Nocturnal Hypoxemia as a Co-Determinant of Sleepiness in Patients with Obstructive Sleep Apnea

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Abstract

The association between nocturnal hypoxemia and subjective sleepiness was studied in 200 recently diagnosed OSA patients (AHI>15).

Four standard hypoxemia measures were extracted from the pulse-oximetry signal, and their linear correlations (individually and in combination) with sleepiness were determined by discriminant and AUROC analyses.

Average ODI and P90 were greater in sleepy patients (Epworth ≥10). Even so, the correlation coefficients for all possible combinations of the hypoxemia measures were low (<0.3), and resulted in low AUROC values (≤0.62).

Nocturnal hypoxemia is only a partial determinant of sleepiness in moderate-to-severe OSA patients.

Introduction

EDS is common in OSA patients. Why EDS occurs in some OSA patients but not others is poorly understood.

In non-sleep-deprived patients, EDS is often attributed to nocturnal hypoxemia (NH), particularly in severe OSA. Nevertheless EDS occurs even after successful treatment of OSA, indicating that NH is probably only a partial explanation for EDS. We studied the strength of this association in newly-diagnosed patients with moderate-to-severe OSA. Specifically, we determined the correlation coefficients between standard measures of NH (both individually and in combination) with subjectively assessed daytime sleepiness.

We planned to interpret statistically significant coefficients ≤0.3, 0.3–0.7, ≥0.7 as respectively indicating a low, medium, and high correlation.

Methods

Patients

Overnight cardiopulmonary studies (Embletta X100, Embla, Broomfield, CO) were performed in the sleep-medicine clinic at the Overton Brooks VAMC using a standard montage; oxyhemoglobin saturation was measured by pulse oximetry at a sampling rate of 10 Hz. Sleep efficiency (SE) was characterized using an actigraphy device (ActiSleep, Actigraph, Pensacola, FL). Subjective sleepiness was assessed using the Epworth Sleepiness Scale Score (ESSS); a score ≥10 points was considered to indicate excessive daytime sleepiness (EDS).

	ESSS < 10	**ESSS ≥ 10**
Number of Patients	73	127
ESS Score	5.7 ± 2.3	*15.6 ± 4.0
Age (years)	61.2 ± 10.2	57.3 ± 11.0
BMI	32.4 ± 5.9	33.1 ± 6.2
Race (%)		
Black (55)	26% (19)	28% (36)
White (145)	74% (54)	72% (91)
AHI (events/hr)	31.5 ± 16.7	*37.7 ± 22.1

Table 1. Demographics of Patient Cohort. Mean ± SD. Inclusion criterion, AHI > 15. *P < 0.05.

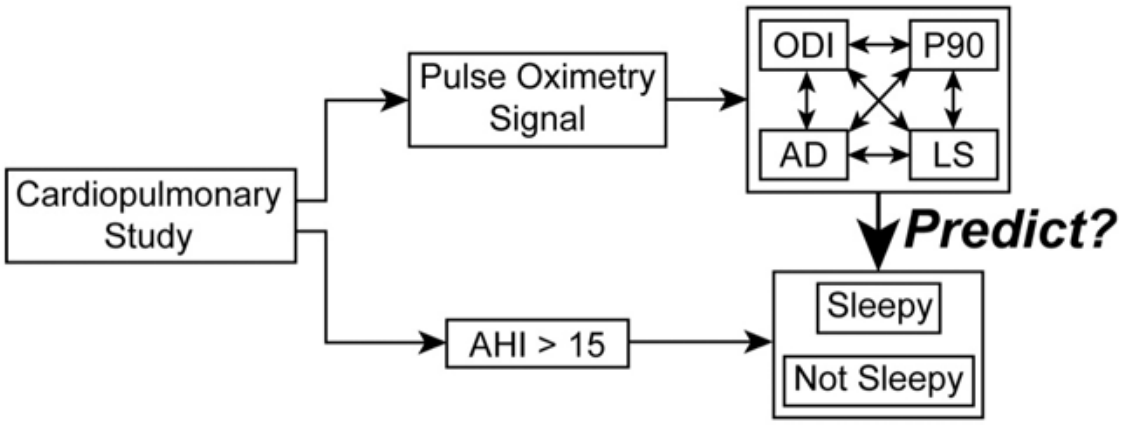

Fig. 1. Study design.

