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Predictors of Obstructive Sleep Apnea-Hypopnea Treatment Outcome

ABSTRACT

Oral appliance therapy is an alternative to continuous positive airway pressure (CPAP) for treating the obstructive sleep apnea-hypopnea syndrome. However, the ability to pre-select suitable candidates for either treatment is limited. The aim of this study was to assess the value of relevant variables that can predict the outcome of oral appliance and CPAP therapy. Fifty-one patients treated with oral appliance therapy and 52 patients treated with CPAP were included. Relevant clinical, polysomnographic, and cephalometric variables were determined at baseline. The predictive value of variables for treatment outcome was evaluated in univariate and multivariate analyses. The outcome of oral appliance therapy was favorable, especially in less obese patients with milder sleep apnea and with certain craniofacial characteristics (mandibular retrognathism in particular). Neither univariate nor multivariate analyses yielded variables that reliably predicted the outcome of CPAP. We conclude that the variables found in this study are valuable for pre-selecting suitable candidates for oral-appliance therapy.

KEY WORDS: sleep apnea syndromes, orthodontic appliances, positive-pressure ventilation, treatment outcome, predictors.

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A supplemental appendix to this article is published electronically only at http://www.dentalresearch.org.

INTRODUCTION

The obstructive sleep apnea-hypopnea syndrome is a common sleep-related breathing disorder characterized by disruptive snoring and repetitive upper airway collapse (Malhotra and White, 2002). Continuous positive airway pressure (CPAP) is the preferred treatment for sleep apnea (Giles *et al.*, 2006). Since maintaining CPAP requires that patients wear an obtrusive device, patients may abandon therapy. Oral appliance therapy is an alternative to CPAP that relieves upper-airway collapse during sleep by modifying the position of the mandible, tongue, and pharyngeal structures (Cistulli *et al.*, 2004). Although there is evidence that oral appliance therapy is effective for sleep apnea, it is generally considered less effective than CPAP (Barnes *et al.*, 2004; Hoekema *et al.*, 2004; Lim *et al.*, 2006). Nevertheless, many patients prefer an oral appliance over CPAP therapy (Hoekema *et al.*, 2004). Therefore, predictors of treatment outcome are important for the selection of suitable candidates who may benefit from either treatment.

Numerous clinical and polysomnographic variables have been reported to correlate with increased effectiveness of oral appliance therapy. For example, the outcome of treatment is generally more favorable in patients who are less obese (Pancer *et al.*, 1999; Liu *et al.*, 2001) and who have a lower apnea-hypopnea index (Rose *et al.*, 2002a). In addition to the fact that specific bony- and soft-tissue features may characterize the upper airway of sleep apnea patients (Okubo *et al.*, 2006), numerous cephalometric variables have also been implicated in the outcome of oral appliance therapy (Horiuchi *et al.*, 2005). Predictors of treatment outcome, however, are not uniformly reported (Henke *et al.*, 2000; Marklund *et al.*, 2004). The majority of these studies incorporate bias, because patients with severe sleep apnea or patients who have not adhered to therapy have been excluded (Marklund *et al.*, 2004). In addition, predictors have not been systematically validated to evaluate their accuracy in a separate population of patients (Lim *et al.*, 2006). Therefore, clinicians' ability to predict treatment outcome and pre-select suitable candidates for a specific treatment modality is still limited.

The aim of this study was to assess the value of relevant clinical, polysomnographic, and cephalometric variables, separately and jointly, to predict the outcome of oral appliance and CPAP therapy.

