Polysomnographic Endotyping to Select Obstructive Sleep Apnea Patients for Oral Appliances

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Abstract

Rationale: Oral appliance therapy is efficacious in many patients with obstructive sleep apnea (OSA) but prediction of treatment outcome is challenging. Small, detailed physiological studies have identified key OSA endotypic traits (pharyngeal collapsibility and loop gain) as determinants of greater oral appliance efficacy.

Objectives: We used a clinically-applicable method to estimate OSA traits from routine polysomnography and identify an endotype-based subgroup of patients expected to show superior efficacy.

Methods: In 93 patients (baseline apnea-hypopnea index [AHI] ≥20 events/hr), we examined whether polysomnography-estimated OSA traits (pharyngeal: *collapsibility* and muscle *compensation*; non-pharyngeal: *loop gain*, *arousal threshold* and ventilatory *response to arousal*) were associated with oral appliance efficacy (percent reduction in AHI from baseline) and could predict responses to treatment. Multivariable regression (with interactions) defined endotype-based subgroups of "predicted" responders and non-responders (based on 50% reduction in AHI). Treatment efficacy was compared between the predicted subgroups (with cross-validation).

Results: Greater oral appliance efficacy was associated with favorable non-pharyngeal traits (lower *loop gain*, higher *arousal threshold* and lower *response to arousal*), moderate (non-mild, non-severe) pharyngeal *collapsibility* and weaker muscle *compensation* (overall R^2=0.30, adjusted R^2=0.19, p=0.003). Predicted responders (N=54), compared with predicted non-responders (N=39), exhibited a greater reduction in AHI from baseline (73[66-79] vs. 51[38-61]%, mean[95%CI], p<0.0001) and a lower treatment AHI (8[6-11] vs. 16[12-20]events/hr,

p=0.002). Differences persisted after adjusting for clinical covariates (including baseline AHI, body mass index, and neck circumference).

Conclusions: Quantifying OSA traits using clinical polysomnography can identify an endotype-based subgroup of patients that is highly responsive to oral appliance therapy. Prospective validation is warranted.

Oral appliances, intraoral devices worn during sleep to protrude the mandible, are increasingly utilized as a treatment alternative for obstructive sleep apnea (OSA).[1] The literature indicates that oral appliance therapy reduces OSA severity (indicated by the apnea-hypopnea index, AHI) by an average of 50-70%.[2-6] Although not as efficacious as continuous positive airway pressure (CPAP) at ameliorating OSA, they have a proven positive impact on sleepiness, blood pressure and quality of life.[7-11] Additionally, studies suggest that treatment outcomes of oral appliances and CPAP are similar,[12] reflecting superior adherence to oral appliance therapy. Efficacy of oral appliance therapy is variable across OSA patients. Without experimental testing in each patient,[13,14] there is currently no clinically-applicable means to predict the likelihood of oral appliance therapy success before treatment prescription.[15]

The variability in oral appliance efficacy across OSA patients may be attributed to the extent to which OSA endotypic traits (pharyngeal: *collapsibility* and muscle *compensation*; non-pharyngeal: *loop gain*, *arousal threshold* and ventilatory *response to arousal*) contribute to the pathogenesis of the condition.[16-25] Small, detailed physiological studies have revealed two key traits associated with reduced oral appliance efficacy. Namely, greater pharyngeal collapsibility, whereby the severity is beyond the scope of treatment,[26] and higher loop gain (i.e. ventilatory control instability) that cannot be resolved with anatomical interventions.[20] Notably, these detailed studies were performed in specialized laboratories using invasive instrumentation, which are out of reach for clinical sleep laboratories.

Recently, our team has developed a method for estimating the key endotypic traits causing OSA from routine diagnostic polysomnography.[27-29] The method is based on automated analysis of a surrogate uncalibrated ventilation signal (derived from nasal pressure) from which

ventilatory drive is estimated and OSA endotypic traits are characterized. In the current study, we applied this method to diagnostic polysomnography of patients treated with oral appliance therapy. We aimed to: 1) determine whether greater oral appliance efficacy is associated with favorable non-pharyngeal OSA endotypes (i.e. lower *loop gain*, higher *arousal threshold*, and lower *ventilatory response to arousal*), with the ultimate goal of 2) defining an endotype-based subgroup of OSA patients (prediction model) who are most likely to benefit from oral appliance therapy (predicted responders).

Methods

Subjects

In this study, we performed a secondary analysis of polysomnographic data from previous oral appliance research studies (which included newly-diagnosed OSA patients with baseline AHI >10 events/hr).[12,30,31] Patients were included in our analysis if they had a baseline polysomnography-derived AHI ≥20 events/hr (pre-specified) which was selected to minimize the influence of night-to-night variability (noise) on the percent reduction in AHI with treatment (efficacy).[32] For example, a 75% reduction in AHI from 20 to 5 events/hr was considered more reliable than the same from 10 to 2.5 events/hr (the latter is within the expected night-to-night variability, i.e. ~10 events/hr).

