tonus and eye movements, in a 30 seconds polysomnography recording.
Figure 11: A > 1.5 seconds Arousal

A shift to alpha for more than 1.5 seconds from sleep stage II associated with eye movement, in a 30 seconds polysomnography recording.
Figure 12: Respiratory Arousal

A shift to alpha for more than 3 seconds from sleep stage II proceeded by an obstructive hypopnea. At the beginning of the arousal, the patient snored twice during 2 inspiratory movements. The paradoxical respiration (abdominal and chest movements are in opposite direction) is abolished during the arousal.
Figure 13: Respiratory Effort-Related Arousal

Example of a Respiratory Effort-Related Arousal (RERA): an arousal proceeded by a sequence of breaths lasting at least 10 seconds and showing a pattern of progressively more negative esophageal pressure, terminated by a sudden change in pressure to a less negative level.
5.6.2 Sleepiness

5.6.2.1 Mild
Unwanted sleepiness or involuntary sleep episodes during activities that require little attention.

5.6.2.2 Moderate
Unwanted sleepiness or involuntary sleep episodes during activities that require some attention.

5.6.2.3 Severe
Unwanted sleepiness or involuntary sleep episodes during activities that require active attention.

5.7 Diagnosis
Patients with sleep apnea usually complain of daytime sleepiness, unrefreshing sleep (Chung SA, Can Fam Physician 2002), choking, nocturia (Umlauf MG, Sleep 2004), depression (Ohayon MM, J Clin Psychiatry 2003) and cognitive deficits (decreased general intellectual functioning, attentional functioning, learning abilities, executive functions, motor performance and memory) (Decary A, Sleep 2000). They may also present to non-sleep specialists with symptoms that are not immediately attributable to the condition.

5.7.1 History

5.7.1.1 Symptoms
Snoring is the most frequent symptom of SDB, occurring in 70–95% of patients (Whyte KF, Q J Med 1989), but it is a poor predictor of SDB (Flemons WW, Am J Respir Crit Care Med 1994). However, the absence of snoring makes SDB unlikely; only 6% of patients with SDB do not report snoring (Viner S, Ann Intern Med 1991). Nevertheless, 75% of patients who deny snoring turn out to snore when this is measured objectively (Hoffstein V, Sleep 1994). Because many patients are not aware of their heavy snoring and nocturnal arousals, OSA may remain undiagnosed; therefore, it is helpful to interview the bedpartner of a patient with chronic sleepiness and fatigue (Victor LD, Am Fam Physician 1999). SDB should also be suspected, in addition with the above mentioned symptoms, in most obese persons, as obesity is an important risk factor (Young T, J Respir Crit Care Med 2002). It is important to obtain information concerning recent weight gain and associated high blood pressure (Lindberg E, Eur Respir J 1998) (Table I).
<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Sleep medicine</th>
<th>Cardiology</th>
<th>Psychiatry</th>
<th>Neurology</th>
<th>Anaesthesia</th>
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<td>Hypertension</td>
<td>Depression</td>
<td>Epilepsy</td>
<td>Difficult intubation</td>
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<td>Respiratory failure</td>
<td>Daytime sleepiness</td>
<td>Nocturnal angina</td>
<td>Anxiety</td>
<td>Stroke</td>
<td>Sensitivity to sedation</td>
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<td>Fatigue</td>
<td>Myocardial infarction</td>
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<td>Hoarse voice</td>
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</tbody>
</table>

References:
1 = Schlosshan D, Thorax 2004
2 = Schnader J, Chest 1999
3 = Chung SA, Can Fam Physician, 2002
4 = Leung RS, Am J Respir Crit Care Med 200;
5 = Naegle B, Sleep 1995
6 = Mohsenin V, Stroke 2001
7 = Loh NK, Arch Intern Med 1999
8 = Loadsman JA, Br J Anaesth 2001
9 = Margel D, Urology 2004
10 = Rosenow F, J Sleep Res 1998
11 = Rombaux P, Acta Otorhinolaryngol Belg 2002
12 = Ing AI, Am J Med 2000
13 = Carlson JT, J Intern Med 1992
5.7.1.2 Questionnaires

5.7.1.2.1 The Basic Nordic Sleep Questionnaire

This questionnaire is largely used to screen SDB. It uses a five-point scale (1 = never, 5 = every night or almost every night) concerning snoring, sleep habits, work habits, daytime hypersomnolence and other sleep related disorders (Partinen M, J Sleep Res 1995).

5.7.1.2.2 Epworth Sleepiness Scale (ESS)

The ESS is a questionnaire that reliably quantifies the severity of daytime sleepiness using a scale from 0 to 24, with an abnormal result being over 7-11 (Johns MW, Sleep 1991). Recently, the author has, however, argued that the ESS does not measure sleepiness, but subjective sleep propensity (Johns MW, J Sleep Res 2000). ESS has a high degree of internal consistency and its scores relate to important clinical outcomes such as road traffic accidents and health-related quality of life (Engleman HM, Chest 1996). Its major advantages are the facts that the test is simple, quick, inexpensive, and has high test-retest reliability (AASM, Sleep 1999). Unfortunately, recent validity testing did not unequivocally support the use of the ESS as a measure of daytime sleepiness, sleep propensity or as a diagnostic tool (Miletin MS, Sleep Med 2003).

5.7.2 Physical Findings

Patients with suspected SDB are usually obese, with a predominance of central obesity and a high neck circumference/height ratio (Dancey DR, Chest 2003). As hypothyroidism may be associated with daytime fatigue, it is important to palpate the thyroid and, when necessary, to check for thyroid function. Clinical signs of acromegaly should be checked, as SDB is very common in this disease (Fatti LM, Pituitary 2001). A systematic check of the naso-pharyngeal sphere for nasal polyps, obstruction or deviated nasal septum, tonsillar enlargement, enlarged uvula, low lying soft palate, lateral peritonsillar narrowing, enlarged tongue and retrognathia is recommended (Zonato AI, Laryngoscope 2003).

Several studies tried to identify predictors of SDB like age, snoring history, witnessed apneas, hypertension, BMI, and neck circumference. The sensitivity and specificity of these predictors, or their combinations, were not satisfactory (Tsai WH, Am J Respir Crit Care Med 2003).

5.7.3 Overnight Studies

OSA is caused by interruptions in upper airway airflow during sleep that lead to oxygen desaturations and disruptions in sleep continuity. The apnea index describes the number of cessations of airflow per hour and the AHI indicates both
cessation and reductions of airflow. The RDI includes AHI plus RERA (AASM, Sleep 1999). An oxygen desaturation index of 4% (ODI_s) is usually used to measure SDB-related oxygen saturation falls.

5.7.3.1 Polysomnography

Traditionally, SDB has been diagnosed using overnight PSG (American Thoracic Society, Am Rev Respir Dis 1989) (Figure 14), monitoring many variables during sleep. These variables include an electroencephalogram, submental electromyogram, and electro-oculogram (all for sleep staging), respiratory airflow, respiratory effort, oxygen saturation, electrocardiogram, snoring, body position, and tibialis electromyogram (to detect nocturnal myoclonus) (Figure 15).

![Figure 14: In-laboratory Polysomnography](image)

The patient is connected to variable electrodes to monitor sleep, respiratory airflow, respiratory effort, oxygen saturation, electrocardiogram, snoring, body position and leg movements.
**Figure 15: Periodic Leg Movements**

A 10 minutes polygraphy recording showing periodic leg movements (nocturnal leg myoclonus) in both legs and a pulse variation. The patient complained of daytime hypersomnolence. The recording showed no sleep disordered breathing. LM = leg movement.

Some patients with disrupted snoring and excessive daytime sleepiness have a normal AHI on standard PSG (Guilleminault C, Ann Intern Med 1994). These patients present high respiratory effort-related arousals with few modifications in oxygen desaturation index. Monitoring esophageal pressure (Pes) during sleep in these patients demonstrates crescendo changes in intrathoracic pressures followed by frequent arousals or microarousals (Guilleminault C, Chest 1993) (Figure 13). In spite of the excellent information of respiratory effort provided by Pes monitoring, few sleep centers use it routinely. Factors preventing the widespread use of this technique include patient refusal or intolerance (Chervin RD, Am J Respir Crit Care Med 1997) and the requirement of additional technical expertise and expense (Argod J, Am J Respir Crit Care Med 2000).

Alternative methods to Pes monitoring include:

a - Semiquantitative analysis of transduced nasal pressure waveform (Norman RG, Sleep 1997) (Figure 7)

b - Quantitative respiratory inductive plethysmography (RIP) measurements based on the detection of changes in the volume of the chest and abdomen over the breathing cycle (Loube DI, Chest 1999) (Figure 7).
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c - Measurement of typical patterns in the high frequency band of static-charge-sensitive bed and end-tidal carbon dioxide (Polo O, Acta Physiol Scand 1992; Kirjavainen T, Eur Respir J 1996) (Figure 7).


e - Peripheral Arterial Tone (PAT) (Pillar G, Sleep Med 2003).

Nevertheless, Pes monitoring is still regarded as the gold standard for measuring respiratory effort (AASM Task Force, Sleep 1999).

The capacity for performing PSG is limited (Flemons WW, Am J Respir Crit Care Med 2004). The American Academy of Sleep Medicine recommends PSG for determining the severity of sleep apnea, and evaluating patients’ response to treatment (ASDA, Sleep 1997). Moreover, the American Thoracic Society recommends PSG for CPAP titration (ATS, Am J Respir Crit Care Med 1994).

If these guidelines were followed, on the basis of incidence estimates alone, 600 polysomnograms per 100,000 people per year would be required. This exceeds the actual capacity for PSG in most countries by a factor of 10 (Flemons WW, Am J Respir Crit Care Med 2004).

5.7.3.2 Oximetry and Other Ambulatory Methods

Pulse oximetry is a well-established tool routinely used in many settings of modern medicine to determine arterial oxygen saturation and heart rate. The decreasing size of pulse oximeters over recent years has broadened their spectrum of use (Netzer N, Chest 2001).

PSG is costly in terms of personnel, time, and money. This has led to attempts to simplify the diagnostic strategy by, for example, only using oximetry (Williams AJ, Chest 1991); however, the results have been conflicting (Netzer N, Chest 2001). Differing results are in part related to the fact that certain persons may show marked desaturations with recurrent apneic events that are easily detected using oximetry, whereas others may show little desaturation with repeated hypopneas that instead lead to arousal and sleep fragmentation (Guilleminault C, Chest 1993). A more important reason, however, for these differing results is the method of analysis of the oximetry data (Pack AI, Ann Intern Med 1993). However, overnight pulse oximetry is a good economical means to detect oxygen desaturation related to sleep apnea (Netzer N, Chest 2001).