MATERIALS & METHODS

Patient Selection

Patients were recruited through the Department of Home Mechanical Ventilation of the University Medical Center Groningen (The Netherlands) for a randomized parallel non-inferiority trial comparing the effects of oral appliance and CPAP therapy (Hoekema *et al.*, 2006). Patients over age 20 years, who underwent polysomnography and were diagnosed as having obstructive sleep apnea-

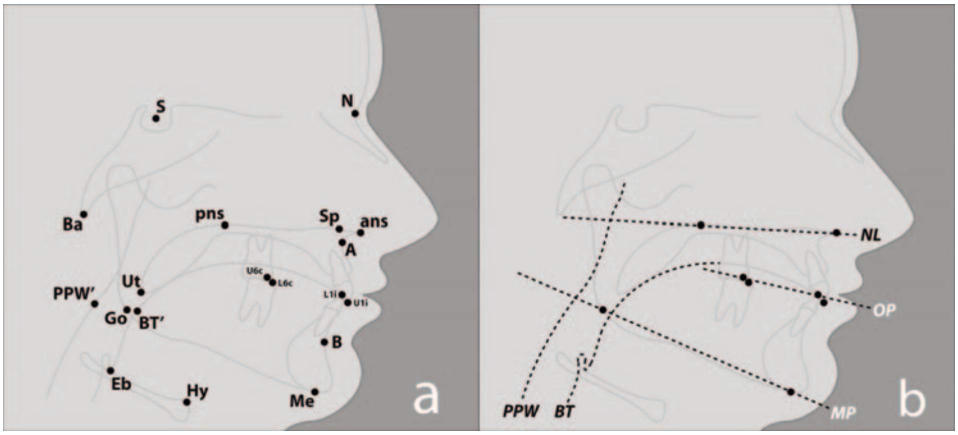

Figure. Cephalometric analysis. **(a)** Reference points traced on lateral cephalograms. The following 19 reference points were identified on lateral cephalograms: A (point A; the deepest midline concavity on the anterior maxilla); ans (anterior nasal spine; the tip of the bony anterior nasal spine); B (point B; the deepest midline concavity on the mandibular symphysis); Ba (basion; the median point of the anterior margin of the foramen magnum); BT′(base of tongue intersection; intersection point of the line connecting B-Go with the base of tongue); Eb (epiglottis base; the point located at the intersection of the epiglottis and the base of tongue); Go (gonion; point on the bony contour of the gonial angle determined by bisecting the angle of the tangents to the body and ramus of the mandible, respectively); Hy (hyoid; the most anterior-superior point on the body of the hyoid bone); L1i (first lower incisor edge); L6c (first lower molar mesial cusp tip); Me (menton; the most inferior point on the mandibular symphysis); N (nasion; the most anterior point on the frontonasal suture); pns (posterior nasal spine; the tip of the bony posterior nasal spine); PPW′ (posterior pharyngeal wall intersection; intersection point of the line connecting B-Go with the posterior pharyngeal wall); S (sella; the midpoint of the pituitary fossa); Sp (spina prim; intersection point of the line connecting ans-pns and the line connecting Me-N); Ut (uvular tip; tip of the velum of the soft palate); U1i (first upper incisor edge); and U6c (first upper molar mesial cusp tip). **(b)** Reference lines traced on lateral cephalograms. The following 5 reference lines were identified on lateral cephalograms: *BT* (base of tongue; the posterior outline of the tongue base extending from the base of the epiglottis to first maxillary molar); *MP* (mandibular plane; line connecting Me and Go); *NL* (nasal line; line connecting the ans and pns); *OP* (occlusal plane; line connecting the midpoint between U1i and L1i with the midpoint between U6c and L6c. The distance between the horizontal and vertical projections of U1i and L1i on the occlusal plane were used to calculate the overjet and overbite, respectively.); and *PPW* (posterior pharyngeal wall; the anterior outline of the posterior pharyngeal wall).

hypopnea syndrome, were eligible (AASM, 1999). Patients were selected based on medical, psychological, and dental criteria. The trial was approved by the Groningen University Medical Center's ethics committee. Written informed consent was obtained from patients before enrollment. Details of the trial are provided in the APPENDIX.

