Sleep Medicine 54 (2019) 187–194

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Mandibular advancement device therapy for obstructive sleep apnea: a prospective study on predictors of treatment success

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ARTICLE INFO

Article history:
Received 30 May 2018
Received in revised form
28 September 2018
Accepted 30 September 2018
Available online 12 November 2018

Keywords:
Obstructive sleep apnea
Mandibular advancement device
Predictors of outcome
Positional sleep apnea
Cephalometry
Acoustic reflectometry

ABSTRACT

Objective: To survey potential predictors of success of mandibular advancement device (MAD) therapy in patients with obstructive sleep apnea (OSA), and in particular, to examine anatomical narrowings and sleep-related collapse levels in the upper airway.
Methods: This was a prospective study of 62 OSA patients (median apnea–hypopnea index [AHI] of 34), who were treated with a custom-made, monobloc MAD. The upper airway was examined by inspection, nasopharyngoscopy, overnight acoustic reflectometry recording collapses, and cephalometry of soft tissue dimensions (in addition to skeletal parameters). MAD treatment was controlled by polysomnography before and after at least five weeks from the beginning of treatment. Independent predictors of actual reduction in AHI and treatment success (reduction in AHI $\geq$ 50% with residual AHI $<$ 10) were determined, using multivariable linear and logistic regression.
Results: Positional OSA (POSA) and nonsupine AHI (adjusted for upper airway narrowness and collapses, together with gender, age, body mass index, neck circumference, and baseline AHI) were the only independent predictors: POSA indicative for success, and nonsupine AHI inversely related to success. Cephalometry was not predictive. Two predictive models were proposed, one based on POSA having a specificity of 70% and sensitivity of 69%, and the other based on nonsupine AHI, generating a receiver operating characteristic (ROC) curve (area under ROC = 0.78). Using the ROC model, specificity could be increased to 80% without lowering sensitivity.
Conclusions: Only variables related to sleep position proved to be independent predictors of success with MAD therapy. The results could be explained by the MAD counteracting the mandible from moving backwards when sleeping supine.

1. Introduction

Continuous positive airway pressure (CPAP) is widely used as first-line treatment for obstructive sleep apnea (OSA). However, a major problem with CPAP is decreasing long-term patient adherence. Accordingly, there is an interest in other treatment modalities. In recent years, an alternative treatment, use of mandibular advancement devices (MAD), has been increasingly used, even as a first-line treatment in patients with mild to moderate OSA (AHI $\leq$ 30). Furthermore, it is well documented that MADs work across even a broader spectrum of OSA severity [1–3]. However, compared to CPAP, the effect is very unpredictable [4,5]. For that reason, there is a need to define which patients may benefit from MAD. Yet, there is currently no consensus about factors predicting treatment outcome.

Several OSA phenotypes have been proposed as a predictor, such as gender [6,7], age [7,8], baseline apnea–hypopnea index (AHI) [1,8], body mass index (BMI) [8,9], neck circumference [1,8],

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https://doi.org/10.1016/j.sleep.2018.09.033
1389-9457/

positional OSA (POSA) [6,10,11], and some cephalometric variables [1,7,9], all with conflicting evidence.

Other OSA phenotypes, based on nonanatomic pathophysiologic features, have been examined in a controlled study by Eckert et al., [12]. They found that abnormalities in ventilatory control, pharyngeal muscle responsiveness, and arousal threshold were present in most OSA patients.

MAD therapy was found to reduce collapsibility of the upper airway in a study performed during sleep [13]. Upper airway collapsibility, assessed by respiratory measurements, has been proposed as a predictor of MAD treatment outcome. One study, using spirometry during wakefulness, found flow volume curves to be predictive [14]. Another study, using pneumotachometry and CPAP during sleep (a setup similar to that of Eckert et al., [12]), found ventilatory control (loop gain) to be especially predictive of failure [15]. Also, the level and degree of collapse has been studied for predictive value. One study, using multisensor catheters for determination of upper airway closing pressures during sleep, found predominant oropharyngeal collapse to be predictive [16]. Another study, using fiberoptic nasopharyngoscopy during drug-induced sleep, found that the degree of collapse resolution by simulated mandibular titration was predictive [17].

The aim of the present study is to provide better evidence for selection of OSA phenotypes that will be useful in the daily clinic to identify those OSA patients likely to benefit from MAD therapy. In particular, this study examines the predictive value of anatomical reduced space in the upper airway and of collapse levels during sleep, using acoustic reflectometry (ie, sound reflections in a flexible tube).

2. Methods

2.1. Patients

A prospective study of 62 OSA patients with a median AHI of 34 (range 6–117), the majority with severe OSA (61%), was conducted. All subjects were recruited from a randomized controlled trial (RCT) of MAD [3] (registered at ClinicalTrials.gov; ID: NCT00243139).The RCT had one group with an active device ($n = 27$) and two control groups, one with a nonadvancement device ($n = 25$) and one without an intervention ($n = 29$). The patients in the two control groups ($n = 54$) were intended according to the protocol to continue the study with a MAD, but one-third from each group discontinued this intervention, as shown in the study profile (Fig. 1). The protocol of the study was approved by the regional research ethics committee (ID: 1998-1-34) and the Danish Data Protection Agency. Written informed consent was obtained from all patients in the study.

