

Prediction of Mandibular Advancement Device Response Using CPAP Pressure in Different Polysomnographic Phenotypes

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Objective: Both continuous positive airway pressure (CPAP) pressure and polysomnographic phenotypes have been associated with mandibular advancement device (MAD) treatment response, but the precise relationship has not been fully elucidated. We hypothesized that utilizing CPAP pressure would predict the MAD response in treatment-naïve patients with moderate-severe obstructive sleep apnea (OSA), and the MAD response would be associated with two polysomnographic phenotypes, including sleep stage dependency and positional dependency.

Methods: OSA treatment-naïve patients with an apnea-hypopnea index (AHI) ≥ 15 /h who declined CPAP treatment and received MAD treatment for 3–6 months were enrolled. The MAD treatment response was defined as 1) residual AHI under MAD (AHI_{MAD}) < 5 /h and 2) AHI_{MAD} < 10 /h. Logistic regression was applied to identify the association between CPAP pressure and MAD treatment responders. The predictability of the MAD responder status utilizing CPAP pressure was assessed with the area under the receiver operating characteristic (AUROC).

Results: A total of 128 enrolled patients (AHI ≥ 30 /h in 74.2%) were recruited, of whom 119 patients and 80 patients were included for analysis of sleep stage and positional dependency, respectively. REM-predominant OSA had lower AHI than stage-independent OSA, while the supine-predominant phenotype had lower anthropometrics than the nonpositional-dependent phenotype. The response rates for AHI_{MAD} < 5 /h and AHI_{MAD} < 10 /h were 25.8% and 48.4%, respectively. Lower anthropometrics, baseline AHI, and supine predominance were associated with the responder status, while CPAP pressure was an independent predictor. The AUROCs for the prediction of AHI_{MAD} < 5 /h and AHI_{MAD} < 10 /h responders were 0.635 and 0.664, respectively. Utilizing a CPAP level > 14 cmH₂O as the cutoff to predict criterion 1 and 2 nonresponders, the sensitivity was 93.9% and 95.2%, respectively.

Conclusion: In treatment-naïve patients with moderate-severe OSA, the supine-predominant phenotype and lower CPAP pressure were associated with the MAD response, while the sleep stage dependency phenotype was not. Utilization of a CPAP level > 14 cmH₂O could be a sensitive measure to identify nonresponders.

Keywords: continuous positive airway pressure, mandibular advancement device, polysomnography, phenotype, sleep apnea, obstructive

Introduction

Obstructive sleep apnea (OSA) is a common disease with a 9–38% prevalence in the general population.¹ It is characterized by the recurrent collapse of the upper airway during sleep, resulting in chronic intermittent hypoxia and

sleep fragmentation. Untreated OSA is associated with hypertension, cardiovascular mortality, motor vehicle accidents, diabetes mellitus, and impaired quality of life.^{2–4} Continuous positive airway pressure (CPAP) therapy is the standard treatment for moderate-severe OSA and can improve daytime sleepiness, quality of life, and blood pressure.^{5–9} However, the efficacy of CPAP is often offset by suboptimal adherence.¹⁰ Mandibular advancement device (MAD) treatment is an alternative for patients who refuse or cannot tolerate CPAP therapy. The response to MAD treatment is defined according to the residual apnea-hypopnea index (AHI) on MAD treatment (AHI_{MAD}) and AHI reduction: criterion 1, $AHI_{MAD} < 5/h$ with a reduction $> 50\%$; criterion 2, $AHI_{MAD} < 10/h$ with a reduction $> 50\%$, and criterion 3, a reduction in AHI $> 50\%$. The response rates to the three criteria have been reported to be 48%, 64%, and 35%, respectively, which highlights the importance of patient selection.^{11,12} Therefore, a biomarker is needed to identify patients who would benefit from MAD treatment.

Factors associated with a favorable response to MAD treatment include younger age, female sex, lower AHI, body mass index (BMI) and neck circumference,^{11–15} craniofacial features (eg, angle between the anterior cranial base and mandibular plane),¹⁶ extent of mandibular advancement,¹⁷ and upper airway response (collapsibility, loop gain, arousal threshold, compensation, and ventilatory response to arousal).¹⁸ Few studies have linked polysomnographic phenotypes, including sleep stage dependency and positional dependency, to MAD treatment response. Three studies have shown that positional-predominant OSA was more likely to have a better response to MAD therapy than non-positional OSA,^{19–21} while one study showed the opposite findings.¹⁴ One study reported that rapid eye movement (REM)-predominant OSA was associated with a lower MAD treatment response,¹⁴ while another reported no association between sleep-stage dependency and MAD treatment response.²² The inconsistencies are partly related to differences in the definitions of sleep stage dependency, positional dependency and MAD type.^{14,15,19–22}

Recent studies have reported that the CPAP pressure was associated with the MAD treatment response.^{23–26} Our previous study identified that higher BMI and higher CPAP pressure were associated with $AHI_{MAD} \geq 15/h$.²⁷ Tsuiki et al reported that a fixed pressure ≥ 10.5 cmH₂O could predict no response to MAD therapy across all three criteria in male Japanese patients adhering to CPAP treatment.²⁶ Sutherland et al reported that a fixed pressure ≥ 13 cmH₂O was predictive of criterion 1 or 2 nonresponders in treatment-naïve Caucasian patients.²⁵ Additionally, Storesund et al reported that a maximum autoadjusting CPAP (APAP) level > 12 cmH₂O could predict criterion 1 and 2 nonresponders in Caucasian patients nonadherent to APAP.²⁴ Moreover, Dort et al reported that CPAP level > 9 cmH₂O, obtained from both fixed pressure and APAP, could predict criterion 1 nonresponders in a variety of Caucasian patients, including those who were treatment naïve; had failed CPAP treatment; had an unsuccessful surgery; and were using a MAD as a temporary alternative.²³ These inconsistencies in CPAP level cutoff values may be related to the heterogeneity of the participants, treatment prior to MAD treatment, and the method of determining the CPAP pressure.

