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A Measure of Ventilatory Variability at Wake-Sleep Transition Predicts Sleep Apnea Severity

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Abstract

Rationale—Increased variability in ventilation may contribute to the pathogenesis of obstructive sleep apnea (OSA) by promoting ventilatory instability, fluctuations of neuromuscular output to the upper airway, and pharyngeal collapsibility. We assessed the association of a measure of ventilatory variability measured at the wake-sleep transition with OSA and associated covariates.

Methods—485 participants in the Cleveland Family Study underwent overnight polysomnography with independent derivation of the Ventilatory Variability Index and the Apnea Hypopnea Index. The Ventilatory Variability Index was calculated from the variability in the power spectrum of the abdominal inductance signal over a 2-minute period beginning at sleep onset.

Results—The Ventilatory Variability Index was strongly correlated with the Apnea Hypopnea Index ($r=0.43$, $p<0.001$). After adjusting for age, body mass index, sex, and race, the Ventilatory Variability Index remained significantly associated with Apnea Hypopnea Index ($p<0.001$). The adjusted odds ratio for obstructive sleep apnea (Apnea Hypopnea Index ≥ 15) with each half standard deviation increase in Ventilatory Variability Index was 1.41 [1.25–1.59]. In a subgroup analysis of obese snorers, to limit analyses to those with a presumed anatomic predisposition for apnea, Ventilatory Variability Index remained associated with an elevated Apnea Hypopnea Index.

Conclusions—Increased ventilatory variability may be a useful phenotype in characterizing obstructive sleep apnea.

Keywords

Sleep apnea syndromes; sleep disordered breathing; polysomnography; apnea

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder associated with significant co-morbidities. Although obesity is the most common risk factor for adult OSA, individual susceptibility to OSA is likely influenced by other factors. These factors include anatomic and physiological traits that individually or jointly result in enhanced airway collapsibility during sleep. Variation in the neuromuscular output to upper airway muscles may represent one such risk factor. Intermittent airway obstruction may result when sleep-related reductions in upper airway dilator muscle tone exceed reductions in chest wall muscle activation. Thus, the ventilatory instability characteristic of periodic breathing may often result in overt obstruction^{1,2}. Although a direct cause-and-effect relationship between ventilatory instability and airway obstruction, or OSA severity, has been demonstrated in small experimental studies^{1,3}, the technical demands of current approaches for measuring such instability has limited research that addresses the role of ventilation in the expression or severity of OSA in the general population.

Periods of state instability, such as during sleep state transitions, have been shown to be associated with fluctuations in ventilation⁴. Taking advantage of this naturally occurring disturbance and using data readily available from routine polysomnography (PSG), we sought to test whether variability of ventilation at wake-sleep transitions may explain a significant portion of the variance in measures of OSA and thus serve as a means to better understand the physiology and risk factors associated with OSA via pathways independent of obesity.

METHODS

Study Population

Subjects were participants in the Cleveland Family Study, a longitudinal community-based study established to evaluate the genetic aspects of OSA. The methods of recruitment and data collection have been previously described⁵. Of the 729 participants who underwent overnight PSG in the last examination cycle, 117 were excluded due to age <18 years, 115 were excluded due to use of Continuous Positive Airway Pressure (CPAP), and 12 were excluded due to artifact in the abdominal signal that would interfere with the accurate calculation of the measure of ventilatory variability. The analytic sample therefore consisted of 485 individuals.

Data Collection

Each participant underwent in-laboratory overnight PSG using the Compumedics E-Series System (Abbotsford, Victoria, Australia) conducted in the General Clinical Research Laboratory at University Hospitals Case Medical Center (Cleveland, OH). Institutional Review Board approval and written informed consent was obtained from each participant. Prior to the PSG, each participant completed the Cleveland Health and Sleep Questionnaire⁶, a standardized and validated questionnaire assessing health and sleep habits.