The study group consisted of 52 male and 10 female subjects with a median age of 51 years (range 27–65 years) and a median BMI of 30 kg/m^2 (range 21–49). Of these subjects, 82% reported daytime sleepiness. With the patient in sitting position, the upper airway was assessed by visual inspection of the nose and pharynx, combined with fiberoptic nasopharyngoscopy, recording marked narrowing of the retropalatal space (ie, narrow velopharyngeal aperture) and of the retrolingual space (ie, enlarged tonsils and/or bulging oropharyngeal side walls and/or narrow hypopharynx).

Examinations with cephalometry, recording soft tissue and skeletal dimensions, and flexible tube reflectometry with a simultaneous polysomnography (PSG) were performed before start of treatment.

2.2. MAD treatment

The MAD was a custom-made acrylic, one-piece device with a 5-mm vertical opening in front. The device was secured to the molars and premolars by four stainless steel Adams clasps in each jaw. The MADs were adjusted during an acclimatization period to obtain the best retention and the most protrusive position and vertical height without discomfort. The adjustments were made by rebuilding the MAD according to a new construction bite. The final protrusion varied from 60% to 89% of the maximum protrusion (mean 74%). The actual advancement varied from 5 to 13 mm (mean 9 mm).

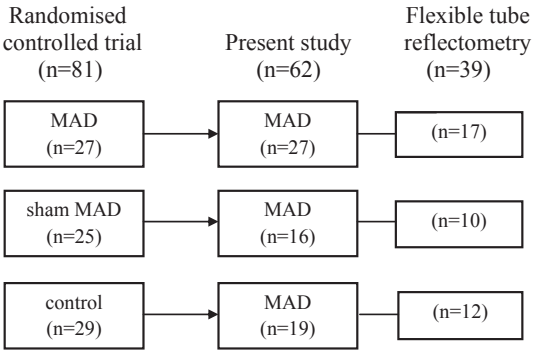

Fig. 1. Study flow chart.

After acclimatization, the patients should have slept with the MAD in position for at least five weeks. The follow-up study was then conducted. The median follow-up time was 13 weeks. There were no dropouts.

2.3. Sleep studies

The sleep study before the start of treatment, and at the follow-up study, was an overnight standard PSG (Embla recording system, ResMed), performed unattended at home. The recording of oronasal airflow was made with a thermistor. The sensor was the standard at the start of the RCT, which is why it was used throughout the whole study, so as to ensure uniformity in signals and scoring rules.

Sleep stages and AHI events were manually scored, and the relation of AHI to supine and nonsupine position was automatically calculated (Somnologica software). Apnea was defined as a drop in the thermal sensor signal by ≥90% with continued inspiratory effort for at least 10 s. Hypopnea was defined as a clear drop in the sensor signal for at least 10 s associated with ≥3% desaturation or terminated by an arousal.

Rapid eye movement (REM)–predominant OSA was defined by an AHI during REM being at least twice the AHI during non-REM.

POSA was defined using the definition by Sunnergren et al., [18]: (1) supine AHI at least twice the nonsupine AHI with supine AHI ≥ 5; and (2) supine time ≥10% and ≤90% of total sleep time (TST).

Treatment success was defined as a reduction in AHI of ≥50% and residual AHI of <10.

2.4. Cephalometry

Lateral profile radiographs were taken with teeth in occlusion and the head in natural position, using a Cephalix cephalostat. An aluminum wedge placed between the cassette and the patient's face and a movable grid were used to increase the sharpness of the image. Exposure data were 80 kV and 32 mA.

The landmarks (Fig. 2) were marked on sheets fixed to the radiographs, digitized on a high-resolution flatbed scanner (PowerLook 1000) and recorded using Viewbox software. Correction was made for the constant linear enlargement of 8.3%.

Reference points and lines for the craniofacial analysis, including the soft tissue dimensions of the phaynx, were defined according to Solow et al., [19].

2.5. Acoustic reflectometry

The method is based on acoustic reflection, using a stable flexible tube (RhinoFlex tube) made of PVC and divided into a hard section, going from outside the nose to the back of the nasal septum, and a soft section ending closed in the esophagus. The proximal end is connected to a probe containing a microphone and a generator of continuous white band noise (Fig. 3).

The method provides information about the patency of the entire pharynx. The noise signals are sent into the flexible tube tube. When an obstruction occurs anywhere in the throat, the soft tissue compresses the flexible tube, changing the sound reflections. The microphone is recording the reflected sound, and then the measuring system (a computer) analyses the reflections in terms of duration of the obstruction and distance to the obstruction site. The equipment used, (SRE2100 and RhinoSleep, RhinoMetrics, Denmark) has been described and validated by Faber et al., [20,21].

The measurements, together with PSG, were performed overnight in-hospital. The longest period (median 262 min, range 86–530 min) with good data quality and PSG-documented sleep was analyzed by automatic software, excluding swallowing events. All obstructive events were calculated by each individual's cephalometric length, the upper part from the posterior edge of the hard palate to the lower border of the soft palate (retropalatal space), and the lower part from the soft palate to the inlet of the esophagus (retroglossal space).

A level was defined as predominant, when three-fourths or more of the obstructive events were located in that area.

