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SCIENTIFIC INVESTIGATIONS

Screening for Obstructive Sleep Apnea in Commercial Drivers Using EKG-Derived Respiratory Power Index

M. Melanie Lyons, PhD, ACNP[1]; Jan F. Kraemer, Dipl-Inform[2]; Radha Dhingra, MD[3]; Brendan T. Keenan, MS[1]; Niels Wessel, PhD[2]; Martin Glos, PhD[4]; Thomas Penzel, PhD[4]; Indira Gurubhagavatula, MD, MPH[1,5,6]

[1]Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Department of Physics, Humboldt-Universitat zu Berlin, Berlin, Germany; [3]Mahatma Gandhi Medical College and Hospital, Jaipur, India; [4]The Centre of Sleep Medicine, Department of Cardiology, Charité Universitätsmedizin, Berlin, Berlin, Germany; [5]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [6]Sleep Disorders Clinic at the Philadelphia CMC VA Medical Center, Philadelphia, Pennsylvania

Study Objectives: Obstructive sleep apnea (OSA) is common in commercial motor vehicle operators (CMVOs); however, polysomnography (PSG), the gold-standard diagnostic test, is expensive and inconvenient for screening. OSA is associated with changes in heart rate and voltage on electrocardiography (EKG). We evaluated the utility of EKG parameters in identifying CMVOs at greater risk for sleepiness-related crashes (apnea-hypopnea index [AHI] ≥ 30 events/h).

Methods: In this prospective study of CMVOs, we performed EKGs with concurrent PSG, and calculated the respiratory power index (RPI) on EKG, a surrogate for AHI calculated from PSG. We evaluated the utility of two-stage predictive models using simple clinical measures (age, body mass index [BMI], neck circumference, Epworth Sleepiness Scale score, and the Multi-Variable Apnea Prediction [MVAP] score) in the first stage, followed by RPI in a subset as the second-stage. We assessed area under the receiver operating characteristic curve (AUC), sensitivity, and negative posttest probability (NPTP) for this two-stage approach and for RPI alone.

Results: The best-performing model used the MVAP, which combines BMI, age, and sex with three OSA symptoms, in the first stage, followed by RPI in the second. The model yielded an estimated (95% confidence interval) AUC of 0.883 (0.767–0.924), sensitivity of 0.917 (0.706–0.962), and NPTP of 0.034 (0.015–0.133). Predictive characteristics were similar using a model with only BMI as the first-stage screen.

Conclusions: A two-stage model that combines BMI or the MVAP score in the first stage, with EKG in the second, had robust discriminatory power to identify severe OSA in CMVOs.

Keywords: commercial motor vehicle drivers, electrocardiography, EKG, obstructive sleep apnea, occupational driving, OSA, respiratory power index, screening, surrogate measure for apnea hypopnea index, truck drivers

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BRIEF SUMMARY

Current Knowledge/Study Rationale: In commercial motor vehicle operators (CMVOs), obstructive sleep apnea (OSA) is often undiagnosed because testing using the gold-standard measure, in-laboratory polysomnography, is expensive, not easily accessible, and time consuming for long-haul drivers who are regularly on the road. However, 28% to 60% of CMVOs have been found to have OSA and ~30% of known CMVO accidents have been related to OSA.

Study Impact: We describe an approach that shows promise in identifying CMVOs who have severe OSA—who are likely to be at risk for a sleepiness-related crash—by using the spectral qualities of electrocardiography with portable diagnostic ability and without requiring overnight in-laboratory polysomnography. Future studies should include larger cohorts of patients.

INTRODUCTION

Characterized by repetitive breathing pauses during sleep, obstructive sleep apnea (OSA) occurs due to a collapse of the pharyngeal muscles, leading to cessation (apnea) or reduction (hypopnea) in airflow. These events are terminated by a sympathetic burst, which leads to a brief arousal from sleep. The resultant sleep fragmentation, intermittent hypoxia, and sympathetic activation have been linked with a number of downstream consequences. One symptom of OSA is daytime sleepiness, which is relevant for commercial motor vehicle operators (CMVOs) because of its association with sleepiness-related crashes.

Indeed, ~30% of commercial vehicle accidents are due to sleepiness.[1–3] OSA is common in CMVOs, with 28% to 60% having the disorder.[4,5] This is because CMVOs tend to be obese, male, and middle-aged, the three most common risk factors for OSA.[6–8] Despite this risk, in most CMVOs

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OSA is undiagnosed and, therefore, no treatment is implemented.[5,8–10] The gold-standard test, polysomnography (PSG)[11] is inappropriate for systematic screening because of its high expense, complexity, and relative inaccessibility, particularly among uninsured patients. Moreover, PSG requires the patient to sleep in a laboratory, which poses inconvenience to long-haul drivers. Therefore, simpler screening tools deserve investigation.

Symptom reporting has been shown to be unreliable in this group,[9,10,12] and so may not be effective for screening. Objective tools include body mass index (BMI), age, and sex. These can be used alone, or in a two-stage fashion, with the second stage test being an ambulatory diagnostic recording that can be done in the CMVO's home or berth of the truck. These tools have included recordings of airflow, respiratory effort, and oxyhemoglobin saturation.

