

Mandibular Advancement Device Treatment Efficacy Is Associated with Polysomnographic Endotypes

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Abstract

Rationale: Mandibular advancement device (MAD) treatment efficacy varies among patients with obstructive sleep apnea.

Objectives: The current study aims to explain underlying individual differences in efficacy using obstructive sleep apnea endotypic traits calculated from baseline clinical polysomnography: collapsibility (airflow at normal ventilatory drive), loop gain (drive response to reduced airflow), arousal threshold (drive preceding arousal), compensation (increase in airflow as drive increases), and the ventilatory response to arousal (increase in drive explained by arousal). On the basis of previous research, we hypothesized that responders to MAD treatment have a lower loop gain and milder collapsibility.

Methods: Thirty-six patients (median apnea–hypopnea index [AHI], 23.5 [interquartile range (IQR), 19.7–29.8] events/h) underwent baseline and 3-month follow-up full polysomnography, with MAD fixed at 75% of maximal protrusion. Traits were

estimated using baseline polysomnography according to Sands and colleagues. Response was defined as an AHI reduction $\geq 50\%$.

Results: MAD treatment significantly reduced AHI (49.7%_{baseline} [23.9–63.6], median [IQR]). Responders exhibited lower loop gain (mean [95% confidence interval], 0.53 [0.48–0.58] vs. 0.65 [0.57–0.73]; $P = 0.020$) at baseline than nonresponders, a difference that persisted after adjustment for baseline AHI and body mass index. Elevated loop gain remained associated with nonresponse after adjustment for collapsibility (odds ratio, 3.03 [1.16–7.88] per 1–standard deviation (SD) increase in loop gain [SD, 0.15]; $P = 0.023$).

Conclusions: MAD nonresponders exhibit greater ventilatory instability, expressed as higher loop gain. Assessment of the baseline degree of ventilatory instability using this approach may improve upfront MAD treatment patient selection.

Clinical trial registered with www.clinicaltrials.gov (NCT 01532050)

Keywords: obstructive sleep apnea; OSA; MAD; personalized medicine; pathophysiology

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Obstructive sleep apnea (OSA) is defined as repetitive upper-airway collapse (apnea) or narrowing (hypopnea) during sleep for a period of at least 10 seconds. OSA affects up to 9% of middle-aged women and 17% of middle-aged men (1) and is associated with several comorbidities, including, but not limited to, cardiovascular sequelae (2). OSA severity is quantified using the apnea-hypopnea index (AHI), capturing the frequency of apneas and hypopneas per hour of sleep (3).

Mandibular advancement device (MAD) therapy is the first-line non-continuous positive airway pressure (CPAP) treatment for patients with moderate-to-severe OSA (AHI ≥ 15 events/h). MAD therapy acts by protruding the lower jaw and increasing pharyngeal patency (4, 5). Typically, treatment involves custom-made, titratable MADs that allow individual treatment optimization (6–9). Although CPAP shows high efficacy in unselected patients, adherence is suboptimal (10, 11). In contrast, MAD adherence is high, but response to MAD treatment is highly patient dependent (12). A recent meta-analysis showed complete resolution of OSA, obtaining an AHI < 5 events/h, under MAD therapy in approximately one-third of patients. Another third showed a decrease in AHI of 50% or more, whereas the last one-third of patients showed negligible improvement in OSA severity (13). Therefore, upfront patient selection could be beneficial.

OSA pathophysiology can be subdivided into different characteristics: upper-airway collapsibility, loop gain, upper-airway muscle responsiveness, arousal threshold, and the ventilatory response to arousal (VRA). However, the gold-standard measurement techniques to assess these traits are rigorous and time consuming, involving multiple CPAP drops during sleep overnight with a sealed mask and pneumotach and/or via esophageal catheters to assess ventilatory drive (14, 15). Therefore, pathophysiological OSA traits are not routinely measured in clinical practice. However, recent research showed that pathophysiological OSA traits affect MAD treatment efficacy (16, 17). Specifically, a recent study by Edwards and colleagues (16) showed that patients with lower loop gain, measured using a gold-standard technique, were more likely to respond to MAD treatment; milder collapsibility was also a predictor (16, 18).

