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Mandibular Advancement Device Treatment Efficacy Is Associated with Polysomnographic Endotypes
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Abstract

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

Objectives: The current study aims to explain underlying individual differences in efficacy using OSA endotypic traits calculated from baseline clinical polysomnography: 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 ventilatory response to arousal (VRA, increase in drive explained by arousal). Based on previous research, we hypothesized that responders to MAD treatment have a lower loop gain and milder collapsibility.

Methods: Thirty-six patients (apnea-hypopnea index [AHI] 23.5[IQR:19.7-29.8]/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 et al. (AJRCCM 2018). Response was defined as AHI reduction ≥ 50%.

Results: MAD treatment significantly reduced AHI (49.7%[23.9-63.6] of baseline, median[IQR]). Responders exhibited lower loop gain (mean[95%CI], 0.53[0.48-0.58] vs. 0.65[0.57-0.73]; p=0.020) at baseline compared to non-responders, a difference that persisted after adjustment for baseline AHI and BMI. Elevated loop gain remained associated with non-response after adjustment for collapsibility (OR: 3.03 [1.16 - 7.88] per 1 SD increase in loop gain [SD=0.15]; p=0.023).
Conclusions: MAD non-responders 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 Registration: The current study is a secondary analysis of the parent clinical trial NCT01532050 (Clinicaltrial.gov)

Abstract word count: 244
Obstructive sleep apnea (OSA) is defined as repetitive upper airway collapse (apnea) or narrowing (hypopnea) during at least ten 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 therapy is the first-line non-continuous positive airway pressure (CPAP) treatment for moderate to severe (AHI ≥ 15/h) OSA patients. 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). While 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/h, under MAD therapy in approximately one-third of patients. Another third showed a decrease in AHI with 50% or more, while 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. 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 effort/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 et al. (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 polysomnography 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 non-responders to upper airway surgery (26). Recently, Bamagoos et al. (17) showed that a combination of the different calculated pathophysiological traits explain AHI reduction after MAD treatment.

In the current study, we aimed to use the pathophysiological OSA traits, calculated from the baseline polysomnography signals, to differentiate between responders and non-responders to MAD treatment. We hypothesized that MAD responders exhibit lower loop gain (primary) and less severe collapsibility (secondary) as per Edwards et al. (16). We also aimed to expand the results to other non-anatomical OSA traits: arousal threshold, ventilatory response to arousal and compensation, as per Bamagoos et al. (17).

**Methods**

**Subjects**

The current study is a secondary analysis of the parent clinical trial NCT01532050 (Clinicaltrials.gov) that was approved by the local ethical committee at 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 moderate to severe OSA patients (all available) were included in this secondary analysis (Figure E1, Online Supplement). As this is a secondary analysis, only data of patients with a complete dataset were selected. In the parent trial, 47 patients consented with an AHI ≥ 15/h. 11 dropped out. Five patients quit the study due to time constraints, 2 failed to return despite several reminders, 1 moved abroad, 2 stopped due to financial reasons, 1 patient preferred to stop treatment due to absence of symptomatic relief and 1 patient quit the study due to an improvement of OSA after weight reduction. In total, 36 (77%) of the patients with an AHI ≥ 15/h completed the parent study.

As described in detail by Verbruggen et al. (27), all patients had underwent a baseline clinical type 1 polysomnography, confirming moderate to severe OSA (AHI ≥ 15/h), at the Antwerp University Hospital. Hypopneas were scored according to the AASM 1999 guidelines (28). For the present analysis, arousal start and end times were manually re-scored using electroencephalography (EEG) since precise arousal timing was not required in the parent clinical trial. Custom-made MAD treatment (RespiDent Butterfly® MAD, Orthodontic Clinics NV, Antwerp, Belgium) was administered (29). For standardization, the MAD was set in fixed 75% of the individual patient’s maximal protrusion without further titration. After three months of MAD treatment, a follow-up visit was scheduled, including a type 1 polysomnography with MAD. Response was defined as ΔAHI ≥ 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 et al. (23-25, 30). The calculated traits included collapsibility (airflow at normal ventilatory drive, $V_{\text{passive}}$), 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 (VRA, increase in drive explained by arousal).

