Upper-Airway Collapsibility and Loop Gain Predict the Response to Oral Appliance Therapy in Patients with Obstructive Sleep Apnea

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Abstract

Rationale: Oral appliances (OAs) are commonly used as an alternative treatment to continuous positive airway pressure for patients with obstructive sleep apnea (OSA). However, OAs have variable success at reducing the apnea–hypopnea index (AHI), and predicting responders is challenging. Understanding this variability may lie with the recognition that OSA is a multifactorial disorder and that OAs may affect more than just upper-airway anatomy/collapsibility.

Objectives: The objectives of this study were to determine how OA alters AHI and four phenotypic traits (upper-airway anatomy/collapsibility and muscle function, loop gain, and arousal threshold), and baseline predictors of which patients gain the greatest benefit from therapy.

Methods: In a randomized crossover study, 14 patients with OSA attended two sleep studies with and without their OA. Under each condition, AHI and the phenotypic traits were assessed. Multiple

linear regression was used to determine independent predictors of the reduction in AHI.

Measurements and Main Results: OA therapy reduced the AHI (30 ± 5 vs. 11 ± 2 events/h; $P < 0.05$), which was driven by improvements in upper-airway anatomy/collapsibility under passive (1.9 ± 0.7 vs. 4.7 ± 0.6 L/min; $P < 0.005$) and active conditions (2.4 ± 0.9 vs. 6.2 ± 0.4 L/min; $P < 0.001$). No changes were seen in muscle function, loop gain, or the arousal threshold. Using multivariate analysis, baseline passive upper-airway collapsibility and loop gain were independent predictors of the reduction in AHI ($r^2 = 0.70$; $P = 0.001$).

Conclusions: Our findings suggest that OA therapy improves the upper-airway collapsibility under passive and active conditions. Importantly, a greater response to therapy occurred in those patients with a mild anatomic compromise and a lower loop gain.

Keywords: upper-airway anatomy; obstructive sleep apnea; ventilation

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At a Glance Commentary

Scientific Knowledge on the

Subject: Currently, for the 50% of patients with obstructive sleep apnea (OSA) that cannot tolerate continuous positive airway pressure or discontinue using it after 6 months, typically clinicians consider oral appliance devices. However, these devices have variable success rates in treating OSA, and previous attempts to predict responses have been poor, largely because they have not considered that OSA is a multifactorial disorder (i.e., patients have OSA for different reasons) and is caused not just by compromised pharyngeal anatomy but also by a confluence of abnormalities in several nonanatomic traits including inadequate upper-airway muscle function, a large ventilatory response to a respiratory disturbance (high loop gain), and a low arousal threshold.

What This Study Adds to the

Field: This physiologic study demonstrates that oral appliances acutely improve the upper-airway collapsibility under passive and active conditions, without affecting muscle function, loop gain, or the arousal threshold. Importantly, those with a better passive upper-airway anatomy/collapsibility and a low loop gain at baseline gained the greatest benefit from oral appliance therapy. This work provides key insight into the physiologic characteristics of those individuals likely to be considered good clinical candidates for oral appliance therapy. Given the recent development of techniques to measure the underlying physiology causing an individual's OSA using routine clinical information, our findings bring clinicians one step closer to individualizing therapy for patients with OSA.

Obstructive sleep apnea (OSA) is a highly prevalent disorder with serious cardiovascular (1–8) and neurocognitive consequences (9), yet only 50% of patients with OSA can tolerate the most commonly prescribed treatment, continuous positive

airway pressure (CPAP) (10, 11).

Importantly, oral appliances (OAs) (12, 13) are often recommended for the treatment of OSA, versus no treatment at all, for CPAP-intolerant patients and those that prefer an alternative to CPAP. Notably, the success rate of OAs varies dramatically (14, 15), making decisions regarding patient selection a clinical challenge.

The key, we believe, to better understanding the variable success rate of OAs, is to recognize that OSA is a multifactorial disorder, and is not simply caused by poor upper-airway anatomy. Recent evidence suggests that several additional nonanatomic traits also contribute to the pathogenesis of OSA (16–20) including but not limited to (1) an inability of the pharyngeal muscles to hold open or stiffen the airway, (2) an oversensitive ventilatory control system (i.e., high loop gain), and (3) a low respiratory arousal threshold. To date, investigations into how OAs alter these traits have focused solely on how they modify one trait: upper-airway anatomy/collapsibility. Such studies have shown that OAs increase the upper-airway size (21–23), which often leads to a reduction in pharyngeal collapsibility and OSA severity (24). Although improving upper-airway anatomy/collapsibility is likely to be a key determinant in predicting the efficacy of these devices, it may not be the only factor involved. To date several investigators have used both clinical and polysomnographic predictors of OA success and have found that patients who gain the greatest benefit are often younger, less obese, have a smaller neck circumference, display a lower baseline apnea–hypopnea index (AHI), and have positional OSA (15, 25–27). However, the prediction models generated by these studies do not have sufficient accuracy to be directly translated into clinical practice (25), and hence alternative prediction methods are needed.

