A tailor made approach to obstructive sleep apnea

Ravesloot, M.J.L.

Citation for published version (APA):
Ravesloot, M. J. L. (2013). A tailor made approach to obstructive sleep apnea

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 1

Introduction

This chapter is partially based on the following publications:


Obstructive sleep apnea (OSA) is the most prevalent sleep disordered breathing problem. The first publication on the clinical features of OSA appeared in 1976.¹

**CLASSIFICATION**

In the *International classification of Sleep Disorders*, OSA falls under the category “sleep disordered breathing”.² This section also includes central sleep apnea syndromes as well as sleep disorders related to hypoventilation or hypoxemia (see Table 1).

*Table 1*: International Classification of Sleep disorders: category sleep related breathing disorders (SBD)

<table>
<thead>
<tr>
<th>1.0 CENTRAL SLEEP APNEA SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary central sleep apnea</td>
</tr>
<tr>
<td>Central sleep apnea due to Cheyne Stokes breathing pattern</td>
</tr>
<tr>
<td>Central sleep apnea due to high-altitude periodic breathing</td>
</tr>
<tr>
<td>Central sleep apnea due to medical condition not Cheyne Stokes</td>
</tr>
<tr>
<td>Central sleep apnea due to drug or substance</td>
</tr>
<tr>
<td>Primary sleep apnea of infancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.0 OBSTRUCTIVE SLEEP APNEA SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea, adult</td>
</tr>
<tr>
<td>Obstructive sleep apnea, pediatric</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.0 SLEEP RELATED HYPOVENTILATION/HYPOXEMIC SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-related non obstructive alveolar hypoventilation, idiopathic</td>
</tr>
<tr>
<td>Congenital central alveolar hypoventilation syndrome</td>
</tr>
<tr>
<td>Sleep-related hypoventilation/hypoxemia due to medical condition</td>
</tr>
<tr>
<td>Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology</td>
</tr>
<tr>
<td>Sleep-related hypoventilation/hypoxemia due to lower airway obstruction</td>
</tr>
<tr>
<td>Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4.0 OTHER SLEEP-RELATED BREATHING DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep apnea/sleep-related breathing disorder, unspecified</td>
</tr>
</tbody>
</table>
In an attempt to facilitate more reliable and accurate reporting in research studies and in clinical practice, the American Academy of Sleep Medicine (AASM) Task Force, defined key features differentiating the various sleep disordered breathing disorders.³

The diagnostic criteria for OSA syndrome are as follows:

The individual must fulfil criterion A or B, plus criterion C

A. Excessive daytime sleepiness that is not better explained by other factors;

B. Two or more of the following that are not better explained by other factors:
   - Choking or gasping during sleep,
   - Recurrent awakenings from sleep,
   - Refreshing sleep,
   - Daytime fatigue,
   - Impaired concentration; and/or

C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep.

Not every patient with an apnea hypopnea index (AHI) \( \geq \) five is symptomatic. These patients are considered to suffer from OSA instead of the OSA syndrome. Many studies have shown adverse health outcomes (discussed later in this chapter) to be associated with patients with frequent episodes of apnea and hypopnea, regardless of the presence of sleepiness.⁴ However, evidence suggests that compliance of treatment is associated with the severity of daytime hypersomnolence and other symptoms on presentation.⁵

The severity of OSA is expressed in the AHI: the calculated sum of total events (apneas and hypopneas) per hour of sleep, as measured by polysomnography (PSG). An AHI of 5 - 15/hour is mild OSA, an AHI of 15 - 30/hour is moderate and AHI > 30/hour is severe OSA, as assessed by PSG.
PREVALENCE

In the general population, it is estimated that 3.3 - 7.5% in men and 1.2 - 3.2% in women meet the diagnostic criteria for OSA syndrome as described previously. Yet, the number of patients who are asymptomatic but have an AHI ≥ 5 is significantly higher: 17 - 27% in men and 5 - 28% in women. The estimated prevalence of an AHI ≥ 15 ranges from 7 to 14% in men and 1.2 to 7%.\(^6-15\) It should be noted that comparison of the results of these epidemiology studies is limited by methodological differences, including variation in used criteria, sleep registration techniques and study methods (e.g. sampling schedules).\(^15\) On the basis of these prevalence estimates, roughly 1 of every 5 adults has at least an AHI ≥ 5 and 1 of every 15 adults at least an AHI ≥ 15.\(^4\) It is estimated that nearly 80% of men and 93% of women with moderate to severe OSA remain undiagnosed.\(^16\)

PATHOPHYSIOLOGY

OSA is characterized by repetitive partial or complete obstruction of the upper airway during sleep, resulting in reduction or cessation of airflow, despite ongoing respiratory effort. This results in repetitive hypoxia and carbon dioxide retention, provoking arousals as to restore upper airway patency and consequently fragmenting sleep.