Briefly, the traits were calculated automatically using overlapping windows of manually-scored polysomnographic data during non-REM 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 ventilatory response to arousal (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). 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 due to anatomical deficit) at normal drive and referred to as $V_{\text{passive}}$; a lower $V_{\text{passive}}$ indicates a greater level of pharyngeal collapsibility. Compensation, a measure of upper airway muscle responsiveness, was taken as the increase in airflow as ventilatory drive rises from normal levels ($V_{\text{passive}}$) 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, The MathWorks, Inc., Natick, Massachusetts, United States) and R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were reported as mean and 95% confidence interval or median and interquartile range. Normality was tested using the Shapiro-Wilk test. To differentiate between responders and non-responders, normally distributed continuous variables were compared using unpaired t-tests, non-normally distributed variables 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 BMI) using multivariable logistic regression (non-responder = 1, responder = 0). For example, percent change in AHI may depend somewhat on baseline AHI. BMI is also a potential confounder between loop gain and MAD response, since those with higher BMI are expected to have higher loop gain (e.g. via lowered functional residual capacity) but also a poorer MAD response. Likewise, collapsibility is a potential confounder for loop gain and MAD response (e.g. 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. 36 patients was expected to have 80% power to detect a 1 SD difference (alpha level 0.05) in loop gain between responders and non-responders (logistic regression); inclusion of uncorrelated confounders were expected to lower statistical power by under 1% per variable (simulations, 10000 iterations). Due to 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 (30). All reported p-values are two-sided. Statistical significance was considered based on p < 0.05.

Results

Data from 36 patients were assessed and all 36 were included in the final analysis (AHI: Median: 23.5, IQR: [19.7 – 29.8]; BMI: 28.8, 95% CI [27.8 – 29.7]; 69% male; age: 48.5 years, 95% CI [45.8 – 51.1]). MAD treatment significantly improved AHI, supine AHI, non-supine 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 (ΔAHI ≥ 50%) in a non-titrated 75% protrusion, 13 (36%) patients reached an AHI < 10, 3 (8%) patients were complete responders (AHI < 5). Five responders (5/18, 28%) had a residual AHI > 10 despite a 50% reduction (baseline AHI = 34.1, 34.6, 23.6, 69.9 and 40.7/h), see Figure 1. No significant differences in baseline characteristics, including baseline AHI and BMI, were present
between responders (n=18; 50%) and non-responders (n=18; 50%) to MAD treatment, MAD responders were slightly younger compared to non-responders (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 – 0.64], V_{passive} 92.7 [95% CI: 91.4 – 94.0] % eupnea, arousal threshold: 122.6 [95% CI: 117.1 – 128.7] % eupnea, compensation: 0.83 [95% CI: -7.1 – 8.8] % eupnea, ventilatory response to arousal: 43.9 [95% CI: 36.7 – 51.2] % eupnea.

**Bivariate Associations with MAD Efficacy**

Compared to responders, non-responders to MAD treatment (ΔAHI < 50%) showed a significantly higher loop gain (odds ratio = 2.16 [1.17 – 3.97] per 1 SD increase in loop gain [SD = 0.15]; p = 0.020) (Table 3 & Figure 2).

**Adjusted Bivariate Associations**

After adjusting for baseline AHI and BMI, differences in loop gain were upheld (odds ratio = 2.17 [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 [1.18 – 3.29] per 1 SD decrease in V_{passive}; p = 0.014) and higher arousal threshold (odds ratio = 1.86 [1.04 – 3.35] per 1 SD increase in arousal threshold [SD = 18.0%]; p = 0.045) in non-responders was also significant after adjusting for baseline AHI and BMI.
**Multivariable Associations**

We further explored whether loop gain remained associated with non-responder status after additional adjustment for collapsibility (potential confounder; AHI and BMI included). Higher loop gain (odds ratio = 3.03 [1.16 to 7.88] per 1 SD increase in loop gain [SD=0.15]; p=0.023) remained associated with non-responder status, independent of more-severe collapsibility (lower $V_{\text{passive}}$: odds ratio = 4.6 [1.1 to 18.5] per 1 SD decrease in $V_{\text{passive}}$ [SD=7.2%]; p=0.032; $R^2 = 0.28$, $\chi^2$-test: $p = 0.008$). Variance inflation factors of the final model were below 2. 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% was obtained to explain non-response.