An alternative to these ambulatory tests that has not been evaluated before is heart rate variability (HRV) using electrocardiography (EKG), which can be summarized using time- or frequency-based metrics.[13] Respiratory activity can affect EKG-derived variables. For example, respiratory movement can induce rotation in the electrical axis,[14] as well as sinus arrhythmia.[15] Additionally, OSA has been associated with cyclic heart rate variability,[16] with patients experiencing a relative bradycardia during the apnea/hypopnea event, followed by a relative tachycardia at event termination, during the sympathetic burst. In addition, the effort to inhale against a closed glottis can lead to fluctuations in EKG voltage, as the chest wall moves away from the heart, followed by an increase in voltage when breathing resumes and the chest wall returns to neutral position. These data may be combined into a single metric that estimates the frequency of apneas and hypopneas per hour of sleep, or apnea-hypopnea index (AHI).

In the current study, we evaluated the utility of single-stage and two-stage risk prediction paradigms leveraging a three-channel EKG in identifying OSA in a cohort of CMVOs, using the AHI derived from PSG as the gold standard. Given that studies have associated severity of OSA with increased risk for motor vehicle crashes,[17] we focused our observations on CMVOs with severe OSA (s-OSA; AHI of ≥ 30 events/h).

METHODS

The Institutional Review Board of the University of Pennsylvania approved the protocol. All participants provided signed informed consent.

Participant Selection

We recruited holders of active commercial driver's licenses through online advertisements from 2009–2011. Participants were required to reside within 40 miles from the Penn Sleep Center and be 18 to 65 years old. We excluded those using positive airway pressure or supplemental oxygen; those with nocturnal hypoxia because of any other illness; or medical or psychiatric conditions that prevented their ability to participate.

Confidentiality

Given that study data can affect employment, the National Institutes of Health granted a Certificate of Confidentiality,[12] enabling us to resist court-ordered subpoenas to release personal health information. We shared this information with all participants.

Demographics, Symptoms, Examination, PSG and Case Definition

We collected demographic data,[12] and self-reported data including medical history, apnea-related symptoms (snoring, choking/gasping, witnessed apneas), and daytime sleepiness (Epworth Sleepiness Scale [ESS]). Study personnel measured and recorded BMI, blood pressure, and neck circumference (NC). PSG tests were 14-channel studies conducted in the participant's home, as described previously,[12] and included electroencephalography (C3, C4, Oz), three-channel EKG, eye, chin, and pretibial electromyography, chest and abdominal plethysmography, nasal and oral airflow by nasal cannula, and oral thermistor and finger oximetry. Scoring was performed by registered PSG technologists, using standards defined by the American Academy of Sleep Medicine (AASM). Per AASM scoring guidelines, hypopneas were defined as a ≥ 30% drop in signal amplitude for at least a 10-second duration and also associated with a ≥ 4% oxygen desaturation from baseline.[18,19] Technologists set up and scored PSG tests while blinded to questionnaire data. We computed the AHI as the number of apneas plus hypopneas divided by hours of sleep time. s-OSA, our main case-definition of interest, was defined as an AHI of ≥ 30 events/h based on PSG.

Determining EKG-Derived Respiratory Power Index: A Surrogate for Apnea-Hypopnea Index

As briefly described previously,[20] we integrated signals based on their estimated spectral power densities. We used the instantaneous respiratory rate to exclude noise in bands not relevant to respiration. We used the resulting integrated spectrum to estimate respiratory power, and from this, we calculated the respiratory power index (RPI), an estimate for the AHI.

To generate the initial estimations of the respiratory signal, we used prior algorithms, such as: amplitude of the R-Peak, P-Wave, and T-Wave, as well as the area of the QRS complex and the change in the heart rate, or respiratory sinus arrhythmia (RSA). We transformed each signal so that all signals show an identical average power. After averaging the calculated spectral power densities, the common respiratory component became dominant. Next, to remove the nonrespiratory parts of the spectrogram, we estimated the instantaneous respiratory frequency on a spectrum that is longitudinally rescaled on the frequency axis. This allowed us to filter out nonrespiratory components, and select the respiratory component. Summing the power density of this component over each time point provided an estimation of the respiratory power. We applied an adaptive[20,21] filtering procedure to exclude artifacts and values related to ectopy.

For further details on this derivation, see **Figure 1**. The variables used in the EKG for calculating[13] the HRV are summarized in **Table 1**.

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Respiratory Power Index

The method used to calculate the RPI has so far only been described preliminarily as a conference contribution; a detailed study will follow.[20] Each of the metrics in **Table 1** was calculated as a weighted average over all EKG segments, the weights being the length of the EKG segment. Multiple independent embeddings of the respiratory activity on the EKG were used to calculate the RPI, which has been used as a surrogate marker for AHI. These embeddings have the physical and rotational properties of the electrical axis, due to respiratory movement as well as neural sources in the case of RSA. As outlined earlier, the RSA depends on the breathing rate. Information from all embeddings was then integrated and controlled for noise, which is often a reason for infrequent sampling. The combination of spectral power densities for these signals along with instantaneous respiratory rate allowed for exclusion of noise not relevant to respiration. The integrated spectrum was used to estimate respiratory power from which RPI could be computed. Further information on extracting RPI and distinguishing RPI signals from artifact is presented in the supplemental material.