RISK FACTORS

Studies have shown that the prevalence of OSA increases with age.\(^6-8, 10, 11, 17-20\) OSA occurs more frequently in men than in women.\(^8, 10, 13, 18, 21, 22\) Possible explanations include differences in fat distribution and pharyngeal anatomy and function between sexes and the effects of hormonal influences affecting muscles of the upper airway and its ability to collapse.\(^15\) In support of the last hypothesis: in women the prevalence is greater in postmenopausal women (without hormone replacement therapy) than in premenopausal women.\(^23, 4, 10\)

In both genders, OSA is more prevalent in overweight and obese subjects.\(^4, 11, 18\) Not everyone with OSA is obese, but most people with
obesity have OSA. Especially in patients undergoing bariatric surgery (BS) it is important to recognize the presence of OSA. To date the value of clinical parameters (body mass index [BMI], neck circumference [NC] and the Epworth Sleepiness Scale [ESS]) to predict the presence of OSA in patients undergoing BS remains to be elucidated. In chapter 4 we aim to measure the prevalence of OSA among patients undergoing BS and test the value of various clinical parameters (BMI, NC and the ESS) to predict the presence of OSA in patients undergoing BS.

Craniofacial and upper airway soft tissue abnormalities each increase the likelihood of having or developing OSA. Examples of such abnormalities include an abnormal maxillary or short mandibular size, a wide craniofacial base, macroglossia, tonsillar hypertrophy and adenoid hypertrophy.

A considerable amount of literature exits on the role of sleep position in OSA. The worst sleeping position is usually, but not always the supine position. In studies from Israel and the Netherlands a remarkable steady 56% of patients with OSA have a difference of 50% or more in apnea index (AI) between supine and non-supine positions. On average patients with positional dependent OSA have a lower BMI and are younger than non-positional OSA patients.

Both sedatives and alcohol are considered important risk factors for OSA due to a reduction in muscle tone and depression of the central nervous system, adversely affecting ventilatory response to hypoxia. Studies have shown that alcohol consumption aggravates OSA, leading to an increase in frequency and duration of hypopneic or apneic events. Lastly, studies show that there is a positive association between tobacco smoking and the presence of OSA.

The Adult OSA Task Force of the AASM recommends that high-risk patients with nocturnal symptoms of OSA should undergo a PSG, including those who are obese, those with systolic or diastolic heart failure, coronary artery disease, treatment refractory congestive heart failure or hypertension, history of stroke or transient ischemic attacks or significant tachyarrhythmias or bradyarrhythmias.
DIAGNOSIS

The cornerstone of the initial diagnosis of OSA is a comprehensive sleep history and physical examination in patients suspected of OSA. Information should be gained concerning intoxications (including tobacco, alcohol and other recreational drug use), medication (sedative use, in particular), change in weight, family history and past medical and surgical history. Further questions to be asked should include a history of possible nocturnal and daily symptoms such as: snoring, observed apneas, choking or gasping episodes during sleep, disturbed unrefreshing sleep, thirst during the night, nocturia, excessive daytime sleepiness not explained by other factors, morning and nocturnal headaches, decreased libido and impotence, decreased concentration and memory and a morning dry mouth. The ESS is a validated method to assess severity of sleepiness. By answering eight questions regarding the patient’s ability to remain awake or the tendency to doze off during certain monotonous situations in daily life, impaired daytime alertness is measured. Not only does a high ESS increase the suspicion of OSA, studies have shown that patients are less likely to accept and be compliant to treatment, unless they can perceive a benefit with a reduction in subjective sleepiness and other symptoms. Studies have shown that the correlation between ESS and OSA severity is weak, but currently the ESS is the best available tool to assess the excessive sleepiness.