Furthermore, recent research showed it is possible to derive the pathophysiological OSA traits using baseline polysomnographic signals, avoiding additional invasive measurements (19–25). These techniques already showed their potential in calculating and estimating the OSA traits to differentiate between responders and nonresponders to upper-airway surgery (26). Recently, Bamagoos and colleagues (17) showed that a combination of the different calculated pathophysiological traits explains AHI reduction after MAD treatment.

In the current study, we aimed to use the pathophysiological OSA traits, calculated from the baseline polysomnographic signals, to differentiate between responders and nonresponders to MAD treatment. We hypothesized that MAD responders exhibit lower loop gain (primary) and less severe collapsibility (secondary), as per Edwards and colleagues (16). We also aimed to expand the results to other nonanatomical OSA traits: arousal threshold, VRA, and compensation, as per Bamagoos and colleagues (17). The results described in this article were presented orally at the 2019 American Thoracic Society International Conference on May 20, 2019, and at the 2019 American Academy of Dental Sleep Medicine Annual Meeting in San Antonio on June 7, 2019, and have been published in abstract form (27, 28).

Methods

Subjects

The current study is a secondary analysis of the parent clinical trial NCT 01532050 (clinicaltrials.gov) that was approved by the local ethical committee at the University of Antwerp and Antwerp University Hospital (11/11/103, Belgian registration number: B300201212961). Written informed consent was obtained from all patients.

Data of 36 patients with moderate-to-severe OSA (all available) were included in this secondary analysis (see Figure E1 in the online supplement). As this is a secondary analysis, only data of patients with a complete data set were selected. In the parent trial, 47 patients with an AHI ≥ 15 events/h consented, but 11 dropped out. Five patients quit the study because of time constraints, two failed to return despite several reminders, one moved abroad, two stopped because of financial reasons,

one patient preferred to stop treatment because of an absence of symptomatic relief, and one patient quit the study because of an improvement of OSA after weight reduction. In total, 36 (77%) of the patients with an AHI ≥ 15 events/h completed the parent study.

As described in detail by Verbruggen and colleagues (29), all patients had undergone a baseline clinical type 1 polysomnography, confirming moderate-to-severe OSA (AHI ≥ 15 events/h), at the Antwerp University Hospital. Hypopneas were scored according to the American Academy of Sleep Medicine 1999 guidelines (30). For the present analysis, arousal start and end times were manually rescored using electroencephalography because precise arousal timing was not required in the parent clinical trial. Custom-made MAD treatment (RespiDent Butterfly MAD; Orthodontic Clinics NV) was administered (31). For standardization, the MAD was fixed at 75% of the individual patient's maximal protrusion without further titration. After 3 months of MAD treatment, a follow-up visit was scheduled, including a type 1 polysomnography with MAD treatment. Response was defined as a change in AHI (Δ AHI) $\geq 50\%$ from baseline.

Pathophysiological Trait Calculation

The pathophysiological traits were calculated from the baseline clinical polysomnography using the previously validated method as described by Sands and colleagues (23–25, 32). The calculated traits included collapsibility (airflow at normal ventilatory drive [V_{passive}]), loop gain (drive response to reduced airflow), arousal threshold (drive preceding arousal), compensation (increase in airflow as drive increases), and the VRA (increase in drive explained by arousal).

Briefly, the traits were calculated automatically using overlapping windows of manually scored polysomnographic data during non-rapid eye movement sleep. The nasal pressure signal was linearized (power = 0.67) (23) and used to generate a breath-to-breath ventilation signal (normalized to 100% of local average). A physiologically constrained chemoreflex control model (parameters: loop gain [gain, response time, delay]; response to arousal) was fit to the ventilation data (input: ventilation) so that the output (estimated ventilatory drive) best fit the ventilation signal when the airway was open (between

scored respiratory events). Loop gain, defined as the change in ventilatory drive in response to a drop in airflow (25), was calculated directly from the best-fit model (taken at 1 cycle/min; median value for each patient used); an elevated loop gain indicates a hypersensitive ventilatory-control system more prone to cyclic ventilatory instability. The VRA was taken from the best-fit model (median value used) and represents the increase in ventilatory drive that is attributed to arousal from sleep (25, 26) as opposed to the increase in chemical drive (attributed to loop gain) (23). The arousal threshold was taken as the ventilatory drive on breaths preceding arousals (24) (median value used); a lower threshold indicates that sleep is more easily disturbed. Collapsibility was taken as the median value of airflow (lowered because of anatomical deficit) at normal drive and referred to as the V_{passive} ; a lower V_{passive} value indicates a greater degree of pharyngeal collapsibility. Compensation, a measure of upper-airway muscle responsiveness, was taken as the increase in airflow as ventilatory drive rises from normal degrees (V_{passive}) to more active conditions (at the arousal threshold). A single value (median) of each trait for each patient was used for statistical analyses.

