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Reliability of Home Nocturnal Oximetry in the Diagnosis of Overlap Syndrome in COPD

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Keywords
Chronic obstructive pulmonary disease · Sleep apnea · Overlap syndrome · Home nocturnal oximetry · Sleep study · Polysomnography · Reliability

Abstract
Background: Chronic obstructive pulmonary disease (COPD) and sleep apnea are common conditions and often coexist. The proper diagnosis of sleep apnea may affect the management and outcome of patients with COPD. ***Objective:*** To determine the accuracy of home nocturnal oximetry to distinguish between nocturnal oxygen desaturation related to COPD alone or to sleep apnea in patients with moderate-to-severe COPD who have significant nocturnal hypoxemia with cyclical changes in saturation. ***Methods:*** This study involved a comparison of home nocturnal oximetry and laboratory-based polysomnography (PSG) in patients with moderate-to-severe COPD considered for inclusion in a trial of nocturnal oxygen therapy. All of the patients had significant nocturnal oxygen desaturation (defined as ≥30% of the recording time with a transcutaneous arterial oxygen saturation <90%) with cyclical changes in saturation suggestive of sleep apnea. ***Results:*** PSG was obtained in 90 patients; 45 patients (mean age = 68 years, SD = 8; 71% men; mean forced expiratory volume in 1 s [FEV_1] = 50.6% predicted value, SD = 18.6%; data from 41 patients) fulfilled the criteria for sleep apnea (mean apnea-hypopnea index = 32.6 events/h, SD = 19.9) and 45 patients (mean age = 69 years, SD = 8; 87% men; mean FEV_1 predicted value 44.6%, SD = 15%) did not (mean apnea-hypopnea index = 5.5 events/h, SD = 3.8). None of the patients' characteristics (including demographic, anthropometric, and physiologic measures) predicted the diagnosis of sleep apnea according to PSG results. ***Conclusion:*** The diagnosis of sleep apnea in patients with moderate to severe COPD cannot rely on nocturnal oximetry alone, even when typical cyclical changes in saturation are seen on oximetry tracing. When suspecting an overlap syndrome, a full-night, in-laboratory PSG should be obtained.

Introduction

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea are prevalent disorders in the general population. Their combination is referred to as the "overlap syndrome" and it is associated with increased

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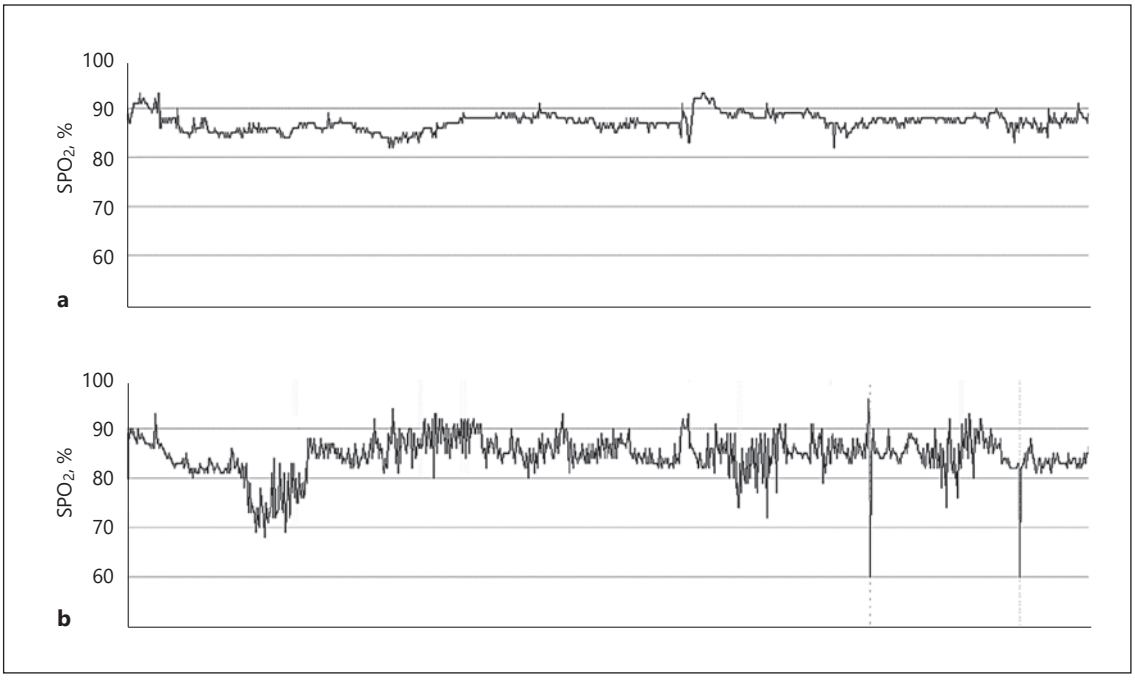

