Clinical Investigations

Respiration

Respiration 2008;76:386–392
DOI: 10.1159/000156861

Received: January 31, 2008
Accepted after revision: May 6, 2008
Published online: September 17, 2008

Mandibular Advancement for Obstructive Sleep Apnea: Dose Effect on Apnea, Long-Term Use and Tolerance

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Key Words
Apnea · Mandibular advancement · Obstructive sleep apnea · Oral appliance · Titration

Abstract
Background: Previous studies have documented an effect of mandibular advancement (MA) on pharyngeal airway size and collapsibility. ***Objectives:*** We aimed to describe the course of the apnea-hypopnea index (AHI) and the snoring index (SI) during progressive MA and to evaluate the long-term efficacy, tolerance and usage of MA therapy after progressive MA titration in sleep apnea patients. ***Methods:*** Sixty-six patients with obstructive sleep apnea syndrome underwent sequential sleep recordings during progressive MA titration. Long-term effectiveness, compliance and side effects of oral appliance (OA) in the titrated position were evaluated by questionnaires. ***Results:*** OA therapy was started at 80% of the maximum MA. Seventy percent of the patients had only one increment in MA with a marked decrease in mean AHI from 36 to 10. In the remaining cases, further increments in MA were associated with a progressive reduction in AHI and an increase in the number of patients responding to treatment. OA in the titrated position resulted in a 70% decrease in AHI, with 54% of patients showing complete responses, 29% partial responses and 17% no response. Daytime sleepiness and quality of life improved, too. Seventeen months after the start of treatment, 82% of the patients declared that they were still using OA almost all nights. Reported side effects including subjective occlusal changes were frequent but mild. ***Conclusions:*** Improvement in AHI during OA is dependent on the amount of MA. Sequential sleep recordings facilitate MA titration. Long-term MA therapy in the titrated position is effective and well tolerated. Reported side effects are frequent but mild.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disease characterized by recurrent episodes of partial or complete obstruction of the upper airways during sleep. Moderate-severe OSAS with an apnea-hypopnea index (AHI) >15/h affects 4% of males and 2% of females in the general population [1]. OSAS is a cause of excessive daytime sleepiness and can pose a significant risk factor for car accidents [2]. There is growing evidence in support of an independent association between OSAS, endothelial dysfunction and cardiovascular disease [3, 4]. Nasal continuous positive airway pressure (CPAP) is the primary treatment of OSAS [5], but many patients are un-

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able or unwilling to comply with this treatment. Five to 50% of OSAS patients recommended for CPAP reject this treatment and 12–25% of the remaining patients can be expected to discontinue CPAP, especially if they have mild OSAS and/or if they are not 'subjectively sleepy' [6, 7]. Over the last decade, mandibular advancement (MA) has emerged as an alternative therapy for various degrees of OSAS [8], including severe OSAS in children [9]. Advancement of the mandible has been shown to improve velopharyngeal airway patency and to reduce upper airway collapsibility [10, 11]. In randomized controlled trials AHI decreased, with an average of 52% of complete responses (AHI <10), and daytime sleepiness improved during MA therapy [12, 13]. In comparison to CPAP, MA devices were less effective in reducing AHI, but were preferred over CPAP in many studies. No significant differences were observed between the two treatment modalities regarding symptom scores. In most randomized studies evaluating MA therapy in OSAS, the degree of MA was arbitrarily set without any titration procedure, e.g. at 80% of the maximal comfortable mandibular protrusion [14]. Previously, a dose-dependent effect of MA on nocturnal oxygen desaturation and pharyngeal collapsibility has been demonstrated [15]. A study based on sequential polysomnographic (PSG) recordings in 7 patients with mild-moderate OSAS demonstrated a reduction in AHI that was proportional to the degree of MA [16]. These previous findings suggest the potential benefit of individual MA titration in patients with OSAS. However, there is no consensual recommendation concerning the procedure of MA titration. We developed an MA titration procedure based on sequential sleep recordings during progressively increasing MA. The aim of this retrospective study was to describe the course of AHI and the snoring index (SI) during progressive MA and to evaluate the long-term efficacy, tolerance and usage of MA therapy after progressive MA titration in sleep apnea patients.