Study Design and Inclusion/Exclusion Criteria

The study was designed to assess how well hypoxemia predicted EDS (Fig. 1). Two hundred consecutive untreated (for OSA) patients having an AHI>15 events/hr were studied (199 males and 1 female). Exclusion criteria were alcohol or drug abuse, medications that could adversely affect sleep or respiration, or other sleep disorders. The cohort consisted of groups with and without daytime sleepiness that were balanced with respect to age, BMI, race, and gender (Table 1).

Measures of Nocturnal Hypoxemia

The hypoxemia variables evaluated were: oxygen desaturation index (ODI); the number of minutes in bed during which oxygen saturation was <90% (P90); average desaturation (AD), expressed as a percent of the time in bed; lowest percent saturation (LS). The measures were extracted from the pulse-oximetry signal (Fig. 2) and scored by proprietary software (RemLogic 1.1). The oximetry signal was also exported as an EDF file, converted to a Matlab-readable format (MathWorks, Needham, MA), and analyzed using a custom code, employing standard definitions for the NH variables. Preliminary studies showed that the results obtained were not materially different than those produced using the proprietary code, the results from which are reported here.

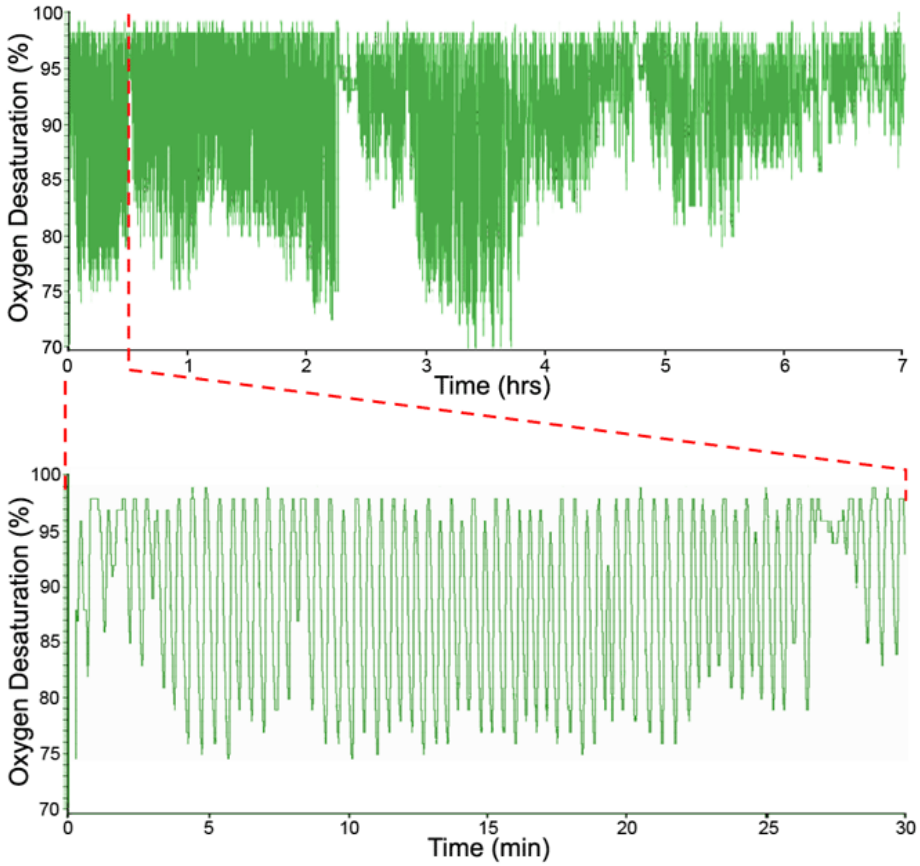

Figure 2. Typical oximetry data from an OSA patient (AHI = 41 events/hr). Top, entire 7-hour oximetry time series. Transducer output sampled at 10 Hz, averaged every 3 points and plotted (~3 points/sec). The oxygen desaturation that occurred during the initial 30 minutes is shown at an expanded time scale in the lower panel.

Statistics

The relationships between the ESSS and the hypoxemia variables and between ESSS and SE were determined by comparing the means of the sleepy and non-sleepy groups using the t test, and by computing the Pearson correlation coefficients (r).

Linear discriminant analysis (LDA) was used to evaluate all possible linear combinations of the NH and SE variables for purposes of determining whether any combination yielded a biomarker that was more strongly correlated with EDS than were the variables individually.

The sensitivity and specificity of the variables to predict sleepiness was evaluated by computing the area under the receiver-operator characteristics curve (AUROC) (AUROC = 0.5, no predictability; AUROC = 1, completely predictable).