Objectively sleepiness can be assessed through the validated Multiple Sleep Latency Test (MSLT). A patient is considered to suffer from pathological sleepiness if a patient falls asleep (using electroencephalogram [EEG] criteria) in a darkened room within 7 minutes, on at least four separate occasions, across one day following instructions to fall asleep. But, MSLT, is not indicated in the initial evaluation and diagnosis of obstructive sleep apnea syndrome, or in assessment of change following treatment with nasal Continuous Positive Airway Pressure (CPAP) as available evidence indicates that routine use of the MSLT does not contribute significantly to diagnosis or assessment of response to treatment for sleep-related breathing disorders.
It should be remembered that not every OSA symptom is present in every OSA case and that many patients with an AHI $\geq 5$ are asymptomatic. Bearing in mind that patients may not be aware of abnormalities during sleep and/or fail to recognize or underplay some of these symptoms, it is often very useful to seek information from the (bed) partner, especially regarding observed apnoeas, snoring and nocturnal restlessness. Furthermore particular attention should be paid to possible secondary conditions resulting from OSA such as cardiovascular disease, decreased daytime alertness and motor vehicle accidents.

On physical examination particular attention should be paid to the weight, NC, mandible and maxilla position and size, facial features, nasal pathology, tonsil size, uvula and palate aspect and tongue size. Presence of obesity, an increased NC, presence of retrognathia, macroglossia, tonsillar hypertrophy, elongated or enlarged uvula and nasal pathology strengthen the likelihood of the presence of OSA.

Clinical symptoms and physical examination alone are insufficient to accurately diagnose OSA. A full night PSG is considered to be the most accurate instrument for measuring the presence and severity of OSA. Sleep architecture [derived from EEG, electrooculogram (EOG) and submental electromyogram (EMG)], respiration (thoracic and abdominal measurement), nasal airflow and the intensity of the snoring (the last two measured by pressure sensor) are recorded. Transcutaneous pulse oximetry is used to monitor oxygen saturation ($\text{SaO}_2$) and heart rate. The latter can also be recorded through an electrocardiogram (ECG). Classification of disordered breathing events, recorded during PSG, have been standardized to guide practice, by the AASM. Obstructive apneas are defined as a cessation of airflow for at least 10 seconds. Hypopneas are defined as periods of reduction of $> 30\%$ oronasal airflow for at least 10 seconds and a $\geq 4\%$ decrease in oxygen saturation. Arousals should not be scored as hypopneas. Respiratory events and indices are summarized in Table 2.

Additional recommended physiologic signals include leg EMG derivations (movements of limbs) and body position monitors. In my opinion, the
latter is essential, especially since the introduction of new generation positional therapy (PT), which successfully prevents patients from adopting the supine position without negatively influencing sleep efficiency.\textsuperscript{75-78} A recent study by van Kesteren et al., advocates dual position sensors placed on both trunk and head, as the results of their study suggest that the occurrence of OSA can be dependent on the position of the head.\textsuperscript{31} It is important to differentiate between habitual snoring and OSA, the latter being associated with considerable complications.

Table 2: Respiratory event definitions and indices of sleep disordered breathing.

<table>
<thead>
<tr>
<th>RESPIRATORY EVENT</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive Apnea</td>
<td>A cessation of airflow for at least 10 seconds</td>
</tr>
<tr>
<td>Obstructive Hypopnea</td>
<td>A reduction in airflow ($\geq 30%$) at least 10 seconds with $\geq 4%$ oxygen desaturation</td>
</tr>
<tr>
<td>Respiratory effort-related arousal (RERA)</td>
<td>Sequence of breaths for at least 10 seconds with increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep when the sequence of breaths does not meet the criteria for an apnea or a hypopnea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INDICES</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea Index (AI)</td>
<td>Number of apneas per hour of total sleep time</td>
</tr>
<tr>
<td>Hypopnea Index (HI)</td>
<td>Number of hypopneas per hour of total sleep time</td>
</tr>
<tr>
<td>Apnea Hypopnea Index (AHI)</td>
<td>Number of apneas and hypopneas per hour of total sleep time</td>
</tr>
<tr>
<td>Respiratory disturbance index (RDI)</td>
<td>Number of apneas, hypopneas, and RERAs per hour of total sleep time</td>
</tr>
<tr>
<td>Oxygen Desaturation Index (DI)</td>
<td>Average number of oxygen desaturation episodes ($\geq 4%$) per hour</td>
</tr>
</tbody>
</table>

Sleep monitoring systems have been divided into 4 categories

Type 1: full attended PSG ($\geq 7$ channels) in a laboratory setting
Type 2: full unattended PSG ($\geq 7$ channels)
Type 3: limited channel devices (usually using 4–7 channels)
Type 4: 1 or 2 channels usually using oximetry as 1 of the parameters
Type I sleep monitoring is the preferred monitoring method for the diagnosis of sleep disorders and considered the most comprehensive and reliable.\textsuperscript{79}

Despite the high costs, time consuming nature and patient burden of PSGs, the task force of the AASM does not advise the use of portable monitoring (PM) for general screening, as there is yet insufficient evidence to guide the use of PM.\textsuperscript{80}