Patients and Methods

Patients

The study population consisted of 66 patients with OSAS diagnosed by full-night PSG (mean AHI: 38.6 ± 20.3) who had been referred for MA therapy according to current practice guidelines [8, 12] and who had no dental or temporomandibular contraindication to MA therapy as assessed by a dentist. In 50 cases, MA therapy had been recommended as a second-line treatment in patients (6 females; mean age: 52 ± 11 years; mean body mass index: 26.4 ± 4.5 kg/m^2) with moderate-severe OSAS (mean AHI: 42 ± 20) who did not tolerate CPAP and decided to abandon this treatment after a few months despite attentive management and correction of side effects. Sixteen patients (3 females; mean age: 49 ± 10 years; mean body mass index: 26 ± 10 kg/m^2; mean AHI: 29 ± 19) had not been treated with CPAP before MA therapy. Ten had mild-moderate OSAS, and 6 had severe OSAS and refused CPAP treatment. All patients had been informed of the procedure of titration and had given their informed consent. According to the French Legislation, agreement of an ethics committee is not required for retrospective collection of data corresponding to current practice. However, the database was made anonymous and complied with the restrictive requirements of the Commission Nationale Informatique et des Libertés, the organization dedicated to privacy, information technology and civil rights in France.

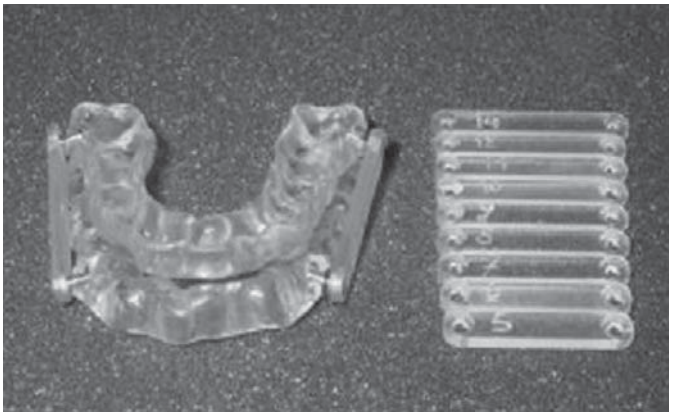

Fig. 1. Photograph of the MA device (AMC™, Dupont Medical, Pantin, France) used in the study. Full-coverage acrylic appliances designed to fit to the upper and lower dental (left) arches are connected by acrylic plates of increasing length (right).

Oral Appliance

Patients were treated with an adjustable bi-bloc acrylic oral appliance (OA) (AMC™; Dupont Medical, Pantin, France; fig. 1). After taking impressions of the upper and lower teeth, separate upper and lower full-coverage acrylic appliances were constructed that could be clipped onto the two dental arches. The two dental arches were connected by attachments allowing the opening, the protrusion and some side-to-side movement of the mandible, but no retrusion. Attachments of various sizes allowed MA titration.

MA Titration

Each patient's maximum protrusive range of movement was measured from the position of maximum intercuspation. The greatest advancement measured on three consecutive maneuvers (i.e. the maximum MA) was adopted. The attachments of the MA device were adjusted on a semi-adjustable articulator to obtain an initial advancement of 80% of the maximum MA. After a 2-week acclimatization period, the mandible was incrementally advanced, by a step of 1 mm every 2 weeks with repeated limited

