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Nocturnal hypoxemia biomarker predicts sleepiness in patients with severe obstructive sleep apnea

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Abstract

Purpose This study aims to assess the association between excessive daytime sleepiness (EDS) and variables extracted from the pulse-oximetry signal obtained during overnight polysomnography.

Methods A cross-sectional design was used to study the relation between four hypoxemia variables and EDS as determined by Epworth Sleepiness Scale scores (ESSS) in 200 consecutive patients, newly diagnosed with obstructive sleep apnea (OSA), as defined by an apnea–hypopnea index (AHI)≥15. Hypoxemia measurements were compared between sleepy (ESSS≥10) and nonsleepy (ESSS<10) patients before and after dichotomizing the cohort for each hypoxemia variable (and for AHI) such that there were 35 (165) patients in each of the corresponding higher (lower) subcohorts. The hypoxemia variables were combined into a biomarker, and its accuracy for predicting sleepiness in individual patients was evaluated. We planned to interpret prediction accuracy above 80 % as evidence that hypoxemia predicted EDS.

Results Hypoxemia was unassociated with sleepiness in OSA patients with AHI in the range of 15 to 50. In patients with AHI>50, the hypoxemia biomarker (but not individual hypoxemia variables) predicted sleepiness with 82 % accuracy.

Conclusion Nocturnal hypoxemia as determined by a polyvariable biomarker reliably predicted EDS in patients with severe OSA (AHI>50), indicating that oxygen fluctuation had a direct role in the development of EDS in patients with severe OSA.

Keywords Hypoxemia · Obstructive sleep apnea · Excessive daytime sleepiness · AUROC · Biomarker

Introduction

Overnight pulse oximetry is one of many data traces obtained during routine polysomnography performed for the purpose of diagnosing obstructive sleep apnea (OSA). Intermittent hypoxia has been shown to produce a selective pro-inflammatory cellular response, with an increased elaboration of substances—such as NF-κB and TNF-α—which are potentially involved in homeostatic sleep drive [1]. Several distinct but related variables derived from the pulse-oximetry signal—including the mean overnight oxygen saturation (SpO_2%), the minimum SpO_2%, the cumulative time spent with SpO_2% less than a threshold amount (e.g., SpO_2%<95 %), and the desaturation index—have been linked with excessive daytime sleepiness (EDS) in patients with OSA [2–9]. However, the associations in many of these studies were weak and inconsistently manifested by any single given hypoxemia variable. Moreover, indices of hypoxemia typically co-migrate with other polysomnographic variables, including apnea–hypopnea index (AHI), arousal index, and sleep stage transitions, making it difficult

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to judge whether measures of hypoxemia can themselves causally explain the presence of EDS.

The limitations could have arisen from an overly broad application of the hypoxemia theory to OSA patients. For example, the frequency of reversible airflow limitation events (as determined by AHI) may influence whether an individual measure of hypoxemia can predict EDS. Another possibility is that analysis of a single descriptive variable (e.g., the minimum $SpO_2\%$) independent of one another may be insufficient to characterize the composite of the burden of intermittent hypoxemia as a physiologic stressor. An alternative approach could be to assume that each variable reflects a different aspect of the complex relationship between EDS and hypoxemia, and that the true predictive power inherent in the pulse-oximetry signal is best captured by means of a predetermined combination of the variables.

We hypothesized that the reports of links between EDS and individual hypoxemia variables in OSA cohorts comprising patients with a wide range of OSA severity (AHI range, 5–120 events/h [2–9] actually reflected a causal association that existed principally in patients with high AHI values (increased burden of intermittent hypoxemia). Our first aim was to compare measurements of hypoxemia variables in sleepy and nonsleepy patients with OSA and then to dichotomize the cohort according to predetermined hypoxemia thresholds, repeating the comparisons in the subcohorts. We expected to find weak differences in the study cohort that could best be explained as resulting from the patients above the thresholds. Our second aim was to compute a hypoxemia biomarker and evaluate its accuracy. We expected that the biomarker would predict sleepiness in the supra-threshold patients more reliably than did the individual hypoxemia variables.