Study Design

Between September, 2002, and May, 2005, 103 eligible sleep apnea patients were enrolled. Fifty-one patients had been randomly allocated to oral appliance therapy (Thornton Adjustable Positioner type-1, Airway Management Inc., Dallas, TX, USA) and 52 to CPAP therapy. At baseline, relevant clinical (Marklund *et al.*, 1998a, 2004; Pancer *et al.*, 1999; Liu *et al.*, 2001; Mehta *et al.*, 2001; Walker-Engstrom *et al.*, 2003) and polysomnographic variables (Pancer *et al.*, 1999; Henke *et al.*, 2000; Mehta *et al.*, 2001; Yoshida, 2001; Rose *et al.*, 2002a; Marklund *et al.*, 2004; Horiuchi *et al.*, 2005) were determined in all patients. We also obtained a lateral cephalogram from patients in the oral appliance group, to determine relevant cephalometric variables (Bonham *et al.*, 1988; Eveloff *et al.*, 1994; Yoshida, 1994; Mayer and Meier-Ewert, 1995; Marklund *et al.*, 1998b; Liu *et al.*, 2001; Rose *et al.*, 2002b; Skinner *et al.*, 2002; Horiuchi *et al.*, 2005). Because CPAP therapy treats upper airway obstructions regardless of underlying anatomical risk factors, cephalometric variables were not evaluated in the CPAP group. All variables were considered relevant, because they had been implicated in the outcome of oral appliance therapy in one or more previous studies.

After patients had used an oral appliance or CPAP for approximately a two- to three-month period, the treatment effect was assessed with polysomnography. At the final follow-up review, treatment was considered effective when the apnea-hypopnea index either was <5 or showed "substantial reduction", defined as reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient who had no symptoms while using therapy (Hoekema *et al.*, 2004). Patients not meeting these criteria at their final review were considered "non-responsive" to treatment. Patients who discontinued treatment for any reason were considered "non-adherent" to treatment.

Clinical Predictors

The following clinical variables were determined at baseline: sex, age, body mass index, neck circumference, and the Epworth sleepiness scale (Johns, 1991). Furthermore, in the oral appliance group, the maximum mandibular advancement was determined at baseline with a George-Gauge™ (H Orthodontics, Michigan City, IN, USA).

Polysomnographic Predictors

The following polysomnographic variables were determined at baseline: apnea-hypopnea index, lowest oxyhemoglobin saturation during sleep, the percentage of non-rapid eye-movement sleep during sleep stages 3 & 4, and the apnea-hypopnea index ratio supine to lateral. Patients were also classified as having non-severe (apnea-hypopnea index 5 to 30) or severe (apnea-hypopnea index > 30) sleep apnea, and supine-dependent (defined by an apnea-hypopnea index < 10 in the lateral position) or non-supine-dependent sleep apnea (Marklund *et al.*, 2004).

Cephalometric Predictors

In each lateral cephalogram, 19 reference points and 5 reference lines were identified (Fig., a,b). The cephalometric analysis yielded 20 predictive variables.

Statistical Analysis

First, in each treatment group, variables were submitted for univariate analysis. Categorical variables (*i.e.*, sex, sleep apnea-severity, and supine-dependence of sleep apnea) were submitted only for multivariate analysis. The univariate analysis consisted of calculation of 'receiver-operating characteristics' curves of each variable, with 'treatment effectiveness' and an 'apnea-hypopnea index < 5 following treatment' being the dependent variables,

Table 1. Univariate Analysis of Clinical and Polysomnographic Variables for Predicting Effectiveness of, or an Apnea-Hypopnea Index < 5 with, Oral Appliance and CPAP Therapy