Importantly, there is no information on how OAs alter the nonanatomic traits responsible for OSA. It is plausible that the variability in response may be related to the ability of OAs to alter the nonanatomic traits. For instance, improving the anatomy/collapsibility may reduce the mechanical load on the airway thereby enabling the upper-airway dilator muscles to be more effective at reopening the airway during periods of airway collapse.

Furthermore, if OAs are successful at immediately reducing OSA severity, this could in turn decrease the arousal threshold (28–30) or loop gain (28, 31), which may perpetuate a further improvement in the disorder. Therefore, using well-described and validated techniques (16), the current study aims to investigate the effect of OA therapy on four key traits responsible for OSA, and determine the baseline physiologic traits of the patients that gained the greatest benefit from OA therapy.

Methods

Participants

Fourteen patients with OSA were recruited from sleep laboratories at the Brigham and Women's Hospital (BWH) and Monash Medical Centre (MMC). All patients had documented OSA (AHI >10 events/h) and were currently being treated with a custom-fitted OA. The degree of mandibular advancement was set by a qualified dentist at the patient's maximal comfortable/tolerable limit. A detailed description of the exclusion criteria is provided in the online supplement. Written informed consent was given before enrolment, which was approved by the Human Research Ethics Committees at both Partners Healthcare and Monash Health.

Experimental Design and Setup

Subjects were randomized to initially spend 2 nights in our sleep laboratory with or without their OA. During these visits patients underwent a clinical polysomnography (PSG) to measure their OSA severity, and a research PSG to measure the four physiologic OSA traits. During both PSGs, subjects were asked to sleep in the supine position. The clinical and research PSGs were then repeated with the opposite intervention (device or no device) at least 1 week later. All subjects were advised to continue to use their device during this “washout” period.

A standard clinical montage was used during the clinical PSG as described in the online supplement. Sleep state and respiratory events were scored by a trained sleep technician according to standard criteria (32). The sleep technician was blinded to the study intervention. During the research PSG, subjects were initially placed on CPAP sufficient to eliminate snoring, flow limitation, and hypopneas (i.e., therapeutic CPAP). Airflow was measured using a nasal

mask (BWH: Respironics, Murrysville, PA; MMC: Resmed, Sydney, Australia) attached to a pneumotachometer (model 3700A; Hans Rudolph, Kansas City, MO). The mask was attached to a positive/negative pressure source (Phillips-Respironics, Murrysville, PA) used to regulate the level of CPAP. A port in the mask (Validyne, Northridge, CA) facilitated the measurement of mask pressure. CO₂ was recorded at the nostril via a capnograph (Vacumed, Ventura, CA). All signals were sampled at 125 Hz and displayed using clinical sleep recording software (BWH: Nihon Kohden, Tokyo, Japan; MMC: Compumedics Graef, Abbotsford, Victoria, Australia) and Spike2 software (Cambridge Electronic Design, Cambridge, UK).

Measuring the Traits Responsible for OSA

The traits were assessed in units of ventilation during supine non-REM sleep

using our previously published and validated method (33), which manipulates CPAP and assesses the consequent changes in ventilation (Figure 1) described as follows:

1. Eupneic ventilation (V_{eupnea}): the asleep ventilatory requirement/demand based on metabolic rate and dead space, quantified as the mean ventilation during optimal therapeutic CPAP.
2. Passive anatomy/collapsibility (V_{passive}): the ventilation through a passive airway (CPAP = 0 cm H₂O) at eupneic ventilatory drive. To determine V_{passive} , a series of step-wise reductions in the CPAP level from the therapeutic pressure for five breaths were performed until apnea was produced. Linear regressions were performed between minute ventilation against mask pressure for breaths 3–5 (if the breaths were flow-limited) after each CPAP drop. The y -intercept of minute

ventilation versus mask pressure regression (zero mask pressure) was taken as V_{passive} .

3. Ventilation that causes an arousal (V_{arousal}): during the gradual CPAP reduction, the upper airway narrows and ventilation is eventually decreased until CO₂ and ventilatory drive have increased to a level that causes respiratory effort-related arousals. The level of CPAP associated with these arousals is referred to as the “minimum tolerable level” (CPAP_{min}). V_{arousal} was measured as the average ventilation over the five flow-limited breaths just before the arousal (defined as >3 s of high-frequency activity on the EEG). The data were excluded if there was no clear flow limitation before the arousal, or if the ventilation was greater than V_{eupnea} (i.e., spontaneous arousal).