Fig. 1. Nocturnal oximetry tracings in patients with COPD not qualifying for long-term oxygen therapy. **a** Steady nocturnal desaturation with nonperiodic variation in saturation throughout sleep. This tracing is not suggestive of underlying sleep apnea. **b** Nocturnal desaturation with cyclical changes in saturation. This tracing is suggestive of sleep apnea.

morbidity and mortality [1–4]. The association of COPD and sleep apnea likely reflects the coincidental occurrence of 2 highly prevalent diseases within the same individual rather than common pathophysiological mechanisms [5]. Even in the absence of sleep apnea, patients with COPD have poor sleep quality, with frequent complaints of fatigue, daytime sleepiness, and disrupted sleep [6]. Patients with COPD have a prolonged sleep latency, a short total sleep time, and frequent arousals and wake after sleep onset; their sleep architecture is characterized by less deep sleep and rapid eye movement (REM) stage [7].

COPD patients are also prone to hypoxemia during sleep due to hypoventilation and increased ventilation-perfusion mismatch [8, 9]. They are especially susceptible to hypoxemia during REM sleep due to a reduction of and variability in tidal volumes, REM-associated skeletal muscle hypotonia, and ineffective contraction of the diaphragm [10–14]. Furthermore, as patients with COPD often have a low baseline saturation in the vicinity of the steepest portion of the oxyhemoglobin dissociation curve, any given change in PaO_2 will result in a greater decline in saturation [6, 9]. As a consequence, >50% of patients with COPD and moderate daytime hypoxemia (daytime PaO_2 in the range of 59–69 mm Hg) have significant nocturnal oxygen desaturation and patients with overlap syndrome have greater desaturations compared to those with either disease alone [3, 15].

In a cohort of 128 patients with moderate-to-severe COPD, we observed 2 different patterns of nocturnal oxygen desaturation on oximetry tracings. The first pattern, seen in 49 patients (38%), consisted of steady nocturnal desaturation with nonperiodic variation in saturation throughout the night. The second pattern, seen in 20 patients (16%), consisted of cyclical changes in saturation than can hardly be distinguished from the one observed in sleep apnea (Fig. 1) [15]. This distinction is of the utmost importance since sleep apnea and isolated nocturnal oxygen desaturation are to be managed very differently. Also, the diagnosis and proper management of sleep apnea in COPD bear on clinical outcomes. Treatment of sleep apnea in COPD patients has been shown to reduce the likelihood of hospitalization due to severe exacerbation and increase survival [4, 16]. However, the optimal screening tools and proper diagnostic methods for sleep apnea in COPD have not yet been determined.

In this study, we took advantage of the International Nocturnal Oxygen (INOX) trial to report on a series of patients with COPD presenting nocturnal desaturation