Polysomnographic data (N=94) were taken from three parent studies: a 3-center randomized cross-over trial[12] comparing health outcomes of CPAP therapy versus oral appliances therapy in patients who were recommended both treatments (N=108 (80% males),

mean±SD age=50±11 years, body mass index [BMI]=30±6 kg/m^2 and AHI=26±12 events/hr), a single-center observational study[30] designed to examine awake-based predictors of oral appliance efficacy in patients to whom MAS therapy were recommended (N=142 (59% males), mean±SD age=56±11 years, BMI=30±5 kg/m^2 and AHI=29±18 events/hr), and an ongoing dual-center observational study[31] that is using MRI-based genioglossus dynamics to explain heterogeneity in oral appliance efficacy (at assessment: N=40 (72% males), mean±SD age=43±11 years, BMI=30±5 kg/m^2 and AHI=27.7±16.9 events/hr). Although some of the parent studies were multi-center, all polysomnographic data included in our analysis were from a single sleep clinic. Key exclusion criteria for the original research studies were previous oral appliance usage, oral appliance contraindications (including insufficient number of teeth, periodontal disease and severe daytime sleepiness that requires urgent intervention) and predominance of central sleep apnea at baseline. Oral appliance efficacy was determined using in-laboratory polysomnography with the oral appliance in-situ. Since all data were de-identified, the current analysis was deemed to be exempt from consent by the Human Research Ethics Committee at North Sydney Local Health District, NSW, Australia and the Partners Institutional Review Board, Boston, MA, USA.

Study Protocol

Patients first attended in-laboratory diagnostic polysomnography (electroencephalography, electrocardiography, electrooculography, chin and leg electromyography, thoracoabdominal plethysmography, pulse oximetry, body position, nasal-pressure airflow and thermistor signals) which were scored according to the AASM criteria 2012[12,33] (30% reduction in airflow with

either 3% oxygen desaturation or cortical arousal) or AASM criteria 2007[30,31,34] (30% reduction in airflow with 4% oxygen desaturation). Models were not adjusted for scoring type as no effect was evident (see Results). All patients were treated with a custom-made oral appliance (SomnoDent, SomnoMed Ltd., Australia) implemented for individual patients under supervision of a treating dentist. Devices were initially set to 70% of the maximal mandibular protrusion from habitual bite. Patients were instructed to incrementally advance the protrusive level of the device until the maximum comfortable limit was reached (approximately 6-8 weeks), which was then confirmed by the treating dentist. A second in-laboratory polysomnography was performed to determine response to therapy.

Oral Appliance Efficacy

Oral appliance efficacy was described by the percent reduction in AHI with treatment relative to baseline (primary outcome, continuous variable). This measure was selected (over absolute reduction or treatment AHI) to maximize statistical power (typically largest mean/SD ratio,[35] correlates least with baseline AHI[36]).

Endotypic Trait Analysis

Raw data. We identified 94 patients who met our pre-specified eligibility criteria for analysis (N=50 excluded for AHI <20 events/hr). For optimal endotyping analyses, a thorough manual check of cortical arousal onset and end times was performed for baseline polysomnography by 3 experienced scorers. Adjustment of arousal timing (if required) was performed blinded to treatment outcome. Raw data and accompanying annotations (staging, arousals and respiratory

events) were exported for each patient. Data from one participant were excluded due to poor nasal pressure signal (automated quality control algorithm, verified visually) leaving 93 for analysis. Analysis of the traits was restricted to non-REM sleep for consistency with previous validation studies using our methods, and to avoid the influence of night-to-night variability in REM duration on the measurements.[27-29] Data from supine and lateral positions were pooled given the interest in predicting changes in the total AHI with treatment, regardless of position.

Quantifying OSA endotypic traits. These methods have been described in detail previously.[27-29,37] Each diagnostic polysomnogram was automatically segmented into 7-min overlapping windows containing non-REM sleep. The analyses were performed for each window separately and median values across windows were used to represent each individual. First, nasal pressure (linearized, square-root) provided an uncalibrated breath-to-breath *ventilation* signal (volume × rate), calibrated such that the mean eupneic ventilation for the window being analyzed =100%.[29] *Ventilatory drive* was defined as the intended ventilation that would be observed if the airway was completely open (i.e. immediately after a scored cortical arousal). Ventilatory drive was estimated by least-squares fitting of a regression model that seeks to predict ventilation (i.e. overshoot between obstructive events) based on previous values of ventilation. This chemoreflex model is physiologically constrained such that 3 key parameters are identified (gain, time-constant and delay[27]). These parameters were used to calculate the *loop gain* (LGn, ventilatory drive response to an oscillatory disturbance at the natural frequency, which captures the combined influence of chemoreflex sensitivity, plant gain, and circulatory delay; a value of 1 would predict central sleep apnoea).[27,37] The ventilatory *response to arousal* (additional ventilatory drive response that accompanies arousal,

independent of the chemoreflex contribution) was found by including the presence of a scored EEG arousal on any breath as a covariate. The *arousal threshold* was calculated as the mean ventilatory drive on the breath immediately preceding scored arousals.[29]

To calculate collapsibility and muscle compensation, an overnight endotype plot[28] was generated, whereby all breath-by-breath values of ventilation and ventilatory drive for the whole night (except breaths in wake, arousals and REM) are tabulated and plotted against each other. The median value of ventilation at eupneic ventilatory drive was taken as a measure of passive *collapsibility* ($V_{PASSIVE}$). A lower $V_{PASSIVE}$ reflects a greater collapsibility. The median value of ventilation at maximal ventilatory drive (at arousal threshold) was taken as a measure of active collapsibility (V_{ACTIVE}). The difference between V_{ACTIVE} and $V_{PASSIVE}$ was used as a measure of pharyngeal muscle *compensation*. Analysis was fully-automated using a custom in-house software (Matlab, Mathworks, Natick MA, USA; Interested users are directed to contact the authors) and visually verified.

