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Physiological Traits and Adherence to Obstructive Sleep Apnea Treatment in Patients with Stroke

To the Editor:

Treatment of obstructive sleep apnea (OSA) in patients with stroke may improve neurological recovery (1, 2). However, trials of OSA treatment are limited by reduced adherence to continuous positive airway pressure (CPAP) (2). Among nonstroke patients, psychosocial factors (e.g., partner support), symptoms (e.g., sleepiness), and comorbidities (e.g., cardiovascular disease) predict adherence (3, 4). Recent reports also indicate that low arousal threshold, a physiologic trait of OSA, is associated with reduced rates of regular CPAP use (5). It is unknown whether arousal threshold or other traits that cause OSA, such as loop gain, pharyngeal collapsibility, and muscle compensation, influence CPAP adherence among patients with stroke.

We therefore hypothesized that *1*) physiologic OSA traits are associated with CPAP adherence (e.g., low arousal threshold associated with decreased adherence), and *2*) addition of these traits will improve models of adherence based on established factors (e.g., demographic, social, comorbidities, symptoms, and polysomnographic metrics). Some of the results of this study have been previously reported in the form of an abstract (6).

Methods

We performed a secondary data analysis of a randomized controlled trial (SleepTight; NCT01446913) of OSA management among patients with acute stroke or transient ischemic attack (TIA) (2). Of the 84 patients who underwent unattended polysomnography and were prescribed CPAP on the basis of the apnea–hypopnea index $\geqslant 5$ events/h, the analytic sample ($n = 60$) was selected by excluding those who did not start CPAP ($n = 4$), had inadequate polysomnography signals to measure OSA traits ($n = 18$), or terminated CPAP use because of acute illness

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(e.g., pneumonia; $n = 2$) (2). The parent study included two intervention arms: "standard" and "enhanced" ("standard" with behavioral CPAP adherence counseling). Patients from both arms were pooled in the analyses because there were no differences in adherence between the two groups (5).

We measured OSA traits using an automated, noninvasive method, as previously described (7). In brief, each polysomnogram was segmented into 7-minute windows of non-REM sleep, with median trait values across windows used to represent each individual. The nasal pressure signal was transformed into a ventilation signal to model ventilatory drive (Vdrive). Loop gain (LG) was quantified as the Vdrive response to ventilatory disturbance. Arousal threshold (ArTH) was calculated as the Vdrive immediately preceding an arousal. Pharyngeal collapsibility (Vpassive) was calculated as ventilation at eupneic Vdrive. Pharyngeal compensation (Vcomp) was taken as the difference between ventilation at maximal Vdrive and Vpassive.

The primary outcome was CPAP adherence, defined as the average CPAP use (h/night) over a 6-month period, measured from CPAP downloads.

To examine whether physiologic traits were associated with CPAP adherence, we first explored associations between adherence and OSA traits using linear regression. Because trait × trait interactions and trait × body mass index (BMI) interaction were previously reported to be relevant to OSA treatment efficacy (8) and CPAP adherence (5), respectively, we also included those terms. Given a relatively small sample size, a parsimonious CPAP adherence model (model 1) was then built, starting with the above traits and interactions using backward selection with Bayesian information criterion (9). We next built an adherence model (model 2) using variables from the domains known to affect CPAP use ("established factors"), selected using Bayesian information criterion. The domains included demographics, social, psychological and medical comorbidities, functional status, symptoms, and polysomnographic indices. Finally, we combined models 1 and 2 to determine whether the addition of the physiologic traits significantly improved the fit of the CPAP adherence model, using a likelihood ratio test (10). Standardized β coefficient values (change in the SD of adherence per SD increase in each continuous exposure term) were determined to show relative effect sizes for each exposure.