To the best of our knowledge, no study has reported the association between MAD treatment response and CPAP pressure and the polysomnographic phenotype of sleep stage and positional dependency. Moreover, it is unclear whether the predictability of the MAD treatment response with CPAP pressure varies across different polysomnographic phenotypes. We hypothesized that the level of CPAP was predictive of the MAD treatment response independent of the polysomnographic phenotype (sleep stage dependency and positional dependency) in treatment-naïve patients with moderate-severe OSA. The present study aimed to test the association between CPAP pressure and MAD treatment responder status across different sleep stages and positional dependency phenotypes. We also tested the predictability of the MAD response utilizing CPAP pressure.

Methods

Study Setting

This retrospective study was conducted at the Center of Sleep Disorder of National Taiwan University Hospital (NTUH). The routine protocol for treating patients with moderate-severe OSA ($AHI \geq 15/h$) has previously been reported.²⁷ Briefly, patients underwent 2-week fixed-pressure CPAP, where therapeutic pressure was obtained by overnight manual titration. Patients who declined CPAP treatment were referred to an orthodontist for MAD treatment. Three to six months after MAD delivery, the patient underwent follow-up polysomnography (PSG) while on MAD to determine the response to MAD treatment.

Participants and Data Collection

Medical records of patients referred for suspected OSA from January 1, 2008, to December 31, 2017, were reviewed for eligibility. Patients who fulfilled all the following inclusion criteria were eligible for the study: 1) age 20–80 years; 2) diagnosed moderate-severe OSA; 3) no previous treatment for OSA; 3) CPAP titration to determine the therapeutic pressure; and 4) refusal of CPAP treatment and subsequent receipt of MAD treatment for 3–6 months. Patients were excluded if they fulfilled one of the following exclusion criteria: 1) failed CPAP titration; 2) residual AHI $\geq 5/h$ at a CPAP level of 20 cmH₂O; 3) MAD treatment period < 3 months; and 4) refusal of follow-up PSG after MAD for 3–6 months ([Figure S1](#)).

Data extracted from collected medical records included demographics, anthropometrics [body mass index (BMI), neck and waist circumference], subjective sleepiness, PSG parameters, and CPAP pressure. All methods were carried out in compliance with the Declaration of Helsinki and the data remained confidential. The study protocol was approved by the Research Ethics Committee of NTUH (protocol number 20161218ORINA). Because it was a retrospective study, the need for consent from the participants was waived by the Research Ethics Committee.

Polysomnographic Phenotype

Full-night PSG (Embla N7000, Medcare Flaga, Reykjavik, Iceland) was performed in the sleep lab following the protocol as previously described.²⁷ Apnea was defined as the absence of airflow for ≥ 10 sec, and hypopnea was defined as a 30% decrease in airflow for ≥ 10 sec associated with a $\geq 4\%$ reduction in arterial oxygen saturation. The oxygen desaturation index was defined as the number of times that pulse oxygen saturation decreased by $\geq 4\%$ per hour.²⁸

The polysomnographic phenotypes in the present study included positional dependency and sleep stage dependency. Patients with a time in supine or nonsupine sleep <15 min were excluded from the analysis of positional dependency, while patients with a time in REM or NREM <15 min were excluded from the analysis of sleep stage dependency. Positional dependency was defined as the ratio of the AHI during supine sleep (AHI_{supine}) to the AHI during nonsupine sleep (AHI_{nonsupine}). Supine-predominant OSA was defined as an AHI_{supine}/AHI_{non-supine} ratio ≥ 2 , and nonpositional OSA was defined as an AHI_{supine}/AHI_{non-supine} ratio < 2.

Sleep stage dependency was defined as the ratio of AHI during REM (AHI_{REM}) to AHI during NREM (AHI_{NREM}). Because the definition of sleep stage dependency was inconsistent across previous reports, two definitions for the sleep stage phenotype were applied in the present study. First, REM-predominant OSA was defined as an AHI_{REM}/AHI_{NREM} ratio ≥ 2 , and NREM-predominant OSA was defined as an AHI_{REM}/AHI_{NREM} ratio ≤ 0.5 . Stage-independent OSA was defined as a ratio between 2 and 0.5.^{14,29,30} Second, REM-related OSA (AHI_{REM}/AHI_{NREM} ratio ≥ 2) and NREM-related OSA (AHI_{REM}/AHI_{NREM} ratio < 2) were defined.^{31–33}

Determination of CPAP Pressure

The therapeutic pressure was determined by overnight manual titration using BiPAP Synchrony™ (Respironics Inc., Murrysville, PA, USA) following a published protocol.²⁷ The manual titration started with the CPAP mode at a pressure of 4 cmH₂O. The pressure was then increased in 1 cmH₂O increments over 10 min to eliminate obstructive events, including apnea, hypopnea, and snoring, and to minimize electroencephalography arousals until 30 min had elapsed without any obstructive events. Optimal pressure was defined as the pressure at which the AHI was < 5/h for 15 min, including supine REM sleep. The choice of interface started with a nasal mask, which was changed to an oronasal mask if a significant mouth leak was detected.

MAD Treatment

The MAD used in the present study was a monobloc that was fabricated as previously described to achieve 75% of the maximum mandibular advancement, and the vertical opening was limited to 5 mm.²⁷ The design of the MAD remained the same during the study period. MAD was delivered four weeks after taking a dental impression. The patients visited the clinic at the 1st, 3rd, 6th, and 12th months after MAD delivery, where the self-reported average nightly usage was recorded at every follow-up visit.

Outcomes

The outcome was the MAD treatment response, which was evaluated by reduction in the baseline AHI and residual AHI (AHI_{MAD}) on the follow-up PSG. The response to MAD treatment was defined by two criteria: criterion 1, residual $AHI_{MAD} < 5/h$ with AHI reduction $> 50\%$; criterion 2, $AHI_{MAD} < 10/h$ with AHI reduction $> 50\%$.^{23,25,26}

Data Analysis

Factors associated with positional dependency were determined by comparing the clinical features between supine-predominant and nonpositional-dependent OSA; between REM-predominant, NREM-predominant, and stage-independent OSA; and between REM-related and NREM-related OSA. Factors associated with MAD treatment response were determined by comparing the clinical features between the responders and nonresponders.