Model Development and Statistical Analyses

The goals of the statistical analyses were two-fold. First, we sought to describe the associations between oral appliance efficacy and OSA endotypic traits (in combination) at baseline to provide insight into mechanistic causes of variability in oral appliance efficacy. A multivariable regression model approach[37] was employed (outlined below). Second, we sought to use the same endotype-based regression model as the basis of a prediction model to examine the extent to which these endotypes could be employed to identify an endotype-based subgroup of

OSA patients who would exhibit greater oral appliance efficacy ("predicted responders") compared with other patients ("predicted non-responders").

Statistical power. Ninety patients were estimated to provide 86% power to detect significant independent associations with R^2 >0.1 (alpha=0.05), and 92% power to detect differences in efficacy between endotypic subgroups of at least 20±40%.

Data transformation. Several variables were not normally distributed (Shapiro-Wilk test) and were transformed accordingly: $V_{PASSIVE}$ and arousal threshold were square-root-transformed via the equations $y=1+(x-1)^{0.5}$ and $y=1-(1-x)^{0.5}$, respectively, where $x=1$ describes 100%.[37] The percent reduction in AHI with treatment vs. baseline (primary outcome variable) was transformed to avoid left skewness via the equation $y=x/(2-x)$, which is equivalent to y=(BaselineAHI−TreatmentAHI) / (BaselineAHI+TreatmentAHI), where x ranges between −1 and +1. This transformation was made so that, for instance, halving or doubling baseline AHI with oral appliance therapy would produce equal and opposite effects on the transformed outcome (y is noted as ΔAHI from now on). Thus, halving baseline AHI (x=0.5) yields a ΔAHI=33% and doubling baseline AHI (x=−1) yields a ΔAHI=−33%. Baseline and treatment AHI were also left skewed and transformed using $y=x^{1/3}$. All variables were back-transformed for presentation.

Bivariate analyses. Simple linear regression analyses were initially performed to evaluate the relationships between ΔAHI and each OSA endotypic trait individually.

Multivariable regression analysis. Initial visual inspection of the data (plots showing responders and non-responders against combinations of collapsibility, loop gain, and arousal threshold; data not shown) suggested complex interactions between multiple traits and oral appliance efficacy that could not be captured appropriately using bivariate regression. We

therefore employed a *quadratic* regression analysis in which the total possible variable terms, i.e. 20 terms, were included. These 20 terms were the 5 individual OSA endotypic traits, the 5 endotypic traits after square-transformation (1 square-transformation per trait) and 10 interaction terms. Significant square-transformed terms would indicate non-linear relationships with efficacy (e.g. U-shaped curve), and interaction terms would imply that the relationship between efficacy and an endotypic trait varies depending on the level of another trait. An example quadratic model expression with just two traits would be $\beta_0 + \beta_1(\text{loop gain}) + \beta_2(V_{PASSIVE}) + \beta_3(\text{loop gain})^2 + \beta_4(V_{PASSIVE})^2 + \beta_5(\text{loop gain} \times V_{PASSIVE})$. To determine which terms should be included, we employed a backward elimination method. We started with a model that included all 20 terms. Subsequently, backward stepwise elimination iteratively removed each term with the highest p-value, if $p>0.157$ (Wald-test, equivalent to Akaike Information Criterion, indicating that the relative quality of the model was not improved with the inclusion of the term[37-41]). This approach was employed on the basis that removal of very weak predictors reduces uncertainty of remaining model coefficients. Terms were accepted as significant at $p<0.05$. For interpreting associations, we did not adjust the P-value threshold for multiple comparisons (e.g. 5-traits: conservative p-threshold=0.01).

Defining endotypic subgroups. Defining the endotypic subgroups of predicted responders and predicted non-responders were based on the above regression model and the following steps. True responders and true non-responders were defined by percent reduction in AHI with treatment (true efficacy cutoff =50%). “Predicted responders” and “predicted non-responders” were defined by determining the optimal cutoff, from the multivariable regression model output, that maximized sensitivity plus specificity (a model-predicted efficacy cutoff

=60% was found; see Results; Note that model-predicted efficacy and true efficacy are not equal). Predicted subgroups were allocated using a "leave-one-patient-out cross-validation" procedure to avoid overestimating predictive performance. This procedure ensured that the outcome status of a given patient was predicted based on a model that included all patients' data except his/her own. Thus, cross-validated results are more conservative (more likely indicative of future re-test performance). For example, allocation of patient #1 to a "predicted responder" subgroup or a "predicted non-responder" subgroup was determined by building a modified model (via re-running backwards elimination regression described above) without the data of patient #1, and then using this modified model to predict patient #1 response. This process was then repeated for all other patients from #2 to #93. The primary statistical comparison for the study was the difference in percent reduction in AHI (primary outcome variable) between the predicted endotypic subgroups.

Adjusting for clinical covariates. Multivariable linear regression was used to determine whether predicted response status (being a predicted responders vs. predicted non-responder) could predict oral appliance efficacy (ΔAHI) independently of clinical covariates (i.e. baseline AHI, BMI, age, gender and neck circumference; baseline REM:NREM AHI and change in REM sleep duration with treatment were also assessed). To perform this test, predicted response status (1 or 0, respectively) was included as an independent variable and clinical covariates were sequentially included-then-removed from the model.

