Mandibular advancement device therapy in obstructive sleep apnea
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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 patients with obstructive sleep apnea (OSA) [1, 2]. 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 apnea-hypopnea index 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 continuous positive airway pressure (CPAP) in the treatment of OSA.

In this chapter, the methodological aspects of this thesis and the main research outcomes are discussed in a broader context, and suggestions for future studies are made.

**Methodological considerations**

One of the main clinical features of OSA patients is excessive daytime sleepiness. It is therefore one of the diagnostic criteria for an OSA diagnosis [3]. Because of its reliability and validity, as well as for its ease of administration, the Epworth Sleepiness Scale was used in our RCT to evaluate excessive daytime sleepiness [4]. When excessive daytime sleepiness is absent, at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force, e.g., complaints of unrefreshing sleep and daytime fatigue, should be present for an OSA diagnosis [3]. It was surprising to notice that measurement methods for these symptoms nor their severity criteria are reported in the literature. As long as this information is not present, we cannot be certain if we are studying groups that have the same diagnostic characteristics as OSA groups that are already described in the literature by others. Future research should therefore focus on the development of evidence-based methods for measuring symptoms of OSA and their severity criteria.

As a consequence of their disturbed sleep condition, OSA patients often complain about daytime symptoms as described above. These symptoms, however, are not specific for OSA and
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General discussion

can be caused by other disorders. Therefore, the diagnosis of OSA requires the combined assessment of relevant clinical features and the objective demonstration of at least five obstructive respiratory events per hour of sleep [3]. The “gold standard” for the objective demonstration of abnormal breathing during sleep in OSA patients is full polysomnography (PSG), which provides detailed information on sleep state and respiratory abnormalities [5]. Therefore, this technique was used in this thesis for diagnostic and therapy evaluation purposes. These full polysomnographic studies, however, are resource-intensive, because they generally require the facilities of a sleep laboratory and a trained technician. Although less comprehensive diagnostic systems have been developed, these systems have not yet been proven to be acceptable replacements for full polysomnography [6]. Nevertheless, the high prevalence figures for OSA make it necessary to consider simplified approaches for the diagnosis of OSA. Future research should therefore focus on the further development of such simplified techniques.

OSA is characterized by repetitive complete or partial collapses of the upper airway during sleep. For the quantification of these upper airway collapses in our RCT, we used the apnea-hypopnea index (AHI). Patients with the so-called “upper airway resistance syndrome” (UARS) show increased inspiratory efforts during sleep without breathing stops, but with frequent arousals. Since such events of respiratory effort-related arousals (RERAs) represent a form of upper airway obstruction, the International Classification of Sleep Disorders recommends that UARS should be considered as a part of OSA, and not as a separate entity [3, 7]. As a consequence, the respiratory disturbance index (RDI) was introduced to be used for the diagnosis of OSA. However, to enable comparison with previously performed RCTs, the AHI was chosen for the diagnosis of OSA in our RCT instead of the RDI.

The appropriate number of apneas and hypopneas for diagnosing clinically relevant OSA is uncertain. While a number of five or more apneas and hypopneas per hour is historically considered abnormal, the rationale for this cut-off value is unclear [8, 9]. It was therefore surprising to see that in the past decades, the AHI was preceded by the apnea index (AI; the number of apneas per hour of sleep), and that it was later replaced by the RDI for the diagnosis of OSA, but that the cut-off value of five events/hour for these indices has never been changed over time. You may question if a patient with, for example, twenty apneas per hour of sleep has the same negative consequences of his/her OSA condition (symptoms and co-morbidities) as a patient with twenty RERAs per hour of sleep. This can only be clarified by investigating the negative consequences of OSA in relation to the value of the used index (viz., AI, AHI, or RDI). In this way, a clinically meaningful diagnostic cut-off criterion for these indices can be established.

When an AHI cut-off point of five events per hour is used in the diagnosis of OSA, it is difficult to diagnose those patients with an AHI value near this cut-off point, because of the natural fluctuation of the AHI over time. If the recorded values of the AHI lie close to the cut-off point, the value may as well lie for one night above this point and for another night below this point. This suggests that conclusions about the presence or absence of OSA can only be drawn when the AHI recording lies far enough away from the cut-off point; that is, outside the limits of a cut-off band surrounding that point. In the study in chapter 2, we therefore suggested to use cut-off bands instead of cut-off points in the diagnosis of OSA. This means that in a research setting, it may be better to exclude those patients that have an AHI inside the cut-off band, because one cannot be certain about their diagnosis. This approach on the usefulness of cut-off bands in the diagnosis of OSA was recognized in the scientific field, as evidenced by an Editorial in “Respiration” [10]. Importantly, also studies on other disorders, for example on sleep bruxism [11], that use variables that are not stable over time, have the same problem in diagnosing these disorders. The use of cut-off bands is therefore recommended for these disorders as well.

