Developments in diagnosis and treatment of obstructive sleep apnea

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1 General introduction and thesis outline

GENERAL INTRODUCTION

Physiological basis of sleep

Since approximately one third of our lifetime is spent sleeping, the impact of sleep quality on our health cannot be underestimated.[1] It is thus not surprising that a wide range of theoretical proposals on the beneficial effects of sleep is available. The ecological hypothesis states that we sleep in order to optimize the timing and effectivity of our activities.[2] Another proposal emphasizes energy conservation, which implies that we sleep to save energy.[3] The recovery hypothesis is based on the belief that sleep removes metabolic waste and restores our neurocognitive and emotional functions.[4] Others think that sleeping reinforces our memories and adaptive immunity.[5,6] Perhaps we sleep in order to maintain our neural networks and immune system's functions.[7] Most of these hypotheses are not mutually exclusive, which makes it evident that sleep is a complex system, with functions ranging from basis physiological needs to complex network-like functions.[8] All these functions should be beneficial for general health. It is therefore worrying that about 30% of people are plagued by excessive daytime sleepiness.[9] Consequently, the interest in sleep medicine and science is rapidly growing and developing across all major clinical specialties.[9,10]

Assessment of sleep disorders

Sleep disorders are common and carry a significant healthcare burden, comparable to those of other major diseases.[11,12] Accurate screening tools and cost-effective treatment, essential in order to treat patients with sleep-related morbidities properly and at the same time reduce consequential economic burden, have been developed.[10] When - in the 1960s - the polysomnography (PSG) was introduced, a need to reach consensus on the definition of sleep disorders arose.[10] The first classification system was proposed in 1972.[13] In 2014, the International Classification of Sleep Disorders was updated to its 3rd edition (ICSD-3) and constitutes the currently available and recommended classification for use by sleep experts. The following categories of sleep disorders are defined:[14]

- Insomnia
- Sleep-related breathing disorders
- Central disorders of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep-related movement disorders
- Other sleep disorders

The estimated prevalence of insomnia alone is already up to 20% of the adult population worldwide.[12] The subject of this thesis is another very prevalent sleep disorder, Obstructive Sleep Apnea (OSA), belonging to the Sleep-Related Breathing Disorders (SRBDs), with a worldwide prevalence of at least 10% in the middle- and older-aged population.[15]

Diagnostic process of sleep-related breathing disorders

Sleep-related breathing disorders (SRBDs) are characterized by disordered respiration during sleep and classified by the ICSD-3 as follows:[16]

- Obstructive Sleep Apnea (OSA) disorders
- Central Sleep Apnea (CSA) syndromes
- Sleep-related hypoventilation disorders
- Sleep-related hypoxemia disorder
- Isolated symptom/normal variant (primary snoring and catathrenia)

SRBDs are a diagnostic challenge because of their broad variety in clinical presentation.[17] For each category, minimal diagnostic criteria exist that should be met.[18] A classification system rather serves as a framework for scientific research, but in clinical reality often more than one sleep disorder is present. The evaluation of a patient with sleep disorders includes three key elements: the history of patient's sleep and daytime complaints, a physical examination, and sleep diagnostic and daytime function tests.[18] Extensive diagnostic work-up completes the foundation of the final diagnosis.[10]

Clinical interviewing consists of identification of main complaints, long-term daytime and nighttime symptoms, and information on medical history and use of medication. Structured interviews and standardized questionnaires can be of significant added value.[18] The obtained information may lead to specific focus areas for physical examination. Assessment of the upper airway, Body-Mass-Index (BMI), blood pressure and pulse, and cardiopulmonary status should always be done to identify potential risk factors.[19]