Results

Group-Level Analysis

Four measures of hypoxemia severity were extracted mathematically from the pulse-oximetry time-series data of hemoglobin oxygen saturation. Both ODI and P90 were greater, on average, in the patients with EDS ($P < 0.05$). In contrast, neither mean AD nor LS differed between the two groups (Table 2). Sleep efficiency (determined by actigraphy) also did not differ on average between the groups (Table 2).

	ESSS < 10	ESSS ≥ 10
ODI (events/hr)	25.0 ± 18.1	*34.8 ± 26.5
P90 (min)	29.2 ± 35.7	*59.9 ± 85.2
Lowest O2 Sat. (%)	79.5 ± 8.0	78.3 ± 8.6
Average Desaturation (%)	6.4 ± 2.1	6.8 ± 2.6
Sleep Efficiency (%)	74.9 ± 15.0	70.7 ± 20.9

Table 2. Measures of Hypoxemia in Patients With and Without Daytime Sleepiness. Mean ± SD. *P < 0.05.

Patient-Level Analysis

ESSS was correlated with ODI and P90 ($P < 0.05$) (Table 3), but not with AD or LS. The relative abilities of ODI and P90 to predict sleepiness (ESSS ≥10) were each similar to that of AHI ($r = 0.209$, AUROC = 0.578). Sleepiness predictability did not improve materially when the variables were considered in combination (Table 3).

Correlated Variables	Correlation Coefficient	AUROC
ESSS/ODI	0.211	0.599
ESSS/P90	0.213	0.588
ESSS/(ODI+P90)	0.235	0.615
ESSS/(ODI+P90+SE)	0.246	0.625

Table 3. Correlations Between Sleepiness and Markers for Hypoxemia. ESSS, Epworth sleepiness scale score; AHI, apnea/hypopnea index (events/hr); ODI, oxygen desaturation index (events/hr); P90, minutes below 90% oxygen saturation; SE, sleep efficiency (%). AUROC, area under the receiver-operator characteristics curve.

Taking sleep efficiency into consideration did not improve the coefficients or AUROC (Table 3), as expected because mean SE did not differ between sleepy and non-sleepy patients (Table 2).

The hypoxemia variables were mildly–strongly correlated with each other, which probably explains why their combinations did not increase predictability (Table 4).

Correlated Variables	Correlation Coefficient
AHI/ODI	0.804
AHI/P90	0.354
ODI/P90	0.455

Table 4. Correlations Between Variables.

The observed correlations resulted almost exclusively from patients with severe OSA, as evidenced by the essentially random distributions of sleepy versus non-sleepy patients except for ODI >40, P90 >75, and AHI >50 (Fig. 3).

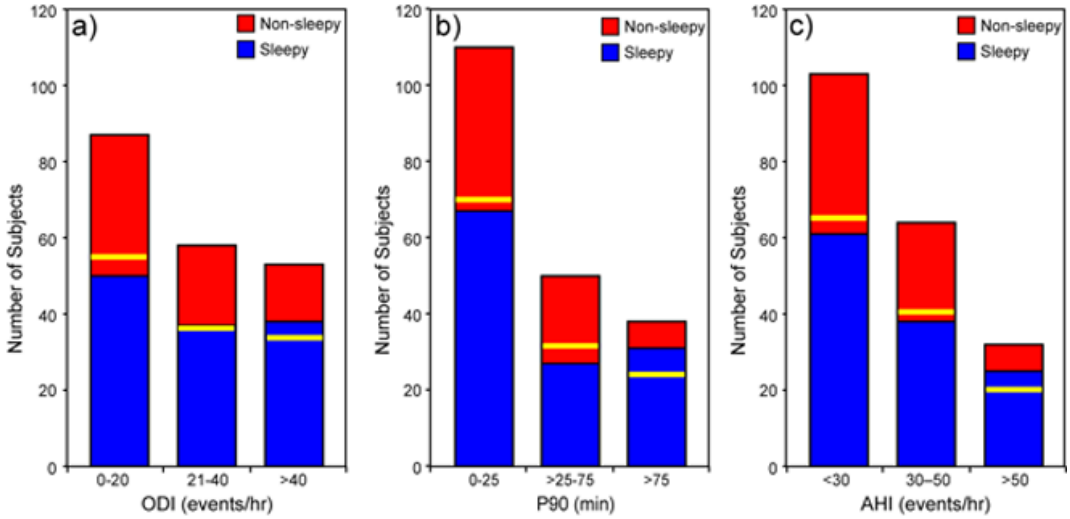

Figure 3. Analysis of relative proportions of sleepy (ESSS ≥10) and non-sleepy (ESSS <10) subjects by level of hypoxemia measure. ODI, oxygen desaturation index. Yellow bar indicates the fraction of sleepy patients expected by chance (73/127 of total bar height).