Correlations between clinical features, CPAP pressure, baseline AHI, and AHI_{MAD} were evaluated using Spearman's correlation analysis. The association between CPAP pressure and MAD treatment response was determined with logistic regression. Multiple logistic regression was conducted with age, sex, BMI, baseline AHI, CPAP pressure, sleep stage dependency, positional dependency, and factors significant at the 0.1 level in univariate analysis entered into the regression model.

The ability of the CPAP pressure to predict the MAD treatment response was assessed using the area under the receiver operating characteristic curve (AUROC). In addition, the best cutoff CPAP level was based on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and accuracy.

Continuous variables are expressed as medians (interquartile ranges [IQRs]), and categorical variables are expressed as numbers (percentages). The Wilcoxon-Mann-Whitney *U*-test, chi-square test or Fisher's exact test with Bonferroni correction, and the Kruskal-Wallis test with the Bonferroni post hoc method were used as appropriate. A two-tailed *P* value < 0.05 was considered to be statistically significant. All statistical analyses were conducted using SPSS version 23 (SPSS, Chicago, IL, USA).

Data Availability Statement

The data of individual subjects that are not publicly available may be obtained from the corresponding author upon reasonable request.

Results

Clinical Features of the Participants

[Figure S1](#) shows the recruitment flowchart. A total of 5796 patients with moderate-severe OSA aged 20–80 years were screened. A total of 4859 patients were newly diagnosed and had never been treated for OSA (treatment-naïve). Among the 1559 who underwent CPAP titration, 53 had titration failure, and 151 had a residual AHI $> 5/h$ at a pressure of 20 cmH₂O. Among the 1355 patients with a residual AHI $< 5/h$, 144 received MAD treatment. A total of 128 patients who completed 3–6 months of MAD treatment and underwent follow-up PSG were recruited for the study.

[Table 1](#) shows the clinical features of these 128 patients. The patients were middle-aged, predominantly male (82%), and overweight-obese with a median BMI of 26.8 kg/m² (IQR, 24.2–28.6). The median baseline AHI was 38.9/h (IQR, 29.3–52.1), with an AHI $\geq 30/h$ observed in 74.2% of the patients. The median CPAP level was 9 cmH₂O (IQR, 7–12), and the median AHI_{MAD} was 10.2/h (IQR, 4.7–20.3). Compared to the male patients, female patients were older, had lower neck and waist circumferences, had more excessive daytime sleepiness (EDS), and had a higher AHI_{REM} .

Polysomnographic Phenotype

Nine patients with time in REM < 15 mins were excluded from the analysis of the sleep stage dependency phenotype. Among the remaining 119 patients, stage independency accounted for 71.4%, while REM predominance and NREM predominance accounted for 16.8% and 11.8%, respectively. Patients with REM-predominant OSA tended to have

Table 1 Comparisons of the 105 Male and 23 Female Enrolled Patients

Feature	All (N=128)	Male (N=105)	Female (N=23)	P
Age (years)	54.5 (48.0–61.8)	53.4 (46.0–60.6)	57.4 (53.6–61.9)	0.037
BMI (kg/m ²)	26.8 (24.2–28.6)	26.8 (24.2–28.6)	27.1 (24.7–28.8)	0.884
Neck circumference (cm)	38.5 (36.0–40.0)	39.0 (37.0–41.0)	33.0 (32.0–36.0)	<0.001
Waist circumference (cm)	91.5 (86.0–96.0)	92.0 (88.0–98.0)	87.0 (78.0–92.0)	0.001
ESS	10 (7–13)	9 (7–12)	11 (9–14)	0.184
EDS, n (%)	46 (35.9)	33 (34.4)	13 (61.9)	0.019
Polysomnographic parameter				
REM (%)	17.0 (11.6–21.5)	16.9 (11.6–21.2)	19.3 (12.1–24.2)	0.507
AHI (/h)	38.9 (29.3–52.1)	39.5 (30.4–51.7)	32.4 (27.4–50.1)	0.446
≥ 30/h, n (%)	95 (74.2)	79 (75.2)	16 (69.6)	0.573
AHI _{REM} (/h) [#]	48.0 (34.5–60.2)	46.7 (33.5–58.9)	59.7 (47.7–63.8)	0.021
AHI _{NREM} (/h) [#]	36.5 (26.8–52.9)	37.2 (28.0–53.5)	29.0 (20.9–45.9)	0.104
AHI _{supine} (/h) ^{&}	48.4 (33.9–65.2)	49.9 (34.3–65.6)	41.7 (32.4–56.2)	0.510
AHI _{non-supine} (/h) ^{&}	28.9 (7.3–53.6)	30.6 (8.9–61.8)	22.1 (5.2–34.6)	0.206
Sleep stage dependency, n [#]	119	98	21	0.083
REM-predominant, n (%)	20 (16.8)	13 (13.3)	7 (33.3)	
NREM-predominant, n (%)	14 (11.8)	12 (12.2)	2 (9.5)	
Stage-independent, n (%)	85 (71.4)	73 (85.9)	12 (57.1)	
Positional dependency, n ^{&}	80	67	13	0.762
Supine-predominant, n (%)	40 (50.0)	33 (49.3)	7 (53.8)	
Nonpositional, n (%)	40 (50.0)	34 (50.7)	6 (46.2)	
CPAP (cmH ₂ O)	9.0 (7.0–12.0)	9.0 (7.0–12.0)	9.0 (7.0–11.5)	0.808
AHI _{MAD} (/h)	10.2 (4.7–20.3)	10.2 (4.3–21.3)	11.1 (6.8–17.8)	0.826

Notes: Data are presented as the median (interquartile range) or number (percentage). [#]Patients with time in REM or NREM <15 minutes were excluded from the analysis; [&]Patients with a time in supine sleep <15 minutes or nonsupine sleep <15 minutes were excluded from the analysis.

Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; REM (%), rapid eye movement percentage of total sleep time; AHI, apnea-hypopnea index; AHI_{REM}, apnea-hypopnea index during the rapid eye movement stage; AHI_{NREM}, apnea-hypopnea index during the nonrapid eye movement stage; AHI_{supine}, apnea-hypopnea index during the supine position; AHI_{non-supine}, apnea-hypopnea index during nonsupine positions; REM, rapid eye movement; NREM, non-rapid eye movement; CPAP, continuous positive airway pressure; AHI_{MAD}, residual apnea-hypopnea index under MAD treatment.

a higher percentage of females and lower baseline AHI than sleep stage-independent patients. Patients with NREM-predominant OSA had a lower percentage of criterion 1 and 2 responders. Age, sex, anthropometrics, and CPAP pressure were similar in the three sleep-stage dependency phenotypes (Table 2). For the other definition of sleep stage dependency, 20 patients had REM-related OSA and 99 had NREM-related OSA, and REM-related OSA had a higher percentage of female patients and lower baseline AHI but a similar percentage of criterion 1 and 2 responders than NREM-related OSA (Table S1).

A total of 48 patients with supine sleep and nonsupine sleep < 15 mins were excluded from the analysis of the positional dependency phenotype. In the remaining 80 patients, supine-predominant and nonpositional OSA accounted

Table 2 Comparison of Patients with Different Sleep Stage Dependency and Positional Dependency Phenotypes

Feature	Sleep Stage Dependency (N=119)				Positional Dependency (N=80)		
	REM-Predominant (N=20)	NREM-Predominant (N=14)	Stage-Independent (N=85)	P	Supine-Predominant (N=40)	Nonpositional (N=40)	P
Age (years)	57.1 (52.7–62.2)	57.8 (49.6–62.9)	52.8 (47.6–58.7)	0.185	57.3 (51.0–62.6)	51.7 (43.1–57.1)	0.024
Male, n (%)	13 (65.0)	12 (85.7)	73 (85.9)	0.083	33 (82.5)	34 (85.0)	0.762
BMI (kg/m ²)	27.4 (26.1–28.4)	26.8 (24.7–27.8)	26.3 (23.8–28.9)	0.339	26.6 (24.0–28.4)	27.3 (24.7–29.5)	0.201
Neck circumference (cm)	38.5 (34.0–40.0)	39.0 (36.0–40.0)	38.0 (36.0–40.0)	0.960	38.0 (36.0–40.0)	39.5 (37.5–41.5)	0.044
Waist circumference (cm)	95.0 (87.5–100.0)	90.5 (87.0–95.0)	91.0 (86.0–98.0)	0.471	90.0 (86.0–95.0)	95.0 (89.0–100.8)	0.014
ESS	10 (8.5–15)	9 (7–12)	9 (6.5–12)	0.372	9 (6–13)	10 (8.5–13)	0.084
EDS, n (%)	7 (43.8)	5 (35.7)	29 (36.7)	0.858	12 (31.6)	16 (44.4)	0.254
Polysomnographic parameter							
REM (%)	20.0 (14.3–24.3)	17.1 (13.6–23.0)	17.1 (11.6–21.0)	0.252	18.5 (14.5–22.5)	14.9 (11.3–21.5)	0.072
AHI (/h)	27.6 (22.6–30.5) ^{^^}	37.4 (26.3–43.9)	44.4 (33.4–58.4)	<0.001	35.9 (30.3–45.2)	36.8 (27.1–50.2)	0.690
≥ 30/h, n (%)	6 (30) [^]	10 (71.4)	74 (87.1)	<0.001	31 (77.5)	28 (70.0)	0.446
AHI _{REM} (/h)	56.7 (49.2–62.7)	13.2 (6.3–16.5) ^{***}	51.5 (38.8–61.3) [§]	<0.001	–	–	
AHI _{NREM} (/h)	19.4 (16.6–22.3) ^{^^}	40.9 (29.1–52.1) ^{***}	42.8 (32.6–58.0)	<0.001	–	–	
AHI _{supine} (/h)	–	–	–		48.4 (35.5–65.5)	46.4 (29.7–65.1)	0.419
AHI _{non-supine} (/h)	–	–	–		7.3 (2.2–14.8)	53.6 (36.1–81.9)	<0.001
CPAP (cmH ₂ O)	7.5 (6.0–12.0)	10.0 (8.0–13.0)	9 (7.0–12.0)	0.440	9.0 (6.0–11.5)	9.0 (8.0–11.0)	0.313
AHI _{MAD} (/h)	10.9 (5.8–17.8)	14.1 (8.1–24.4)	9.9 (4.2–20.4)	0.232	10.7 (4.0–20.1)	14.2 (7.9–22.9)	0.058
AHI _{MAD} <5/h, reduction >50%, n (%)	4 (20)	0	26 (30.6) [§]	0.043	14 (35.0)	3 (7.5)	0.003
AHI _{MAD} <10/h reduction >50%, n (%)	9 (45.0)	4 (28.6)	43 (50.6)	0.304	19 (47.5)	14 (35.0)	0.256

Notes: Data are presented as the median (interquartile range) or number (percentage). Kruskal–Wallis test with the Bonferroni post hoc method: ***REM-predominant vs NREM-predominant; $p < 0.001$; [§]NREM-predominant vs stage independent; $p < 0.001$; ^{^^}Stage independent vs REM-predominant; $p < 0.001$. Chi-square test with Bonferroni correction: [^]Stage independent vs REM-predominant; $p < 0.017$; [§]NREM-predominant vs stage-independent; $p < 0.017$.

Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; REM (%), rapid eye movement percentage of total sleep time; AHI, apnea-hypopnea index; AHI_{REM}, apnea-hypopnea index during the rapid eye movement stage; AHI_{NREM}, apnea-hypopnea index during the nonrapid eye movement stage; AHI_{supine}, apnea-hypopnea index during supine sleep; AHI_{non-supine}, apnea-hypopnea index during nonsupine sleep; CPAP, continuous positive airway pressure; AHI_{MAD}, residual apnea-hypopnea index under MAD treatment.