Results

The majority of patients were men with a mean age of 60.8 ± 10.6 years and BMI of 29.5 ± 5.9 kg/m^2 (Table 1). Most (82%) had a stroke, with 52% being able to carry out all usual activities after the event (Modified Rankin Scale score, 0–1). The median apnea–hypopnea index was 18 events/h, and the median time with oxygen saturation as measured by pulse oximetry < 90% was 1% of total sleep time. The mean nightly CPAP use over 6 months was 2.2 ± 2.4 h/night.

The final CPAP adherence model combining physiologic OSA traits (model 1) and "established factors" (model 2) is shown in Table 2. The parsimonious model 1 was composed of ArTH, LG, Vpassive, Vcomp, ArTH × BMI, and LG × Vpassive terms and explained 35% of CPAP adherence variance ($R^2 = 0.35$; all P values < 0.02; data not shown). When added to model 2, only pharyngeal muscle compensation (Vcomp), ArTH, and BMI remained significantly associated with CPAP adherence. Specifically, increasing pharyngeal muscle compensation was inversely related to adherence. Decreasing ArTH, particularly at lower BMIs (reflected by the negative coefficient of the ArTH × BMI interaction term), was associated with reduced CPAP adherence. The addition of physiologic traits significantly improved the adherence model based on "established factors" (likelihood ratio test P value = 0.013; addition of model 1 to model 2 increased R^2 from 0.50 to 0.65). Among "established factors," baseline sensory deficit and prescription of physical activity/rehabilitation were associated with higher CPAP adherence. There was a suggestion for an association between being married and higher adherence; however, this was not statistically significant (P value = 0.06). Conversely, a history of TIA, chronic pain, and post-stroke disability (Modified Rankin Scale score ⩾ 2) were associated with lower CPAP use. Given the association of CPAP use with chronic pain and the potential for opioid use to affect CPAP adherence, we explored the association between opioid use and CPAP adherence. No significant relationship was identified (data not shown). Finally, none of the traditional polysomnographic indices (listed in Table 1) were significantly associated with adherence (data not shown), suggesting that physiologic OSA traits provide unique information about the relationship between OSA physiology and CPAP use.

Significance

A novel finding of our work is that the physiological traits that cause OSA are also associated with adherence to CPAP in patients with stroke with OSA. Specifically, decreasing ArTH by 8% (% eupneic ventilation) and increasing pharyngeal muscle compensation by 33% were associated with a clinically meaningful 1-hour reduction in CPAP use. Importantly, this relationship was comparable in magnitude to, and independent of, established adherence factors such as marital status and post-stroke disability. Because physiologic OSA traits vary across individuals, this finding suggests that they may be used to personalize prediction of CPAP adherence.

Recent studies show that physiologic OSA traits predict responsiveness to non-CPAP treatments such as oral appliances (8). Our study is the first to show that measuring the traits may also help predict CPAP use. Prior reports indicate that a surrogate of a single trait, low ArTH, is associated with low CPAP adherence in nonobese patients (5, 11). These observations are consistent with our findings that low ArTH, particularly in those with lower BMI, was associated with poor adherence. We extend these observations by identifying a new relationship between pharyngeal muscle compensation and adherence. This lays the groundwork for investigations to understand the mechanisms by which traits may influence CPAP adherence.

We identified other novel factors relevant to CPAP adherence among patients with stroke/TIA. For example, that chronic pain is associated with lower CPAP adherence (1.8 h) highlights the potential benefits of assessing and treating pain in this population. Although disability from stroke adversely affected adherence, a prescription for physical activity was associated with improved CPAP use, suggesting that rehabilitation may be important for stroke recovery via both direct effects through physical activity and through adherence to OSA treatment.

We acknowledge that present analysis among patients with stroke and TIA in a small sample ($n = 60$) may limit the power to detect significant relationships for some of the traits (type 2 error) and may not be reproducible in other populations. Although an analogous relationship between ArTH and CPAP adherence was identified in prior work (5), these limitations highlight the need to assess the trait's role in adherence in larger samples and different populations. Similarly, lack of classification for nearly half of strokes in our study did not allow us to assess impact of event type on CPAP adherence.