Validation of this technique was performed using an independent PSG data set.[22] This information is summarized in the supplemental material. For determination of AHI ≥ 30 events/h, the coefficient of determination was calculated as, $R^2 = 0.90$ with $P < 10^{-10}$. Using a threshold of RPI > 12.23 for the determination of OSA (AHI ≥ 30 events/h) in this dataset, the RPI would show sensitivity of 1 and specificity of 0.75. Similarly, for determination of AHI > 15 events/h, the coefficient of determination was calculated as, $R^2 = 0.74$. Using a threshold of 10 for the determination of OSA (AHI > 15 events/h) in this dataset, the RPI would show sensitivity of 0.93 and specificity of 0.75.

Computation of Risk

Single-Stage Strategies to Determine Risk

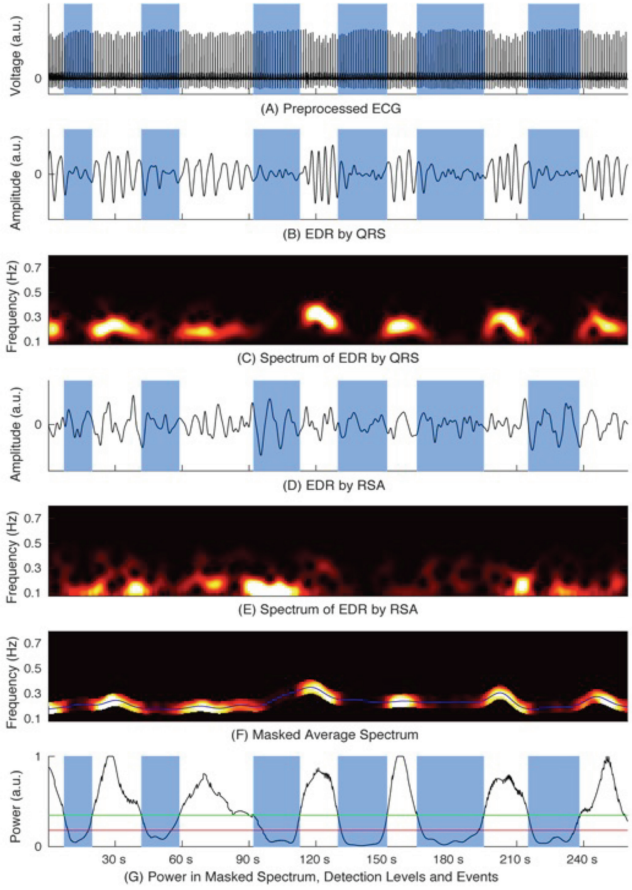
We first determined risk scores for single-stage models. These models included assessments of BMI, age, ESS, NC, and all 13 aforementioned EKG-derived metrics (**Table 1**). In addition, we assessed the performance of a previously derived Multi-Variable Apnea Prediction (MVAP) score[23] which combines BMI, age, sex, and the average responses (ranging from 0–4) on three specific OSA-symptom frequency questions: (1) snorting or gasping; (2) loud snoring; and (3) breathing stops, choking, or struggling for breath. In addition to the overall MVAP score, we examined the predictive ability of the symptom score average (Index 1) alone.

Two-Stage Strategies to Determine Risk

We employed a two-stage risk prediction strategy, as described previously.[8,24,25]

We categorized participants into high, intermediate, or low probability groups for risk of s-OSA based on first-stage risk scores (BMI, age, NC, ESS, MVAP Index 1, and MVAP). Using a previously described, iterative, optimization method, we chose an upper-bound value of each risk score to separate participants who could be at high risk for s-OSA from those at intermediate risk, and a lower-bound value to separate intermediate risk from low-risk participants.[26] We predicted that participants with a risk score that was greater than the upper-bound cutoff point would have s-OSA, whereas participants with a risk score of less than the lower-bound cutoff point would be predicted not to have s-OSA. In our model, CMVOs

Figure 1—Exemplary illustration of the methods behind the electrocardiographically derived respiratory power index (RPI).



The nighttime electrocardiograph recordings are preprocessed, including detection of fiduciary points and an estimation of signal-to-noise ratio (SNR), and are cut into segments of limited length (4–10 minutes) and high SNR **(A)**. Segments of insufficient quality are discarded. Multiple embeddings of respiration into the ECG are used to derive electrocardiographically derived respiration (EDR) signals based on, e.g., the amplitudes of the peaks of the r-, p-, and t-wave **(B)**, the respiratory sinus arrhythmia (RSA) **(D)**. The spectrograms calculated from these signals **(C,E)** are normalized and averaged to amplify the common, ie, respiration based, component. In this case the RSA is not dominant as a source of modulation of the heart rate variability and shows mostly uncorrelated components that are reduced in the averaging process. The averaged spectrum is then analyzed to derive an estimate for the instantaneous respiratory frequency and masked to further reduce nonrespiration-related power in the spectrum **(F)**. The power at each time-step is then calculated together with two levels used in the selection of events **(G)**. The green line is the maximum level that determines the extent of an event if it lasts longer than a minimum amount of time and falls below the red level at least once. Time spans that indicate an event are underlaid blue on all time series. The amount of detected events, in relation to the analyzed time, is the RPI.

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Table 1—Description of variables used in electrocardiography.