Table 3 Comparison of Criterion 1 and 2 Responders and Nonresponders

Feature	AHI _{MAD} <5/h, Reduction >50%			AHI _{MAD} <10/h, Reduction >50%		
	Responder (N=33)	Nonresponder (N=95)	P	Responder (N=62)	Nonresponder (N=66)	P
Age (years)	57.1 (49.9–62.0)	53.7 (47.8–60.5)	0.299	54.2 (45.8–60.3)	54.5 (50.0–62.2)	0.507
Male, n (%)	29 (87.9)	76 (80.0)	0.310	52 (83.9)	53 (80.3)	0.599
BMI (kg/m ²)	23.9 (23.4–27.1)	27.3 (25.4–29.0)	<0.001	25.5 (23.6–27.4)	27.7 (25.8–29.4)	<0.001
Neck circumference (cm)	37.0 (35.0–39.0)	39.0 (36.0–41.0)	0.023	37.0 (35.0–39.0)	39.5 (36.3–42.0)	0.003
Waist circumference (cm)	88.0 (83.5–92.5)	93.0 (88.0–100.0)	0.004	89.0 (84.5–93.5)	95.0 (89.0–100.8)	0.001
ESS	11 (8–15)	9 (7–12)	0.156	10 (7–13.5)	9.5 (6–12)	0.470
EDS, n (%)	17 (51.5)	29 (34.5)	0.090	23 (39.0)	23 (39.7)	0.941
Polysomnographic parameter						
REM (%)	17.2 (13.3–21.3)	16.8 (11.3–21.7)	0.571	17.2 (12.3–21.5)	16.8 (11.5–21.5)	0.754
AHI (/h)	36.6 (30.4–47.4)	39.5 (28.6–54.0)	0.479	32.4 (26.2–46.8)	43.4 (32.3–57.6)	0.005
≥ 30/h, n (%)	25 (75.8)	70 (73.7)	0.815	40 (64.5)	55 (83.3)	0.015
AHI _{REM} (/h) [#]	46.4 (39.1–59.1)	51.5 (34.3–60.9)	0.886	44.4 (29.4–58.5)	54.4 (37.9–63.2)	0.071
AHI _{NREM} (/h) [#]	34.8 (28.0–43.3)	37.3 (26.6–56.7)	0.377	34.0 (24.4–43.1)	43.3 (29.1–57.7)	0.018
AHI _{supine} (/h) ^{&}	38.0 (35.4–60.7)	49.9 (31.8–65.2)	0.724	36.1 (28.4–52.9)	53.0 (40.2–66.8)	0.002
AHI _{non-supine} (/h) ^{&}	4.1 (1.5–14.3)	34.4 (13.9–65.7)	<0.001	7.7 (2.2–34.7)	34.9 (14.7–71.7)	0.001
Sleep stage dependency, n [#]	30	89	0.043	56	63	0.304
REM-predominant, n (%)	4 (13.3)	16 (18.0)		9 (16.1)	11 (17.4)	
NREM-predominant, n (%)	0	14 (15.7) ^o		4 (7.1)	10 (15.8)	
Stage-independent, n (%)	26 (86.7)	59 (69.3) ^o		43 (76.8)	42 (66.7)	
Positional dependency, n ^{&}	17	63	0.003	33	47	0.256
Supine-predominant, n (%)	14 (82.4)	26 (41.3)		19 (57.6)	21 (44.7)	
Nonpositional, n (%)	3 (17.6)	37 (58.7)		14 (42.4)	26 (55.3)	
CPAP (cmH ₂ O)	8.0 (5.0–11.0)	9.0 (7.5–12.0)	0.020	8.0 (6.0–11.0)	9.5 (8.0–13.0)	0.001
AHI _{MAD} (/h)	2.2 (0.9–3.4)	13.5 (9.2–24.2)	<0.001	4.6 (2.1–6.9)	20.0 (13.1–35.3)	<0.001

Notes: Data are presented as the median (interquartile range) or number (percentage). [#]Patients with time in REM or NREM ≤15 min were excluded from the analysis; [&]Patients with time in supine sleep ≤15 min or non-supine sleep ≤15 min were excluded from the analysis. Chi-square test with Bonferroni correction: ^oResponder vs nonresponder: $p < 0.017$.

Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; REM (%), rapid eye movement percentage of total sleep time; AHI, apnea-hypopnea index; AHI_{REM}, apnea-hypopnea index during the rapid eye movement stage; AHI_{NREM}, apnea-hypopnea index during the nonrapid eye movement stage; AHI_{supine}, apnea-hypopnea index during supine sleep; AHI_{non-supine}, apnea-hypopnea index during non-supine sleep; CPAP, continuous positive airway pressure; AHI_{MAD}, residual apnea-hypopnea index under MAD treatment.

for half each. Compared with the patients with nonpositional OSA, those with supine-predominant OSA were older, had lower neck and waist circumferences, and had a higher percentage of criterion 1 responders (Table 2).

Response to MAD Treatment

The percentages of criterion 1 and 2 responders were 25.8% and 48.4%, respectively. For criteria 1 and 2, responders had lower anthropometrics and lower CPAP pressure but a similar age and percentage of males compared with nonresponders. Compared with nonresponders, criterion 2 responders had a lower baseline AHI, lower percentage of severe OSA, and lower AHI_{NREM}, AHI_{supine} and AHI_{non-supine}, while AHI_{non-supine} was lower in criterion 1 responders. Regarding