Multiple evaluation techniques have been used to examine an individual’s pattern of upper airway obstruction; indicated when surgery or MRA therapy is being considered as a treatment option by the patient and physician, such as the Mueller maneuver, cephalometric radiology, computed tomography (CT), magnetic resonance imaging (MRI). Visualization of the level of obstruction is not mandatory if CPAP, weight loss or PT is being considered. OSA surgical evaluation techniques are commonly performed during wakefulness and include largely static observations rather than dynamic assessments. As such, they may not be ideal methods to assess the upper airway during breathing and sleep. The variety and complexity of vibrations and collapse events in the upper airway during sleep depend on multiple factors. Sleep stages, muscle tone, body position, head and neck position, and lung volumes are some of the variables that affect upper airway collapsibility. To support this theory, studies have shown that CT, MRI and cephalometric radiology do not accurately differentiate patients with OSA from normal subjects, despite evaluating the size and shape of the upper airway.\textsuperscript{81-84}

Drug-induced sleep endoscopy (DISE) has been performed for decades, in many, leading centres in Europe as well as selected centres in other parts of the world. Introduced by Croft and Pringle in 1991, the evaluation requires pharmacologic induction of sedation and flexible fiberoptic endoscopy to visualize upper airway obstruction and/or snoring.\textsuperscript{85, 86} As opposed to most surgical evaluation techniques, DISE not only uniquely offers a dynamic evaluation of the upper airway during conditions that ideally mimic natural sleep but also enables visualization of specific structures that contribute to upper airway obstruction (see \textbf{Figures 1 - 4}).
Drugs commonly used for DISE are propofol and/or midazolam. Anesthetic depth is of key importance. The target depth of sedation is the transition from consciousness to unconsciousness (loss of response to verbal stimulation). Because individuals have differential susceptibilities to propofol, the required dosage can vary widely. Slow stepwise induction is required to avoid oversedation. Deeper levels of sedation are associated with progressive decreases in upper airway dilator muscle tone and neuromuscular reflex activation that both increase airway collapsibility, and the transition to unconscious sedation may be a closer approximation to natural sleep. Previous research using propofol has shown that the transition to unconsciousness is associated with changes in upper airway collapsibility (passive critical closing pressure), Bispectral Index Score readings (based on frontal EEG activity), and genioglossus muscle tone; normals have decreases in genioglossus tone to 10% of maximum awake activity, which is one-half to one-third of the level in normals but greater than during REM sleep in normals and OSA. While unconscious sedation under propofol may not a perfect simulation of natural sleep, pharyngeal dilator muscle activity appears to lie somewhere between NREM and REM sleep.

During the DISE, maneuvers such as a chin lift (a manual closure of the mouth) or a jaw thrust (or Esmarch maneuver) can be performed, with reassessment of the airway after each maneuver (see Figure 5 and 6). A jaw thrust is a gentle advancement of the mandible by up to approximately 5 mm, mimicking the effect of a mandibular repositioning appliance. It is thought that, using DISE, one can predict the likelihood that an appliance would be effective by examining the changes in the airway.
The recently introduced VOTE Classification system for reporting DISE findings (see Table 3), focuses on the primary structures that contribute to upper airway obstruction, either alone or in combination: the velum, oropharyngeal lateral walls (including the tonsils), tongue, and epiglottis, as well as the degree (partial or complete) and configuration of airway obstruction (anteroposterior, circumferential or lateral). 

The shared use of the VOTE Classification can facilitate the scientific evaluation of DISE in individual centers and, just as importantly, the collection of data across multiple centers. With these data we can compare results across studies and increase our knowledge and find supporting evidence whether DISE is indeed beneficial to the outcomes of existing and novel treatments for snoring and OSA. In an attempt to further unravel and understand the pathogenesis of OSA, in chapter 2 we report on the distribution of sites of obstruction as observed through DISE, investigate associations between patient characteristics, PSG and DISE findings and evaluate the feasibility of the VOTE classification.
DIFFERENTIAL DIAGNOSIS

Various conditions as summarized in Table 1 are distinguished by disordered breathing during sleep, whether of an obstructive or central nature.\textsuperscript{2} Central sleep apnea is characterized by an absence in respiratory effort due to nervous system or cardiopulmonary dysfunction, resulting in an absence of airflow. OSA should furthermore be distinguished from habitual snoring. Other potential causes of excessive daytime sleepiness include: narcolepsy, depression, insufficient sleep (sleep deprivation, fragmented sleep), shift work, hypothyroidism, sleep related movement disorders (e.g. periodic limb movements), excessive alcohol or drug use (sedatives, β-blockers, selective serotonin reuptake inhibitors) or neurological conditions (dystrophica myotonica, previous encephalitis, previous head injury, parkinsonism).\textsuperscript{3, 15, 67}