**Discussion**

The current study showed that non-responders 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 non-response, independent from baseline AHI, BMI, and collapsibility (logistic regression), with a 1 SD increase in loop gain yielding a 3-fold increase in likelihood of being a non-responder. 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$_2$O or more, reflecting a highly collapsible upper airway, are more likely to be non-responders to MAD
therapy (31). Likewise, other studies found greater MAD efficacy in patients with lower BMI (32), a surrogate of less-severe collapsibility (33). Results obtained in the study of Edwards et al. (16), using gold standard measurement techniques to define each pathophysiological trait, showed that patients with lower loop gain have increased probability for favorable MAD response. In a recent study by Bamagoos et al. (17), loop gain and collapsibility were also found to be associated with AHI reduction under MAD treatment (although only in non-linear multivariable models rather than bivariate analyses). In the present study, we demonstrated an increased odds for MAD treatment non-response in patients with high loop gain, independent of collapsibility, showing that loop gain might be the main trait that is able to differentiate between responders and non-responders 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 increased likelihood for non-response to MAD treatment, 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, 31, 32, 34-37). However, as discussed, previous and current research shows other traits also play a role in MAD treatment efficacy (16, 17, 31). We showed that it is now feasible to calculate these traits in a clinical setting using baseline polysomnography 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 non-response to MAD could be identified based on their pathophysiology (higher loop
gain), as such reducing the time needed to guide patients towards their optimal treatment. These results highlight that pathophysiological endotyping might be a useful approach for predicting non-CPAP treatment efficacy in general.

This study has several strengths and limitations. First, the results of this study confirm the results of Edwards et al. (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 et al. (17), in which a greater reduction in AHI was associated with lower loop gain, higher arousal threshold, lower response to arousal, moderate collapsibility and weaker muscle compensation. However, in contrast to this study, our dataset 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 mandibular advancement devices were fixed at 75% of the individual patient’s maximal protrusion without further titration. Further titration might have
increased response rates, but the authors argue that this approach was needed to allow for an objective and reproducible comparison between patients.

Fourth, all patients were fitted with the same mandibular advancement device (Respident Butterfly). This MAD type consists of two clips attached to each other via a screw system located in the frontal teeth area. As such it avoids mouth opening during sleep, thereby obviating backwards and downwards 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 DC-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 AASM 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 $V_{\text{passive}}$, as similar models were published previously. (16, 17). Due to this limited sample size, further exploration of effect modification by age and gender was also not possible. Future larger studies, with the current results as primary outcome, are needed to confirm these findings and enable MAD treatment outcome prediction.

Second, the OSA patients included in this study are in a narrow range concerning OSA severity, BMI (< 35 kg/m²), age and do not show ethnic diversity. While these patient
characteristics are rather typical to the patients presenting in our sleep clinic for MAD therapy, this limits the generalizability of the current results towards patients outside these ranges with e.g. higher BMI and other race. To allow clinical application outside this patient range, future studies are needed with a broader range in OSA severity and patient characteristics.

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 controls) 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 towards an optimal protrusion in the individual patient. In our clinical practice, most patients end up around 80% of their maximal comfortable protrusion. Therefore, more optimal results could have been obtained with further titration. However, the authors 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. Severe OSA patients who are classified as responder using this definition, might not be complete responders ($\text{AHI} < 5/\text{h}$). However, the authors preferred this liberal definition as they 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 (37, 38), and 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 increased AHI with MAD (37). Furthermore, expiratory pinching, associated with palatal prolapse was, together with increased event depth, shown to be associated with MAD non-response (39). Although PPV and NPV values of the current study are only moderate, these values are in line with previously researched methods like cephalometry and phrenic nerve stimulation (40, 41). Combining different prediction methods and, e.g., including information on site of obstruction (e.g. using the airflow signal (19, 20, 22, 39)) may help improve the predictive value to the levels needed for clinical application.