Once the differential diagnosis is established, the appropriate diagnostics tools/tests are selected, based on a cost-benefit basis according to clinical suspicion and best scientific evidence. Assessment of sleepiness through investigation of sleep and wakefulness should include subjective scales and objective test, and should always be interpreted in the context of the full clinical picture.[13] Careful assessment of SRBDs

can only be achieved by an overnight sleep test. such as a PSG (in laboratory or ambulatory), Polygraphy (PG), limited-channel devices (i.e., only heart-rate, oxygen-saturation levels), and home-based sleep studies. Selecting the proper test should be based on resource availability and pretest probability of OSA. The indication for a PSG includes suspected sleep apnea, including suspected OSA despite a low level of clinical suspicion, clinical signs of a comorbid sleep disorder, or known significant pulmonary, cardiovascular, or neuromuscular comorbid disease.[10]

A PSG provides detailed information on sleep stages, arousal from sleep, respiratory abnormalities, hypopnea, periodic leg movements, and other indices obtained by electroencephalogram, electro-oculogram, and electromyogram of the submental muscle.[14,20] The latter is measured because sleep bruxism is characterized by rhythmic masticatory muscle activity and related to OSA.[21] Respiration is measured in many simultaneous ways: by a nasal cannula, a pulse oximeter to determine oxygen saturation levels, and a respiratory effort belt to measure thoracoabdominal excursions. In addition, a position sensor determines body position. In case of automatized analysis of the PSG recording, manual corrections, using the AASM scoring manual, are essential. It must be noted that the latter can create considerable inter-observer variability in the scoring of events.[14] In addition, night-to-night variability in respiratory variables may be considerable.[22] This variability is most likely related to the time spent in supine sleeping position, in which the AHI is typically higher. Other causes/factors include the variation in sleep stage, degree of nasal congestion, alcohol and/or drug consumption causing relaxation, the so called first night effect (i.e. decreased total sleep time, lower sleep efficiencies, reduction in REM sleep, and longer REM latencies on the first night of testing), and environmental factors (e.g. noises, bedpartner, light).[20] An apnea is defined as a ≥90% decrease in peak signal excursion for at least 10 seconds; a hypopnea is an drop in airflow by ≥30% for at least 10 seconds in combination with ≥3% oxygen desaturation.[14] The scoring rules to be used are still a matter of discussion, and for this reason the reference for the scoring procedure used should always be mentioned.[13]

Obstructive sleep apnea

The criteria for the OSA diagnosis according to the ICSD-3 are shown in Table 1.[16] OSA severity is internationally classified by the apnea-hypopnea index (AHI), assessed by PSG or PG, where 5-14 events/hr is defined as mild, 15-29 events/hr as moderate and ≥30 events/hr as severe OSA. The Epworth Sleepiness Scale (ESS) is used to indicate evident daytime sleepiness.[23]

Table 1. Diagnostic criteria for OSA, adults.[14]

A	The presence of ≥1 of the following: • Complaints of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms • Breath holding, gasping or chocking symptoms which causes waking -up • Reported habitual snoring and/or breathing interruptions by bed partner • Diagnosis with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, CHF, atrial fibrillation, or type 2 diabetes mellitus
B	PSG or out of center sleep testing demonstrates ≥5 predominantly obstructive respiratory events per hour of sleep
C	PSG or out of centre sleep testing demonstrates ≥15 predominantly obstructive respiratory events per hour of sleep

(A and B) or C satisfy the criteria

Epidemiology and risk factors

A recent study on global prevalence of OSA in adults aged 30-69 years estimated the existence of almost a billion cases with an AHI ≥5 events/hr.[11] Within the Netherlands, the same study estimated 49% of the middle-aged population to have an AHI≥5 events/hr and 28.5% with an AHI≥15 events/hr.[11] It must be noted that this study did not take into account whether patients where symptomatic. An explanation for the world-wide increasing prevalence of OSA could be its direct relation to obesity, ageing, and usage of adjusted criteria to define an apnea or hypopnea. More than 70% of the patients with OSA are obese.[24] Weight gain of 10% causes an AHI increase of approximately 32%, and increases the chance of having an AHI≥15 events/hr with a factor of six.[25] The ratio of men versus women having OSA is 2:1. This difference might be explained by the negative effect of androgens on the collapsibility of the upper airway. Progesterone has the opposite effect, which explains why after menopause and during pregnancy, when these levels are low, the prevalence of OSA amongst women increases. Another risk factor is age. OSA prevalence increases with age until the age of 70 years, after which a plateau is reached.[26]