Because in-home studies have the potential to reduce costs, a number of equipment manufacturers have developed various devices that are largely used at home instead of full in-laboratory PSG (Flemons WW, Am J Respir Crit Care Med 2004). These include a device that monitors heart rate variation, oximetry, body position, and snoring, primarily for screening purposes (Stoohs R, Chest 1992), a device that monitors all respiratory variables (Redline S, Chest 1991) and devices that record all variables, including the electroencephalogram, in the home (Figure
16). Several recent reviews and policy documents (ASDA, Sleep 1994; Rose SD, AHCPR Publication No. 99–E002, 1999; Flemons WW, Chest 2003; Cheson AL, Sleep 2003) indicate however, that the use of ambulatory approaches to diagnosis instead of full laboratory PSG cannot be recommended (Pack AI, Am J Respir Crit Care Med 2004).

5.7.3.3 Additional Methods for Evaluating SDB

Narrowing of the pharyngeal airway as a result of alterations in craniofacial morphology has been suggested in the etiology of SDB (Hoekema A, J Oral Rehabil 2003). Therefore, a number of techniques are available to determine the level of obstructive predominance in snoring and in OSA: lateral cephalography, awake endoscopy, awake endoscopy with the Muller maneuver, endoscopy

**Figure 16: Ambulatory Polysomnography**

A portable PSG (Embla®) that records all usual variables, including the electroencephalogram, in the home.
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during sleep, endoscopy with nasal continuous positive airway pressure during sleep, fluoroscopy, computed tomography scanning, magnetic resonance scanning, manometry, and acoustic reflections (Hoekema A, J Oral Rehabil 2003). Meanwhile, there is no reference standard for the determination of the predominant obstructive level during obstructive events (Faber CE, Sleep Breath 2003).

Cephalometric studies in SDB patients reveal alterations in the maxillomandibular complex (Battagel JM, European Journal of Orthodontics 1996), a more inferiorly positioned hyoid bone, a larger gonial angle, a smaller anterior cranial base, and altered anterior and posterior facial heights (Hoekema A, J Oral Rehabil 2003) (Figure 17).

5.7.4 Objective Measurement of Daytime Hypersomnolance

Objective tests for measuring daytime sleepiness have obvious advantages over subjective tests (for example, the ESS questionnaire) but are time consuming and may not reflect everyday activity (Schloshan D, Thorax 2004).

5.7.4.1 Multiple Sleep Latency Test

The Multiple Sleep Latency Test (MSLT) was designed to provide information concerning sleepiness and the presence of abnormal sleep-onset REM episodes. The subject lies in a quiet, dark, temperature-controlled room during a daytime PSG and is asked not to resist falling asleep. A minimum of four tests at 2-hour intervals beginning 1.5-3 h after wake-up are performed. A mean sleep latency of < 5 minutes indicates a pathological level of daytime sleepiness (Carskadon MA, Sleep 1986).

5.7.4.2 Maintenance of Wakefulness Test

The Maintenance of Wakefulness Test (MWT) is a daytime PSG procedure which quantifies wake tendency by measuring the ability to remain awake during soporific circumstances. The subject is instructed to remain awake for the 40 minutes testing period. A mean sleep latency of < 20 minutes indicates a pathological level of daytime sleepiness (Sangal RB, Chest 1992)

5.7.4.3 OSLER Test

The Oxford Sleep Resistance (OSLER) test (Figure 18) represents a simple alternative to the MWT (Bennett LS, J Sleep Res 1997). The occurrence of sleep is assessed behaviorally rather than by EEG monitoring. The subject is seated in quiet, dark, temperature-controlled room and is asked to respond by hitting a
**Figure 17: Cephalometry**

Diagrammatic representation of landmarks and uvuloglossopharyngeal measurements: ANS- Me = anterior lower facial height = distance between anterior nasal spine (ANS) and menton (Me); Na-Me = distance between nasion (Na) and menton; ph1-ph2: minimal distance between base of the tongue and posterior pharyngeal wall; U1-U2 = minimal distance from tip of uvula to posterior pharyngeal wall; PAS = posterior airway space; Sp1-Sp2 = width of soft palate; Tongue length = distance between the tip (T ant) and the intersection of mandible and pharyngeal surface of the tongue (T gon); Tongue height = thickness of the tongue (T sup to T ant - T gon line); S-Na/MP = angle between the anterior cranial baseline and mandibular line.

button each time a dim light flashes. The light-emitting diode flashes regularly for 1 second every 3 seconds. The subject is instructed to remain awake for the maximum testing period of 40 minutes. The test consists of four periods of 40 minutes each. When the subject fails to respond for 21 seconds (i.e., seven consecutive illuminations), the test ends and it is assumed that the subject has fallen asleep. Thus, the OSLER test reproduces many of the MWT characteristics, with the advantage of being a simpler and less expensive tool which does not require the presence of a trained technician (Mazza S, Am J Respir Crit Care Med 2002). A mean sleep latency of < 20 minutes indicates a pathological level of daytime sleepiness (Bennett LS, J Sleep Res 1997).
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\textbf{Figure 18: Osler Test}

The Oxford Sleep Resistance Test (OSLER) is a behavioral test that measures the patient's ability to maintain wakefulness. The subject is seated in a dark and quite room and asked to respond by hitting a button each time a dim light flashes. The light-emitting diode flashes regularly for 1 second every 3 seconds. The subject is instructed to remain awake for a maximum testing period of 40 minutes. The test consists of four periods of 40 minutes each. When the subject fails to respond for 21 seconds (i.e., 7 consecutive illuminations), the test is ended and it is assumed that the patient has fallen asleep.

\section*{5.8 Therapy}

CPAP is the mainstay of apnea treatment (Malhotra A, Lancet 2002), nevertheless, other (non-CPAP) treatments should be considered in three situations (Malhotra A, Lancet 2002).

\begin{itemize}
  \item[a] Individuals with clearly reversible causes for OSA (e.g., anatomical deformities such as adenotonsillary hypertrophy) should be considered for surgery.
  \item[b] Individuals who have failed or refuse CPAP treatment.
  \item[c] Patients with mild OSA. While treatment of mild apnea is the subject of many debates (Barnes M, Am J Respir Crit Care Med 2002). Malhotra et al, (Lancet 2002) believe that despite the potential advantages of conservative measures treatment with CPAP should be considered for such patients.
\end{itemize}
5.8.1 Conservative Measures

Conservative measures should always be emphasized (Laitenen LA, Respir Med 2003). Obesity is thought to be a major factor causing upper airway obstruction during sleep and is present in most patients with OSA (Aubert G, Sleep 1992). Weight loss of more than 3 kg has significantly reduced the frequency of snoring (Braver HM, Chest 1995). Moreover, a mean weight loss of 11 kg was associated with a significant reduction in ODI<sub>5</sub>, but the amount of weight loss needed for improvement of sleep apnea was unique to each individual (Lojander J, J Intern Med 1998). Meanwhile, dieting is a very difficult challenge for many individuals, and a weight loss of 10 kg is obtained by only half of the obese subjects with sleep apnea (Smith PL, Ann Intern Med 1985). Recently, a cognitive-behavioral weight loss program gave a satisfactory weight loss associated with improvement of OSA, while adding CPAP in the initial phase of the weight reduction program did not result in significantly greater weight loss (Kajaste S, Sleep Med 2004).

As upper airway resistance during sleep is higher in the supine than in the lateral position (Jordan AS, Am J Respir Crit Care Med 2003), avoiding the supine position may reduce snoring (Matsuzawa Y, Intern Med 1995) and the severity of sleep apnea (Victor LD, Am Fam Physician 2004). Individuals with documented positional apnea should be encouraged not to sleep on their backs (Malhotra A, Lancet 2002).

As nasal obstruction is a strong independent risk factor for habitual snoring (Young T, J Allergy Clin Immunol 1997), it is recommended that nasal patency be maintained in the treatment of snoring and sleep apnea (Matsuzawa Y, Intern Med 1995; Staevska MT, Curr Allergy Asthma Rep 2004).

Stopping smoking may also reduce the frequency of snoring (Shin C, Chest 2003). Nevertheless, smoking does not seem to be associated with increased apneic activity during sleep (Hoffstein, Sleep 2002; Casasola GG, Sleep Breath 2002). Avoidance of alcohol, hypnotics and sedatives is also recommended (Victor LD, Am Fam Physician 2004) as they may increase the tendency of an unstable upper airway to collapse (Dawson A, Alcohol Clin Exp Res 1997).

In OSA patients minimum SpO<sub>2</sub> may worsen after sleep deprivation (Desai AV, Sleep 2003), and both sleep fragmentation and sleep deprivation can exacerbate sleep pathology by increasing the length and pathophysiology of sleep apnea (Bonnet MH, Sleep Med Rev 2003). Moreover, the circadian timing system can potentially amplify or suppress sleep-related breathing abnormalities (Stephenson R, Sleep Med Rev 2003). Therefore, it is to wise to advise these patients to follow a regular sleep rhythm and to try to get sufficient sleep (Victor LD, Am Fam Physician 2004).
5.8.2 Continuous Positive Airway Pressure

In 1981, Sullivan et al. (Lancet 1981) reported reversal of OSA by continuous positive airway pressure applied through the nose (Figure 19). The CPAP pressure provides a pneumatic splint for the nasopharyngeal airway. It is a safe and simple treatment for OSAS (Sullivan CE, Lancet 1981). CPAP has remained the treatment of choice for OSA because of its effectiveness in elimination of apnea and improvements in apnea sequelae (Faccenda J, Am J Respir Crit Care Med 2001; Jenkinson C, Lancet 1999). Results of randomized trials have shown substantial improvements in both the sleepiness and neurocognitive performance of patients on nasal CPAP compared with those on placebo or subtherapeutic CPAP (Malhotra A, Lancet 2002). Treatment of SDB with CPAP also relieved erectile dysfunction in one-third of patients (Karacan I, J Sex Marital Ther 1995), and was followed by a reduction in motor vehicle collisions (George CF, Thorax 2001). Finally, treatment of obstructive sleep apnea should include a trial of CPAP in most cases (Malhotra A, Lancet 2002).