Presentation. Data are presented as mean±SD for descriptive variables and mean±SEM for comparisons. Back transformed data were presented as mean [95% confidence interval]. Data were described as median [25^{th} - 75^{th} centile] for non-normally-distributed data as

appropriate. Significance was accepted at $p<0.05$. Figures were created using custom MATLAB software (MathWorks, Natick, MA, USA).

Results

Baseline Characteristics

Data from 93 participants (56% males) were analyzed. Baseline vs. treatment characteristics for the overall group are presented in Table 1. On average, participants were middle-aged (56.2±11.0 years), obese (30.5 ±5.3 kg/m^2) with moderate to severe OSA (30.6 [24.4 – 43.5] events/hr).

Oral Appliance Therapy

The final protrusion provided by the oral appliance was, on average, 89% (range: 44-100%) of the maximal mandibular protrusion. Overall, treatment lowered AHI by a median of 67% and had favorable effects on arousal frequency and oxygenation (Table 1). Forty-three patients were responders (>50% reduction in AHI).

Bivariate Analyses

Using simple linear regression analyses, we observed no bivariate associations between oral appliance efficacy (percent reduction in AHI transformed; ΔAHI) and any of the individual endotypic traits at baseline ($R^2<0.01$ for all). There were also no associations between oral appliance efficacy and baseline AHI, BMI, age, gender or neck circumference.

Multivariable Regression Analysis

When endotypic traits were considered in combination (multivariable regression), we found that greater oral appliance efficacy was associated with: moderate $V_{PASSIVE}$ (non-severe and non-mild), lower pharyngeal compensation and more favorable non-pharyngeal traits (i.e. lower loop gain, higher arousal threshold and lower response to arousal), see Table 2 and Figure 1. Several interaction variables were also associated with treatment efficacy (see Table 2 and Figure 1 for interpretation of each of the 12 terms included in the model).

Defining Endotypic Subgroups

Use of the above multivariable regression model to define endotype subgroups of predicted responders and predicted non-responders revealed the following:

***Before cross-validation*.** Predicted responders (N=57), compared with predicted non-responders (N=36), exhibited a greater reduction in AHI from baseline (76[70-80] vs. 42[28-55]%, mean[95%CI], p<0.0001) and had lower treatment AHI (8[6-10] vs. 18[14-23] events/hr, p<0.0001). Positive and negative predictive values were 83% and 56%, respectively; accuracy was 72%.

***After cross-validation (main results)*.** Differences in responses between subgroups remained clinically significant after cross-validation: Predicted responders (N=54), compared with predicted non-responders (N=39), exhibited a greater reduction in AHI from baseline (73[66-79] vs. 51[38-61]%, mean[95%CI], p<0.0001) and had lower treatment AHI (8[6-11] vs. 16[12-20] events/hr, p=0.002), see Figure 2. Positive and negative predictive values were 78% (42:12) and 46% (18:21), respectively, (p=0.02, Fisher exact test); accuracy was 65%.

Further analyses. Adjusting for covariates (baseline AHI, BMI, age, gender, neck circumference, baseline REM:NREM AHI and change in REM sleep duration with treatment) did not attenuate the differences between groups. Notably, baseline AHI was similar between groups (predicted responders: 34[30-38] vs. predicted non-responders: 33[29-37] events/hr, mean[95%CI], p=0.5). Additionally, none of the above clinical covariates were significantly associated with oral appliance efficacy (ΔAHI) when considered individually (linear regression) or in combination (multivariable regression, total R^2=0.08).

Adjusting for scoring type had no impact (<1% change in model coefficient) on the association between endotypic subgroup and oral appliance efficacy and was not associated with efficacy (p=0.9).

Altering the cutoff of "true responder" from >50% to >70% reduction in AHI yielded similar results, with group differences in efficacy of 22% (cross-validated, p=0.0006) becoming 20% (p=0.0011). Positive and negative predictive values became 65% (30:16) and 72% (34:13), respectively, (p=0.0004, Fisher exact test); and accuracy was 69%.

Discussion

The current study is the first to demonstrate that the endotypic traits causing OSA, estimated from routine diagnostic polysomnography, have utility in defining a subgroup of patients who are more likely to respond to oral appliance therapy. Our study shows that a greater treatment efficacy is associated with favorable non-pharyngeal traits (lower loop gain, higher arousal threshold and lower ventilatory response to arousal), moderate collapsibility (not mild nor

severe, U-shaped) and weaker pharyngeal muscle compensation. Using measurements of the traits alone, “predicted responders”, on average, exhibited half the residual AHI (8 events/hr, ~quarter of baseline) compared with “predicted non-responders” (16 events/hr, ~half of baseline), despite similar baseline AHI. Moreover, 78% of patients in the predicted responders group exhibited at least a 70% reduction in AHI. These results provide a basis for future identification of patients who could potentially be prioritized for personalized therapy with oral appliances based on the OSA endotypic traits estimated from diagnostic polysomnography.