Statistical Analysis

Statistical analysis was performed using the software packages MATLAB (MATLAB and Statistics Toolbox Release 2018a; MathWorks) and R (R: A language and environment for statistical computing, 2016; R Core Team, R Foundation for Statistical Computing). Descriptive statistics were reported as the mean and 95% confidence interval (CI) or median and interquartile range (IQR). Normality was tested using the Shapiro-Wilk test. To differentiate between responders and nonresponders, normally distributed continuous variables were compared using unpaired t tests, and nonnormally distributed variables were compared using the Wilcoxon signed-rank or Mann-Whitney U test. Loop gain was considered the primary determinant. Associations were also adjusted for potential confounders (baseline AHI and body mass index [BMI]) using multivariable logistic regression (nonresponder = 1; responder = 0). For example, the percentage Δ AHI may depend somewhat on the baseline AHI. The BMI is also a potential confounder between loop gain and MAD

response because those with a higher BMI are expected to have not only higher loop gain (i.e., via lowered functional residual capacity) but also a poorer MAD response. Likewise, collapsibility is a potential confounder for loop gain and MAD response (i.e., via possible acquired increases in loop gain over time with more severe recurrent obstruction); thus, further adjustment for collapsibility was also performed to assess the extent to which loop gain is associated with MAD response, independent of collapsibility. The 36 patients were expected to have 80% power to detect a 1-standard deviation (SD) difference (α level = 0.05) in loop gain between responders and nonresponders (logistic regression); inclusion of uncorrelated confounders was expected to lower statistical power by under 1% per variable (simulations: 10,000 iterations). Because of the limited sample size of this study, multivariable analysis with multiple traits was considered exploratory. However, we also expected that the bivariate relationships may be strengthened by concurrent inclusion of loop gain and collapsibility, as seen previously (32). All reported P values are two-sided. Statistical significance was considered to be present at $P < 0.05$.

Results

Data from 36 patients were assessed, and all 36 patients were included in the final

analysis (median AHI, 23.5 [IQR, 19.7–29.8] events/h; median BMI, 28.8 kg/m² [95% CI, 27.8–29.7]; 69% male; median age, 48.5 yr [95% CI, 45.8–51.1]). MAD treatment significantly improved AHI, supine AHI, nonsupine AHI, minimum oxygen saturation, oxygen desaturation index, and Epworth sleepiness scale after 3 months of MAD treatment (Table 1). In total, 18 out of the 36 patients (50%) were classified as responders (Δ AHI \geq 50%) in a nontitrated 75% protrusion, 13 (36%) patients reached an AHI < 10 events/h, and 3 (8%) patients were complete responders (AHI < 5 events/h). Five responders (5 of 18, 28%) had a residual AHI > 10 events/h despite a 50% reduction (baseline AHI = 34.1, 34.6, 23.6, 69.9, and 40.7 events/h; see Figure 1). No significant differences in baseline characteristics, including baseline AHI and BMI, were present between responders ($n = 18$; 50%) and nonresponders ($n = 18$; 50%) to MAD treatment, and MAD responders were slightly younger than nonresponders ($P = 0.04$; Table 2). No patients reported temporomandibular joint problems after treatment start-up.

Pathophysiological traits were calculated in all 36 patients, yielding the following average values for the entire group: loop gain, 0.59 (95% CI, 0.54 to 0.64); V_{passive} , 92.7% (95% CI, 91.4% to 94.0%) eupnea; arousal threshold, 122.6% (95% CI, 117.1% to 128.7%) eupnea; compensation, 0.83% (95% CI, -7.1% to 8.8%) eupnea; and VRA, 43.9% (95% CI, 36.7% to 51.2%) eupnea.