Methods

Patients

The participants were recruited from patients seen in the sleep-medicine clinic at the Overton Brooks Veterans Affairs Medical Center who underwent an overnight cardiopulmonary study (Embletta X100, Embla, Broomfield, CO). The recording montage consisted of a nasal pressure transducer cannula, nasal–oral thermistor sensor, thoracic and abdominal respiratory effort bands, body-position sensor, and a fingertip pulse oximetry. Sleep efficiency was determined by actigraphy, expressed as the percent ratio of the immobility signal to the total recording time (ActiSleep, Actigraph, Pensacola, FL).

Apneas were defined as a ≥90 % decrease in airflow, measured by nasal–oral thermistor, lasting at least 10 s. Hypopneas were defined as airflow reductions of >50 %,

as measured by the nasal pressure transducer sensor, lasting at least 10 s and producing a ≥3 % decrease in the $SpO_2\%$ [10]. Apneas and hypopneas were scored manually by a certified sleep technologist and reviewed by a board-certified sleep-medicine physician. The AHI was the sum of apneas and hypopneas per hour of sleep, as computed by actigraphy.

The polysomnograms from 200 consecutive patients meeting inclusion and exclusion criteria were analyzed. Studies in which the AHI was ≥15 events/h were included. Exclusion criteria included a current history of known alcohol or drug abuse, the presence of medications that could adversely affect sleep or respiration, history of prior treatment for OSA, and a known diagnosis of other identifiable sleep disorders. Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS); EDS was defined as an ESS score (ESSS) of ≥10. All patient-related procedures were approved by the institutional review board for human experimentation.

Hypoxemia variables

Pulse-oximetry traces were evaluated to determine four individual variables: (1) the percent of recorded time during which arterial oxygen saturation was <90 % (P90); (2) the oxygen desaturation index (ODI), defined as the hourly rate of oxygen desaturations of ≥4 % (threshold incorporated into the Embletta software); (3) the average percent desaturation (AD); (4) the lowest percent saturation (LS).

Fig. 1 Experimental design. Four hypoxemia variables were extracted from the pulse-oximetry signals recorded during overnight sleep studies on 200 patients with OSA (AHI≥15). The relationship of the particular variables (and their combination in a biomarker) and sleepiness (*ESS*) was determined using group-level statistics (means, correlation coefficient, and odds ratio) and individual-level statistics (area under the receiver operating characteristics curve), both before and after dichotomizing the study cohort based on severity thresholds for each hypoxemia variable (corresponding AHI threshold, >50 events/h)

Table 1 Pertinent demographics for the study cohort and the SHHS dataset [12]

	This study	SHHS dataset
Number of patients	200 (199 M, 1 F)	390 (201 M, 189 F)
White/Black (%)	73/27	89/11
Age (years)	58.8±10.8	64.0±9.3
BMI (kg/m^2)	32.5±6.9	28.7±4.7
AHI range (events/h)	15–120	0–76

Mean±SD

All values were extracted from the pulse-oximetry signal and scored by proprietary software (RemLogic 1.1, Embla). The pulse-oximetry signal was exported as an EDF file, converted to a MatLab-readable format (MathWorks, Needham, MA), and analyzed using a custom code. Preliminary studies showed that the computed hypoxemia values were not materially different than those produced by the proprietary software; the latter results are reported here.

Experimental design

The study cohort was evaluated as a whole and after dichotomization based on thresholds for each of the hypoxemia variables (Fig. 1). The thresholds were identified by ordering the values for each variable from least to most hypoxemic and then arbitrarily dividing the distributions (N=200) into subcohorts consisting of the lower (N=165) and higher (N=35) hypoxemia values (82/18 %). The process resulted in thresholds of P90=18 %, ODI=50 events/h, AD=8 %, and LS= 86 %. The corresponding thresholds for the AHI and hypoxemia biomarker (see below) were 50 and 0.75 events/h, respectively. The consequences of the arbitrary

choice for dividing the study cohort were examined empirically.