Consistency with Available Literature and Novel Physiological Insights

Our findings confirm previous work in that OSA endotypes can be estimated from routine diagnostic polysomnography and provide insight into therapeutic outcomes.[26-29,42] In concordance with physiological principles and our recent small, detailed physiology study, we confirmed the finding in a larger dataset that lower loop gain contributes significantly to greater oral appliance efficacy.[20] We emphasize, however, that in the current study, unlike our prior work, we did not find a strong bivariate relationship between loop gain and oral appliance efficacy. However, the requirement for multiple interacting endotypic predictors to be considered in combination is consistent with our previous study.[37]

Previous studies have also found that severe collapsibility is associated with reduced oral appliance efficacy.[15,20,26,43-45] Oral appliance therapy typically reduces critical collapsing pressure by 3-5 cmH_2O[26,46-48] and, therefore, is unlikely to resolve OSA in patients with severe collapsibility at baseline. Greater collapsibility (lower $V_{PASSIVE}$), higher BMI, non-positional OSA (a marker of greater collapsibility) and higher CPAP requirement have each been shown to predict

poor response to oral appliance therapy,[15,20,26,43-45] although these are not robust predictors individually. The current study found a U-shaped relationship between collapsibility and response to oral appliances. As expected, more-severe collapsibility predicted reduced responses to oral appliance therapy. Milder collapsibility, unexpectedly, also predicted a reduced response to treatment. We consider that these individuals, rather than being an "easier to treat", have a more "non-pharyngeal" mechanisms underpinning their sleep apnea. We emphasize that while we initially considered that the U-shaped relationship could be spurious, we noted that a large proportion of patients were non-responders with mild collapsibility (and high loop gain or low arousal threshold, see Figure 1), such that this unexpected U-shaped effect at the mild end of the spectrum was unlikely to be attributable to low sample size.

We also found that elevated loop gain, lower arousal threshold and greater ventilatory response to arousal also contributed to a reduced oral appliance efficacy. These non-pharyngeal factors contributing to breathing instability are unlikely to be corrected by mandibular advancement.[20] Indeed, it was precisely this subgroup of patients that responded preferentially to supplemental oxygen in our recent study[37]. Furthermore, we found that reduced pharyngeal compensation was associated with a higher oral appliance efficacy. According to physiological principles, a stronger pharyngeal dilator muscle compensation will act to mask a more severely collapsible airway. Therefore, attempts to improve collapsibility via oral appliance therapy will be partially counteracted by attenuation of the pharyngeal dilator muscle activity as airway obstruction is mitigated. Thus, our findings that poor compensation is associated with a higher oral appliance efficacy is consistent with physiological principles.

Our study shows no significant predictive value of routine clinical variables (such as baseline AHI, BMI, neck circumference, age or gender) whether individually or in-combination with OSA endotypic traits. These data confirm the difficulty in using routine clinical variables to predict outcomes of oral appliances therapy.[44] Our study also supports the concept that baseline severity of OSA (AHI) is not a useful predictor of responses to therapy.

Clinical Implications

The current study sought to advance knowledge for future precision sleep medicine. In the context of heterogeneous oral appliance efficacy in unselected patients, a major goal of our work was to enable the identification of a subgroup of (moderate-to-severe) OSA patients who have a superior treatment efficacy compared with other OSA patients whose average efficacy is more modest. We used an automated clinical tool to estimate the key endotypic traits causing OSA from routine diagnostic polysomnography and combined these traits to define two endotype-based subgroups of patients. On average, the "predicted responders" subgroup exhibited good treatment efficacy (~75% reduction in AHI) which, when coupled with the reported high adherence to therapy[12], appears sufficient to justify offering oral appliances as a first-line therapy in selected (moderate-to-severe) OSA patients (specifically those who have a preference for this intervention). Although our results were based on unseen 'hold-out' data (leave-one-patient-out cross-validation), these findings require replication in a larger prospective study for this method to be adopted for routine clinical use. Notably, even the "predicted non-responders" subgroup had, on average, 50% reduction in AHI (residual AHI ~16 events/hr). While this level of efficacy seems unlikely to show superior health benefit compared

to CPAP, the considerable improvement in non-responders is likely to confer benefit over no therapy, justifying prescription of oral appliance therapy as a second-line option even in this subgroup (e.g. in CPAP intolerant patients).

Our automated method has several advantages as a clinical tool for predicting outcomes. It is based on OSA endotypes, e.g. rather than demographic factors, and therefore has a close connection with the underlying mechanisms. The approach used here is inexpensive, not dependent on specialized equipment or physiological interventions and can produce results rapidly. The data used for analysis in the current study were also clinical in nature supporting clinical generalizability and translatability of physiological endotypes. Data were extracted from standard clinical sleep studies (rather than research studies) acquired by a commercially-available sleep recording system (Profusion PSG, Compumedics Ltd., Australia). Since the analysis was retrospective, there was no opportunity to pay extraordinary attention to nasal pressure quality beyond AASM standards (unfiltered nasal pressure). Other challenges for widespread implementation of our tool in clinical practice include: 1) incorporation of endotyping methods into commercial systems, and 2) requirement for re-scoring of arousal timing (not performed clinically). Neither obstacle is insurmountable.

Methodological Considerations

There are several limitations of our work. First, the endotypic traits described here are not based on gold standard measurements but rather estimated from a nasal pressure surrogate of ventilatory airflow and a mathematically-estimated ventilatory drive signal. However, it would be a highly challenging endeavor to perform gold standard measurements of physiology (via

CPAP drops or esophageal catheterization) in such large numbers of patients undergoing a specific treatment regimen. Thus, a strength and novelty of our work is obtaining such measures in a sample size of >90 oral-appliance-treated OSA patients. Second, we studied patients with baseline AHI >20 events/hr (average AHI 30 events/hr) and, thus, our results are relevant to those with similar OSA severity and may not apply to many patients with milder condition who seek oral appliance therapy. Indeed, a major goal of our work was to identify patients who might exhibit favorable outcomes of oral appliance therapy despite a more-severe OSA. Further investigation is needed to identify those with milder OSA (AHI <20 event/hr) who might be suitable for oral appliance therapy regardless of their endotypic characteristics.

