ABSTRACT

The prevalence of snoring is high and snoring affects one’s quality of life. Snoring can also be a symptom of obstructive sleep apnea (OSA). Snoring has traditionally been measured to predict OSA, but it has not been quantified in the same way as sleep disordered breathing events are. The objective diagnosis of snoring requires a sleep study. Simple and cost-effective systems are needed to screen for snoring and OSA. Upper airway symptoms are frequent in snorers and patients with obstructive sleep apnea syndrome (OSAS) already prior any treatment. The treatment of choice for obstructive sleep apnea is continuous positive airway pressure (CPAP). Although CPAP treatment is effective for OSA, the challenge is to improve treatment adherence.

To evaluate the value of a Moving Picture Experts Group Layer-3 Audio (MP3) recorder device in screening of snoring, we recorded snoring sounds during polysomnography (PSG) in 200 consecutive patients referred for suspected obstructive sleep apnea (OSA). Snoring was recorded during the PSG with two microphones and with the MP3 device. We compared the results of the MP3 snoring recordings to the snoring recordings in PSG.

To investigate the frequency of upper airway symptoms in subjects referred for a sleep study, we enrolled 524 consecutive patients and asked them to complete a questionnaire inquiring about current upper airway symptoms and any history of nasal and pharyngeal disorders prior the sleep study. Moreover, we examined 385 consecutive OSAS patients referred for CPAP initiation and ask the patients to complete questionnaires about upper airway symptoms before beginning CPAP and after two months of CPAP treatment.

To evaluate predictors of later CPAP use, we finally followed 580 consecutive OSA patients scheduled for CPAP initiation for one year. Patients completed a self-efficacy questionnaire (5 = low, 25 = high score) before CPAP initiation. Immediately after CPAP initiation, we asked about the patients’ satisfaction with the CPAP trial as well as their eagerness and willingness to continue CPAP therapy (0 = unsatisfied, uneager or refused CPAP, 100 = satisfied, eager or willing to continue CPAP treatment).

MP3 recording was technically successful for 87% of the patients. The Pearson correlation between PSG snoring and MP3 snoring was significant at 0.77 (p < 0.001). More than half of the sleep study subjects suffered from throat, mouth and nose dryness as well as from nasal stuffiness. The patients with moderate or severe OSAS (apnea-hypopnea index ≥ 15 and an Epworth sleepiness scale score ≥ 10) more often experienced mouth dryness (71% vs. 40%, p < 0.01) than did those with mild or no OSAS. In addition, patients with moderate to severe OSAS who were
beginning CPAP treatment frequently suffered daily or almost daily from upper airway symptoms: dryness of mouth (61%), throat (54%) and nose (51%), nasal stuffiness (52%), sneezing (30%), mucus in the throat (24%), rhinorrhea (17%), and nose bleeds (6%). In CPAP users there was shown a significant reduction in the number of patients with frequent mouth (37%), throat (34%) and nose (28%) dryness and nasal stuffiness (24%). Finally, of the 580 patients 377 (65%) continued CPAP therapies beyond one year. Altogether 77 patients had a low score (< 50) for willingness to continue CPAP treatment after a brief initiation, and only 7 of them used CPAP > four hours daily after one year, yielding a specificity of 97% in predicting CPAP failure.

In conclusion, recording snoring with an MP3 device offers reliable information about the patients’ snoring. Subjects referred for a sleep study often presented with upper airway symptoms. Nasal stuffiness and airway dryness in particular bothered snorers even before the development of sleep apnea. The most common upper airway symptoms in patients with untreated OSAS were associated with mucosal dryness. These symptoms improved during CPAP treatment. Finally, a low score for willingness to continue CPAP therapy after a short trial predicted CPAP failure and poor CPAP adherence after one year.
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This thesis is based on the following original communications, which are referred to in the text by the Roman numerals I-IV, and also presents some unpublished data. The original publications appear here with the permission of their copyright owners.


IV  Kreivi HR, Maasilta P, Bachour A. Willingness score obtained after a short CPAP trial predicts CPAP use at 1 year. Sleep Breath. 2013; Jun 28. [Epub ahead of print]
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
</tr>
<tr>
<td>ASV</td>
<td>adaptive servoventilation</td>
</tr>
<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
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<tr>
<td>AUDIT</td>
<td>alcohol use disorders identification test</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<td>DEPS</td>
<td>depression scale</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<td>EOG</td>
<td>electro-oculography</td>
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<td>EMG</td>
<td>electromyography</td>
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<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>ESS</td>
<td>Epworth sleepiness scale</td>
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<tr>
<td>LAUP</td>
<td>laser-assisted uvulopalatoplasty</td>
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<tr>
<td>MAD</td>
<td>mandibular advancement device</td>
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<tr>
<td>MMA</td>
<td>maxillo-mandibular advancement</td>
</tr>
<tr>
<td>MP3</td>
<td>moving picture experts group layer-3 audio</td>
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<tr>
<td>MSLT</td>
<td>multiple sleep latency test</td>
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<td>MWT</td>
<td>maintenance of wakefulness test</td>
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<tr>
<td>OA</td>
<td>oral appliance</td>
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<tr>
<td>ODI</td>
<td>oxygen desaturation index</td>
</tr>
<tr>
<td>ODI₄</td>
<td>oxygen desaturation (≥ 4%) index</td>
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<tr>
<td>OSA</td>
<td>obstructive sleep apnea</td>
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<td>OSAS</td>
<td>obstructive sleep apnea syndrome</td>
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<td>PSG</td>
<td>polysomnography</td>
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<td>PAP</td>
<td>positive airway pressure</td>
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<td>RDI</td>
<td>respiratory disturbance index</td>
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<td>RFA</td>
<td>radiofrequency ablation</td>
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<tr>
<td>RERA</td>
<td>respiratory effort-related arousal</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>SDB</td>
<td>sleep-disordered breathing</td>
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<tr>
<td>UARS</td>
<td>upper airway resistance syndrome</td>
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<tr>
<td>UPPP</td>
<td>uvulopalatopharyngoplasty</td>
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1. INTRODUCTION

Snoring, apneas and hypopneas are signs of increased upper airway resistance usually due to anatomical factors that narrow upper airway. Snoring patients represent a range of clinical and sleep study findings from nonsleepy nonapneic snoring to severe obstructive sleep apnea syndrome (OSAS) (Figure 1). Upper airway resistance syndrome (UARS) occupies an intermediate position in this spectrum (Figure 1).

Figure 1 A simple schematic illustration of the association of apneas and hypopneas, daytime sleepiness, and snoring to sleep apnea. Modified from Obstructive Sleep Apnoea Syndrome – Report from a joint Nordic Project.

The prevalence of snoring is high and snoring can significantly impact on quality of life (Baldwin et al. 2010, Svensson et al. 2008). The objective diagnosis of snoring usually requires a sleep study. Recently, of the conditions causing sleep-disordered breathing, particularly OSAS, have received increasing attention in affluent societies. Patients with OSAS suffer from a complete or partial airway obstruction caused by pharyngeal collapse during sleep, which leads to loud snoring or choking, frequent awakenings, disrupted sleep and excessive daytime sleepiness. Untreated OSAS is an important health problem that leads to poor quality of life, to increased risk for other diseases – particularly the risk for cardiovascular diseases is increased – and to risk for higher mortality (Mannarino et al. 2012, Marin et al. 2005, Marti et al. 2002). Moreover, OSAS patients are at increased risk for traffic accidents (Mulgrew et al. 2008, Tregear et al. 2009). Because about 4% of men and 2% of women have OSAS (Young et al. 1993), questions about risks, diagnosis and treatment options for OSAS are important for both clinicians and health care planners.
The gold standard for diagnosing OSAS is the overnight polysomnography (PSG) (American Academy of Sleep Medicine Task Force 1999). However, it is an expensive, time-consuming and cumbersome examination. In addition, the demand for sleep studies is constantly growing, as are the waiting lists for examinations in the sleep laboratories (Flemons et al. 2004). One way to improve access to appropriate care for patients with more severe and complex diseases could be to improve the preliminary screening of obstructive sleep apnea (OSA) and snoring.

The treatment of choice for sleep apnea is nasal continuous positive airway pressure (CPAP) treatment. CPAP is effective in eliminating snoring, apneas and hypopneas, thereby improving sleep quality and reducing daytime sleepiness as well as other symptoms of OSAS (Giles et al. 2006, Kakkar & Berry 2007, McDaid et al. 2009). Common side-effects of CPAP treatment are upper airway symptoms such as dryness of the nose and mouth, rhinorrhea, nasal stuffiness and sneezing (Brander et al. 1999, Pepin et al. 1995). Some have noticed in clinical practice that snorers and OSAS patients often suffer from airway symptoms long before any treatment. No previous studies have evaluated the frequency of upper airway symptoms in snorers and OSAS patients prior to treatment. Studies have shown that during CPAP treatment, upper airway complaints, particularly rhinorrhea and sneezing, increase (Brander et al. 1999); in fact these it upper airway symptoms may even lead to treatment cessation.

Although CPAP is an effective treatment for OSA, many patients refuse to continue CPAP treatment or fail to use the device sufficiently. Predictors of CPAP use are still poorly understood (Weaver & Grunstein 2008). The factors affecting CPAP adherence are multifaceted (Weaver & Grunstein. 2008) and can be related to the patient himself/herself, severity of the disease, the treating physician or other healthcare personal, the equipment used, or the patient’s family (Sawyer et al. 2011, Shapiro & Shapiro 2010).

The aim of this study was as a part of the development of home sleep testing to evaluate the diagnostic performance of an MP3 recording device in the screening for snoring. In addition, we also studied the prevalence of upper airway symptoms in snorers and OSAS patients prior to treatment and during the CPAP treatment. Moreover, we assessed CPAP adherence as well as the association between patient satisfaction with the CPAP trial and his or her willingness and eagerness to continue CPAP treatment after the initiation trial.
2. REVIEW OF THE LITERATURE

2.1 Background

A healthy person normally breathes through the nose, although resistance to the airflow is lower when respiration follows the oral route. Physiological variation in nasal patency, the nasal cycle, is also active during sleep (Hudgel & Robertson 1984). The role of the nose is to moisten and clear inspired air and to regulate the muscles of the upper airway. During sleep, the upper airway becomes narrower, the muscle tone in the upper airway decreases, and increased nasal resistance can cause the upper airway to collapse. Depending on the individual susceptibility to snoring due to narrowing of the upper airway, upper airway resistance syndrome (UARS) or obstructive sleep apnea (OSA) may develop. Opening the mouth increases the collapsibility of the upper airway during sleep (Meurice et al. 1996), and while asleep, upper airway resistance is higher when breathing orally than with breathing nasally (Fitzpatrick et al. 2003). Factors that increase inflammation (e.g. viral flu, allergic rhinitis and smoking) increase nasal resistance in the supine position (Stroud et al. 1999). Reduced lower nasal airflow is more often measured in snorers than in non-snorers (Young et al. 1997).

In snorers and in patients with OSA, upper airway symptoms are common, especially mouth and throat dryness and nasal stuffiness (Brander et al. 1999, Pepin et al. 1995). Nasal obstruction is probably a risk factor for snoring and sleep apnea (Young et al. 1997, Young et al. 2001). For example, inflammatory diseases such as allergic or non-allergic rhinitis, infectious rhinitis or rhinosinusitis, or abnormalities of anatomical structure, such as nasal septal deviation or nasal polyps, can cause obstruction. Studies have discovered an association between sleep apnea and allergic rhinitis (Lofaso et al. 2000, McNicholas et al. 1982), and the use of topical nasal steroids has led to significant improvement in nasal obstruction and in the apnea hypopnea index (AHI) (Kiely et al. 2004). Adults with nasal obstruction due to allergy and nasal stuffiness were 1.8 times more likely to have moderate to severe sleep-disordered breathing than were adults with no nasal symptoms (Young et al. 1997).

2.2 Snoring

Snoring is sound generated from the upper airway due to vibration of the uvula and soft palate. Snoring is associated with changes in the calibre of the upper airway, which reduces airflow and indicates increased pharyngeal airflow resistance.
2.2.1 PREVALENCE OF SNORING

Snoring is extremely common, and its prevalence in middle-aged adults is between 11-59% (Fitzpatrick et al. 1993, Hiestand et al. 2006, Pevernagie et al. 2010, Svensson et al. 2008, Young et al. 1993). This variability may stem from different study populations, different questionnaires used and whether they asked the spouse about the anamnesis of snoring. The prevalence of snoring is higher among smokers and passive smokers than among non-smokers (Franklin et al. 2004, Virkkula et al. 2005). Despite the high prevalence of snoring, an official definition of snoring and valid methods to quantify it are lacking (Rice & Strollo 2011, Stuck et al. 2010). Snoring is usually measured as a predictive factor for OSA, but not quantified in the same way as hypopneas and apneas are (Rice & Strollo 2011). Although perceptions of snoring are known to vary depending on the observer (Hoffstein et al. 1994, Hoffstein et al. 1996), physicians in clinical work have traditionally relied on questionnaires addressed to the patients or their bed partner (Virkkula et al. 2005).

2.2.2 CONSEQUENCES OF SNORING

Snoring may be a symptom of OSA (Bliwise et al. 1991, Deegan & McNicholas 1996, Romero et al. 2010, Stuck et al. 2010), and studies have demonstrated that the intensity of snoring increases with the severity of OSA (Maimon & Hanly 2010). However, a long-term epidemiological observational study demonstrated that simple snoring does not appear to be a significant risk factor for cardiovascular disease (Marin et al. 2005). The association of vascular disease with simple snoring was previously believed to be only a marker for OSA linked to sleep fragmentation, intermittent hypoxemia and intrathoracic pressure changes (Kohler & Stradling 2010). Recent studies, however, have reported that snoring itself seems to lead to vibration of the upper airway, which is then transmitted to the carotid artery, thus possibly resulting in vibration injury to the artery (Amatoury et al. 2006, Cho et al. 2011). Therefore, snoring itself is now believed to represent a risk for vascular diseases. Even if snoring was mostly harmless, those affected by snoring often suffer significantly, and snoring surely impairs their quality of life.

2.2.3 TREATMENT FOR SNORING

There is no clear evidence that early treatment of snoring in adults can prevent its progression to obstructive sleep apnea, so the need for invasive treatment of snoring must be assessed carefully (Stuck et al. 2010). Conservative treatments for snoring include weight loss in obese patients, position therapy, avoidance of alcohol and sedatives, and smoking cessation. There is no evidence of the efficacy of pharma-
Review of the literature

cological interventions for snoring (Stuck et al. 2010). Continuous positive airway pressure (CPAP) is effective in eliminating snoring, but not for pure snoring as it is too cumbersome and costly. Intraoral devices can successfully serve to treat snoring (Stradling et al. 1998) by enlarging the pharynx in the anterior-posterior dimension.