Figure 19: Autotitration CPAP

A seance of CPAP titration with an autotitrating device (AutoSet™). The patient receives a continuous positive airway pressure applied through the nose. Nasal air pressure, body position, SpO₂, and respiratory movements are monitored. The CPAP pressure provides a pneumatic splint for the nasopharyngeal airway that prevents snoring and obstructive apneas.
CPAP therapy is traditionally given via a nose mask. Patients should ideally keep their mouth closed; however, during sleep the mouth may fall open and leak may occur in 10-15% of cases (Rapoport DM, Sleep 1996). Adherence to CPAP therapy is far from optimal (Sin DD, Chest 2002; Pepin JL, Chest 1995). Low long-term adherence rates (60-70%) have to be regarded as a major challenge warranting further effort to ameliorate treatment of SDB (Verse T, Am J Respir Med 2003). Increased age and a prior uvulopalatopharyngoplasty (UPPP) are risk factors for low CPAP adherence (Janson C, Respiratory Medicine 2000). Recently, to increase patient comfort, alleviate nasal symptoms and improve CPAP adherence, a vast variety of masks have been made available. The use of oral (Beecroft J, Chest 2003) and fullface masks (Prosise GL, Chest 1994) are proposed (Figure 20). Moreover, addition of heated humidification devices to the ventilation circuit (Martins De Araújo, Chest 2000), intensive educational

![Figure 20: Fullface CPAP Mask](image)

A fullface CPAP mask is usually used to control mouth-leak with CPAP. It covers both the nose and mouth.
and behavioral support and regular follow-up have increased CPAP adherence (Chervin RD, Sleep 1997).

Newer positive pressure devices have gained popularity, and include bilevel positive airway pressure machines (different inspiratory and expiratory pressure) and autotitrating devices which provide variable pressure levels based on snoring, flow limitation, vibration, for example (Meurice JC, Am J Respir Crit Care Med 1996) (Figure 19). Results of clinical trials (Reeves-Hoche MK, Am J Respir Crit Care Med 1995) do not support the use of bilevel positive airway pressure over CPAP, since patient adherence is generally similar. Nevertheless, patients needing high CPAP pressures to eliminate disordered breathing events who complain about the expiratory work of breathing often prefer bilevel positive airway pressure (Berry RB, Sleep Med 2000). Results of studies assessing autotitrating devices have shown improved adherence in only a few trials however, with most finding little effect (Berry RB, Sleep Med 2000). Thus, routine use of such devices is difficult to justify because of their increased costs (Hudgel DW, Sleep 2000; Stradling, Thorax 1997; Berthon-Jones M, Sleep 1993).

5.8.3 Oral Devices

Oral appliances should be considered for (Ferguson KA, Clin Chest Med 2003; Malhotra A, Lancet 2002):

a - Patients who have failed or refused CPAP treatment.
b - Those with snoring or mild OSA.
c - Those who do not respond to surgery.

Mandibular advancing (Figure 21) and tongue retaining (Figure 22) devices are mechanical devices designed to prevent retroglottal collapse (Ferguson KA, Am J Respir Crit Care Med 1997). Although CPAP is clearly more effective than such devices, especially for severe symptoms, oral appliances also have a role in the treatment of OSA (Malhotra A, Lancet 2002). When directly compared in randomized trials, oral appliances are generally preferred by patients over CPAP, even when only partly successful in the elimination of disordered breathing events (Ferguson KA, Clin Chest Med 2003; Malhotra A, Lancet 2002). Short-term side effects are generally minor and are related to excessive salivation, jaw and tooth discomfort, and occasional joint discomfort. Serious complications are uncommon (Ferguson KA, Clin Chest Med 2003).

5.8.4 Pharmacotherapy

SDB is a prevalent disorder associated with substantial cardiovascular and neurobehavioral morbidity. Yet this is a disorder for which there are no widely effective pharmacotherapies. The pathophysiology of OSA, namely normal
respiration in waking with disordered breathing only in sleep, suggests that this disorder should be readily amenable to drug therapy (Veasey SC, Am J Respir Med 2003).

5.8.4.1 Hormone Replacement Therapy

Estrogen replacement therapy in postmenopausal women decreases the occurrence and frequency of sleep apnea but has no effect on partial upper airway obstruction or arterial oxyhemoglobin saturation (Polo-Kantola P, Obstet Gynecol 2003).

5.8.4.2 Ventilatory Stimulants

a- Medroxyprogesterone

It was reasoned that if medroxyprogesterone increased central responsiveness to CO$_2$ or hypoxia then the apnea cycle would be interrupted due to inhibition of the hypoventilatory portion of the apneic cycle (Hudgel DW, Am J Respir Crit Care Med 1998). Except in some hypercapnic OSA patients, however, the usefulness of medroxyprogesterone in the treatment of OSA has not been proven (Hudgel DW, Am J Respir Crit Care Med 1998).
**Review of the Literature**

**Figure 22: Tongue Retaining Device**

The device is attached to upper teeth during sleep. The U-shape attached posterior part goes down to hold the tongue in an anterior position, increasing the retroglossal space.

b- Thyroxine

Hypothyroidism is associated with sleep disordered breathing (Massumi RA, Am J Med 1964). Thyroid replacement treatment in patients with myxedema may ameliorate SDB, nevertheless it may not be totally effective in obese SDB patients with myxedema (Hudgel DW, Am J Respir Crit Care Med 1998).

c- Acetazolamide

Acetazolamide induces metabolic acidosis, which stimulates ventilation. Therefore, it has been hypothesized that acetazolamid would improve SDB. Meanwhile, several studies have shown that it may be helpful in those with central apnea (White DP, Arch Intern Med 1982).

d- Theophylline

Theophylline has some effect on central apnea, periodic breathing and OSA (Hudgel DW, Am J Respir Crit Care Med 1998). This effect could be explained, at least in part, by inhibiting the ventilatory depressant effect of adenosine, which has been found to be elevated in the peripheral blood of OSA patients (Findley LJ, J Appl Physiol 1988). In addition, theophylline may stimulate ventilation by other
mechanisms: increasing metabolic rate, stimulating hypoxic and hypercapnic ventilatory drives, and by improving respiratory muscle performance (Hudgel DW, Am J Respir Crit Care Med 1998). Theophylline also has a positive inotropic action on the cardiovascular system, which may indirectly improve the stability of breathing by decreasing circulation time, at least in congestive heart failure. These properties have led to its use in sleep-disordered breathing (Hudgel DW, Am J Respir Crit Care Med 1998).

e- Nicotine

Transdermal nicotine has been shown to worsen sleep quality and does not improve the apnea index (Zevin S, Am J Ther 2003; Davila DG, Am J Respir Crit Care Med 1994).

f- Opioid Antagonists

Suratt et al. (Bull Eur Physiopathol Respir 1986) found that doxapram infusion decreased the length of apneas, but it did not change the apnea index in four male OSA patients.

g- CO₂

The administration of CO₂ in a closed mask system has decreased obstructive apneas considerably (Hudgel DW, Am J Respir Crit Care Med 1998). Moreover, CO₂ may also be useful in the treatment of central sleep apnea. The ventilatory stimulation produced by CO₂ would eliminate the hypocapnia that leads to hypopnea and periodic breathing (Villiger PM, Neurology 1993).

5.8.4.3 Psychotropic Agents

Protriptyline, by decreasing the REM time, reduces the apnea time and the severity of arterial oxygen desaturation in patients with REM-associated OSA (Brownell LG, N Engl J Med 1982).

5.8.4.4 Medications for Weight Reduction

Weight reduction may improve SDB (Kajaste S, Sleep Med 2004). Researchers are using different distinct strategies with innovative anti-obesity drugs (Nisoli E, J Endocrinol Invest 2002): first, to reduce energy intake; second, to increase energy expenditure; third, to alter the partitioning of nutrients between fat and lean tissue. Orlistat (Xenical, Hoffmann-La Roche) is a powerful inhibitor of gastrointestinal lipase, reducing fat absorption (Ballinger A, Expert Opin Pharmacother 2000). In clinical trials, orlistat (120 mg t.i.d.) in combination with lifestyle modification and a hypocaloric diet induced significantly more weight loss than did diet alone (Ballinger A, Expert Opin Pharmacother 2000).
5.8.4.5 Medications to Improve Nasal Patency

Patients with SDB and rhinitis showed subjective improvements in nasal congestion and daytime alertness with fluticasone. Nevertheless, snoring noise and sleep quality were unchanged (Kiely JL, Thorax 2004).

5.8.4.6 Future Directions

a- Serotonin

Serotonin delivery to upper airway dilator motor neurons is reduced in sleep, and this contributes to sleep-related reductions in dilator muscle activity and upper airway obstruction (Veasey SC, Am J Respir Med 2003). Serotonin receptors are also found within central respiratory neuronal groups. Drugs that modulate these receptors may have a future role in the treatment of sleep apnea (Veasey SC, Am J Respir Med 2003).

b- Cholinesterase Inhibitor

Recently, it was reported that OSA is related to a thalamic cholinergic deficit in multiple system atrophy (Gilman S, Neurology 2003). Hedner et al. (Am J Respir Crit Care Med 1993) infused physostigmine, a cholinesterase inhibitor, during sleep and noticed a reduction in the number of obstructive apnea events, primarily during REM sleep.

c- Modafinil

Modafinil is a somnolytic that acts directly to block the sleep-promoting system (Pack AI, Am J Respir Crit Care Med 2003). It is a safe compound, with only minor side effects, considered to be a wake-promotion medication different from amphetamines, and used for patients with narcolepsy (US Modafinil in Narcolepsy Multicenter Study Group, Neurology 2000). Modafinil was recently proposed to reduce residual sleepiness in SDB patients on CPAP (Pack AI, Am J Respir Crit Care Med 2001). However, a Pro vs con debate has arisen over its role in the treatment of SDB (Black J, Am J Respir Crit Care Med 2003; Pollak PP, Am J Respir Crit Care Med 2003; Douglas NJ, Am J Respir Crit Care Med 2003). There is a concern that its use would decrease adherence to CPAP when daytime hypersomnolence is decreased by medication (Douglas NJ, Am J Respir Crit Care Med 2003). Modafinil is not yet available in Finland.

5.8.5 Surgery

The most common surgical procedure for OSA has been uvulopalatopharyngoplasty (UPPP), in which the uvula and redundant soft tissue of the soft palate are resected (Malhotra A, Lancet 2002). Several other surgical procedures have recently been developed.
5.8.5.1 Nasal Surgery

Nasal airway reconstruction may aid in the treatment of OSA, because increased nasal resistance and obstruction may significantly increase the negative pressure of the upper airway, leading to collapse of the velopharyngeal, base-of-tongue, and hypopharyngeal regions (Aragon SB, Dent Clin North Am 2001). Nasal valve surgery by open-septorhinoplasty and lateral cartilage grafts has decreased snoring assessed by the patient and bed partner. Nevertheless, there was no change in active anterior and posterior rhinomanometry values (Bertrand B, Acta Otorhinolaryngol Belg 2002). In recent unpublished data, nasal surgery did not reduce snoring time in mild OSA patients (Virkkula P et al.)