Pathophysiology

OSA is characterized by varying obstructions of the upper airway, which causes cessations (apneas) or reductions (hypopneas) of the respiratory flow. These breathing disturbances are associated with oxygen desaturations, activation of the central nervous system (arousals), and/or excretion of stress hormones. The predisposition for developing OSA depends upon the collapsibility (diameter) of a segment of the

upper airway, which is not completely stiffened by bony and cartilaginous structures.[27] The degree of collapsibility is characterized by the balance between the occluding (extraluminal) pressure of the surrounding tissue and the dilating positive (intraluminal) pressure which can be quantified by the critical closing pressure (Pcrit). The Pcrit determines the threshold between free and interrupted airflow.[28] The diameter of the upper airway (degree of obstruction) varies depending on, for instance, sleep stage and body-position.[10] In addition, the occluding pressure (decrease in diameter) increases in patients with morphological malformations (such as the position of the mandible), fat deposition, enlargement of the tonsils, uvula or tongue, or fluid accumulation in the soft tissues.[29] The dilating positive pressure (increase in diameter) depends on upper airway muscles, especially the m. genioglossus, the muscle tone of which might be impaired in OSA.[27] Muscle relaxation during sleep is also present in healthy people, in particular during REM sleep, although it does not cause a clinically relevant reduction of the diameter of the upper airway.[30] In OSA patients, increased muscle activity compensates the occluding pressure on the upper airway, and this mechanism fails during sleep, possibly due to structural damage and the influence of individual muscle responsiveness.[28] The described pathophysiology of the upper airway obstructions is reflected by PSG outcomes. Decrease in diameter of the upper airway leads to decreased inspiratory flow (flattening flow curve on PSG). Respiration through narrowed airways and the rapid increase of respiration after reopening of the airway causes vibrations of the soft tissue (snoring and/or sharp increase in respiration on PSG). While the upper airway is obstructed, paradoxical breathing occurs; the thorax and abdomen not fully move in phase (also shown on PSG). Obstructive disturbances appear more likely during Rapid Eye Movement (REM) sleep.[31] The precise analysis of the individually relevant components of the pathophysiology can be helpful with the selection of the treatment options. These mechanical, pharmaceutical, and functional treatment options may address morphology, the central nervous influence, the muscle function, and the ventilatory response.

Clinical picture and diagnosis

SRBDs have both similarities and differences in their clinical presentation. If OSA is suspected, it is therefore recommended to follow the standardized diagnostic work-up as previously described. The clinical symptoms in OSA are often heterogeneous and can be divided into daytime and nighttime symptoms. During sleep, complaints include snoring, observed apneas by a bed partner, dry mouth, sore throat, chocking and dyspnea, nocturia, nocturnal sweating, and frequent awakenings.[10] The

majority of OSA patients (95%) report disruptive snoring, however the predictive value of this symptom is low due to the high prevalence of snoring complaints in the general population.[32] Regularly occurring apneas are reported by bed partners in 75% of the OSA population and are consequently a better diagnostic predictor.[10] OSA symptoms during wakefulness include excessive sleepiness, non-restorative sleep, fatigue, cognitive dysfunction, emotional imbalance, depressive symptoms, decreased libido, and morning headaches.[10] Only 25% of the OSA population reports excessive daytime sleepiness as primary symptom, which is more pathognomonic for OSA than symptoms like exhaustion or fatigue, which are reported by half of the population as main symptom.[33] Because symptoms progress gradually, many patients underestimate the severity of their sleepiness until their daytime function and activities are severely affected. All of these symptoms can negatively influence their quality of life and professional performance, and increases – for instance – their risk to become involved in vehicle accidents. However, attention must be drawn to the fact that having an AHI≥5 events/hr without any symptomatology is common as well.[34]