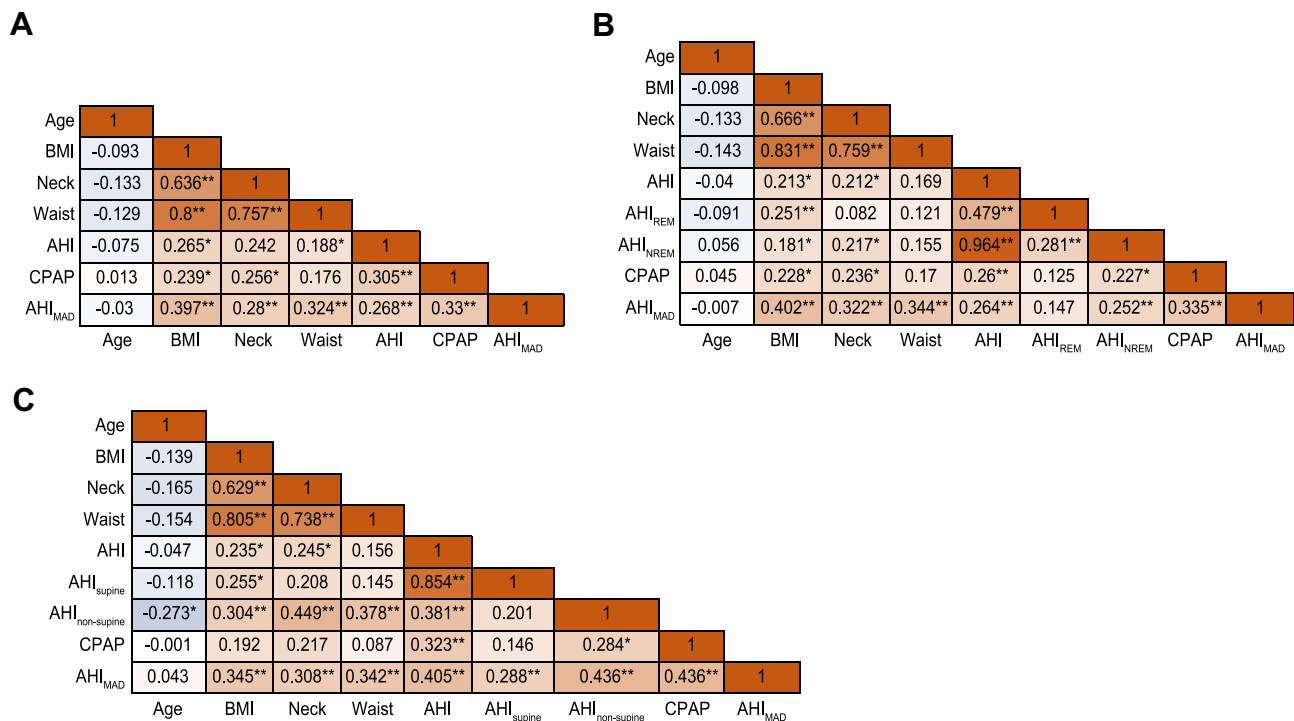


Figure 1 Heatmap of the correlation between clinical features, CPAP pressure, and AHI_{MAD} in (A) all 128 patients and (B) 119 patients included for analysis of sleep stage dependency (C) 80 patients included for analysis of positional dependency. **p <0.01, *p <0.05. **Abbreviations:** BMI, body mass index; Neck, neck circumference; Waist, waist circumference; AHI, apnea-hypopnea index; AHI_{REM}, apnea-hypopnea index during the rapid eye movement stage; AHI_{NREM}, apnea-hypopnea index during the nonrapid eye movement stage; AHI_{MAD}, residual apnea-hypopnea index during mandibular advancement device treatment.

sleep stage dependency, stage-independent OSA was the most common phenotype in both responders and nonresponders for both criterion 1 and 2. For criterion 1 responders, there was a higher percentage of stage-independent and no NREM-predominant OSA. For criterion 1 responders, the percentage of supine-predominant OSA was higher than that of nonresponders (Table 3).

Factors Associated with the MAD Treatment Response

Spearman's correlation showed that the AHI_{MAD} was positively correlated with BMI, neck and waist circumferences, baseline AHI, and CPAP pressure. CPAP pressure was correlated with BMI, neck circumference, and baseline AHI (Figure 1A). For patients included in the analysis of sleep stage dependency, AHI_{NREM} was correlated with both AHI_{MAD} and CPAP pressure, while the AHI_{REM} was not (Figure 1B). For patients included in the analysis of positional dependency, AHI_{supine} and AHI_{non-supine} were correlated with AHI_{MAD}, while AHI_{non-supine} was correlated with CPAP pressure (Figure 1C).

Univariate analysis revealed that BMI, neck circumference, and baseline AHI were associated with CPAP, while age, sex, and waist circumference were not in all patients. Neither the sleep stage dependency nor positional dependency phenotype was associated with CPAP pressure (Table S2). Lower anthropometrics and CPAP pressure were associated with criterion 1 and 2 responders, while lower baseline AHI was associated with criterion 2 responders. Compared with stage-independent OSA, REM-predominant and NREM-predominant OSA has similar associations with responders. Compared with nonpositional OSA, supine-predominant OSA was associated with criterion 1 responders (Table S3).

Multivariable analysis was applied to identify the association between CPAP pressure and MAD treatment responders. The unadjusted model showed that lower CPAP pressure was associated with the MAD treatment response. For criterion 1 responders, the association was not observed after adjustment for BMI in either all groups or patients included for analysis of sleep stage dependency. However, for patients included for positional

Table 4 Multivariable Logistic Regression to Identify the Association Between CPAP and MAD Treatment Responder