Table 1. Baseline and 3-month follow-up patient characteristics

Outcome Parameter	Baseline PSG ($n = 36$)	Follow-Up PSG (3 M) ($n = 36$)
Apnea-hypopnea index, events/h*	23.5 (19.7–29.8)	12.8 (7.9–21.7)
Supine apnea-hypopnea index, events/h*	40.9 (29.0–62.4)	22.1 (10.4–38.8)
Nonsupine apnea-hypopnea index, events/h*	16.5 (11.03–21.0)	7.0 (4.4–15.6)
Mean Sa _O ₂ *	94.6 (93.9–95.7)	95.2 (94.1–95.7)
Minimal Sa _O ₂ †	85.3 (83.8–86.8)	87.5 (86.3–88.7)
Oxygen desaturation index, events/h*	10.6 (6.3–16.6)	3.7 (1.4–8.0)
Body mass index, kg/m ² †	28.8 (27.9–29.7)	29.0 (28.0–30.0)
Epworth sleepiness scale*	7 (5–14)	6 (3–9)
Visual analog scale*	7 (6–9)	7 (5–9)
Age, yr†	48.5 (45.8–51.1)	—
Sex, M/F, %M	31/5, 86% M	—

Definition of abbreviations: F = female; M = male; PSG = polysomnography; Sa_O₂ = arterial oxygen saturation.

One patient did not have follow-up minimal O₂ saturation ($n = 35$).

*Data are presented as medians (interquartile ranges).

†Data are presented as means (95% confidence intervals).

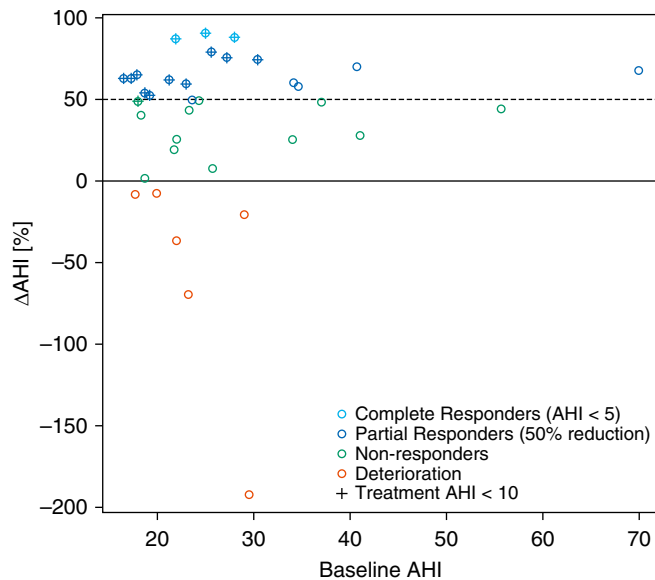


Figure 1. Dot plot showing the Δ AHI as a function of the baseline AHI. Deteriorating patients (treatment AHI > baseline AHI) are shown in red, nonresponders (Δ AHI < 50%) are shown in green, partial responders (Δ AHI \geq 50% but treatment AHI > 5) are shown in dark blue, and complete responders (treatment AHI < 5) are shown in light blue. Patients with a treatment AHI < 10 events/h are depicted with crosses. The dotted line shows the Δ AHI 50% threshold. AHI = apnea-hypopnea index.

Bivariate Associations with MAD Efficacy

Compared with responders, nonresponders to MAD treatment (Δ AHI < 50%) showed a significantly higher loop gain (odds ratio, 2.16 [95% CI, 1.17–3.97] per 1-SD increase in loop gain [SD, 0.15]; $P=0.020$) (Table 3 and Figure 2).

Adjusted Bivariate Associations

After adjusting for baseline AHI and BMI, differences in loop gain were upheld (odds ratio, 2.17 [95% CI, 1.22–3.88] per 1-SD increase in loop gain [SD, 0.15]; $P=0.013$; Table 3). Furthermore, greater collapsibility (odds ratio, 1.97 [95% CI, 1.18–3.29] per 1-SD decrease in V_{passive} ; $P=0.014$) and

a higher arousal threshold (odds ratio, 1.86 [95% CI, 1.04–3.35] per 1-SD increase in arousal threshold [SD, 18.0%]; $P=0.045$) in nonresponders was also significant after adjusting for baseline AHI and BMI.