Historical cohort

As a control for the potential role of the particular demographics of the study cohort (Table 1), we compared the relationship between sleepiness and AHI in the study cohort with the corresponding relationship in a cohort formed during the Sleep Heart Health Study (SHHS), a multicenter study of the cardiovascular and other consequences of sleep-disordered breathing [11]. An SHHS dataset collected in 2001 and 2003 was searched and the AHI, ESS scores, and pertinent demographic information were obtained for all persons in the dataset who had no heart failure, emphysema, chronic bronchitis, or hypertension (Table 1) [12]. The results were presented without regard to gender because preliminary analyses of the AHI/ESSS relationship revealed no gender-related differences (N=390).

Statistics

Differences in means and in variances were evaluated using the t and F tests, respectively. When effects on variance were found, the data were evaluated using the Mann–Whitney U test. In these instances, the results were the same as those found using the t test; for simplicity, therefore, all reported differences were based on the t test. Linear correlations were assessed using Pearson's correlation coefficients (r) and evaluated for statistical significance using the t test. Discriminant analysis [13] was used to compute the optimal biomarker function (B) for sleepiness based on a combination of the four hypoxemia variables. The procedure resulted in a mathematical expression for B in which the input was the set of four hypoxemia values for a

Table 2 Group- and individual-level analyses of sleepiness (ESS score≥10) in the study cohort

Hypoxemia variable	Group-level analyses			Individual-level analysis
	Mean±SD		Sleepiness-HV correlation	Sleepiness prediction accuracy
	ESSS<10	ESSS≥10	r	AUROC
P90 (%)	13.3*±19.0**	6.4±7.6	0.18*	58
ODI (events/h)	34.8*±26.5**	25.0±18.1	0.17*	59
AD (%)	6.8±2.6	6.4±2.1	0.18*	52
LS (%)	78.3±8.6	79.5±8.0	0.11	54
B (0–1 scale)	0.66±0.13*	0.59±0.09*	0.24*	68

Mean±SD

HV hypoxemia variable, *r* Pearson's correlation coefficient, *AUROC* area under the receiver operating characteristics curve, *B* value of the biomarker function formed from all four hypoxemia variables, *P90* percent of bedtime when oxygen saturation was <90 %, *ODI* rate of oxygen desaturation, *AD* average desaturation, *LS* lowest saturation

*P<0.05, t test; **P<0.05, F test

Table 3 Group-level and individual-level analyses of sleepiness in sub-cohorts of the study cohort

Hypoxemia variable threshold (T)	Group-level analyses			Individual-level analysis	
	HV–sleepiness correlation (r)		HV-related increased sleepiness	Sleepiness prediction accuracy (AUROC)	
	Below T	Above T	OR	Below T	Above T
P90=18 %	~0	0.30	3.3*	50	74
ODI=50 events/h	~0	0.15	3.3*	52	70
AD=8 %	~0	0.38	1.3	50	69
LS=86 %	0.1	0.38	1.4	52	57
B=0.75	0.14	0.37	3.4*	56	82

Mean±SD

HV hypoxemia variable, *AUROC* area under the receiver operating characteristics curve, *OR* odds ratio, *B* value for biomarker function formed from all four hypoxemia variables, *r* Pearson correlation coefficient, *P90* percent of bedtime when oxygen saturation was <90 %, *ODI* rate of oxygen desaturation, *AD* average desaturation, *LS* lowest saturation

*$P<0.05$, Chi-square test

particular patient, and the output was the probability that a specific patient was sleepy (ESSS≥10). Details regarding the determination of B are provided in the Appendix.

The accuracy of the B for predicting sleepiness was evaluated by computing the area under the receiver operating characteristics curve (AUROC), which provides an overall characterization of the sensitivity and specificity of predictions (in our case, sleepiness) [13]. An AUROC of 50 would indicate that B was no better than a guess for predicting sleepiness. An AUROC of 100 would indicate that the predictions can be made with perfect accuracy for each patient (a reliable clinical test typically has an AUROC of >80–90 %).

The a priori probability for rejecting the null hypothesis was $P<0.05$. The a posteriori P values were not listed because no hypotheses were based on actual P values. The hypoxemia variables were regarded as independent; consequently no corrections were made for multiple tests.