Third, the incomplete-data nature of retrospective studies precluded full assessment of the impact of some other relevant variables. For example, we did not have systematic data at baseline and on-therapy for supine sleep duration. Controlling for body position would likely reduce a source of undesirable variability. Nonetheless, the influence of endotypes on efficacy is unlikely to be confounded by differences in body position at baseline and on-therapy (i.e. no plausible mechanism by which treatment-related changes in supine sleep duration could influence endotypic traits of OSA and, thus, oral appliance efficacy). We also did not have systematic measures of daytime sleepiness (e.g. Epworth Sleepiness Scale), and, thus, could not assess the role of daytime sleepiness in the context of the endotypic traits. However, we found a relationship between lower arousal threshold and reduced oral appliance efficacy, suggesting that a higher propensity for arousal from sleep might render oral appliance treatment less efficacious. Further investigation along these lines is warranted.

Fourth, we used the percent reduction in AHI as a continuous outcome measure and a single cutoff (i.e. 50% reduction in AHI) to define the "true" response subgroups. However, changing the cutoff (e.g. to a 60% or 70% reduction in AHI) did not alter the findings substantially. We also note that proportions of patients defined as *complete responders* (≥50% reduction in AHI and residual AHI<10events/hr), *partial responders* (≥50% reduction in AHI and residual AHI ≥10events/hr) and *non-responders* (<50% reduction in AHI) were 30:12:12 in predicted responders and 10:11:18 in predicted non-responders (p=0.01, Fisher exact test), respectively. Fifth, while subgroup differences in efficacy appear clinically-relevant, the overall model accuracy is modest (as noted above, predicted non-responders show an average of 50% reduction in AHI). Thus, at present we are unable to identify a subgroup of OSA patients who may exhibit negligible benefit. Incorporation of additional information on site/structure of pharyngeal obstruction (e.g. through coupling of our approach with other polysomnographic methods such as airflow shape[49]) may further improve the model precision and predictive performance.

Finally, we caution that the non-invasive measurements of endotypic traits were validated against gold standard values in relatively small samples (N=28-41) and would benefit from further refinement and validation studies, including efforts to improve reliability (e.g. incorporating respiratory inductance plethysmography to handle mouth leak) and make the measurements independent of manual scoring (e.g. quantitative EEG analysis[50]).

Conclusions

In the largest study to date, we elucidated the relationships between the pathophysiological traits causing OSA and oral appliance treatment efficacy. Although bivariate linear associations between efficacy and endotypes were not evident, our multivariable analyses showed that greater oral appliance efficacy is associated with favorable non-pharyngeal endotypic traits of OSA at baseline (including lower loop gain, higher arousal threshold and lower ventilatory response to arousal). Greater efficacy was also associated with moderate (non-mild or non-severe) collapsibility and weaker dilator muscle compensation. Combining endotypic traits identified a "predicted responders" subgroup of patients who exhibited good treatment efficacy and could potentially be targeted judiciously for early oral appliance intervention compared with a "predicted non-responders" subgroup. Further studies are needed to prospectively validate our predictive model for clinical use. We anticipate that identifying endotypes from routine diagnostic polysomnography will allow patient selection for oral appliance therapy in OSA.

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Table 1: Patient characteristics

Characteristic	Baseline	Oral Appliance	p-value
Sex (M:F)	52:41		
Age (years)	56.2 ± 11.0		
BMI (kg/m^2)	30.5 ± 5.3		
Neck circumference (cm)	40.2 ± 4.1		
Max possible advancement (mm)	10.4 ± 3.4		
Final advancement (mm)	9.2 ± 3.0		
Mandibular advancement (%max)	88.5 ±14.8		
AHI, total (events/hr)	30.6 [24.4 – 43.5]	11.3 [5.5 – 19.1]	<0.001
Percent reduction (ΔAHI)	67.4 [42.5 - 83.1]		
AHI, non-REM (events/hr)	31.4 [21.5 – 48.6]	7.3 [3.1 – 16.9]	<0.001
AHI, REM (events/hr)	48.8 [29.1 – 66.1]	25.6 [6.1 – 45.3]	<0.001
AHI, supine* (events/hr)	52.9 [33.0 – 72.4]	16.7 [8.7 – 38.4]	<0.001
Arousal Index (events/hr)	43.5 [35.7 – 54.6]	9.9 [4.4 – 16.5]	<0.001
Minimum Oxygen Saturation (%)	80 [76 – 84]	87 [81 – 90]	<0.001
Total sleep time (minutes)	356 ± 65	363 ± 65	0.43
REM sleep time (%TST)	16.8 ± 6.2	17.6 ± 6.9	0.45
Supine sleep time* (%TST)	40.1 [26.3 – 69.3]	37.0 [21.2 – 80.6]	0.83

On average, participants were typical OSA patients, middle aged, predominantly obese with moderate-to-severe OSA. Continuous variables are presented as mean ± SD or median [25th - 75th centile]. BMI, body mass index; AHI, Apnea hypopnea index; TST, total sleep time. *Data available in N=62.