CONSEQUENCES OF UNTREATED OSA

First and foremost untreated OSA causes impairment of quality of life. Epidemiological studies have shown significant independent associations between OSA (with or without symptoms) and hypertension, coronary artery disease, arrhythmias, heart failure, and stroke.\textsuperscript{91} The point at which the AHI becomes harmful remains unclear. He\textit{et al}/reported an acceleration of harm when the AHI rises above 20 - 25.\textsuperscript{92} Furthermore, patients with OSAS often suffer from excessive daytime sleepiness leading to impaired
professional and cognitive performance and a greater probability of having a traffic accident and accidents at the workplace than patients without OSA.\textsuperscript{93-102} Especially the serious risk factor for traffic accidents has led to national lobbying actions, mainly in the European Union, resulting in modified driving license regulations.\textsuperscript{15} Since 2008, in the Netherlands, patients with OSAS are declared unsafe to drive personal vehicles, buses or lorries unless the patient has been successfully treated for at least two consecutive months. In the case of professional drivers, three consecutive months is mandatory. A patient is considered successfully treated when the AHI is reduced to below 15.\textsuperscript{103, 104}

**TREATMENT**

In the infancy of this new diagnosis, treatment options were limited to tracheostomy and weight loss.\textsuperscript{105} Currently, the therapeutic armamentarium for OSA comprises several treatment options. To provide effective treatment for OSA, careful consideration of the individual patient, available medical and surgical therapies, and inherent risks and complications of those interventions must be taken into account.

Treatment is generally approached in a stepwise manner and begins with behaviour modification, indicated for all patients with a modifiable risk factor.\textsuperscript{25}

**WEIGHT LOSS**

Even modest weight loss can be effective in reducing OSA severity, but there is a poor correlation between the amount of weight loss and the clinical response.\textsuperscript{67, 106-111} In patients who fail conservative treatment, such as dietary modification and exercise, BS can be considered. Various studies have reported significant improvement of OSA in obese patients after BS.\textsuperscript{111-129} Bearing in mind that that weight loss following BS, is rapid in the first few months, but it can take at least 1 year or more to reach the final result, we were interested to measure the effect of BS on OSA at two postoperative intervals: at least 6 and 12 months after surgery.\textsuperscript{126} The results are described in chapter 5. To the best of our knowledge, this is the first report describing the effect of BS on OSA at two intervals.
postoperatively. Small-scale studies suggest that the effect of BS on OSA is long lasting, but regaining of weight is associated with the reappearance of OSA.\textsuperscript{114, 125, 130}

**ALCOHOL, TOBACCO AND SEDATIVE ABSTINENCE**

Studies have shown that alcohol consumption aggravates OSA: an increase in frequency and duration of hypopneic or apneic events.\textsuperscript{41-46, 49-60} Therefore abstinence is recommended.

Tobacco smoking is a risk factor for the presence of OSA, but there is no evidence that cessation is effective in reducing apneic events.\textsuperscript{62, 63}

**AVOIDANCE OF WORST SLEEPING POSITION**

Various techniques have been developed to prevent patients from sleeping in the worst position and are described at length in chapter 6. In an attempt to decrease discomfort and improve compliance, recent developments have seen the introduction of a new generation of PT, most often a small neck- or trunk-worn device, which when worn, triggers a vibration when a supine position is adopted until a new position is adopted. Recent studies suggest that these devices successfully prevent patients from adopting the supine position without significantly reducing sleep quality or disrupting sleep with almost 100\% compliance after 1 month.\textsuperscript{76-78} It is to be expected that PT will gain momentum in the scope of OSA treatment. Besides the efficacy of the treatment modality, further advantages include that if the treatment is not effective, the appliance can be returned to the distributor and used by another patient (unlike an MAD which is custom made), acceptable costs and that there is a learning effect of PT.\textsuperscript{77} Studies suggest that patients may learn to avoid the supine position following PT and therefore do not need to use PT on a regular basis.\textsuperscript{77, 131}

