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HYPOXIA • SHORT COMMUNICATION

Do T90 and SaO_2 nadir identify a different phenotype in obstructive sleep apnea?

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Abstract

Introduction Severity of obstructive sleep apnea (OSA) is commonly based upon the apnea-hypopnea index (AHI). However, patients with similar AHIs may demonstrate widely varying comorbidities and risk for cardiovascular disease. These varying manifestations of disease may be related to nocturnal hypoxia and not AHI. We hypothesize that parameters of oxygenation may identify a different phenotype in OSA.

Purpose To explore potential associations between lowest SaO_2 (SaO_2 nadir) and total sleep time spent with arterial oxygen saturation (SaO_2) < 90% (T90) with comorbidities and mortality in patients with moderate and severe OSA.

Method This was a retrospective study of patients between 2009 and 2014, with a new diagnosis of moderate-to-severe OSA without a concomitant respiratory disease. Data collection included demography, comorbidities, sleep study parameters, and mortality over a 5-year interval. Patients were categorized into two groups for analysis, group 1: SaO_2 nadir < 75%, and group 2: T90 > 20%.

Results Of the 365 patients, 163 (45%) recorded SaO_2 nadir < 75% and 127 (35%) recorded T90 > 20%. These oxygenation parameters were associated with more severe OSA by AHI ($p < 0.001$). T90 > 20% was associated with an increased risk of hypertension (HT) OR 2.95 (CI 1.87–4.76, $p < 0.001$) in patients with both moderate and severe OSA. T90 > 20% was also associated with an increased risk of type 2 diabetes mellitus (T2DM) OR 2.14 (CI 1.35–3.38, $p = 0.001$) and mortality 2.70 (CI 1.37–5.22, $p = 0.0048$).

Conclusion The findings demonstrate a correlation between SaO_2 nadir < 75% and T90 > 20% and increased severity of OSA. The findings also show a strong association between SaO_2 nadir < 75% and T90 > 20% and increased risk for comorbidities of HT and T2DM as well as mortality at 5 years. This analysis suggests that parameters of oxygenation should be used to describe a high-risk phenotype of OSA.

Keywords Comorbidities · Sleep apnea · Obstructive · Hypertension · Cardiovascular

Introduction

Obstructive sleep apnea (OSA) is a major public health problem [1]. Current clinical practice guidelines specify using the apnea-hypopnea index (AHI) to diagnose and categorize the degree of severity of OSA in polysomnography and home sleep apnea tests (HSAT) [2, 3]. However, some patients with moderate and severe OSA also demonstrate severe nocturnal hypoxemia. The variable of hypoxemia is not routinely part of the severity valuation even though there may be substantial clinical differences and worse prognoses due to nocturnal hypoxemia [4].

Biomarkers of oxidative stress are elevated in patients with OSA who show an arterial oxygen saturation (SaO_2) nadir < 75% or a total sleep time spent with SaO_2 < 90% (T90) for 20% or more of sleep time [5, 6]. The aim of this study was to explore the possible association between nocturnal hypoxemia (either SaO_2 nadir < 75% or T90 > 20%) and risk of hypertension (HT), type 2 diabetes mellitus (T2DM), and mortality in patients with newly diagnosed moderate to severe OSA.

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Methods

This retrospective study included patients being evaluated in a sleep clinic for suspected OSA between 2009 and 2014. Patients with central apnea, positional apnea, or incomplete data were excluded. Patients with other respiratory diseases such as chronic obstructive pulmonary disease (COPD), asthma/COPD overlap syndrome, and pulmonary fibrosis were also excluded.

Data collection included baseline demography, body mass index (BMI), history of HT or T2DM, sleepiness measured by Epworth Sleepiness Scale (ESS), and neck circumference. Data from home sleep apnea tests (HSAT using Embletta® MPR equipment, Natus sleep products, USA) were analyzed manually according to the American Academy of Sleep Medicine for level III studies [3]. Data extraction included AHI, SaO_2 nadir, oxygen desaturation index (ODI), and T90. Mortality over the 5 years since HSAT was also obtained by consulting the national register of mortality (www.registrocivil.cl).

