Mandibular advancement device therapy in obstructive sleep apnea

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Chapter 1

General Introduction

Obstructive sleep apnea (OSA) is a condition characterized by repetitive complete or partial obstruction of the upper airway during sleep [1]. These obstructions manifest themselves as a complete cessation or reduction of airflow, despite ongoing inspiratory efforts, and are often terminated by arousals from sleep. The lack of adequate ventilation during an obstructive event usually results in oxygen desaturation.

OSA patients often complain about daytime symptoms, such as excessive daytime sleepiness, unrefreshing sleep, poor concentration, and fatigue [2-4]. Loud snoring is another typical feature of OSA and is commonly reported by the patient's sleep partner or family [5]. Based on available population-based studies, the prevalence of obstructive sleep apnea is approximately 3-7% for adult men and 2-5% for adult women in the general population [6-11].

There is evidence that links OSA to long-term cardiovascular morbidity, including hypertension, myocardial infarction, and stroke [12-17]; and to an increased risk of motor vehicle accidents [18, 19]. These cardiovascular co-morbidities and motor vehicle accidents result in an increased risk of mortality in OSA patients [20, 21]. Hence, untreated OSA is associated with serious medical consequences, which underlines the importance of timely recognition, accurate diagnosis, and effective treatment of this disorder.

Pathogenesis and risk factors

The pathogenesis of upper airway closure in patients with OSA is still not fully understood [22, 23]. OSA is thought to result from a combination of anatomical upper airway predisposition and changes in neural activation mechanisms [22]. OSA patients tend to have an anatomically compromised upper airway, resulting from skeletal abnormalities (e.g., retrognathia), soft tissue abnormalities (e.g., macroglossia), or a combination of these factors. During wakefulness, the activity of pharyngeal dilator muscles compensates for these anatomic characteristics. This compensatory effect is substantially diminished when the action of upper airway reflexes and pharyngeal dilator muscles decreases during sleep [24].

Obesity is the main risk factor of OSA [25, 26]. Fat deposition around the upper airway may narrow the upper airway lumen and increase the collapsibility of the pharynx [27]. Craniofacial anomalies like retrognathia or micrognathia, which may be a result of a genetic syndrome, are accompanied by posterior positioning of the tongue and can thus result in narrowing of the upper airway lumen [28-32]. Further, thickening of the pharyngeal wall, tongue, and tonsils also causes upper airway narrowing [33]. Older age can be considered a risk for developing OSA [34]. Mechanisms proposed for the age-related increase in OSA prevalence include increased deposition of fat in the parapharyngeal area and lengthening of the soft palate, which both result in a narrowed upper airway, and a deterioration of upper airway neuromuscular reflexes [35, 36].

OSA prevalence is higher in diabetes and in metabolic syndrome patients (i.e., insulin-resistance syndrome; an emerging disorder associated with accelerated atherosclerosis) [37-39]. The mechanisms underlying the predisposition to diabetes in OSA patients are not clear [34]. An association between OSA and the metabolic syndrome is suggested, although a unequivocal causality between the two has not been demonstrated yet [40].

OSA is more common in males, in patients with polycystic ovary syndrome, as well as in postmenopausal patients [41]. Although the exact mechanisms are unknown, gender differences in hormones and in fat deposition around the upper airway are thought to play a role [42]. Progesterone increases the activity of the upper airway dilator muscles and therefore plays a protective role against collapse of the upper airway in premenopausal women [41].Obese men are more susceptible to the development of OSA than obese women, most likely because of more fat deposition in the neck, causing narrowing of the pharyngeal lumen [24].

Smoking and alcohol are both considered risk factors for OSA [34]. Airway inflammation due to cigarette smoke could alter the mechanical and neural properties of the upper airway and increase its collapsibility during sleep [34, 43]. Alcohol relaxes upper airway dilator muscles, which in turn increases upper airway resistance, and may thus induce OSA [44].

Diagnosis

The diagnosis of OSA requires the combined assessment of relevant clinical features and the objective demonstration of abnormal breathing during sleep [1, 5]. Signs and symptoms suggestive of OSA include, amongst others, snoring, witnessed apnea and/or gasping by family or bed partner, obesity, excessive daytime sleepiness, a positive family history, non-restorative sleep, and hypertension [45]. An objective measure of sleep-disordered breathing at night is generally required to confirm the diagnosis of OSA. The "gold standard" for the objective demonstration of abnormal breathing during sleep in OSA patients is full polysomnography, which provides detailed information on sleep state, respiration, and gas exchange abnormalities, in addition to a host of other variables including body position, heart rate and rhythm, and snoring sounds [46] (Fig. 1).