Time-Domain Methods	
Metric	**Definition**
SDNN (milliseconds)	Standard deviation of all NN intervals.
RMSSD (milliseconds)	The square root of the mean squared differences of successive NN intervals.
SDANN (milliseconds)	Standard deviation of the averages of NN intervals in all minute segments of the entire recording.
% NN interval differences < 10 millisecond	The percentage of beat-to-beat interval differences that were less than 10 milliseconds.
Frequency-Domain Methods	
Power-spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency. The methods used for determining heart rate variability:	
Total power (ms^2)	The variance of all NN intervals.
High frequency (ms^2)	Power in the high frequency range (0.15–0.4 Hz).
Low frequency (ms^2)	Power in the low frequency range (0.04–0.15 Hz).
Very low frequency (ms^2)	Power in the very low frequency range (0.003–0.04 Hz).
Low frequency/high frequency (LF/HF)	Ratio of LF to HF powers.
Symbolic Dynamics Method	
Polvar10	The percentage of occurrence of sequences of beat-to-beat intervals that were less than 10 milliseconds.
WSDVAR	Symbolic dynamics; word sequence variance.
Wpsum02	Symbolic dynamics; symbol probability for symbols 0 and 2.

For more information, see Wessel N, Malberg H, Bauernschmitt R, Kurths J. Nonlinear methods of cardiovascular physics and their clinical applicability. *Int J Bif Chaos*. 2007;17:3325–3371. NN = normal to normal beat-to-beat interval.

falling between these ranges would be expected to undergo the second-stage test (EKG), and have the RPI value compared against a threshold RPI. Those with RPI values at or above the RPI threshold would be deemed to be at high risk for s-OSA, and those whose values were below the threshold would be predicted not to have OSA.

Computation of Model Parameters

We computed predictive characteristics of our single- or two-stage prediction models based on derived optimal model parameters. Single-stage models classified s-OSA or no s-OSA based on a single parameter, which was the optimal cutoff point for the variable being examined. The two-stage strategies had three parameters: the upper and lower bound for the first-stage test, and the threshold value of RPI in the second stage. We defined the optimal parameter set for each model by using an iterative algorithm that minimized the sum of false positives and twice the false negatives (ie, missed cases). We weighted missed cases more heavily because of the potential risk of drowsiness-related crashes in this group. In the case that multiple cutoff points met our selection criteria, we chose as the optimal parameter set the one that which also maximized specificity. Our method has been detailed previously.[24–26]

We determined area under the receiver operating characteristic curve (AUC) for single-stage models using continuous cutoff points for each single-stage predictor. For two-stage models, we calculated the AUC using logistic regression models with s-OSA as an outcome. We utilized the optimal parameter set for each model to compute sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (−LR), positive posttest probability (PPTP), and negative posttest probability (NPTP). To estimate the expected accuracy of our estimates, we calculated nonparametric confidence intervals (CI) based on 1,000 bootstrapped samples of the dataset. That is, we generated 1,000 random samples (chosen with replacement) of equal size to the original population and obtained a distribution of 1,000 predictive characteristics; the nonparametric 95% CI for each measure were calculated as the 2.5th to 97.5th percentiles of these distributions.

General Statistical Methods

Unless otherwise noted, we summarized continuous variables using mean and standard deviation (SD) and categorical variables using frequency and percent. We used a natural log or square-root transformation, when appropriate and if needed for continuous variables to meet parametric modeling assumptions, and compared between s-OSA and non-s-OSA groups using *t* tests. Categorical variables were compared between groups using chi-square or Fisher exact tests.

RESULTS

Sample Characteristics

Of the 95 participants who met our inclusion criteria and had EKG data available, 89 (93.7%) were male. We present demographic data in **Table 2**. The mean (SD) BMI, age, NC, and systolic and diastolic blood pressure were: 34.2 (8.2) kg/m^2, 43 (8.5) years, 43 (3.9) cm, 133.2 (11.5) mmHg and 78.8 (14.6) mmHg, respectively. Most participants (70.5%) had obesity or were considered to have morbid obesity. These data are consistent with studies in prior truck driver cohorts[5,8,27] and with established OSA risk factors.[28–30]

Compared to individuals with AHI < 30 events/h, participants with s-OSA were older, more likely to have obesity, had larger NC, higher diastolic blood pressure, and worse

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Table 2—Demographic characteristics of the sample, overall and stratified by AHI.

Characteristic	Overall (n = 95)	AHI < 30 (n = 69)	AHI ≥ 30 (n = 26)	*P**
Age, years	43.8 ± 8.5	42.4 ± 8.7	47.3 ± 6.8	.0115
Male, %	93.7	92.8	96.2	> .999
BMI, kg/m^2	34.2 ± 8.2	32.6 ± 7.7	38.3 ± 8.0	.0019
Normal (20 to < 25), %	9.5	13.0	0.0	.0228
Overweight (25 to < 30), %	20.0	23.2	11.5	
Obese (30 to < 35), %	33.7	34.8	30.8	
Morbid I (35 to < 40), %	20.0	18.8	23.1	
Morbid II (≥ 40), %	16.8	10.1	34.6	
Weight, lbs.	238.1 ± 59.0	229.6 ± 60.5	260.7 ± 49.2	.0214
Height, in.	70.0 ± 3.4	70.3 ± 3.3	69.4 ± 3.5	.2660
Neck circumference, cm	43.0 ± 3.9	42.4 ± 3.9	44.7 ± 3.6	.0119
Race, %				
White	51.6	52.2	50.0	.8004
Black	43.2	43.5	42.3	
Other	5.3	4.4	7.7	
Systolic BP, mmHg	133.2 ± 11.5	132.4 ± 11.7	135.4 ± 10.9	.2486
Diastolic BP, mmHg	78.8 ± 14.6	76.6 ± 11.6	84.6 ± 19.7	.0589
Current smoker, %	29.5	27.5	34.6	.4998
Married, %	39.0	39.1	38.5	.9525
Bed partner, %	55.8	53.6	61.5	.4886
ESS score	6.5 ± 4.7	5.9 ± 4.0	8.2 ± 5.8	.0630
ESS > 10, %	11.6	8.7	19.2	.1659
ESS > 15, %	7.4	2.9	19.2	.0155
AHI, events/h	25.2 ± 21.4	14.5 ± 8.2	53.8 ± 19.2	< .0001
Control (< 5), %	10.5	14.5	0.0	< .0001
Mild (5 to < 15), %	30.5	42.0	0.0	
Moderate (15 to < 30), %	31.6	43.5	0.0	
Severe (≥ 30), %	27.4	0.0	100.0	
RPI, events/h	15.0 ± 9.8	11.5 ± 4.9	24.3 ± 13.1	< .0001