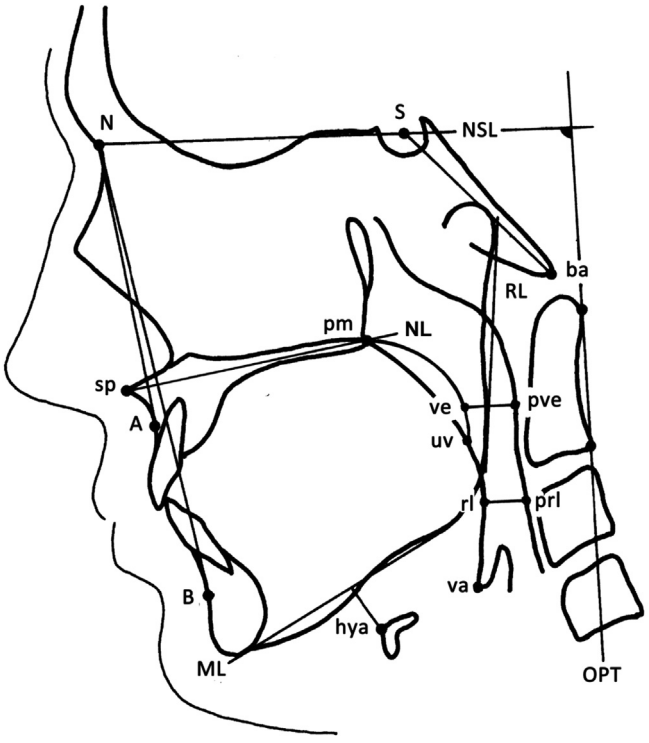

Fig. 2. Cephalometric points and lines used in the study. N, nasion; S, sella; ba, basion; A, subspinale; B, supramentale; hya, anterosuperior point of hyoid bone; pm, posterior nasal spine; rl, radix linguae, closest to pharyngeal wall; sp, anterior nasal spine; uv, inferior point of uvula; va, vallecula epiglottica; ve, velum palatini, closest to pharyngeal wall; pve and prl, dorsal pharyngeal wall closest to ve and rl; NSL, nasion-sella line; ML, mandibular line; RL, ramus line; OPT, odontoid process tangent.

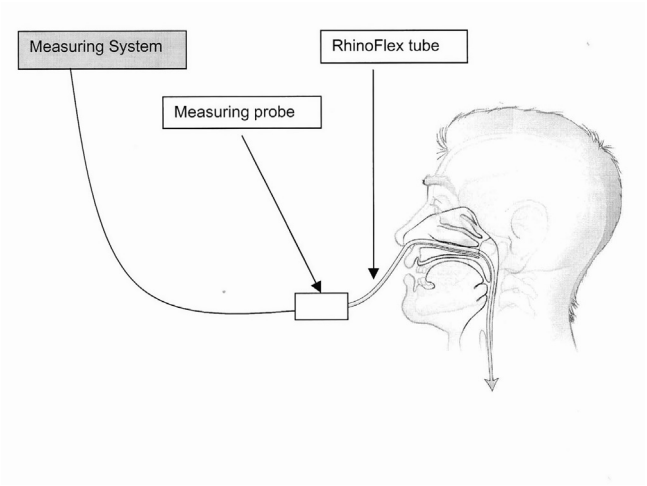

Fig. 3. The Rhinoflex System. The probe is generating continuous acoustic wide band noise, and a microphone in the probe is recording the reflected sound. The measurement system (a computer) is calculating the distance to the obstruction site and storing a graphic description for later analysis.

2.6. Statistical analysis

Continuous explanatory variables were compared using the Kruskal–Wallis test and the χ^2 test for categorical variables. The associations of the binary outcome measures with the explanatory covariates were analyzed using logistic regression analysis. Univariable analysis was performed for each explanatory variable, and multivariable analysis was performed including covariates with a univariable p value of less than 10%. A final model was selected by reducing the full multivariable model, using the residual χ^2 for the stopping rule, and requiring a p value of less than 5% (Lawless and Singhal [22]) with fivefold cross-validation to assess the final model. The results are presented as odds ratios with 95% confidence intervals as well as sensitivity and specificity for the final model. A p value of less than 5% was considered significant. All calculations were done using SAS (version 9.4; SAS Institute, Cary, NC) and R (Frank E Harrell Jr [2015]; Rms: regression modeling strategies; R package version 4.3–1.http://CRAN.R-project.org).

3. Results

The major outcomes of the MAD treatment are shown in Table 1, indicating that the MAD was efficient both in the supine and the lateral positions. The median reduction in AHI was 62% (range −42% to +98%) in patients with mild to moderate OSA and 71% (range −29% to +100%) in patients with severe OSA. The proportion of POSA patients was the same before and during MAD therapy. The median AHI was 26 in the POSA group and 51 in the non-POSA group.

For comparison with other studies, we have shown the treatment response rates with different AHI targets used as success criteria (Table 1).

No association was found between the duration of follow-up and treatment success ($p = 0.86$).

Table 1
Treatment outcomes of mandibular advancement device (MAD) in 62 patients.