In summary, our results indicate that ArTH and pharyngeal muscle compensation are associated with CPAP adherence in

Table 1. Characteristics of Included Patients with Acute Cerebrovascular Disease Who Were Randomized to CPAP ($n = 60$)

Characteristic	
Demographics and social characteristics	
Age, yr	60.8 ± 10.6
Sex, M	43 (71.7)
Race	
White	38 (63.3)
Black	20 (33.3)
Other	2 (3.4)
Marital status (married vs. other)	29 (48.3)
Education level (high school or higher)	40 (66.7)
Employment (full or part time)	29 (48.3)
Living with spouse or family (vs. alone)	41 (68.3)
Sleeps with partner (vs. alone)	41 (68.3)
Anthropometry, symptoms, and polysomnographic characteristics	
Body mass index, kg/m^2	29.5 ± 5.9
Epworth sleepiness scale score*	8.0 (4.0–9.0)
AHI, No./h	17.7 (13.1–36.9)
Sleep duration, min	317.1 ± 106.2
Sleep efficiency, %	79.0 (62.5–86.2)
Arousal index, No./h	20.1 (15.5–30.7)
CAI, No./h	0.00 (0.0–0.2)
PLMI, No./h	0.00 (0.0–0.0)
T< 90% (% of sleep time)	1.00 (0.2–2.9)
Nadir oxygen saturation, %	86 ± 5
OSA physiologic traits	
Arousal threshold (% Veupnea)	113.0 (104.3–126.3)
Loop gain	0.62 (0.48–0.78)
Pharyngeal collapsibility (Vpassive, % Veupnea)	96.2 (92.6–97.8)
Pharyngeal muscle compensation (Vcomp, % Veupnea)	5.7 (3.5–12.4)
Baseline psychological and medical comorbidities	
Anxiety*	8 (13.3)
PTSD*	2 (3.3)
Depression*	15 (25)
PHQ-9 depression total score	
0–4 (minimal)	36 (60.0)
5–14 (mild to moderate)	22 (36.7)
⩾14 (moderately severe to severe)	2 (3.3)
Alcohol (current use)	29 (43.3)
Tobacco (current use)	15 (25.0)
TIA	7 (11.7)
Stroke	10 (16.7)
Visual field deficit	7 (11.7)
Auditory deficit	12 (20.0)
Sensory deficit	9 (15.0)
Hemiplegia or motor deficit	1 (1.7)
Hypertension	37 (61.7)
Diabetes mellitus	14 (23.3)
Chronic kidney disease	5 (8.3)
Acute kidney injury*	4 (6.7)
Myocardial infarction	10 (16.7)
Other CAD*	11 (18.3)
Congestive heart failure	2 (3.3)
Atrial fibrillation	5 (8.3)
Cancer diagnosis	5 (8.3)
Chronic pain	14 (23.3)
Asthma	5 (8.3)
COPD*	3 (5.0)
Other chronic lung disease*	11 (18.3)
Event characteristics, functional status, and treatment	
Stroke	49 (81.7)
TIA	11 (18.3)
Event type	
Atherothrombotic/large vessel (e.g., carotid stenosis)	5 (8.3)
Cardioembolic	14 (23.3)
Lacunar	11 (18.3)
Other classified (e.g., dissection)	2 (3.3)
Unclassified	13 (21.7)
Missing	15 (25.0)
MRS score	
0–1 (no disability)	31 (51.7)
⩾2 (slight or worse disability)	29 (48.3)
Alteplase administration	9 (15.0)
Cardiac rehabilitation*	7 (11.9)
Physical activity/rehabilitation*	31 (51.7)
OSA treatment characteristics	
CPAP use characteristics over 6 mo	
CPAP adherence, h/night	1.6 (0.2–3.9)
CPAP adherence, h/night	2.2 ± 2.4
Adherent (>4 h for >70% of nights)	11 (1)
Residual AHI_{CPAP}, No./h	4.2 (1.9–6.6)
Large leak, min/night	2.0 (0.2–9.3)