* = *P* value from *t* test for continuous variables and chi-square of Fisher exact tests for categorical variables, comparing AHI groups. AHI = apnea-hypopnea index, BMI = body mass index, ESS = Epworth Sleepiness Scale, RPI = respiratory power index.

sleepiness (see **Table 2**). In this group, mean (SD) AHI was 53.8 (19.2) events/h, compared to 14.5 (8.2) events/h in the non-s-OSA group. Participants with s-OSA had a higher RPI than those without s-OSA (24.3 [13.1] versus 11.5 [4.9] events/h; $P < .0001$), supporting the strong association between the RPI and AHI from PSG.

Electrocardiogram Derived RPI Metrics Are Associated With Severe OSA

We observed statistically significant or suggestive associations between select EKG-derived metrics and severe OSA (see **Table 3**). Specifically, CMVOs with s-OSA had significantly lower high frequency band to total power ratio ($P = .0304$) and average beat-to-beat interval ($P = .017$) compared to individuals with AHI < 30 events/h. In addition, s-OSA individuals had suggestively higher percentages of NN (normal to normal) beat-to-beat interval differences < 10 ms ($P = .063$) and occurrence of NN sequences < 10 ms ($P = .070$). As shown in **Table 3**, RPI was the most significantly associated metric with severe OSA; thus, this was chosen as our primary EKG-derived measure in our modeling strategies to identify s-OSA.

Single-Stage Strategy: RPI Is Associated With Severe OSA

The discriminatory power of all single-stage models is shown in **Table 4** and **Table S1** in the supplemental material, along with optimal cutoff points, AUC, sensitivity, specificity, +LR, −LR, PPTP, and NPTP. When examining the AUC statistic, the RPI was the best predictor of s-OSA, followed by the MVAP score. Specifically, RPI had an overall AUC of 0.872 (95% CI: 0.791–0.942). The optimal cutoff point of RPI ≥ 12.23 yielded a high sensitivity of 88.5% (75.0% to 100.0%) and specificity of 63.8% (52.4% to 75.0%). The MVAP score was the second best performing model in terms of AUC (0.813 [0.702–0.910]) and showed similar sensitivity (87.5% [74.6% to 100%]) and specificity (63.6% [51.7% to 75.0%]) as the RPI, based on an optimal cutoff point of 0.616. The improved performance of both the RPI and MVAP when compared to other single-stage models (eg, BMI, age, ESS, NC, or MVAP Index 1) appears

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Table 3—Summary statistics for electrocardiogram-derived respiration and heart rate variability characteristics.

Characteristic	Overall (n = 95)	AHI < 30 (n = 69)	AHI ≥ 30 (n = 26)	*P**
Respiratory power index	15.0 ± 9.8	11.5 ± 4.9	24.3 ± 13.2	< .0001
Low noise segments	36.9 ± 10.5	37.3 ± 10.4	35.8 ± 11.0	.5254
Total power	242.8 ± 245.0	226.4 ± 204.4	286.2 ± 330.8	.7498 †
High frequency band : total power	0.17 ± 0.08	0.18 ± 0.09	0.15 ± 0.06	.0304
Low frequency band : total power	0.34 ± 0.07	0.34 ± 0.07	0.35 ± 0.07	.3971
Very low frequency band : total power	0.48 ± 0.08	0.48 ± 0.09	0.50 ± 0.08	.2568
Low frequency : high frequency	4.40 ± 3.49	4.09 ± 3.09	5.25 ± 4.33	.1020 †
Average beat-to-beat intervals	890.1 ± 139.4	911.0 ± 142.6	834.8 ± 115.7	.0168
SDNN	53.5 ± 23.8	53.3 ± 22.1	53.9 ± 28.3	.8117 †
RMSSD	35.1 ± 22.1	36.1 ± 22.0	32.4 ± 22.4	.2220 †
% NN interval differences < 10 ms	0.34 ± 0.17	0.32 ± 0.16	0.39 ± 0.18	.0630
% occurrence of NN sequences < 10 ms	0.04 ± 0.07	0.03 ± 0.07	0.06 ± 0.07	.0697 ‡
Word sequence variance	1.35 ± 0.38	1.32 ± 0.36	1.43 ± 0.44	.2222
Symbol probability (0 & 2)	0.51 ± 0.21	0.52 ± 0.20	0.50 ± 0.22	.7748

* = *P* value from *t* test comparing mean values between AHI groups. † = *t* test based on natural log transformed variable. ‡ = *t* test based on square root transformed variable. AHI = apnea-hypopnea index, NN = normal to normal beat-to-beat interval, RMSSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals, SDNN = standard deviation of all NN intervals.