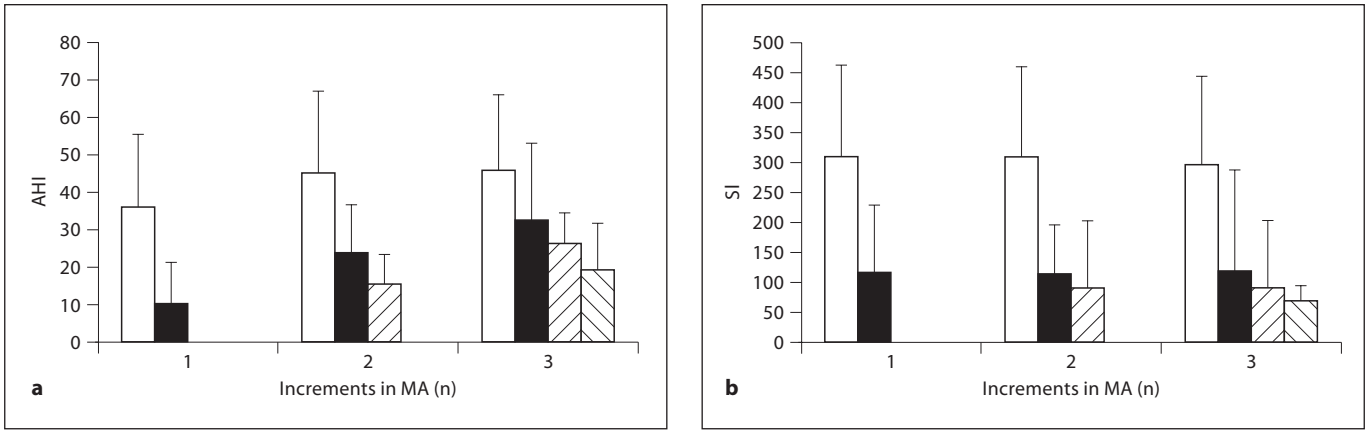

Fig. 2. AHI (**a**) and SI (**b**) at baseline (events/h of sleep) and during progressive MA increment (events/h of recording). Means ± SD. AHI and SI at baseline PSG (□), and during the limited sleep study after the first (■; mean MA: 8.5 ± 1.7 mm), second (▨; mean MA: 9.9 ± 1.5 mm) and third MA increment (▧; mean MA: 12 ± 1.7 mm).

sleep study during progressive MA. MA was increased until either reduction of AHI to <10 events/h or attainment of the maximum comfortable limit of advancement was achieved. Then, a follow-up visit was planned for quality-of-life questionnaires and standard PSG during OA at the final MA. A complete response was defined as a ≥50% reduction in AHI with an AHI <10 during OA at the final MA. A partial response was defined as a ≥50% reduction in AHI with an AHI ≥10. No response to MA therapy was defined as a <50% reduction in AHI.

Sleep Recordings

Standard PSG (CID 102; Cidelec, Angers, France) at baseline and at the final MA was performed as previously described [17] and scored according to standard criteria [18]. Limited sleep studies (CID 102L; Cidelec) were performed during progressive MA with recording of nasal airflow (nasal cannulae), tracheal sounds (suprasternal microphone), thoracic and abdominal movements and oxygen saturation (SaO_2; finger pulse oximetry). Respiratory events were scored manually. Apnea was defined as cessation of airflow for at least 10 s. Hypopnea was defined as a >50% reduction in airflow or a <50% reduction in airflow accompanied by a 3% decrease in oxygen saturation. Snoring was defined as a signal of >76 dB in the transducer chamber with a frequency between 20 and 200 Hz. Both standard PSG and limited sleep studies were performed in the sleep laboratory.

Questionnaires

Specific questionnaires were used at baseline and at the final MA. Daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS) [19]. Quality of life was evaluated by the Nottingham Health Profile (NHP) [20]. The NHP includes 38 items exploring six dimensions of perceived health: energy, pain, sleep, physical mobility, emotional reactions and social isolation. For each item, the answer is either yes (= 1) or no (= 0). Each item was weighted and a final score was calculated for each dimension by adding the weighted answer for each item. For each dimension, the score ranged from 0 (excellent perception of health) to 100 (very poor perception of health). Regarding the effect of OA on snoring, patients were asked to evaluate the evolution of snoring under treatment as follows: high improvement, moderate improvement, unchanged or increase in snoring.

Reported side effects (i.e. jaw pain, tooth pain, muscle stiffness, mucosal dryness, hypersalivation and occlusal change) and global satisfaction were assessed during a telephone interview, 16.6 ± 7.7 months after treatment start, using a 0–10 interval scale. Treatment compliance was assessed by questioning the patient on the usage of MA therapy (h/night and days/week).