During the flow-limited stable breathing between arousals, CPAP was

Figure 1. Technique for determining the physiologic traits using continuous positive airway pressure (CPAP) manipulations. The obstructive sleep apnea traits are measured by manipulating CPAP during supine non-REM sleep (A) and measuring the changes in ventilation (B). After determining ventilation on optimum CPAP (V_{eupnea} ; i), a series of step-wise reductions (inset) in the CPAP from the therapeutic pressure was produced, and V_{passive} (ii) was taken as the y -intercept of the minute ventilation versus mask pressure regression (zero mask pressure). CPAP was then lowered until flow limitation started (iii) and arousals occurred intermittently. Ventilation just before arousal (iv) was defined as the “ventilation causing arousal” (V_{arousal}). During stable breathing between arousals, CPAP was dialled down or up to obtain V_{active} (v) and loop gain (vi), respectively. V_{active} is the ventilation at CPAP = 0 when pharyngeal muscles are maximally activated. Loop gain is the ventilatory response (overshoot in ventilation above V_{eupnea}) divided by the ventilatory disturbance (reduction in ventilation below V_{eupnea}). (C) Illustration of how these four ventilations can be used to calculate the arousal threshold and upper-airway (UA) response (or gain), and how all four traits interact to manifest the absence or presence of obstructive sleep apnea. Once the patient’s loop gain is known, the ventilation that causes arousal was translated into the ventilatory drive that causes the arousal, which is referred to as the arousal threshold (i.e., 9 L/min). Once the arousal threshold is known, starting at V_{passive} , as ventilatory drive is increased to a level near the arousal threshold, then the pharyngeal muscles activate and increase V_{passive} to the measured level V_{active} . The slope of this line is called the upper-airway gain and is a measure of the upper-airway muscle function. The steeper this slope, the better the upper-airway response to an increase in ventilatory drive, and the larger the distance between the V_{active} and V_{passive} . To not have obstructive sleep apnea (i.e., achieve stable breathing), V_{active} must be above V_{arousal} . CPAP_{min} = minimum tolerable level of continuous positive airway pressure; V_{passive} = passive anatomy/collapsibility.

dialled-down or up to measure V_{active} and loop gain, respectively.

4. Ventilation on zero CPAP when the upper-airway muscles are maximally active (V_{active}): represents the ventilation that can be achieved through a maximally active airway without arousal. When ventilatory drive is at or near the arousal threshold, the pharyngeal muscles are maximally active during sleep, thereby permitting more airflow than during the passive condition. After raising drive by lowering CPAP to CPAP_{min}, CPAP was dropped to zero to measure V_{active} ; the difference between V_{passive} and V_{active} reflects the amount of compensatory ventilation that can be generated by the upper-airway muscles.
5. Ventilatory control sensitivity (i.e., loop gain): the increase in ventilatory drive (measured as the ventilatory overshoot following a switch to optimal CPAP) in response to a steady-state reduction in ventilation. During CPAP_{min}, ventilation often becomes stably reduced below baseline levels despite the raised ventilatory drive. Loop gain was calculated by abruptly returning the CPAP back to the therapeutic pressure and measuring the overshoot in ventilation, which is a quantitative reflection of the increased ventilatory drive. Loop gain was defined as the ratio of the rise in ventilatory drive (V_r) in response to a persistent reduction or disturbance in ventilation (V_d). Thus loop gain = V_r/V_d .

Multiple measurements of each ventilation/trait were averaged to produce a single value for each patient. The mean of these four ventilations together with the loop gain can then be incorporated in a model that allows the arousal threshold and the effectiveness of the upper-airway muscles (i.e., upper-airway gain) to be calculated. The difference between V_{arousal} and V_{active} , which we refer to as the physiologic “gap,” predicts whether stable breathing is possible or if patients will exhibit OSA. A positive “gap” quantifies the degree of ventilatory insufficiency and predicts the presence of OSA. In other words, the ventilation needed to avoid arousal cannot be achieved through the activated airway ($V_{\text{active}} < V_{\text{arousal}}$). A negative “gap” quantifies the degree of ventilatory reserve, and predicts that stable

breathing is possible without arousal ($V_{\text{active}} > V_{\text{arousal}}$).

Statistics

Paired *t* tests or Wilcoxon rank sum tests were used to assess the effects of OA therapy depending on whether or not the data were normally distributed. Multivariate regression was used to determine significant predictors of the reduction in AHI. Lastly, to determine the physiologic characteristics of patients that gained the greatest benefit from OA therapy, patients were categorized as responders to therapy using three commonly used definitions: (1) if their treatment AHI was reduced by greater than or equal to 50% of the baseline value, (2) criterion 1 plus a treatment AHI of less than 10 events per hour, and (3) a treatment AHI of less than five events per hour. All statistical analyses were performed using SigmaPlot (Systat Software, San Jose, CA) with *P* less than or equal to 0.05 considered significant. Values are presented as means $\pm$ SEM or medians (interquartile range) unless stated otherwise.