The added value of carefully addressing the symptoms is to identify specific phenotypes and endotypes. A phenotype is an observable characteristic with no direct relationship to a disease process. An endotype is a specific biological pathway that explains the observable properties of a phenotype. The identification of these pheno- and endotypes contribute to a better understanding of the pathophysiology, provides guidance through the diagnostic procedures, and facilitates tailored treatment (recommendations) and prediction of treatment outcome.[35]

Phenotype

Gender[36,37]

- Age 20-55 years: male>female
- Age >55 years: male = female
- Snoring and apneas: male>female
- Fatigue, headache, depression: female>male

Positional OSA[38]

- AHI in supine sleeping position is twice as high as in non-supine position
- >56% of the OSA population has position-dependent OSA
- Severity is often mild to moderate

REM-related OSA[30]

- AHI in REM is twice as high as in non-REM in these patients, symptoms and OSA severity are often mild
- Better prediction cardiometabolic disease risk by using REM-AHI compared to non-REM measurements

Endotype

Decreased neuromuscular function[35]

- Impaired neuromuscular (genioglossus) response to hypoxia and hypoxemia
- In 36% of the OSA population

Anatomy[39] (66% of the OSA population)

- Obesity (most frequent)
- Bone structures inferior positioning of the hyoid bone, retro positioning of the mandible, smaller cranial base
- Abnormal upper airway soft tissue morphology (large tonsils or uvula)

Arousal threshold[40]

- Low arousal threshold reduces dilator activity of the upper airway
- In 37% of the OSA population

Loop gain[41]

- Higher degree of response to a ventilatory stimulus (desaturation)

Examination of the upper airway is of added value in the diagnostic process and as to screen for treatment eligibility.[23] Certain findings are more common in patients with OSA, and in some cases a treatable underlying cause can be present. Findings include nasal abnormalities, which may cause a decreased nasal airflow and can be associated with snoring, a higher predisposition of OSA, and decreased effectiveness of Continuous Positive Airway Pressure (CPAP).[42] In the pharynx, the presence of a voluminous tongue, webbing of the soft palate, enlarged uvula, increased soft tissue of the lateral walls of the oropharynx, and hypertrophic tonsils can all contribute to an increased risk of developing OSA.[23] The presence of retrognathia and an arched palate should also be noted.[43]

As previously mentioned, better insight in the complex underlying pathophysiology potentially helps to increase treatment success by choosing targeted treatment. Assessment of the collapsibility of the upper airway during sleep by a drug-induced sleep endoscopy (DISE) can be of additional value.[44] Currently, DISE is mainly done if upper airway surgery or upper airway stimulation is considered to treat OSA. Many scientist are currently investigating the added predictive value of DISE with regard to non-invasive treatment options such as positional therapy (PT) or a mandibular advancement device (MAD. During DISE, a ''natural'' sleeping situation is simulated by the use of, most often, propofol administration to reach the desired level of sedation.[44] With the appropriate depth of sedation, patients should temporary not be able to respond to verbal stimuli while they maintain their own respiration activity. Such an endoscopy is executed in a quiet and dark room. On average, patients are asleep for 15 minutes. With a flexible laryngoscope, introduced through the nose, in particular the collapsible segment of the upper airway is examined, preferably with the patient in lateral head-and-trunk position and subsequently in supine position. In both positions, four potential obstruction levels of the upper airway are investigated, with and without a manually performed jaw-thrust with an estimated 70% of maximal protrusion of the mandible.[44,45] To systematically report on the DISE findings, the VOTE scoring system was created.[45] This abbreviation refers to the four potential obstructed levels of the upper airway: namely velum (V), oropharynx (O), tongue base (T), and epiglottis (E).[45] The obstruction severity is defined as no collapse (zero, <50% obstruction), partial collapse (one, 50% - 75% obstruction), or complete collapse (two, >75% obstruction).[45] The configuration of the collapse is either anterior-posterior (AP), lateral, or concentric.[45] Research on the predictive value of DISE has found a negative relationship between complete concentric collapse on soft palate level and surgical success.[46] In addition, data from DISEs have shown that the phenomenon of floppy epiglottis is very rare in the lateral position, but when present in supine position, could cause CPAP failure.[47] The suspicion of enlarged tonsils as the cause of the OSA could also be confirmed by DISE.[48,49] All these findings can be of added value in order to determine targeted treatment.[48,50] In this thesis, we will also discuss the, more controversial, predictive value of the lateral head-and-trunk position, the jaw-thrust maneuver, and the use of a temporary MAD during DISE regarding non-surgical treatment outcome.[51,52]

