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Clinical Predictors of the Respiratory Arousal Threshold in Patients with Obstructive Sleep Apnea

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Abstract

Rationale: A low respiratory arousal threshold (ArTH) is one of several traits involved in obstructive sleep apnea pathogenesis and may be a therapeutic target; however, there is no simple way to identify patients without invasive measurements.

Objectives: To determine the physiologic determinates of the ArTH and develop a clinical tool that can identify patients with low ArTH.

Methods: Anthropometric data were collected in 146 participants who underwent overnight polysomnography with an epiglottic catheter to measure the ArTH (nadir epiglottic pressure before arousal). The ArTH was measured from up to 20 non-REM and REM respiratory events selected randomly. Multiple linear regression was used to determine the independent predictors of the ArTH. Logistic regression was used to develop a clinical scoring system.

Measurements and Main Results: Nadir oxygen saturation as measured by pulse oximetry, apnea-hypopnea index, and the fraction

of events that were hypopneas ($F_{\text{hypopneas}}$) were independent predictors of the ArTH ($r^2 = 0.59$; $P < 0.001$). Using this information, we used receiver operating characteristic analysis and logistic regression to develop a clinical score to predict a low ArTH, which allocated a score of 1 to each criterion that was satisfied: (apnea-hypopnea index, <30 events per hour) + (nadir oxygen saturation as measured by pulse oximetry $>82.5\%$) + ($F_{\text{hypopneas}} >58.3\%$). A score of 2 or above correctly predicted a low arousal threshold in 84.1% of participants with a sensitivity of 80.4% and a specificity of 88.0%, a finding that was confirmed using leave-one-out cross-validation analysis.

Conclusions: Our results demonstrate that individuals with a low ArTH can be identified from standard, clinically available variables. This finding could facilitate larger interventional studies targeting the ArTH.

Keywords: sleep apnea; respiratory-induced arousals; arousal threshold; phenotype traits; lung

Obstructive sleep apnea (OSA) is a common disease with major neurocognitive and cardiovascular sequelae (1–3). Despite its high prevalence and well-recognized

consequences, treatment of OSA remains unsatisfactory because of poor adherence (e.g., continuous positive airway pressure) and variable efficacy of existing therapies

(e.g., surgery, oral appliances) (4), creating a need for further research into underlying mechanisms to identify new therapeutic targets.

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*Both authors contributed equally to this work.

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At a Glance Commentary

Scientific Knowledge on the

Subject: A low respiratory arousal threshold is one of several physiologic traits involved in the pathogenesis of obstructive sleep apnea and may be a therapeutic target. However, there is currently no practical way to identify such patients without using invasive measurement approaches (e.g., an epiglottic or esophageal pressure catheter).

What This Study Adds to the

Field: This study provides a simple, easily implementable clinical screening tool to help identify patients with obstructive sleep apnea with a low respiratory arousal threshold. Such predictive capabilities take us one step closer to being able to noninvasively characterize the multiple causes of obstructive sleep apnea so that treatments can be directed according to the underlying pathophysiology.

The hallmark of OSA is the collapse of the upper airway during sleep, which raises CO₂ and leads to increased ventilatory drive and increasingly negative pharyngeal pressure. These respiratory stimuli can activate the upper airway dilator muscles to restore pharyngeal patency during sleep, which can protect against OSA (5–9). However, restoration of sufficient airflow can only occur if ventilatory drive can build up during sleep without an arousal (5, 10, 11). Instead, in approximately one-third of patients with OSA (8), respiratory events are terminated early because of a low respiratory arousal threshold (ArTH), preventing the opportunity for ventilatory drive to build up and restore pharyngeal patency during sleep. In this subset of patients, strategies to raise the ArTH could potentially resolve OSA (12). Accordingly, there are a substantial number of patients with OSA who could potentially benefit from certain sedatives to reduce their OSA severity and improve sleep quality.

Currently, however, we have no reliable way to identify patients with a low ArTH using clinically available metrics (e.g., anthropometric indices or polysomnography variables). Instead, invasive procedures, such as an epiglottic

or an esophageal pressure catheter, are required. Previous studies suggest that a high ArTH is associated with more severe OSA (higher apnea-hypopnea index [AHI]), lower nadir oxygen saturation, and a higher arousal index (ArI) (13, 14). A major limitation of many of these studies, however, is that they either involved a small number of participants or were conducted in patients with homogenous disease severity (predominately severe OSA). Thus, there is a need to quantify the ArTH in a large number of patients with a broader range of OSA severity to define adequately the clinical predictors of a low respiratory ArTH. As such, the aims of the current study were to determine the physiologic determinates of the respiratory ArTH and use this information to develop a clinical tool that can identify patients with a low ArTH.