Results

The demographics of the 14 patients are displayed in Table 1, and the details of the patients' OA devices (i.e., device type, degrees of mandibular advancement, and vertical opening) are provided in the online supplement (see Table E1 in the online supplement). The effects of OA therapy on both sleep architecture and sleep-disordered breathing (determined from clinical PSG) are summarized in Table 2.

Table 1. Baseline Participant Characteristics

Variable	
Age, yr	51.8 $\pm$ 2.3
Sex, M/F, n	11/3
Height, cm	175.9 $\pm$ 2.3
Weight, kg	89 (78.5–98)
BMI, kg/m ²	28.8 $\pm$ 1.1

Definition of abbreviation: BMI = body mass index.

Values are provided as median (interquartile range) or mean $\pm$ SEM unless otherwise indicated.

Effect of OA Therapy on the OSA Traits

The number of measurements used to quantify the OSA traits was similar between the OA and baseline nights (24 ± 2 vs. 24 ± 4 ; *P* = 0.7). The effects of OA therapy on the traits are displayed in Table 3. OA therapy significantly increased the V_{passive} (*P* = 0.002) and the V_{active} (*P* < 0.001). These improvements resulted in a significant reduction in the physiologic gap (*P* = 0.003) between the level of ventilation that leads to arousals (V_{arousal}) and the maximum ventilation achievable without arousal (V_{active}). Notably, there was considerable variability in the improvements in V_{passive} (2.8 ± 2.7 L/min; mean, $\Delta V_{\text{passive}} \pm$ SD) and V_{active} (3.8 ± 3.4 L/min; mean $\Delta V_{\text{active}} \pm$ SD). OA therapy did not significantly alter the eupneic ventilation (V_{eupnea}), upper-airway gain, loop gain, or arousal threshold. The difference between V_{active} and V_{passive} also remained unchanged.

The group average of the four physiologic traits were combined graphically using our mathematical model (16, 33) to illustrate how the traits interact to manifest the absence or presence of OSA in Figure 2. Note that OA therapy (Figure 2B) abolished the gap indicating that, on average, the device successfully treated the physiologic deficits responsible for their OSA (in non-REM sleep).

Predictors of Response to Therapy

Linear regression demonstrated that loop gain (at baseline) was a significant predictor of the percent reduction in AHI with an OA ($r^2 = 0.57$; *P* = 0.001) (Figure 3A). It was also noted that there was a near significant trend for the percent reduction in AHI to be associated with the baseline V_{passive} (Figure 3B). None of the other traits showed any relationship with the percent reduction in AHI. However, when using multiple linear regression, both baseline V_{passive} and loop gain were significant independent predictors of the percent reduction in AHI (Table 4) ($r^2 = 0.70$; adjusted $r^2 = 0.64$; *P* = 0.001). When comparing whether these physiologic indices predict response to therapy even after controlling for age, body mass index (BMI), and baseline AHI (variables that have commonly been used in previous predictive models), only AHI and loop gain remained strong predictors ($r^2 = 0.87$;

Table 2. Effect of Oral Appliance Therapy on Sleep Architecture and Sleep-Disordered Breathing

Variable	Baseline	Oral Appliance Therapy	P Value
Sleep architecture			
TIB, min	424.1 ± 14.3	435.1 ± 18.2	0.31
TST, min	340.7 ± 13.9	363.4 ± 10.8	<0.0001
% Sleep efficiency (TST/TIB)	80.7 (65.4 to 97.1)	84.1 (68.7 to 97.5)	0.008
N1 duration, min	66.7 ± 11.7	53 ± 7.9	0.21
N2 duration, min	199 ± 14.0	213 ± 9.1	0.28
N3 duration, min	19 (0 to 62.5)	23.3 (0 to 71.5)	0.37
non-REM duration, min	289.5 ± 7.8	294.1 ± 7.8	0.63
REM duration, min	51.7 ± 7.8	66.9 ± 7.1	0.03
Sleep-disordered breathing			
Total AHI, events/h	29.6 ± 5.3	10.6 ± 2.3	<0.001
AHI _{NREM} , events/h	30.6 ± 5.5	9.0 ± 1.8	<0.001
Therapy reduction in AHI _{NREM} , %		62.6 ± 7.5	
AHI _{REM} , events/h	23.0 ± 5.9	18.8 ± 6.1	0.32
Therapy reduction in AHI _{REM} , %		13.4 (−4.7 to 69.4)	
Obstructive apnea index, events/h	4.1 ± 1.5	1.0 ± 0.4	0.06
Hypopnea index, events/h	25.4 ± 5.1	9.5 ± 2.0	0.01
Respiratory event arousal index, events/h	13.0 ± 2.0	5.3 ± 1.6	<0.001
Lowest SaO ₂ , %	84.6 ± 1.5	88.0 ± 1.7	0.05

Definition of abbreviations: AHI = apnea–hypopnea index; NREM = non-REM; TIB = time in bed; TST = total sleep time.