5.8.5.2 Pharyngeal Procedures

5.8.5.2.1 Uvulopalatopharyngoplasty (UPPP)

In a meta-analysis, only about 41% of patients who undergo UPPP obtain an RDI of < 20/hour (Hudgel DW, Chest 1997). In many cases snoring will stop after the operation, but disordered breathing continues, leading to silent apneas (Malhotra A, Lancet 2002).

5.8.5.2.2 Lateral Pharyngoplasty

This operation consists of microdissection of the superior pharyngeal constrictor muscle within the tonsillar fossa, sectioning of this muscle, and suturing of the laterally-based muscle flap created to the same-side palatoglossus muscle (Cahali MB, Laryngoscope 2003). This procedure has resulted in a significant improvement in snoring, and a reduction in RDI. However, a short period of swallowing disturbances may follow the surgery (Cahali MB, Laryngoscope 2003).

5.8.5.2.3 Modified Uvulopalatopharyngoplasty

More recently, a modified UPPP was performed on 33 patients with OSA (Li HY, Am J Otolaryngol 2003). The surgery consisted of bilateral tonsillectomy, dissection and removal of submucosal adipose tissue of the soft palate and supratonsillar area, imbrication, and reposition of the denuded uvulopalatal flap. Six months after surgery RDI decreased from 42 to 13/hour (Li HY, Am J Otolaryngol 2003).

5.8.5.2.4 Newer Surgical Approaches

Laser-assisted palatal procedures and radiofrequency thermal ablation (RFTA) have shown disappointing results in the treatment of OSA (Powell NB, Clin Chest Med 1998). However, for patients whose main complaint is snoring, with little or
no apnea found on formal testing, these procedures may be considered (Malhotra A, Lancet 2002). Meanwhile, longer-term follow-up did not suggest sustained alleviation of snoring. Thus, caution should be exercised in recommending their use (Malhotra A, Lancet 2002).

5.8.5.3 Maxillofacial Surgery

With more aggressive surgery (eg, genioglossal advancement and maxillomandibular advancement) few authors reported better results than with classical interventions in the treatment of SDB (RileyRW, Otolaryngol Head Neck Surg 1993 and Otolaryngol Head Neck Surg 1994). However, the generalizability of these results is unclear and these procedures have not gained widespread acceptance (Malhotra A, Lancet 2002).

5.8.5.4 Surgery for Weight Reduction

Weight loss may improve OSA and clinicians regularly recommend dieting to their patients with SDB. No more than 5–10% of body weight is lost through dieting, exercise, and the few available antiobesity medications, however, recidivism after dietary weight reduction is nearly universal (Yanovski SZ, N Engl J Med 2002; Bray GA, Nature 2000). At present, malabsorptive bariatric surgery (Jejunoileal bypass, biliopancreatic diversion, duodenal switch) is the most effective method to achieve major, long-term weight loss (Brolin RE, JAMA 2002; Mun EC, Gastroenterology 2001; Cummings DE, J Clin Endocrinol Metab 2004). Weight reduction following surgery is associated with significant improvements in RDI an average of 28 months after surgery (Guardiano SA, Chest 2003). However, some studies have shown a recurrence of apnea in the absence of substantial weight gain (Pillar G, Chest 1994). Thus, the role of surgery for obesity in the management of OSA is unclear, even though surgery is increasing in popularity (Malhotra A, Lancet 2002).

5.8.5.5 Tracheostomy

Tracheostomy is very efficient in treating OSA (Weitzman ED, Sleep 1980; Partinen M, Chest 1990). Because of its social and medical drawbacks, however, it is performed only in very selective medical situations such as in morbidly obese patients (BMI > 55 kg/m²) (Gross ND, Laryngoscope 2002) and in those with craniofacial abnormalities (Curran AJ, J Laryngol Otol 1993).
5.9 Consequences of Sleep Disordered Breathing

Obstructive sleep apnea was clinically recognized more than 30 years ago (Guilleminault, Annu Rev Med 1976), but awareness of this condition outside the field of sleep medicine was slow to develop. The situation changed drastically when population-based studies uncovered an unexpectedly high prevalence of OSA in adults (Bearpark H, Sleep 1993; Gislason, J Clin Epidemiol 1988; Kripke DF, Sleep 1997; Young T, N Engl J Med 1993). Attention appropriately turned to the health significance of frequent episodes of apnea and hypopnea. Even in subjects with mild forms of SDB, with an RDI of > 5/h, hypertension, sleepiness, and motor vehicle accidents may occur (Young T, Sleep 1997b).

5.9.1 Social Consequences

Loud intrusive snoring affects bed partners, family, and even neighbors. Noise pollution and its resulting social disability, relationship disharmony and threat of marriage break-up are important reasons why patients, often pressured by their partners, seek medical attention (Schlosshan D, Thorax 2004).

5.9.2 Sleepiness and Motor Vehicle Accidents

Fragmentation of sleep is common in OSA and can lead to daytime hypersomnolence, reduction in neurocognitive function, decrease in the quality of life, and increased risk of motor vehicle and occupational accidents (Flemons WW, Chest 2003). Several studies revealed a strong association between OSA and reported car accidents (Lavie P, Sleep 1995; Stoohs RA, Sleep 1993; Hoffstein V, Lancet 1994; Teran-Santos J, N Engl J Med 1999; Lindberg E, Am J Respir Crit Care Med 2001). Moreover, patients with OSA made significantly more errors than did controls in driving simulators (Findley LJ, Am Rev Respir Dis 1989) and treatment with CPAP resulted in a reduction in motor vehicle collisions (George CF, Thorax 2001).

5.9.3 Impact on Work Capacity

In one study, 32 patients with OSA were assessed with an overnight Polysomnography (PSG), multiple sleep latency test, maximal exercise test, and fatigue severity scale. They reported a high level of fatigue, and exercise testing revealed decreased physical work capacity, but objective and subjective indicators of fatigue were not significantly correlated with apnea severity (Aguillard RN, Appl Psychophysiol Biofeedback 1998). Moreover, it has been reported that patients with OSA have a decrease in general intellectual functioning, in learning
abilities, in executive functions and in motor performance, which all have an impact on work capacity (Decary A, Sleep 2000).

5.9.4 Systemic Hypertension

The association between snoring, OSA and systemic hypertension has been investigated in several studies. Epidemiological studies showed that snoring is an independent risk factor for the development of hypertension among males aged < 50 yrs (Lindberg E, Eur Respir J 1998). Moreover, in a population-based sample of hypertensive males, OSA was associated with increased urinary concentrations of extraneuronal metabolites of catecholamines, suggesting increased sympathoadrenal activity (Elmasry A, Eur Respir J 2002). Peppard et al. (N Engl J Med 2000) found a dose-response association between SDB at base line and the presence of hypertension 4 years later. Recently, even the early stages of sleep apnea were reported to be associated with high blood pressure and cardiovascular consequences (Sharabi Y, Curr Opin Nephrol Hypertens 2004). Meanwhile, Escourrou et al. (Chest 1990) found no association of OSA with raised blood pressure.

5.9.5 Cardiac Arrhythmias

The prevalence of cardiac arrhythmias was reported to be higher in patients with OSA than in nonapneic snoring patients (Hoffstein, Chest 1994). Nevertheless, some authors did not confirm this high prevalence (Flemmons, Am Rev Respir Dis 1993). It was recently reported that patients with untreated OSA have higher recurrence of atrial fibrillation after cardioversion than patients without OSA (Kanagala R, Circulation 2003).

5.9.6 Stroke

Several studies (Palomaki H, Stroke 1991; Smirne S, Eur Respir J 1993) have reported an association between snoring and development of stroke. Meanwhile, it was recently reported (Davies DP, J Sleep Res 2003) that ‘simple’ snoring without daytime hypersomnolence may not be an independent risk factor for the development of stroke.

5.9.7 Other Cardiovascular Consequences

An association has been reported between the apnea index and coronary heart disease (Moee T, Chest 1996), pulmonary hypertension (Laks L, Eur Respir J 1995) and right heart failure (Bradley T, Am Rev Respir Dis 1985). More recently, Nieto et al. (Am J Respir Crit Care Med 2004) found a statistically significant linear association between the hypoxemia index and the diameter of the brachial
artery in patients with OSA. Moreover, values of impaired endothelium-dependent vascular relaxation (FMD), a prognostic marker of cardiovascular disease, were decreased in OSA compared to controls, and CPAP therapy increased FMD values (Ip MSM, Am J Respir Crit Care Med 2004). These two studies add to a growing body of evidence linking sleep apnea with vascular dysfunction. Partinen et al (Chest 1990) demonstrated a more significant decrease in vascular morbidity after tracheostomy but not with conservative therapy.

5.9.8 Impact on Pregnancy

There are conflicting results regarding the potential impact of OSA on pregnancy outcomes (Young T, Am J Respir Crit Care Med 2002). Case reports of OSA during pregnancy suggest a possible association with both intrauterine growth retardation and pre-eclampsia (Lefcourt LA, Obstet Gynecol Surv 1996). Franklin et al. (Chest 2000) found that women who reported snoring often or always during the week prior to delivery were more than twice as likely to have pregnancy-induced hypertension (14% versus 6%) and pre-eclampsia (10% versus 4%) than women without frequent snoring. They were more than twice as likely to give birth to an infant small for gestational age (7.1% versus 2.6%) or with an Apgar score < 7 at both 1 and 5 minutes.

5.9.9 Mortality

Results of cohort studies concerning the association between apnea-hypopnea scores and mortality are controversial (Bliwise, Am J Public Health 1988; Ancoli-Israel S, Chest 1989). Lindberg et al. (Thorax 1998) showed an increased risk of mortality associated with the combination of snoring and excessive daytime sleepiness, although neither snoring nor excessive daytime sleepiness alone was independently associated with mortality. It was recently reported that adequately treated OSA may confer little, if any, mortality risk (Richie RC, J Insur Med 2003).
Aims of the Present Study

6 Aims of the Present Study

I - To evaluate the effect of obesity on SDB during pregnancy.

II - To find a cost-effective system for the diagnosis of mild SDB, by comparing the results of ORO with PSG.

III - To study the effect of a mouth-closing device (chinstrap) on mouth-leak with CPAP in SDB patients.