**CONTINUOUS POSITIVE AIRWAY PRESSURE**

CPAP first introduced by Sullivan in 1981, is regarded as the gold standard in the treatment of moderate and severe cases and is the most efficacious treatment modality of OSA.\textsuperscript{132} CPAP functions as a pneumatic splint to
maintaining upper airway patency. CPAP is considered successful when the AHI is reduced to below 5 when CPAP is used. In a meta-analysis of the Cochrane Collaboration, compared with control, CPAP was shown to be significantly effective in reducing the AHI as well as improving measurements of quality of life, cognitive function and objective and subjective measures of sleepiness.\textsuperscript{133} Despite the efficacy of CPAP it is, however, a clinical reality that the use of CPAP is often cumbersome. Patients seem to either tolerate the device well or not at all—a bimodal distribution.\textsuperscript{134} Studies have shown that 29% - 83% of patients are non-adherent, when adherence is defined as at least 4 hours of CPAP use per night.\textsuperscript{5} More support and care is needed to improve compliance, especially on a long-term basis, such as addressing CPAP side effects. Possible side effects can be related to the interface (skin abrasion from contact with the mask, claustrophobia, mask leak, irritated eyes), pressure (nasal congestion and rhinorrhea with dryness or irritation of the nasal and pharyngeal membranes, sneezing, gastric and bowel distension, recurrent ear and sinus infections) and negative social factors.\textsuperscript{15, 135}

**MANDIBULAR ADVANCEMENT DEVICE**

Mandibular advancement devices (MAD), also known as mandibular reposition appliances (MRA) or oral appliances (OA) have become increasingly popular as a treatment alternative.\textsuperscript{136} By advancing the mandible and its attached soft tissue structures forward they aim to increase upper airway size.\textsuperscript{137} MADs have been found to be effective in reducing the AHI, especially in patients with mild to moderate OSA. Studies have shown that MADs are more effective when compared to “control devices” (which do not protrude the mandible), in reducing the AHI.\textsuperscript{136, 138-142} When compared to CPAP, there was a significant effect in favour of CPAP compared with MADs.\textsuperscript{143-146} Objective usage data are harder to collect than for CPAP, but self reported treatment compliance is high.\textsuperscript{138, 141, 145, 147, 148} To my best knowledge there are no standardized compliance criteria for MAD treatment.

Side effects have been reported with use of MADs: excessive salivation or dryness of the mouth, gum irritation, discomfort of the temperomandibular
joint, teeth or facial musculature, bite change and temporomandibular disorders. Long-term treatment with an MAD can result in changes in dental morphology.

**SLEEP SURGERY**

Sleep surgery aims to increase the surface area of the upper airway, to bypass the pharyngeal airway or to remove a specific pathology. Despite the vast amount of medical literature on sleep surgery, high level evidence is scarce: there are but few randomized control trials assessing different surgical techniques with inactive and active control treatments. The majority of publications evaluate single procedures or procedure combinations in case series designs (level 4 evidence).

Conventionally, a tracheotomy is considered the gold standard surgical treatment modality for OSA. A tracheostoma relieves OSA by completely bypassing the portion of the airway that narrows or collapses in OSA and is therefore the most effective treatment modality for OSA – a near 100% success rate. But, since the introduction of other treatment options, a tracheotomy is now considered a last resort, due to the significant morbidity and associated psychosocial problems and inconvenience of a tracheostoma. Surgical procedures for OSA performed nowadays are generally less effective, but associated with less morbidity. Surgical procedures developed to treat OSA can predominantly be classified according to site of intervention, mechanism of action and invasiveness.

The first surgical alternative, the uvulopalatopharyngoplasty (UPPP) was first introduced in 1979 by Fujita et al and is still the most commonly performed surgical procedure for OSA. The technique was a modification of a similar procedure introduced by Ikematsu in 1963 to treat snoring. The procedure aims to increase the retropalatal lumen and reduce the collapsibility of the pharynx, by resection of the free edge of the uvula and soft palate, often in combination with a tonsillectomy.

The preliminary results of the first randomized controlled trial (RCT) comparing UPPP and tonsillectomy against a control group (no treatment)
were recently published. Twenty-one patients with an AHI greater than 15/hour, CPAP intolerance, tonsil hypertrophy and palatal obstruction were included. Blinding of the patients and the surgeons is not feasible, but evaluation of the PSG and questionnaires was blinded (observer-blind). The preliminary results of this study show a significant effect in favour of UPPP and tonsillectomy. In the surgery group the AHI was reduced from 27.8 ± 15.1/hour to 7.4 ± 9.5/hour in comparison to a reduction from 39.3 ± 20.8/hour to 30.6 ± 16.2/hour in the control group).