Methods

A detailed description of the methodology is provided in the online supplement.

Participants

We recruited 146 individuals from the community (control subjects) and our sleep clinic at Brigham and Women's Hospital. Individuals recruited from the clinic were either recently diagnosed untreated patients with OSA or were suspected to have OSA. Written informed consent was obtained before the study, which was approved by the Partners' Human Research Committee.

Experimental Design and Protocol

All subjects completed the Epworth Sleepiness Scale (ESS) on arrival. Each subject then underwent an in-laboratory polysomnogram (PSG) using a standard clinical montage for evaluation of OSA. To assess the respiratory ArTH, subjects were additionally instrumented with an epiglottic pressure catheter (model MCP-500; Millar, Houston, TX). Once all the equipment was in place, subjects were asked to sleep in the supine position and were provided with an 8-hour sleep opportunity. All signals were sampled at 125 Hz via a Power1401 data acquisition interface and displayed using Spike 2 software (Cambridge Electronic Design Ltd., Cambridge, UK).

Data Analysis

Sleep was staged according to standard criteria (15); arousals and respiratory events were scored according to the American Academy of Sleep Medicine Criteria (16). OSA was defined as mild (AHI, 5–14.9 events per hour), moderate (15–29.9 events per hour), or severe (≥ 30 events per hour). Throughout this article the term “arousal threshold” refers to the summative neuromuscular-mechanical pressure present at the end of the apnea-hypopnea that causes a cortical arousal from sleep (defined as >3 s of high-frequency activity on the EEG). The ArTH was quantified as the nadir epiglottic pressure immediately preceding arousal using established criteria (Figure 1; see online supplement for details) (12, 17–19). Lastly, we defined a low ArTH as an overall ArTH less negative than -15 cm H₂O and a high ArTH as more negative than -15 cm H₂O (8, 12).

Statistical Procedures

A chi-square test was used to assess differences in the proportions of OSA and control subjects with low versus high respiratory ArTHs. To assess which variables were associated with ArTH, we first performed univariate linear regression comparing the overall (non-REM and REM) ArTH (dependent variable) against several independent variables, which consisted of patient demographics (age, body mass index [BMI], ESS) and clinical PSG characteristics (AHI, nadir oxygen saturation, ArI, the percentage of respiratory events that were hypopneas, and respiratory event duration). All regressions were repeated using non-REM and REM ArTHs. To determine independent predictors, multiple linear regression was then performed. For all three models, age, sex, and BMI were included *a priori* as independent variables. PSG variables were selected for inclusion based on a univariate r^2 greater than 0.2.

To provide a simple clinical screening tool to identify patients with OSA with a low ArTH, receiver operating characteristic (ROC) curves were calculated for each of the PSG characteristics that were independent predictors (as determined via multivariate regression) to derive cut-off values. These cut-offs were then used in a multiple logistic regression model to determine which predictors would be included in the clinical scoring tool, and what weighting they were