Multivariable Associations

We further explored whether loop gain remained associated with nonresponder status after additional adjustment for collapsibility (potential confounder; AHI and BMI included). Higher loop gain (odds ratio, 3.03 [95% CI, 1.16–7.88] per 1-SD increase in loop gain [SD, 0.15]; $P=0.023$) remained associated with nonresponder status, independent of more severe collapsibility (lower V_{passive} ; odds ratio, 4.6 [95% CI, 1.1–18.5] per 1-SD decrease in V_{passive} [SD, 7.2%]; $P=0.032$; $R^2=0.28$; χ^2 test-derived $P=0.008$). Variance inflation factors of the final model were below two. With this model, a sensitivity of 66.7%, a specificity of 72.2%, a positive predictive value of 70.6%, and a negative predictive value of 68.4% were obtained to explain nonresponse.

Discussion

The current study showed that nonresponders to MAD treatment have a more hypersensitive (less stable) ventilatory-control system, reflected by a higher baseline loop gain observed using routine clinical polysomnography (Figure 2). A higher loop gain was associated with nonresponse, independent of baseline AHI, BMI, and collapsibility (logistic regression), with a 1-SD increase in loop gain yielding a threefold increase in the likelihood of being a nonresponder. Determining the ventilatory-control stability at baseline could thus potentially help predict MAD treatment response.

In previous research, increased collapsibility of the upper airway was found to have an effect on MAD treatment efficacy. Patients with an optimal CPAP pressure of 10.5 cm H_2O or more, reflecting a highly collapsible upper airway, are more likely to be nonresponders to MAD therapy (33). Likewise, other studies found greater MAD efficacy in patients with a lower BMI (34), a surrogate of less severe collapsibility (35). Results obtained in the study of Edwards and colleagues (16), using gold-standard measurement techniques to define each pathophysiological trait, showed that

Table 2. Baseline characteristics for responders and nonresponders

Outcome Parameter	Responders (n = 18)	Nonresponders (n = 18)	P Value
Apnea-hypopnea index, events/h*	24.3 (19.7–29.8)	23.3 (20.4–29.5)	0.9
Supine apnea-hypopnea index, events/h†	42.4 (28.3–56.5)	52.2 (41.1–63.3)	0.3
Nonsupine apnea-hypopnea index, events/h*	16.4 (12.1–21.0)	16.5 (9.7–20.7)	0.5
Mean Sa_{O_2} *	94.4 (93.3–95.4)	94.9 (94.1–95.8)	0.3
Minimal Sa_{O_2} †	85.1 (82.5–87.7)	85.4 (84.0–86.8)	0.8
Oxygen desaturation index, events/h*	8.4 (3.6–14.8)	10.9 (8.5–18.2)	0.16
Body Mass index, kg/m ² †	28.8 (27.4–30.2)	28.7 (27.4–30.0)	0.9
Age, yr†	45.7 (42.7–48.8)	51.2 (47.2–55.3)	0.04
Sex, M/F‡	14/4	17/1	0.34
Epworth sleepiness scale*	9 (6–16)	7 (3–13)	0.3
Visual analog scale*	7 (6–9)	8 (6–9)	0.9

Definition of abbreviations: F = female; M = male; Sa_{O_2} = arterial oxygen saturation.

Significant values are shown in bold.

*Data are presented as medians (interquartile ranges), and the Mann-Whitney U test was used.

†Data are presented as means (95% confidence intervals), and an unpaired t test was used.

‡Data are presented as ratios, and the Fisher exact test was used.