Ventilation was measured using an oro-nasal thermistor, nasal cannula for pressure measurement, and abdominal and thoracic inductive plethysmography sampled at 32 Hz. Apneas and hypopneas were defined using Sleep Heart Health Study criteria modified to include the nasal pressure signal⁷. Respiratory events were identified as a decline in respiratory effort (from inductive respiratory bands) or airflow (from the thermocouple or nasal pressure) for ≥ 10 seconds and associated with at least a 3% drop in oxygen saturation. Arousals were scored according to American Academy of Sleep Medicine criteria⁸. The Apnea Hypopnea Index (AHI), Central Apnea Index, and Arousal index were defined as the number of apneas plus hypopneas, central apneas, or cortical arousals, respectively, per hour of sleep. OSA was defined as an AHI ≥ 15 events/hour of sleep.

The Ventilatory Variability Index (VVI) was designed to quantify ventilatory variability measured at the first wake-sleep transition (algorithm developed by NeuroWave Systems Inc). The abdominal inductance plethysmography signal was used as the measure of ventilation in these analyses, since this channel contained the fewest artifacts or periods of lost data among the ventilatory measurements available (Figure 1). A Fast Fourier transform was performed on this signal in a 10 second sliding window over a two minute period beginning with sleep onset. Sleep onset was defined as the time at which three consecutive epochs of stage I occurred or the first epoch of any other stage. A weighted measure of the normalized power in the 0.1 – 1 Hz range, the aggregate signal power (ASP), was computed such that frequencies in the 0.1 – 0.3 Hz range contributed 90% and frequencies in the 0.3 – 1.0 Hz range contributed 10% to the ASP. The ASP was computed at each second across the 2 minutes and the coefficient of variation in the ASP was used to measure the variability in ventilation in this frequency range. Because preliminary results suggested this metric varied nonlinearly with the AHI, the Ventilatory Variability Index (VVI) was defined as the square root of this coefficient of variation to provide a more linear relationship to the AHI.

The computation of the VVI was performed by individuals blinded to the scoring of the AHI. Examples of data analysis from subjects with normal breathing (AHI=2, VVI 1.6), moderate apnea (AHI=17, VVI 18), and severe apnea (AHI=68, VVI 39) are shown in Figure 2.

Statistical Analysis

Descriptive statistics were performed on sample characteristics using means, standard deviations, medians, and inter-quartile ranges for continuous variables, and frequency and percentage for categorical variables. Because of the non-normal distribution of the VVI, Spearman correlation coefficients were used to assess the correlation with continuous covariates.

Two outcomes were analyzed: the log-transformed AHI and the binary outcome, OSA, defined as an AHI ≥ 15 . The association of each outcome with the VVI was assessed using linear mixed models and Generalized Estimating Equations, respectively, using a compound symmetry correlation structure to account for the intra-familial dependence. Adjusted analyses included age, body mass index (BMI), sex, and race as covariates. Geometric means of the VVI, calculated using linear mixed models, unadjusted and adjusted for covariates, were derived to use in a graphical assessment of the association of VVI with severity of sleep disordered breathing. The change in the area under the Receiver Operator Characteristic (ROC) curve was used as a metric of model improvement for the addition of VVI to the regression model for OSA. This area is interpreted as the probability of correctly identifying an individual with OSA over an individual without OSA.

RESULTS

Table 1 shows characteristics of the sample. Over 30% of the cohort met criteria for OSA (AHI ≥ 15). Overall, subjects were obese, middle-aged, consisted of approximately equal proportions of men and women, and included a slight predominance of African-Americans. Of note, the frequency of central apneas was very low. As expected, compared to subjects without OSA, those with OSA were heavier, older, and consisted of a proportionally greater number of men.

Spearman correlation coefficients shown in Table 2 demonstrated that the VVI was positively associated with age and BMI, as well as AHI, central apnea index, arousal index, and time in desaturation. Of all these variables, the VVI was most strongly associated with AHI ($r = 0.43$, $p < 0.001$). After controlling for age, BMI, sex, and race, VVI remained significantly associated with AHI ($p < 0.001$).

Figure 3 displays the geometric means of VVI with increasing level of OSA severity. A significant increase in VVI with increasing severity of OSA was demonstrated ($p < 0.001$ for trend). This relationship persisted after adjusting for age, BMI, sex, and race.