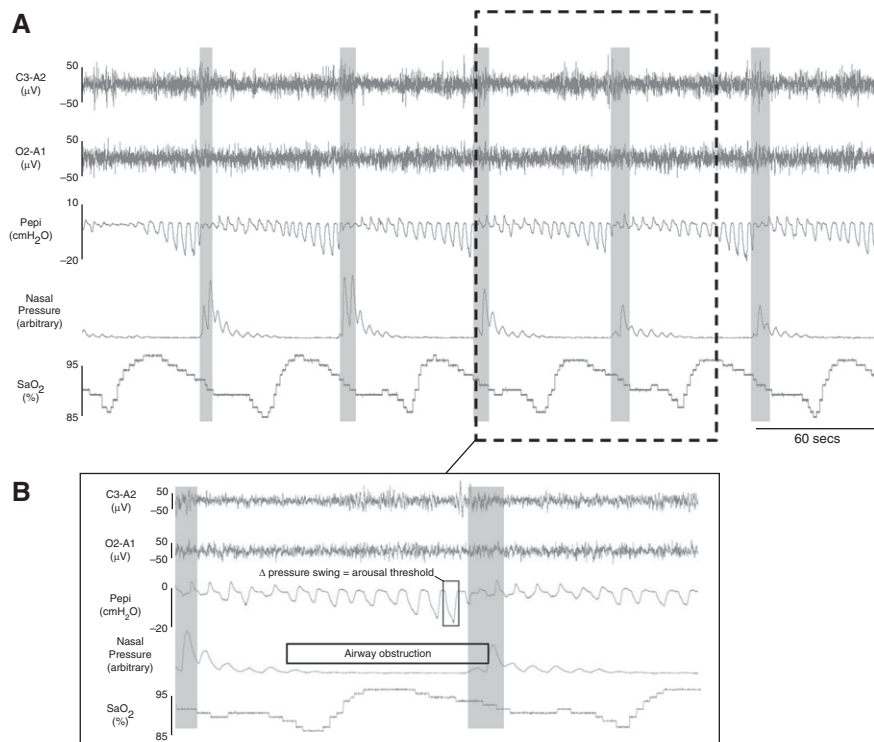


Figure 1. Determining the arousal threshold during an in-laboratory polysomnogram. (A) Representative example taken from an overnight polysomnogram recording in a male patient with severe obstructive sleep apnea (apnea-hypopnea index, 56 events per hour) to demonstrate how the arousal threshold was calculated. Note the progressive increase in the negative pressure swings on the epiglottic pressure trace (Peppi) during periods of obstruction indicating an increased effort to breathe. (B) The respiratory arousal threshold was taken as the delta pressure swing (-16.7 cm H₂O in this example) immediately before arousal (*gray shading*). C3-A2 and O2-A1 are electroencephalograms.

given. The sensitivity and specificity of our tool was then tested. Cross-validated estimates of sensitivity and specificity were also obtained by the “leave-one-out” method.

All statistical analyses were performed using SigmaPlot (Systat Software, San Jose, CA) with P less than or equal to 0.05 considered statistically significant. Values

are presented as means \pm SD or medians (25th percentile–75th percentile) as appropriate.

Results

Of the 146 participants enrolled, 127 were included in the final analysis cohort (*see the*

online supplement). Of these, 26 were healthy control subjects and 101 had OSA. The demographics of the 127 participants are shown in Table 1. ArTH measurements were made in 121 (95%) and 81 (64%) subjects in non-REM and REM, respectively. Non-REM and REM ArTHs were strongly correlated ($r^2 = 0.81$; $P < 0.001$). On average, the overall ArTH measurements were derived from 3 (2–5) events (arousals) in control subjects and 20 (15–24) events in the patients with OSA.

Proportion of Patients with a Low ArTH

Figure 2 shows the proportion of control subjects and patients with OSA that had a low overall ArTH; most control subjects had a low ArTH, whereas approximately half of the patients with OSA had a low ArTH ($P = 0.005$). Multiple logistic regression demonstrated that compared with the proportion of healthy control subjects with a low ArTH, the proportion of mild and moderate patients with OSA with a low ArTH was not statistically different. However, there was a significantly smaller proportion of severe patients with OSA with a low ArTH (odds ratio, 21.1 [5.3–83.8]; $P < 0.001$) (Figure 2B).

Physiologic Determinants of the ArTH in Patients with OSA

Univariate regression demonstrated that the overall ArTH correlated weakly with BMI and ESS but not age (Figure 3). The polysomnographic characteristics that strongly correlated with the ArTH were AHI, nadir oxygen saturation as measured by pulse oximetry (Sp_{O_2}), the fraction or percentage of all respiratory events that were hypopneas rather than apneas ($F_{\text{hypopneas}}$), and the ArI (Figure 4). ArTH was not associated with longer event

Table 1. Anthropometric Data of the Study Cohort

Characteristics	Entire Group ($n = 127$)	Control Group ($n = 26$)	OSA Group ($n = 101$)
Male:female	81:46	10:16	71:30
Age, yr	45 \pm 14.3	28 (22.8–47.3)	48 (39.5–58.0)*
Body mass index, kg \cdot m ⁻²	30.9 \pm 8.7	28.2 (24.9–34.9)	29.2 (25.1–34.4)
ESS, /24	8.7 \pm 4	9.0 \pm 3.4	8.6 \pm 4.1
AHI total, h ⁻¹	31.2 \pm 29.1	2.8 (1.6–3.7)	32.8 (13.8–57.9)*
Mild:moderate:severe, n			26:23:52

Definition of abbreviations: AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea.

Data presented as mean \pm SD or medians (25th percentile, 75th percentile) as appropriate.

* $P < 0.05$ versus control group (Mann-Whitney rank sum test).