Because not all the data on the success rates of surgical interventions have been sufficiently evaluated, some have recommended that only minimally invasive surgical procedures with low peri- and postoperative morbidity and risk for complications should be used to treat snoring (Stuck et al. 2010). For the nose, no surgical interventions are available to treat specifically snoring. Nasal surgery is recommended only for snoring patients suffering from nasal obstruction (Elshe-rif & Hussein 1998). Operative treatment for mainly structural nasal obstruction has failed to reduce snoring intensity, snoring time or sleep-disordered breathing despite significantly decreasing nasal resistance (Virkkula et al. 2006). Minimally invasive procedures to stiffen the soft palate and/or to cut off excessive soft tissue, such as laser-assisted uvuloplasty (LAUP) and radiofrequency surgery, are the most widespread procedures for treating snoring. Although studies have documented the efficacy of LAUP for the treatment of snoring (Krespi et al. 1994, Wareing & Mitchell 1996), the long-term follow-up data show that the benefits of LAUP seem to diminish with time (Berger et al. 2001, Iyngkaran et al. 2006). Radiofrequency surgery on the soft palate is a safe procedure and more effective than placebo, at least in a short-term follow-up, although it cannot necessarily cure snoring (Back et al. 2009, Stuck et al. 2005). Soft palate implants are also effective in decreasing the severity of snoring; however, improvements seem to diminish over time (Maurer et al. 2005, Rotenberg & Luu 2012).

2.3 Upper airway resistance syndrome (UARS)

Since Guilleminault and colleagues described the term upper airway resistance syndrome (UARS) in 1993 (Guilleminault et al. 1993), speculation has ensued about whether UARS is an independent disease entity or a subgroup of obstructive sleep apnea syndrome. So far, the American Academy of Sleep Medicine (AASM) has included UARS under its definition of OSA (American Academy of Sleep Medicine Task Force 1999). Population-based studies of the prevalence of UARS are still lacking, however. Pathophysiology is specific to low collapsibility of the upper airway and preserved pharyngeal reflexes (Pepin et al. 2012). UARS patients suffer from typical symptoms of OSAS and may snore despite typically showing no hypopneas or apneas in sleep study. UARS is defined by the occurrence of excessive daytime sleepiness associated with partial airway obstruction and more than 50% of respiratory events being nonapneic and nonhypopneic (Pepin et al. 2012). Snoring and repetitive respiratory effort-related arousals (RERAs) without oxygen desaturation may lead to a significant disease with symptoms (Pepin et al. 2012). RERAs can
be assessed by measuring esophageal pressure or changes in pulse transit time (Pepin et al. 2012). In respiratory flow, inspiratory flow limitation may become evident when using nasal cannulae (Ayappa et al. 2000). CPAP therapy improves excessive sleepiness, but the problem is often due to poor treatment compliance (Exar & Collop 1999, Pepin et al. 2012). Oral appliances have also been used to treat UARS (Pepin et al. 2012).

2.4 Obstructive sleep apnea (OSA)

2.4.1 DEFINITIONS OF SLEEP APNEA

Obstructive sleep apnea is a condition characterized by repeated episodes of upper airway closure during sleep. Total closures are known as obstructive apneas (no inspiratory airflow), and partial closures (reduced inspiratory airflow), obstructive hypopneas. Obstructive apnea is defined as a drop in the breathing signal during the peak signal excursion by ≥ 90% of the pre-event signal with ever increasing inspiratory effort throughout the entire period of no airflow and when the duration of the drop in the sensor signal exceeds 10 seconds (Berry et al. 2012). Central apnea is scored if the episode meets the criteria of an apnea and is associated with an absence of inspiratory effort throughout the entire period of no airflow. Mixed apnea is scored if the episode meets apnea criteria and is associated with an absence of inspiratory effort in the initial portion of the event, followed by the resumption of inspiratory effort during the second portion of the event (Berry et al. 2012). The previous American Academy of Sleep Medicine (AASM) criteria recommended defining hypopnea as at least a 30% reduction in breathing amplitude for at least 10 seconds, associated with oxygen desaturation of at least 4% or alternatively as at least a 50% reduction in breathing amplitude with at least 3% oxygen desaturation from the pre-event baseline or the event is associated with arousal (American Academy of Sleep Medicine Task Force 1999). According to the latest AASM Scoring Manual, hypopnea in adults is scored when the peak signal excursions drop by ≥ 30% from the pre-event baseline for ≥ 10 seconds in association with either arterial oxygen saturation ≥ 3% or arousal (Berry et al. 2012). The apnea-hypopnea index (AHI) is the mean number of apneas and hypopneas per hour of sleep. An AHI greater that 5/h is considered pathological. The definition of obstructive sleep apnea syndrome entails five or more episodes of apnea or hypopnea per hour of sleep with associated symptoms (e.g. excessive daytime sleepiness, fatigue or impaired cognition) or an AHI greater than 15/h regardless of associated symptoms (American Academy of Sleep Medicine Task Force 1999).
2.4.2 PREVALENCE AND INCIDENCE OF OBSTRUCTIVE SLEEP APNEA

Epidemiological studies indicate that 4% of men and 2% of women in Western countries have OSAS (Punjabi 2008, Young et al. 1993). Because not all OSA patients are symptomatic, the number of people with OSA with no clinical syndrome is higher. In a general population sample of adults with moderately severe sleep-disordered breathing (SDB), the five-year incidence was estimated to be about 7.5%, and for mild to moderately severe SDB 16% (Tishler et al. 2003). The number of patients suffering from OSA has grown recently due to the increasing prevalence of obesity, the most important risk factor for OSA (Leger et al. 2012, Punjabi 2008). The prevalence of OSA has a tendency to increase with age, but its clinical significance and severity decreases (Bixler et al. 1998). After the age of 65, the prevalence of OSAS seems to plateau (Young et al. 2002). The prevalence of OSA in women increases after menopause, but hormone replacement appears to be associated with reduced risk for sleep apnea (Bixler et al. 2001, Shahar et al. 2003).

2.4.3 PATHOPHYSIOLOGY

The pathophysiology of OSA is still poorly understood, but both anatomic and neuromuscular factors are involved in its development. Several factors lead to the obstruction of the upper airway during sleep. A narrow upper airway is more vulnerable to collapse than a larger one. Imaging studies have demonstrated that during wakefulness, the cross-sectional area of the upper airway in OSA patients is smaller than in control subjects (Schwab et al. 2003). OSA is associated with a number of variable alterations in upper airway anatomy, such as tonsillar or tongue hypotrophy, rithrognathia or the inferior displacement of the hyoid bone, which reduces the size of the pharynx. Pathological and insufficient reflex activation of the upper airway dilator muscles and the greater likelihood of collapsibility of the passive airway also contribute to upper airway collapse. Upper airway dysfunction begins with snoring and flow limitation, which can lead to mechanical trauma that progressively injures the upper airway tissues. Studies have shown the chemical control system to be more unstable in patients with severe OSA than in patients with milder disease (Younes et al. 2001). Consequently, this instability of ventilatory control is a potential contributing factor in the development of obstructive events.

2.4.4 RISK FACTORS

Obesity is the most important risk factor for OSA. A 10% weight gain increases the risk for OSA six-fold (Peppard et al. 2000a). Obesity is believed to predispose one to OSAS by narrowing airway because of fat in the pharyngeal tissues. Volu-
metric magnetic resonance imaging has shown that patients with OSA may have smaller-calibre upper-airway lumen than healthy controls (Schwab et al. 2003). However, not all OSAS patients are obese. Patients with OSA are more often male (Schwab, 1999), although a number of differences between the sexes may explain why men are more prone to OSA (Al Lawati et al. 2009). For example, upper airway muscle activity in men differs from that in women, upper airway fat deposition may be greater in men, men tend to have an androgenic pattern of fat distribution to the upper body, and upper airway soft tissue structures are larger in men. Moreover, sex hormones may affect neurologic control of the upper airway muscles and ventilation (Redline et al. 1994). Postmenopausal women are at higher risk for developing OSA than premenopausal women are, and hormone replacement appears to be associated with reduced risk (Bixler et al. 2001). Sleep-disordered breathing also seems to be more severe in postmenopausal than in premenopausal women (Anttalainen et al. 2006, Resta et al. 2003). The effect of body mass index (BMI) on OSA seems to decrease with age (Young et al. 2002). Smoking relates to sleep apnea in a dose-response relationship: heavy smokers are at the greatest risk, whereas former smokers are at no greater risk for SDB (Wetter et al. 1994).

2.4.5 CLINICAL FEATURES

The clinical presentation for OSA includes signs of upper airway obstruction during sleep and excessive daytime sleepiness (Epstein L.J. et al. 2009). At the time of diagnosis, the patients have typically suffered from the symptoms of OSAS for years. Obstructive breathing symptoms at night include snoring, snorting, gasping and choking (American Academy of Sleep Medicine Task Force 1999, Epstein L.J. et al. 2009). Patients often complain of awakenings and fragmented sleep, insomnia, reduced total sleep time or early morning awakenings (Epstein L.J. et al. 2009, Krakow et al. 2001, Lavie 2007). Headache, difficulty concentrating, memory loss, decreased libido, and nocturia are common (Epstein L.J. et al. 2009, Park et al. 2011). The severity of the symptoms usually progress over the years and may become more severe if the patient gains weight, ages or reaches menopause (Mannarino et al. 2012).

2.4.6 CONSEQUENCES OF UNTREATED OBSTRUCTIVE SLEEP APNEA

al. 2006), stroke (Marin et al. 2005, Yaggi et al. 2005), pulmonary hypertension (Galie et al. 2009), and impaired neurocognitive function (Aloia et al. 2004). Studies have also documented increased mortality risk in OSA patients (Marin et al. 2005, Marshall et al. 2008, Young et al. 2008). CPAP therapy seems to protect OSA patients against death from cardiovascular diseases (Doherty et al. 2005, Marin et al. 2005). In another study, patients with untreated OSA were at increased mortality risk, due largely to cardiovascular and respiratory causes, than was the general population, whereas the mortality in treated OSA patients seemed to show no increase (Martí et al. 2002). The pathophysiological interaction between OSA and cardiovascular diseases is complex and remains poorly understood. Several risk factors, such as obesity, male gender and age, are also risk factors for cardiovascular diseases. However, part of the association between OSA and cardiovascular diseases is independent of traditional cardiovascular risk factors. Other suggested mechanisms include increased sympathetic activity, endothelial dysfunction, metabolic dysregulation, oxidative stress and inflammation (Bradley & Floras 2009, Caples et al. 2007).

2.4.7 TRAFFIC AND SLEEP APNEA

Research has shown that drivers with OSA are at increased risk for motor vehicle accidents (Mulgrew et al. 2008, Tregear et al. 2009). However, daytime sleepiness and the severity of sleep apnea do not seem to correlate with crash risk (Ellen et al. 2006). Successful treatment of OSA improves driver performance, which would seemingly decrease the risk for motor vehicle accidents (Ellen et al. 2006, Hartenbaum et al. 2006).

2.4.8 SEVERITY OF SLEEP APNEA SYNDROME

The severity of OSAS involves two components: the results of an overnight sleep study and the severity of daytime sleepiness. The severity rating of OSAS is based on the most severe component. Overnight polysomnography registers 5 to 15 apneas and/or hypopneas per hour in mild disease, 15 to 30 apneas and/or hypopneas per hour in moderate disease, and more than 30 apneas and/or hypopneas per hour in severe disease (American Academy of Sleep Medicine Task Force 1999) Sleepiness is mild if unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. In moderate sleepiness, unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. In severe sleepiness, the symptoms lead to significant impairment in social or occupational function: unwanted sleepiness occurs during activities that require active attention (American Academy of Sleep Medicine Task Force 1999).
2.4.9.9 DIAGNOSIS OF SLEEP APNEA

A diagnosis of OSA requires the presence of repetitive apneas and hypopneas during sleep and a history of OSA symptoms. A diagnosis of OSA requires four levels of sleep studies. Level 1 is an attended sleep laboratory polysomnography (PSG), level 2 an unattended PSG, level 3 a respiratory polygraphy, and level 4 includes one or two respiratory variables and pulse oximetry (Chesson et al. 2003, Collop et al. 2007). In the recommendations, the minimum examination for diagnosing OSA is a type 3 portable monitoring device that includes airflow monitoring, thoracoabdominal bands and oximetry (Collop et al. 2007).

The severity of daytime sleepiness can be quantified with questionnaires. The most widely used sleepiness test is the Epworth Sleepiness Scale (ESS), which comprises eight questions about the patient’s likelihood to fall asleep during the daytime (Johns 1991). The test is validated and score is based on a 0- to 24-point scale, with higher scores representing greater levels of sleepiness. The Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) may serve to objectively measure sleepiness and alertness. MSLT measures the number of minutes it takes the study subject to fall asl sleep while lying down in a dark room (Carskadon et al. 1986, Littner et al. 2005) and MWT measures the subject’s ability to stay awake during specific conditions, such as sitting in a dark room (Littner et al. 2005, Sangal et al. 1992).

2.4.9.1 Polysomnography (level 1)

Overnight PSG is expensive, time-consuming and cumbersome (American Sleep Disorders Association 1997, Kushida et al. 2005). The demand for sleep studies is growing with the increase in awareness of sleep apnea (Flemons et al. 2004). Techniques are therefore available to examine patients with fewer and simpler signals with relatively acceptable reliability without the need for EEG recordings (Chesson et al. 2003, Collop et al. 2007). AASM recommends portable monitoring devices in patients with a high pre-test probability of moderate to severe OSA, but with no significant comorbitudes or indications of other sleep disorders (Collop et al. 2007, Nelson 2013). If testing the high-risk patient with a portable monitoring device turn out negative or fails technically, a PSG is a recommended second-line examination. At a minimum, portable monitoring devices measure airflow, respiratory effort and oxygen saturation (Figure 2). Sleep time is approximated as recording time or as time-in-bed. This approach includes a risk for underestimating the average number of apneas/hypopnes per hour of sleep, because recording time and time-in-bed usually exceeds sleep time.
2.4.9.2 Polygraphy (level 3)

Overnight PSG is expensive, time-consuming and cumbersome (American Sleep Disorders Association 1997, Kushida et al. 2005). The demand for sleep studies is growing with the increase in awareness of sleep apnea (Flemons et al. 2004). Techniques are therefore available to examine patients with fewer and simpler
signals with relatively acceptable reliability without the need for EEG recordings (Chesson et al. 2003, Collop et al. 2007). AASM recommends portable monitoring devices in patients with a high pre-test probability of moderate to severe OSA but with no significant co-morbidities or suspicion of other sleep disorders (Collop et al. 2007, Nelson 2013). If testing with portable monitoring device in the high-risk patient is negative or fails technically, a PSG is recommended as second-line examination. At minimum, in portable monitoring devices airflow, respiratory effort and oxygen saturation are measured (Figure 2). Sleep time is approximated as recording time or as time-in-bed. This approach includes a risk for underestimating the average number of apneas/hypopnes per hour of sleep because recording time and time-in-bed is usually longer than sleep time.