Table 3. Baseline pathophysiological traits for responders and nonresponders

Endotypic Trait	Responders [Mean (95% CI)]	Nonresponders [Mean (95% CI)]	Difference [Mean (95% CI), <i>P</i> Value]	Adjusted Difference [Mean (95% CI), <i>P</i> Value]
Loop gain	0.53 (0.47 to 0.59)	0.65 (0.58 to 0.71)	-0.12 (-0.21 to -0.02), 0.019	-0.12 (-0.21 to -0.03), 0.013
Collapsibility, Vpassive	94 (93 to 95)	91 (90 to 93)	<i>2.5 (0.0 to 4.5), 0.055</i>	2.6 (0.7 to 4.3), 0.014
Arousal threshold	118 (112 to 125)	128 (121 to 137)	<i>-10 (-19 to 1), 0.074</i>	-11 (-18 to -1), 0.045
Compensation	0.74 (-9.9 to 11.4)	0.90 (-9.7 to 11.5)	<i>-0.5 (-16.1 to 15.0), >0.9</i>	<i>0.2 (-14.3 to 14.6), >0.9</i>
Ventilatory response to arousal	38 (28 to 48)	50 (40 to 60)	<i>-11.6 (-25.3 to 2.0), 0.104</i>	<i>-11.9 (-25.4 to 1.6), 0.094</i>

Definition of abbreviations: CI = confidence interval; Vpassive = airflow at normal ventilatory drive.

An unpaired *t* test was used. Adjusted differences and *P* values take into account the baseline apnea-hypopnea index and body mass index (potential confounders). The primary trait for analysis was loop gain. Vpassive and arousal threshold values were transformed (square-root) to provide normally distributed data for analysis; back-transformed results are shown for presentation. Significant values are in bold, and nearly significant values are in italics.

patients with lower loop gain have increased probability for a favorable MAD response. In a recent study by Bamagoos and colleagues (17), loop gain and collapsibility were also found to be associated with AHI reduction under MAD treatment (although only in nonlinear multivariable models rather than in bivariate analyses). In the present study, we demonstrated an increased odds for MAD treatment nonresponse in patients with high loop gain, independent of collapsibility, showing that loop gain might be the main trait that can be used to differentiate between responders and nonresponders to MAD treatment.

Furthermore, recently, loop gain was found to be a predictor for response to upper-airway surgery using the same algorithm to calculate pathophysiological traits from the baseline clinical polysomnography (26). As the results in our study show, an association between higher loop gain and an increased likelihood of nonresponse to MAD treatment suggest that similar patients might be suitable for MAD therapy and upper-airway surgery.

In current clinical practice, MAD patient selection, if it is done at all, is mainly based on the site of collapse and surrogates of collapsibility (5, 33, 34, 36–39). However, as discussed, previous and current research shows other traits also play a role in MAD treatment efficacy (16, 17, 33). We showed that it is now feasible to calculate these traits in a clinical setting using baseline polysomnographic data, without the need for invasive, labor-intensive techniques. Pending future validation of our results in a larger sample, we consider that patients at elevated risk of nonresponse to MAD could be identified on the basis of their pathophysiology (higher loop gain), as such

reducing the time needed to guide patients toward their optimal treatment. These results highlight that pathophysiological endotyping might be a useful approach for predicting non-CPAP treatment efficacy in general.

Strengths and Limitations

This study has several strengths. First, the results of this study confirm the results of Edwards and colleagues (16) obtained using the gold-standard measurement techniques ($n = 14$) showing that MAD treatment outcome is associated with a low loop gain at baseline and a less collapsible upper airway. In contrast to that study, the endotypic traits in the current study were derived from a standard baseline clinical polysomnography, avoiding the more invasive and labor-intensive aspects of measuring these traits with the gold-standard techniques.

Second, our results are in line with the results as described by Bamagoos and colleagues (17), in which a greater reduction in AHI was associated with lower loop gain, a higher arousal threshold, a lower response to arousal, moderate collapsibility, and weaker muscle compensation. However, in contrast to this study, our data set showed a bivariate association between baseline loop gain and MAD response that was sustained after correcting for baseline covariates and collapsibility. As in our smaller sample, the loop gain findings were retained; a lower loop gain might be the most important parameter in explaining MAD response.

A third strength is the well-designed study protocol. All patients followed a standardized methodological protocol with fixed study dates. As there is no gold-

standard titration protocol available for MAD treatment (7), all MADs were fixed at 75% of the individual patient's maximal protrusion without further titration. Further titration might have increased response rates, but we argue that this approach was needed to allow for an objective and reproducible comparison among patients.

Fourth, all patients were fitted with the same MAD (RespiDent Butterfly). This MAD type consists of two clips attached to each other via a screw system located in the frontal area of the teeth. As such, it avoids mouth opening during sleep, thereby obviating backward and downward movement of the upper jaw that could reduce treatment efficacy.