IV - To evaluate the hypothesis that SDB patients who breathe mainly through their mouth during sleep would have more mouth-leak during CPAP, and therefore lower adherence to CPAP therapy, than those who occasionally breathe through their mouth.
7 Materials and Methods

7.1 Patients and Control Subjects

In the first study, 11 obese but otherwise healthy pregnant women were recruited from the Helsinki region. Obesity was defined as a BMI > 30 kg/m² prior to pregnancy. Eleven healthy, non-obese (normal weight = BMI 20 to 25 kg/m² prior to pregnancy) pregnant women were recruited in a similar manner. Subjects were ineligible if they were receiving any medication other than vitamin or iron supplements or if they had smoked > 20 pack-years. Obese and non-obese pregnant women had mean ± SD ages of 31 ± 2 and 32 ± 1 years, BMI 34 ± 1 and 23 ± 1 kg/m², neck circumference 37 ± 2 and 32 ± 2 and Epworth Sleepiness Scale (ESS) 7 ± 3 and 6 ± 3, respectively (Table II).

In the second study, during the period 1998-2000, we investigated 457 patients with a history of snoring and excessive daytime sleepiness. Mild OSA was suspected on a clinical basis, by a pulmonary physician trained in sleep medicine, in 187 patients. Pes monitoring during PSG was planned for 174 patients but was proposed to 110. Of the 88 patients for which Pes monitoring was successful, 79 slept more than two hours and were included in the study (Figure 23). This group comprised 51 men and 28 women. Their mean ± SD was age 49 ± 10 years, BMI 28 ± 5 kg/m², neck circumference 39 ± 4 cm, and ESS 9 ± 4 (Table II).

In the third study, 15 consecutive patients (1 woman) with observed mouth-leak and complaining of mouth dryness and nasal obstruction with CPAP were investigated. Patients served as their own controls. They had a mean ± SD age of 54 ± 12 years, BMI 31 ± 5 kg/m², neck circumference 43 ± 3 cm, and ESS 8 ± 4 (Table II).

In the fourth study, we investigated 231 consecutive CPAP-naive patients referred for snoring and a variable degree of daytime sleepiness. We excluded 119 with RDI < 15/hour and another 19 patients for various reasons: 3 with a stroke < 1 year previously, 2 with severe psychiatric illness, 5 with a prior UPPP, 3 with persistent nasal symptoms, 1 who refused CPAP, and 5 to whom nasal surgical intervention was proposed. Patients were checked by an otolaryngologist. A decision for nasal surgical intervention (septoplasty, chryotherapy or radio frequency thermo-ablation) was based on the presence of nasal symptoms, abnormal nasal structure, and abnormal rhinomanometry findings. We excluded 42 patients whose percentage of mouth breathing fell between 30% and 70% of total sleep time (TST). We studied 51 patients without nasal symptoms: 30 were considered mouth-breathers (MBs) with mouth breathing > 70% of TST, and 21 nose-breathers (NBs) with mouth breathing < 30% of TST (Figure 24). Their mean ± SD ages were 51 ± 2 and 51 ± 2 years, BMI 32 ± 1 and 31 ± 1 kg/m², neck circumference 43 ± 1 and 42 ± 1cm, and ESS 8 ± 1 and 8 ± 1 (Table II).
### Table II. Characteristics of Patients and Control Subjects

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<th>Study</th>
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<td>III</td>
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BMI: body mass index, NC: neck circumference, ESS: Epworth Sleepiness Scale (0: no sleepiness, 24: maximal sleepiness).
Figure 23: Pool of Patients in Study II

7.2 Methods

7.2.1 Protocols

In the first study all pregnant women were referred for the first PSG after their first routine obstetric ultrasound examination at 12 weeks of pregnancy. The second PSG was performed after 30 weeks. A pre-study decision was made to propose CPAP to all women with RDI > 10/hour. A follow-up PSG was planned 6 months postpartum for those with major pathologic findings (Table III). In connection with both PSGs, venous blood was drawn for estradiol and progesterone measurement. Furthermore, routine obstetric and delivery data were noted, as were data on the newborn.

In the second study all patients underwent a PSG including Pes monitoring. A diagnosis of OSA was made when RDI > 5/hour. From the same PSG recording
only esophageal pressure, respiratory flow and movement and oximetry (ORO) were made available for manual scoring to a chest physician trained in sleep medicine, who was blinded to the PSG results but did have access to the patient’s file. A diagnosis of OSA was made when the esophageal index (OI) for the ORO system was > 5/h. The costs were analysed with the help of two diagnostic algorithms (Figure 25). In algorithm A, ORO served as the initial screening test, and all patients with abnormal ORO (OI > 5/h) results went on to PSG for definitive diagnosis. For algorithm B, all patients had an initial PSG. In both algorithms, all patients diagnosed as having SDB underwent a one-night CPAP titration for treatment. During PSG, the additional cost of monitoring Pes was estimated to be equivalent to the additional cost caused by CPAP titration. The cost reported for ORO was 250€ per patient; the costs for interpreted PSG with CPAP titration or with esophageal pressure monitoring amounted to 400€.
Table III. Study Protocols

<table>
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<td>-</td>
<td>evaluation of RDI scoring MB</td>
<td>CPAP titration</td>
<td>CPAP fixed pressure scoring MB</td>
<td>3-month scoring MB</td>
<td>one year after CPAP initiation</td>
</tr>
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PSG: polysomnography; ORO: esophageal pressure, respiratory movements and airflow, and oximetry; RDI: respiratory disturbance index; MB: mouth breathing.
Materials and Methods

Figure 25: Diagnostic Algorithm in Study II

Two diagnostic algorithms used for the cost analysis of ORO. In algorithm A, all patients with an esophageal index (OI) > 5/h went on to PSG for definitive diagnosis. In algorithm B, PSG was done as the initial test. All patients with RDI > 5/h underwent a one-night CPAP titration for treatment.
In the third study, all the 15 SDB patients with observed mouth-leak during CPAP underwent two consecutive overnight PSGs, one with a chinstrap, in random order. The nasal CPAP pressure had been chosen during a previous CPAP titration for each subject and remained constant over the two-night period. Six patients were also randomly selected to undergo cephalometry. Acceptance of the chinstrap at six months was evaluated by a questionnaire. Patients were asked whether mouth dryness and nasal obstruction had improved considerably, moderately, mildly, or not at all (Table III).

In the fourth study, 30 patients with mouth breathing > 70% of TST (MBs) and 21 patients with mouth breathing < 30% of TST (NBs) were followed up for one year after starting CPAP. PSG was performed at baseline, at 2 nights of CPAP titration, and at 3 months. CPAP adherence (mean daily CPAP use in hours) was calculated at one month, 3 months, and the last follow-up visit (Table III).

### 7.2.2 Polysomnography

We used a computerized 24-channel polygraph (Alice 3, Healthdyne Technologies, Marietta, GA, USA) (Figure 14). This included a four-channel electroencephalogram (C3A2, C4A1, O1A2 and O2A1), electro-oculogram, and submental and leg electromyogram. Heart rate was monitored through standard leads. Nasal airflow was scored using a thermistor (Healthdyne Technologies, Marietta, GA) placed near the patient’s nostrils, and during CPAP using a pneumotachometer (Hans Rudolph Inc., MO, USA) attached between the nasal mask and the CPAP generator. Mouth airflow was scored using a thermistor placed in front of the mouth. Thoracic and abdominal belts (Healthdyne effort sensor) were used for respiratory movement detection. Pulse oximetry and nasal expired CO₂ were monitored (BCI Capnochec Plus, BCI International, Waukesha, WI, USA). Snoring was detected with a microphone attached to the subject’s throat, and the analog signal was transferred to the monitor screen. Another microphone was attached to the ceiling, 2 meters from the patient’s head, to record sounds on videotape (Figure 26). Subjects were asked to snore as loud as they could while lying supine during the calibration process before the start of the recording. The maximal snoring signal during calibration was given a value on an arbitrary scale from 0 to 100. With a snoring signal of < 50, no snoring was heard on the videotape. During PSG calibration with CPAP, patients were asked to breathe strongly through the mouth while a trained nurse verified that the thermistor was activated (Figure 27).

Sleep was manually scored in epochs of 30 seconds according to Rechtschaffen and Kales criteria (Rechtschaffen A, A manual of standardized terminology, CA: BIS/BIR, UCLA, 1968). Periodic leg movement scoring was based on American Sleep Disorders Association Task Force recommendations (ASDA, Sleep 1993)
Materials and Methods

Figure 26: Video Recording during PSGs
During polysomnography studies the patient’s sound is recorded on videotape using a microphone attached to the ceiling, 2 meters from the patient’s head. Two video cameras with an infrared light are also used.

(Figure 15). An arousal was defined as an EEG frequency shift into the alpha range for at least 3 seconds (ASDA, Sleep 1992) (Figure 10).

7.2.3 Esophageal Pressure Measurement
An esophageal catheter (Figure 28) (a piezoresistor pressure sensor, Synectics FTC catheter, French size F8/2.7mm. Synectics Medical AB, Stockholm, Sweden) was calibrated regularly, inserted through the nose after local anesthesia and fixed about 38 cm from the nostril (Figure 29). This maneuver was abandoned if the patient complained of discomfort. The catheter was removed during the recording when requested by the patient.

7.2.4 Setting of Mouth Breathing
To prevent activation of the mouth thermistor during nasal breathing, a 3 x 6 cm silicon transversal diaphragm was fixed at the nasal thermistor (Figure 30). During CPAP, the nasal mask also acts as diaphragm (Figure 31). During PSG
Materials and Methods

Figure 27: Calibration and Attending Overnight Recording
A qualified person attended all overnight polysomnographies.

Figure 28: Esophageal Catheter
A French size F8/2.7mm and 260 cm long catheter with two piezoresistor pressure sensors at 25 cm distance for measuring esophageal and pharyngeal pressure.
Materials and Methods

Figure 29: Insertion of Esophageal Catheter

The esophageal catheter is inserted through the nose after local anesthesia and fixed about 38 cm from the nostril. The patient is seated in upright position and instructed to drink water when the tip of the catheter touches the posterior pharyngeal wall. Then the catheter is quickly inserted and fixed. Thereafter, its position is verified and adjusted.

calibration, patients were asked to breathe strongly through the mouth while a trained nurse verified that the mouth thermistor was activated.

7.2.5 Scoring of Respiratory Events

An apnea was defined as cessation of nasal/oral airflow for at least 10 seconds without regard to either arousal or oxygen desaturation (Figure 6).

A hypopnea was defined as a > 50% decrement in nasal/oral airflow for at least 10 seconds, associated with either an arousal or oxygen desaturation > 3%.

An oxygen desaturation index of 4% (ODI₄) was automatically registered by the polygraph and validated manually when there was a 4% drop in oxygen saturation during sleep.