	Baseline	With MAD	*p*
AHI (events/h)	34 (22–56)	11 (4–29)	<0.001
AHI supine	61 (36–78)	19 (6–62)	<0.001
AHI nonsupine	25 (8–45)	6 (0–19)	<0.001
ODI 3%	30 (19–52)	9 (3–27)	<0.001
Average desaturation	6 (5–8)	6 (4–7)	<0.001
Supine time (%TST)	31 (17–46)	32 (15–50)	0.96
POSA (no.)	30/62 (48%)	27/62 (44%)	0.72
ESS score	11 (9–14)	9 (6–11)	<0.001
Treatment response rates by different AHI targets	All patients	REM-OSA	NREM-OSA
Reduction AHI ≥ 50%	38/62 (61%)	6/10 (60%)	32/52 (62%)
and residual AHI < 10	29/62 (47%)	4/10 (40%)	25/52 (48%)
and residual AHI < 5	19/62 (31%)	2/10 (20%)	17/52 (33%)

Quantitative values are given as the median with 25th and 75th percentiles and were tested by the Wilcoxon signed rank test. Binary values were tested by the Fisher exact test.
AHI, apnea–hypopnea index; ESS, Epworth Sleepiness Scale (ranges from 0 to 24, with 24 as the highest score of sleepiness); NREM-OSA, non–REM-predominant OSA; ODI 3%, oxygen desaturation index (at least 3% desaturations); OSA, obstructive sleep apnea; POSA, positional obstructive sleep apnea; REM-OSA, REM-predominant.
REM, rapid eye movement; TST, total sleep time.

3.1. Cephalometric analysis

The number of craniofacial variables included in this study are summarized in Table 2. Among the skeletal parameters, maxillary and mandibular retrognathia were found to have a potential, albeit nonsignificant, association with treatment success.

A subgroup analysis of non-obese (BMI ≤ 30) versus obese subjects was performed. Non-obese subjects (58%) had significantly more maxillary and mandibular retrognathia and a shorter soft palate, but these differences were small and not correlated with treatment success of MAD.

3.2. Acoustic reflectometry analysis

These examinations were performed in 53 of the 62 patients. Of the examinations, 14 (26%) had to be excluded because of low quality of the signals or problems with accepting the flexible tube (Fig. 1). However, there were no statistical differences between the potential predictive factors in the successful examined group ($n = 39$) and the remaining group ($n = 23$), except for more severe OSA in the former group (Table 3).

The median analyzed sleep time was 305 min (range 86–530 min), and median number of obstructive events was 159 (range 39–430). Retropalatal obstructions were predominant in 18 of 39 patients (46%), and retroglossal in 14 of 39 patients (36%). The rest of the obstructive events were equally distributed between the two levels (isolated predominant oropharyngeal obstructions were seen only in one case).

The predominant obstructions, either retropalatal or retroglossal, did not have predictive value, as shown in the table of screening variables (Table 4).

Correlation analysis showed no significant associations between the level of obstructions by the flexible tube and the narrowness of the pharynx by physical examination or cephalometric soft tissue measurements.

3.3. Predictive analyses

The screening analyses revealed five significant and four borderline-significant variables. All of these were included in a multivariable logistic regression analysis (Table 4).

Among the nine potential predictors, only non-supine AHI remained significant (odds ratio = 0.67, 95% confidence interval = 0.48–0.93). Nonsupine AHI and POSA are closely related variables (Spearman correlation coefficient −0.68), and when nonsupine AHI was removed from the multivariable analysis, POSA became the only significant variable ($p = 0.040$; odds ratio = 3.59, 95% confidence interval = 1.06–12.16). If both nonsupine AHI and POSA were removed, baseline AHI became borderline significant, but the rest of the potential predictors remained nonsignificant. A predictive model based on a receiver operating characteristic (ROC) curve of nonsupine AHI

Table 2
Screening cephalometric variables for predictive factors related to outcome of mandibular advancement device in 60 patients.[a]

	Success	Failure	*p*
	$n = 29$	$n = 31$	
SNA, position of maxilla (deg)	79.5 (77.6–82.1)	81.8 (79.4–83.5)	0.083[b]
SNB, position of mandibula (deg)	76.6 (74.9–78.6)	77.4 (76.0–81.0)	0.088[b]
NSL/ML, mandibular inclination (deg)	32.0 (27.4–38.6)	30.0 (24.4–36.4)	0.17
NSL/NL, maxillar inclination (deg)	9.6 (6.6–11.9)	7.7 (5.1–9.7)	0.18
N-S, anterior cranial base (mm)	69.9 (66.8–72.4)	70.4 (68.7–72.1)	0.71
length maxilla, sp-pm (mm)	53.6 (49.7–55.0)	53.4 (51.5–56.0)	0.60
NS/basion, cranial base angulation (deg)	131.4 (125.6–137.8)	130.1 (126.5–133.5)	0.32
position hyoid bone, hya-ML (mm)	21.8 (19.2–26.3)	22.0 (19.1–23.9)	0.62
ML/RL, mandibular shape (deg)	121.0 (117.7–129.7)	120.2 (114.7–125.8)	0.53
NSL/OPT, head posture (deg)	103.3 (98.5–108.2)	103.4 (98.6–108.8)	0.84

Values are given as the median with 25th and 75th percentiles. deg, Degrees.
NS $p > 0.05$; [b]$0.10 > p > 0.05$ (Mann–Whitney test).
[a] Cephalometry missed in two cases.

Table 3
Baseline characteristics of patients successfully completing flexible tube reflectometry and the remaining group of excluded ($n = 14$) and unexamined ($n = 9$) patients.