Comorbidities

Intermitted hypoxia and sleep fragmentation caused by upper airway obstruction induce oxidative stress.[53] In response to this sympathetic over-activity, inflammation

and endothelial dysfunction occur.[53] These chain reactions consequently can cause an increase of comorbidities throughout life.[40] Many studies have proven that untreated OSA acts as the modulator of the occurrence, severity, and progression of cardiovascular and metabolic diseases.[53,54] Severe OSA could cause a four to six times increased risk of mortality, irrespective of factors such as age, diabetes, or high cholesterol.[55] In addition to the direct health consequences of these comorbidities, OSA may also lead to chronic pain, a decrease in activities, lack of social interaction, and increased mortality.[56] Another important risk of untreated OSA is a higher change of being involved in a traffic accident because of excessive daytime sleepiness[33]. As previously described, OSA and other sleep-disorders such as insomnia and restless legs syndrome often co-occur. Many theories exist on the pathophysiology and developmental course of these co-morbid sleep-disorders. It is recommended to address them, in order to optimize OSA treatment effect[55].

Treatment

New concepts of personalized medicine emphasize the importance of pathophysiological considerations in a tailored treatment strategy.[57] The precise analysis of the individually relevant components will assist in the selection of the best (combination of) treatment options. Consequently, there is no standard approach for treatment of OSA. Therapeutic management consists of lifestyle recommendations, treatment of associated comorbidities, oral appliances, CPAP, positional therapy, surgical interventions, including neurostimulation and, more experimental, drug treatment.[10] Choices should not only be based on clinical and pathophysiological characteristics, but also on patients' preference by the concept of shared decision making to improve treatment adherence.[58] Treatment should be aimed towards the reduction of symptoms, while reduction of the AHI could be a measure to monitor treatment effect. It must be noted that the latter not always correlates with reduction of symptoms. Prevention of comorbidities should also be taken into account. Patient education regarding OSA is key for successful treatment, because the apneic events occur during sleep and are therefore often not recognized, and because of the often lifelong treatment that OSA requires.

Lifestyle recommendations

Because of the common interaction between insomnia and OSA, practitioners should always promote healthy sleep. An example of good sleep hygiene is avoidance of

sleep-disturbing habits prior to bed time, such as excessive exercise and consumption of caffeine, nicotine, and alcohol.[59] In addition, hypnotic and opioid pharmaceuticals should be avoided due to their myorelaxant effects, which may negatively influence OSA severity.[60,61] As previously mentioned, obesity is closely related to OSA. Weight loss counteracts the caused anatomical abnormalities.[62] Replacement of fatty tissue with muscle can improve both the AHI and sleepiness, even if the BMI does not decrease.[63]

Indication

Before starting specific therapy, these lifestyle interventions should be encouraged. In addition, existing comorbid sleep disorders, including insomnia, restless legs syndrome, chronic pain or depression, should be addressed.