Table 4—Predictive characteristics of single variable models with bootstrap confidence intervals.

Predictor	Cutoff Point	Estimate (Bootstrapped 95% CI)						
		AUC	Sensitivity	Specificity	+LR	−LR	PPTP	NPTP
BMI	27.91	0.723 (0.607, 0.834)	0.962 (0.875, 1.00)	0.261 (0.163, 0.366)	1.301 (1.122, 1.526)	0.147 (0.00, 0.544)	0.329 (0.228, 0.434)	0.053 (0.00, 0.176)
Age	37.45	0.662 (0.541, 0.770)	0.962 (0.864, 1.00)	0.261 (0.164, 0.365)	1.301 (1.110, 1.533)	0.147 (0.00, 0.544)	0.329 (0.229, 0.434)	0.053 (0.00, 0.176)
Neck circumference	42.00	0.669 (0.543, 0.785)	0.846 (0.692, 0.968)	0.464 (0.347, 0.582)	1.578 (1.201, 2.104)	0.332 (0.061, 0.701)	0.373 (0.259, 0.492)	0.111 (0.023, 0.231)
ESS	3.00	0.610 (0.489, 0.740)	0.923 (0.800, 1.00)	0.203 (0.110, 0.306)	1.158 (0.979, 1.364)	0.379 (0.00, 1.120)	0.304 (0.209, 0.406)	0.125 (0.00, 0.308)
MVAP Index 1	0.330	0.653 (0.522, 0.779)	0.917 (0.800, 1.00)	0.273 (0.169, 0.393)	1.260 (1.039, 1.551)	0.306 (0.00, 0.835)	0.314 (0.209, 0.431)	0.100 (0.00, 0.255)
MVAP	0.616	0.813 (0.702, 0.910)	0.875 (0.746, 1.00)	0.636 (0.517, 0.750)	2.406 (1.719, 3.607)	0.196 (0.00, 0.435)	0.467 (0.325, 0.615)	0.067 (0.00, 0.143)
RPI	12.23	0.872 (0.791, 0.942)	0.885 (0.750, 1.00)	0.638 (0.524, 0.750)	2.442 (1.805, 3.632)	0.181 (0.00, 0.419)	0.479 (0.333, 0.627)	0.064 (0.00, 0.146)

−LR = negative likelihood ratio, +LR = positive likelihood ratio, AUC = area under the curve, BMI = body mass index, CI = confidence interval, ESS = Epworth Sleepiness Scale, MVAP = Multi-Variable Apnea Prediction, MVAP Index 1 = Multi-Variable Apnea Prediction Index, NPTP = negative posttest probability, PPTP = positive posttest probability, RPI = respiratory power index.

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to be driven by higher specificity, as several of these single-stage models had higher sensitivity estimates, but lower AUC. When examining posttest probabilities, the RPI model showed a NPTP of 0.064 (0.00–0.146), suggesting only a 6.4% probability of s-OSA if the screening test predicts an absence of OSA. However, the PPTP was 0.479 (0.333, 0.627), suggesting that slightly < 50% of individuals screening positive will have s-OSA. This difference reflects the overweighting of missed cases when we chose our optimal cutoff point. Similarly, the MVAP showed an NPTP of 6.7% and a PPTP of 46.7% in our sample at the optimal cutoff point.

EKG-derived metrics other than RPI had relatively low AUCs (ranging from 0.511 to 0.668), indicating that they are less useful for predicting s-OSA (see **Table S1**).

Two-Stage Strategy: RPI Increases Discriminatory Power for Predicting Severe OSA When Used In Tandem With Established Risk Factors

Table 5 shows the discriminatory power of RPI when used in tandem with the six variables known for their established association with OSA risk: BMI, age, NC, ESS, MVAP Index 1, and MVAP. Specifically, RPI was used as a second-stage screen among individuals predicted to have intermediate risk using the clinical measures as a first-stage screen.

We observed that using the two-stage strategy improved the discriminatory power of each clinical single-stage model in predicting s-OSA. The best model used MVAP in the first stage, followed by RPI (cutoff point of 16 events/h) for the group with intermediate values of MVAP (scores between 0.22

Table 5—Predictive characteristics of two-stage models with bootstrap confidence intervals.