	Completing ($n = 39$)	Remaining ($n = 23$)	p
AHI (events/h)	39 (26–59)	26 (14–51)	0.026
AHI non-supine	26 (12–44)	21 (4–46)	0.38
Supine time (%TST)	35% (20–51)	21% (15–42)	0.11
POSA (no.)	20/39 (51%)	10/23 (43%)	0.61
Gender (M:F)	34/39 (87%)	18/23 (78%)	0.48
Age	50 (41–56)	51 (40–59)	0.72
BMI (kg/m^2)	30 (27–34)	30 (27–36)	0.84
Neck circumference (cm)	43 (40–45)	42 (39–44)	0.56
ESS score	11 (8–13)	11 (9–14)	0.69

Quantitative values are given as the median with 25th and 75th percentiles and were tested by the Wilcoxon rank sum test. Binary values were tested by the Fisher exact test. AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale (ranges from 0 to 24, with 24 as the highest score of sleepiness); F, female; M, male; POSA, positional obstructive sleep apnea; TST, total sleep time.

as the response variable was constructed (Fig. 4). Six clinically relevant specificities were selected, and, using the ROC curve, the corresponding sensitivities and cutpoints of nonsupine AHI for success were calculated (Table 5). The maximum specificity with an acceptable sensitivity was 80%, and the corresponding nonsupine AHI of <17 resulted in a false-positive rate of 24%. Even a modest improvement of the sensitivity would significantly reduce the specificity and thereby increase the false-positive rate.

For comparison, a simple model based on POSA as success resulted in a specificity of 70% and a false-positive rate of 33% (Table 6).

A multivariable linear regression analysis (not shown) based on the actual percentage reduction in AHI as response variable, instead of the binary success criterion, again showed that nonsupine AHI and POSA were the only independent predictors, POSA for treatment success ($p = 0.0006$) and nonsupine AHI for treatment failure ($p = 0.0073$).

4. Discussion

The effectiveness of MAD therapy in reducing AHI was comparable with that in randomized placebo-controlled studies [1–3].The outcome of the present study cannot be explained by change in sleep position from supine to lateral (Table 1). The proportion of POSA patients did not decrease during treatment, which contrasts with the findings of Dieltjens et al., [23]. A possible explanation could be that changes in sleep position are independent of MAD therapy.

The variables related to the sleep position were the strongest and only independent predictors of treatment success. This is most directly expressed by POSA, but nonsupine AHI reflects the same thing, being negatively correlated with treatment success. The

Table 4
Screening baseline variables for predictive factors related to outcome of mandibular advancement device in 62 patients.

	Success ($n = 29$)	Failure ($n = 33$)	p_1	OR (95% CI)	p_2	p_3
Gender (M:F)	23:6	29:4	0.36	0.53 (0.13–2.10)		
Age (year)	51 (45–56)	49 (40–58)	0.42	1.02 (0.97–1.07)		
BMI (kg/m^2)	29 (27–32)	31 (29–37)	0.077	0.91 (0.82–1.01)	0.97	0.77
Neck circumference (cm)	41 (39–43)	44 (41–46)	0.017	0.81 (0.69–0.96)	0.98	0.77
AHI baseline (events/hr)	30 (16–44)	46 (28–61)	0.0055	0.96 (0.93–0.99)	0.97	0.08
AHI supine	56 (33–75)	69 (40–80)	0.64	1.00 (0.98–1.01)		
AHI non-supine	11 (4–28)	36 (19–57)	0.0012	0.95 (0.92–0.98)	0.018	
Supine time (%TST)	37% (21–47)	24% (13–45)	0.67	1.01 (0.98–1.03)		
POSA (no.)	20/29 (69%)	10/33 (30%)	0.0031	5.11 (1.73–15.08)	0.98[a]	
ESS score	11 (9–14)	11 (8–14)	0.78	1.02 (0.90–1.14)		
SNA (deg)	79.5 (77.6–82.1)	81.8 (79.4–83.5)	0.083	0.89 (0.77–1.03)	0.96	0.70
SNB (deg)	76.6 (74.9–78.6)	77.4 (76.0–81.0)	0.088	0.89 (0.78–1.02)	0.94	0.78
Upper airway examinations						
Physical examination ($n = 62$)						
Narrowness						
Retropalatally (no.)	8/29 (28%)	13/33 (39%)	0.33	0.59 (0.20–1.71)		
Retrolingually (no.)	12/29 (41%)	14/33 (42%)	0.93	0.96 (0.35–2.63)		
Low palatal arch (no.)	10/29 (34%)	9/33 (27%)	0.54	1.40 (0.48–4.15)		
Fexible tube reflectometry measuring						
predominant obstructive events ($n = 39$)						
Retropalatally (no.)	9/17 (53%)	9/22 (41%)	0.46	1.62 (0.45–5.82)		
Retrolingually (no.)	6/17 (35%)	8/22 (36%)	0.95	0.95 (0.25–3.58)		
Cephalometry ($n = 60$)						
Narrowest width						
Retropalatally (mm)	5.1 (3.5–7.5)	5.4 (4–7)	0.87	1.02 (0.82–1.26)		
Retrolingually (mm)	9.8 (6.9–12.1)	10.5 (7–12.5)	0.94	0.99 (0.87–1.14)		
Length of soft palate (mm)	42.7 (40.2–45)	44.8 (42.4–51.2)	0.061	0.91 (0.82–1.00)	0.95	0.75
Length of pharynx (mm)	84.7 (79.9–89.8)	85.5 (81.5–88.7)	0.89	0.99 (0.92–1.08)		
Ratio soft palate/pharynx	0.52 (0.47–0.53)	0.54 (0.5–0.57)	0.016	0.00 (0.00–0.05)	0.59	0.28