Modification of the classic UPPP have been described by Woodson, Friedman, Coleman and Pang, among others, such as the laser assisted UPPP, (extended) uvulopalatal flap, lateral pharyngoplasty, Z-palatoplasty in tonsillectomised patients, expansion sphincter palatoplasty and transpalatal advancement pharyngoplasty. Current research suggests that modifications of the classic UPPP are more effective, but more higher level evidence is needed.

Unfortunately UPPP is often misused as the first line of surgical therapy for OSA, without adequate assessment of obstruction site(s) and regardless of predictive factors such as obesity. As a result, an isolated UPPP is often unsuccessful in treating OSA, especially in badly selected patients. Palatal surgery is indicated in patients who have airway collapse at the level of the velum. There are no widely accepted standardized methods or algorithms to identify suitable candidates. In general patients with large tonsils, elongated uvula and palatal redundancy position without the presence of other obstruction sites are considered good candidates for palatal surgery. The impression is that surgical success rates in patients selected by DISE are better than average, although this has to be confirmed by more studies. In chapter 3 we test the hypothesis that DISE variables can predict the outcome of upper airway surgery in OSA patients.

In a literature review by Sher et al, published in 1996, an overall response rate of 40.7% was reported (with response defined as a 50% decrease in the respiratory disturbance index [RDI] and a postoperative RDI of 20, or as a 50% decrease in the AI and a postoperative AI of 10) in patients with
OSA treated with UPPP alone, regardless of site of obstruction. In patients with suspected hypopharyngeal obstruction the response rate was a mere 5.3%, whilst in patients with suspected palatal narrowing alone, the response rate increased to 52.3%.

As in all surgery, meticulous patient selection is crucial. The type and extent of surgical intervention mainly depends on the severity of the disease and the site(s) of obstruction as well as patient characteristics, sleep position dependence, comorbidity, and the patient’s preference. Even more so since, in almost 50% of patients with either socially unacceptable snoring or OSA, a multilevel obstruction is observed on DISE.

This has prompted the development and/or improvement of obstruction site evaluation techniques, palatal sleep surgery and modalities to treat other obstruction sites such as the base of tongue. Over the years the scope of surgical treatment modalities has broadened significantly – a list too long to be covered in its entirety in this introduction.

No surgery is without risks. Possible late complications, in order of descending frequency, of UPPP are: Pharyngeal dryness and hardening, postnasal secretion, dysphagia, incapability of initiating swallowing, prolonged angina, taste disorders, speech disorders, numbness of tongue, permanent velopharyngeal incompetence and nasopharyngeal stenosis. Furthermore, although more clarification is needed, studies suggest that the response to UPPP for OSA decreases progressively over the years after surgery.

Treatment modalities designed to prevent obstruction at the level of the hypopharynx vary from minimally invasive, such as radiofrequency ablation of the base of tongue to invasive, genioglossal advancement (GA) or maxillomandibular advancement (MMA) for example. An evidence-based medicine review reported a success rate ranging from 20 - 83% achieved in patients undergoing tongue radiofrequency, 25 - 83% in reports on midline glossectomy and 39 - 78% on GA. Surgical success was defined as a reduction in AHI of 50% or more and an AHI of less than 20. It should be noted that overall the patients were overweight or obese and the range of OSA severity was predominantly moderate or severe. Four studies reported on the efficacy of hyoid suspension.
In 3 studies the success rate ranged from 52 - 78% but in one study the success rate was a poor 17%. Patients in this study had a higher BMI and a lower minimum oxygen saturation (SaO₂).\textsuperscript{180} In a prospective, randomized, small-scale trial, MMA was found to be just as effective as APAP after 1 year.\textsuperscript{181}

Nasal procedures are unlikely to significantly improve OSA, but may be indicated to facilitate adherence to nasal CPAP therapy.\textsuperscript{182} In a randomized controlled study setting, 49 patients with OSA (mean AHI 30.1 ± 16.3/hour) and symptomatic nasal obstruction due to a deviated septum were randomly assigned to either surgery (submucous resection of the deviated nasal septum with or without submucous resection of the bilateral inferior turbinates) or sham surgery. The AHI as a primary endpoint remained unchanged after surgery or sham surgery, despite a significant reduction in nasal resistance to airflow in the surgery group as measured per rhinomanometry.\textsuperscript{169, 183}

The success rates for sleep surgery decrease as the BMI and age increases.\textsuperscript{184} On a last and final note, surgery in patients with OSA is not without risks, especially when general anaesthesia and intubation are required. Comorbid conditions may contraindicate surgical treatment.\textsuperscript{15} Studies have shown that patients with OSA are at an increased risk for per- and postoperative complications.\textsuperscript{185}