Group data (n = 14) from the clinical polysomnography. Values are mean ± SEM or median (interquartile range). Bold text highlights the values that are significantly different.

adjusted $r^2 = 0.79$; $P = 0.002$). Both BMI and V_{passive} dropped out because they were correlated with each other ($r^2 = 0.48$; $P = 0.006$), as evidenced by the high variance inflation factors. Repeating the analysis after removing BMI from the regression model (because of its having the highest variance inflation factors) showed that baseline AHI, V_{passive} , and loop gain were significant predictors of the percent reduction in AHI (Table 4) ($r^2 = 0.83$; adjusted $r^2 = 0.75$; $P = 0.002$).

A total of 7 (50%) and 6 (43%) out of the 14 patients were classified as responders to therapy using criteria 1 and 2, respectively. Findings using criterion 3 were

similar to criterion 1 and are presented in the online supplement (see Table E2). The baseline clinical and physiologic characteristics (i.e., traits) of responders and nonresponders using both criteria are summarized in Table 5. Baseline loop gain was the sole predictor of successful therapy using criterion 1, with those showing the greatest improvement in OSA severity having a low or normal loop gain (3.0 ± 0.5 vs. 5.4 ± 0.7 ; $P = 0.02$). When using criterion 2, baseline loop gain ($P = 0.012$) remained different between groups, whereas V_{passive} (normalized to V_{eupnea}) now became an additional predictor ($P = 0.048$) of those likely to improve with OA therapy

(Figure 4). Regardless of responder criteria used, the improvement in both V_{passive} and the V_{active} achieved with the OAs was not different between the groups. Further analysis also illustrated the combinations of loop gain and upper-airway collapsibility (Figure 5) that would be expected to respond to OA therapy. Receiver operating characteristic curve analyses using the predicted reduction in AHI derived from the combination of loop gain and V_{passive} correctly predicted the response to OA therapy (defined using criterion 2) with a sensitivity of 100% and a specificity of 87.5%. The cutoff that best separated the groups was a predicted reduction in AHI of 63.4%; this cutoff reflected a treatment AHI of 6.5 ± 1.9 events/h in responders versus 16.0 ± 3.9 events/h in nonresponders ($P = 0.034$). Similar receiver operating characteristic curve results were also seen when the response to OA therapy was defined using criterion 1 or 3 (see Table E3).

Discussion

Despite the widespread use of OAs for the treatment of OSA, there remains considerable uncertainty about their precise mechanisms of action on the underlying physiology. The major novel findings of our study were that OA therapy significantly

Table 3. Effects of Oral Appliance Therapy on the Physiologic Traits Causing OSA

Variable	Baseline	Oral Appliance Therapy	P Value
V_{eupnea} , L/min	6.8 ± 0.3	7.0 ± 0.3	0.24
V_{arousal} , L/min	5.8 ± 0.3	6.0 ± 0.3	0.38
V_{active} , L/min	2.4 ± 0.9	6.2 ± 0.4	<0.001
V_{passive} , L/min	1.9 ± 0.7	4.7 ± 0.6	0.002
Loop gain	4.2 ± 0.5	4.5 ± 0.8	0.61
Arousal threshold, L/min	10.4 ± 0.7	11.0 ± 0.9	0.41
Upper-airway gain	0.5 ± 0.4	0.5 ± 0.2	0.92
$V_{\text{arousal}} - V_{\text{active}}$ (the gap), L/min	3.4 ± 0.9	−0.2 ± 0.5	0.003
$V_{\text{active}} - V_{\text{passive}}$, L/min	0.5 ± 0.7	1.5 ± 0.6	0.18

Definition of abbreviations: OSA = obstructive sleep apnea; V_{active} = ventilation on zero continuous positive airway pressure when the upper-airway muscles are maximally active; V_{arousal} = ventilation that causes an arousal; V_{eupnea} = eupneic ventilation; V_{passive} = passive anatomy/collapsibility. Group data from the research polysomnography. Values are mean ± SEM. The bold text highlights the values that are significantly different.