	Oral Appliance			CPAP		
Variable	Baseline[a] (n = 49)	Area under the Curve: Effectiveness[b]	Area under the Curve: Apnea-Hypopnea Index < 5	Baseline[a] (n = 50)	Area under the Curve: Effectiveness[b]	Area under the Curve: Apnea Hypopnea Index < 5
Age (yrs)	49.2 ± 9.5	0.57[c]	0.52[d]	49.4 ± 9.6	0.61[c]	0.64[c]
Body mass index (kg/m2)[e]	32.2 ± 6.1	0.72[d]*	0.71[d]*	33.0 ± 5.6	0.60[c]	0.56[c]
Neck circumference (cm)	43.8 ± 3.6	0.58[d]	0.65[d]	44.5 ± 3.5	0.50[d]	0.56[d]
Epworth sleepiness scale	12.8 ± 5.6	0.53[c]	0.59[d]	14.5 ± 5.4	0.69[c]	0.61[c]
Maximum mandibular advancement (mm)	12.8 ± 1.9	0.65[c]	0.75[c]*	—	—	—
Apnea-hypopnea index (events/hr)	38.0 ± 29.8	0.63[d]	0.78[d]*	40.8 ± 28.0	0.59[c]	0.59[d]
Lowest oxyhemoglobin saturation during sleep (%)	78.0 ± 8.6	0.69[c]	0.69[c]	77.8 ± 10.0	0.62[d]	0.56[c]
Non-rapid eye movement, sleep stages 3 & 4 (%)	13.5 ± 9.1	0.66[c]	0.65[c]	12.9 ± 11.6	0.60[d]	0.51[d]
Apnea-hypopnea index ratio supine/lateral[f]	2.0 (1.2-5.2)	0.61[c]	0.64[c]	2.1 (1.1-6.8)	0.63[d]	0.54[c]

* Variables with at least fair predictive ability for the outcome of therapy.
[a] Plus-minus values are means ± standard deviations; values with additives in parentheses are medians with interquartile ranges.
[b] Treatment was considered effective when the apnea-hypopnea index either was < 5 or showed "substantial reduction", defined as reduction in the apnea-hypopnea index of at least 50% from the baseline value to a value of < 20 in a patient who had no symptoms while using therapy.
[c] Larger value of variable associated with a more positive response to treatment.
[d] Smaller value of variable associated with a more positive response to treatment.
[e] The body mass index is the weight (kg) divided by the square of the height (m).
[f] This item could be determined in 39 patients in both the oral appliance and CPAP groups. Abbreviation: CPAP = continuous positive airway pressure.

respectively. To obtain a summary measure for the predictive ability of each variable, we calculated the area under the curve of each 'receiver-operating characteristics' curve. The predictive ability of a variable was classified based on the area under the curve (excellent = 0.9 to 1, good = 0.8 to 0.9, fair = 0.7 to 0.8, poor = 0.6 to 0.7, or non-discriminative = 0.5 to 0.6) (Swets, 1988). All variables with at least fair predictive ability were admitted for logistic regression analyses. By excluding variables stepwise backward, we constructed predictive models in both the oral appliance and CPAP groups, with 'treatment effectiveness' and an 'apnea-hypopnea index < 5 following treatment' being the dependent variables, respectively. Logistic regression analyses also produced odds ratios associated with each predictor value. We used a discriminant analysis to select the predictive model that classified the highest percentage of patients correctly. Subsequently, the selected model was cross-validated in another discriminant analysis by the application of a "leave-one-out classification".

RESULTS

Two patients in both the oral appliance and CPAP groups did not return for the follow-up review. The median period to final review was 68 (interquartile range, 60-96) days in the oral appliance group and 63 (interquartile range, 60-88) days in the CPAP group ($p > 0.05$). At final follow-up review, mean advancement of the mandible with the oral appliance was 81 ± 19% of maximum advancement. Mean CPAP pressure was 8.1 ± 1.9 cm H_2O at final review. Oral appliance therapy was effective for 39 patients (79.6%). Of the other 10 patients, eight were "non-responsive", and two were "non-adherent" to treatment. In the CPAP group, treatment was effective for 43 patients (86.0%). Of the other seven patients, two were "non-responsive", and five were "non-adherent" to treatment. Oral appliance therapy yielded an apnea-hypopnea index < 5 in 29 of the 49 patients (59.2%). CPAP therapy yielded an apnea-hypopnea index < 5 in 40 of the 50 patients (80.0%).

Clinical and Polysomnographic Predictors

A smaller body mass index had fair ability to predict the effectiveness of oral appliance therapy (Table 1). In prediction of an apnea-hypopnea index < 5 following oral appliance therapy, a smaller body mass index, more extended maximum mandibular advancement, and a smaller apnea-hypopnea index had fair predictive ability. In prediction of the effectiveness of, or an apnea-hypopnea index < 5 with, CPAP therapy, all variables had a poor predictive ability or were non-discriminative.

