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The Effect of Hypopnea Scoring on the Arousal Threshold in Patients with Obstructive Sleep Apnea

To the Editor:

A low respiratory arousal threshold ($ArTH_{Resp}$) is one of several endotypes that contribute to the pathogenesis of obstructive sleep apnea (OSA). Accordingly, it has emerged as a potential “drugable” target to treat OSA (1). Notably, Edwards and colleagues (2) developed a clinical screening tool to identify OSA patients with low $ArTH_{Resp}$ based on three predictive variables obtained from standard overnight sleep studies (i.e., polysomnograms [PSGs]): 1) nadir oxygen saturation $>82.5\%$, 2) apnea-hypopnea index (AHI) <30 events/hour, and 3) percentage of respiratory events that are hypopneas (%hypopnea) $>58.3\%$ that correctly predicted the presence of a low $ArTH_{Resp}$ in 84% of patients.

However, a key limitation of this tool is that it was developed using hypopnea scoring rules from the older “Chicago” (AASM₁₉₉₉) criteria (3), which have since been updated to the current American Academy of Sleep Medicine (AASM) “Recommended” (AASM_{2012Rec}) and “Acceptable” (AASM_{2012Acc}) criteria. The AASM_{2012Rec}-defined hypopneas are associated with a $\geq 3\%$ oxygen desaturation or EEG arousal, whereas AASM_{2012Acc} requires a stricter $\geq 4\%$ oxygen desaturation and does not consider arousals (4). Though it is established that differing scoring criteria impact the AHI and %hypopnea (5–7), we recently demonstrated that scoring criteria also influence the measurement of another key OSA endotype (8), the sensitivity of the ventilatory control system. However, the extent to which changes in scoring criteria impact the predictive utility of the $ArTH_{Resp}$ score is unknown. Accordingly,

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Table 1. Multiple Linear Regression Models to Predict Low Respiratory Arousal Threshold as Measured by Epiglottic Pressure (cm H₂O) across Different Hypopnea Scoring Criteria

Variable	1999 Chicago (Adjusted $r^2 = 0.590^*$)		2012 Recommended (Adjusted $r^2 = 0.593^*$)		2012 Acceptable (Adjusted $r^2 = 0.595^*$)	
	β	P Value	β	P Value	β	P Value
Age, yr	0.075	0.25	0.073	0.26	0.055	0.41
Sex, M	0.153	0.04	0.139	0.06	0.129	0.08
BMI, kg/m ²	-0.024	0.74	-0.021	0.77	-0.022	0.77
AHI, events/h	-0.275	0.002	-0.315	0.001	-0.421	<0.001
%hypopnea	0.271	0.004	0.228	0.02	0.144	0.07
SpO ₂ nadir, %	0.446	<0.001	0.441	<0.001	0.452	<0.001

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; %hypopnea = percentage of respiratory events that are hypopneas; SpO₂ = blood oxygen saturation as measured by pulse oximetry.

Bold indicates significant predictors.

1999 Chicago (Original) = (age · 0.064) + (sex · 3.688) + (BMI · -0.031) + (AHI · -0.108) + (%hypopnea · 0.091) + (SpO₂ nadir · 0.534) - 65.402.

2012 Recommended = (age · 0.062) + (sex · 3.364) + (BMI · -0.027) + (AHI · -0.123) + (%hypopnea · 0.075) + (SpO₂ nadir · 0.528) - 63.382.

2012 Acceptable = (age · 0.047) + (sex · 3.162) + (BMI · -0.029) + (AHI · -0.164) + (%hypopnea · 0.051) + (SpO₂ nadir · 0.548) - 61.23.

* $P < 0.001$.

we aimed to determine the influence that the 2012 scoring criteria has on the tool's performance.

An investigator rescored the PSGs of 101 patients with OSA from the original study (2). Hypopneas that did not meet the AASM_{2012Rec} criteria were removed. A second pass was then performed to remove hypopneas not meeting the AASM_{2012Acc} desaturation criteria. Area under the curve, sensitivity, and specificity of the ArTH_{Resp} score produced from both AASM 2012 scoring criteria were evaluated. Values are reported as mean ± SD.

The AASM₁₉₉₉ AHI (39.3 ± 28.6 events/h) was significantly higher than both the AASM_{2012Rec} (37.9 ± 28.6 events/h; $P < 0.01$) and AASM_{2012Acc} (30.7 ± 28.7 events/h; $P < 0.0001$). Similarly, %hypopnea was significantly lower for the AASM_{2012Acc} (35.0 ± 31.5%; $P < 0.0001$) and AASM_{2012Rec} (54.0 ± 33.3%; $P < 0.05$) compared with the AASM₁₉₉₉ (54.9 ± 32.8%). Notably, 20 patients were no longer considered to have OSA (AHI < 5 events/h) using the AASM_{2012Acc} criteria.