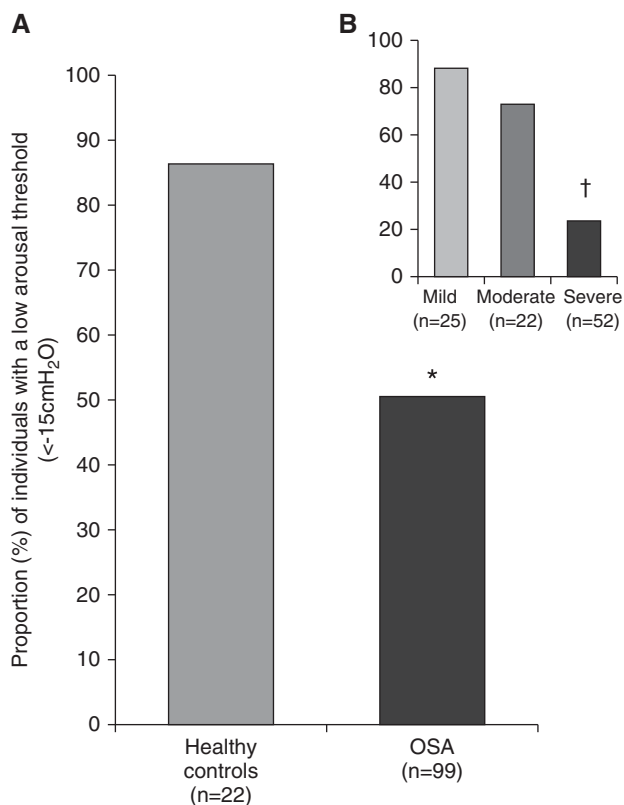


Figure 2. Proportions of individuals with a low arousal threshold. (A) Most control subjects (86.4%, gray bar) had a low respiratory arousal threshold (defined as a peak epiglottic pressure of -15 cm H_2O or less) compared with the 50.5% of patients with obstructive sleep apnea (OSA) (black bar). (B) When dividing up the patients with OSA according to apnea severity, the proportions of patients with a low arousal threshold decreased as severity increased; mild = 88% (light gray bar), moderate = 72.7% (dark gray bar), and severe = 23.1% (black bar). *Significantly reduced compared with control subjects (chi-square test, $P = 0.005$). †Significant difference compared with control subjects (multiple logistic regression, $P < 0.001$).

duration. To account for potential heteroscedasticity in our univariate correlations, univariate regression models using the log-transformed ArTH were also performed as a sensitivity analysis (see online supplement). The statistical trends were very similar using this approach. Therefore, the untransformed ArTH was used for clinical interpretability. When a multivariate analysis with the variables of age, sex, BMI, AHI, nadir Sp_{O_2} , $F_{\text{hypopneas}}$, and ArI was performed, a high degree of colinearity was found between the AHI and ArI; therefore, all multiple linear regressions were run excluding the ArI. Multivariate analysis demonstrated that sex, AHI, nadir Sp_{O_2} , and the $F_{\text{hypopneas}}$ were significant independent predictors of the ArTH (adjusted $r^2 = 0.59$; $P < 0.001$) (Table 2). When we examined the ArTH by sleep state, we found that the AHI, nadir Sp_{O_2} , and the $F_{\text{hypopneas}}$ were significant

predictors for the non-REM ArTH (adjusted $r^2 = 0.57$; $P < 0.001$), whereas the AHI and nadir Sp_{O_2} were predictors of the REM ArTH (adjusted $r^2 = 0.62$; $P < 0.001$) (Table 3). Sex was no longer a significant predictor in the separate non-REM or REM analyses.

Screening Tool to Identify Patients with a Low ArTH

ROC curves for each of the independent PSG predictors yielded the following cut-off values: AHI, 30 events per hour; nadir Sp_{O_2} , 82.5%; and $F_{\text{hypopneas}}$, 58.3%. Multiple logistic regression (using these cut-offs) demonstrated that the AHI, nadir Sp_{O_2} , and $F_{\text{hypopneas}}$ remained significant predictors (Table 4). These three predictors were then used to create the following clinical score, which allocated a score of 1 (based on the observation that the β values and odds ratios for each of the predictors in the

logistic regression were similar) to each criterion that was satisfied:

$$\begin{aligned} \text{Low arousal threshold score} \\ = (\text{AHI} < 30 \text{ events/hr}) \\ + (\text{nadir } Sp_{O_2} > 82.5\%) \\ + (F_{\text{hypopneas}} > 58.3\%) \quad (1) \end{aligned}$$

After a score was calculated for each patient, we found that the best cut-off to detect the presence of a low ArTH was a score of greater than or equal to two (ROC analysis). This score correctly predicted a low ArTH in 84.1% of participants with a sensitivity of 80.4% and a specificity of 88.0% (positive predictive value, 87%; negative predictive value, 81%). Furthermore, compared with using the individual parameters alone to predict a low ArTH, the three-parameter score yielded the best sensitivity and specificity (see online supplement). Use of “leave one out” cross-validation analysis confirmed the excellent predictive power of this clinical tool (sensitivity, 82.2%; specificity, 84.0%). Even in severe patients with OSA, in whom the proportion of those with a low ArTH is small, our test had good predictive power (positive predictive value, 80%; negative predictive value, 85%).

To assess whether the ability of our scoring system to predict a low ArTH was altered by dichotomizing our predictor variables, an additional multiple logistic regression model to predict a low/high ArTH using the three continuous clinical predictors (AHI, nadir Sp_{O_2} , and $F_{\text{hypopneas}}$) and the covariates (age, sex, and BMI) was performed; the results of this model yielded a similar sensitivity (84%) and specificity (84%).