![Figure 4](image.png) A screen print (5 minutes) of a polygraphy. Channels: ECG = electro-cardiography, nasal pressure, thermistor, SpO2 = oxygen saturation, thorax and abdomen belts, left and right leg, snoring microphone, pulse, position.

### 2.4.10 SCREENING

There is a continuous and growing need for sleep studies, and the sleep laboratories that are already available are having difficulties meeting this growing demand (Flemons et al. 2004). Therefore, a wide spectrum of less sophisticated screening devices are available that are designed to screen for snoring and sleep apnea. These devices are developed to aid the physician in screening for SDB, but should be used prudently.

In patients with suspected OSA, studies have shown limited monitoring with a nasal cannula flow signal and oximetry to detect a respiratory disturbance index (RDI) similar to that obtained in full nocturnal PSG (Ayappa et al. 2004). ApneaLink™, a single-channel screening device based on the pressure-transduced measurement of nasal flow, has also been compared with PSG; ApneaLink proved
to be an accurate screening tool for particularly moderate to severe sleep apnea in a population with a high prevalence of the disorder (Ragette et al. 2010).

Acoustic analysis of the sound spectrum of snoring has served to distinguish simple snorers and sleep apnea patients. Compared to simple snorers, OSA patients vary more during snoring epochs (Cavusoglu et al. 2008, Sola-Soler et al. 2005). It is also possible to classify sleep-disordered breathing with tracheal sound analysis. In detecting sleep apnea in adults, tracheal sound analysis has been used with relatively good results (Nakano et al. 2004). Higher frequencies of the tracheal sound spectrum are believed to indicate obstruction in the upper airway (Herzog et al. 2008a, Herzog et al. 2008b).

In addition, SleepStrip™, a small device comprising oral and nasal thermistors worn underneath the nose and above the upper lip, can serve as an initial screening tool for OSA (Shochat et al. 2002). Moreover, the measurement of volatile organic compounds with an electronic nose is an innovative method that identifies distinct molecular patterns of exhaled breath in different patient groups. The pharyngeal washing fluids of OSAS patients revealed higher levels of alpha-1-antitrypsin and markers of extracellular remodeling than have controls, thus showing that the electronic nose can distinguish between OSAS patients and controls with high accuracy (Greulich et al. 2012).

### 2.4.11 TREATMENT

Behavioral, medical and surgical treatment options are available to treat OSA. In mild disease with few symptoms, lifestyle modification – particularly weight reduction in obese patients – is the cornerstone of OSA treatment. In moderate to severe OSA, and in mild disease when lifestyle modification fails to improve the symptoms, the nasal continuous positive airway pressure (CPAP) is the treatment of choice. A multidisciplinary approach in treatment is often necessary.

#### 2.4.11.1 Lifestyle modification

Of all OSA patients, about 70% are overweight or obese (Lindberg & Gislason 2000). Weight loss is a primary treatment option for OSA in overweight patients and should be recommended for all overweight patients regardless of other treatment modes. A low-energy diet combined with active lifestyle counselling results in weight reduction and an improved apnea-hypopnea index (AHI) more than does traditional, routine lifestyle counselling in mild disease (Tuomilehto et al. 2009). In moderate to severe OSA, treatment with a low-energy diet improves OSA in obese men, with the greatest effect in patients with severe disease: AHI decreased by 67% in the intervention group, compared with no change in the control group (Johansson et
Research has shown that intensive lifestyle intervention in obese patients with type 2 diabetes leads to weight loss, thus resulting in significantly improved apnea-hypopnea index (Foster et al. 2009). Because weight reduction is associated with improved breathing patterns, quality of sleep, and daytime sleepiness, weight reduction is recommended to reduce the risk for developing OSA.

Lack of exercise is associated with increased severity of sleep-disordered breathing (Peppard & Young 2004). Exercise training seems to result in moderate improvements in AHI and oxygen desaturation index (ODI) in overweight or obese adults, improvements attained despite a lack of change in body weight (Kline et al. 2011).

Simple positional treatment with a ball or backpack in positional OSA has proven to be an effective alternative treatment to CPAP in mild or moderate OSA, at least in the short term (Jokic et al. 1999). CPAP proved to be superior to positional treatment in reducing AHI and desaturations, although it yielded no functional improvement (Jokic et al. 1999). According to the European Respiratory Society (ERS) task force for non-CPAP therapies for OSA, positional treatment can only be recommended for carefully selected patients, and during the treatment, control sleep studies should be carried out to document treatment success (Randerath et al. 2011). Patients whose OSA improves with positional therapy tend to be younger, to have lower AHI, and to be less obese.

Smoking negatively impacts both nasal resistance and improvement of AHI, and worsens airway obstruction by nasopharyngeal edema and airway inflammation (Blomster et al. 2011, Kim et al. 2012). Consequently, conservative approaches to OSA treatment include smoking cessation, as well as abstinence from alcohol and sedatives.

2.4.11.2 Continuous positive airway pressure (CPAP)

Sullivan et al. (Sullivan et al. 1981) introduced CPAP in 1981. CPAP acts as a physical pressure splint that prevents partial or complete collapse of the upper airway during sleep by pushing the soft palate and tongue forward and away from the posterior oropharyngeal wall. Pressure from the device is applied to the upper airways through a nasal or oronasal mask or nasal pillows (Figure 5).
2.4.11.2.1 Effects of CPAP

There is strong evidence that CPAP treatment decreases AHI and improves subjective and objective sleepiness (Gay et al. 2006, Giles et al. 2006, Kakkar & Berry 2007, McDaid et al. 2009). CPAP also improves quality of life (Avlonitou et al. 2012, Jenkinson et al. 1999, Montserrat et al. 2001), decreases blood pressure (Barbe et al. 2010, Bazzano et al. 2007), reduces pulmonary arterial hypertension (Arias et al. 2006), reduces the risk for cardiovascular events (Doherty et al. 2005, Marin et al. 2005), the risk for car accidents (Tregear et al. 2010), and the risk for atrial fibrillation recurrence after cardioversion (Fein et al. 2013, Kanagala et al. 2003), as well as improves ejection fraction in patients with congestive heart failure (Egea et al. 2008). Moreover, CPAP reduces the sleep disturbance of an OSA patient’s bed partner and improves their quality of life as well (Parish & Lyng 2003).

2.4.11.2.2 Side effects of CPAP

Adverse effects of CPAP are common, but usually mild. Nevertheless, they can cause patients discomfort and even lead to treatment cessation despite improvements in
OSAS symptoms (Baltzan et al. 2009, Brander et al. 1999, Lojander et al. 1999, Pepin et al. 1995). Table 1 summarizes the side effects and adverse effects of CPAP studies from recent years. In earlier studies, side effects were more common than nowadays. With more robust devices and simpler masks, the main complaints of patients and bed partners have been the noise of the blower and the discomfort of the treatment (Hoffstein et al. 1992, Kribbs et al. 1993, Meslier et al. 1998, Pepin et al. 1995, Rolfe et al. 1991). Local side effects related to interface, such as pressure sores, skin ulcerations, air leaks, mask dislodgement, claustrophobia and local allergic skin reactions, have been documented in as many as 50% of patients (Kakkar & Berry 2007, Pepin et al. 1995). Side effects in the upper airway are also common. More than half of patients have reported mouth, nose and throat dryness during CPAP treatment (Brander et al. 1999, Meslier et al. 1998, Pepin et al. 1995).

2.4.11.2.3 Adherence to CPAP treatment

Despite the effectiveness of CPAP to improve upper airway obstruction in sleep apnea, variable adherence to treatment limits the effectiveness of treatment. Patients’ failure to adhere to CPAP therapy is a major limitation to treatment success (Engleman & Wild 2003). This is clinically important, as CPAP has proven to normalize sleep architecture, to improve symptoms of OSAS, to enhance daily functioning, to elevate mood, to decrease blood pressure, to reduce risk for cardiovascular morbidities and to normalize the risk for traffic accidents (Gay et al. 2006, Giles et al. 2006, Kakkar & Berry 2007, McDaid et al. 2009). Many factors, including the severity of the disorder, side effects, therapeutic response, claustrophobia, patients’ perceptions of the severity of the disease, psychological and social factors, family support and cost, are known to influence adherence to CPAP treatment (McArdle et al. 1999, Sawyer et al. 2011, Shapiro & Shapiro 2010).

The commonly used definition of adequate CPAP adherence is the usage of ≥ 4 h per night for ≥ 70% of days (Engleman & Wild 2003, Gay et al. 2006, Kribbs et al. 1993). Table 2 reviews studies of adherence to CPAP treatment. Non-acceptance rates have ranged from 5% to 50% (Engleman & Wild 2003). Another 12-15% of CPAP patients quit CPAP treatment within three years (Engleman & Wild 2003). Early studies of patients’ CPAP use relied on self-reports, but many patients tend to overestimate their CPAP use (Kribbs et al. 1993, Reeves-Hoche et al. 1994). Therefore, an objective measurement of CPAP use, such as the use of memory cards for the devices, is essential. AASM also recommends routine assessment of CPAP use (Epstein L.J. et al. 2009, Kushida et al. 2006).
### Table 1  Adverse effects of CPAP

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Rolfe I 1991| Retrospective                    | 168 M/F 145/23 | - 26/61 non-users, intolerance of mask  
- 16/61 non-users, inconvenience of treatment |
| Hoffstein S 1992 | Questionnaire-based study | 96        | - 65% mask too tight  
- 48% hurts the ridge of the nose and the upper lip  
- 47% blower too noisy  
- 21% blower too heavy  
- 10% felt claustrophobic |
| Kribbs NB 1993 | Prospective questionnaire-based study | 35 M/F 29/6 | - 54% inconvenience of CPAP  
- 46% stuffy nose  
- 32.3% slept poorly  
- 31.3% disturbs sleep  
- 31.3% less intimacy with bed partner  
- 28.1% claustrophobia  
- 28.1% irritates the face  
- 27.6% expense |
| Pepin JL 1995 | Prospective questionnaire-based study | 193 M/F 165/28 | - 50% of patients complained of side effects of the nasal mask (allergic reaction on the face, air leaks, abrasions on the ridge of the nose)  
- 65% of patients had dry nose or mouth in the morning  
- 35% experienced sneezing and nasal drip  
- 25% suffered from nasal congestion |
| Meslier ET 1998 | Retrospective questionnaire-based study | 3225 M/F 2796/429 | - 52.2% dry mouth and throat  
- 47% noise disturbed bed partner  
- 28% red eyes or conjunctivitis  
- 27% nasal soreness  
- 26% nasal congestion  
- 24% runny nose |
| Lojander J 1999 | Retrospective questionnaire-based study | 151 M/F 128/23 | - 46% dry nose  
- 37% nasal stuffiness  
- 35% sneezing  
- 27% rhinorrhea |
| Brander PE 1999 | Prospective questionnaire-based study | 49 M/F 37/12 | - 75% sneezing  
- 57% rhinorrhea  
- 50-75% nasal stuffiness, mucus in throat, dry nose, mouth and throat |
| Baltzan MA 2009 | Prospective questionnaire-based study | 89 M/F 68/21 | - 39.5% dry upper airway  
- 32.9% mouth leaks  
- 23.6% mask removal during sleep  
- 20.3% nasal congestion  
- 15.9% runny nose  
- 12.4% pain with nCPAP mask  
- 11.2% disturbed by noise of nCPAP  
- 10.1% sense of uncomfortable pressure  
- 9.3% morning headache  
- 8.8% sneezing  
- 6.8% sneezing  
- 5.6% claustrophobia |
Table 2  Studies of adherence to CPAP treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Follow-up</th>
<th>Hours / night</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kribbs NB 1993</td>
<td>35</td>
<td>3 months</td>
<td>4.8 h ± 1.96 h</td>
<td>Average use per night</td>
</tr>
<tr>
<td>Engleman HM 1994</td>
<td>54</td>
<td>3 months</td>
<td>4.7 h ± 0.4 h</td>
<td>Average use per night</td>
</tr>
<tr>
<td>Reeves-Hoche MK 1994</td>
<td>47</td>
<td>6 months</td>
<td>4.7 h (0-10.2 h)</td>
<td>Average use per night</td>
</tr>
<tr>
<td>Pepin JL 1995</td>
<td>193</td>
<td>19 ± 17 months</td>
<td>6.5 ± 3 h</td>
<td></td>
</tr>
<tr>
<td>Krieger J 1996</td>
<td>575</td>
<td>39 months</td>
<td>5.7 h</td>
<td></td>
</tr>
<tr>
<td>Meslier ET 1998</td>
<td>3225</td>
<td></td>
<td>6 h 35 min ± 2 h 15 min</td>
<td>Average use per night. Retrospective study, CPAP use ≥ 6 months</td>
</tr>
<tr>
<td>McArdle N 1999</td>
<td>1103</td>
<td>median 22 (12-16) months</td>
<td>5.6 h (3.8-7 h)</td>
<td>Median use per night at the most recent clinic visit</td>
</tr>
<tr>
<td>Grote L 2000</td>
<td>149</td>
<td>30 (25-30) months</td>
<td>4.4 h ± 2.4 h</td>
<td>Average use per night at 30 months</td>
</tr>
<tr>
<td>Popescu 2001</td>
<td>209</td>
<td>1 year</td>
<td>5.0 h ± 2.3 h</td>
<td>Average use per night</td>
</tr>
<tr>
<td>Sin DD 2002</td>
<td>296</td>
<td>6 months</td>
<td>5.8 h</td>
<td>Average CPAP use per night</td>
</tr>
<tr>
<td>Kohler M 2010</td>
<td>639</td>
<td>median 3.9 years</td>
<td>6.2 h (4.5-7.3 h)</td>
<td>Average use per night at the most recent clinic visit</td>
</tr>
</tbody>
</table>

2.4.11.2.4 Tools to improve CPAP adherence

Technical advances in positive airway pressure (PAP) have led to the development of new modes of therapy, such as automatic and pressure relief technologies. During autoadjusting PAP, treatment pressure is significantly lower than during fixed CPAP (Berry et al. 2002, Haniffa et al. 2004). No compliance or clinical benefits have been demonstrated in CPAP-naive patients (Ayas et al. 2004, Nilius et al. 2006, Nolan et al. 2007). Individual patients, however, may benefit from a change in pressure mode. Autoadjusting PAP devices can also serve to determine effective treatment pressure. Moreover, use of an autoadjusting PAP device eliminates the need for pressure titrations in long-term treatment.