Figure 2. Integrative model of the obstructive sleep apnea (OSA) traits demonstrating how oral appliance therapy improves the physiology causing OSA. (A) The traits at baseline are consistent with OSA. Stable breathing is not possible because the achievable ventilation (V_{active}) is below the level needed to prevent arousal (V_{arousal}). (B) Oral appliance therapy restores stable breathing and abolishes OSA. This improvement is driven by the dramatic improvement in both V_{passive} and V_{active} . V_{active} = ventilation on zero continuous positive airway pressure when the upper-airway muscles are maximally active; V_{arousal} = ventilation that causes an arousal; V_{eupnea} = eupneic ventilation; V_{passive} = passive anatomy/collapsibility.

improves the passive anatomy/collapsibility (i.e., V_{passive}) and the ventilation achieved when the pharyngeal muscles are maximally activated (i.e., V_{active}), while also demonstrating that the nonanatomic traits (i.e., loop gain, arousal threshold, and upper-airway gain) remain unchanged. In addition, we report that baseline anatomy/collapsibility (i.e., V_{passive}) and loop gain were independent predictors of patients likely to gain the greatest benefit from OA therapy. More specifically, patients who showed the greatest reduction in their AHI had a less collapsible airway (i.e., higher V_{passive}) and a low/normal loop gain at baseline. Although nonresponders had their anatomy improved by similar amounts to the responders, these individuals still had residual OSA due to nonanatomic causes (i.e., a high loop gain). Importantly, the current work has provided the first comprehensive assessment of the mechanisms and effect size by which OAs alter the physiologic traits causing OSA. These findings, taken together with the knowledge that a combination of baseline upper-airway collapsibility and loop gain

predicts successful treatment, suggest that *a priori* knowledge of an individual's underlying OSA pathophysiology would be useful in helping physicians determine which patients should be selected for OA therapy.

The Effect of OA Therapy on OSA Severity

Similar to the previous investigations (for review, see Reference 34), the current study confirmed that OA therapy significantly reduced the overall AHI. Furthermore, the proportion of our patients who had their OSA completely resolved (i.e., AHI < 5 events/h), and those whose treatment AHI was less than 10 events/h, is consistent with previously published data (13, 15, 25, 26, 35). Interestingly, the current study reported that the improvement in the AHI was driven solely by an improvement in the non-REM AHI, because the REM AHI remained unchanged with OA therapy. This is in contrast to the results of Sutherland and colleagues (25), which demonstrated in a large number ($n = 425$) of patients that OA therapy causes a significant reduction in both non-REM (by

61%) and REM (by 39%). Although the reduction in non-REM observed in the current study was almost identical, we speculate that we may have been underpowered to detect a difference in REM. It is also noteworthy that our data showed a trend for responders to have more severe OSA (Table 5) without their device, which is counter to the common perception that baseline AHI is the best predictor of response. Nonetheless, this finding is consistent with our result that baseline AHI is only a modest predictor of treatment response, and complete or partial response to OA may still occur in all severities of OSA.

The Effect of OA Therapy on the Physiologic Traits Causing OSA

The current study is the first to document the effect of OA therapy on four of the phenotypic traits known to cause OSA. Previous investigations have solely focused on how OAs have altered the anatomy/collapsibility trait. Studies using imaging techniques (i.e., magnetic resonance imaging) in awake patients with OSA have consistently reported that OAs improve the cross-sectional area of the upper airway, which is expected to decrease the susceptibility to airway collapse during sleep (23, 36). In addition to these studies, Ng and colleagues (24) assessed the passive upper-airway closing pressure (a direct measure of the pressure at which airway collapse occurs) in patients with OSA during sleep, and reported that OAs decreased the closing pressure by 144%. Although we used a different technique for assessing airway collapsibility, we saw a strikingly similar improvement (140%) in the passive anatomy/collapsibility.

A major novel finding of the present study was that the ventilation achieved when pharyngeal muscles were active (V_{active}) was improved by OA therapy. Thus, both V_{active} and V_{passive} were increased, and the magnitudes of their increase were comparable, indicating that the effect of the pharyngeal muscles is preserved with OA therapy. We considered the possibility that there may be a synergistic effect of OA therapy and dilator muscles, manifest as a greater ability for the upper-airway muscles to dilate and restore flow with a reduction in mechanical load on OA therapy. However, we found no change in upper-airway gain, and the magnitude of muscle compensation between active and passive conditions was similar on OA therapy.

Figure 3. Physiologic predictors of response to therapy. (A) The relationship between loop gain at baseline and percentage reduction in apnea–hypopnea index (AHI). Baseline loop gain (represented as the ratio of a ventilatory response/ventilatory disturbance) was the only significant predictor of the percent reduction in AHI ($P = 0.001$). A lower baseline loop gain (loop gains closer to zero) was associated with a greater percent reduction in AHI, indicating those with a low/normal loop gain were likely to have a greater improvement in their obstructive sleep apnea severity when treated with an oral appliance. (B) There was a near significant trend for the percent AHI reduction to be associated with passive anatomy/collapsibility (V_{passive}) at baseline. Negative values of V_{passive} indicate an airway that collapses despite positive airway pressure.

Thus, our evidence suggests that OA therapy does not have a substantial impact on OSA pathophysiology through improving dilator muscle effectiveness. Lastly, the current study also showed for the first time that the other nonanatomic traits (i.e., loop gain and arousal threshold) were not altered by OA therapy.