Upper airway collapse during sleep is prevented by the MAD by both opening and protruding the mandible. In chapter 4, we used an MAD with a constant vertical dimension in different mandibular protrusions to investigate the pure influence of mandibular protrusion (i.e., a movement in the horizontal plane) on OSA signs and symptoms. The study described in chapter 4 demonstrated a dose-response relationship for a relatively wide range of protrusion positions.
Ferguson et al. indicated in a review of the literature that a larger mandibular protrusion will produce a larger decrease in OSA events [12], which was corroborated in our study. However, in that review, reference is made to studies that did not investigate a wide range of mandibular protrusion positions during sleep [13-16]. Consequently, there was not enough scientific evidence for a recommendation in which protrusion position an MAD treatment should be started. On the basis of the study in chapter 4, we can now recommended to start an MAD treatment in the 50% protrusion position.

RCT

In the RCT described in chapter 5, there were three patients in the MAD group that did not respond to the MAD therapy. The changes in airway configuration produced by MADs show inter-individual differences, which is likely a major factor in the inconsistent clinical response [17, 18]. A recent study showed that these airway configuration changes could not be predicted from the anatomical characteristics of the upper airway in OSA patients at baseline [18]. The mechanism of action of an MAD is generally considered to relate to the anterior movement of the mandible and the consequent increase in the cross-section area at the level of the velo-, oro- and/ or hypopahrynx [18-21], and to an improvement in the collapsibility of the upper airway [22]. However, the precise mechanism of action of an MAD appears to be rather complex and is not yet completely understood. This is not surprising, because the pathogenesis of upper airway closure in patients with OSA is not fully understood either [23, 24]. Therefore, one of the main objectives of future research should be the clarification of the relative contributions of the different morphological and pathophysiological factors to the development of recurrent sleep-rated collapse of the upper airway in OSA patients [25]. Such research could lead to improvement in our selection of OSA patients for an MAD treatment. Moreover, this kind of research could also result in the development of new treatments of OSA that would target the specific pathways that lead to upper airway collapse.

Based on our RCT described in chapter 5, it was concluded that there is no clinically relevant difference between MAD and nasal CPAP (nCPAP) in the treatment of mild-to-moderate OSA, which corresponds with the findings of a recent study [26]. Although in most previous cross-over studies MADs were considered less effective in reducing the AHI value than CPAP in mild-to-moderate OSA patients [e.g., 27-30], similar improvements in subjective and objective measures of daytime sleepiness were found. Therefore, the question remains whether the differences found between MAD and CPAP in the reduction of AHI in these studies are really clinically relevant. Further, it should be noted that these studies also indicated that, in general, patients find MADs a more acceptable treatment compared to CPAP. This means that although a small difference in efficacy between MAD and CPAP may be present, the better acceptance by patients of MADs can result in better treatment adherence and can thus provide comparable or even better treatment results than CPAP. Moreover, the follow-up study in chapter 6 showed that the difference between both therapies in treatment effect remained to be clinically irrelevant over a one-year period. Therefore, based on the outcomes of this RCT, we can recommend the use of MADs as a primary treatment in patients with mild-to-moderate OSA.

Conclusions

The following conclusions can be drawn from this thesis:

- It should be taken into account that in the diagnosis and therapy evaluation of OSA, there is considerable intra-individual variability between AHI recordings (chapter 2).
- It is recommended to start an MAD treatment in the 50% protrusion position in the treatment of mild-to-moderate OSA (chapter 3 and chapter 4).
- There is no clinically relevant difference between MAD and nCPAP in the treatment of mild-to-moderate OSA, neither at the short-term (chapter 5) nor at the long-term (chapter 6).
Clinical recommendations

Based on the outcomes of this thesis, MADs may be considered a primary treatment for mild-to-moderate OSA patients. Importantly, the dentist should only treat OSA patients on referral of a physician. Following this referral, the primary tasks of the dentist are a comprehensive dental assessment of the patient, and the selection and fitting of the MAD. After a period of acclimatization to the device, a medical review and an objective overnight assessment are required to determine the effects of the treatment. Regular visits of the patient to their physician and dentist are required to monitor the treatment response, adverse effects, and compliance.

References