Fifth, our laboratory collected high-quality nasal pressure signals, sampled at ≥ 100 Hz, with true direct-coupled data acquisition (no inherent high-pass “drift-correction” that creates artificial variability in the zero-flow baseline and conflates inspiration and expiration), without digital high-pass filtering (or low-pass “smoothing”) or signal clipping. These data are a rare sample that were able to meet American Academy of Sleep Medicine recommendations and standards for physiological trait estimation.

Our study also has some limitations. First of all, a potential limitation of our study is the rather low sample size of 36 patients. Hence, the multivariable analysis should be considered exploratory. However, it was of particular interest to demonstrate the association between MAD response and loop gain after adjusting for Vpassive, as similar models were published previously (16, 17). Because of this limited sample size, further exploration of effect modification by age and sex was also not possible. Future

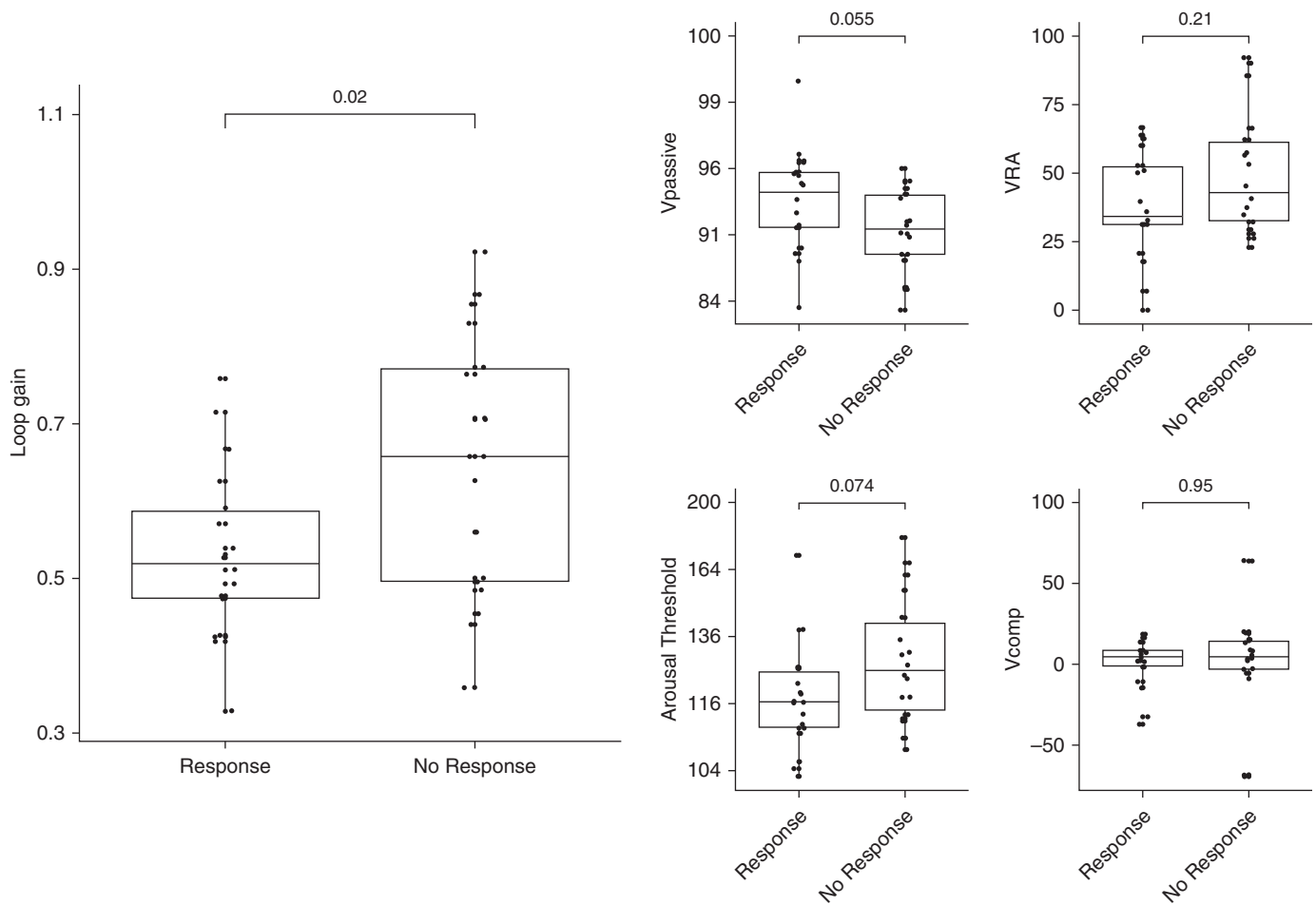


Figure 2. Bivariate analysis showed that nonresponders to mandibular-advancement-device treatment had a significantly higher loop gain than responders. Without adjustment for apnea-hypopnea index and body mass index, there was no significant difference between responders and nonresponders for any of the other traits. After adjustment for apnea-hypopnea index and body mass index, nonresponders exhibited significantly greater collapsibility (lower V_{passive}) and a higher arousal threshold. V_{passive} and arousal-threshold values were transformed (square-root) to provide normally distributed data for analysis; back-transformed results are shown for presentation. V_{comp} = ventilatory compensation; V_{passive} = airflow at normal ventilatory drive; VRA = ventilatory response to arousal.

larger studies, with the current results as the primary outcome, are needed to confirm these findings and enable MAD treatment outcome prediction.

Second, the patients with OSA included in this study are in a narrow range concerning OSA severity, BMI ($<35 \text{ kg/m}^2$), and age and do not show ethnic diversity. Although these patient characteristics are rather typical of the patients presenting in our sleep clinic for MAD therapy, this limits the generalizability of the current results to patients outside these ranges (e.g., higher BMI and other ethnicities). To allow clinical application outside this patient range, future studies with a broader range in OSA severity and patient characteristics are needed.

Third, the current study does not include an untreated control group, as it was a retrospective analysis of a previous prospective study. Prospective validation of our findings would ultimately require demonstration of greater efficacy (vs. untreated control patients) in patients with favorable endotypes.