Linear regression was used to examine relationships between the gold-standard measure of the ArTH_{Resp} (i.e., epiglottic pressure) with the AHI and %hypopnea across all scoring criteria. The AHI generated from both 2012 criteria correlated with the ArTH_{Resp} (AASM_{2012Rec} [$R^2 = 0.412$; $P = 0.0001$] and AASM_{2012Acc} [$R^2 = 0.481$; $P = 0.0001$]) and were similar to the originally

described relationship ($P = 0.73$). The relationship between ArTH_{Resp} and %hypopnea was comparable between the original AASM₁₉₉₉ ($R^2 = 0.332$; $P < 0.0001$) and AASM_{2012Rec} ($R^2 = 0.339$; $P < 0.0001$) but was substantially attenuated when using the AASM_{2012Acc} ($R^2 = 0.09$; $P = 0.003$), a difference confirmed via analysis of covariance ($P = 0.02$). Multiple linear regression was performed to assess individual relationships between the three predictive variables and the ArTH_{Resp}. All three variables were independent predictors under AASM_{2012Rec} criteria (Table 1). The %hypopnea derived from AASM_{2012Acc} was no longer a predictor of ArTH_{Resp}. Receiver operating characteristic analysis and a DeLong's test were used to assess and compare the predictive performance of the low ArTH_{Resp} score between the different scoring criteria using the original score thresholds. The area under the curve was similar between the original AASM₁₉₉₉ and AASM_{2012Rec} criteria ($P = 0.96$) but lower for AASM_{2012Acc} when compared with both AASM₁₉₉₉ ($P = 0.02$) and AASM_{2012Rec} ($P = 0.009$; Table 2). Removing the 20 patients without OSA from the AASM_{2012Acc} data set reduced the accuracy by another 10%.

Patients with a low ArTH_{Resp} typically exhibit shallow reductions in breathing (and/or oxygen levels) before arousing from sleep because they poorly tolerate minor increases in

Table 2. Comparison of the Clinical Screening Tool's Performance to Accurately Predict the Presence of a Low Respiratory Arousal Threshold Across Different Hypopnea Scoring Criteria

AASM Scoring Criteria	Sensitivity	Specificity	Accuracy	Area Under Curve
1999 Chicago (Original)	80%	88%	84%	0.89* [0.81–0.94]
2012 Recommended	82%	88%	85%	0.89* [0.81–0.94]
2012 Acceptable	76%	80%	78%	0.83* [0.75–0.90]
2012 Acceptable (OSA only [†])	62.5%	82%	74%	0.79* [0.68–0.87]

Definition of abbreviations: AASM = American Academy of Sleep Medicine; OSA = obstructive sleep apnea.

Area under curve [95% confidence interval].

* $P < 0.001$.

[†]Excluding $n = 20$ that no longer had OSA (defined as an apnea-hypopnea index <5/h) using the AASM 2012 Acceptable criteria.

ventilatory effort, regardless of why ventilatory drive was increased (i.e., resistive load, hypercapnia, and/or hypoxia) (9). Hypopnea scoring that captures multiple features of increased ventilatory effort such as the AASM_{2012Rec} criteria (which is sensitive to reductions in flow [i.e., resistive load] and oxygen desaturation [hypoxia] leading to arousal), would be expected to correlate well with the ArTH_{Resp}. In contrast, the AASM_{2012Acc}-scored hypopneas are solely driven by the frequency of desaturation >4% (5) irrespective of whether an arousal occurs and, as such, only capture one source of increased ventilatory effort: hypoxia. It is therefore understandable that the %hypopnea determined using the AASM_{2012Acc} were weakly associated with the ArTH_{Resp} (epiglottic pressure_{nadir}) and was not an independent predictor of a low ArTH_{Resp}.