The VVI was also found to be associated with the binary outcome, OSA (Table 3). After adjusting for age, BMI, sex, and race, each 0.5 SD increase in the VVI was associated with an approximately 40% increased odds of OSA. In comparison, 0.5 SD increases in age and BMI were associated with approximately 50% and 60% increases in the odds of OSA, respectively. The addition of VVI to the model that only included age, BMI, sex, and race significantly increased the correct classification of OSA by 2.6% (81.5% vs. 84.1%, $p = 0.0095$). Similar results were observed when OSA was defined as an $AHI \geq 5$ (data not shown).

In order to better assess whether VVI represented a measure of OSA propensity independent of airway anatomy, we performed a secondary analysis restricted to the subgroup of obese snorers (individuals with $BMI \geq 30 \text{ kg/m}^2$ who reported snoring at least 3–4 times per week; $n=256$). We hypothesized that in this subgroup, most individuals would have some anatomic predisposition for apnea. However, those with clinically elevated AHI levels ($AHI \geq 5$) would be distinguished from non-apneic snorers by differences in physiological traits. This hypothesis was supported by the finding of a higher VVI in the group with $AHI \geq 5$ compared to obese non-apneic snorers (34.6 vs. 23.2; $p = 0.0002$). Again, these results persisted after adjustment for covariates (Figure 4).

DISCUSSION

OSA is a complex phenotype which likely results from interplay between both anatomic and physiologic risk factors, the relative contributions of which may differ among individuals. Attempts at individualizing treatment programs, understanding OSA-related outcomes, and discovering the genetic bases for this disease have been hindered by this heterogeneity.

Studies of heterogeneous conditions such as OSA may benefit from quantifying intermediate phenotypes, i.e. traits that describe specific causal pathways of risk factor domains. For example, the use of IgE levels in the study of asthma has allowed for the identification of an atopic subgroup whose genetic risk factors for asthma are different and whose response to specific treatments (e.g., omalizumab) may vary from non-atopic asthmatics. Further understanding the etiology of OSA may also be enhanced by the development of tools that allow the anatomic and physiological intermediate phenotypes that are risk factors to be reliably quantified in large populations.

One of the physiologic traits implicated to play an important role in OSA pathogenesis is ventilatory control stability. Younes reported chemical control of the respiratory system was more unstable in patients with severe OSA than in patients with milder OSA⁹. Similarly, Wellman et al. identified loop gain of the ventilatory control system as a predictor of OSA severity¹⁰. Unfortunately, the methods used to study ventilatory control instability in these works have been both time and labor intensive making them impractical for the study of large cohorts.

We hypothesized that increased ventilatory variability measured at the wake-sleep transition may provide a simple surrogate for variation in neuromuscular output which is relevant to the pathogenesis of OSA. It therefore could serve as an intermediate OSA phenotype. To test this hypothesis, we analyzed data from a large sample of research polysomnograms obtained on a population with a wide range of AHI. Our analyses demonstrated that even after considering demographic factors, the VVI was significantly associated with AHI and predicted OSA severity status. The strength of the association was only modestly attenuated by BMI

adjustment suggesting that the VVI is associated with OSA through an obesity-independent pathway.

The improvement in OSA prediction with inclusion of the VVI (from 82% to 84%) was modest compared to the information already present in the baseline model with age, sex, BMI, and race. These data would suggest that factors such as obesity play a more important role than ventilatory phenotypes in defining OSA susceptibility at a population level. However, this does not take away from our findings that ventilatory traits can explain differences in OSA risk between individuals with the same age, gender, race, and BMI. Furthermore, the importance of ventilatory control may have been underestimated in these analyses because some of the OSA-promoting effects of increased age, male gender, etc may be mediated via this pathway.

As opposed to prior studies of ventilatory control that utilized a standardized external disturbance, our study capitalized on a naturally occurring disturbance, the wake-sleep transition, to assess variability in ventilation. Multiple studies have demonstrated that the state change from wake to sleep is associated with large fluctuations in ventilation providing a strong signal from which to measure variability^{11–13}. Furthermore, ventilatory fluctuations at the wake-sleep transition have been measured to occur abruptly and influence upper airway resistance and ventilation in a reciprocal fashion¹⁴. The VVI was derived to capitalize on this state-related variability in neuromuscular respiratory output.