Fourth, the fixed 75% protrusive position is an advantage for scientific consistency but may not fully reflect the current clinical practice with titration toward an optimal protrusion in the individual patient. In our clinical practice, most patients end up at around 80% of their maximal comfortable protrusion. Therefore, more optimal results could have been

obtained with further titration. However, we advocate that the fixed 75% protrusive position was imperative for a more objective and comparable study design, as it removes a potential confounder or source of unrelated variability.

Fifth, the response definition used ($\Delta\text{AHI} \geq 50\%$) is rather liberal. Patients with severe OSA who are classified as responders using this definition might not be complete responders ($\text{AHI} < 5 \text{ events/h}$). However, we preferred this liberal definition, as we believe a drop in AHI of more than 50% is a clinically meaningful response. For patients without complete response, MAD treatment might be a valuable component for combination therapy.

Another limitation is that the endotyping approach used here does not incorporate site-of-obstruction information. For example, recent research showed that patients with tongue-base collapse show increased odds for being a responder to MAD treatment (39, 40) and that those with complete concentric collapse at the level of the palate or a complete lateral wall collapse at the level of the oropharynx were at risk of an increased AHI with MAD treatment (39). Furthermore, expiratory pinching associated with palatal prolapse was, together with increased event depth, shown to be associated with MAD nonresponse (41). Although positive and negative predictive values of the current study are only moderate, these values are in line with those derived from previously researched methods like cephalometry and phrenic-

nerve stimulation (42, 43). Combining different prediction methods and including information on the site of obstruction (e.g., using the airflow signal [19, 20, 22, 41]) may help improve the predictive value to the amounts needed for clinical application.

Conclusions

The current study showed that hypersensitive ventilatory control (higher loop gain) is associated with a greater odds for nonresponse to MAD therapy, even after consideration of baseline AHI, BMI, and collapsibility ($V_{passive}$), as calculated from standard clinical polysomnography.

The current results confirm the results as obtained in previous research using the gold-standard measurement methods. Our

findings show that it may be possible to use the pathophysiological OSA traits from signals collected at a standard baseline clinical polysomnography to differentiate between responders and nonresponders to MAD treatment (23). As such, pending validation in a larger study, this technique potentially makes the findings reported previously by Edwards and colleagues (16) available for clinical practice. ■

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