Table 2: Traits associated with oral appliance efficacy: multiple regression

Variable	Beta	SEM	Beta Std.	p-value	Interpretation
Constant	47.1	5.1	1.4	<0.0001	
Pharyngeal traits					
$V_{PASSIVE}$	-0.771	0.325	-0.47	0.02	Not severe and not mild collapsibility → Success
$V_{PASSIVE}^2$	-0.0293	0.0095	-1.1	0.003	
Compensation^2	0.0215	0.0067	0.94	0.002	Higher compensation → Failure particularly when arousal threshold is low or response to arousal is high
Compensation x Arousal threshold	0.0486	0.0107	1.4	<0.0001	
Compensation x Response to arousal	-0.0171	0.0064	-0.41	0.009	
Non-pharyngeal traits					
Loop gain	-112	41	-0.37	0.008	Higher loop gain → Failure particularly when compensation or response to arousal are high
Loop gain x Compensation	-6.95	2.23	-0.52	0.003	
Loop gain x Response to arousal	-8.79	2.52	-0.70	0.0008	
Arousal threshold	0.420	0.233	0.32	0.076	Lower arousal threshold → Failure
Arousal threshold^2	0.0151	0.0055	0.51	0.007	
Response to arousal	-0.514	0.193	-0.34	0.009	Higher response to arousal → Failure
Response to arousal x $V_{PASSIVE}$	-0.0212	0.0115	-0.50	0.069	

Oral appliance efficacy is defined as the percentage reduction in apnea-hypopnea index with treatment compared to baseline (transformed, see Methods). The Table describes final results (12/20 terms) after backward stepwise elimination (P-to-remove=0.157) which began with five traits, their squares and all interaction terms. Note that significance level was $p<0.05$ in 10/20 terms and $P<0.01$ in 9/20 terms. Traits were mean-subtracted before terms were generated and applied to the model (see below). *Beta Std.* describes the number of SDs of change in treatment efficacy per SD increase in each term (1.3 SD is needed to move a typical non-responder to a typical responder). Mean values of the endotypic traits before mean substraction: $V_{PASSIVE}$=79.0±20.8, Loop gain=0.43±0.11, Compensation=-9.5+27.0%, Arousal threshold=141.8±26.0%, Response to Arousal=36.3±22.6%. A regression model cutoff of 60% (predicted reduction in AHI, untransformed) was used to define predicted responders and predicted non-responders (maximized sensitivity plus specificity). *SEM*=standard error of the mean. Overall R^2=0.30, adjusted R^2=0.19, p=0.003.