We further explored the hypothesis that ventilatory instability, as measured by the VVI, impacts OSA risk through mechanisms independent of anatomy. We found VVI was a predictor of OSA even after controlling for BMI. In addition, VVI predicted OSA in analyses restricted to those presumed to have an anatomic predisposition for OSA (i.e., in the group of obese habitual snorers).

The physiological basis for the VVI relates to its quantification of relative changes in airflow or volume. Since quantitative data on ventilation are not required, data from most respiratory signals can be used to derive estimates of breathing variability. We chose the abdominal inductance signal for analysis based on it having fewer artifacts than other respiratory signals available to us. This choice is supported by research showing that data from individual band signals may better capture breathing pattern than the sum signal¹⁵. In addition, although the wake-sleep perturbation is likely not constant across subjects, it is a physiologically relevant perturbation that occurs in all subjects.

Because sleep pressure is greatest at the beginning of the night, we theorized the wake – sleep transition (and the corresponding change in ventilatory control) would occur fastest at this time point. As a result, the perturbation on ventilation would be greatest at this first transition providing the greatest signal for detecting differences across individuals. We, therefore, chose to analyze only the first wake – sleep transition. Future studies assessing the reproducibility of the VVI measured at multiple sleep – wake transitions across the night or across multiple nights as well as studies of the effect of OSA treatment on the VVI would be useful in confirming whether ventilatory variability represents an intrinsic phenotype. Strengths of our study include the large sample that included a wide AHI range. In addition, the VVI and standard measures of apnea severity were independently derived. A limitation of this index, however, is that it is empirically derived and does not delineate the precise mechanisms for ventilatory variability, including assessment of the extent to which it is sensitive to differences in the drive to upper airway as compared to differential drive to the diaphragm. This study did not address the potential utility of the VVI as a clinical predictor of OSA. Rather, we have examined its utility as an intermediate trait potentially informative for studies where quantifying ventilatory variability in large numbers of individuals may be useful.

In summary, our analyses demonstrate that a simple measure of ventilatory variability, assessed during the initial wake-sleep transition, has a moderate to strong correlation with AHI. This index predicted OSA independent of conventional OSA risk factors, suggesting its potential utility to provide information on physiological traits relevant to OSA in large clinic and population studies for OSA. Additional research validating the predictive utility of this measure in other samples, and research aimed at dissecting the physiological basis and consequences for ventilatory variability will further clarify the utility of this new phenotype.

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ABBREVIATIONS

AHI	Apnea Hypopnea Index
VVI	Ventilatory Variability Index
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
CPAP	Continuous Positive Airway Pressure

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Figure 1. Derivation of the Ventilatory Variability Index

A Fast Fourier transform was performed on the abdominal signal in a 10 second sliding window over a two minute period beginning with sleep onset. A weighted measure of the normalized power in the 0.1 – 1 Hz range, the aggregate signal power (ASP), was computed. The ASP was computed at each second across the 2 minutes and the coefficient of variation in the ASP was used to measure the variability in ventilation in this frequency range. Ventilatory Variability Index (VVI) was defined as the square root of this coefficient of variation.

FFT: Fast Fourier Transform

ASP: Aggregate Signal Power

CV_{ASP} : Coefficient of Variation of Aggregate Signal Power

SOT: Sleep Onset Time

VVI: Ventilatory Variability Index

Figure 2. Data Analyses of Subjects with Varying Degrees of Sleep Apnea

The plot of the aggregate signal power (ASP) is displayed over the 2 minute window beginning at sleep onset for three participants with varying severity of apnea severity. The ASP fluctuates to a greater extent with an increasing severity of apnea resulting in a greater ventilatory variability index (VVI).

Figure 3. Association of Ventilatory Variability Index and Sleep Disordered Breathing Category
 A significant increasing trend was found between ventilatory variability index and obstructive sleep apnea categories ($p < 0.001$).