Statistical Analysis

Statistical analysis was performed using SPSS software for Windows (version 10.1; SPSS; Chicago, Ill., USA). All values were summarized by descriptive statistics and expressed as means ± SD. Sleep recording and questionnaire data at baseline and during OA therapy were compared using the Wilcoxon test for paired samples or Friedman's ANOVA for multiple comparisons. The Mann-Whitney U test was used for comparisons between two groups. $p < 0.05$ was regarded as statistically significant.

Results

Mean maximum MA was 8.7 ± 1 mm. Treatment was started with a mean of 7.1 ± 1.1 mm MA and mean final MA was 9.54 ± 1.93 mm (i.e. 108.3 ± 26.8% of the maximum MA). Figure 2 shows the course of AHI (fig. 2a) and SI (fig. 2b) over consecutive sleep studies during progressive increments in MA. Forty-six patients (70%) had only one increment in MA with a marked decrease in AHI from 36 ± 19 at baseline PSG to 10.1 ± 11.2 during

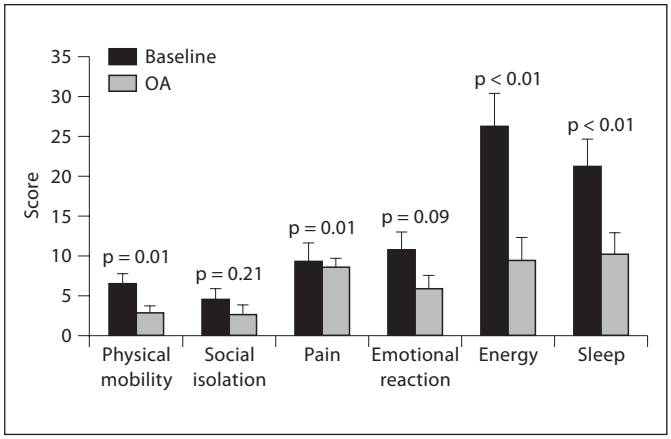

Fig. 3. Comparison of quality of life evaluated by the NHP questionnaire at baseline and during OA at the final MA. Means ± SD.

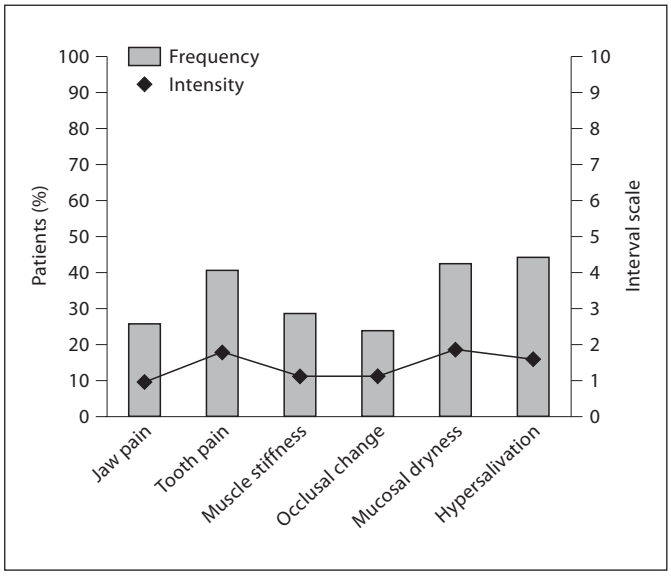

Fig. 4. Mean frequency and intensity of side effects reported during OA at the final MA.

the limited sleep study ($p < 0.001$). In the 16 (24%) patients who had two increments in MA, mean AHI decreased from 24 ± 13 to 15 ± 8 ($p = 0.02$) in consecutive limited sleep studies. Between the first and the second increment in MA, the number of complete responses increased from 2 to 5, partial responses increased from 7 to 8 and non-responses decreased from 7 to 3. In the 4 patients (6%) who had three increments in MA, mean AHI was 32 ± 20, 26 ± 14 and 19 ± 12 (p = nonsignificant), respectively, in consecutive limited sleep studies. Between the first and the third increment in MA, 2 non-responses became partial responses and 1 partial response became a complete response to MA therapy. Regarding snoring measurements, an important reduction in SI was observed at the first level of MA but further increments in MA had little impact on SI.