Contraindication

Not applicable.

Drug treatment

In treatment OSA, currently no licensed medications are available. However, pharmaceuticals that improve associated conditions of OSA might be helpful. Antimuscarinergic and andrenergic drugs may stabilize upper airway muscles, while other pharmaceuticals may influence respiratory drive or arousability.[64]

Indication

The definite place of drug treatment in OSA is still to be determined.

Contraindication

The definite place of drug treatment in OSA is still to be determined.

Positional therapy

In the majority of OSA population the following applies: the lower the AHI, the higher the prevalence of patients with position-dependent OSA.[65] The most often used definition is having twice as many apneic events in supine position than in the other sleeping positions.[66] Positional Therapy (PT) has been developed to prevent patients from sleeping in this position. The new-generation PT consist of a small device worn on the chest during the night which vibrates if the patient sleeps on the back, consequently stimulating the patient to choose another sleeping position.[67,68]

Indication

PT can be used for patients with position-dependent OSA (POSA) as standalone treatment. In some non-positional patients, if OSA following treatment remains as a less severe POSA, PT can be used as combined therapy.[69,70] A floppy epiglottis, observed during DISE, is a phenomenon occurring in the supine position and rarely in non-supine sleeping positions, and is therefore well responsive to PT.[47]

Contraindication

If the AHI in non-supine position exceeds 10 events/hr, the effect of PT could be suboptimal, in which case this form of therapy could be used as combined treatment.[69] In patients with physical issues, in whom the supine sleeping position is the only preferred position, other treatment options should be considered. In patients with co-existing insomnia, OSA care givers should pay attention to the effect of the vibrations on this complaint.

Oral appliances

The practical guideline for oral appliances states that these modalities should be considered in adult patients requesting treatment for primary snoring or denying or not tolerating CPAP treatment.[32] The appliance should be a custom-made titratable device, provided by a specialized dentist.[32,71] A Mandibular Advancement Device (MAD) is the most commonly prescribed type of oral appliances. It consists of two adjustable elements ("duobloc"), covering the teeth, in order to advance the lower jaw. By moving the mandible forward, it counteracts the effects of anatomical abnormalities that decrease the volume of the upper airway.[72] It remains difficult to predict the needed amount of mandibular protrusion in order to decrease the AHI.[73] Although MADs have a lower efficacy than CPAP, due to better adherence on MADs therapy, it's reported to have the same effectiveness as CPAP.[74,75] Possible explanation for the better adherence is more patient comfort.[76] The reported treatment outcomes of MADs range widely. A recent review reported complete success (AHI <5 events/hr) rates of 29% to 71% among studies.[77] This underlines the need for research on potential variables influencing treatment outcome.

Indication

MADs improve the pharyngeal collapsibility.[78] Since treatment success of MADs varies, potential predictors for success are widely studied.[79] Low BMI, lower age, female sex, snoring, mild to moderate OSA, and POSA are positive predictors.[80]

Contraindication

Oral appliances should not be prescribed to patients with an insufficient number of teeth to anchor the appliance, periodontal disease, limited mouth opening, extreme gag reflex, or restriction of mandibular advancement.[81] A complete concentric collapse and collapse of the lateral walls, observed during DISE, are associated with negative treatment outcomes.[82] MADs seem not to affect loop gain, arousal threshold, and dilator muscle activity.[78]