Quantitative values are given as the median with 25th and 75th percentiles. AHI, apnea–hypopnea index; BMI, body mass index; CI, confidence interval; ESS, Epworth Sleepiness Scale (ranges from 0 to 24, with 24 as the highest score of sleepiness); F, female; M, male; OR, odds ratio; POSA, positional obstructive sleep apnea; SNA, position of maxilla; SNB, position of mandibula; TST, total sleep time.
p_1: Univariable logistic regression analysis; p values are given with OR and CI for success versus failure.
p_2: <Multivariable logistic regression analysis; p values are the results of a stepwise reduction process, and OR for success versus failure is presented for the only significant and final selected predictive model (OR is calculated for a difference of 10 in nonsupine AHI).
p_3: p Values after removing nonsupine AHI and POSA from the multivariable analysis.
[a]When removing nonsupine AHI from the multivariable analysis, POSA became significant ($p = 0.040$; OR = 3.59, 95% CI = 1.06–12.16).

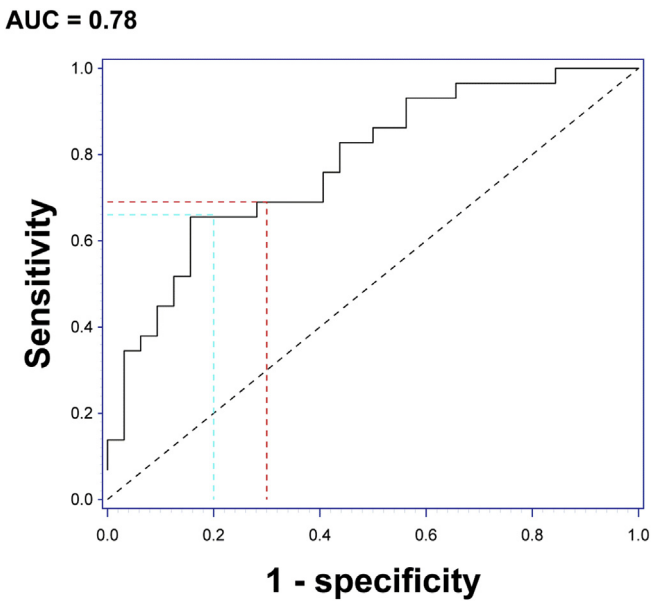

Fig. 4. Receiver operating characteristic (ROC) curve for the final model based on the nonsupine apnea–hypopnea index (AHI). The diagonal line represents the curve for no effect of the marker. Dotted lines show the sensitivity for the chosen specificities of 70% and 80%. AUC, area under ROC curve.Red: specificity 70%, cyan: specificity 80 %.

higher the nonsupine AHI, the greater the risk of failure with MAD therapy. The advantage of using nonsupine AHI is that the values are continuous, allowing for the generation of an ROC model and the choice of the clinically most relevant combination of specificity and sensitivity, with the associated cutoffs of nonsupine AHI for success.

The accuracy of the predictive model based on nonsupine AHI was good, as indicated by an area under the ROC curve of 0.78. The POSA model is easier to use but has some limitations. It is rigid, not allowing a choice between the most appropriate specificity and sensitivity. Furthermore, because the values are binary, information about treatment outcomes with AHI reductions close to the chosen success target is lost. Also, the POSA model does not take into account the impact of REM sleep. Half of the false-positive results were due to REM sleep overlapping with supine position.

In a large but retrospective study, Sutherland et al., [8] found that REM-predominant OSA was associated with a lower treatment response rate than non–REM-predominant OSA. In the present study, only 10 patients had this OSA phenotype, and therefore it does not make sense to compare the rate of treatment response between the two subgroups (Table 1).

Some of the false positive and negative rates could probably be an influence from clinically important OSA phenotypes such as BMI, neck circumference and retrognathia. This assumption is supported by the finding that the rate of treatment success was markedly reduced with a BMI > 33 kg/m^2 and a neck circumference > 43 cm, the cutpoints corresponding to the 75% percentiles. However, these variables were not significant in the predictive analyses, and the values varied considerable within both the success and the failure groups.

Table 6
Predictive model based on POSA as success in 61 patients.[a]

Specificity	0.70
Sensitivity	0.69
PPV	0.67
NPV	0.72
False-positive	0.33
False-negative	0.28

NPV, negative predictive value; POSA, positional obstructive sleep apnea; PPV, positive predictive value.
[a] Failed recording of body position in one case.

The finding that POSA is an independent predictor of MAD treatment success is consistent with some other studies [6,10,11,24] despite different criteria for POSA and treatment success. Some studies could not identify POSA as a predictor of treatment success [8,23]. These studies have used duoblock devices allowing mouth opening. By contrast, in the present study and the other studies that found that POSA to be predictive of treatment success, mouth opening was counteracted using a monobloc [6,10,24] or a duoblock device fixed in the front [11]. Furthermore, two randomized controlled trials found the monobloc generally to be more effective than a duoblock device that allowed mouth opening [25,26]. The high prevalence of POSA (48% in the present study) has also been found in other studies, all using almost the same POSA definition [10,11,27].

Since POSA was mostly related to mild-to-moderate OSA, as also found by Oksenberg et al., [27] one might expect that baseline AHI could also be a good predictor. However, in multivariable logistic regression analysis, baseline AHI became borderline significant only when nonsupine AHI and POSA were removed from the analysis (Table 4). The finding that baseline AHI was not predictive has also been reported in some other studies [1,7]. Alternately, in the present study, treatment success was not achieved with a baseline AHI above 64, and the success rate was markedly better with an AHI < 56 (the 75% percentile of baseline AHI) compared to an AHI > 56 (60% vs. 7%).