Bilevel positive airway pressure treatment enables the delivery of separately adjustable levels of pressure in inspiration and expiration, and is an effective alternative to CPAP in patients with OSA and coexisting chronic obstructive pulmonary
disease (COPD), restrictive lung disease, and Cheyne-Stokes respiration and nocturnal hypoventilation syndromes associated with hypercapnia (Kushida et al. 2006).

In patients with complex sleep apnea syndrome, a condition involving the coexistence or appearance and persistence of central apneas or hypopneas in patients with OSA upon successful restoration of airway patency, CPAP treatment often proves insufficient; these patients may require treatment with adaptive servoventilation (ASV) devices (Kuzniar & Morgenthaler 2012).

Humidification often accompanies CPAP treatment to augment CPAP adherence and to reduce upper airway side effects. Heated humidification delivers more moisture than does cool humidification. Heated humidification increases objectively measured adherence to CPAP (Massie et al. 1999, Neill et al. 2003). However, heated humidification has failed to increase satisfaction with CPAP treatment (Massie et al. 1999) or to improve subjective sleepiness (Neill et al. 2003). In contrast, heated humidification effectively alleviates upper airway symptoms (Mador et al. 2005, Martins De Araujo et al. 2000, Wiest et al. 1999).

Often finding a suitable interface that does not leak can be a major obstacle for the success of CPAP treatment. A variety of different interfaces are available: nasal, oronasal, total facemasks, nasal pillows or oronasal pillow masks. Sometimes, several types of masks need to be tried to find the most comfortable mask.

2.4.11.3 Drug therapy, oral appliances and surgery

Intranasal steroids have proved effective in improving mild to moderate OSA in patients with coexisting rhinitis in terms decreasing the AHI and improving nasal resistance (Kiely et al. 2004). The ERS Task Force for non-CPAP therapies for OSAS does not recommend intranasal steroids as a single intervention, although they can serve as concomitant therapy especially in CPAP patients with symptoms of rhinitis (Randerath et al. 2011). Other pharmacological treatments, such as tricyclic antidepressants and serotonic agents to improve pharyngeal dilator muscle tone, methylxanthine and opioid antagonists to increase ventilatory drive, and oximethazoline to reduce airway resistance, have also been studied in patients with OSA. Thus far, there is no clear evidence that drugs are likely to benefit an unselected patient with OSA; consequently, they are not recommended for patients with OSA (Randerath et al. 2011).

Oral appliances (OAs) and upper airway surgery are both used in patients with mild to moderate OSA, and as a backup against CPAP failure. OAs, also known as mandibular advancement devices (MADs), move the lower jaw forwards and downwards during sleep, thereby increasing the airway space, stabilizing the position of mandibula, advancing the position of tongue, and reducing the collapsibility of the upper airway. OAs reduce apneas during sleep and daytime sleepiness, even though CPAP is more effective than oral appliances in improving OSA (Lim
et al. 2006). OAs are recommended for non-obese patients with mild to moderate OSA, and for those whose CPAP treatment fails (Randerath et al. 2011). OAs are not the first choice therapy for severe OSA (Lim et al. 2006). According to guidelines, treatment success with OA should always be re-evaluated with a sleep study (Randerath et al. 2011).

Upper airway or facial surgery is often considered as an alternative treatment for OSA. Various surgical operations have been performed for decades as treatments for OSA (Fujita et al. 1981). Still, controlled studies are few, and the results of these studies are controversial. To bypass the upper airway, tracheostomy is a possible treatment option. However, tracheostomy is rather cumbersome and, nowadays, is very seldom used. Uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatoplasty (LAUP), maxillo-mandibular advancement (MMA) or tonsillectomy, for example, can now serve to enlarge the oropharyngeal airspace. UPPP involves excision of the tonsils and posterior palatal/uvula as well as closure of the tonsillar pillars. UPPP is effective only in patients with obstruction limited to the oropharyngeal area and is associated with possible long-term side effects, such as abnormal swallowing, dry throat and velopharyngeal insufficiency (Randerath et al. 2011). After UPPP, increased leaks and mouth dryness often compromise the success of CPAP treatment. UPPP is recommended only in carefully selected patients (Randerath et al. 2011). LAUP involves a series of laser incisions and vaporizations in order to shorten the uvula, as well as to modify and tighten the soft palatal tissue (Caples et al. 2010). LAUP has demonstrated no significant improvement in the severity or symptoms of OSA, and is therefore not recommended (Randerath et al. 2011). Maxillo-Mandibular Advancement (MMA) is multilevel skeletal surgery that enlarges the velo-orahypopharyngeal airway without direct manipulation of the pharyngeal tissues. MMA can be considered in patients with hypopharyngeal and/or velo-orohypopharyngeal narrowing, which is common in patients with skeletal hypoplasia and rethrognathia (Caples et al. 2010). MMA operations have shown some promising results in treating OSA (Caples et al. 2010).
3. **AIMS OF THE STUDY**

I  To evaluate the diagnostic performance of a Moving Picture Experts Group Layer-3 Audio (MP3) recording device in screening for snoring.

II  To evaluate the frequency of upper airway symptoms in subjects referred for sleep studies.

III To evaluate the prevalence of upper airway symptoms in obstructive sleep apnea syndrome patients before and during nCPAP treatment.

IV  To determine whether CPAP adherence can be predicted before or immediately after CPAP trial.
4. STUDY SUBJECTS AND METHODS

This study consists of four parts. The first study and the fourth study were carried out at the Sleep Unit, Department of Pulmonary Medicine at the Helsinki University Central Hospital, Helsinki, Finland, which is a teaching hospital that serves a population of 600 000; all sleep apnea patients treated in communal care are treated at the Sleep Unit.

Studies II and III were carried out at the Division of Pulmonary Medicine at Hyvinkää Hospital, Hospital District of Helsinki and Uusimaa, Hyvinkää Finland. Hyvinkää Hospital serves a population of 165 000; all patients with suspected sleep apnea referred for communal care in the Hyvinkää area are investigated primarily at the sleep laboratory of Hyvinkää Hospital.

The local ethics committee approved all the study protocols.

4.1 Study subjects

4.1.1 STUDY SUBJECTS (I,IV)

For Study I, we enrolled 200 consecutive adult patients referred to the Sleep Unit for polysomnography between May 2008 and September 2009. Patients complaining of daytime sleepiness and snoring were referred for suspected OSA. Of the study patients, 58% were men. Their age, mean ± standard deviation (SD) was 50 ± 13 years, with a Depression Scale (DEPS) score of 5 ± 6, and on the Alcohol Use Disorders Identification Test (AUDIT), 6 ± 6. Of the study subjects, 18% were current smokers and 23% were ex-smokers. Table 3 reports other important patient characteristics.

In Study IV, we followed 580 consecutive adult patients with OSA admitted for CPAP initiation in Sleep Unit, Helsinki University Central Hospital for one year (between May 2010 and December 2012). All patients had an AHI ≥ 5, based on an overnight AASM type III (Embletta, EMBLA, ResMed Corp., San Diego, CA, USA) sleep study, and suffered from daytime sleepiness. Table 3 lists the most important patient characteristics. We were missing follow-up data for 40 patients because they had either moved to another district, failed to attend the follow-up visit, postponed their follow-up appointment or had forgotten their CPAP device at home when they came for their follow-up visit.
Table 3  Patient characteristics (Studies I and IV)

<table>
<thead>
<tr>
<th></th>
<th>Study I (N = 200)</th>
<th>Study IV (N = 580)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 6</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>AHI/hour</td>
<td>17 ± 20</td>
<td>34 ± 22</td>
</tr>
<tr>
<td>ODI4/hour</td>
<td>14 ± 20</td>
<td>30 ± 23</td>
</tr>
<tr>
<td>ESS</td>
<td>6 ± 6</td>
<td>9 ± 4</td>
</tr>
</tbody>
</table>

Data appear as mean ± standard deviation (SD), unless indicated otherwise. Abbreviations: BMI = body mass index, ESS = Epworth sleepiness scale (0-24), AHI = apnea-hypopnea index, ODI4 = oxygen desaturation index, SD = standard deviation.

4.1.2 STUDY SUBJECTS (II, III)

The study population consisted of consecutive adult patients referred to Hyvinkää Hospital for a diagnostic limited overnight sleep study for suspected sleep apnea and CPAP pressure titration.

We enrolled 524 consecutive patients who were referred to Hyvinkää Hospital for a diagnostic limited overnight sleep study during a two-year period (2003-2004) for Study II. Table 4 demonstrates patient characteristics.

For Study III, we enrolled 385 consecutive patients admitted to the Hyvinkää Hospital for CPAP initiation from January 2003 to December 2004. All the patients had undergone a diagnostic limited overnight sleep study (Embletta ®, Flaga, Reykjavik, Iceland) before enrolling in the study. Patient characteristics appear in Table 4.

Table 4  Patient characteristics (Studies II and III)

|                                | Sleep study patients (Study II) | CPAP study (study III) |
|                                | N 524                          | 385                    |
| Men/Women %                    | 69/31                          | 79/29                  |
| Age, years                     | 51 ± 12                        | 52 ± 19                |
| BMI, kg/m²                     | 31 ± 6                         | 33 ± 7                 |
| ESS                            | 9 ± 5                          | 9 ± 4                  |
| AHI                            | 15 ± 21                        | 33 ± 7                 |
| ODI4                           | 16 ± 22                        | 32 ± 24                |

Data appear as mean ± standard deviation (SD), unless indicated otherwise. BMI = body mass index, ESS = Epworth sleepiness scale (0-24), AHI = apnea-hypopnea index, ODI4 = oxygen desaturation index.
4.2 Methods

4.2.1 STUDY I

In Study I, we evaluated the diagnostic performance of an MP3 recording device (Figure 6) in screening for snoring by recording snoring sounds with the MP3 device during PSG. We compared the results of our MP3 snoring recording to the recordings of snoring with PSG. For PSG, we used a 32-channel polygraph Embla N7000 (Embla, Denver, CO, USA). We manually scored each sleep stage according to the criteria of Rechtschaffen and Kales (Rechtschaffen & Kales 1968) and respiratory parameters according to the AASM 2007 recommendations (Iber et al. 2007). We scored apneas if airflow stopped completely for ≥ 10 seconds, and scored hypopneas if nasal airflow decreased by ≥ 50% for ≥ 10 seconds accompanied by a ≥ 3% decrease in oxygen saturation. The apnea and hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep.

![Figure 6](image.png) MP3 device for recording of snoring

4.2.1.1 Detection of snoring in PSG

During PSG, we detected snoring with two microphones: a calibrated skin microphone (Pro-Tech P1696 piezo snore sensor, Philips Respironics, Murraysville, PA, USA) set to a 10-Hz sampling rate was attached to the patient’s throat, and another microphone, attached to the ceiling two meters from the patient’s head, recorded snoring sounds on videotape. We asked the subject to imitate snoring sounds while lying supine during calibration, and the maximal snoring signal from the neck...
sensor during calibration was assigned a value of 100 on an arbitrary scale from 0 to 100 (Figure 7). With a snoring signal of 50, no snoring was audible on the videotape. To be certain that the snoring signal scored on the PSG was audible to the human ear, a snoring signal was scored visually if the signal strength was at least 50% that of the calibration signal. At least one snoring event was included in a snoring episode, and a snoring event terminated when no snoring event occurred for two breathing cycles. We calculated the length of snoring episodes and called them it as PSG snoring. We excluded wakefulness and movement and calculated the percentage of snoring time as follows: PSG snoring time x 100 / total sleep time.

Figure 7  Scoring of snoring in polysomnography. A snoring signal was scored visually if the signal strength was at least 50% that of the calibration signal.

4.2.1.2  Detection of snoring with an MP3

The MP3 recording device (Creative Zen Stone Plus 2GB, Creative Labs Inc., Singapore) we used to record snoring sounds had a built-in microphone for voice recording (sampling frequency 8,000 Hz). We attached the device to the patient’s collar. A sleep technician began recording about three minutes before the “lights off” time for PSG and finished recording at the “lights on” time. We downloaded the data from the MP3 recorder to a PC and used FMJ Awave Studio commercial software (www.fmjsoft.com) to convert the audio signals to digital values. The digital values were amplitude-integrated (with an epoch of 0.1 seconds), analyzed with previous algorithms developed for sleep apnea recordings (Salmi et al. 1989), and finally displayed on a computer screen (Figures 8 and 9). To exclude unaffiliated sounds, we deleted the first five minutes of the recorded data. First, we analyzed the snoring when the signal exceeded a threshold of one, two, three, and four times the median value of the acoustic signal for the entire recording. Finally, we considered values
of the MP3 snoring signals that exceeded the threshold of twice the median value of the acoustic signal to be snoring. Moreover, we considered signals exceeding the threshold of four times the median to be loud snoring. To identify possible sleep apnea patterns in the snoring, we calculated an intermitted snoring index, which we defined as an episode during which a snoring signal is recorded for 5-15 seconds followed by a 5- to 15-second absence of snoring. We calculated percentages of the MP3 snoring as follows: MP3 snoring x 100 / MP3 recording time. We chose to arbitrarily consider the patient a snorer if the snoring time exceeded 5% of the total sleeping time in PSG.

![Figure 8](image)

**Figure 8** A screen print of the MP3 snoring analysis program. One line represents five minutes of recording. The green color represents the basic sound, the blue color represents snoring, and the red lines represent periods of snoring and loud snoring. The snoring threshold was set to twice the median value of the acoustic signal of the entire recording, and that for loud snoring, to four times the median value.
4.2.2 STUDIES II AND III

Publications II and III are prospective questionnaire-based studies. In Study II, all the study subjects underwent a diagnostic limited overnight sleep study that included the simultaneous monitoring of nasal airflow with a nasal cannulae/pressure transducer system, respiratory movements, finger pulse oximeter, and body position detection (Emblett®®, Flaga, Reykjavik, Iceland) throughout the study period. All the sleep recordings, analyzed manually, recorded both AHI per hour and decrease in oxygen saturation ≥ 4% per hour (ODI4). Apneas were defined as a complete cessation of airflow for ≥ 10 seconds. Hypopneas were defined as a ≥ 50% decrease in the amplitude of breathing for ≥ 10 seconds accompanied by an oxygen desaturation of 3% (American Academy of Sleep Medicine Task Force 1999). We defined the apnea and hypopnea index (AHI) as the number of apneas and hypopneas per hour of sleep. Based on the results of the sleep studies, we divided the subjects into four groups: 1) normal sleep study (AHI < 5), mildly abnormal (AHI 5-15), moderately abnormal (AHI 15-30), and severely abnormal (AHI > 30). Patients were considered OSA patients if their AHI was ≥ 5 (American Academy of Sleep Medicine Task Force 1999), and defined moderate and severe OSAS as AHI ≥ 15 and ESS ≥ 10. Subjects with an AHI < 5 and an ESS < 10 were considered nonapneic and nonsleepy snorers. We measured daytime sleepiness with ESS and considered an ESS score ≥ 10 abnormal (Johns 1991). We also measured weight and height and calculated each subject’s body mass index (BMI).