Standard PSG during OA at the final MA was performed 6.8 ± 4.7 months after the beginning of treatment. On average, OA reduced the AHI from 39 to 12 (i.e. 70%). Table 1 shows the comparison of PSG data at baseline and during OA at the final MA in complete responders (n = 36; 54%), partial responders (n = 19; 29%) and non-responders (n = 11; 17%) to MA therapy. Mean AHI decreased by 83% in patients with complete response, 71% in those with partial response and 19% in the non-responders. A significant improvement in the micro-arousal index, SI and mean nocturnal oxygen saturation was also observed in both complete and partial responders. The periodic leg movement index also decreased significantly in these two groups. Comparison of complete, partial and non-responders showed a significant difference for AHI, which was higher in partial responders. Conversely, there was no significant difference between these three groups regarding age, body mass index and ESS.

Comparison of daytime sleepiness at baseline and during OA showed a significant decrease in ESS from 8.9 ± 5.1 to 5.9 ± 3.8 ($p < 0.001$) for the whole group. The improvement in ESS was significant in both complete and partial responders, but there was no significant improvement in daytime sleepiness in the non-responders. Comparison of the NHP data at baseline and during OA demonstrated a significant improvement in four of the six dimensions assessing quality of life (fig. 3) for the whole group. In the non-responders, only the 'sleep' dimension of the NHP improved significantly ($p = 0.04$). According to patient's subjective evaluation, snoring was highly improved in 51% of cases, moderately improved in 38%, unchanged in 6% and increased in 5%.

Compliance, satisfaction and side effects were assessed during a telephone interview 16.6 ± 7.7 months after treatment start. Among the 66 patients, 6 were lost to follow-up, 6 had abandoned the treatment after a mean duration of 10 months, and 54 (82%) were still using OA on average 6.3 ± 1.6 days a week and 7.5 ± 1.1 h/night. Mean global satisfaction on the 0–10 interval scale was 8.1 ± 1.3. Seventy percent of the patients reported at least one side effect during OA. The most frequently reported side effects were hypersalivation (44%), mucosal dryness

Table 1. Comparison of PSG data at baseline and during OA at the final MA in patients with complete, partial and no response

	Complete response (n = 36, 54%)		Partial response (n = 19, 29%)		No response (n = 11, 17%)	
	baseline	OA	baseline	OA	baseline	OA
TST, min	405 ± 53	427 ± 53*	371 ± 58	395 ± 54	426 ± 35	427 ± 58
S I + II, %	62 ± 8	59 ± 10*	65 ± 13	58 ± 12*	62 ± 14	56 ± 9
S III + IV, %	18 ± 7	20 ± 8	16 ± 7	19 ± 10	19 ± 7	18 ± 6
REM, %	19 ± 5	20 ± 6	18 ± 10	20 ± 5	18 ± 8	25 ± 6*
MAI, events/h	33 ± 16	18 ± 8**	42 ± 12	25 ± 9**	30 ± 14	26 ± 16
PLMI, events/h	20 ± 33	10 ± 26*	23 ± 25	12 ± 18*	32 ± 24	25 ± 31
SI, events/h	303 ± 162	78 ± 89**	364 ± 147	145 ± 194**	235 ± 101	241 ± 189
AHI, events/h	30 ± 15	5 ± 2**	59 ± 17	17 ± 8**	32 ± 12	26 ± 14*
Mean SaO_2, %	93 ± 1	94 ± 1*	93 ± 1	94 ± 1*	93 ± 1	93 ± 1

Means ± SD. TST = Total sleep time; S I + II = stage I + II sleep; S III + IV = stage III + IV sleep; REM = rapid eye movement sleep; MAI = microarousal index; PLMI = periodic leg movement index; SaO_2 = arterial oxygen saturation; * $p < 0.05$, ** $p < 0.01$, vs. baseline.

(42.3%) and tooth pain (40.6%). Mean frequency and intensity of side effects are presented in figure 4. They did not significantly differ between complete responders, partial responders and non-responders.

Discussion

Our findings demonstrate a dose effect of MA on AHI in sleep apnea patients. Using a titration procedure based on sequential sleep recordings during progressive MA, we also confirmed that OA is a well-tolerated and effective treatment for OSAS reducing AHI and daytime sleepiness and improving quality of life.