In 1999, the American Academy of Sleep Medicine Task Force reported standard definitions, criteria, and severity ratings for abnormal breathing events during sleep [1]. Apnea is defined as a cessation of airflow for at least of 10 seconds. Hypopnea is a decrease in nasal-oral airflow of more than 50% for at least 10 seconds, or a substantial decrease of less than 50% in nasal-oral airflow if associated with an arousal and/or an oxygen desaturation of greater than 3%. The apnea-hypopnea index (AHI) is the number of apneas and hypopneas per hour of sleep [1]. An AHI of at least 5 events/hour and the presence of excessive daytime sleepiness (measured objectively or subjectively) that is not explained by other factors, are commonly used for an OSA diagnosis (based on the American Academy of Sleep Medicine Task Force report, 1999). When excessive daytime sleepiness is absent, at least two symptoms, e.g., recurrent complaints of unrefreshing sleep and daytime fatigue, should be present. Based on the AHI, the American Academy of Sleep Medicine Task Force classified the severity of OSA in mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI >30) [1].

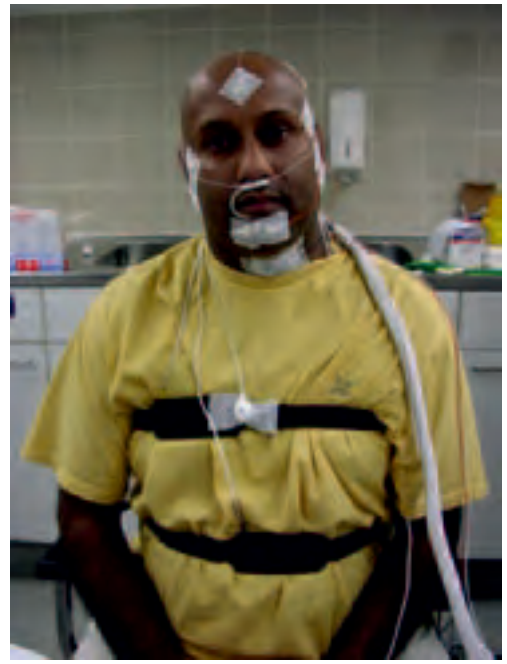

Fig. 1a. An obstructive sleep apnea patient prepared for a full polysomnographic recording. The different electrodes measure variables like sleep state, respiration, body position, heart rate and rhythm, and snoring sounds.

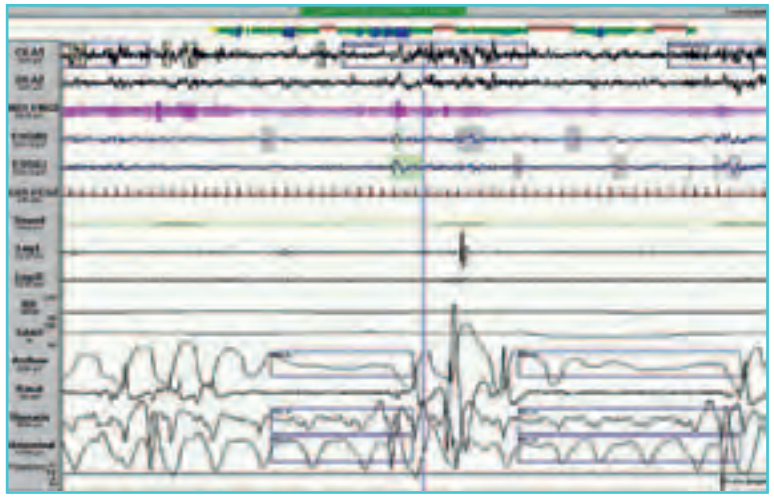

Fig. 1b. The output of a full polysomnographic recording. Two obstructive apneas are highlighted with blue squares in the airflow channel. The graph represents an increment of 60 seconds.

Treatment strategies

Most common treatment options for OSA include behavioral strategies, such as weight reduction, alcohol avoidance, smoking cessation, and alteration of sleeping position [47-50]; a range of surgical procedures of the upper airway [51]; continuous positive airway pressure (CPAP); and oral appliances [52, 53]. In this thesis, an oral appliance is compared with CPAP in the treatment of OSA. Therefore, only oral appliance therapy and CPAP therapy are further introduced below.

CPAP is generally considered the "gold standard" treatment for OSA [52]. CPAP is administered through a nasal or facial mask, held in place by straps around the patient's head. The mask is connected by a tube to a small air compressor (Fig. 2). The CPAP machine sends air under pressure through the tube into the mask. This essentially "splints" the upper airway open and keeps it from collapsing during sleep [54]. In several short-term randomized controlled trials (RCTs), CPAP has been proven to normalize sleep architecture, reduce daytime sleepiness, enhance daily function, elevate mood, reduce automobile accidents, and decrease blood pressure and other cardiovascular consequences [52, 55]. Although CPAP is a highly efficacious treatment, there is nevertheless a need for other treatment options, because the effectiveness of CPAP is often limited by poor patient acceptance and tolerance, and suboptimal compliance [56, 57].

Nowadays, oral appliances are widely prescribed for the treatment of mild and moderate OSA [53]. Most of the prescribed oral appliances are mandibular advancement devices (MADs) (Fig. 3). The rationale behind the efficacy of MADs is that advancement of the mandible and tongue improves upper airway patency during sleep by enlarging the upper airway and by decreasing upper airway collapsibility, thereby preventing collapse during sleep [58-61]. There are many types of MADs, and they all have the potential advantages over CPAP that they are unobtrusive, make no noise, do not need a power source, and are potentially less costly [62]. Further, they are often considered by patients to be a more acceptable treatment modality compared to CPAP [63].