In Study III, we started CPAP treatment during one-night CPAP pressure titration at the ward by using an autotitrating CPAP device (Autoset®, Resmed, Sydney, NSW, Australia). For the devices that patients used at home, the fixed pressure was
set to a pressure that eliminated 95% of obstructive apneas and hypopneas, snoring and flow limitation. The nurses individually adjusted the interfaces, and patients used full-face masks if nasal masks proved intolerable. The patients received detailed instructions about CPAP treatment and were also informed of possible side effects of the therapy. Moreover, we advised the patients in how to treat possible upper airway symptoms with topical medications, such as oily or saline drops, and recommended temporary use of a nasal decongestant during viral infections. All our patients received a prescription for intranasal steroids along with the recommendation to take the medication if nasal symptoms became problematic during CPAP treatment. We included a humidifier in the treatment only if local treatment proved insufficient to improve upper airway side effects. In practice, we added the humidification to the treatment no earlier than the first follow-up visit.

4.2.3 STUDY IV

Study IV is also a prospective questionnaire-based study. A sleep specialist decided whether to carry out the CPAP trial at the hospital or at home. We used Resmed Autoset CPAP devices (Resmed Corp., San Diego, CA, USA) to perform the home titrations, set the pressure between 4-20 cm H2O, and attached a Reslink (Resmed Corp., San Diego, CA, USA) device with a pulse oximetry to the CPAP device to monitor the oxygen saturation during initiation. Those who underwent a manual CPAP pressure titration at the Sleep Unit had a history of uvulopalatoplasty. The sleep nurse manually increased the CPAP pressure to eliminate apneas, hypopneas, flow limitation and snoring. For those with reduced mobility or restricted learning ability, we carried out the CPAP initiation at the Sleep Unit with the Autoset CPAP device. To monitor the patients at the Sleep Unit during manual or automatic titration, we used an Embla N7000 cardiorespiratory sleep study device (Resmed Corp., San Diego, CA, USA). To download data on CPAP use, we used ResScan software (Resmed Corp., San Diego, CA, USA) during initiation and later during CPAP therapy. Dividing the total hours of use by the length of the CPAP period in days, including days with no CPAP use, yielded the average daily CPAP use. Median daily CPAP use indicated the median number of hours per day only for those days with CPAP use. We scheduled follow-up visits at three months and at one year after CPAP initiation. Initially, we offered heated humidification in the treatment to all patients suffering from any troublesome upper airway symptoms and to those who used regularly nasal steroids. Later we added humidification to the treatment if their upper airway symptoms increased during CPAP treatment. After CPAP initiation, the sleep nurse went through the results of the initiation in the ResScan report, checked the mask fit, and offered additional instructions in CPAP treatment as needed.
4.2.4 QUESTIONNAIRES

In all studies, we assessed daytime sleepiness with the ESS questionnaire (Johns 1991). ESS is a validated eight-item measure of daytime sleepiness that asks respondents to estimate how likely they are to doze off in eight different situations. The score is based on a 0- to 24-point scale, with higher scores representing greater levels of sleepiness.

4.3.4.1 Study I

In Study I, in addition to the ESS questionnaire, the patients completed questionnaires inquiring about depression (Depression Scale – DEPS) and alcohol consumption (Alcohol Use Disorders Identification Test – AUDIT).

4.3.4.2 Studies II and III

In Study II, the study subjects completed the questionnaires (Appendix: Questionnaire 1) in the evening before the sleep study.

In Study III, the patients completed Questionnaire 1 (Appendix: Questionnaire 1) in the evening before CPAP pressure titration, and Questionnaire 2 (Appendix: Questionnaire 2) during the first follow-up visit after two months of treatment.

Questionnaire 1 comprised two sections: 1) current upper airway symptoms (dryness of throat, mouth and nose, nasal bleedings, nasal stuffiness, rhinorrhea, postnasal drip and sneezing) and 2) history of upper airway disorders, operations, allergic rhinitis, and medications reported by the patients. We evaluated the frequency of their upper airway symptoms by asking how often they experienced the symptoms. We used a scale from 1 to 4 (1 = never, 2 = occasionally, 3 = often (i.e. on most weekdays), 4 = all the time (i.e. every day)). Questionnaire 2 contains the same questions about upper airway symptoms occurring during CPAP treatment as Questionnaire 1. In Questionnaire II, we also asked the patients whether they had had sinusitis after the initiation of CPAP treatment, whether the CPAP treatment made them feel as if they were choking, whether they had slept with CPAP and for how many hours per night, whether they benefited from CPAP treatment, whether CPAP treatment caused more trouble for them than benefit, and whether they wanted to continue CPAP treatment. We combined the four upper airway symptom scores into two categories: 1 or 2 = no symptoms present, 3 or 4 = symptoms present. For analysis, we used both the original and the combined scores. We also divided the upper airway symptoms in two categories: 1) symptoms of airway dryness (dryness of throat, mouth, and nose, and nasal bleeding) and 2) symptoms of rhinitis (nasal stuffiness, rhinorrhea, postnasal drip, and sneezing). We also wanted
to assess the stability of the symptoms, and because 98 of the original sleep study subjects began using CPAP during the study period, we asked them to complete the same questionnaire on upper airway symptoms again.

4.3.4.3 Study IV

In Study IV, we used a self-efficacy questionnaire to inquire about patients’ preparedness and willingness to begin CPAP treatment (scale 5-25) (Steponowsky et al. 2002), which they completed prior to CPAP initiation. The questions were: 1) Are you confident you can use CPAP regularly? 2) Do you have the ability to use CPAP regularly? 3) Are you confident you will use CPAP regularly even if you do not feel like it? 4) Are you confident you will use CPAP regularly even if you experience uncomfortable side effects? 5) Can you operate the CPAP machine to make it more comfortable for you? Patients also completed the ESS questionnaire to evaluate their daytime sleepiness prior to and after the CPAP trial. After the CPAP trial, the patients completed a questionnaire (Appendix: Questionnaire 3) with visual analogue scales on their satisfaction with CPAP initiation (0 = I am very disappointed, 100 = I am very satisfied with it), their eagerness to continue CPAP treatment (0 = I am not eager at all, 100 = I am very eager), and their willingness to continue CPAP therapy at home (0 = I am not ready to continue CPAP under any circumstances, 100 = I would like to continue). We classified patients as uneager, unsatisfied and unwilling if their corresponding score was under 50. Later, to predict CPAP adherence at one year, we ran a receiver-operative characteristics curve using scores for eagerness, satisfaction, willingness, and self-efficacy.

4.2.5 STATISTICAL METHODS

In all studies, two-sided values of p < 0.05 were considered significant.

In Study I, PSG served as the gold standard. We used the Pearson correlation coefficient to evaluate the relationship between PSG and MP3 snoring time. We assessed agreement between these data with the Bland Altman test and created a ROC for the MP3 to detect snoring. To compare differences between separate patient groups, we performed an independent samples t-test. We used SPSS 18.0 for Microsoft Windows (SPSS Inc. Chicago, IL, USA) for statistical analyses.

In Studies II and III, we used the independent samples t-test, the x²-test, and Mann-Whitney U statistics to compare differences between the patient groups. We used McNemar’s test to identify differences in the number of symptomatic patients between two assessments. In Study II, we used the method recommended by Bland and Altman to analyze intraindividual agreement between the symptoms scores. We
also calculated correlation coefficients and used SPSS statistical software, versions 15.0 and 19.0 (SPSS Inc. Chicago, IL, USA), to perform computations.

In Study IV, we tested differences between patient groups with the independent samples t-test, the $x^2$-test and the Mann-Whitney U-test. We also calculated receiver-operating characteristics (ROC) curves for scores of self-efficacy and patient satisfaction and of eagerness and willingness to continue CPAP at home to detect CPAP use during three-month and one-year follow-up visits. We used SPSS 20.0 for Microsoft Windows (SPSS Inc. Chicago, IL, USA) for the statistical analyses.
5. RESULTS

5.1 Study I

No technical failures were reported with the PSG recordings, and 27 of the 200 MP3 recordings (13.5%) failed for technical reasons. MP3 recording underestimated snoring time by a mean ± standard deviation (SD) of 32 ± 55 min. The mean MP3 snoring time was 62 ± 53 min, and the mean PSG snoring time was 96 ± 86 min. The Pearson correlation coefficient r-value was 0.77 (p < 0.001) between the MP3 and PSG snoring data. Values for MP3 snoring time varied according to the threshold used: 241 ± 82, 47 ± 46, and 39 ± 41 minutes for a threshold of one, three, or four times the median, respectively.

Patients with OSA (AHI > 5) snored significantly longer than did simple snorers (AHI < 5) (mean ± SD MP3 snoring time 79 ± 55 minutes vs. 30 ± 28 minutes, p < 0.001). We also found a significant correlation between MP3 snoring time and the severity of OSA (r = 0.49, p < 0.001). We found no correlation between the intensity of snoring (loud snoring) and the severity of OSA, nor between the intermittent snoring index and the severity of OSA.

We considered 148 patients (74%) to be snorers, since, according to the PSG, they snored for more than 5% of their sleeping time. The sensitivity and specificity of the MP3 recorder to identify a subject as a snorer was 92% and 60%, respectively, with a high area-under-the-curve (AUC) value of 0.857. The positive predictive value of the MP3 recorder in detecting snoring was 89%, and its negative predictive value, 68%, respectively.

The mean PSG AHI was 17 ± 20/hour. In total, 136 patients (68%) had an AHI > 5/hour of sleep, 77 patients (39%) an AHI > 15/hour of sleep, and 38 patients (19%) an AHI > 30/hour of sleep in PSG. Total sleep time was a mean 368 ± 88 minutes, and wakefulness after sleep onset was a mean 67 ± 69 minutes. Sleep efficiency was a mean 85 ± 15%, and 139 (70%) patients had a sleep efficiency of over 80%. We found no correlation between snoring times and BMI or values of DEPS and AUDIT.
5.2 Study II

Of our 524 sleep study patients, 144 (28%) were nonapneic nonsleepy snorers (AHI < 5 and ESS < 10), and 80 patients (15%) had moderate to severe OSAS (AHI ≥ 15 and ESS ≥ 10).

The study subjects frequently reported upper airway disorders: 139 subjects (26%) had allergic rhinitis, 106 subjects (20%) had constant rhinorrhea, 84 subjects (16%) had a septum deviation, and 29 subjects (6%) had nasal polyps. Altogether, 134 subjects (26%) had undergone tonsillectomy or adenoidectomy or both, 34 subjects (7%) septoplasty, 23 subjects (5%) polypectomy and 21 subjects (4%) sinus surgery. To improve their snoring, 33 subjects (6%) had undergone palatal/pharyngeal surgery, and 80 (15%) subjects used regular medication for rhinitis (intranasal steroid).

The study subjects were divided into different groups by AHI, and we compared the frequency of nasal and pharyngeal symptoms between the groups (Figure 10). Upper airway symptoms, especially nasal stuffiness and airway dryness, were also common in primary snoring (AHI < 5) and mild OSA (Figure 10); mouth dryness increased with OSA severity (Figure 10). Nasal stuffiness and rhinorrhea showed no significant change with OSA severity: 58% of patients with AHI < 5 reported symptoms of rhinitis (nasal stuffiness and/or rhinorrhea), as did 63% of patients with AHI 5-15, 53% of patients with AHI 15-30, and 62% of patients with AHI < 30. Nonapneic, nonsleepy snorers (AHI < 5 and ESS < 10) had significantly less mouth dryness than did patients with moderate or severe OSAS (AHI ≥ 15 and ESS ≥ 10) (40% vs. 71%, p < 0.01). In addition, patients with moderate or severe OSAS experienced not only throat dryness slightly more often than did nonapneic, nonsleepy snorers (65% vs. 51%), but also nose dryness (59% vs. 48%). However, the difference in the frequency of symptoms did not reach statistical difference (p > 0.05). As many as 20% of the nonapneic nonsleepy snorers used rhinitis medication, whereas only 4% of patients with moderate to severe OSAS (AHI ≥ 15 and ESS ≥ 10) regularly used medication for nasal symptoms.

We analyzed the intraindividual variability of symptom scores for 98 sleep apnea patients who completed the questionnaire on nasal and pharyngeal symptoms twice. The mean (± SD, range) time interval between the sleep recording and CPAP titration was 2.8 (± 1.9, 0-10) months. For the whole group of patients, we found no significant difference in symptoms between the two assessments. The means and differences between the two measurements of symptom scores for each patient and correlation coefficients appear in Table 5.
Figure 10  Study subjects with frequent upper airway symptoms based on the apnea-hypopnea index (% of patients)

Table 5  Repeatability of symptom scores inquired during the sleep study and at CPAP titration. Frequency of symptoms was evaluated on a scale from 1 to 4 (1 = never, 2 = occasionally, 3 = often (i.e. during most of the days of the week), 4 = all the time i.e. every day) by inquiring how often the symptom occurred.

<table>
<thead>
<tr>
<th>Pairs of measurements (N)</th>
<th>Dry mouth</th>
<th>Dry throat</th>
<th>Dry nose</th>
<th>Nose bleeds</th>
<th>Nasal stuffiness</th>
<th>Rhinorrhea</th>
<th>Postnasal drip</th>
<th>Sneezing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>97</td>
<td>98</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>Mean value of pair(^1)</td>
<td>2.90</td>
<td>2.83</td>
<td>2.75</td>
<td>1.41</td>
<td>2.79</td>
<td>1.93</td>
<td>2.22</td>
<td>2.42</td>
</tr>
<tr>
<td>Difference in symptom score (average)</td>
<td>0.01</td>
<td>0.13</td>
<td>0.05</td>
<td>-0.10</td>
<td>0.08</td>
<td>0.08</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>Correlation coefficient(^2)</td>
<td>0.64</td>
<td>0.43</td>
<td>0.58</td>
<td>0.64</td>
<td>0.64</td>
<td>0.54</td>
<td>0.48</td>
<td>0.42</td>
</tr>
</tbody>
</table>

\(^1\) [Symptom score at sleep study – symptom score at CPAP titration]/2.
\(^2\) Spearman correlation coefficient (\(r\)) between symptom score at sleep study and at CPAP titration.