**OUTCOME MEASURES OF OSA TREATMENT**

When reporting on the efficacy of treatment, the AHI is the most frequently reported outcome measure. Some clinicians argue that other PSG variables could be used as an outcome measure; e.g., desaturation index (DI) as a measure of intermittent hypoxia. The latter is also considered to be less susceptible to nightly variability.\textsuperscript{186, 187} Others argue that clinical outcomes may be more appropriate, such as sleepiness, daytime functioning, blood pressure and cardiovascular outcomes. There are more dimensions to consider in clinical management of OSA than AHI alone, e.g., side-effects, partner acceptance, or cost-effectiveness. To complicate matters, different definitions of successful therapy are
being used for the different treatment options. In surgery, traditionally, success is defined as a postoperative reduction of AHI to < 20 and > 50% postoperative reduction in AHI. Others have later proposed to tighten these criteria to a postoperative AHI to < 15 (regarded as “clinically relevant” OSA), < 10, and recently even < 5 (as in CPAP therapy).

CPAP and intraoral devices are regarded as successful if the AHI drops below 5 while the devices are used; an AHI below 5 is the bar for CPAP adjustment. Current arbitrary trends define CPAP compliance as 4/ hours/night as an average over all nights observed. The effectiveness of conservative treatment regarding the reduction of AHI depends both on its impact on airway obstruction and compliance. Presently, the second aspect is often overlooked. Currently, when reporting on treatment effectiveness of conservative treatment, the reduction in AHI whilst using CPAP in laboratory situations is documented. An artificial compliance of 100% is assumed. In chapter 7 we compare non-optimal use of optimal therapy (CPAP) with the continuous effect (100%) of often non-optimal therapy (surgery). In chapter 8 of this thesis we provide evidence for change - we propose that treatment adherence should be taken into account when reporting outcomes of treatment of OSA with regard to the AHI and comparing effects of different treatment options.

**OUTLINE OF THIS THESIS**

The first two chapters focus on DISE. In chapter 2 we report the results of our prospective study aimed at documenting the results of 100 consecutive DISE procedures and investigating associations between patient characteristics, PSG and DISE findings. We test the hypothesis, in chapter 3, whether DISE variables can predict the outcome of upper airway surgery in OSA patients.

The following 2 chapters address the results of a large prospective, multidisciplinary, single center, observational study including consecutive patients undergoing bariatric surgery. Chapter 4 focuses on the prevalence of obstructive sleep apnea among patients undergoing bariatric surgery and the predictive value of various clinical parameters: BMI, NC and ESS.
The follow-up study results are described in chapter 5. We report the effect of surgical weight loss on OSA at two post-operative time intervals.

Chapter 6 reviews the current literature on positional sleep apnea and its therapy.

In the last section, we advocate that OSA treatment effects on the AHI should no longer be reported under conditions of artificial compliance only, but in consideration of the individual compliance to the treatment. This is of particular importance when different treatment options are compared. Although the AHI is only a surrogate marker for this disease, it remains the most frequently reported outcome measure in OSA. The effectiveness of conservative treatment regarding the reduction of AHI depends both on its impact on airway obstruction and compliance. Momentarily, the second aspect is often overlooked. Currently, when reporting on treatment effectiveness of conservative treatment, the reduction in AHI whilst using CPAP in laboratory situations is documented. An artificial compliance of 100% is assumed. The study described in chapter 7 aimed to compare non optimal use of optimal therapy (CPAP) with the continuous effect (100%) of often non-optimal therapy (surgery). In chapter 8 we provide evidence for change.

Chapter 9 describes the main findings of the studies described from chapter 2 through chapter 8 in broader context, draws general conclusions and provides suggestions for future research.

Chapter 10 provides a summary of this thesis in English and Dutch.
Figure 1: Velum obstruction. (A) No obstruction; (B) partial anteroposterieur (AP) obstruction; (C) complete AP obstruction; (D) concentric obstruction

Figure 2: Oropharynx and tonsil obstruction. (A) No obstruction; (B) partial obstruction by tonsils; (C) complete lateral collapse; (D) complete obstruction by kissing tonsils; (E) kissing tonsils view in the oral cavity
Figure 3: Tongue base obstruction. (A) partial AP obstruction; (B) complete AP obstruction

Figure 4: Epiglottis obstruction. (A) Anteroposterior; (B) Lateral
REFERENCES


32. Schwab RJ. A quantum advance in PSG recordings: the importance of head position in mediating the AHI. *Sleep* 2011;34:985-986.