Fig. 2. An obstructive sleep apnea patient using nasal continuous positive airway pressure during sleep.

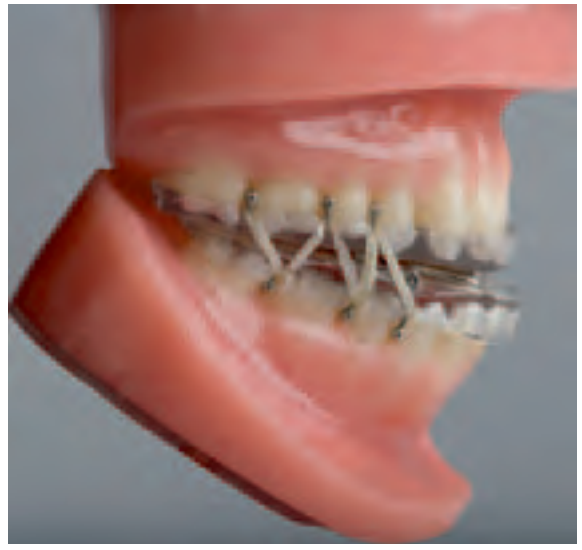

Fig. 3. Lateral view of a mandibular advancement device (MAD).

In 2002, when we started with our randomized placebo-controlled trial (RCT), especially case series were published on the therapeutic efficacy of mandibular advancement devices (MADs) in OSA patients [60, 64]. Consequently, there was not enough sound scientific evidence for the efficacy of MADs. Therefore, we decided to investigate three important aspects of MAD therapy in an RCT: (1) the time-variant nature of the AHI and its consequences for diagnosis and therapy evaluation in OSA patients; (2) the influence of mandibular

protrusion on OSA signs and symptoms; and (3) the short-term and long-term effects of both MAD and CPAP in the treatment of OSA.

In most studies, the AHI is used as the main outcome variable in the diagnosis and therapy evaluation of OSA. When using the AHI for these purposes, it is of importance that the AHI is stable over time. In studies investigating the AHI variability during consecutive nights, considerable variability was observed on the individual level [65-71]. The numerical consequences of this variability for diagnosis and therapy evaluation, however, were not elaborated in these studies. Therefore, the aim of the study in **chapter 2** of this thesis was to determine the variability of AHI during a follow-up of 10 weeks, and to describe a mathematical technique to assess its possible consequences for diagnostic and therapy evaluation purposes.

In a recent, evidence-based review regarding the use of oral appliances in the treatment of OSA, Ferguson et al. indicated that more information is needed about the key design elements of oral appliances that are related to the observed improvements of OSA signs and symptoms [63]. For example, the role of vertical opening remains a controversy [72, 73]. Therefore, it is of importance to keep this variable constant when investigating the effects of a gradual increase in mandibular advancement on OSA. As a first step for this thesis, an adjustable MAD was therefore developed with a constant vertical dimension at different mandibular positions. In **chapter 3** of this thesis, the initial efficacy of this MAD in a group of OSA patients was assessed in a pilot study. Further, it was aimed to evaluate the patients' compliance to the MAD therapy and to determine the feasibility of the procedures of this pilot trial for use in a future RCT. In **chapter 4** of this thesis, the influence of four mandibular protrusion positions, at a constant vertical dimension, on OSA signs and symptoms was assessed. The hypothesis thereby was that larger protrusions would yield larger improvements in OSA characteristics.

After the start of our RCT, several other RCTs have addressed the efficacy of mandibular advancement devices (MADs) in the treatment of OSA (e.g., 74-78). Their common control condition, CPAP, was found to be superior to MAD therapy. However, in these studies, only CPAP was titrated objectively (i.e., by using polysomnography). To enable an unbiased comparison between both treatment modalities, the

MAD should be titrated objectively as well. Therefore, the aim of the study in **chapter 5** of this thesis was to compare the effects of an MAD with those of nasal CPAP (nCPAP), following polysomnographically controlled titration of both treatment modalities. To control for a possible placebo effect in subjective outcome variables like excessive daytime sleepiness and health perception, an intra-oral placebo device served as passive control condition for both active conditions. Although the short-term therapeutic efficacy of MADs has been compared with CPAP in several RCTs (e.g., 74-79), long-term parallel-group trials are needed to capture information regarding the persistence of efficacy and loss to follow-up [52]. Therefore, the aim of the study in **chapter 6** of this thesis was to compare these treatment aspects between MAD and nCPAP in a one-year follow-up.

Synopsis

The topic of this thesis is the effects of mandibular advancement device (MAD) therapy on obstructive sleep apnea (OSA). The objectives were:

1. To determine the apnea-hypopnea index variability over time, and to discuss its consequences for diagnosis and therapy evaluation in OSA patients (**chapter 2**).
2. To assess the influence of four mandibular protrusion positions on OSA signs and symptoms (**chapter 3 and 4**).
3. To compare the short-term and long-term effects of an MAD with those of nasal continuous positive airway pressure in the treatment of OSA (**chapter 5 and 6**).

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