CPAP

Continuous positive airway pressure through the (oro)nasal route is used to improve airflow to the lungs and constitutes the gold standard therapy for OSA.[42] Preferably, CPAP is administered via the nose with the interface.[83] Contemporary technology has contributed to improvement of the machine and interface/mask over the years. CPAP should now be easily portable, sturdy though light weight, quite silent, and above all comfortable. The choice of mask depends on anatomical features and personal preference. Air leaks should be avoided as they lead to sub-optimal treatment and discomfort.[83] Nasal pressure of 4.5-10 cm H_2O increases intraluminal pressure in the upper airway, consequently exceeding the critical closing pressure and therefore preventing passive collapses of the upper airway during sleep [42]. The effective pressure level, directly related to the collapsibility of the upper airway, provides predictive information on responsiveness to alternative treatment.[84,85] Other potential effects of CPAP include decreased work of breathing, improved stability of the central respiratory drive, improved cardiac function due to reductions in preload and afterload.[86] Adequate CPAP compliance is defined as usage of ≥4 hours/night, 70% of the nights. However, between 46% and 83% patients with OSA insufficiently use CPAP as defined.[83] Support from family members at home and appropriate usage during the initial weeks will improve long-term adherence.[87]

Indication

The adherence and therefore effectiveness of CPAP therapy is better in the more severe cases of the disease (AHI) and in the presence of daytime sleepiness.

Contraindication

Recent base of skull surgery, facial emphysema, severe facial eczema.[88,89]

Upper airway surgery

Upper airway surgery acts on the volume of the upper airway by elevating structural abnormalities in the pharyngeal airway and consequently increasing its volume. In addition, surgery could correct specific anatomical abnormalities which compromise adherence to non-surgical treatment options for OSA[90]. DISE is recommended to optimize patient selection and consequently treatment success.[44] Nasal surgery has no effect on OSA severity, although improvement of nasal patency might improve CPAP compliance.[91] Adenoidectomy and tonsillectomy are, in particular in the pediatric population, very effective in reducing the AHI if the adenoid and tonsils are evidently enlarged.[92] Lateral pharyngoplasty, barbed reposition pharyngoplasty, and expansion sphincter pharyngoplasty are relatively new surgical interventions which remodel the pharyngeal tissues instead of the previously performed resections.[93] For obstructions regarding the tongue, radiofrequency ablation to stiffen the tongue base and trans oral robotic surgery (TORS) to reduce the volume of the tongue base could be the remedy.[94,95] Another way to improve the volume of the upper airway is by stimulating the genioglossus muscle, a non-anatomical but physiological targeted type of therapy. With a relatively new surgical treatment, this upper airway dilatator muscle is activated by hypoglossal nerve stimulation (HNS), which causes opening of the upper airway at the tongue base by protrusion of the tongue and also on soft palate level during inspiration.[96,97]Maxillomandibular advancement (MMA) surgery protrudes both jaws to affect the configuration of the soft tissues and consequently enlarge the volume of the upper airway.[98] This type of surgery urges intensive pre- and postoperative orthodontic treatment to prevents malocclusion. In very severe, therapy resistant OSA cases, bypassing the upper airway obstruction with a tracheostomy is a very effective and permanent therapeutic solution. It must be noted this is a last resort treatment option because of its specific nursing requirements and impact on social life. Since obesity and OSA are evidently related, and weight reductions commonly fail, bariatric surgery nowadays is increasingly being applied. Due to the perioperative complications caused by OSA, all bariatric patients should be screened in advance and treated with CPAP perioperative in case of moderate to severe OSA.[99] Bariatric surgery substantially reduces the weight and AHI, however many patients still require additional treatment for their (less severe) OSA.

Indication

In case of mild OSA and evident anatomical abnormalities, surgery could be first-line therapy. In more severe cases, surgery is only indicated if non-surgical therapies do not have favorable outcomes.

Contraindication

A complete concentric collapse of the soft palate during DISE is a contraindication for the majority of surgical interventions. In addition, a high BMI (>35 kg/m^2) has been associated with negative treatment outcomes.