Results

The means and variances for P90 and ODI were greater ($P<0.05$) in the sleepy patients (Table 2). With the exception of LS, the hypoxemia variables were each significantly ($P<0.05$) but weakly ($r<0.2$) correlated with ESS score. The hypoxemia variables did not predict sleepiness for individual patients substantially better than a guess, as indicated by the low AUROC values (50=chance, 100=certainty). When the hypoxemia variables were combined by discriminant analysis to form a B for sleepiness, prediction accuracy increased but remained below potentially useful clinical levels (Table 2).

The hypothesis that sleepiness and hypoxemia were causally linked principally in patients with relatively severe hypoxemia was tested by examining the associations in subcohorts formed by dividing the study cohort at thresholds for each hypoxemia variable such that 18 % (35/200) of the values were above and 82 % (165/200) were below the

Fig. 2 Relationship between sleepiness and oxygen desaturation index (*ODI*). **a** Scatterplot for ODI. **b** Percent sleepiness in subcohorts below and above ODI=50 events/h. *r* Pearson's correlation coefficient, *AUROC* area under the receiver operating characteristics curve, *OR* odds ratio. *Patients at or above the dotted line* were regarded as sleepy

threshold. As expected, the hypoxemia variables were each essentially unrelated to the ESS score ($r \approx 0$) in the subcohorts below the threshold but were related in the subcohorts above the threshold as indicated by the modest r values, odds ratios for sleepiness, and AUROC values. The predictive accuracy of B was 82 (scale, 50 to 100), which exceeded the accuracy achieved using the variables individually (Table 3; Fig. 5). When BMI was added as a factor to the biomarker function, prediction accuracy increased to 84 % (data not shown).

Scatter plots for individual hypoxemia variables visually confirmed that a relationship with ESSS was apparent only for patients above the thresholds (Figs. 2, 3, and 4).

When the threshold for dividing the cohort (82 %) was changed by ±5 % (78–87 %), the overall results were similar to those found using the 82 % threshold (Tables 2 and 3). For thresholds of >87 %, the severe hypoxemia subcohorts became too small to permit meaningful statistical analysis; for thresholds of <78 %, the statistical distinctions between the subcohorts became progressively weaker (data not shown).

Patients with AHI<50 events/h (82 % threshold) were more likely than not to be sleepy (Fig. 5a, green bar), but the

Fig. 4 Relationship between sleepiness and biomarker (B). **a** Scatterplot for B. **b** Percent sleepiness in subcohorts below and above $B=0.75$. r Pearson correlation coefficient, *AUROC* area under the receiver operating characteristics curve, *OR* odds ratio. *Patients at or above the dotted line* were regarded as sleepy. The two highlighted points (*arrows*) are examples of a false-positive ($B=0.79$) and a true-positive ($B=0.97$) prediction of sleepiness (see Appendix)

ESS scores were uncorrelated with the AHI ($r \approx 0$) (Fig. 5). The percent of sleepy patients was greater among patients with an AHI≥50 events/h (OR=2.7, $P<0.05$), but AHI did not predict sleepiness (AUROC=55). AHI was 37.5±22.1 events/h ($N=127$) and 31.5±16.7 events/h ($N=73$) for the sleepy and nonsleepy patients, respectively ($P<0.05$); the difference originated almost entirely from patients with AHI≥50 events/h (Fig. 5a).

The SHHS historical cohort was less obese and probably healthier than the study cohort (Table 1). Nevertheless, the SHHS cohort exhibited a relationship between AHI and ESSS similar to that in the study cohort (Fig. 6 compared with Fig. 5). For both cohorts, there was essentially no sleepiness-EDS correlation except among the patients with severe OSA, even though percent sleepiness increased when patients were stratified by AHI range (Figs. 5b and 6b).