Effect of Sex and Sleep State on the ArTH

As a subanalysis, the effects of both sex and sleep state on the ArTH were assessed (see online supplement). Briefly, both the non-REM ($P = 0.13$) and REM ($P = 0.34$) ArTHs were not different between sexes. This finding remained even after we compared the ArTHs between a subgroup of participants matched for age, BMI, and AHI. The ArTH was significantly altered by sleep state ($P < 0.001$); the N2 ArTH was significantly higher than both the N1 ($P < 0.05$) and REM ArTH ($P < 0.05$), but the ArTH in N1 versus REM did not differ.

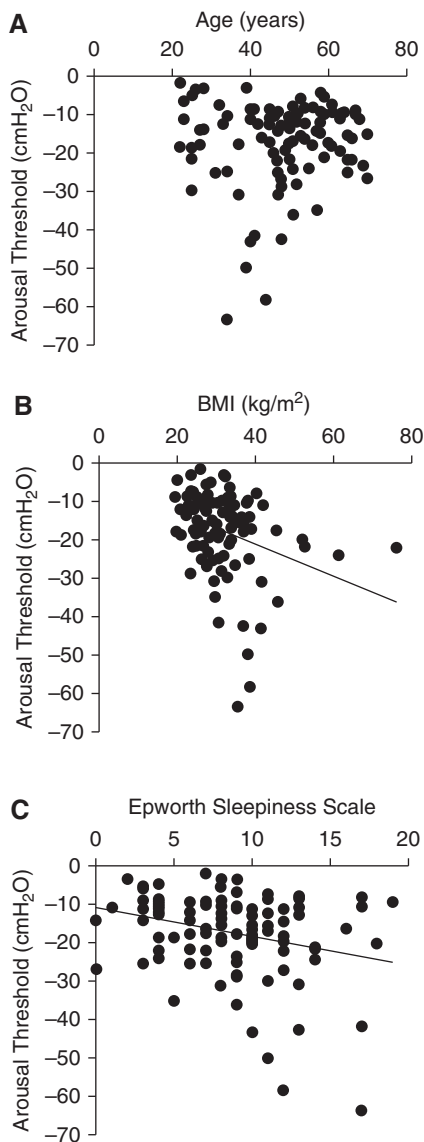


Figure 3. Univariate associations between age, body mass index (BMI), and Epworth Sleepiness Scale (ESS) and the arousal threshold. (A) Age was not related to the arousal threshold ($r^2 = 0.002$; $P = \text{NS}$), whereas both (B) BMI ($r^2 = 0.103$; $P = 0.001$) and (C) ESS ($r^2 = 0.078$; $P = 0.005$) were weakly correlated with the arousal threshold. Similar correlations were seen whether the non-REM arousal threshold (age [$r^2 = 0.001$; $P = 0.72$], BMI [$r^2 = 0.08$; $P = 0.005$], ESS [$r^2 = 0.09$; $P = 0.003$]) or the REM arousal threshold (age [$r^2 = 0.017$; $P = 0.76$], BMI [$r^2 = 0.08$; $P = 0.02$], ESS [$r^2 = 0.09$; $P = 0.013$]) were used.

Discussion

The major findings of our study were that the ArTH is strongly related to several markers of sleep apnea severity. We also

demonstrated that the ArTH is not different between sexes and is higher in N2 compared with N1 or REM (*see* online supplement). In our view, the most important and clinically useful aspect of the current work is the development of a novel, simple clinical screening tool to help identify patients with OSA with a low ArTH. Importantly, our tool demonstrates that in patients with severe OSA, the presence of a low ArTH can be predicted by both the nadir SpO_2 greater than 82.5% and $F_{\text{hypopneas}}$ greater than 58% criteria,

whereas in mild-moderate OSA failing both of these criteria indicates a high ArTH. Such predictive capabilities take us one step closer to being able to noninvasively characterize the varying causes of patients with OSA so that novel treatments can be directed according to underlying mechanisms.