Model	Model Variable	AHI _{MAD} <5/h, Reduction >50%			AHI _{MAD} <10/h, Reduction >50%		
		OR (95% CI)	P	R ²	OR (95% CI)	P	R ²
All (N=128)							
1	CPAP	0.885 (0.783–1.000)	0.049	0.050	0.848 (0.763–0.943)	0.002	0.108
2	Model 1 and age and sex	0.882 (0.782–0.995)	0.041	0.089	0.848 (0.763–0.943)	0.002	0.113
3	Model 2 and BMI	0.912 (0.805–1.033)	0.145	0.221	0.870 (0.780–0.970)	0.012	0.209
4	Model 3 and baseline AHI	0.905 (0.796–1.029)	0.128	0.223	0.881 (0.788–0.984)	0.025	0.218
Sleep stage dependency (N=119)							
1	CPAP	0.874 (0.767–0.995)	0.042	0.059	0.847 (0.759–0.945)	0.003	0.110
2	Model 1 and age and sex	0.871 (0.767–0.991)	0.035	0.085	0.849 (0.760–0.948)	0.004	0.116
3	Model 2 and BMI	0.896 (0.784–1.024)	0.108	0.235	0.870 (0.776–0.975)	0.016	0.224
4	Model 3 and baseline AHI	0.896 (0.783–1.026)	0.113	0.235	0.882 (0.786–0.989)	0.032	0.237
5	Model 4 and sleep stage dependency	0.919 (0.798–1.059)	0.242	0.320	0.890 (0.791–1.001)	0.052	0.265
Positional dependency (N=80)							
1	CPAP	0.745 (0.592–0.938)	0.012	0.172	0.776 (0.657–0.915)	0.003	0.202
2	Model 1 and age and sex	0.745 (0.591–0.939)	0.013	0.215	0.770 (0.648–0.915)	0.003	0.215
3	Model 2 and BMI	0.744 (0.583–0.951)	0.018	0.287	0.783 (0.653–0.938)	0.008	0.318
4	Model 3 and baseline AHI	0.754 (0.587–0.968)	0.027	0.290	0.824 (0.668–0.987)	0.035	0.392
5	Model 4 and position dependency	0.779 (0.609–0.996)	0.047	0.366	0.828 (0.689–0.995)	0.044	0.402

Abbreviations: CPAP, continuous positive airway pressure; BMI, body mass index; AHI, apnea-hypopnea index; OR, odds ratio.

dependency, a lower CPAP pressure was associated with responder status, even with further adjustment for position dependency. For criterion 2, CPAP pressure was associated with responder status after full adjustment, including age, sex, BMI, baseline AHI, and sleep stage dependency or positional dependency (Table 4).

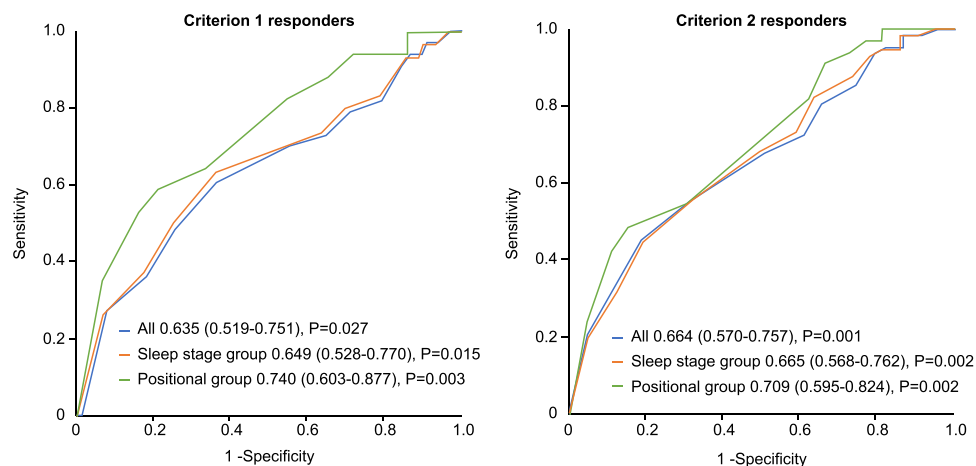


Figure 2 AUROC in the prediction of MAD responder status with CPAP pressure.

Table 5 Utilizing CPAP to Predict MAD Treatment Nonresponders with Criteria 1 and 2 According to Different Cutoff Values

Pressure Cutoff (cmH ₂ O)	8	9	10	11	12	13	14	15
CPAP >cutoff, no.	74	53	43	35	26	18	15	12
AHI_{MAD} <5/h, reduction >50%								
Sensitivity (%)	60.6	69.7	72.7	78.8	81.8	90.9	93.9	93.9
Specificity (%)	64.2	45.3	35.8	29.5	21.1	15.8	13.7	10.5
PPV (%)	37.0	30.7	28.2	28.0	26.5	27.3	27.4	26.7
NPV (%)	82.4	81.1	79.1	80.0	76.9	83.3	86.7	83.3
LR+	1.69	1.27	1.13	1.12	1.04	1.08	1.09	1.05
LR-	0.61	0.67	0.76	0.72	0.86	0.58	0.44	0.58
Accuracy (%)	63.3	51.6	45.3	42.2	36.7	35.2	34.4	32.0
AHI_{MAD} <10/h, reduction >50%								
Sensitivity (%)	54.8	67.7	72.6	80.6	85.5	93.5	95.2	95.2
Specificity (%)	69.7	50.0	39.4	34.8	25.8	21.2	18.2	13.6
PPV (%)	63.0	56.0	52.9	53.8	52.0	52.7	52.2	50.9
NPV (%)	62.2	62.3	60.5	65.7	65.4	77.8	80.0	75.0
LR+	1.81	1.35	1.20	1.24	1.15	1.19	1.16	1.10
LR-	0.65	0.65	0.70	0.56	0.56	0.30	0.27	0.35
Accuracy (%)	62.5	58.6	55.5	57.0	54.7	56.3	55.5	53.1

Abbreviations: CPAP, continuous positive airway pressure; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

Prediction of MAD Responder Status with CPAP Pressure

Using CPAP pressure alone, the AUROC was 0.635 (95% CI, 0.519–0.751; $P=0.027$) and 0.664 (95% CI, 0.570–0.757; $P=0.001$) in predicting criterion 1 and 2 responders, respectively (Figure 2). To maximize the sensitivity in identifying patients who may benefit from MAD treatment, CPAP level >14 cmH₂O was selected as a cutoff value to predict both criterion 1 and 2 nonresponders, in which the minimal pressure reached the highest sensitivity. The prediction model of criterion 1 nonresponders had a sensitivity of 93.9%, specificity of 13.7%, and accuracy of 34.4%. The prediction model of criterion 2 nonresponders had a sensitivity of 95.2%, specificity of 18.2%, and accuracy of 55.5% (Table 5).