Conclusion

The current study showed that hypersensitive ventilatory control (higher loop gain) is associated with a greater odds for non-response to mandibular advancement device therapy, even after consideration of baseline AHI, BMI, and collapsibility (V_{passive}), as calculated from a 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 non-responders to MAD treatment (23). As such, pending validation in a larger study, this technique makes the findings reported previously by Edwards et al.(16) potentially available for clinical practice.
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References


Figure Legends

**Figure 1**: Dot plot showing ΔAHI in function of the baseline AHI. Deteriorating patients (treatment AHI > baseline AHI) are shown in red, non-responders (ΔAHI < 50%) in green, partial responders (ΔAHI ≥ 50% but treatment AHI > 5) in dark blue, complete responders (treatment AHI < 5) in light blue. Patients with a treatment AHI < 10/h are depicted with crosses. The dotted line shows the ΔAHI 50% threshold.

**Figure 2**: Bivariate analysis showed non-responders to MAD treatment had a significantly higher loop gain compared to responders. Without adjustment for AHI and BMI, there was no significant difference between responders and non-responders for any of the other traits. After adjustment for AHI and BMI, non-responders exhibited significantly greater collapsibility (lower $V_{\text{passive}}$) and a higher arousal threshold.
Table 1: Baseline and 3 month follow-up patient characteristics

<table>
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<th>Outcome parameter</th>
<th>Baseline PSG</th>
<th>Follow-up PSG (3M)</th>
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<tr>
<td></td>
<td>n = 36</td>
<td>n = 36</td>
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<td>7.0 [4.4 – 15.6]</td>
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<td>95.2 [94.1 – 95.7]</td>
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<td>87.5 [86.3 – 88.7]</td>
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<td>Oxygen desaturation index (/h)</td>
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<td>6 [3 - 9]</td>
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<td>7 [6 - 9]</td>
<td>7 [5 - 9]</td>
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<td>Age (years)$^2$</td>
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<tr>
<td>Gender (M/F, %male)</td>
<td>31/5, 86% male</td>
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Table 1: Baseline and 3 month follow-up patient characteristics. Median and interquartile ranges ($^1$) or mean and 95% confidence interval ($^2$). All parameters were compared using the Wilcoxon signed rank test ($^1$), except minimal oxygen saturation and body mass index which was compared using a paired t-test ($^2$). One patient did not have follow-up minimal O$_2$ saturation (n = 35). PSG: polysomnography; SaO$_2$: oxygen saturation. Significant values in bold, nearly significant in italics.
Table 2: Baseline characteristics for responders and non-responders

<table>
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<tr>
<th>Outcome parameter</th>
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<th>Non-responders n = 18</th>
<th>p-value</th>
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<tbody>
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<td>23.3 [20.4 – 29.5]</td>
<td>0.9</td>
</tr>
<tr>
<td>Supine apnea-hypopnea index (/h)(^2)</td>
<td>42.4 [28.3 – 56.5]</td>
<td>52.2 [41.1 – 63.3]</td>
<td>0.3</td>
</tr>
<tr>
<td>Non-supine apnea-hypopnea index (/h)(^1)</td>
<td>16.4 [12.1 – 21.0]</td>
<td>16.5 [9.7 – 20.7]</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean SaO(_2) (%)(^1)</td>
<td>94.4 [93.3 – 95.4]</td>
<td>94.9 [94.1 – 95.8]</td>
<td>0.3</td>
</tr>
<tr>
<td>Minimal SaO(_2) (%)(^2)</td>
<td>85.1 [82.5 – 87.7]</td>
<td>85.4 [84.0 – 86.8]</td>
<td>0.8</td>
</tr>
<tr>
<td>Oxygen desaturation index (/h)(^1)</td>
<td>8.4 [3.6 – 14.8]</td>
<td>10.9 [8.5 – 18.2]</td>
<td>0.16</td>
</tr>
<tr>
<td>Body Mass Index (kg/m(^2))(^2)</td>
<td>28.8 [27.4 – 30.2]</td>
<td>28.7 [27.4 – 30.0]</td>
<td>0.9</td>
</tr>
<tr>
<td>Age (years)(^2)</td>
<td>45.7 [42.7 – 48.8]</td>
<td>51.2 [47.2 – 55.3]</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (M/F)(^3)</td>
<td>14/4,</td>
<td>17/1</td>
<td>0.34</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale(^4)</td>
<td>9 [6 - 16]</td>
<td>7 [3 - 13]</td>
<td>0.3</td>
</tr>
<tr>
<td>Visual Analogue Scale(^1)</td>
<td>7 [6 - 9]</td>
<td>8 [6 - 9]</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 2: Baseline characteristics for responders and non-responders. No significant differences were present. Median [Q1 – Q3] \(^1\) or mean [95% confidence interval] \(^2\). \(^1\): Mann-Whitney U test, \(^2\): unpaired t-test, \(^3\) Fisher exact test.
**Table 3:** Baseline pathophysiological traits for responders and non-responders