Clinical Predictors of the Respiratory ArTH

Our study shows that the strongest independent clinical predictors of both the

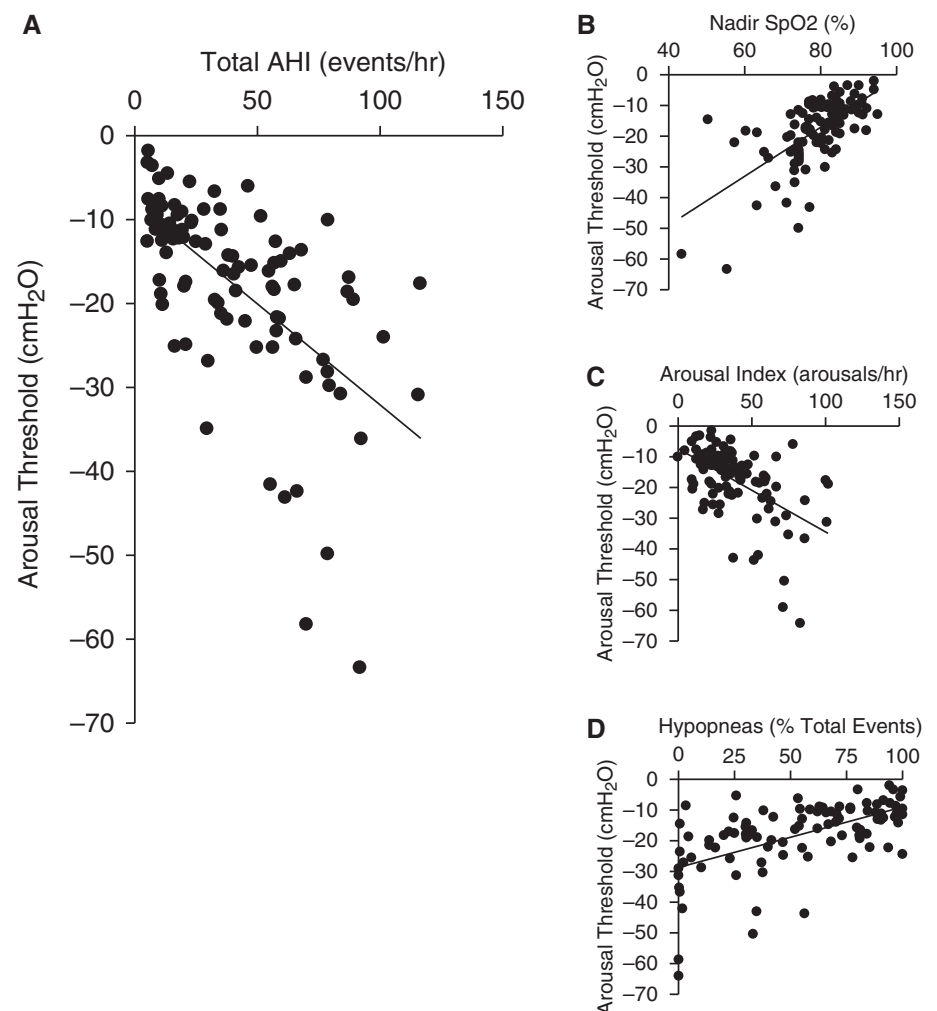


Figure 4. Clinical determinants of the overall arousal threshold. (A) Apnea–hypopnea index (AHI) ($r^2 = 0.37$; $P < 0.0001$), (B) nadir oxygen saturation ($r^2 = 0.43$; $P < 0.0001$), (C) the arousal index ($r^2 = 0.29$; $P < 0.001$), and (D) percentage of respiratory events that were hypopneas ($r^2 = 0.35$; $P < 0.001$) were the strongest variables from the clinical polysomnogram report that were correlated with the overall arousal threshold. Similar correlations were seen whether the non-REM arousal threshold (AHI [$r^2 = 0.36$; $P < 0.001$], nadir oxygen saturation [$r^2 = 0.42$; $P < 0.001$], arousal index [$r^2 = 0.26$; $P < 0.001$], % hypopneas [$r^2 = 0.35$; $P < 0.001$]) or the REM arousal threshold (AHI [$r^2 = 0.45$; $P < 0.001$], nadir oxygen saturation [$r^2 = 0.43$; $P < 0.001$], arousal index [$r^2 = 0.37$; $P < 0.001$], % hypopneas [$r^2 = 0.35$; $P < 0.001$]) were used. SpO_2 = oxygen saturation as measured by pulse oximetry.

Table 2. Multiple Linear Regression Model Investigating Physiologic Determinants of the Overall Arousal Threshold

	Overall Arousal Threshold			
	β	SE of β	β_{std}	P Value
Age, yr	0.06	0.05	0.08	0.25
Male sex	3.69	1.75	0.15	0.04
BMI, $\text{kg} \cdot \text{m}^{-2}$	-0.03	0.09	0.02	0.74
AHI total, h^{-1}	-0.11	0.03	-0.28	0.002
Nadir SaO_2 , %	0.53	0.09	0.45	<0.001
$F_{\text{hypopneas}}$	0.09	0.03	0.27	0.004

Definition of abbreviations: AHI = apnea hypopnea index; BMI = body mass index; $F_{\text{hypopneas}}$ = fraction of the respiratory events that were hypopneas.

Bold indicates significant predictors.