Cephalometric Predictors

In predicting the effectiveness of oral appliance therapy, a larger intermaxillary discrepancy (*i.e.*, higher angle between the lines connecting point A with Nasion and point B with Nasion [ANB]) had good predictive ability, and a greater mandibular deficiency (*i.e.*, smaller angle between the lines connecting Sella with Nasion and Nasion with point B [SNB]), a larger overjet and overbite, and a greater upper anterior face height had fair predictive ability (Fig., a; Table 2). In predicting an apnea-hypopnea index < 5 following oral appliance therapy, all cephalometric variables had poor predictive ability or were non-discriminative.

Multivariate Analysis

The logistic regression analysis for predicting the effectiveness of oral appliance therapy yielded a model providing an 84%

Table 2. Univariate Analysis of Cephalometric Variables for Predicting Effectiveness of, or an Apnea-Hypopnea Index < 5 with, Oral Appliance Therapy

		Oral Appliance	
Variable	Baseline[a] (n = 48)	Area under the Curve: Effectiveness[b]	Area under the Curve: Apnea-Hypopnea Index < 5
Cranial Base			
S-N (mm)	71.9 ± 7.6	0.52[c]	0.52[c]
Ba-S-N (mm)	178.9 ± 20.4	0.61[c]	0.58[c]
Sagittal Jaw Relationships			
SNA (degrees)	79.1 ± 4.7	0.51[d]	0.56[c]
SNB (degrees)	76.7 ± 4.6	0.74[d]*	0.57[d]
ANB (degrees)	2.5 ± 2.7	0.80[c]*	0.64[c]
Overjet (mm)	4.0 ± 3.0	0.79[c]*	0.66[c]
Overbite (mm)	4.4 ± 3.0	0.80[c]*	0.64[c]
Vertical Craniofacial Dimensions			
N-Me; anterior face height (mm)	126.5 ± 14.8	0.62[c]	0.54[d]
S-Go; posterior face height (mm)	83.8 ± 11.0	0.52[c]	0.53[c]
Me-Sp; lower anterior face height (mm)	72.9 ± 9.5	0.53[c]	0.59[d]
N-Sp; upper anterior face height (mm)	53.7 ± 6.5	0.72[c]*	0.59[c]
Posterior face height : anterior face height (ratio)	0.66 ± 0.06	0.55[d]	0.58[c]
Upper anterior face height : lower anterior face height (ratio)	0.74 ± 0.08	0.63[c]	0.64[c]
MP-SN; mandibular plane angle (degrees)	34.9 ± 7.6	0.56[c]	0.59[d]
Pharyngeal Dimensions and Hyoid Bone Position			
pns-Ut; uvular length (mm)	42.8 ± 7.5	0.51[c]	0.58[d]
Ut-*PPW* (perpendicular); retropalatal airway space (mm)	8.2 ± 2.9	0.51[c]	0.57[c]
PPW´ -BT´; posterior airway space (mm)	10.1 ± 3.7	0.50[d]	0.58[c]
pns-Eb; vertical airway length (mm)	82.3 ± 10.1	0.56[c]	0.55[c]
Hy-*MP* (perpendicular) (mm)	26.1 ± 6.2	0.55[c]	0.52[c]
Hy-Me (mm)	48.6 ± 8.4	0.60[d]	0.53[d]

* Variables with at least fair predictive ability for the outcome of therapy.
[a] Plus-minus values are means ± standard deviations. Cephalometric radiographs were available for 48 of the 49 patients completing the follow-up review for oral appliance therapy.
[b] Treatment was considered effective when the apnea-hypopnea index either was < 5 or showed "substantial reduction", defined as reduction in the apnea-hypopnea index of at least 50% from the baseline value to a value of < 20 in a patient who had no symptoms while using therapy.
[c] Larger value of variable associated with a more positive response to treatment.
[d] Smaller value of variable associated with a more positive response to treatment.

correct classification of responders and non-responders. Variables included in the model were the apnea-hypopnea index, SNB angle, and ANB angle (Table 3). When the selected model was cross-validated, 80% of the patients were classified correctly. The logistic regression analysis for predicting an apnea-hypopnea index < 5 with oral appliance therapy yielded a model providing an 80% correct classification of responders and non-responders. Variables included in the model were the apnea-hypopnea index and the maximum mandibular advancement (Table 3). When the selected model was cross-validated, 80% of patients were classified correctly.