5.3 Study III

In Study III, 370 of the 385 patients attending the CPAP pressure titration continued CPAP treatment at home. Prior to the first follow-up visit after two months of CPAP treatment, 88 (22%) patients had abandoned the treatment. Another 51 (14%) patients abandoned the treatment before or at the one-year follow-up visit.
After one year, 237 patients (64%) continued CPAP treatment. At the first follow-up visit, the patients used CPAP a mean ± SD 3.2 ± 2.6 hours/day, and 52% of the patients were using CPAP for more than 4 hours/day. At the one-year follow-up, the patients used CPAP a mean ± SD 3.9 ± 2.4 hours/day, and 58% of the patients used CPAP more than 4 hours/day. At the two-month and one-year follow-ups, those patients who chose to continue CPAP after that follow-up (“users”) used CPAP significantly longer than did those who terminated the treatment after that follow-up (“non-users”) (4.5 ± 2.3 hours/day vs. 1.0 ± 0.7 hours/day, p < 0.01 and 4.5 ± 2.2 hours/day vs. 1.0 ± 1.4 hours/day, p < 0.01, respectively). The users at the two-month and one-year follow-ups were more obese at baseline than were the non-users (BMI 34 ± 7 vs. 31 ± 5, p < 0.01 and 34 ± 7 vs. 31 ± 5, p < 0.01, respectively), and their sleep apnea was more severe (AHI 35 ± 24 vs. 26 ± 21, p < 0.01 and 36 ± 25 vs. 26 ± 21, p < 0.01, respectively). The users also reported benefit from the treatment more often than did non-users (after two months, 84% vs. 6%, p < 0.001; after one year, 96% vs. 5%, p < 0.001).

A history of allergic diseases and upper airway treatments was common among subjects in Study III: 27% of the patients had allergic rhinitis, 14% had asthma bronchiale, 18% used intranasal corticosteroids, 6% had undergone polypectomy, 4% sinus surgery, 12% nasal septal surgery, 26% adenoidectomy/tonsillectomy, and 8% palatal surgery. Prior to CPAP treatment, patients often suffered from upper airway symptoms. Only 36 patients reported no upper airway symptoms before CPAP treatment, whereas 54% of all the patients complained of throat dryness, 61% mouth dryness, 51% nose dryness, 6% nose bleeds, 52% nasal stuffiness, 17% rhinorrhea, 24% postnasal drip, and 30% sneezing. At the two-month follow-up visit, 43% of the patients had throat dryness, 45% mouth dryness, 44% nose dryness, 7% nose bleeds, 48% nasal stuffiness, 22% rhinorrhea, 22% postnasal drip, and 30% sneezing. Throat, mouth and nose dryness had decreased significantly during CPAP therapy (p < 0.05). Prior to CPAP treatment, however, there were no differences in upper airway symptoms between the patients who continued CPAP treatment after one year (users) and those who had terminated CPAP treatment (non-users) (Figure 11). At the two-month follow-up visit, CPAP users less often suffered mouth, throat and nose dryness and/or nasal stuffiness, whereas rhinorrhea increased significantly among non-users (Figure 11). At the two-month follow-up visit, non-users reported nasal stuffiness more often than did CPAP users (45% vs. 41%, p < 0.05). Of those patients who quit CPAP treatment at any time during the study period, 23% reported nasal problems as the main reason for treatment cessation. For 42 patients (11%), heated humidification was added to their CPAP treatment during or after the first follow-up visit. Those patients reported no more upper airway symptoms prior to CPAP treatment than did those who needed no humidification; moreover, those patients who received humidification were no more likely to continue treatment at one year than were those who received no humidification.
Figure 11 Sleep apnea patients with frequent upper airway symptoms prior to CPAP treatment and at the first follow-up after two months of CPAP treatment. * p < 0.05.

5.4 Study IV

Of the 580 patients referred for CPAP initiation, 558 (95%) were CPAP naive, and 17 (3%) patients had undergone uvulopalatopharyngoplasty (UPPP). Of all the patients, 50 (9%) had begun CPAP in the ward at the Sleep Unit, and 530 (91%) had begun their therapy at home. Of all the patients, 44 (8%) refused to continue their CPAP therapy immediately after initiation. By three months, 96 patients had abandoned CPAP. Later, 23 patients discontinued their CPAP therapy, and 377 (65%) patients continued after one year.

During the CPAP initiation period, average CPAP use was 5.1 ± 2.4 hours/day, at three months 3.0 ± 2.4 hours/day, and at one year 4.1 ± 2.3 hours/day. The corresponding values for median CPAP use were 5.4 ± 2.3 hours/day, 5.0 ± 2.1 hours/day and 5.7 ± 1.8 hours/day, respectively. The mean ± SD self-efficacy score at CPAP initiation was 21 ± 4. The mean ± SD eagerness score was 75 ± 28, the mean satisfaction score was 69 ± 29, and the mean willingness score was 81 ± 26. A receiver-operating characteristics (ROC) curve for scores of self-efficacy in the detection of CPAP use at one year showed an area under the curve (AUC) value of 0.635. Corresponding values for satisfaction, eagerness and willingness were 0.738, 0.746 and 0.724, respectively, and in the detection of treatment success (CPAP use > 4 hours/night) at one year showed AUC values of 0.612, 0.581 and 0.601, respectively.

Of all the patients, 77 expressed a low willingness (score < 50) to continue CPAP therapy immediately after the CPAP trial. At one year, 24 of them were still using
Results

CPAP, but only 7 were using CPAP more than four hours daily. Thus, a low willingness score obtained immediately after CPAP initiation not only predicts whether the patient will stop CPAP therapy by one year with a specificity of 94%, but also predicts poor CPAP use (< 4 hours/day) with a specificity of 97%. The sensitivity score for low willingness was low (32% and 21%, respectively).

By one year, 63% of patients expressing a low satisfaction score (< 50) at their initial CPAP trial had abandoned CPAP, whereas only 18% of satisfied patients (score ≥ 50) had done so (p < 0.001). This same significant (p < 0.001) trend to quit CPAP therapy occurred among groups of patients with low willingness (score < 50) (69% vs. 24%, p < 0.001) and eagerness (score < 50) (66% vs. 20%, p < 0.001) scores. Patients who continued CPAP treatment after one year had significantly higher scores on the self-efficacy questionnaire after one year than did non-users: a mean ± standard deviation (SD) 21 ± 3 vs. 19 ± 4 (p < 0.001) prior to CPAP trial. Patients continuing CPAP treatment after one year also had significantly higher scores on questionnaires they completed after the trial which inquired about their satisfaction with the CPAP trial (75 ± 26 vs. 44 ± 33, p < 0.001), as well as their eagerness (80 ± 26 vs. 48 ± 37, p < 0.001) and willingness to continue CPAP treatment (85 ± 23 vs. 56 ± 37, p < 0.001). Patients with a score > 20 on the self-efficacy questionnaire had higher CPAP use at three months than did patients with a score < 20 (average use, 3.5 hours ± 2.5 hours vs. 2.3 hours ± 2.3 hours, p < 0.001). At one year, patients with a score > 20 used CPAP more often than did patients with a score < 20 (average use 4.4 hours ± 2.2 hours vs. 3.7 hours ± 2.3 hours, p < 0.001). The mean satisfaction score was significantly lower than the willingness score (69 ± 29 vs. 81 ± 26, p < 0.001), and the two scores showed a significant correlation (r 0.70, p < 0.001).

CPAP use at three-month and one-year follow-up visits did not significantly differ between groups of those who initiated CPAP therapy at home and those who initiated CPAP at the hospital: 2.5 ± 2.4 hours/day vs. 2.8 ± 2.7 hours/day (p > 0.05), and 4.0 ± 2.3 hours/day vs. 4.0 ± 2.3 hours/day (p > 0.05), respectively. Patients with more severe OSA showed better treatment adherence at one year (pre-treatment AHI in CPAP users 38 ± 23 vs. 27 ± 18 in non-users, p < 0.001 and pre-treatment ODI4 33 ± 24 vs. 24 ± 20, p < 0.001, respectively). With CPAP treatment, ESS scores dropped significantly from 9 ± 4 to 7 ± 4 (p < 0.001) at one year.
6. DISCUSSION

6.1 Materials

In Europe, it is common to begin with a simple sleep study (AASM type 3) when the pre-test probability for sleep apnea is high (Collop et al. 2007). Consequently, our Study I subjects comprised a group of special patients who had been referred to the sleep unit for PSG because the initial examination, usually a polygraphy, had failed to identify the disease or the subject presented clinical findings suggesting a low pre-test probability for sleep apnea. As a result, many of our patients were female, young, and not very obese. We assume that the MP3 recording would have shown better sensitivity in detecting snoring had we examined unselected sleep unit patients.

Study II reports for the first time the prevalence of upper airway symptoms of rhinitis and airway dryness in primary snoring and in patients with mild OSA. In Study II, we considered patients with an AH1 < 5 and an ESS < 10 to be nonapneic nonsleepy snorers. However, we did not specifically verify snoring. Consequently, this group of patients may include patients with other sleep disorders or even healthy subjects. Earlier data on upper airway symptoms related to sleep apnea and CPAP treatment have originated mostly from relatively small patient series and most have been retrospective (Table 1). The strength of Study III is that its study population consists of a larger group of patients (385 patients) than earlier prospective studies demonstrating the side effects of CPAP treatment (Baltzan et al. 2009, Brander et al. 1999, Kribbs et al. 1993). All patients in Studies II and III were unselected, and consecutive patients were referred to Hyvinkää Hospital for a sleep study (Study II) and for CPAP initiation (Study III). All patients referred for suspected sleep apnea to communal care in the Hyvinkää area are examined and treated primarily at the sleep unit of Hyvinkää Hospital.

For Study IV, we prospectively enrolled a large group (580 patients) of consecutive patients referred for CPAP initiation. In Helsinki, all CPAP initiations take place at the Sleep Unit. Therefore, our study subjects consisted of a large group of unselected OSAS patients. CPAP follow-up data were missing for small groups of patients (7%), they had moved to another district, failed to participate in the follow-up visit, postponed their follow-up appointment or had forgotten their CPAP device at home.
6.2 Methods

6.2.1 SCREENING FOR SNORING

Snoring is a common symptom than can indicate OSA. The gold standard for diagnosing OSA is polysomnography, which is an expensive and time-consuming examination (American Sleep Disorders Association 1997, Kushida et al. 2005). To improve access to appropriate treatment for patients with more complex diseases, we aimed to improve preliminary screening of OSA. We developed a method that uses a simple MP3 recording device to analyze snoring sounds, and in our study, we found that an MP3 recorder can accurately detect snoring sounds. We also found a close correlation between snoring sounds detected by the MP3 recorder and those detected by PSG. In addition, we found a significant correlation between snoring time and the severity of OSA.

Vibration of the soft tissue in the upper airway during respiration causes snoring. It is triggered by muscle relaxation of the upper airway dilators during sleep. The tendency of the soft tissue to vibrate increases, and the diameter of the upper airway decreases, modifying the air velocity (Stuck et al. 2010). There are no accepted standardized methods for recording and classifying snoring (Pevernage et al. 2010), and the definition of a snorer is arbitrary (Stuck et al. 2010). Recordings of snoring vary in the directionality, placement, and sensitivity of the recorder, body position, possible nasal obstruction, and surgical modification of the upper airway.

In our study, we chose to consider a person to be a snorer if the patient’s snoring time exceeded a threshold of 5% of the total sleeping time based on the PSG results. Compared to the PSG results, the MP3 recorder successfully identified 92% of the snorers. We also attempted to use a threshold of 10% to define a snorer, but failed because doing so improved the sensitivity of the MP3 device to screen for a snorer.

We documented that the MP3 device identified snoring effectively, even though it underestimated the snoring time by a mean ± SD of 32 ± 55 minutes. The MP3 device records all acoustic sounds in the patient’s environment, including sounds such as talking, coughing, or noise from the medical personnel, which leads to a higher median threshold value. Consequently, this slightly reduces t sensitivity of the MP3 device in detecting snoring sounds. We chose to adopt the threshold for snoring, defined as twice the median value, after an initial analysis of the results with thresholds of 1, 2, 3 and 4 times the median value. In addition, all the portable home monitoring devices, including the MP3 recorders, reflect a total recording time that is not the true time the patient is asleep. Underestimation of the MP3 snoring time stems partly from the fact that our patients had a mean sleep efficiency of 85%, reflecting the MP3 device’s tendency to include a mean of at least 15% of the recording time in which no snoring occurred. We also attached the MP3 microphone to the patient’s collar, and the PSG microphone directly to the patient’s neck. Depending on the patient’s position, this may also have lead to the underestimation of snoring
time. On the other hand, the MP3 device may also have overestimated the snoring
time in some subjects who have noisy breathing, but without “real” snoring on the
PSG. We analyzed the sleep data using the old Rechtschaffen and Kales rules at
the time of Study IV. This had no effect on our results, however, because studies
have shown the methods to be identical in detecting total sleeping times (Moser

Intermittent snoring may indicate apneas. So, we attempted to predict sleep
apnea from the MP3 recording. Unfortunately, our single channel recording fai-
led to predict the patient’s apnea and hypopnea index. Manual scoring may have
improved the accuracy of a single channel device, as reported earlier (Nigro et al.
2011), but it would also have restricted this method to use by trained personnel
only, which was not the aim of this study; we wanted to evaluate MP3 as a scree-
ning method for snoring.

Although, recording snoring sounds with an MP3 recorder is quite simple, we
encountered some technical failures in initiating the recording. Switching the re-
corder on was surprisingly difficult, partly because the accessory bag slightly covers
the recording button. In addition, the device and the screen are quite small, and the
time lag between clicking a button on the control pad and the appearance of the
next item in the highlighted was troublesome. Moreover, the editing possibilities
for the MP3 recording were limited to the beginning and the end of the recording.
Presumably, replacing the device with a more advanced model and instructing the
nurses and patients more carefully could have minimized technical failures with
the MP3 device. Another limitation of our study is that, although the MP3 device
is designed to record one person’s snoring at a time, it may also record the bed
partner’s sounds, which can confound the result.

6.2.2 QUESTIONNAIRES

For this thesis, we used a variety of questionnaires. Some possible factors can reduce
the reliability of questionnaire-based studies: the respondent can misunderstand
the question, provide a dishonest answer, remember the facts incorrectly or the
answer can vary depending on the mood of the respondent or time of the day or year.

We used ESS to measure daytime sleepiness in all studies. ESS is a validated and
widely used questionnaire measuring daytime sleepiness (Johns 1991). In Studies
II and III, we used two questionnaires (Appendix: Questionnaire 1 and 2), which
we created ourselves, to evaluate upper airway symptoms in snorers and in OSAS
patients before and during CPAP treatment. These questionnaires have not yet
been validated. In Questionnaire 1, we inquired about the history of upper airway
disorders and operations. One study limitation was that the disorders were not
confirmed by physicians; rather, we had to rely on the answers given by the study
subjects. To assess the stability of the symptoms and the repeatability of the ques-
tions, we asked 98 of the original sleep study subjects, who began CPAP during the study period, to complete the same questionnaire on upper airway symptoms and found no significant difference in symptom scores between the two assessments.