An esophageal event was registered when a pattern of progressively more negative esophageal pressure lasted for 10 seconds or longer ended with a sudden return to the baseline, regardless of whether it was associated with apnea or hypopnea.
Materials and Methods

**Figure 30: Setting of Mouth Breathing without CPAP**

To prevent the activation of the mouth thermistor during nasal breathing, a 3 x 6-cm silicon transversal diaphragm is fixed at the nasal thermistor. The mouth thermistor is placed in front of the mouth.

(Figure 32). The minimal increase in the negative esophageal pressure at the end of the esophageal event was at least 5 cm H$_2$O or more than 50% of the baseline level.

The esophageal index (OI) was calculated by the following formula: number of esophageal events x 60/total time in bed (minutes).

A mouth-leak event was scored visually when the deviation from baseline was at least 10% of the calibrated signal.

A mouth-leak episode, scored over a period of 30 seconds, contained at least one mouth-leak event. Only events during epochs scored as sleep were considered.

Mouth-leak, as a percentage of TST, was calculated as follows: total mouth-leak episodes x 0.5 x 100/TST (minutes).

A respiratory effort-related arousal (RERA) event was scored when it was not caused by apnea or hypopnea, lasted 10 seconds or longer with a pattern of progressively more negative esophageal pressure, and was terminated by a sudden change in pressure to a less negative level and an arousal (Figure 13).
Materials and Methods

Figure 31: Setting of Mouth Breathing with CPAP

A pneumotachometer is attached between the nasal mask and the CPAP generator for measuring nasal airflow. The nasal mask prevents nasal ventilation from activating the mouth termistor.

The respiratory disturbance index was calculated by the following formula: number of apneas + hypopneas + RERA / TST (hours).

A respiratory event was scored when diminution of flow amplitude was observed for > 10 s associated with paradoxical chest and abdominal movement, sometimes with a crescendo pattern of snoring.

A respiratory arousal (RA) was scored when an arousal was preceded by an apnea, a hypopnea, or a respiratory event (Figure 12).

The respiratory arousal index (RA index) was calculated by dividing the total number of RAs by TST in hours.

Arousals that started during a mouth-leak episode or within 2 seconds of a mouth-leak event were considered to be leak arousals.

A snoring event was scored visually if the signal was at least 50% of the calibration signal.

A snoring episode included at least one snoring event and terminated when no snoring event was detected for two breathing cycles.
Materials and Methods

Figure 32: Esophageal Event
A 1 minute polygraphy recording showing a 32 seconds esophageal event with a pattern of progressively more negative esophageal pressure ending with a sudden return to the baseline. The pressure at the baseline is -12 cm H₂O and at the end of the esophageal event -19 cm H₂O.

Snoring time: time spent in snoring episodes x 100/TST.
Breathing irregularity was scored visually in epochs of 5 minutes. Irregular breathing was noted when either the respiratory frequency or the respiratory amplitude changed for > 50% of the epoch.

7.2.6 Mouth Closing Device
We used a chinstrap with a chin cradle (Respirronics, Inc., Murrysville, PA, USA). The chinstrap was applied according to the manufacturer’s instructions. Both sides of the strap were attached to the headgear of a nasal mask near the temples (Figure 33). Attention was directed at placing the straps as far forward as possible to prevent the patient’s jaw from being pushed backwards. The strap and chin cradle were adjusted for optimal comfort while simultaneously preventing the mouth from opening. The positioning of the nasal mask and the chinstrap were checked regularly by the attending nurse and were adjusted when necessary. The chinstrap was removed if requested by the patient.

7.2.7 CPAP Titration
Patients underwent a session of familiarization with the CPAP device and mask. On the initial titration night, pressure was increased manually to correct respiratory
Materials and Methods

![Image](image_url)

**Figure 33: Chinstrap**

Both sides of the chinstrap are attached to the headgear of the nasal mask near the temples. Attention is directed at placing the straps as far forward as possible to prevent the patient’s jaw from being pushed backwards. The strap and chin cradle are adjusted for optimal comfort while simultaneously preventing the mouth from opening.

...continued...

7.2.8 Cephalometry

Cephalometry with and without a chinstrap was randomly performed on 6 patients. Lateral cephalometric radiographs were obtained while the patient was supine and awake, and at a constant pillow height of 5 cm and with the nasal mask disconnected from the CPAP device. The x-ray was taken when the jaws were relaxed or when the opening of the mouth was inhibited by a chinstrap. The exposure was performed at the end of an expiration. The orthodontist who conducted the cephalometric analysis of pharyngeal and skeletal structures was blind to the clinical and PSG data (Figure 17).
7.2.9 Sleep Habits and Daytime Sleepiness

Prior to each PSG, the subjects were asked to keep a sleep diary for 2 weeks. A sleep questionnaire based on the Basic Nordic Sleep Questionnaire (Partinen M, J Sleep Res 1995) was completed before the first sleep study. A shorter follow-up questionnaire was completed prior to the next studies.

The severity of daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS) (Johns MW, Sleep 1991) and classified clinically according to AASM recommendations (AASM, Task Force, Sleep 1999).

The alcohol consumption risk was evaluated by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders JB, Addiction 1993).

7.3 Statistical Analysis

Results were expressed as mean ± SD (standard deviation). The Mann-Whitney U test, z-adjusted for ties, and Yates corrected $\chi^2$ test were used to compare findings between groups of small number, and a Student’s t-test for larger groups. Spearman’s Rank Correlation was used for correlation analysis. Wilcoxon matched pair signed-rank tests or Student’s paired t-tests were also used.

To evaluate the diagnostic accuracy of ORO we used overnight PSG as the gold standard. We evaluated the sensitivity (true positive/ [true positive + false negative]), the specificity (true negative/ [true negative + false positive]), the positive predictive value (true positive/ [true positive + false positive]), and the negative predictive value (true negative/ [true negative + false negative]). We also drew a receiver-operating curve (ROC) for ORO in the detection of SDB with an OI value between 0.2 and 30.

A reduction in mouth-leak with the chinstrap of at least 30% of the initial value was considered to be clinically significant. We also considered as significant any difference of 1.5 hours of daily CPAP use between MBs and NBs at 3 months.

We used a commercial statistical package (Statistica v.5, StatSoft, Tulsa, OK) for all analyses, p < 0.05 was considered significant.

7.4 Ethical Aspects

All subjects gave their written informed consent. The Research and Ethics Committee of the Department of Internal Medicine at our hospital approved all the study protocols. Written consent was given for publication of the photos.
Results

8 Results

8.1 Patient Compliance

Three obese pregnant women and two control subjects refused to undergo a second PSG in late pregnancy (Study I). All patients that were randomized for chinstrap attended their exams (Study III). Four MBs (one woman) refused to use CPAP at home immediately after the titration but are included in analyses. Their mean ± SD age was 45.7 ± 7.4 years, BMI 35.9 ± 7.1 kg/m2, RDI 50.2 ± 33.7/hour, and ESS 7.8 ± 5.1, and two had an AUDIT score exceeding 10. No NB refused CPAP after the titration (Study IV).

8.2 Differences at Baseline

8.2.1 Pregnant Women

The BMI differences between the obese and control subjects were highly significant (p < 0.001) at any assessment point. BMI and neck circumference before pregnancy were significantly higher (p < 0.001) in obese pregnant women, 34 ± 1 kg/m² and 37 ± 2 cm, than in controls, 23 ± 1 kg/m² and 32 ± 2 cm respectively (Table II).

8.2.2 Mouth-breathers and Nose-breathers

MBs and NBs did not differ with respect to age, sex, BMI, neck circumference, ESS, AUDIT, TST, TST while supine, REM sleep, wakefulness after sleep onset, sleep efficiency, RDI while supine, or SpO₂ awake. Meanwhile, total arousal, respiratory arousal, RDI, and ODI₁ were higher in MBs, but amount of delta sleep was lower. By design, the percentage of mouth breathing by MBs was higher than by NBs. (Table II).

8.3 Impact of Obesity on SDB during Pregnancy (Study I)

8.3.1 Weight Gain

During pregnancy, women in the obese group gained 12.5 ± 3.6 kg and controls 15.9 ± 2.2 kg.
8.3.2 Impact on Sleep

No significant differences in sleep characteristics appeared between obese pregnant women and controls during early or late pregnancy in regard to their TIB, TST, REM, SWS, sleep efficiency, wakefulness after sleep onset, or movement time. Nevertheless, obese and non-obese women all slept significantly less (p < 0.01) in the supine position in late pregnancy: for obese pregnant women in early and late pregnancy 38 ± 5% and 15 ± 4% of TST, and for controls 47 ± 7%, 25 ± 7% respectively.

8.3.3 Impact on Blood Oxygenation

8.3.3.1 Mean Awake Oxygen Saturation
Mean awake SpO₂ were 95.8 ± 0.6% and 95.8 ± 0.6% in the obese women and 96.9 ± 0.5% and 96.3 ± 0.4% in the non-obese women during the two PSGs.

8.3.3.2 Time with Oxygen Saturation < 90%
In late pregnancy, one obese woman slept 6% of the time (corresponding AHI, 0.2 events per hour), and three obese women and one control slept 1% of the time at an oxygen saturation < 90%; all other values were > 90%.

8.3.3.3 Oxygen Desaturation index 4%
ODI₄ was significantly higher (p < 0.005) in obese than in controls both in early (5.3 per hour vs 0.3) and late pregnancy (8.9 per hour vs 0.5). In late pregnancy, ODI₄ increased significantly (p < 0.01) from 5.3 ± 2.8 to 8.9 ± 3.1 in the obese women.

8.3.4 Impact on Apnea-Hypopnea Index
We found a significant (p < 0.05) difference in AHI between the obese and non-obese women in early pregnancy, (1.7 events per hour vs 0.2), although all indices were < 10 events. Moreover, this significant difference persisted in late pregnancy (2.6 events per hour vs 0.1).

8.3.5 Impact on Snoring
Obese women snored for 32% of their sleeping time during the first recording, whereas control women snored only 1% of the time (p < 0.001). In late pregnancy, snoring time increased significantly (p < 0.01) in the obese women.
**Results**

8.3.6 **Impact on Respiratory Arousals**
The RA indices differed significantly between obese and control women (p < 0.001), 7.4 and 0.8 in early pregnancy and 13.6 and 1.4 in late pregnancy. The RA index increased in obese women from 7.4 ± 1.7 per hour to 13.6 ± 4.1 in late pregnancy.

8.3.7 **Impact on Respiration Rhythm**
Irregular breathing as a percentage of TST was significantly more common (p < 0.05) in the obese women than controls in both early (36.2 ± 5.8% vs 13.3 ± 4.2) and late pregnancy (48.4 ± 6.7% vs 29.3 ± 3.4).

8.3.8 **Other Associated Complications**

8.3.8.1 **Gestational Diabetes**
Gestational diabetes developed significantly (p < 0.05) more often in the obese women (8 of 11 women) than in the control group (1 of 11 women), however, no medication was needed.