Fig. 3 Relationship between sleepiness and average desaturation (*AD*). **a** Scatterplot for AD. **b** Percent sleepiness in subcohorts below and above AD=8 %. r Pearson's correlation coefficient, *AUROC* area under the receiver operating characteristics curve, *OR* odds ratio. *Patients at or above the dotted line* were regarded as sleepy. *NS* not significant

Discussion

The character of the relation between nocturnal hypoxemia and sleepiness in patients with OSA (AHI=15–120 events/h) was studied. We expected to find a direct link,

Fig. 5 Relation between sleepiness and AHI in the study cohort (*N*=200). *r* Pearson's correlation coefficient, *AUROC* area under the receiver operating characteristics curve, *OR* odds ratio. *Patients at or above the dotted line* were regarded as sleepy

but only in patients with high AHI values. The hypothesis was tested by dichotomizing an OHA cohort at predetermined thresholds for hypoxemia variables extracted from the pulse-oximetry signal, and comparing statistical measures of association obtained from the subcohorts. We planned to conclude that a causal link had been shown if (1) associations occurred only in subcohorts above the thresholds and (2) sleepiness was reliably predictable in the patients in those subcohorts, based solely on the values of their hypoxemia variables.

The means and variances of individual hypoxemia variables differed between sleepy and nonsleepy patients (Table 2, group level analyses), but interpatient variability prevented the use of the data for reliable prediction of sleepiness (the hallmark of a mechanistic relationship) (Table 2, AUROC values). Both results were only marginally improved when the variables were combined into a biomarker (Table 2). But when the cohort was dichotomized with respect to the hypoxemia variables, a different picture of the hypoxemia–sleepiness relationship emerged (Table 3). Sleepiness was essentially unrelated to hypoxemia for

values below the thresholds. Above the thresholds, there was some indication of a relationship (the correlation coefficients and the AUROC levels), but the strongest evidence was the finding that the hypoxemia biomarker yielded an AUROC of 82. Taken together, the results indicated that EDS and hypoxemia were directly related in the more severely hypoxemic patients and that these patients could be identified based on a biomarker computed from a group of four conventional hypoxemia measures.

The rationale for the choice of a threshold level stemmed from the need to define subcohorts that exhibited differing levels of hypoxemia. Dichotomization at the highest 18 % was chosen arbitrarily, and the consequences of the choice were examined. Small increases had no effect on the study conclusion. Above 23 %, the means of the hypoxemia variables in the subcohorts were not sufficiently distinct to permit the study hypothesis to be tested (the subcohorts were not materially different). For example, dichotomization at 50 % (which corresponded to AHI subcohorts of 15–37, >37) failed to reveal the effect of oxygen fluctuation on EDS. The consequences of choosing higher thresholds indicated that the link

Fig. 6 Relation between sleepiness and AHI in the SHHS cohort (*N*=390). *r* Pearson's correlation coefficient, *AUROC* area under the receiver operating characteristics curve, *OR* odds ratio (computed with respect to AHI 0–5 group). *Patients at or above the dotted line* were regarded as sleepy

Fig. 7 Published reports of group-level analyses of the association between hypoxemia and sleepiness in patients with OSA

between hypoxemia and EDS found in the cohort was limited to patients with an AHI>50.

The results were consistent with prior research, and helps elucidate the variability of results regarding the relationship between hypoxemia and EDS found in earlier studies [2–9]. Hypoxemia variables in OSA patients were commonly associated statistically with symptomatic sleepiness, depending on demographic factors including BMI, age, gender, and

comorbid conditions (Fig. 7). These studies had explored putative relationships under the assumption that a linear statistical relationship between sleepiness and hypoxemia existed across the full spectrum of OSA severity (AHI>5 events/h). Our results suggested that below an OSA severity threshold—50 events/h in our study but probably higher or lower in other cohorts having different demographics—hypoxemia and sleepiness were associated only as co-effects caused by other physiological factors, but were associated as cause–effect above the threshold.

The variables commonly used to characterize the pulse-oximetry signal have each proved useful, but none to the extent of marginalizing the others, perhaps because each captures a different facet of hypoxemia. We hypothesized that a biomarker combining multiple features of the pulse oximetry trace would allow a more robust association between $SpO_2\%$ and EDS to be demonstrated. The evidence obtained supported this hypothesis (Table 3; Fig. 4).