The logistic regression analysis for predicting the effectiveness of CPAP therapy yielded a model providing a 65% correct classification of responders and non-responders. Variables included in the model were the body mass index, apnea-hypopnea index, sleep apnea-severity, and supine-dependence of sleep apnea (Table 3). When the selected model was cross-validated, 54% of patients were classified correctly. The logistic regression analysis for predicting an apnea-hypopnea index < 5 with CPAP therapy yielded a model providing a 65% correct classification of responders and non-responders. Variables included in the model were the body mass index and apnea-hypopnea index (Table 3). When the selected model was cross-validated, 65% of patients were classified correctly.

DISCUSSION

Univariate analysis demonstrated that a lower body mass index, more extended maximum mandibular advancement, smaller apnea-hypopnea index, higher ANB angle, smaller SNB angle, and more pronounced overjet, overbite, and upper anterior face height were the best predictors for outcome of oral appliance therapy. Our results concur with those of previous studies that demonstrated that these clinical (Marklund *et al.*, 1998a; Pancer *et al.*, 1999; Liu *et al.*, 2001), polysomnographic (Pancer *et al.*, 1999; Henke *et al.*, 2000; Mehta *et al.*, 2001), and cephalometric (Yoshida, 1994; Mayer and Meier-Ewert, 1995; Liu *et al.*, 2001) variables correlate with increased effectiveness of oral appliance therapy. Except for upper anterior face height, the cephalometric predictors found in the present study primarily relate to mandibular retrognathism. Contrary to other reports, variables including supine dependence of sleep apnea (Yoshida, 2001; Marklund *et al.*, 2004) or pharyngeal dimensions and hyoid bone position (Yoshida, 1994; Mayer and Meier-Ewert, 1995; Liu *et al.*, 2001; Mehta *et al.*, 2001; Rose *et al.*, 2002b; Skinner *et al.*, 2002; Horiuchi *et al.*, 2005) could not be implicated in the outcome of oral appliance therapy. These results indicate that patients who are less obese, have milder sleep apnea, and have certain craniofacial characteristics (mandibular retrognathism in particular) respond more favorably to oral appliance therapy.

Multivariate analysis yielded predictive models that, following cross-validation, classified the outcome of oral appliance therapy correctly in 80% of patients. Variables included in the predictive models were maximum mandibular advancement, apnea-hypopnea index, and the SNB and ANB angles. Recent studies have suggested an important role for more sophisticated techniques to predict the outcome of oral appliance therapy. For instance, a remotely controlled mandibular positioner (Tsai *et al.*, 2004) or upper airway imaging techniques, including sleep nasendoscopy (Battagel *et al.*, 2005) or magnetic resonance imaging (Sanner *et al.*, 2002), have been shown to be highly predictive of the patients' response to oral appliance therapy. Although these techniques may be of additional value in the selection of suitable candidates, they are generally costly, laborious, or sensitive to a specific operator. The present study aimed at constructing a predictive model convenient for the clinical situation. By using variables that are relevant and that can be easily determined, we obtained two predictive models that allow for a reliable prediction of the effectiveness of, or an apnea-hypopnea index < 5 with, oral appliance therapy.