For comparisons, patients were categorized into groups according to (1) SaO_2 nadir < 75% and (2) T90 > 20%. Quantitative data are expressed as mean and standard deviation (SD). Qualitative variables were expressed as percentages (%). For comparisons, unpaired students *t* test was used for quantitative data and chi-square test and fisher's exact test were used to compare percentages of patients with HT and T2DM. Data analysis was performed to calculate odds ratios (OR) using GraphPad PRISMA8® software (San Diego, CA, USA).

This retrospective study was approved by the Ethics Committee of the Institution (Institutional Review Board, Clinica Las Condes).

Results

Of the 365 patients recently diagnosed with moderate-to-severe OSA, 126 (35%) had moderately severe OSA with AHI between 15 and < 30 events/h and 239 (65%) had severe OSA with AHI ≥ 30 events/h. Mean age (± SD) for the group was 56.3 (± 14.0) years, BMI was 32.3 (± 5.7) kg/m^2, and neck circumference was 43.1 (± 4.1) cm. Mean ESS was 11.4 (± 5.7) points and mean AHI was 41.0 (± 13.0) events/h. Mean SaO2 nadir was 75% (± 10), mean ODI was 38.2 (± 21.8) events/h, and average T90 was 21% (± 26).

Of the 365 patients, 163 (45%) recorded SaO_2 nadir < 75% and 127 (35%) reported T90 > 20%. The group of patients with SaO2 nadir < 75% had a younger age, lower neck circumference, and lower BMI. They also reported less HT, albeit more sleepiness, worse AHI, worse ODI, and greater mean T90. T90 > 20% was associated to older age, greater neck circumference, higher BMI, more frequent HT and T2DM, and higher mean AHI, higher ODI, and lower SaO2 nadir. A summary of comparisons between the groups are reported in the Table 1.

Nocturnal hypoxemia is associated to an increased risk of hypertension, in this group of patients with moderate to severe OSA. The SaO_2 nadir < 75% was associated with HT with an OR 1.56 (CI 1.02–2.38, $p = 0.043$). Patients with moderate OSA showed an association with HT with an OR 1.89 (CI 1.11–3.17, $p = 0.02$). Patients with severe OSA showed an association with HT with an OR 1.18 (CI 0.69–2.00, $p = 0.591$). There was no statistically significant association between SaO_2 nadir < 75% and risk of T2DM.

T90 > 20% was associated with increased risk of HT in patients with moderate to severe OSA with an OR 2.95 (CI 1.87–4.76, $p < 0.001$). Patients with moderate OSA had risk

Table 1 Differences between patients with moderate-to-severe OSA categorized by SaO_2 nadir < 75% and T90 > 20%

	SaO_2 nadir > 75% ($n = 202$)	SaO_2 nadir < 75% ($n = 163$)	*p* value	T90 < 20% ($n = 238$)	T90 > 20% ($n = 127$)	*p* value
Age (year)	58.0	55.0	*0.036*	54.7	59.3	*0.003*
Gender, male	81%	75%	0.2	81%	75%	0.23
Neck circumference (cm)	43.8	42.6	*0.0047*	42.2	45.1	*< 0.001*
ESS (points)	10.5	12.4	*0.0028*	10.8	12.5	*0.0094*
BMI (kg/mt$^{2)}$	33.5	31.2	*0.0002*	30.8	35.0	*< 0.001*
HT (%)	62	51	*0.045*	47	72	*< 0.001*
T2DM (%)	25	32	*0.16*	23	39	*0.001*
Dead (%)	9	14	*0.13*	8	18	*0.0045*
AHI (events/h)	33.7	50.2	*< 0.001*	34.8	52.8	*< 0.001*
ODI	33.7	50.2	*< 0.001*	29.5	54.5	*< 0.001*
T90	8.5	36.9	*< 0.001*	5.6	50.4	*< 0.001*
SaO2 nadir	82.0	65.7	*< 0.001*	79.2	66.4	*< 0.001*