In Study IV, we chose to use a self-efficacy questionnaire by Stepnowsky et al. (Stepnowsky et al. 2002). Another more detailed self-efficacy questionnaire introduced by Weaver et al (Weaver et al. 2003) is also available, but in our study, we chose to use the simpler questionnaire by Stepnowsky et al., which fit more easily into our daily practice. For Study IV, we also used a questionnaire (Appendix: Questionnaire 3) with visual analogue scales to evaluate satisfaction with CPAP initiation, eagerness to continue CPAP treatment, and willingness to continue CPAP therapy at home. We created the questionnaire ourselves and we used it for the first time in Study IV. It has not been validated yet.

6.3 Results

6.3.1 SCREENING FOR SNORING

In our study, we found the closest agreement between the MP3 and the PSG in subjects presenting with a short snoring time. Longer snoring times raised the median acoustic MP3 threshold and led to a progressive reduction in the sensitivity of the method. Clinically, however, it was easier to identify a heavy snorer than an occasional snorer.

Having a history of snoring and the presence of OSA shows a strong association (Romero et al. 2010). The association of snoring with cardiovascular diseases may stem from consequences of OSA and is linked to intermittent hypoxemia, sleep fragmentation, and intrathoracic pressure changes (Kohler & Stradling 2010). However, snoring itself seems to lead to vibration of the upper airway, which is transmitted to the carotid artery, possibly resulting in direct vibration injury to the artery (Amatoury et al. 2006, Cho et al. 2011). Therefore, researchers have attempted to analyze audio recordings of snoring to diagnose OSA. Research has shown that a method to analyse the acoustic characteristics of the snoring can identify significant differences in the sound power spectrum of the snoring sound between subjects with simple snoring and OSAS (Fiz et al. 1996). In our study, we found significant differences in the duration of snoring between simple snorers and OSA. A long snoring time (within a one-night study) may indicate the presence of OSA. Unlike Wilson and colleagues, who showed that snoring sound intensity is closely related to AHI during sleep (Wilson et al. 1999), we found no correlation between the intensity of the snoring sound. This might result from our strict method to score snoring with PSG in which we exclude all inaudible snoring signals.

Morris and colleagues have introduced a simple clinical screening test for OSA in snoring patients by asking them questions about their snoring severity and by
measuring their BMI; they showed that these two parameters provided rapid risk stratification for OSA (Morris et al. 2008). However, we found no correlation between snoring time and BMI. Moreover, an earlier study has reported that BMI is an independent risk factor for snoring in women (Li et al. 2009), and more recently, a study by Nagayoshi and colleagues (Nagayoshi et al. 2011) also reported that both BMI and alcohol consumption were associated with habitual snoring. In our study, we found no correlation between snoring time and the AUDIT score, which quantifies the greater risks for alcohol consumption. The fact that we objectively quantified the snoring time in our study may explain the differences in the reported results.

The strength of our screening method is that it can work with any computer capable of downloading MP3 data. We aimed to develop a simple method to detect snoring sounds and to make it available to any computer user who only needs to download MP3 data and then define values over twice the median threshold. The challenge is to find a suitable program to convert musical data to mathematical data that the user can use.

Our aim was not to try to replace the need for a sleep study; rather, we demonstrated how a single channel recording from a music-recording device could help in evaluating and screening for snoring. Obesity is a growing problem, and it is causing the snorer population to grow (Li et al. 2009, Nagayoshi et al. 2011). Therefore, the population needs to be informed about snoring and its risks, and we must find ways to screen for snoring with simple and inexpensive methods. If the patient does not snore during MP3 screening, no further examinations are needed unless a sleep disorder other than snoring is suspected. However, if snoring is detected during MP3 recording, OSA should be excluded by a sleep study before undergoing surgical procedures to eliminate snoring. Professionals should therefore use MP3 screening with prudence.

The strengths of the device are that one can obtain a more accurate perception of snoring with minimal additional cost, because one can easily repeat a recording with an MP3 device several times at home. This method could also prove helpful in following up on snorers without OSA both before and after treatment therapies. Moreover, because the recorder is non-invasive and low-cost, this method of screening for snoring also has potential for plenty of other applications in sleep medicine.

### 6.3.2 UPPER AIRWAY SYMPTOMS, SNORING AND SLEEP APNEA

Prospective Studies II and III showed that before treatment, nasal and pharyngeal symptoms were common in both primary snorers and OSAS patients. In both studies, more than half of the study subjects suffered from throat, mouth and nose dryness as well as nasal stuffiness. Both snorers and OSAS patients often exhibited nasal symptoms. The frequency of mouth dryness, however, was related to OSA se-
Discussion

Verity. After initiating CPAP treatment, the frequency of most common upper airway dryness symptoms (e.g. nose, throat and mouth dryness) decreased significantly.

Earlier studies reveal that upper airway symptoms are common in sleep apnea patients during CPAP treatment: more than half of the patients reported mouth, nose and throat dryness during CPAP treatment (Brander et al. 1999, Meslier et al. 1998, Pepin et al. 1995). In addition, studies have shown that upper airway symptoms – particularly, symptoms of upper airway dryness, nasal stuffiness, post nasal drip, sneezing and rhinorrhea – are also common in untreated OSAS patients (Brander et al. 1999, Lojander et al. 1999). In prospective Study III, we also demonstrated that upper airway symptoms related to mucosal dryness are common in OSAS patients even before treatment. For the first time, we showed in Study II the prevalence of upper airway symptoms in snorers and in mild OSA and found that about half of them often suffered from nasal stuffiness and upper airway dryness. The frequency of mouth dryness was related to the severity of OSA, whereas the frequency of nasal stuffiness and dryness showed no significant increase with the severity of OSA. Because upper airway symptoms were common in both primary snorers and OSAS patients, predicting OSAS based on nasal and pharyngeal symptoms appears to be impossible. Earlier, however, researchers noted that mouth dryness is associated with OSAS (Oksenberg et al. 2006). In Study II, we also noticed that sleep study proved normal more often in patients with no mouth and throat dryness than in those who had dryness symptoms.

In Study II, over 50% of the snorers experienced frequent nasal stuffiness. An earlier study evaluating the predictors and prevalence of OSA in middle-aged men revealed that 10.4% of the study subjects reported nasal stuffiness (Stradling & Crosby 1991). In a large population-based study, Young and colleagues also reported that 17.4% of their study subjects often suffered from nasal stuffiness (Young et al. 2001). In addition, a questionnaire-based study comprising over 3000 employees in Pakistan revealed that 5.8% of the responders reported suffering from nasal congestion almost daily (Hussain et al. 2010). Therefore, the results of our study suggest that nasal stuffiness is much more common in snorers than in the general population. One of the typical symptoms of nasal stuffiness is nasal dryness. Exhalation through the mouth dries and cools the nasal mucosa, which may cause inflammation (Martins De Araujo et al. 2000) and exacerbate nasal symptoms. In our study, we noticed that nonapneic nonsleepy snorers used nasal steroids regularly more often than did patients with OSAS. This could be due to the possibility that OSAS patients adapted to their nasal symptoms during the development of the disease.

Upper airway symptoms in snorers and patients with OSAS have many potential causes. Increased nasal airflow resistance may lead to the development of upper airway obstruction during sleep (Deegan & McNicholas 1995, Rappai et al. 2003). Previous studies have also demonstrated an association between snoring or OSA and nasal obstruction (Lofaso et al. 2000, Young et al. 1997, Young et al. 2001).
Various kinds of rhinitis or anatomical abnormalities such as septal deviation or nasal polyps can cause nasal obstruction. Breathing during sleep is normally nasal rather than oral (Fitzpatrick et al. 2003). The humidity of inhaled air increases to 80-100% when air passes through nasal cavity (Huizing E H & de Groot J A M 2002). Patients with OSA often have a tendency to breathe through the mouth, which may expose them to dryness of the mouth and throat (Ruhle & Nilius 2008), as exhaling through the mouth prevents the return of humidity from the lungs back to the nasal mucosa. We hypothesized that untreated OSAS may explain the upper airway symptoms from which OSAS patients suffer prior to CPAP treatment, and that the change from mouth breathing to nasal breathing during CPAP treatment may alleviate these symptoms.

Airflow during nasal CPAP leads to changes in the nasal mucosa, and the degree of inflammation and fibrosis increases during CPAP treatment (Saka et al. 2012). However, a study by Gelardi and colleagues (Gelardi et al. 2012) showed that nasal inflammation/infection occurred frequently in OSAS, but regular CPAP treatment with a humidifier significantly reduced cell infiltration (neutrophils, eosinophils, lymphocytes and muciparous cells). In addition, Kotsourelakis and colleagues (Koutsourelakis et al. 2011) have demonstrated that nasal obstruction in OSA patients is inflammatory in origin, and that adding heated humidification to the CPAP treatment reduced nasal resistance and mucosal inflammation.

Dryness of the upper airway seems to resolve even without humidification. Nasal stuffiness does not always indicate greater nasal resistance and can occur in the presence of dry nasal mucosa (Farmer et al. 2009, Garcia et al. 2007). Because oral breathing decreases during CPAP treatment, dryness of the nasal mucosa diminishes, thereby alleviating nasal stuffiness.

An earlier study by Brander and colleagues (Brander et al. 1999) showed that sneezing and rhinorrhea increased significantly during CPAP treatment. No such increase was observed in this present study (III), perhaps because of the different study designs and treatment practices. The earlier study had fewer patients (49 vs. 385) and different follow-up times and procedures for assessing symptoms. During the earlier study, CPAP devices and masks were less comfortable, no humidifiers were used, and autoadjusting CPAP devices were unavailable. The fixed treatment pressure was determined by using an overnight oximeter and manual titration. Treatment pressures were therefore higher. In addition, treating the side effects of the treatment was less effective than nowadays, when all the patients are told how to treat nasal symptoms, all study patients receive a prescription for nasal steroids, and the treatment included a humidifier if the patient complained of persistent upper airway symptoms that local medications did not alleviate. In an earlier study by Brander and colleagues (Brander et al. 1999), the frequency and severity of sneezing and rhinorrhea increased more profoundly in winter. In the present Study (III), we found no seasonal effect on symptoms.

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Discussion

Several studies have documented that heated humidification effectively decreases upper airway symptoms (Martins De Araujo et al. 2000, Massie et al. 1999, Neill et al. 2003, Ryan et al. 2009, Wiest et al. 1999, Worsnop et al. 2010). Humidification seems to reduce the drying effect of mouth leaks and to increase the humidity of inhaled air during CPAP treatment (Martins De Araujo et al. 2000), which reduces upper airway dryness (Wiest et al. 1999). However, the effect of humidification on CPAP adherence remains unclear. Studies have shown that heated humidification increase objectively measured adherence to CPAP (Massie et al. 1999, Neill et al. 2003). However, other studies show that adding humidification to the treatment does not significantly improve CPAP adherence despite a reduction in upper airway symptoms (Mador et al. 2005, Ryan et al. 2009, Worsnop et al. 2010). Consequently, the routine use of humidifiers cannot be recommended. In Finland, we do not provide every patient with a humidifier. Humidification slightly complicates treatment and increases its cost. During Study III, if the patient complained of persistent upper airway symptoms, we added humidification to the treatment at the two-month follow-up visit or later. Regardless of whether humidification was introduced, we noticed a significant reduction in upper airway symptoms after two months of CPAP treatment. However, one might speculate that adding humidification would have reduced the frequency of symptoms even more.

According to the results of Study III, the frequency of upper airway symptoms prior to CPAP treatment seems to show no association with long-term adherence to CPAP treatment. Therefore, one should not overestimate impaired nasal breathing as a cause of poor CPAP compliance. For example, some nasal stuffiness may have an allergic component, but mouth leak can also be an important cause for nasal symptoms. Mouth leak results in a unidirectional flow to the nose, causing drying of the nasal mucosa, which can also lead to symptoms of rhinitis, dry mouth and nose. The inconvenience of the CPAP machine and mask may also lead to unsuccessful treatment. Given the number of CPAP interfaces used, only a few studies have compared various interfaces. Recently, Bachour and colleagues (Bachour et al. 2012) noted that patients are generally satisfied with their CPAP interfaces, and that users of Resmed, Respironics, or F&P interfaces showed no significant differences in satisfaction rates. Moreover, they noticed that leaks disturbed more than half of the patients, but found no differences between oronasal and nasal masks with regard to comfort or leaks (Bachour et al. 2012). In contrast, however, Teo and colleagues have demonstrated that nasal masks were more comfortable than oronasal masks, and that fewer leaks were associated with nasal masks than with oronasal masks (Teo et al. 2011). In Study III, we collected no data on the type of mask used and so cannot determine the possible in-symptom prevalence between patients using different kinds of interfaces.

An earlier study by Kiely and colleagues (Kiely et al. 2004) has shown that fluticasone nasal spray reduced AHI in OSA patients. However, no patients with OSA were cured. Non-apneic patients also showed greater daytime alertness (Kiely et
al. 2004), presumably because topical steroids may improve the upper airway side effects of CPAP treatment, and because CPAP patients frequently receive steroids to avoid nasal complaints. All of our CPAP patients received intranasal steroids, but unfortunately we did not record how many of our patients actually used them. Moreover, the results of recent studies do not support the beneficial effect of nasal steroids. Ryan and colleagues demonstrated that nasal steroid treatment added to CPAP treatment failed to reduce the frequency of nasal symptoms (Ryan et al. 2009). In addition, Strobel and colleagues (Strobel et al. 2011) showed that topical nasal steroids failed to reduce CPAP-induced unwanted nasal side effects, and that they offered no beneficial effect on CPAP compliance.

Although the side effects of CPAP treatment are usually mild, they can affect CPAP acceptance and adherence. Thus, treating side effects effectively is of great importance. Side effects due to the mask, such as air leaks and skin abrasions, can be avoided by careful mask fitting. Dryness of the upper airway can be alleviated by adding humidification to the treatment and by treating nasal symptoms properly. For patients suffering from pressure intolerance, changing the device to an autoadjusting PAP or bilevel PAP may prove helpful and be worth a try.

6.3.3 PREDICTORS OF CPAP ADHERENCE

In Study IV, we aimed to find new methods to predict CPAP adherence and non-adherence. We used a questionnaire to evaluate patients’ willingness to continue CPAP therapy immediately after a short CPAP trial. We noticed that a low willingness score, reflected by a score of less than 50, predicted poor CPAP adherence at one year with a specificity of 97%. However, we were unable to predict good adherence with an acceptable score.