Several studies performed during wakefulness have documented that the effect of MAD is due to enlargement of the pharyngeal airway, particularly in the lateral dimensions [28–32]. Therefore, one might expect to find that upper airway narrowings and collapse levels are correlated with the MAD treatment effect.

Yet, none of the three upper airway examination methods were of predictive value. Acoustic reflectometry was expected to be the most informative, as it probably provides a true image of the pharyngeal collapse levels during sleep; however, even this method did not have predictive value. Furthermore, the flexible tube method was resource-demanding and unpleasant for some of the patients: at least half of the failed examinations were due to disturbances from the flexible tube.

Table 5
Predictive model based on ROC curve of nonsupine AHI as response. Variable in 61 patients.[a]

Specificity %	Sensitivity %	PPV %	NPV %	False-positive	False-negative	Cutpoints of AHI nonsupine for success
0.60	0.69	0.63	0.69	0.37	0.31	26
0.70	0.69	0.69	0.72	0.31	0.28	24
0.75	0.66	0.73	0.71	0.29	0.29	18
0.80	0.66	0.76	0.72	0.24	0.28	16
0.85	0.52	0.79	0.67	0.21	0.33	11
0.90	0.41	0.80	0.63	0.20	0.37	7

AHI, apnea–hypopnea index; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.
[a] Failed recording of body position in one case.

The unsuccessful results of all the examination methods indicate that the search for a certain level of anatomical narrowing or collapses in the upper airway is without predictive value, probably because MADs obviously and effectively can enlarge the upper airway, both the upper and lower part, as documented by several studies as follows: (1) velopharynx (Ryan et al., using video-endoscopy [28]; Chan et al., using magnetic resonance imaging [31]; Marcussen et al., using cone-beam computed tomography [32]); (2) oropharynx (Haskell et al., using cone-beam computed tomography [30]); and (3) both retropalatal and retroglossal region, that is, velopharynx and oro-hypopharynx (Kyung et al., using ultrafast computed tomography [29]).

Nonetheless, studies of collapsibility based on nonanatomical pathophysiologic features [14,15] are promising with regard to future selection of predictors. The method based on spirometry [14] is relatively simple, whereas the method based on pneumotachometry and CPAP [15] seems to be complicated and resource-demanding. The same can be said about the method that is based on direct inspection of upper airway collapses during manipulated mandibular titration [17].

Apart from retrognathia, the cephalometric skeletal parameters had no potential predictive value. The modest benefit from cephalometry makes it unsuitable in the daily clinic. The cephalometric results are in accordance with many other studies that have searched for cephalometric predictors of MAD outcome. Mostafiz et al., [33] found no significant cephalometric differences between successfully and unsuccessfully treated patients, as did Denolf et al., [34] in a recent systematic review. Recently, however, it has been found that upper spine morphological deviations, diagnosed on lateral cephalograms and cone-beam computed tomography, may be a predictive factor for MAD treatment success and may contribute to the phenotypic differentiation of OSA patients [9,35,36].

5. Conclusion

In conclusion, anatomical reduced space in the upper airway, including collapse levels during sleep, was not predictive of the success of MAD; nor were external conditions of importance for upper airway space conditions (BMI, neck circumference, retrognathia) and severity of OSA (expressed by AHI). All factors were outperformed by variables related to sleeping supine (POSA positively, and nonsupine AHI negatively correlated to outcome). The predictive power of POSA and nonsupine AHI could be explained by the ability of the MAD to counteract obstruction by the tongue when sleeping supine. The benefit from enlargement of the pharyngeal airway space by the MAD could more or less be lost if the MAD design does not counteract the mandible from moving backwards in supine position.

Not all patients with POSA will benefit from MAD, but the false-positive rate can probably be reduced by improving the predictive model.

Our results may contribute to further promoting the concept of OSA as having different pathophysiological causes, thereby highlighting the importance of different phenotypes of OSA for the type of treatment. Further research may uncover and explore those that might usefully be included in the predictive model.

Acknowledgements

The study was supported financially by the following: East Danish Health Science Research Forum; Medical Research Fund, Region 3; Danish Dentistry Association Fund; Copenhagen Trial Unit, Centre for Clinical Intervention Research; Memorial Fund of Edith & Henrik Henriksen; Fund of Director Ib Henriksen; Fund of Director E. Danielsen & Wife. The sponsors had no role in the conception or design of the trial, collection of data, analyses, interpretation, or drafting of the manuscript.

Conflict of interest

None of the authors have a conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.033.