Previous studies in small cohorts of normal subjects or sleep apnea patients have documented a dose effect of MA on pharyngeal airway size [10, 21, 22] and physiological outcomes such as upper airway resistance and collapsibility [11, 23]. Using repeated home overnight oximetry in 37 patients with mild-severe OSAS, Kato et al. [15] found that the oxygen desaturation index improved by 20% for each 2-mm increment of MA. In a subgroup of patients under general anesthesia, MA was found to produce a dose-dependent closing pressure reduction in all pharyngeal segments. More recently, a study based on sequential PSG recordings in 6 patients with mild-moderate OSAS demonstrated that AHI reduction was related to the amount of MA [16]. Mean AHI was 13.2 at baseline, 9.5 with 60% of maximum MA, 7.2 with 60% of maximum MA + 2.4 mm and 6.5 with 60% of maximum MA + 5.3 mm. To our knowledge, our study is the first to describe the course of AHI and SI on sequential sleep recordings during progressive MA in a large clinical population of sleep apnea patients. As described in previous randomized studies evaluating MA therapy in OSAS [14], the degree of MA was initially set at 80% of maximum MA. This may explain that a high proportion (70%) of our patients had only one increment in MA beyond this initial setting, with a marked decrease in mean AHI from 36 to 10. However, in the remaining cases, further increments in MA were associated with a progressive reduction in AHI, and an increase in the number of partial and complete responders, but they had little impact on SI.

On average, OA improved AHI by 70% and SI by 60% at final MA. In 54% of complete responders and 29% of partial responders, AHI decreases of 83 and 71%, respectively, were found at the end of the titration procedure. Improvement in AHI was comparable to that obtained by Fleury et al. [24] in a recent study using a similar device and a titration procedure combining sequential home oximetry and clinical assessment. In comparison, in a recent review of pooled data of 74 studies including 2,816 patients [25], the mean reduction in AHI during OA was only 55%, and the mean reduction in snoring was 45%. In most studies included in this review, the degree of MA had been arbitrarily set without any individual titration procedure.

Seventy-five percents of our patients had previously been treated with CPAP and decided to abandon this treatment despite attentive management and correction of side effects. This may explain that our population was mildly sleepy according to ESS since the risk of CPAP

discontinuation has been found to be higher in sleep apnea patients without subjective daytime sleepiness [6]. However, we observed a significant improvement in the ESS score both in complete and partial responders, and in four domains of the NHP quality of life questionnaire, including 'energy' and 'sleep' during OA. Furthermore, 82% of our patients declared that they were still using OA almost all nights, 16.6 months after the start of treatment. Long-term treatment compliance was similar to that obtained in a study including a titration procedure with a similar device by Fleury et al. [24]. At present, there is no way to record objective daily use of OA. We used reported daily compliance assessed by questionnaire. Previous studies have demonstrated that subjective use of CPAP significantly overestimated the actual running time of the device at the effective pressure [26]. Thus, it cannot be excluded that our patients overestimated actual daily use of OA. Several studies have documented various dental-skeletal effects of long-term use of OA including changes in the degree of vertical and horizontal overlap of the teeth [25]. Recent reports suggested that orthodontic effects of OA might be predictable on the basis of initial characteristics in dental occlusion and the design of the device [27]. We did not perform any objective assessment of orthodontic changes in our study. Seventy percent of our patients had at least on side effect under OA, with non-significant differences between complete, partial and non-responders. However, reported side effects including subjective occlusal changes were found to be of mild intensity and did not constitute an obstacle to long-term regular use of OA.

In this study, we used a custom-made bi-bloc acrylic OA individually fabricated after taking impressions of the upper and lower teeth. Potential disadvantages of these devices are the cost and the time required to construct the device. Furthermore, 17% of our patients were non-responders at the end of a titration procedure that was longer than that required for CPAP titration. Immediately adapted thermoplastic OA may be an alternative strategy to 'screen' response to MA therapy [28].

In conclusion, improvement in AHI during OA is dependent on the amount of MA. Sequential sleep recordings facilitate MA titration. Long-term MA therapy in the titrated position is effective. Reported side effects are frequent but of mild intensity.

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