Italicized values represent statistical significance (*p*-value < 0.05)

AHI apnea-hypopnea index, *HT* hypertension, *T2DM* type 2 diabetes mellitus, *ODI* oxygen desaturation index, *ESS* Epworth Sleepiness Scale, *BMI* body mass index

for HT with an OR 2.55 (CI 1.53–4.21, $p = 0.0004$), and patients with severe OSA had risk for HT with an OR 8.64 (CI 2.50–28.58, $p = 0.003$). T90 > 20% was also associated with an increased risk of T2DM. In this study population, T2DM was reported in 39% of patients with T90 > 20% compared to 23% in patients with T90 < 20%, with an OR 2.14 (CI 1.35–3.38, p value = 0.001).

After 5 years of follow-up, risk of mortality was increased for patients with T90 > 20%. A total of 8% of patients died compared with 18% for T90 > 20%, OR 2.70 (CI 1.37–5.22, $p = 0.0048$).

Discussion

In this study, the findings show similar levels of AHI; there are differences between subjects who have indicators of severe nocturnal hypoxemia, such as TST-90, ODI, and SaO_2 nadir. There is a strong association between T90 > 20% and SaO_2 nadir < 75% and increased severity of OSA, associated increased risk of comorbidities such as hypertension and T2DM, as well as 5-year mortality.

The diagnosis of OSA is established by the AHI. This parameter has known prognosis for cardiovascular and mortality outcomes in patients with OSA who are not treated [7]. However, in recent years, different phenotypes of OSA have been identified which may have better power to predict comorbidities relevant to clinical practice. In a previous communication, we reported that subjects with postural OSA are predominantly women and that these patients have lower severity of OSA as well as a lower frequency of hypertension [8]. In addition, there are parameters reported in the HSAT that allow prediction of a population with higher risk of chronic intermittent hypoxia. The AHI alone does not appear sufficient to distinguish OSA of different severities [5, 6].

Previous studies have shown the value of measuring parameters of hypoxemia. Patients with hypoxemia have been shown to have a greater expression of proinflammatory markers [9]. In a study by Yilmaz et al. [9], 297 patients with similar AHI were evaluated, comparing a group with greater parameters of hypoxia such as T90 and SaO_2 nadir. These parameters were associated with higher concentrations of high-sensitivity C-reactive protein (hsCRP), higher platelet count, and endothelial stiffness.

Oxygenation parameters may also account for systemic inflammation in women with OSA, where it is known that AHI underestimates systemic inflammation [5]. Gouveris et al. studied 46 women comparing them with 167 men and found that while the AHI was higher in men, SaO_2 nadir and hypopneas were better parameters of inflammatory stress in women [5].

In a study by Zhang et al., the expression of hsCRP in men with severe OSA (AHI > 30 events/h) was evaluated. Multivariate analysis on data from this group of 152 men showed that elevated levels of hsCRP were independently associated with the T90 > 20%, with the association being higher than with AHI [6].

Ding and colleagues studied 415 subjects assessing the prevalence of fatty liver in patients with OSA of different severities. These investigators showed that fatty liver disease was associated with both insulin resistance, measured with the HOMA-R index, as well as elevated T90 and reduced SaO_2 nadir [10].

Weaknesses of the current study include the retrospective design and insufficient data retrieval on patient adherence to prescribed continuous positive airway pressure (CPAP). Nevertheless, the findings of this study suggest that there is value in further exploration of predictor variables in OSA that may improve our ability to predict outcomes and potentially to define subgroups or "phenotypes" of patients with an increased risk of complication from this common disorder.

Author's contribution Dr. Labarca: principal investigator, data extraction, data analysis, manuscript redaction, and final approval. Dr. Campos, Thibaut: data extraction, data analysis, and final approval. Dr. Jorquera, Dreyse: data acquisition, data synthesis, critical analysis, and final approval.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee from Clinica Las Condes, Santiago, Chile, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For the retrospective cohort included in this study, formal consent from patients was not required.

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