Stage 1 Variable	Cutoff Point		Stage 2	Estimate (Bootstrapped 95% CI)						
	Low	High	RPI	AUC	Sensitivity	Specificity	+LR	−LR	PPTP	NPTP
BMI	25	39	16	0.860 (0.787, 0.924)	0.923 (0.810, 1.00)	0.797 (0.702, 0.892)	4.549 (3.019, 8.366)	0.097 (0.00, 0.250)	0.632 (0.476, 0.790)	0.035 (0.00, 0.090)
Age	37	55	10	0.749 (0.676, 0.814)	0.962 (0.864, 1.00)	0.536 (0.424, 0.647)	2.073 (1.649, 2.744)	0.072 (0.00, 0.272)	0.439 (0.311, 0.571)	0.026 (0.00, 0.093)
Neck circumference	38	46	16	0.783 (0.695, 0.860)	0.923 (0.750, 1.00)	0.681 (0.579, 0.791)	2.895 (1.989, 4.277)	0.113 (0.00, 0.373)	0.522 (0.367, 0.651)	0.041 (0.00, 0.138)
ESS	2	14	10	0.734 (0.658, 0.800)	0.962 (0.870, 1.00)	0.478 (0.396, 0.622)	1.843 (1.535, 2.551)	0.080 (0.00, 0.273)	0.410 (0.298, 0.545)	0.029 (0.00, 0.088)
MVAP Index 1	0.33	3.40	10	0.739 (0.618, 0.800)	0.917 (0.705, 0.963)	0.561 (0.463, 0.700)	2.086 (1.486, 2.905)	0.149 (0.060, 0.531)	0.431 (0.299, 0.567)	0.051 (0.022, 0.187)
MVAP	0.22	0.87	16	0.883 (0.767, 0.924)	0.917 (0.706, 0.962)	0.848 (0.767, 0.936)	6.050 (3.434, 13.15)	0.098 (0.045, 0.348)	0.688 (0.519, 0.842)	0.034 (0.015, 0.133)

−LR = negative likelihood ratio, +LR = positive likelihood ratio, AUC = area under the curve, BMI = body mass index, CI = confidence interval, ESS = Epworth Sleepiness Scale, MVAP = Multi-Variable Apnea Prediction, MVAP Index 1 = Multi-Variable Apnea Prediction Index, NPTP = negative posttest probability, PPTP = positive posttest probability, RPI = respiratory power index.

and 0.87). The model yielded an AUC of 0.883 (95% CI: 0.767–0.924), as well as high sensitivity (0.917 [0.706–0.962]) and specificity (0.848 [0.767–0.936]) in our sample. Importantly, the two-stage model involving the MVAP and RPI had a low NPTP, suggesting only 3.4% (1.5% to 13.3%) of individuals screening negative have s-OSA; PPTP was moderately high at 68.8% (51.9% to 84.2%). Although the combination of MVAP and RPI showed the highest AUC, this model was followed closely by the two-stage model using only BMI as a first-stage screen. Specifically, lower and upper bounds for BMI of 25 kg/m^2 and 39 kg/m^2, respectively, and an RPI of 16 events/h, yielded an AUC of 0.860 (0.787–0.924), 92.3% sensitivity, and 79.7% specificity, as well as a similar NPTP (3.5% [0.00% to 9.0%]) and slightly lower PPTP (63.2% [47.6% to 79.0%]) when compared to the MVAP two-stage model. Given that BMI is included as part of the MVAP, these results suggest that BMI may be a primary driver for the strong associations in the two-stage MVAP model.

DISCUSSION

This study had two important novel findings. First, a metric derived from spectral analysis of the EKG, which we called the RPI, had strong ability to discriminate s-OSA in a sample of CMVOs. This metric can be obtained easily using ambulatory EKG recordings to determine s-OSA risk. Second, although the RPI provided excellent discriminatory power to screen for s-OSA, this metric, when used in tandem with first-stage clinical measures of BMI alone or the MVAP score, also worked effectively.

Previous studies from our group[12,27,31] and others[5,32] have observed that despite a high prevalence of s-OSA in CMVOs and its association with sleepiness-related vehicular crashes,[17,32] numerous challenges persist in screening and identifying this at-risk population. The use of EKG-derived signals, in particular, HRV, to classify sleep apnea has vastly improved over the past four decades. In particular, recent advances in the utility of cardiorespiratory coupled nonlinear signals in addition to clinical parameters have been shown to determine both sleep stages and sleep disorders.[33–38]

Ours is the first study to investigate screening for s-OSA based on estimations of an EKG-based RPI in CMVOs. Further, to strengthen our screening tool we analyzed multiple metrics in stages to determine the best measure for development of a more robust model for screening for s-OSA in this high-risk population. Across our analyses, the optimal single-stage model was based on RPI alone, while the best performing two-stage models utilized BMI or MVAP as a first-stage screen, followed by RPI among those that had intermediate risk after the initial screen. We note that AUC values were similar across all three models (ranging from 0.860 to 0.883), as were the model sensitivities (ranging from 88.5% to 92.3%). Despite these similarities, importantly, the two-stage model has the added benefit of limiting the number of individuals who require more intensive EKG by utilizing more easily obtainable clinical measures as an initial screen; this would be expected to improve efficiency in both diagnosis and treatment, as well as reduce the costs associated with diagnosing OSA in CMVOs. In addition, we observed a 15% to 20% improvement in specificity for our two-stage models when compared to the single-stage RPI model, suggesting that the two-stage did a better job in correctly identifying CMVOs who did not have OSA.