Because CPAP treatment effectively eliminates snoring, apneas and hypopneas, improves sleep quality, and reduces daytime sleepiness and other symptoms of OSAS, it is the standard treatment for OSAS (Kakkar & Berry 2007, McDaid et al. 2009). Exactly how much CPAP use yields optimal outcomes and defines good adherence remains unclear. Many patients refuse to continue CPAP therapy or their use of the device is insufficient. However, mortality rates in OSAS patients who refuse CPAP therapy are higher than in those who use CPAP therapy (Campos-Rodriguez et al. 2005, Marti et al. 2002). The success of CPAP therapy is multifaceted (McArdisle et al. 1999, Shapiro & Shapiro 2010), as the factors affecting CPAP use can be related to patient and disease characteristics, the treating physician and nurses, the devices used, and the patient’s family (Sawyer et al. 2011, Shapiro & Shapiro 2010). Previous studies have not fully confirmed suggested predictive factors of CPAP use in clinical work (Aloia 2011). No good method to identify patients who are more or less likely to adhere to CPAP treatment is available. The results
of Study IV contribute to our understanding of this complicated issue of how to predict poor adherence.

Adverse effects from CPAP treatment are common, but usually mild. However, adverse effects can lead to treatment cessation despite improvements in OSAS symptoms (Baltzan et al. 2009, Brander et al. 1999, Pepin et al. 1995). There are some conflicting results regarding the association between upper airway symptoms and CPAP adherence. As already noted above, in Study III, we found no association between the frequency of upper airway symptoms and long-term CPAP adherence. Previously, a small retrospective study also reported that nasopharyngeal symptoms did not affect treatment continuation (Lojander et al. 1999). However, an earlier study by Brander and colleagues (Brander et al. 1999) reported that in a few patients, nasopharyngeal symptoms led to treatment cessation.

The severity of OSA influences long-term CPAP use (Kohler et al. 2010), a phenomenon we also noticed in our study. Early CPAP use is a predictor of long-term use (Bachour & Maasilta 2004, Popescu et al. 2001). Daytime sleepiness, assessed by ESS, seemed to have no effect on CPAP adherence in the patients in our study. Kohler and colleagues have also published similar results (Kohler et al. 2010), whereas the results of earlier studies by Waldhorn and colleagues (Waldhorn et al. 1990) and McArdle and colleagues (McArdle et al. 1999) have suggested that daytime sleepiness may affect treatment adherence. Although our patients were not particularly sleepy, we noticed in them a significant decline in their ESS scores during CPAP treatment. Unfortunately, we were unable to collect the ESS scores of those patients who quit CPAP treatment.

Some researchers have previously noted the frequent association between poor CPAP adherence in adults and black ethnicity and lower socioeconomic status (Billings et al. 2011); studies of children have shown that CPAP adherence is related mostly to family and demographic factors rather than to the severity of sleep apnea or measures of psychosocial functioning (DiFeo et al. 2012). We were unable to collect data on the socioeconomic status of the patients, but in Finland, socioeconomic differences are known to be small, and almost all of our patients were of the same ethnicity.

Patients’ attitudes are also a significant predictor of CPAP adherence. In an earlier study, Lewis and colleagues have shown that a single question about problems during CPAP initiation asked after CPAP titration predicted CPAP adherence at one month (Lewis et al. 2004). Recently, Balachandran and colleagues were able to predict 30-day CPAP adherence by inquiring about patients’ experiences and beliefs in the morning after CPAP titration (Balachandran et al. 2013). In our study, we evaluated the attitudes of our patients by asking about their willingness and eagerness to continue CPAP treatment as well as their satisfaction with the CPAP trial. In addition, our patients completed a self-efficacy questionnaire introduced by Stepnowsky et al. (Stepnowsky et al. 2002).
In addition to patients’ attitudes, their expectations of CPAP treatment also influence their treatment adherence. A recent study reported that the expectation of benefit is part of a placebo effect caused by patients who infer benefit from the treatments they choose to use (Crawford et al. 2012). We found that the expectations of our patients were high before the CPAP trial, since their scores on the self-efficacy questionnaires were high. The relatively lower satisfaction score compared to their willingness score immediately after the CPAP trial reflects their high expectations of benefit and their slight disappointment afterwards.

The results of earlier studies (Stepnowsky & Moore 2003) estimate long-term adherence in CPAP treatment to be quite poor, and that about 40-60% of those who begin CPAP treatment will still be using it a year later. Our results are similar in that 57% of our patients in Study IV continued their treatment after one year, and 64% of the patients in Study III continued CPAP treatment over one year. In Study IV, some of our patients were willing to abandon their CPAP therapy, but nevertheless chose to continue. This may stem from their fear of quitting an efficient therapy. In Finland, hospitals provide CPAP devices to patients free of charge, so continuing or abandoning CPAP treatment has no financial impact on the patients themselves. A recent study has also demonstrated that free access to CPAP therapy influences a patient’s decisions regarding the treatment (Krucien et al. 2012).

The cost-effectiveness of CPAP treatment depends on adherence rates. Prior to receiving a diagnosis of OSA and a recommendation for OSA treatment, OSA patients have higher health-care utilization, but treating OSA effectively results in a reduction in their health-care utilization (Albarrak et al. 2005, Bahammam et al. 1999). Nevertheless, the cost of CPAP therapy is already enormous and growing steadily with no corresponding in budget. Therefore, focusing treatment on those who are most likely to succeed and to benefit from the treatment has financial advantages.
7. SUMMARY AND CONCLUSION

We developed a method for recording and analyzing snoring sounds with an MP3 recorder and found that an MP3 device can accurately detect snoring sounds and provide reliable information on a patient’s snoring. This method offers a simple and low-cost screening method for snoring.

Secondly, we studied upper airway symptoms in patients referred for a sleep study and for CPAP initiation and found that more than half of the patients reported suffering from nasal stuffiness and throat, nose and mouth dryness. The frequency of mouth dryness was related to the severity of OSAS. The frequent nasal symptoms, particularly nasal dryness and stuffiness, were already common in snorers and show no significant increase with mild to severe sleep apnea. During CPAP treatment, symptoms of dry nose, mouth and throat decreased. In patients who terminated their CPAP therapy before the one-year follow-up, only rhinorrhea seemed to increase after two months of CPAP treatment. Upper airway symptoms appeared not to predict long-term adherence to CPAP treatment.

Finally, we investigated long-term adherence to CPAP use. We showed that a low willingness score to continue CPAP therapy after a short initiation period had very high specificity in predicting CPAP failure and poor CPAP adherence at one year.
8. FUTURE DIRECTIONS

There is a clear need for simple and cost-effective screening methods for snoring and sleep apnea, since obesity is a growing burden worldwide. To ensure appropriate treatment and care for more difficult and complex diseases by sleep specialists in sleep units, preliminary screening methods for OSA and snoring should be developed, improved and tested in unselected community samples.

Because Study I aimed to use a simple and practical device, we did not analyze the sound spectrum. Most studies have ignored the vibration effects of snoring, and snoring measurements have usually focused on the acoustic effects, as we did in this study. Determining whether the acoustic and the vibrating effects of snoring correlate would require additional research.

Improving CPAP adherence is difficult. Moreover, exactly how much CPAP use yields optimal treatment outcomes remains unclear. Improvements in sleepiness should not be the only target of treatment, but patients should also actively receive information about the potential consequences, particularly cardiovascular events, of untreated OSAS. A number of studies have already attempted to evaluate the interventions used to improve CPAP adherence. Many interventions are often used at the same time, making it difficult to determine the importance of each individual intervention (Kakkar & Berry 2007). Possible methods to improve CPAP adherence are to provide more extensive information on OSAS and its potential consequences without proper treatment, to offer patients more extensive education on CPAP treatment, devices, and interfaces, to ensure easy access to sleep units for the questions that arise at home regarding CPAP treatment, and to provide early interventions for side effects, as well as objective monitoring of treatment adherence.
The studies for this PhD study were carried out at the Division of Pulmonary Medicine, Department of Medicine at Hyvinkää Hospital, Hospital District of Uusimaa and at the Division of Pulmonary Medicine, Department of Medicine at the Helsinki University Central Hospital.

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Hanna-Riikka Kreivi


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APPENDICES

Questionnaire 1:
Questionnaire on upper airway symptoms and disorders for sleep study subjects and for nasal-CPAP patients before the treatment

UPPER AIRWAY SYMPTOMS AND DISORDERS BEFORE NASAL CPAP TREATMENT
occasionally = for example during a flue or less than twice a month
often = at least once a week
all the time = every day

Have you had recently (during last weeks and months):
1) Nasal stuffiness
   a) never    b) occasionally   c) often    d) all the time

2) Throat dryness
   a) never    b) occasionally   c) often    d) all the time

3) Feeling of mucus in throat / postnasal drip
   a) never    b) occasionally   c) often    d) all the time

4) Sneezing
   a) never    b) occasionally   c) often    d) all the time

5) Rhinorrhea
   a) never    b) occasionally   c) often    d) all the time

6) Mouth dryness during the night
   a) never    b) occasionally   c) often    d) all the time

7) Nasal dryness
   a) never    b) occasionally   c) often    d) all the time

8) Nasal bleeding
   a) never    b) occasionally   c) often    d) all the time
9) Locking of ears
a) never   b) occasionally   c) often   d) all the time

10) Do you normally breath through you nose or through you mouth?
 a) through the nose  b) through the mouth  C) I do not know

DO YOU HAVE UPPER AIRWAY DISORDERS OR HAVE YOU UNDERGONE UPPER AIRWAY OPERATIONS AS AN ADULT:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>11) Allergic rhinitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>12) Constant rhinitis</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>13) Nasal polyps</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>14) Frequent tonsillitis</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>15) More than one sinusitis</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>16) Chronic sinusitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17) Maxillary sinus punction for sinusitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>18) Sinus operation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>19) Septum deviation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>20) Septoplasty</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>21) Polypectomy</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>22) Tonsillectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>23) Adenoidectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>24) Palatal Pharyngeal surgery for snoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>25) Nasal fracture</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
26) Regular medication for rhinitis

Yes  No  I do not know / remember

**Questionnaire 2**
Upper airway symptoms during nasal CPAP treatment

**UPPER AIRWAY SYMPTOMS AND DISORDERS DURING NASAL CPAP TREATMENT**
occasionally = for example during a flue or less than twice a month
often = at least once a week
all the time = every day

**Have you had recently, after the initiation of CPAP treatment:**

1) **Nasal stuffiness**
   a) never  b) occasionally  c) often  d) all the time

**Nasal stuffiness**
a) has increased during CPAP treatment  b) has not increased during CPAP treatment

2) **Throat dryness**
   a) never  b) occasionally  c) often  d) all the time

**Throat dryness**
a) has increased during CPAP treatment  b) has not increased during CPAP treatment

3) **Feeling of mucus in throat / postnasal drip**
   a) never  b) occasionally  c) often  d) all the time

**Feeling of mucus in throat / postnasal drip**
a) has increased during CPAP treatment  b) has not increased during CPAP treatment

4) **Sneezing**
   a) never  b) occasionally  c) often  d) all the time

**Sneezing**
a) has increased during CPAP treatment  b) has not increased during CPAP treatment

5) **Rhinorrhea**
   a) never  b) occasionally  c) often  d) all the time
Appendices

**Rhinorrhea**
a) has increased during CPAP treatment  
b) has not increased during CPAP treatment

6) **Mouth dryness during the night**
a) never  
b) occasionally  
c) often  
d) all the time

**Mouth dryness during the night**
a) has increased during CPAP treatment  
b) has not increased during CPAP treatment

7) **Nasal dryness**
a) never  
b) occasionally  
c) often  
d) all the time

**Nasal dryness**
a) has increased during CPAP treatment  
b) has not increased during CPAP treatment

8) **Nasal bleeding**
a) never  
b) occasionally  
c) often  
d) all the time

**Nasal bleeding**
a) has increased during CPAP treatment  
b) has not increased during CPAP treatment

9) **Locking of ears**
a) never  
b) occasionally  
c) often  
d) all the time

**Locking of ears**
a) has increased during CPAP treatment  
b) has not increased during CPAP treatment

10) **Do you normally breath through you nose or through you mouth?**
a) through the nose  
b) through the mouth  
c) I do not know

**Have you had sinusitis after starting CPAP treatment?**
a) yes  
b) no

**Does nasal CPAP device make you feel like you were choking?**
a) yes  
b) no

**Have you slept with the CPAP device for most of the nights (at least 4 nights a week)?**
a) yes  
b) no
How many hours, in average, do you estimate yourself that you have slept with CPAP device?
(a) 0-2 hours /night  (b) 2-4 hours / night  (c) 4-7 hours / night  (d) more than 7 hours / night

Have you benefited from CPAP treatment?
(a) yes  (b) no
If yes, explain how?

CPAP treatment has cause me more troubles than benefit.
(a) yes  (b) no  (c) I do no know

I want to continue CPAP treatment.
(a) yes  (b) no
If you do not want to continue CPAP treatment, explain why?

Questionnaire 3
A questionnaire on eagerness to continue CPAP treatment (0= I am not eager at all, 100 = I am very eager ), on satisfaction with CPAP trial (0 = I am very disappointed, 100 = I am very satisfied with it), and willingness to continue CPAP therapy at home (0= I am not ready to continue CPAP at any circumstances, 100 = I would like to continue).

How eager are you to continue CPAP treatment at home after the CPAP trial
I----------------------------------------------------------------------------------I
0  I am not eager at all               100  I am very eager

Are you satisfied with the CPAP trial?
I----------------------------------------------------------------------------------I
0  I am very disappointed            100  I am very satisfied

Are you willing to continue CPAP treatment at home?
I----------------------------------------------------------------------------------I
0  I am not ready to continue        100  I would like to continue CPAP at any circumstances
tongue hypotrophy = hypertrophy

2.4.9.1 Polysomnography (level 1)

The reference standard for diagnosing sleep apnea is an attended overnight level I PSG in a sleep laboratory (American Sleep Disorders Association 1997, American Academy of Sleep Medicine Task Force 1999, Kushida et al. 2005) (Figure 2 and 3). Total sleep time, sleep stages, sleep efficiency, sleep latency, arousals and awakenings are measured with electroencephalography (EEG), electro-oculography (EOG) and chin electromyography (EMG). According to AASM recommendations, for apnea detection, nasal airflow should be measured with an oronasal thermal airflow sensor, and for hypopnea detection, airflow should be monitored with a nasal pressure transducer (Berry et al. 2012). Oxygen saturation is measured by finger or ear oximetry. Chest and abdominal piezo sensors, strain gauges or esophageal pressures measure respiratory effort to differentiate between obstructive and central apneas. The study also included electrocardiography (ECG) and a body position sensor. Nowadays, apneas, hypopneas, and sleep stages are scored manually according to AASM rules (Berry et al. 2012). Previously, sleep stages were analyzed according to the rules of Rechtschaffen and Kales (Rechtschaffen & Kales 1968).