β and β_{std} represent the nonstandardized and standardized regression coefficients, respectively. SE of β = standard error of the nonstandardized regression coefficient. The standardized regression coefficient is expressed in units of standard deviations and represents the estimates resulting from an analysis carried out on independent variables that have been standardized so that the variance is 1.

non-REM and REM ArTH were the overall AHI and nadir SpO_2 . Furthermore, the $F_{\text{hypopneas}}$ was also a significant predictor for the non-REM but not REM ArTH. Our work has the major advantage over previous investigations in that we included patients with a wide spectrum of OSA severity. Previous studies in predominantly severe patients with OSA have reported modest univariate correlations between the non-REM ArTH and the AHI (13, 14, 20) and other markers of OSA severity including the minimum SpO_2 and ArI (13) and the ESS (21). Taken together, these findings suggest that the ArTH is strongly related to severity of disease, which is consistent with our physiologic understanding. For instance, we expect that

an individual with a low ArTH should wake up before a severe gas exchange abnormality (low SpO_2) has developed. Likewise those whose anatomy is better (indicated by less severe airflow obstruction, higher $F_{\text{hypopneas}}$) should be more likely to have a nonanatomic deficiency causing OSA, such as a low ArTH. However, the exact factors responsible for the increase in the ArTH with increasing severity are yet to be identified conclusively. To date, both chronic sleep fragmentation (22) and intermittent hypoxia (23) have been implicated.

Consequence versus Cause?

The finding that the ArTH increases with increasing OSA severity, coupled

together with the data demonstrating that the ArTH is lowered with continuous positive airway pressure treatment (although the responses varied greatly) (24–26), supports the concept that an elevated ArTH is, in part, a consequence of disease rather than a cause in many individuals. However, our results highlight that approximately 50% of untreated patients with OSA have a low ArTH (defined as an epiglottic pressure on the breath before arousal greater than $-15 \text{ cm H}_2\text{O}$), which would not likely fall with continuous positive airway pressure therapy (14, 24). Thus, there are a substantial number of patients with OSA in whom a low ArTH could well contribute to their disease; this could occur because the repeated arousals either (1) do not allow enough time for respiratory stimuli to recruit the pharyngeal muscles and reopen the airway before arousal; (2) induce a robust ventilatory response, which can promote dynamic ventilatory instability (27), which may contribute to the perpetuation of subsequent respiratory events; or (3) fragment sleep and prevent the individual from achieving slow wave (i.e., stabilizing) sleep (14). Consistent with the idea that a low ArTH can be causal, we have also shown previously that increasing the ArTH pharmacologically can reduce OSA severity, particularly if patients have a low initial ArTH (12). Such findings suggest that in specific individuals, the ArTH is likely to be a contributing factor in their OSA pathogenesis, emphasizing that the ArTH may be a cause in some and a consequence of disease in others (28).

Clinical Implications

It is well established that OSA has a multifactorial pathogenesis. OSA also remains untreated in millions of patients because of a lack of therapeutic options beyond those that act to improve upper airway mechanics and anatomy (e.g., positive airway pressure and surgery). Despite the ongoing discovery of promising nonanatomic therapies (e.g., sedatives, oxygen, acetazolamide) (12, 29, 30), the field has been hampered by a lack of simple measurement tools to target novel therapies directed at specific nonanatomic contributors to OSA (8). We and others strongly believe that measuring the physiologic

Table 3. Multiple Linear Regression Model Investigating Physiologic Determinants of the non-REM and REM Arousal Thresholds

	Non-REM Arousal Threshold				REM Arousal Threshold			
	β	SE of β	β_{std}	P Value	β	SE of β	β_{std}	P Value
Age, yr	0.07	0.06	0.08	0.26	0.06	0.07	0.06	0.42
Male sex	3.78	1.99	0.14	0.06	3.93	2.16	0.15	0.07
BMI, $\text{kg} \cdot \text{m}^{-2}$	0.03	0.11	0.02	0.81	-0.19	0.11	-0.14	0.10
AHI total, h^{-1}	-0.11	0.04	-0.26	0.005	-0.17	0.05	-0.40	<0.001
Nadir SaO_2 , %	0.58	0.11	0.45	<0.001	0.49	0.11	0.40	<0.001
$F_{\text{hypopneas}}$	0.10	0.03	0.29	0.003	0.05	0.04	0.14	0.22

Definition of abbreviations: AHI = apnea hypopnea index; BMI = body mass index; $F_{\text{hypopneas}}$ = fraction of the respiratory events that were hypopneas.

Bold indicates significant predictors.

β and β_{std} represent the nonstandardized and standardized regression coefficients, respectively. SE of β = standard error of the nonstandardized regression coefficient. The standardized regression coefficient is expressed in units of standard deviations and represents the estimates resulting from an analysis carried out on independent variables that have been standardized so that the variance is 1.