Discussion

This study aimed to test the association between CPAP pressure and MAD treatment responders across different sleep stages and positional dependency phenotypes in treatment-naïve patients with moderate-severe OSA. Our results showed that CPAP pressure was independently associated with responder status independent of sleep stage and positional dependency. Utilizing CPAP level >14 cmH₂O identified nonresponders to MAD treatment with a sensitivity of 93.9–95.2%. Moreover, supine-predominant OSA might be associated with the MAD treatment response.

The strength of our study included our recruitment of patients with moderate-severe OSA with AHI ≥ 30 /h in 74.2%. In this population, CPAP is superior to MAD for AHI reduction, and MAD is an alternative treatment for those who refuse or cannot tolerate CPAP treatment. Hence, a parameter of high sensitivity may maximize the chance of identifying candidates for MAD treatment. Moreover, only patients whose time in supine sleep, nonsupine sleep, REM and NREM ≥ 15 min were

included for analysis of sleep stage dependency and positional dependency, which enhanced the robustness of the phenotyping. Our results showed that CPAP pressure was a sensitive measure in identifying candidates for MAD treatment across different polysomnographic phenotypes.

In the present study, the response rates for criterion 1 and 2 were 25.8% and 48.4%, respectively. These rates were lower than the 53.8% and 69.2% reported in the study by Sutherland et al, who recruited 78 treatment-naïve Caucasian patients.²⁵ It was also lower than the 35.6% and 64.4% reported by Storesund et al, who recruited 87 Caucasian patients with moderate-severe OSA who were CPAP non-adherent.²⁴ This discrepancy may be related to the older age, higher baseline AHI, monoblock device use, longer duration of MAD treatment, and Asian ethnicity of our patients. Older age and higher baseline AHI have been associated with a poor response to MAD treatment,¹⁵ while Asian ethnicity has been associated with a higher craniofacial risk and higher AHI than BMI-matched Caucasians. These discrepancies may contribute to the lower response rate in the present study. Our response rate was similar to the result reported by Tsuiki et al. However, Tsuiki included patients who adhered to CPAP, whose upper airway may have less collapsibility and need a lower CPAP pressure. In contrast, we included treatment-naïve patients whose airway may have had higher collapsibility and who needed higher CPAP pressure to stent the airway. The difference in upper airway physiology was supported by the higher cutoff of CPAP level (14 cmH₂O) in the present study than that (10.5 cmH₂O) reported by Tsuiki et al.²⁶

Supine position-related fallback of the mandible, tongue, and soft palate could compromise the upper airway during sleep and could be reversed by mandibular protrusion with MAD treatment. Our study revealed that supine-predominant OSA was associated with a higher criterion 1 response, which is in line with the study by Chung et al.²¹ Both studies excluded patients with inadequate nonsupine sleep time, which may enhance the robustness of the definition of positional dependency. Sutherland et al¹⁴ reported that patients with supine-predominant OSA had a lower response rate, which was in contrast to the findings of our and other studies.^{19–21} The higher BMI and lower percentage of supine-predominant OSA in the study by Sutherland et al may contribute to the paradoxical findings.

Very few studies have investigated the association between stage-dependent OSA and MAD treatment response. Our results showed that the response rate was similar between different sleep stage dependencies for two definitions, which is in line with the findings of the study by Nishio et al.²² Our finding is in contrast with that reported by Sutherland et al, who showed that REM-predominant OSA had a lower response rate than NREM-predominant and stage-independent OSA.¹⁴ A possible explanation for the discrepancy in the results is that participants included in the study by Sutherland had more elderly females, higher BMI, and lower AHI, which may contribute to a higher percentage of REM-predominant OSA and higher residual AHI at REM. Despite the difference in response rate, all three studies confirmed that sleep stage dependency was not associated with MAD treatment response.

There were several limitations to this study. First, it is a retrospective study with a small cohort consisting of a small number of each polysomnographic phenotype, which may underestimate the power of the study. However, despite the possibility of underestimation, our study still confirmed the association between MAD response, positional dependency and CPAP pressure. Such an association may be more significant in the larger cohort. Second, patients with residual AHI $\geq 5/h$ at a CPAP level of 20 cmH₂O were excluded, and thus, our findings may not apply to patients treated with BPAP. Third, the MAD in the present study was a nontitratable monobloc with tongue backing. Even though a monobloc MAD has been reported to be noninferior to a titratable bibloc in reducing AHI,^{34,35} the CPAP pressure cutoff may be different between the two designs. Fourth, all participants were of Asian ethnicity recruited from a single-center hospital, and our findings need to be validated in a large-scale prospective study with a multiethnic population. Fifth, craniofacial features were not analyzed in the present study. However, craniofacial phenotyping has been demonstrated to have limited utility in enhancing models based on clinical variables alone,³⁶ and there is no universal standard to evaluate craniofacial features.¹⁵ Sixth, the CPAP pressure in the present study was obtained by overnight manual titration, which may limit the generalizability of its implications. Further study to validate the predictability of MAD treatment response utilizing pressure obtained from APAP may promote feasibility.

In conclusion, in patients with moderate-severe OSA who were treatment-naïve, CPAP pressure may be a sensitive predictor for identifying candidates for MAD treatment, and the predictability was consistent across the different polysomnographic phenotypes. Further study with the CPAP pressure obtained from APAP in a large-scale and multi-ethnicity cohort to validate the findings of the present study is warranted.

Rationale

Mandibular advancement devices (MADs) are alternative treatments to continuous positive airway pressure (CPAP) for patients with moderate-severe obstructive sleep apnea (OSA) who cannot tolerate CPAP therapy. Both CPAP pressure and positional phenotype (supine vs nonsupine) have been associated with the response to MAD treatment. However, the interplay between CPAP, polysomnographic phenotype (sleep stage dependency, positional dependency), and MAD treatment response has not been fully elucidated.

Study Impact

In patients with moderate-severe OSA who were treatment-naïve, the response rates for residual AHI under MAD ($AHI_{MAD} < 5/h$ and $AHI_{MAD} < 10/h$) were 25.8% and 48.4%, respectively. Supine dependency was associated with responders, while sleep stage dependency was not. CPAP pressure was an independent predictor, and utilization of CPAP level > 14 cmH_2O could be a sensitive measure for identifying nonresponders.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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