One kind of limitation on this study involves the possibility that patients recruited from a population with different demographics may yield different results. For example, race may affect the development of EDS; prior research has demonstrated higher ESSS among black patients, compared with whites, independent of effects of disease severity or BMI [14, 15]. But the similarities between the study cohort and that of the SHHS probably indicated that the demographics of the OSA population chosen for this study affected the level (rather than the existence) of the hypoxemia threshold at which a link was created (or at least became clinically meaningful). Both cohorts exhibited progressively elevated rates of sleepy patients with greater AHI (Figs. 5 and 6), and in both cohorts, there was an absence of correlation and predictability between sleepiness and AHI levels within the patient groups stratified by AHI.

Our results provided evidence of a causal association but not evidence of its direction. We assumed that nocturnal hypoxia caused sleepiness, but the sleepiness data were obtained prior to the hypoxemia data, and the designation of which was the cause and which the effect was made on the basis of general physiological considerations, not observation. The possibility remains that sleepiness caused hypoxemia.

Known contributors to the pathophysiology of EDS other than hypoxemia were not explicitly considered. The macroarchitecture of sleep (particularly the extent of light sleep) was not determined, and sleep efficiency was only estimated, using actigraphy. Additionally, the consequences of sympathetic activation on the complexity of EDS were not assessed. The Sisyphean task of satisfactorily explaining EDS will ultimately depend on a coordinated interpretation of multiple polysomnographic signals and appropriate biochemical data. Even so, data extracted from a single physiological signal were good predictors of the occurrence of

EDS in some patients with OSA, and the formal definition of the link (Appendix) may be useful in identifying at-risk patients.

The Epworth scale is subjective and therefore arguably not the optimal measure of sleepiness. We think that this limitation is probably not significant because the symptoms quantified by the Epworth scale were precisely what we sought to relate to hypoxemia. We did not address the issue of the cellular mechanisms linking $SpO_2\%$ to sleepiness. The role of intermittent hypoxemia in the development of inflammatory mediators known to be involved with homeostatic sleep drive, and in the development of damage to neuronal structures critical for proper functioning of the ascending reticular activating system, is a mechanism that has been described by prior publications [1, 16, 17].

In conclusion, in OSA patients with AHI>50 events/h, four standard hypoxemia variables combined into a biomarker reliably predicted the presence of EDS. For patients with AHI≤50 events/h, the $SpO_2\%$ data could not predict sleepiness better than a guess, implying that nonhypoxemia variables are likely responsible for sleepiness in patients with milder degrees of OSA. We conclude that nocturnal hypoxemia is likely to be causally related to sleepiness in OSA patients only when the burden of intermittent hypoxemia is marked, as in patients with severely elevated AHI.

Conflicts of interest The authors declare no conflicts of interest.

Appendix

Using Fisher's linear discriminant analysis, we determined the coefficients of the biomarker function B that combined the hypoxemia variables in a way that best separated the sleepy (ESS score, ≥10) and nonsleepy (ESS score, <10). The result was:

$$B = 0.04 \times P90 + 0.02 \times ODI + 0.01 \times AD + 0.05$$
$$\times LS - 3.$$

The logit of B was used to scale the value for each patient to the 0–1 range. For example, when the actual values of P90, ODI, AD, and LS were 29.4, 46, 9, and 70 (units in percent except events per hour for ODI), B was 1.756, and its logit was 0.787. A 10-fold cross-validation process was used to evaluate the prediction accuracy of B. Initially, 90 % of the data was used to determine B and the remaining 10 % was used to evaluate prediction accuracy. Then the process was repeated ten times (with differing choices for the composition of the training and evaluation sets), and the results averaged. The prediction accuracy (determined by AUROC) was greater than 80 %.

B reliably predicted sleepiness only when the logit of B was greater than 0.75 (Fig. 4). Above this threshold,

prediction accuracy was 82 % (determined by AUROC), and the optimal combination of whose sensitivity and specificity were 0.87 and 0.67, respectively. Below the threshold, B was no better than a guess.

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