Table 4. Using Multiple Logistic Regression to Create Our Screening Tool's Scoring Criteria

	β	SE	Odds Ratio	Lower CI	Upper CI	P Value
AHI	1.98	0.57	7.27	2.37	22.35	<0.001
Nadir SaO ₂	1.53	0.58	4.63	1.48	14.47	0.008
F _{hypopneas}	1.55	0.57	4.69	1.53	14.43	0.007

Definition of abbreviations: AHI = Apnea hypopnea index; β = regression coefficient; CI = confidence interval; F_{hypopneas} = fraction of the respiratory events that were hypopneas; SE = standard error of the regression coefficient.

Bold indicates significant predictors.

To assess the relative contributions of our three independent variables we performed multiple logistic regression.

mechanisms contributing to OSA in the clinic is essential for making individualized, phenotype-based, therapy a reality.

To date, the effects of sedatives on either the ArTH, OSA severity, or both have been assessed in a few studies involving relatively small numbers of participants (12, 14, 31–34). The ArTH consistently increases (becomes more negative) with sedatives, although the effects on AHI have been inconsistent. Major limitations of these studies were that sedatives were predominantly given to unselected patients and some agents may impair upper airway muscle activity. Our previous study demonstrated that the sedative eszopiclone did produce clinically significant reductions in the AHI in patients with a low ArTH. This suggests that targeted therapy to underlying causes is beneficial. However, this approach will likely require information about all of the traits responsible for OSA, because a patient with OSA with a highly collapsible airway will likely have OSA regardless of whether there are abnormalities in any of the other physiologic traits (i.e., low ArTH). In such patients, we would predict that increasing the ArTH will be of little benefit to the patients in terms of reducing the AHI. In fact, raising the ArTH in such patients may even be harmful, particularly if they are prone to severe blood-gas disturbances during sleep. Thus, identification of patients in whom sedatives will work is going to be the key to improved therapy options. If nonmyorelaxant sedatives could be targeted toward patients with OSA without severe anatomic

abnormalities and with a low ArTH, this approach may yield a more consistent benefit.

Currently, very few sleep programs have the ability to quantitatively measure epiglottic or esophageal pressure as a marker of respiratory drive (i.e., respiratory ArTH). This is a major barrier for clinical trials to examine new or old pharmaceuticals that could be used to increase the ArTH to reduce OSA severity. This barrier also reduces the number of possible sites that could participate in a trial and greatly increases the expense and technical expertise required to conduct such a study. Importantly, our newly developed scoring criteria could now be used to provide a simple and effective clinical tool to identify individuals with a low ArTH from either attended in-laboratory PSGs or most home sleep tests. Identification of such individuals could then be used to facilitate larger interventional studies targeting the ArTH. Thus, we believe that the screening tool developed in the current study is a key step toward developing personalized targeted treatment plans for patients with OSA.

Methodologic Considerations

There are several limitations that must be considered when interpreting our findings. First, it is possible that the scoring criterion developed is only uniquely applicable to the current dataset, although the cross-validation results argue against this. Nonetheless, our scoring system requires validation in a large independent dataset. Prospective validation studies could also assess how well the current scoring criteria perform and whether or not modifications

are required according to the various approaches in which respiratory events are scored (35). Second, we only studied subjects in the supine position. Thus, we cannot determine whether the epiglottic pressure before arousal is altered by sleeping in the lateral position. Although the lateral position is often associated with an improvement in OSA severity (36), a previous study reported no position-dependent changes in respiratory effort before arousal (within the same sleep stage) (21). Thus, position is unlikely to affect the ArTH. Third, we were only able to obtain measurements of the ArTH in all stages (N1, N2, and REM) in just over half of the participants. Thus, there may be a potential bias in our measurements, particularly if the missing data are not at random. Lastly, we noted that there was a large degree of variability in our measurements of the ArTH (coefficients of variation were 0.36 ± 0.14 and 0.25 ± 0.13 for non-REM and REM, respectively; see online supplement). However, the variability observed in our study is consistent with the average coefficient of variability in the measurements of the ArTH from a recent review of the literature (14) that consisted of more than 500 severe patients with OSA (compared with 0.38 ± 0.14 and 0.44 ± 0.10 for non-REM and REM, respectively). Thus, we are confident that our observed methodologic and biologic variability is consistent with expectations.

Conclusions

In summary, our findings provide insight into the factors influencing the ArTH, which we have used to construct a simple screening tool that may be helpful in identifying patients clinically that have a low ArTH. Our ability to identify the roughly 50% of patients with OSA potentially amenable to therapies designed to increase the ArTH takes us one step closer to being able to individualize care for patients with OSA. ■

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