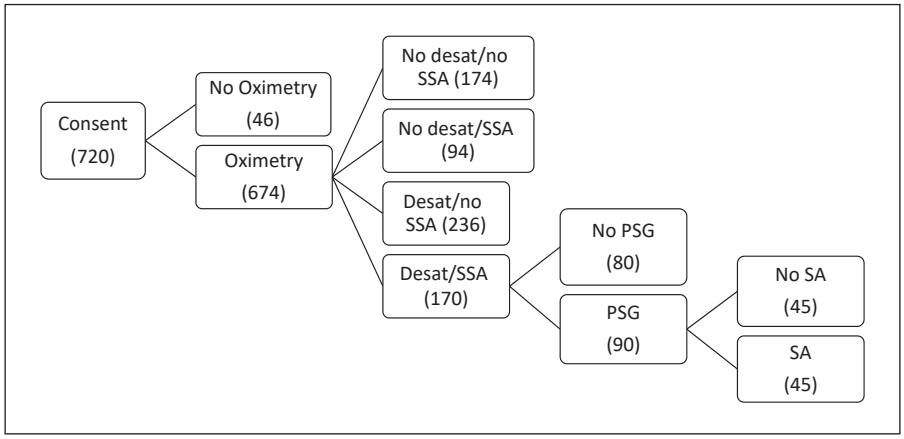

Fig. 2. Recruitment and investigation of patients in the INOX trial. Desat, desaturation (≥30% of the recording time with a transcutaneous pulse oxygen saturation [SpO_2] <90%). Ninety patients were submitted to PSG. SA, sleep apnea; SSA, suggestive of sleep apnea.

and cyclical desaturations suggestive of sleep apnea according to ambulatory oximetry recording [17]. Our objective was to determine in this population the accuracy of home nocturnal oximetry to distinguish between nocturnal oxygen desaturation related to COPD alone or to sleep apnea. More specifically, we wished to calculate the proportion of patients with sleep apnea in those who tested positive on nocturnal oximetry (i.e., its positive predictive value), and to investigate differences in patient characteristics between "pure" COPD and overlap patients.

Methods

Patients

The INOX trial is a 4-year, multicenter, randomized, double blind, placebo-controlled trial of nocturnal oxygen therapy in patients with COPD and nocturnal oxygen desaturation (ClinicalTrials.gov ID: NCT01044628) [17]. COPD was defined as airflow limitation on spirometry (forced expiratory volume in 1 s [FEV_1] <70% predicted, FEV_1/forced vital capacity [FVC] <70% and a total lung capacity by body plethysmography >80% predicted) in patients with a history of smoking. Patients had to be nonsmokers for at least 6 months at study entry. Those with a prior diagnosis of sleep apnea and those who met the criteria for LTOT were excluded. Patients were screened for eligibility in the trial using nocturnal oximetry. All of the patients underwent 2 oximetry studies at home ≤2 weeks apart using PalmSAT 2500™ oximeters (Nonin Medical Inc., Plymouth, MN, USA). Oximetry tracings were all interpreted by one of the investigators (F.S.). On both occasions, recordings of at least 4 h were mandatory. Significant nocturnal oxygen desaturation was defined as ≥30% of the recording time with a transcutaneous pulse oxygen saturation (SpO_2) <90% [18]. Suspicion of sleep apnea was noted according to the visual inspection of oximetry tracings showing cyclical changes in saturation (Fig. 1b). Patients in whom at least 1 oximetry tracing was suggestive of sleep apnea could be submitted off-protocol to complete laboratory-based polysomnography (PSG) in order to rule out sleep apnea before randomization. The present study was therefore limited to those patients who had full PSG.

Polysomnography

PSG recordings minimally consisted of continuous acquisition of electroencephalogram, naso-oral airflow with thermistors, nasal pressure with a nasal cannula, chest and abdominal movements with impedance plethysmography, and electrocardiogram and sleep position monitoring. Sleep apnea was considered to be significant (i.e., moderate to severe) when the apnea/hypopnea index was ≥15 events/hour of sleep. PSG were interpreted in each participating center and reviewed at the coordinating center when sleep apnea was excluded and patients were thought to be eligible to participate in the trial.

Other Measures

In addition, all of the patients underwent spirometry according to American Thoracic Society/European Respiratory Society requirements [19]. The predicted values currently used within each laboratory were accepted. Arterial blood gases were obtained from puncture of the radial artery and measured while breathing room air.

Statistics

We performed standard descriptive statistics (means, SD, proportions) on patients' baseline characteristics and data obtained from the nocturnal oximetry and full-night PSG. To compare "pure" COPD and overlap patients, *t* tests and χ^2 tests were performed as appropriate. We planned to apply logistic regression to identify predictors of sleep apnea depending on the results of the univariate comparisons. We also correlated the oxygen desaturation indices obtained with nocturnal oximetry and during PSG using Spearman's coefficient of correlation. The threshold of statistical significance was adjusted according to the number of comparisons involved.