Definition of abbreviations: AHI = apnea hypopnea index (hypopnea defined as 30% flow decrement associated with an arousal or 3% oxygen desaturation); AHI_{CPAP} = residual AHI determined by CPAP device; CAD = coronary artery disease; CAI = central apnea index; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; MRS = Modified Rankin Scale; OSA = obstructive sleep apnea; PHQ-9 = Patient Health Questionnaire 9; PLMI = periodic limb movements of sleep index; PTSD = post traumatic stress disorder; T = time; TIA = transient ischemic attack; Vcomp = higher values reflect higher compensation; Veupnea = ventilatory drive or intended ventilation observed if the airway is completely open; Vpassive = lower values reflect higher collapsibility.
Data are presented as mean ± SD, median (interquartile range), or *n* (%).
*Missing data for the following variables were imputed (12): Epworth Sleepiness Scale score ($n = 4$), and CAD, COPD, other chronic lung disease, acute kidney injury, anxiety, depression, PTSD, cardiac rehabilitation, and physical activity/rehabilitation all with ($n = 1$) missing.

patients with TIA or stroke and that this relationship persists after adjustment for established adherence factors. Although prospective validation is needed, our findings suggest that physiologic OSA traits may improve and help personalize prediction of CPAP adherence when incorporated along with the established factors, such as psychosocial characteristics, symptoms, and comorbidities. ■

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Table 2. Factors Associated with CPAP Adherence at 6 Months among Patients with TIA or Stroke: Multivariate Regression Model ($n = 60$, $R^2 = 65\%$)

Variable	β	SEM	β Std.	*P* Value
Constant	−29.62	15.08	−1.96	0.056
Physiologic OSA traits (model 1)				
Vcomp	−0.03	0.01	−0.31	0.033
Vpassive	0.14	0.15	0.40	0.359
LG	20.08	17.66	1.88	0.262
LG1 × Vpassive	−0.19	0.19	−1.62	0.305
ArTH	0.13	0.05	1.33	0.011
ArTH × BMI	<0.01	0.00	−1.90	0.010
BMI, kg/m^2	0.66	0.22	1.68	0.004
Factors from established CPAP adherence domains (e.g., social, demographic, comorbidity, etc.; model 2)				
Marital status (reference: single)	1.00	0.52	—	0.061
TIA	−2.22	0.77	—	0.006
Sensory deficit	1.91	0.72	—	0.011
Acute kidney injury	1.49	0.98	—	0.138
Chronic pain	−1.76	0.58	—	0.004
Cardiac rehabilitation	−1.10	0.75	—	0.147
Physical activity/rehabilitation	1.22	0.49	—	0.016
Disability: MRS score ⩾2 (reference: 0–1)	−1.23	0.49	—	0.016

Definition of abbreviations: AHI = apnea–hypopnea index; ArTH = arousal threshold; β Std. = change in the SD of adherence per SD increase in each continuous exposure term; BMI = body mass index; CPAP = continuous positive airway pressure; LG = loop gain; MRS = Modified Rankin Scale; OSA = obstructive sleep apnea; TIA = transient ischemic attack; Vcomp = pharyngeal muscle compensation; Veupnea = ventilatory drive or intended ventilation observed if the airway is completely open; Vpassive = pharyngeal collapsibility.
Model generated by adding factors from "physiological trait" CPAP adherence model (e.g., ArTH and loop gain; model 1) to CPAP adherence model consisting of factors in the social, psychological, medical comorbidity, functional status, symptom, and polysomnographic domains (model 2). Variables for each domain are shown in Table 1. A likelihood ratio test showed that addition of physiological factors significantly improved nonphysiological CPAP adherence model (*P* value = 0.013; change in sum of squares of 29%; R^2 increase from 50% to 65%). Sensitivity analyses including residual AHI and mask leak did not meaningfully change model results (data not shown). β Std. describes the number of SDs of change in CPAP adherence (h/night; SD = 2.3 h) per SD increase in each term. This can be used for comparison between trait effects and β coefficients for dichotomous variables (e.g., chronic pain). For example, lowering ArTH by 1 SD (an absolute of 24% of Veupnea) is associated with 1.33 × 2.3 = 3.1-hour reduction of CPAP adherence. Analogously, the 8% absolute reduction of ArTH is associated with 1-hour reduction in adherence, in comparison to 1.8-hour reduction in presence of chronic pain. SD for Vcomp was 23.1 (%Veupnea), with an increase of Vcomp of that magnitude associated with 0.8-hour reduction of CPAP adherence. Analogously, a 33% increase of Vcomp is associated with a 1-hour decline in CPAP adherence.