Table 3. Logistic Regression Model for Predicting Effectiveness of, or an Apnea-Hypopnea Index < 5 with, Oral Appliance and CPAP Therapy

	Logistic Regression Analysis[a]		
Variable	Coefficient	Standard Error	Odds Ratio (95% confidence interval)
Effectiveness of Oral Appliance Therapy[b]			
Apnea-hypopnea index (events/hr)	-0.014	0.014	0.99 (0.96 to 1.01)
SNB (degrees)	-0.162	0.120	0.85 (0.67 to 1.08)
ANB (degrees)	0.507	0.220	1.66 (1.08 to 2.56)
Constant	13.58	9.476	
-2 Log Likelihood = 31.6			
Apnea-Hypopnea Index < 5 with Oral Appliance Therapy			
Apnea-hypopnea index (events/hr)	-0.038	0.015	0.96 (0.94 to 0.99)
Maximum mandibular advancement (mm)	0.544	0.217	1.72 (1.13 to 2.64)
Constant	-5.137	2.711	
-2 Log Likelihood = 43.6			
Effectiveness of CPAP Therapy[b]			
Body mass index (kg/m^2)	0.118	0.127	1.13 (0.88 to 1.44)
Apnea-hypopnea index (events/hr)	0.059	0.050	1.06 (0.96 to 1.17)
Sleep apnea severity (severe = 1, non-severe = 0)	-2.342	2.283	0.10 (0.00 to 8.44)
Supine-dependence sleep apnea (non-supine-dependent = 1, supine-dependent = 0)	-1.396	1.364	0.25 (0.02 to 3.59)
Constant	-2.089	3.835	
-2 Log Likelihood = 32.2			
Apnea-Hypopnea Index < 5 with CPAP Therapy			
Body mass index (kg/m^2)	0.100	0.095	1.11 (0.92 to 1.33)
Apnea-hypopnea index (events/hr)	-0.027	0.016	0.97 (0.94 to 1.01)
Constant	-0.763	2.777	
-2 Log Likelihood = 4.1			

[a] Due to missing variables, the multivariate analysis included 45 patients from the oral appliance group and 43 patients from the CPAP group.

[b] Treatment was considered effective when the apnea-hypopnea index either was < 5 or showed "substantial reduction", defined as reduction in the apnea-hypopnea index of at least 50% from the baseline value to a value of < 20 in a patient who had no symptoms while using therapy. Abbreviation: CPAP = continuous positive airway pressure.

Contrary to oral appliance therapy, clinical and polysomnographic variables had poor predictive value for the outcome of CPAP therapy. Moreover, multivariate analysis yielded predictive models for an effective treatment and apnea-hypopnea index < 5 with CPAP therapy that, following the cross-validation, classified only 54% and 65% of patients correctly, respectively. These results indicate that patients in whom CPAP therapy does not have a favorable outcome cannot be easily pre-selected. Unfortunately, in clinical practice, these patients are usually deemed the best candidates for oral appliance therapy (Lim *et al.*, 2006). The limited predictive ability of the predictive models is possibly best explained by the fact that CPAP therapy was effective and yielded an apnea-hypopnea index < 5 in the majority of patients.

One may question the extent to which the results found in this study can be extrapolated to other types of oral appliances. Although different aspects in the design of oral appliances may affect patient preference, clinical effects of different oral appliances that reposition the mandible are usually remarkably consistent (Hoekema *et al.*, 2004). Moreover, the present study evaluated only variables that had been implicated in the outcome of oral appliance therapy in previous studies. We therefore believe that the results from this study also apply for predicting the outcome of most other types of oral appliances that reposition the mandible. A second aspect that requires consideration is the fact that cephalograms were obtained from patients in the upright position. The use of supine rather than upright cephalograms has been reported to account for the influence of posture on upper airway dimensions (Johal and

Battagel, 1999). This may explain why pharyngeal dimensions and hyoid bone position could not be implicated in the outcome of oral appliance therapy. However, the added value of supine cephalometry should also be considered in the light of its time-consuming and operator-sensitive character.

Finally, it should be recognized that we evaluated primarily predictors of the effect of therapy on the apnea-hypopnea index. Other important outcomes—like effects on neurobehavioral or cardiovascular parameters (*e.g.,* sleepiness or hypertension) or therapeutic compliance—were not evaluated in the present study.

In conclusion, the outcome of CPAP therapy could not be predicted reliably with the clinical and polysomnographic variables evaluated in this study. Conversely, predictive variables obtained from the univariate and multivariate analysis, including obesity, disease severity, and certain craniofacial characteristics (mandibular retrognathism in particular), were valuable for pre-selecting suitable candidates for oral appliance therapy.

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