Previous studies have examined time-dependent and spectral analysis of HRV in OSA and found significant associations with severity of OSA.[35,38–40] In a study of males with mild and severe OSA, after controlling for age and BMI, Aydin and colleagues showed that metrics described in **Table 1** such as standard deviation of all NN intervals (SDNN) and high frequency (HF) were attenuated, whereas the ultra-low frequency (ULF), very low frequency (VLF), low frequency (LF), and the ratio of low-frequency and high-frequency powers (LF/HF) were increased during a 24-hour timeframe compared to patients without OSA.[35] These findings were present in the presence of

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common comorbidities such as hypertension, which is prevalent in CMVOs.[35] Roche and colleagues analyzed seven HRV metrics, and found that observed differences between daytime and nighttime values of SDNN index and the square root of the mean of the sum of the squares of differences between adjacent NN intervals were significant, independent predictors for OSA.[38]

Busek et al.[39] observed that select HRV metrics varied by sleep stage. Total spectrum power, VLF, LF/HF ratio, and the LF spectral component were higher during rapid eye movement (REM) compared to stage N2 and stage N4 of nonrapid eye movement (NREM) sleep, whereas the HF spectral band was increased in stage N2 and N4 of NREM sleep. Whether HRV metrics, including RPI and severity of s-OSA, are influenced by the disrupted nature of sleep architecture and circadian dysregulation that may be prominent in evening/night shift work for CMVOs remain unknown. Another method, which combines oximetry with HRV indices,[41] may be a potential screening tool as well, given that oximetry has also been shown to be an effective second-stage screening tool in CMVOs.[8]

Studies have shown that the most noticeable differences in HRV in patients with OSA are observed in stage N3/N4 sleep and REM sleep stages in human[3,39,42] and animal models.[43] Given the decrease in metabolic activity, stages N3 and N4 sleep are associated with a substantial decline in the VLF component of HRV.[39,43] In participants with OSA, VLF values during wake did not differ from those during light sleep. This equalization of values (known as "non-dipping"[44] during sleep) may be a consequence of OSA. After 3 months of continuous positive airway pressure (CPAP) therapy, the difference in VLF values between wake and light sleep was restored, resembling values seen in control participants without OSA.[42] This supports the view that long-term CPAP treatment could be detected by EKG markers of parasympathetic activity.[45]

Our study had several strengths, including its prospective design and confirmation of all OSA cases with full PSG. The tool we propose, in contrast to PSG, is more amenable to mass screening because it is inexpensive and allows self-application. Moreover, EKG may be more acceptable to long-haul drivers, as it can be applied in the berth or at home, and can be dispensed and retrieved by mail, thus avoiding reliance on overnight sleep in a laboratory. Our study limitations include small sample size, which limits the ability to control for potential confounding variables, such as the use of beta-adrenergic blockers, which can restrict HRV. The RPI may not be suitable for use in such groups, nor in groups with significant comorbidities such as sick sinus syndrome, myocardial infarction, diabetic neuropathy, and cardiac failure. These conditions, however, may not pertain to many employed CMVOs, who must meet fitness-for-duty requirements mandated by the Federal Motor Carrier Safety Administration during a medical evaluation that must occur every 2 years.[31,45,46] Thus, CMVOs with predetermined diseases such as uncontrolled diabetes, hypertension or heart disease are disqualified from obtaining a license.[31,45] Nevertheless, any disease condition that may parlay a high sympathetic tone could change HRV and respiration. However, the RPI method utilized in this study includes only noise-free episodes, and a decreased RSA does not alter the estimated EKG-derived respiration (**Figure 1**). Another issue that could arise with our model is that of chain of custody, that is, ensuring that the intended participant is the one who actually wore the device. Solutions to chain-of-custody issues have already been introduced and their utility analyzed with respect to portable home sleep apnea testing devices; these solutions may also be applicable to EKG.[11,47] Further, independent studies should evaluate the predictive characteristics and performance of optimal cutoff points described here within independent populations.

Future studies should also explore the use of HRV/RPI as a screening tool using in a prospective, randomized design and evaluate its cost-effectiveness in the diagnosis of s-OSA. Such an evaluation should account for not only the costs of screening, but also the cost savings through prevented crashes, and the costs related to crashes that may result from missed cases. Other at-risk groups should also be explored, such as CMVOs who engage in night-shift driving and may be at even higher risk for crashes.[48,49]

In conclusion, the model presented here provides an efficient and accurate paradigm for detecting severe OSA within a commercial driver population. This can improve screening and diagnosis, facilitate timely treatment, prevent negative health consequences to individual drivers and reduce the risk of sleepiness-related crashes. Additional prospective studies to assess this approach in the commercial driver and other populations are warranted.

ABBREVIATIONS

−LR, negative likelihood ratio
+LR, positive likelihood ratio
AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
AUC, area under the curve
BMI, body mass index
CI, confidence intervals
CMVO, commercial motor vehicle operator
CPAP, continuous positive airway pressure
EKG, electrocardiography
ESS, Epworth Sleepiness Scale
HF, high frequenc
HRV, heart rate variability
LF, low frequency
LF/HF, ratio of low-frequency and high-frequency powers
MVAP, Multi-Variable Apnea Prediction
NC, neck circumference
NPTP, negative posttest probability
NREM, non-rapid eye movement
OSA, obstructive sleep apnea
PPTP, positive posttest probability
PSG, polysomnography
REM, rapid eye movement
RPI, respiratory power index
RSA, respiratory sinus arrhythmia
s-OSA, severe OSA
SD, standard deviation

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SDNN, standard deviation of all NN intervals
ULF, ultra-low frequency
VLF, very low frequency

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Address correspondence to: M. Melanie Lyons, PhD, The Ohio State University, Division of Pulmonary, Critical Care and Sleep Medicine, #218, 2012 Kenny Drive, Columbus, OH 43210; Email: mlyons@upenn.edu

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