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Risk-stratified Management to Remove Low-Risk Penicillin Allergy Labels in the ICU

To the Editor:

Between 8% and 15% of the U.S. population carries a penicillin allergy label, yet <5% of these can be verified by allergy testing (1). A false label has a negative impact on care, including use of broader-spectrum and second-line antibiotics, increased healthcare utilization, surgical site infections, and treatment failure for common infections, delayed antimicrobial therapy, and longer lengths of stay (1, 2). β-Lactam allergy labels also affect antimicrobial stewardship and are associated with increased infections with *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* (3–6).

Penicillin allergies are commonly diagnosed in childhood and go unquestioned throughout life (7). However, these allergy diagnoses are largely inaccurate, explained instead by viral exanthems, drug–viral interactions, or nonallergic side effects. Even for penicillin allergies verified by skin testing, ⩾10% lose reactivity every year without evidence of resensitization (8, 9).

Patients admitted to a medical ICU (MICU) often have chronic illnesses or altered immunity, increasing their need for immediate antibiotic use. We sought to determine whether MICU patients with low-risk penicillin allergy history could be challenged directly with amoxicillin to have their allergy label safely removed during an acute inpatient stay. Some results of this study have been reported in abstract form (10).

Methods

Penicillin allergy risk stratification tool. We developed a history-based risk-stratification tool to identify patients with a penicillin allergy label at low risk of having a true allergy (2). During routine clinical encounters in our outpatient drug allergy clinic, patients provide a history of their index reaction to penicillin and are appropriately skin tested using a standardized panel of reagents. After a negative skin test, patients proceed to an observed oral challenge with amoxicillin 250 mg. When oral challenge is asymptomatic after a 1.5-hour observation period and a 24-hour follow-up nursing phone call to assess delayed skin test reactions and symptoms, a patient's penicillin allergy label is removed. Data from these visits were used to derive and validate our risk-stratification algorithm. This project was approved by the Vanderbilt institutional review board (#181180 and #181734).

Data from 318 consecutive patients seen from 2014 to 2018 were collected using standardized chart review and data collection and were categorized via historical assessment by a physician into one of three groups: *1*) highest risk-delayed reactions (blistering, mucosal involvement, severe rash, and/or immune-mediated organ injury); *2*) moderate to high risk, where patients reported symptoms consistent with standard anaphylaxis criteria; or *3*) low risk, where patients reported symptoms that were inconsistent with either of the higher-risk criteria (Figure 1). The outcomes of allergy testing in the clinic were compared with history-based risk criteria to estimate the negative predictive value for a positive penicillin allergy skin test and oral challenge among low-risk patients.

Penicillin allergy delabeling study. All patients admitted to the MICU between March 31, 2019, and October 31, 2019, who were both hemodynamically stable and could provide a history of their index reaction were screened. Those whose reported index reaction was consistent with a low-risk penicillin allergy were offered direct challenge with 250 mg oral amoxicillin followed by 1-hour observation. Consent for the clinical procedure was obtained

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Data-sharing statement: Individual, deidentified participant data (including data dictionaries) will be shared on written request to the corresponding author and execution of appropriate data use agreements.

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