8.3.8.2 **Pre-eclampsia**
In late pregnancy, one woman in the obese group had pre-eclampsia. She also developed mild OSA (AHI, 12 events per hour).

8.3.9 **Hormonal Results**
There were no significant differences in estradiol and progesterone levels between obese pregnant women and control at any assessment point. As expected, within both groups, levels of both hormones increased significantly (p < 0.05) between early and late pregnancy, with a difference in progesterone level during late pregnancy at 298 ± 39 nmol/L in the obese women and at 437 ± 57 nmol/L in the control women.

8.4 **Cost-effectiveness of ORO (Study II)**

8.4.1 **Effectiveness**
The ability of ORO to detect OSA varied according to the diagnostic criteria used. For an OI of 5 per hour, sensitivity was 64%, specificity 78%, positive predictive value 81% and negative predictive value 60%. This accuracy did not differ significantly between obese and non-obese women. With a variable
diagnostic criterion of OI ranging from 0.2 to 30, the sensitivity decreased from 96% to 0%, and the specificity increased from 6% to 100% (Figure 34).

A diagnosis of OSA was made by PSG in 47 of 79 patients (Figure 25).

### 8.4.2 Costs

The cost of algorithm A, where ORO was employed as a screening test for the diagnosis of mild OSA, was 58400 €. The cost of algorithm B, with PSG as the initial test was 63800 €. Use of ORO as a screening test prior to PSG, rather than initial PSG testing, would have saved 5400 € per 100 patients evaluated, if all patients with mild OSA had required a second-night of study for CPAP titration (Figure 25).

Although this method reduced costs, 17 of the 42 patients with normal ORO results had mild OSA missed by screening ORO alone; their mean age was 51.8, BMI 29.3, RDI 9.0, RERA-I 5.2, and AI 1.5. We found no significant difference (p > 0.05) in these variables between these patients and the general population.

![Figure 34: Receiver Operating Curve](image)

A receiver-operating curve of ORO using an esophageal index between 0.2 and 30/h for diagnosis of mild OSA.
Results

8.5 Mouth-leak (Study III, IV)

8.5.1 Chinstrap and Mouth-leak

8.5.1.1 Chinstrap, Mouth-leak and Arousals

Application of a chinstrap during CPAP significantly decreased (p < 0.05) both mouth-leak (Figure 35) and the arousal index (Figure 36) from 42.9 ± 23.5% to 23.8 ± 13.3% of TST and from 33.4 ± 18.6 to 23.6 ± 9.3/hour, respectively. Nevertheless, mouth-leak and the arousal index remained unacceptably high.

Figure 35: Chinstrap and Mouth-Leak

With the chinstrap mouth-leak decreased significantly.
Changes in mouth-leak correlated positively ($r = 0.86$, $p < 0.001$) with changes in the arousal index. The arousal index was significantly higher ($p < 0.0001$) during leak periods (with or without chinstrap) than during no-leak periods, 48.1 ± 17.3 versus 16.8 ± 8.8/ hour (Figure 36).

8.5.1.2 Chinstrap and Snoring
Snoring time increased significantly ($p < 0.005$) with the chinstrap from $6.7 \pm 14.3\%$ to $24.0 \pm 13.2\%$ of TST.

8.5.2 Chinstrap and Sleep
With the chinstrap, no significant changes were found in TST, sleep time in a supine position, wakefulness after sleep onset, REM sleep, delta sleep, sleep efficiency, or the ODI$_a$.

8.5.3 Chinstrap and Cephalometry
Because the chinstrap closed the lower jaw, significant ($p < 0.05$) decreases were detected in the anterior lower facial height (ANS-Me), from 79.3 ± 3.4 mm to

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**Figure 36: Chinstrap and Arousals**
The arousal index was significantly higher ($p < 0.0001$) during leak periods (with or without chinstrap) than during no-leak periods. With the chinstrap the arousal index decreased significantly due to reduction in mouth-leak time.
Results

70.4 ± 3.0 mm, the distance between the nasion and the menton (Na-Me), from 133.8 ± 7.3 mm to 125.6 ± 3.7 mm and the angle between the anterior cranial baseline and the mandibular line (S-Na/MP), from 36.0 ± 5.8° to 32.8 ± 5.7°. Soft tissue structures showed a significant (p < 0.05) increase in the minimal distances between the base of the tongue and the posterior pharyngeal wall (ph1-ph2) from 7.8 ± 3.4 mm to 9.7 ± 3.7 mm, and between the tip of the uvula and the posterior pharyngeal wall (U1-U2), from 2.3 ± 3.6 mm to 6.4 ± 3.3 mm (Figure 17).

8.5.4 Mouth-leak in Mouth- and Nasal-breathers

In MBs on CPAP, mouth breathing decreased significantly (p < 0.001), from 84.5 ± 8.9% at baseline to 30.0 ± 18.9% and to 21.4 ± 17.5% of TST on the second titration night and at 3 months, respectively. Mouth breathing also decreased significantly (p < 0.05) in NBs from 19.9 ± 7.8% at baseline to 7.7 ± 7.7% and to 11.1 ± 13.5% of TST on the second titration night and at 3 months. Mouth breathing remained, however, significantly higher (p < 0.05) in MBs than in NBs at the two follow-up time-points.

8.6 CPAP Pressure and Titration

The prescribed CPAP pressure for MBs ranged from 6 to 15 cm H₂O and for NBs from 6 to 14 cm H₂O. No significant difference existed in residual (on CPAP therapy) RDI or ODI₁ or in arousal index between MB and NB at the second CPAP titration night or the 3-month assessment.

8.7 Follow-ups

8.7.1 Postpartum Follow-up

In Study I the babies’ weights in the obese pregnant women and control groups were 3506 ± 223g and 3622 ± 128g, respectively. Their corresponding lengths were 49.2 ± 0.8 cm and 50.5 ± 0.7 cm. The woman with mild OSA gave birth to a normal child. No baby had significant malformations. An obese woman who spent 6% of her sleep time with an oxygen saturation < 90% in late pregnancy had a baby weighing 3 SDs below the mean. A follow-up PSG was performed for the two women with abnormal findings in the second recording. At 6 months post-partum, sleep-related breathing had normalized in both women, although the woman with mild OSA during pregnancy still snored 59% of TST.
8.7.2 Chinstrap Follow-up

In Study III, based on PSG results, the chinstrap was proposed for regular home use for six patients who had manifested a significant reduction in mouth-leak and the arousal index. However, because two of them needed to be awakened during the PSG to keep the chinstrap correctly positioned, they judged themselves as unable to use the chinstrap on their own at home; one of these patients had a beard. Thus, for the four patients who did use the chinstrap at home, the CPAP pressure was increased, as an estimate, by 2 cm H₂O to abolish snoring. All experienced subjective improvement in mouth dryness and nasal obstruction at the six-month follow-up.

8.7.3 Follow-up and Adherence to CPAP

In Study IV, total follow-up period for CPAP use was 51.6 ± 42.5 weeks for all patients. Adherence to CPAP was significantly better (p < 0.05) in NBs. Of 30 MBs, 11 (37%) used CPAP for a mean of > 4 hours per night at 3 months, as did 9 of 30 MBs (30%) at the last follow-up visit, whereas 16 NBs (76%) used CPAP for > 4 hours per night at 3 months, as did 15 NBs (71%) at the last follow-up visit. We found a significant correlation (R = 0.87, p < 0.001) for MBs and NBs between use of CPAP at 1 month and at 3 months or at the last follow-up visit.

At 3 months of CPAP therapy, we found a significant (p < 0.01) reduction in ESS in both MBs, from 7.9 ± 5.2 to 5.7 ± 4.2, and NBs from 7.9 ± 3.5 to 4.9 ± 2.7.
Discussion

9 Discussion

9.1 Methodological Considerations

9.1.1 Restrictions Related to Subject Selection

9.1.1.1 Number of Subjects

The number of subjects required was calculated prior to each prospective study. The recruitment period for Study I was long; we analyzed the data, for 11 obese pregnant women and 11 controls, 3 years after starting (Study I). Medical care professionals were over-represented in the control group (Study I). For Study III and IV we obtained the required number of subjects. Study II was retrospective.

9.1.1.2 Selection Criteria

For the cost-effectiveness of ORO (Study II) we included subjects with a clinical suspicion of mild SDB. In such a group of patients, diagnosis requires the monitoring of respiratory effort with an accurate device, such as an esophageal catheter (Guilleminault C, Chest 1993). Several studies that tried to identify predictors of SDB and its severity gave unsatisfactory results (Tsai WH, Am J Respir Crit Care Med 2003). Only about half of our suspected patients had SDB by PSG. Our results confirm the findings of previous studies that PSG is still necessary for the diagnosis of mild SDB (Epstein, Chest 1998; Douglas NJ, Lancet 1992; Yamashiro, Sleep 1995; Levy, Chest 1996), and agrees with Rowley’s report (Sleep 2000) that a clinician’s subjective impression or the use of predictive models is not sufficiently accurate to discriminate between patients with or without SDB.

To evaluate adherence to CPAP in MBs and NBs (Study IV) we excluded patients with mild SDB, as the benefits of CPAP treatment for such patients are less clear (Barnes M, Am J Respir Crit Care Med 2002). Moreover, 94% of our MBs and NBs were males. Therefore, our findings may not apply to women. We agree that the low ESS scores of our MBs and NBs may have reduced their adherence to CPAP, as was recently suggested (Sin DD, Chest 2002).
9.1.2 Restrictions Related to the Methodology

9.1.2.1 Measurement of Respiratory Events
Thermistors used for monitoring nasal and oral airflow at baseline provide measurements more qualitative than quantitative (Farré R, Eur Respir J 1998). Therefore, our methodology with thermal sensors may have underestimated the number of hypopneas, which probably also explains the difference between AHI and ODI values.

9.1.2.2 Measurement of Mouth breathing
When scoring mouth breathing, we did not distinguish mouth-opening at the end of apnea caused by choking and oral-breathing. As choking is more frequent in severe SDB, it may explain the higher RDI in our MBs. Nevertheless, we could not consider mouth breathing as a marker of SDB severity, because no significant correlation appeared between RDI and mouth breathing. In a recent review, Rappai et al. (Rappai M, Chest 2003) postulated that the switch to oronasal breathing that occurs with chronic nasal conditions is a final common pathway for SDB.