THESIS OUTLINE

In the field of obstructive sleep apnea (OSA), the healthcare industry is constantly developing and optimizing diagnostic tools and treatment modalities. The general aim of this thesis was to investigate the value of some recent developments, which potentially can contribute to appropriate care: optimization of screening and treatment outcome in patients with OSA. Choice of diagnostic tools and treatment depends, amongst other things, on OSA severity and patient preference, complaints and characteristics. Given the wide range of diagnostic tools and treatment modalities, in some patients there are multiple suitable options. For both, the patient and the physician, the main goal is to achieve the highest possible treatment outcome. To accomplish that goal, it is of added value to identify potential predictors influencing OSA severity and treatment outcome. Consequently, treatment success will increase by choosing targeted treatment. In all chapters, predictors for OSA severity and parameters influencing treatment outcome are ascertained. In **chapter 2,** the association between demographic, anthropometric and acoustic factors and the obstruction sites of the upper airway is described. We hypothesize that snoring sounds may have a predictive value with regard to site and configuration of upper airway obstruction and therefore might, in specific cases, be a viable screening alternative to drug-induced sleep endoscopy (DISE), which is more time consuming and expensive. In **chapter 3** we explore whether clinical observable dental parameters including profile, molar classification, overjet, overbite, maximal retrusion, and protrusion in patients with OSA influence or predict OSA severity and mandibular advancement device (MAD) treatment outcome.

As described in the general introduction, MAD treatment success ranges widely. In the literature it has been reported a high body-mass index (BMI) or high pretreatment apnea-hypopnea index (AHI) negatively influence MAD treatment outcome. In **chapters 3-7,** we investigate potential predictors for treatment outcome, which could be used in the future for screening purposes with regard to treatment eligibility. In **chapters 3 and 4**, specific dental characteristics and position-dependent OSA (POSA) are explored as potential predictive phenotypes for MAD treatment outcome.

DISE is a widely used screening tool in patients with OSA can provide additional information on collapse patterns of the upper airway, it is especially performed if upper airway surgery is considered. Although more controversial, DISE might

also predict treatment success of a MAD and/or Positional Therapy (PT). Based on the outcomes of various studies, our DISE protocol was adjusted as an attempt to better mimic the effect of a MAD, PT, or combination of both. The aim of the studies in **chapters 5 and 6** was to verify whether our adjustments would increase the value of DISE as a screening tool. In **chapter 5**, we study the predictive value of passive maneuvers, performed during DISE, including lateral head-and-trunk rotation, jaw thrust and a temporary MAD, in patients eligible for positional therapy and MAD treatment. We hypothesize that DISE could be carried out more widely than only for upper airway surgery. Subsequently, in **chapter 6,** we focus in a prospective manner on the predictive value of this temporary MAD applied during DISE on MAD treatment outcome, measured by polysomnography (PSG) after 3 months. Treatment success not only depends on selecting suitable patients, also optimization of treatment modalities is of great importance to improve adherence and consequently treatment outcome. In **chapter 7**, two types of MADs – custom versus non-custom – are compared with regard to objective and self-reported outcomes. We hypothesize that if the treatment efficacy is comparable, a non-custom MAD could be used as a selection tool for MAD treatment eligibility to improve treatment outcome of a more expensive, custom MAD.

The other investigated treatment option for OSA in this thesis is hypoglossal nerve stimulation (HNS). For the majority of treatment options, pre-treatment OSA severity is a predictor for success; the more severe, the less the chance on successful treatment. In **chapter 8** we report on pre-treatment OSA severity (AHI) and its influence on HNS treatment success. After implantation and activation of HNS, titrations are performed to optimize its effectiveness. Traditionally, these titrations are performed during an in-laboratory overnight PSG. In **chapter 9** we report on an alternative, daytime titration, hypothesizing that the latter might be a valuable and viable alternative for conventional overnight titrations. As daytime titrations are cheaper, associated with easier logistics and better work circumstances for somnotechnologists without jeopardizing titration quality.

In **chapter 10** the main findings and their consequences are described, in addition suggestions for clinical implementation and future research are provided.

Chapter 11 contains a summary of this thesis in English and in Dutch.

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