The data presented are geometric mean $\pm$ standard error.

Unadjusted and adjusted (for age, body mass index, sex, and race) p-values from comparison of least square means from linear mixed model predicting log Ventilatory Variability Index.

BMI: Body Mass Index

AHI: Apnea Hypopnea Index

VVI: Ventilatory Variability Index

Figure 4. Association of Ventilatory Variability Index in Simple Snorers versus Apneics among Obese Subjects

Even when restricted to individuals with obesity, there remained a persistent difference between simple snorers and those with an AHI ≥ 5 ($p = 0.002$).

The data presented are geometric mean $\pm$ standard error.

Unadjusted and adjusted (for age, body mass index, sex, and race) p-values from comparison of least square means from linear mixed model predicting log Ventilatory Variability Index.

BMI: Body Mass Index

AHI: Apnea Hypopnea Index

VVI: Ventilatory Variability Index

Table 1

Sample Characteristics *

Covariate [†]	Entire Sample N=485	AHI < 15 N=334 (68.9%)	AHI ≥ 15 N=151 (31.1%)	p-value
Age (y)	46.0 ± 17.0	42.8 ± 16.8	53.0 ± 15.5	<0.001
BMI (kg/m ²)	32.6 ± 8.0	30.9 ± 7.4	36.4 ± 7.9	<0.001
Male Sex	201 (41.4%)	113 (33.8%)	88 (58.3%)	<0.001
African American Race	278 (57.3%)	190 (56.9%)	88 (58.3%)	0.774
Sleep characteristics				
AHI	6.8 (1.8, 19.3)	2.9 (1.1, 7.1)	28.7 (20.7, 50.2)	
Central Apnea Index	0.0 (0.0, 0.3)	0.0 (0.0, 0.3)	0.1 (0.0, 0.6)	<0.001
Arousal Index	17.3 ± 10.5	13.7 ± 6.3	25.4 ± 13.4	<0.001
Average SaO ₂ (%)	94.7 ± 2.4	95.4 ± 2.0	93.2 ± 2.5	<0.001
% Sleep Time S _a O ₂ < 90%	0.0 (0.0, 2.0)	0.0 (0.0, 0.1)	4.0 (1.0, 13.0)	<0.001

* Normally distributed variables are presented as Mean ± SD and categorical covariates are presented as N (%); non-skewed variables are presented as median and inter-quartile ranges.

[†] AHI = Apnea Hypopnea Index; BMI = Body Mass Index; S_aO₂ = Arterial oxygen saturation.

Table 2

Spearman Correlations between Ventilatory Variability Index and Subject Characteristics *

Covariate	Spearman Correlation Coefficient	p-value
Age (y)	0.23	<0.001
BMI (kg/m ²)	0.23	<0.001
AHI	0.43	<0.001
Central Apnea Index	0.16	<0.001
Arousal Index	0.26	<0.001
% Sleep Time S _a O ₂ < 90%	0.36	<0.001

* AHI = Apnea Hypopnea Index; BMI = Body Mass Index; S_aO₂ = Arterial oxygen saturation.

Table 3

Predictors of Obstructive Sleep Apnea

Predictors *	Unadjusted OR [†] (95% CI)	Adjusted [‡] OR (95% CI)
VVI	1.61 (1.42 – 1.81)	1.43 (1.27 – 1.61)
Age (y)	1.36 (1.24 – 1.49)	1.42 (1.26 – 1.61)
BMI (kg/m ²)	1.42 (1.27 – 1.59)	1.58 (1.38 – 1.80)
Male Sex	2.64 (1.76 – 3.97)	3.84 (2.37 – 6.21)
African-American Race	1.06 (0.68 – 1.65)	1.31 (0.79 – 2.19)

Results of generalized estimating equations, modeling obstructive sleep apnea as the outcome.

* BMI = Body Mass Index; VVI = Ventilatory Variability Index.

[†] Odds Ratios for continuous variables (VVI, age, BMI) based on a change of 0.5 standard deviation.

[‡] Each covariate is adjusted for all other covariates in the model.