Furthermore, when using the AASM_{2012Acc} criteria, a proportion of patients (19.8%; $n = 20$) from the original cohort no longer had OSA. Of these individuals, 90% had a low ArTH_{Resp}. Moreover, these 18 patients were predominately female (37% of total female sample; $n = 30$) and lean (13/20 had BMI ≤ 27 kg/m²). Consistent with this observation, Won and colleagues reported that women have a lower ArTH_{Resp} than men and also experienced more arousal-predominant hypopneas with minimal falls in their oxygen levels. Furthermore, they also found the AASM_{2012Acc} criteria underestimated the AHI for women (10). Likewise, leaner patients have also been reported to have fewer or less severe falls in their oxygen levels and were also less likely to be diagnosed with OSA under the AASM_{2012Acc} criteria despite being symptomatic and treatment responsive (11). These findings, together with our own, suggest that when scoring PSGs under the AASM_{2012Acc} rules, we are losing (or perhaps ignoring) some of the physiological information contained within these recordings, which is to the potential detriment of patient subgroups amenable to treatment.

Ultimately, to answer the question of what is and what is not a hypopnea requires hard outcome measures to determine whether they are harmful and require intervention. This issue cannot be addressed if subtle hypopnea information is discarded. Indeed, though debate continues over what constitutes a hypopnea, it would be prudent to err on the side of caution and use an AHI based on hypopnea criteria that maximizes diagnostic sensitivity and physiological insight among a highly heterogeneous patient population. Another implication of our new findings is that strategies to raise the arousal threshold (e.g., sedatives) may preferentially resolve the more subtle hypopneas; the clinical impact of such interventions thus requires careful study.

In summary, the ArTH_{Resp} score remains a clinically useful tool to predict the presence of a low ArTH_{Resp} in patients with OSA when using the AASM_{2012Rec} hypopnea scoring criteria. However, caution is advised if using data scored with the AASM_{2012Acc} criteria. Furthermore, AASM_{2012Acc}-scored cohort studies are at risk of underrepresenting patients with OSA with a low ArTH_{Resp} using this tool, which may lead to biased clinical and research outcomes. ■

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Time-Dependent Confounding in Tuberculosis Treatment Outcome Analyses: A Review of a Source of Bias

To the Editor:

In 2018, 484,000 people became sick with tuberculosis (TB) resistant to at least rifampin, the most effective drug to treat TB (1). Patients with rifampin-resistant or multidrug-resistant TB (MDR-TB) must be

treated for up to 24 months with ≥ 4 drugs, many of which are toxic (2). Research priorities for MDR-TB treatment are evolving rapidly, compromising the relevance of randomized controlled trials (RCTs) that take 5–10 years from planning to reporting (3). RCT evidence remains the gold standard in assessing causal effects. Observational studies may also be used to infer causality when they generate high-quality data, specify potential sources of bias, and employ appropriate analytic methods to account for such threats like confounding.

Time-dependent confounding affected by previous treatment, henceforth “time-dependent confounding,” can introduce substantial bias in longitudinal studies. Such confounding occurs when a time-varying covariate is a risk factor for the outcome, predicts subsequent treatment, and is affected by past treatment (Figure 1) (4, 5). Early studies in HIV that failed to account for time-dependent confounding led to the finding that antiretroviral therapy (ART) increased mortality; appropriately accounting for this bias revealed a protective effect, as seen in RCTs (4). Time-dependent confounding is likely a concern in longitudinal TB-treatment studies, particularly for longer MDR-TB regimens, which are individualized and change based on events throughout treatment (i.e., adverse events, resistance, and bacteriologic response) (Figure 1). These events that predict treatment changes also predict treatment outcomes. Conventional longitudinal analysis techniques, such as time-dependent Cox regression or generalized estimating equations that model time-varying covariates, cannot

Figure 1. Abbreviated graphic of time-dependent confounding by sputum culture result, as applied to an analysis of the effect of multidrug-resistant tuberculosis treatment regimen composition on end-of-treatment outcome. Consider a patient who is sputum culture positive at treatment initiation (time $[t] \ i = 0$, where i indicates a specified treatment month). A positive sputum culture collected in Month 6 (sputum culture result $_{t(6)}$) is predictive of poor end-of-treatment outcome and may also influence a provider to change the patient's treatment when the sputum culture result is available in Month 7 or 8 (treatment regimen $_{t(7 \text{ or } 8)}$). Finally, a positive sputum culture collected in Month 6 (sputum culture result $_{t(6)}$) is dependent on the treatment a patient received in Months 1–6 (treatment regimen $_{t(1-6)}$). A complete graphic of this relationship can include as many time points as there are months of treatment for multidrug-resistant tuberculosis (6 to 24+ months).

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adequately control for time-dependent confounding (5). Rather, analytic methods that consider time-varying treatment–confounder feedback, such as inverse probability weighting in marginal structural models, g-formula, and g-estimation (6), must be used.

Here, we quantify the number of longitudinal cohort studies assessing the effect of TB treatment on TB outcomes that used the aforementioned methods of interest to control for time-dependent