References

[1] Mehta A, Qian J, Petocz P, et al. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. Am J Respir Crit Care Med 2001;163:1457–61.
[2] Gotsopoulos H, Chen C, Qian J, et al. Oral appliance therapy improves symptoms in obstructive sleep apnea. Am J Respir Crit Care Med 2002;166:743–8.
[3] Petri N, Svanholt P, Solow B, et al. Mandibular advancement appliance for obstructive sleep apnoea: results of a randomised placebo controlled trial using parallel group design. J Sleep Res 2008;17:221–9.
[4] Engleman HM, McDonald JP, Graham D, et al. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 2002;166:855–9.
[5] Lam B, Sam K, Mok WY, et al. Randomised study of three non-surgical treatments in mild to moderate obstructive sleep apnoea. Thorax 2007;62:354–9.
[6] Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring. Chest 2004;125:1270–8.
[7] Ng AT, Darendeliler MA, Petocz P, et al. Cephalometry and prediction of oral appliance treatment outcome. Sleep Breath 2012;16:47–58.
[8] Sutherland K, Takaya H, Qian J, et al. Oral appliance treatment response and polysomnographic phenotypes of obstructive sleep apnea. J Clin Sleep Med 2015;8:861–8.
[9] Svanholt P, Petri N, Wildschiødtz G, et al. Influence of craniofacial and upper spine morphology on mandibular advancement device treatment outcome in patients with obstructive sleep apnoea: a pilot study. Eur J Orthod 2015;37:391–7.
[10] Marklund M, Persson M, Franklin KA. Treatment success with mandibular advancement device is related to supine-dependent sleep apnea. Chest 1998;114:1630–5.
[11] Chung JW, Enciso R, Levendowski DJ, et al. Treatment outcomes of mandibular advancement devices in positional and nonpositional OSA patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:724–31.
[12] Eckert DJ, White DP, Jordan AS, et al. Defining phenotypic causes of obstructive sleep apnea. Am J Respir Crit Care Med 2013;188:996–1004.
[13] Ng AT, Gotsopoulos H, Qian J, et al. Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. Am J Respir Crit Care Med 2003;168:238–41.
[14] Zeng B, Ng AT, Darendeliler MA, et al. Use of flow-volume curves to predict oral appliance treatment outcome in obstructive sleep apnea. Am J Respir Crit Care Med 2007;175:726–30.
[15] Edwards BA, Andara C, Landry S, et al. Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2016;194:1413–22.
[16] Ng AT, Qian J, Cistulli PA. Oropharyngeal collapse predicts treatment response with oral appliance therapy in obstructive sleep apnea. Sleep 2006;29:666–71.
[17] Vroegop AV, Vanderveken OM, Dieltjens M, et al. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. J Sleep Res 2013;22:348–55.
[18] Sunnergren O, Broström A, Svanborg E. Positional sensitivity as a confounder in diagnosis of severity of obstructive sleep apnea. Sleep Breath 2013;17:173–9.
[19] Solow B, Skov S, Ovesen J, et al. Airway dimensions and head posture in obstructive sleep apnoea. Eur J Orthod 1996;18:571–9.
[20] Faber CE, Grymer L, Norregaard O, et al. Flextube reflectometry for localization of upper airway narrowing—a preliminary study in models and awake subjects. Respir Med 2001;95:631–8.
[21] Faber CE, Hilberg O, Jensen FT, et al. Flextube reflectometry for determination of sites of upper airway narrowing in sleeping obstructive sleep apnoea patients. Respir Med 2001;95:639–48.
[22] Lawless JF, Singhal K. Efficient screening of nonnormal regression models. Biometrics 1978;34:318–27.
[23] Dieltjens M, Braem MJ, Van de Heyning PH, et al. Prevalence and clinical significance of supine-dependent obstructive sleep apnea in patients using oral appliance therapy. J Clin Sleep Med 2014;9:959–64.
[24] Takaesu Y, Tsuiki S, Kobayashi M, et al. Mandibular advancement device as a comparable treatment to nasal continuous positive airway pressure for positional obstructive sleep apnea. J Clin Sleep Med 2016;12:1113–9.

[25] Bloch KE, Iseli A, Zhang JN, et al. A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. Am J Respir Crit Care Med 2000;162:246–51.
[26] Zhou J, Liu YH. A randomised titrated crossover study comparing two oral appliances in the treatment for mild to moderate obstructive sleep apnoea/hypopnoea syndrome. J Oral Rehabil 2012;39:914–22.
[27] Oksenberg A, Silverberg DS, Arons E, et al. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic and multiple sleep latency test data. Chest 1997;112:629–39.
[28] Ryan CF, Love LL, Peat D, et al. Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake caliber of the velopharynx. Thorax 1999;54:972–7.
[29] Kyung SH, Park YC, Pae EK. Obstructive sleep apnea patients with the oral appliance experience pharyngeal size and shape changes in three dimensions. Angle Orthod 2005;75:15–22.
[30] Haskell JA, McCrillis J, Haskell BS, et al. Effect of mandibular advancement device (MAD) on airway dimensions assessed with cone-beam computed tomography. Semin Orthod 2009;15:132–58.
[31] Chan AS, Sutherland K, Schwab RJ, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 2010;65:726–32.
[32] Marcussen L, Henriksen JE, Thygesen T. Do mandibular advancement devices influence patients snoring and obstructive sleep apnea? A cone-beam computed tomography analysis of the upper airway volume. J Oral Maxillofac Surg 2015;73:1816–26.
[33] Mostafiz W, Dalci O, Sutherland K, et al. Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. Chest 2011;139:1331–9.
[34] Denolf PL, Vanderveken OM, Marklund ME, et al. The status of cephalometry in the prediction of non-CPAP treatment outcome in obstructive sleep apnea patients. Sleep Med Rev 2016;27:56–73.
[35] Sonnesen L, Petri N, Kjaer I, et al. Cervical column morphology in adult patients with obstructive sleep apnoea. Eur J Orthod 2008;30:521–6.
[36] Sonnesen L, Petersson A, Berg S, et al. Pharyngeal airway dimensions and head posture in obstructive sleep apnea patients with and without morphological deviations in the upper cervical spine. J Oral Maxillofac Res 2017;8:e4.