Discussion

Two of four standard measures of hypoxemia extracted from the pulse-oximetry signal were significantly (P<0.05) correlated with ESSS. Nevertheless the correlation coefficients were low, and biomarkers formed from all possible combinations of the measures did not materially improve the correlation with sleepiness. Overall the results

indicated that the standard hypoxemia measures alone (however combined) are unlikely to explain sleepiness in patients with moderate-to-severe OSA.

One possibility is that novel nonlinear measures of hypoxemia designed to quantify the dynamic behavior of oxygen desaturation may be extractable from the pulse-oximetry time series (Fig. 2).

Another possibility is that nocturnal hypoxemia, regardless of how well characterized, simply cannot capture enough of the complex physiological processes associated with OSA (Fig. 4). In this view, depending on the OSA sub-group of interest, other independent variables must be considered jointly to create a biomarker that predicts EDS. For example, in OSA patients successfully treated using CPAP (as assessed by AHI) but who continue to exhibit EDS, explicit consideration of the duration and severity of the OSA (surrogates for brain hypoxia and resulting neuronal death) might strengthen the association between NH and EDS.

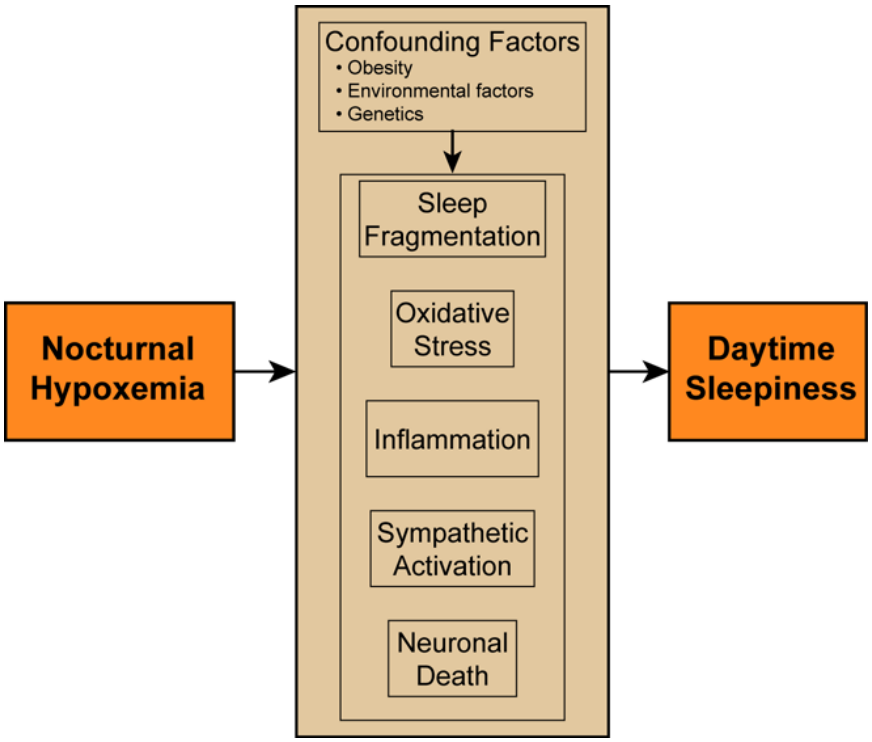

Figure 4. Possible intermediate processes affecting the link between NH and EDS in OSA.

Conclusion

Nocturnal hypoxemia and sleepiness are weakly correlated in male patients with moderate-to-severe OSA.

Abbreviations

AD	Average desaturation
AHI	apnea/hypopnea index
AUROC	Area under the receiver-operator characteristics curve
BMI	body mass index
CPAP	Continuous positive airway pressure
EDF	European data format
EDS	Excessive daytime sleepiness
ESSS	Epworth sleepiness scale score
LDA	Linear discriminant analysis
LS	Lowest percent saturation
NH	Nocturnal hypoxemia
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
P90	Minutes below 90% oxygen saturation
SE	sleep efficiency