9.1.2.3 Patient’s Position
Night to night variation in PSG results may relate to head position, body position or the amount of REM sleep (Littner MR, Chest 2003). We did not describe the patient’s head position with and without chinstrap during sleep; however, head position was strictly regulated during cephalometric radiographs. In addition, we observed no difference in the amount of sleep in the supine position. Moreover, contrary to Teschler et al. (Eur Respir J 1999), we found no increase in REM sleep when mouth-leak was reduced. They had sealed the mouth during bilevel ventilatory assistance to completely suppress mouth-leak. By contrast, the chinstrap used in our study effectively decreased mouth-leak in most patients but did not eliminate it altogether. The chinstrap merely keeps the jaw closed during sleep, having no effect on positioning of the lips, and thus, some mouth-leak can still occur. In fact, Teschler et al. (Eur Respir J 1999) observed large leaks without any obvious opening of the mouth, as air escaped through a corner of the mouth.

9.1.2.4 Selection of Materials
We used a chinstrap with a cradle, which ensures good stability around the chin. The cradle does, however, have a tendency to facilitate the chin being pushed up and backwards. One of the chinstrap’s main drawbacks is the reappearance of snoring. This side-effect might be expected to manifest particularly in patients with a sizeable submandibular fat deposition, as the chinstrap can push submandibular
Discussion

soft tissue up and backwards, reducing upper airway dimensions and facilitating the recurrence of snoring or apnea. Nevertheless, the cephalometric analysis did not confirm this hypothesis. However, our cephalometric radiographs were taken while awake with no CPAP pressure applied. All patients supported use of the chinstrap in PSG studies; the reappearance of snoring could not be explained by an overly tight strap.

Our patients did not receive heated humidity or a full face mask with CPAP (Martins De Araujo, Chest 2000). Our findings may not apply when humidiers or full face mask are employed.

Our method for detecting mouth breathing requires a special setting not commercially available. An “easy-to-use” setting to separate mouth from nasal airflow needs to be developed.

9.2 Obesity as Risk Factor for SDB During Pregnancy (Study I)

We showed significantly more sleep-related disordered breathing in obese pregnant women than in normal-weight control counterparts, a finding not explained by differing sleep characteristics or sleep positions. These differences were observed even during early pregnancy and persisted thereafter. One obese mother, who had mild nocturnal hypoxemia, gave birth to a baby with growth retardation.

The control group gained more weight during pregnancy than the obese group, meaning that weight gain cannot explain the difference observed in sleep-related breathing parameters. However, the obese women experienced more complications.

Because obesity is increasing as a health problem for women in many parts of the world (Kopelman PG, Nature 2000) these findings may have potentially serious implications for the health of their fetuses. As expected in late pregnancy, both groups of women spent less time in REM and SWS sleep and in the supine position. The poor sleep quality was further manifested in more arousals and more awake time during late pregnancy.

Our obese pregnant women had greater AHI and ODI indices than the controls, even during early pregnancy. Nevertheless, indices fell within current reference values (Douglas NJ, Am J Respir Crit Care Med 2000). These differences in sleep-related parameters are even more pronounced with regard to snoring. The control group did not snore in either recording period, whereas the obese women spent 30% to 50% of their sleeping time snoring. In this study, the polygraph recorded snoring. Unfortunately, to our knowledge no data exist on the correlation between recorded and self-reported snoring. Studies looking at self-reported snoring during pregnancy have found a prevalence at 14% to 23% (Loube MDI, Chest 1996;
Franklin KA, Chest 2000), and snoring to be either a risk for growth retardation of the fetus (Franklin KA, Chest 2000) or no risk for the newborn (Loube MDI, Chest 1996).

The high circulating level of progesterone during pregnancy is suggested to prevent sleep-related disordered breathing by increasing ventilatory drive (Yannone, Am J Obstet Gynecol 1968), however, the mechanism leading to snoring and sleep apnea in obese pregnant women is still unclear.

9.3 Cost-effectiveness of ORO (Study II)

Applying a diagnostic algorithm utilizing ORO as a screening tool to guide decisions on which patients should undergo PSG did result in small cost savings over the use of PSG alone. However, the consequence of ORO for screening was that a significant number of patients with sleep disorders that cause excessive sleepiness would have remained undiagnosed and untreated. The high cost of sleepiness-related motor vehicle, work-related, and home-based accidents could negate these small cost savings (Leger D, Sleep 1994).

There are some likely explanations for the failure of ORO to recognize SDB in some patients. Poor Pes monitoring may disturb the scoring of an esophageal event. In fact, it is known that the quality of Pes monitoring is related to the position of the pressure sensor in the esophageal lumen and also to the patient’s position. Poor quality Pes data during a portion of the recording have been found in 18 out of 40 study patients (Yu DU, Sleep Research 1997). Difficulties in scoring esophageal events and RERAs may lead to their underestimation. This risk has little effect on RDI, as apneas and hypopneas are scored regardless of Pes swings. It is known that Pes swings are more prominent during obstructive apnea than during a respiratory event with partial upper airway obstruction. Patients with mild SDB may have more partial obstructions than real obstructive apneas. Meanwhile, the presence of an arousal at the end of a respiratory event with partial obstruction may alert the physician to the importance of this respiratory event. Therefore, such small Pes swings are scored as RERAs in PSG but probably missed in ORO. Although obesity may reduce the Pes swings, we found that the accuracy of ORO in detecting OSA was low in both obese and non-obese subjects.

Pes monitoring, although regarded as the gold standard for measuring respiratory effort (AASM Task Force, Sleep 1999), is however, not without drawbacks. It is invasive, often uncomfortable for the patient, and may not be tolerated. In addition, evidence exists that an esophageal catheter may modify pharyngeal airway dynamics (Chervin RD, Am J Respir Crit Care Med 1997), and it has been suggested that its presence may itself impair the quality of sleep (Chediak RD, Sleep 1990), although this remains disputed (Whitney CW, Sleep 1998).
Discussion

9.4 Effects of Chinstrap on Mouth-leak (Study III)

The use of a chinstrap was found to reduce mouth-leak and the arousal index in patients with SDB receiving CPAP treatment. To the author’s knowledge, this is the first randomized PSG study to show an effect of the chinstrap. Our results support those of Teschler et al. (Eur Respir J 1999) who reported that a reduction in mouth-leak is associated with a decrease in the arousal index. Moreover, during mouth-leak periods the arousal index was significantly higher than during no-leak periods.

9.5 Mouth-leak and Adherence to CPAP (Study IV)

Our results showed that in patients with SDB, a high percentage of mouth breathing during sleep represents a risk for low adherence to CPAP. Furthermore, although mouth breathing decreases considerably when patients are put on nasal CPAP, MBs still have considerably more mouth breathing on CPAP than do NBs. We also found a significant correlation in all patients between use of CPAP at 1 month and its long-term use. These findings are consistent with others, that mouth-leak may compromise CPAP therapy (Berry RB, Sleep Med 2000; Mortimore IL, Am J Respir Crit Care Med 1996), and that the first period of CPAP use predicts long-term adherence (Popescu G, Thorax 2001).

Our study showed that adherence to CPAP was significantly lower in MBs than in NBs. We postulate that MBs have more difficulties in accepting a new breathing pattern, one exclusively nasal, than do NBs, resulting in more mouth-leak with CPAP. Furthermore, our 4 patients who refused CPAP after titration were all MBs. Because sleep and respiratory parameters were significantly better on CPAP for all patients in this study, the low adherence of MBs cannot be attributed to CPAP inefficiency, nor to the difference in patient age or gender, as has been suggested (Sin DD, Chest 2002).

The real cause of mouth breathing in SDB patients is not fully known. We excluded patients with nasal problems and thus may assume that mouth breathing, at the time of the exam, was unrelated to nasal obstruction. Nevertheless, one recent theory is that mouth breathing is related to SDB (Rappai M, Chest 2003) and that medical treatment of rhinitis alleviates SDB (Kiely JL, Thorax 2004).

9.6 Future Investigations

Our study evaluating the risk of obesity and weight gain on SDB during pregnancy did not include investigation of the effect of other possible risk factors, eg,
Discussion

craniofacial characteristics. This issue needs to be resolved in future, larger studies. Moreover, because gestational diabetes is not known to affect respiration (Kjos SL, N Engl J Med 1999) it is unlikely that the difference in its incidence in our study groups had an effect on the differences observed in sleep-related breathing parameters. However, a larger study will be needed to clarify conclusively the role of these complications on sleep-related breathing during pregnancy.

New devices with alternative means of predicting arousal and respiratory effort variation, like those that measure the pulse transit time PTT (Argod J, Am J Respir Crit Care Med 2000), and the peripheral arterial tone PAT (Pillar G, Sleep Med 2003), should be evaluated for cost-effectiveness in screening for mild SDB.

As the use of a chinstrap may increase snoring time and worsen SDB in some patients, consideration of these potential effects is important before taking the chinstrap into regular home use.

We recommend the detection of mouth breathing during sleep, not only for predicting adherence to CPAP therapy, but also for avoiding the use of CPAP titration devices that use nasal mask pressure-vibration detection as their only mode of pressure setting; such devices fail to recognize all respiratory events in patients with significant mouth breathing (Lofaso F, Eur Respir J 1996). Whether mouth breathing predicts nasopharyngeal anatomic obstruction and, in turn, predisposes to more severe SDB, needs further investigation.
Conclusion

10 Conclusion

We first studied whether obesity, a known and important risk factor for SDB in the general population, constitutes a risk factor for SDB during pregnancy. We also tried to find a cost-effective way to diagnose mild SDB. Thereafter we analyzed the effect of closing the patient’s mouth with a chinstrap in preventing mouth-leak with CPAP. Finally we tried to predict the adherence to CPAP therapy by measuring mouth breathing during sleep. We have come to the following conclusions:

Obesity is a risk factor for SDB even during pregnancy. Nevertheless, weight gain during pregnancy in our study population was not important enough to induce SDB. Moreover, SDB offers one possible explanation for the adverse outcomes of pregnancy reported in the obese women. We also showed the importance of PSG in the diagnosis of mild SDB. Our ORO system (esophageal pressure, respiratory flow and movement and oximetry) was not cost effective for the diagnosis of mild SDB. In addition, we showed that the chinstrap, by closing the mouth during CPAP, reduces mouth-leak and therefore the arousal index in most patients. Nevertheless, mouth-leak and the arousal index remained unacceptably high. The chinstrap may also increase snoring and, in rare cases, can worsen the respiratory disturbance index. Finally, we demonstrated that patients with moderate to severe SDB with a high percentage of mouth breathing during sleep would adhere less to nasal CPAP therapy than would patients with a low percentage of mouth breathing during sleep. Our finding is compelling, clinically important, and may be of considerable economic benefit, because it may predict the likely success of CPAP before its initiation.
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13  Original publications (I-IV)
Original publications (I-IV)