<table>
<thead>
<tr>
<th>Endotypic Trait</th>
<th>Responders</th>
<th>Non-responders</th>
<th>Difference (p-value)</th>
<th>Difference (adjusted) (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop gain</td>
<td>0.53 [0.47 – 0.59]</td>
<td>0.65 [0.58 – 0.71]</td>
<td>-0.12 [-0.21 to -0.02]</td>
<td>-0.12 [-0.21 to -0.03]</td>
</tr>
<tr>
<td>Collapsibility, $V_{\text{passive}}$</td>
<td>94 [93 - 95]</td>
<td>91 [90 - 93]</td>
<td>2.48 [0.04 to 4.51]</td>
<td>2.64 [0.69 to 4.31]</td>
</tr>
<tr>
<td>Arousal Threshold</td>
<td>118 [112 - 125]</td>
<td>128 [121-137]</td>
<td>-10 [-19 to 1], 0.074</td>
<td>-11 [-18 to -1], 0.045</td>
</tr>
<tr>
<td>Compensation</td>
<td>0.74 [-9.9 – 11.4]</td>
<td>0.9 [-9.7 – 11.5]</td>
<td>-0.5 [-16.12 to 15.04]</td>
<td>0.2 [-14.3 to 14.6], &gt;0.9</td>
</tr>
<tr>
<td>Ventilatory Response to Arousal</td>
<td>38 [28 - 48]</td>
<td>50 [40 - 60]</td>
<td>-11.6 [-25.27 to 2.03]</td>
<td>-11.88 [-25.37 to 1.61]</td>
</tr>
</tbody>
</table>

Table 3: Baseline pathophysiological traits for responders and non-responders during the entire night. Mean [95% confidence interval]. Unpaired t-test. Adjusted differences and p-values take into account baseline AHI and BMI (potential confounders). Primary trait for analysis was loop gain. $V_{\text{passive}}$ and Arousal threshold values were transformed (square-root) to provide normally-distributed data for analysis; back-transformed results are shown for presentation.
Figure 1: Dot plot showing ΔAHI in function of the baseline AHI. Deteriorating patients (treatment AHI > baseline AHI) are shown in red, non-responders (ΔAHI < 50%) in green, partial responders (ΔAHI ≥ 50% but treatment AHI > 5) in dark blue, complete responders (treatment AHI < 5) in light blue. Patients with a treatment AHI < 10/h are depicted with crosses. The dotted line shows the ΔAHI 50% threshold.
Figure 2: Bivariate analysis showed non-responders to MAD treatment had a significantly higher loop gain compared to responders. Without adjustment for AHI and BMI, there was no significant difference between responders and non-responders for any of the other traits. After adjustment for AHI and BMI, non-responders exhibited significantly greater collapsibility (lower Vpassive) and a higher arousal threshold.
Mandibular Advancement Device Treatment Efficacy is Associated with Polysomnographic Endotypes

Online Supplement

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Supplemental Figures

**Inclusion**

**Baseline PSG**  
\( n = 47 \) patients consented with \( \text{AHI} \geq 15/h \)

**Start MAD treatment**  
75% of maximal protrusion

**3-month follow-up PSG**  
\( n = 36, 11 \) patients dropped out

<table>
<thead>
<tr>
<th>Response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{AHI} \geq 50% )</td>
</tr>
<tr>
<td>No response:</td>
</tr>
<tr>
<td>( \Delta \text{AHI} &lt; 50% )</td>
</tr>
</tbody>
</table>

**Figure E1:** Study protocol.

PSG: polysomnography, MAD: mandibular advancement device, AHI: apnea-hypopnea index