Predictors of Treatment Success

It is well known that OAs resolve OSA in only a proportion of patients and that success rates vary dramatically, which presents an important clinical barrier to patient selection. As such, there has been an

intensive research interest into the patient characteristics or phenotypes that reliably predict treatment success. Previous studies examining clinical and polysomnographic predictors of OA success have reported that patients who gain the greatest benefit are often younger, less obese, have a smaller neck circumference, and display a lower baseline AHI (15, 25). However, these predictors of treatment success are not completely accurate, because treatment success with OAs can also occur in heavier patients (37) and those with severe OSA (38). The key to providing better predictors of OSA resolution with OA therapy is

to understand how these devices impact the underlying physiology. Interestingly, studies assessing the anatomic and functional characteristics of the upper airway with and without an OA during sleep (24) (or using simulated mandibular advancement using drug-induced sleep [39]) have suggested that the change in upper-airway collapsibility/patency may have good predictive value.

The current work extends these previous studies by demonstrating that not only is a patient's baseline upper-airway anatomy/collapsibility important, but suggests that the nonanatomic trait loop gain also plays a major role in predicting treatment success. Notably, these two traits explained the overwhelming majority (70%) of the variance in the AHI reduction. More specifically, this study demonstrated for the first time that responders (defined using criterion 2, because it has the widest applicability for clinical practice) had a less collapsible airway and lower loop gain compared with nonresponders. These findings suggest that responders to OA therapy have primarily milder anatomic deficiencies, a finding that is congruent with the known associations between upper-airway collapsibility and the previously used predictors age (40) and BMI (41), and that nonresponders have a moderate-severe anatomic abnormality that is also accompanied by deficiencies in the nonanatomic traits (most notably loop gain). Importantly, the identification of such novel predictors of treatment success may be useful either alone (Figure 5) or added to existing predictive models (25, 38), in assisting clinicians to better stratify which patients with OSA should be referred for this intervention.

Clinical Implications and Study Limitations

The current work suggests that assessment of the underlying physiology causing an individual's OSA may allow for the successful identification of the patient subgroup most likely to respond to OA therapy. The main constraint to such a prediction methodologies is the requirement to quantify an individual's baseline physiologic traits. Although currently this requires a physiologic PSG, a great deal of progress has been made in quantifying the traits from existing clinical data. Novel research has recently established a method that can reliably

Table 4. Multiple Linear Regression Models Investigating the Baseline Physiologic Determinants of the Percentage Reduction in AHI with Oral Appliance Therapy

	Model 1			Model 2		
	β	SE of β	P Value	β	SE of β	P Value
V_{passive} , L/min	4.0	1.9	0.05	4.6	1.7	0.028
Loop gain	10.6	2.5	0.001	10.2	2.2	0.001
Baseline AHI, events/h				0.6	0.2	0.049
Age, yr				0.1	0.6	0.875

Definition of abbreviations: AHI = apnea–hypopnea index; V_{passive} = passive anatomy/collapsibility. β represents the nonstandardized regression coefficients; SE of β = SE of the nonstandardized regression coefficient; the linear regression for model 1 is given by $\text{Reduction in AHI (\%)} = (4.0 \times V_{\text{passive}}) - (10.6 \times \text{loop gain}) + 94.6$. The bold text highlights the values that are significantly different.

Table 5. Clinical and Physiologic Characteristics of Responders to Therapy

Variable	Criteria #1 (50% Reduction in AHI)		Criteria #2 (50% Reduction in AHI and AHI _{therapy} <10 events/h)	
	Responders (n = 7)	Nonresponders (n = 7)	Responders (n = 6)	Nonresponders (n = 8)
Clinical characteristics				
Age, yr	51 ± 4	52 ± 3	53 ± 4	51 ± 3
Sex, M:F, n	6:1	5:2	4:2	7:1
BMI, kg/m ²	28.7 ± 1.3	28.9 ± 1.9	27.4 ± 1.3	29.8 ± 1.6
CPAP requirement, cm H ₂ O	8.1 ± 1.3	7.1 ± 1.0	7.6 ± 1.4	7.7 ± 1.0
Total AHI, events/h	37.1 ± 9.3	22.0 ± 3.9	32.3 ± 11.1	27.5 ± 4.8
Physiologic characteristics				
V _{eupnea} , L/min	6.9 ± 0.5	6.7 ± 0.2	6.5 ± 0.6	6.9 ± 0.3
V _{arousal} , % V _{eupnea}	84.0 ± 4.0	86.6 ± 2.0	80.7 ± 3.4	88.7 ± 2.2
V _{active} , % V _{eupnea}	35.4 ± 21.0	38.2 ± 17.0	46.7 ± 23.3	29.3 ± 15.4
V _{passive} , % V _{eupnea}	36.6 ± 9.7	23.0 ± 18.7	51.6 ± 8.6	13.5 ± 14.7*
Loop gain	3.0 ± 0.5	5.4 ± 0.7*	2.8 ± 0.5	5.3 ± 0.6*
Arousal threshold, % V _{eupnea}	145.7 ± 12.8	159.3 ± 5.0	153.9 ± 13.0	151.5 ± 7.9
Upper-airway gain	0.3 (−0.4 to 1.2)	0.2 (−0.1 to 0.6)	0.0 (−0.3 to 0.9)	0.3 (−0.1 to 0.7)
V _{arousal} − V _{active} (the gap), % V _{eupnea}	48.6 ± 20.0	48.4 ± 17.3	34.0 ± 20.9	59.4 ± 15.9