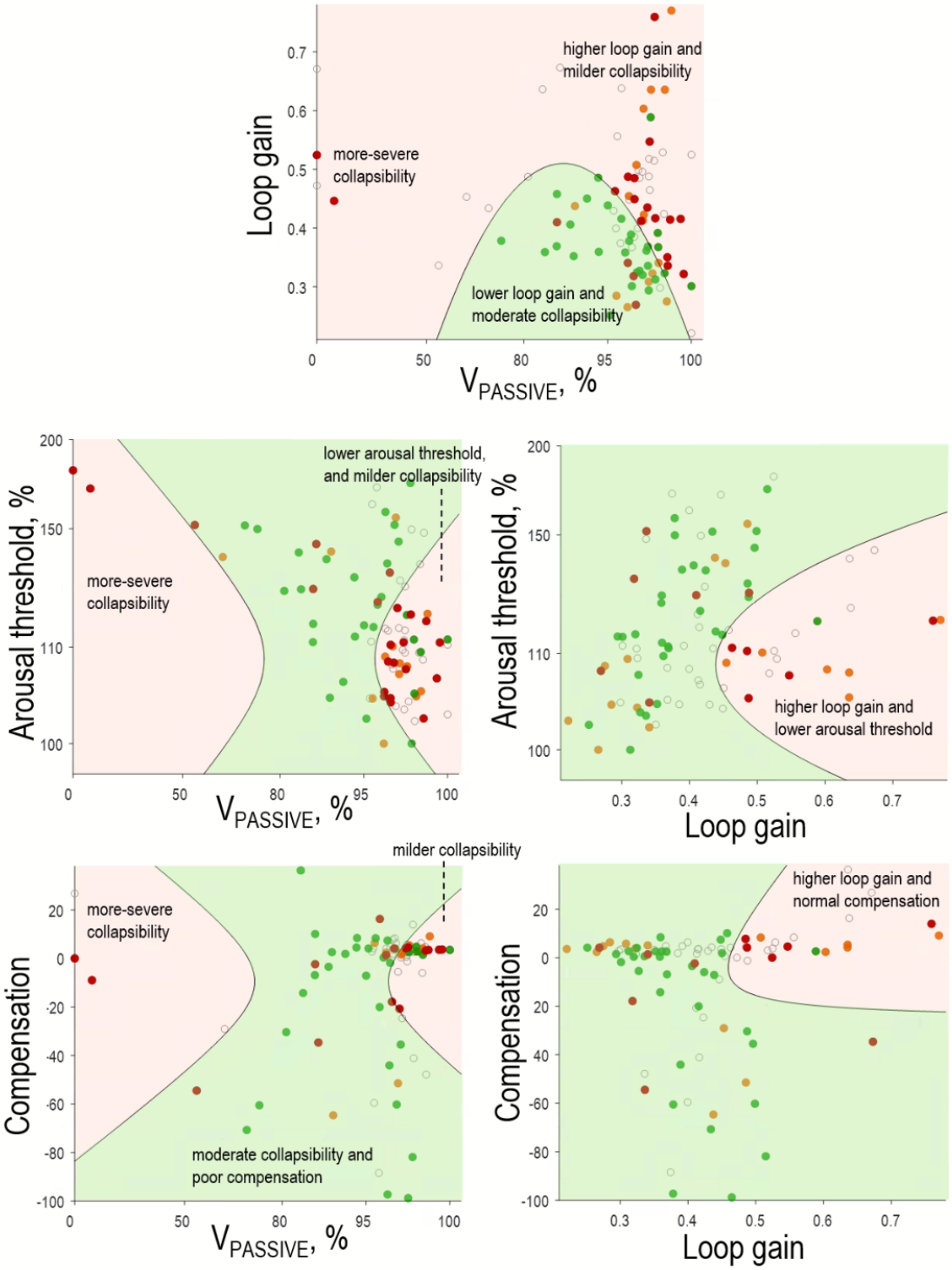
Figures Legends

Figure 1. Key aspects of the 5-trait multivariable model (Table 2) illustrating how combinations of traits may influence oral appliance efficacy. Each plot depicts a 2-trait "cross-section" of the full model drawn at the mean values of the remaining three traits. Dots represent "true" response observations of individual patients: red for non-responders (<50% reduction in AHI with treatment), orange and green for responders (50-70% reduction in AHI and >70% reduction in AHI, respectively). Background regions represent "predicted" response subgroups (light-green for predicted responders and light-red for predicted non-responders). *Top and left*: A U-shaped relationship between collapsibility (Vpassive) and efficacy is evident. For example, in Top, the light-green shading indicating predicted responders are only seen in a mid range of "moderate" collapsibility, and at lower loop gain. Note that non-responders with high Vpassive (mild collapsibility) tend to have high loop gain, low arousal threshold, higher compensation (see dense regions of red dots). *Top and right*: A higher loop gain is associated with reduced treatment efficacy, particularly in milder collapsibility (high Vpassive), but also in the presence of a lower arousal threshold and higher compensation. Open gray circles on each plot represent individual patients whose values for the three remaining traits were too far from the mean to be fairly represented in the simplifed two-trait view (i.e. 2-trait prediction differed from the full model prediction).

Figure 2. Based on combined endotype traits, predicted responders (black), compared with predicted non-responders (gray)**,** exhibited a greater oral appliance efficacy indicated by a

greater reduction in apnea-hypopnea index (untransformed) from baseline **(A)** and a lower residual apnea-hypopnea index on treatment **(B).** Error bars llustrate 95% confidence in the mean. Results are based on cross-validated analysis, whereby the endotypic subgroup allocation for each individual patient was based on a modified regression model using data from all other patients. Thus, group differences are not guaranteed by definition based on the regression model results in Table 2.

Figure 1:


Loop gain
higher loop gain and
milder collapsibility
more-severe
collapsibility
lower loop gain and
moderate collapsibility
$V_{PASSIVE}$, %
Arousal threshold, %
lower arousal threshold,
and milder collapsibility
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collapsibility
$V_{PASSIVE}$, %
Arousal threshold, %
higher loop gain and
lower arousal threshold
Loop gain
milder collapsibility
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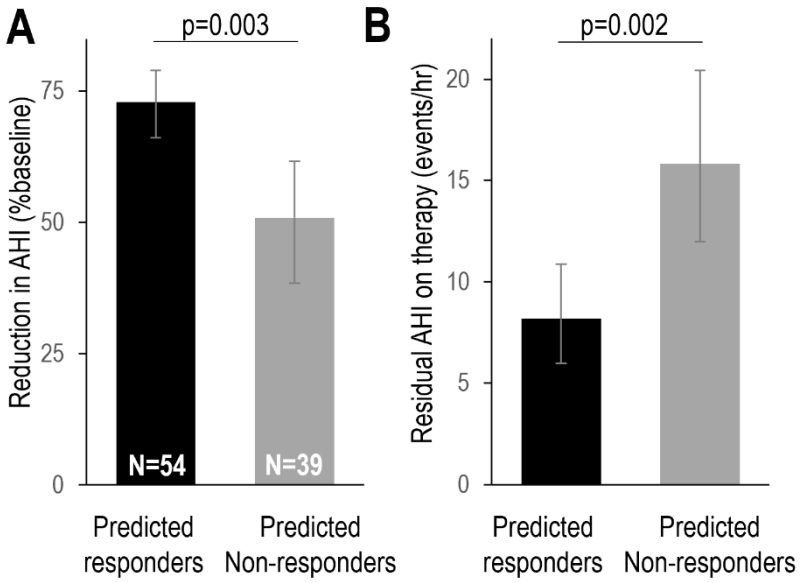
collapsibility
moderate collapsibility and
poor compensation
$V_{PASSIVE}$, %
Compensation
higher loop gain and
normal compensation
Compensation
Loop gain

Figure 2:


A
p=0.003
Reduction in AHI (%baseline)
75
50
25
0
N=54
N=39
Predicted responders
Predicted Non-responders
B
p=0.002
Residual AHI on therapy (events/hr)
20
15
10
5
0
Predicted responders
Predicted Non-responders