Definition of abbreviations: AHI = apnea–hypopnea index; AHI_{therapy} = apnea–hypopnea index on oral appliance therapy; BMI = body-mass index; CPAP = continuous positive airway pressure; V_{active} = ventilation on zero continuous positive airway pressure when the upper-airway muscles are maximally active; V_{arousal} = ventilation that causes an arousal; V_{eupnea} = eupneic ventilation; V_{passive} = passive anatomy/collapsibility.

Values are mean ± SEM or median (interquartile range). Bold text highlights the values that are significantly different.

*P ≤ 0.05.

determine an individual's loop gain (42) and arousal threshold (43) from clinical PSG data alone, and there are preliminary data suggesting that the other traits may also be measurable using the same PSG

data. Thus, although the development of these techniques provides a promising and cost effective identification toolbox for enabling appropriate treatments targeted toward a patient's individual

phenotype, the utility of this approach in the clinical setting remains to be confirmed.

Our study has several potential limitations that need to be considered. First, we studied a relatively small number of subjects, which could have weakened our power in certain assessments. However, robust, statistically significant outcomes were observed in many domains. Second, the type of OA device was not standardized, because each patient wore their own previously configured device. Despite these limitations our results showed almost identical improvements in the polysomnographic variables (including the AHI) and a similar number of responders to therapy as previous studies (14, 15, 25), regardless of how a responder was defined (i.e., AHI <5 events/h, 50% reduction; AHI <10 events/h, or 50% reduction only). Therefore, we believe that our sample is representative of patients with OSA, and that our results can be extrapolated to a general OSA population.

Another potential limitation we encountered was the ability of our patients to tolerate PAP during the research PSGs. During this PSG, we often observed an increased sleep latency, mouth breathing, and multiple awakenings throughout the night that impacted the amount of time available for physiologic measurements.

Figure 4. Baseline physiologic characteristics of responders to therapy. Responders to therapy (using criterion 2) had (A) a lower loop gain and (B) a less collapsible airway under passive conditions (V_{passive}; expressed as a percentage of V_{eupnea}). Non-R = nonresponders; R = responders; V_{eupnea} = eupneic ventilation; V_{passive} = passive anatomy/collapsibility.

Figure 5. Loop gain and passive upper-airway collapsibility (V_{passive}) combine to predict the response to oral appliance (OA) therapy. Responders have a significantly lower loop gain and less severe collapsibility (higher V_{passive}) than nonresponders (see multiple linear regression). Note that the patients with the two lowest loop gain values did not respond well to therapy; their poor responses are explained by the more severe collapsibility. The *dashed line* describes the multiple linear regression, shown here at a 67% reduction in apnea-hypopnea index (best approximating criterion 2, which is used to define responders and nonresponders here). The *shaded region* describes the region of predicted responders.

Despite these challenges, total sleep time did not significantly differ between the two research PSGs ($P = 0.89$) indicating the time available to take measurements was equivalent between nights with and without the OA. Furthermore, a similar number of measurements were taken on both research PSGs and there were equivalent levels of variance seen in the

traits on both nights. Thus, we are confident that despite these limitations our measurements of the physiology are robust and repeatable. Lastly, our study was conducted in patients already receiving treatment rather than newly diagnosed patients. It is possible that such prior treatment may have had an impact on the underlying physiologic traits (see online

supplement for further discussion). Thus, for our findings to be directly translatable into clinical practice, future work needs to confirm the present findings in a prospective validation study in treatment-naïve patients.

Conclusions

The current study is the first to examine how OAs alter the four physiologic traits known to cause OSA. Our findings demonstrate that OA therapy improves upper-airway collapsibility under both passive and active conditions, illustrating that OA therapy and upper-airway dilator muscles act in an additive manner to improve collapsibility and airflow. Muscle dilator effectiveness, loop gain, and arousal thresholds were not affected by OA therapy. Interestingly, although nonresponders had their upper-airway anatomy/collapsibility improved, these patients still had residual OSA due to nonanatomic causes (i.e., high loop gain). Given the recent expansive development of techniques to measure a patient's underlying physiology using routine clinical information, the major clinical implication of this study is that measurement of phenotypic traits will take clinicians one step closer to individualizing therapy for patients with OSA. ■

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