Results

In the INOX trial, 674 patients were screened by overnight oximetry. Overall, 170 (25%) patients had cyclical nocturnal desaturation suggestive of sleep apnea on overnight oximetry. Of them, 90 were submitted to PSG (Fig. 2). The remaining 80 patients had no fur-

Table 1. Baseline clinical characteristics

	Nocturnal desaturation without sleep apnea (n = 45)	Nocturnal desaturation with sleep apnea (n = 41)	p value
Age, years	68.8±7.6	68.3±7.9	0.79
Males	39 (86.7)	29 (70.7)	0.11
Caucasians	45 (100)	40 (100)	–
BMI	26.8±5.3	28.5±6.7	0.19
Pack-years	61.6±36.3	57.9±29.1	0.60
Left heart failure	2 (4.4)	4 (9.8)	0.42
Cardiovascular disease	10 (22.2)	8 (19.5)	0.80
Cerebrovascular disease	3 (6.7)	0 (0)	0.24
Atrial fibrillation	3 (6.7)	1 (2.4)	0.62
Arterial hypertension	22 (48.9)	23 (56.1)	0.52
Dyspnea MRC			0.8
I	1±2.2	1±2.4	
II	9±20.0	10±24.4	
III	20±44.4	16±39.0	
IV	10±22.2	12±29.3	
V	5±11.1	2±4.9	
Resting systolic blood pressure, mm Hg	130.2±16.4	132.0±15.6	0.61
Resting diastolic blood pressure, mm Hg	75.3±9.4	74.8±11.0	0.81
Medication, number of patients			
Theophylline	5 (11.1)	2 (4.9)	0.44
Diuretics	12 (26.7)	14 (34.2)	0.49
Long-acting anticholinergics	40 (88.9)	35 (85.4)	0.75
Long acting β-agonists	44 (97.8)	38 (92.7)	0.34
Oral steroids	7 (15.5)	4 (10.0)	0.53
Benzodiazepine	12 (26.7)	4 (9.8)	0.06
Opiates	1 (2.2)	2 (4.9)	0.60

Values are presented as means ± SD or numbers (%). MRC, Medical Research Council dyspnea scale.

ther evaluation. Overall, the demographic and clinical characteristics of those who underwent PSG and those who did not were similar, with few exceptions. Those who underwent PSG were slightly younger and were more often on long-acting β-agonists than those who did not; atrial fibrillation was also less prevalent in those who were tested (online suppl. Tables 1S–3S; see www.karger.com/doi/10.1159/000505299 for all online suppl. material).

Of the 90 patients who underwent PSG, 45 patients fulfilled the criteria for moderate to severe sleep apnea (positive predictive value: 50%). The data of 4 sleep studies (all in patients with a final diagnosis of sleep apnea) were not available for analysis, leaving 41 patients in this group contributing to the analysis. Patients' characteristics according to the presence or absence of sleep apnea along with PSG results are shown in Table 1. Patients were mostly Caucasian men with a mean age of 68 years. All were former smokers as per the inclusion criteria of the INOX trial. Most patients had exertional dyspnea and were treated with long-acting bronchodilators, alone or in combination. Patients without obstructive sleep apnea had more severe airway obstruction (FEV_1/FVC = 45 vs. 55%; FEV_1 = 45 vs. 51% predicted), although the difference in FEV_1 was not statistically significant (Table 2). None of the baseline characteristics could clearly differentiate between patients with and without sleep apnea. No logistic regression analysis was therefore attempted.

Nocturnal Oximetry

There was no difference in terms of recording time, 3% oxygen desaturation index, average saturation, and percentage of recording time with saturation below 90% between patients with and without sleep apnea on PSG (Table 3).

Table 2. Pulmonary function tests results

	Nocturnal desaturation without sleep apnea (n = 45)	Nocturnal desaturation with sleep apnea (n = 41)	p value
FEV_1, % predicted	44.6±15.9	50.6±18.6	0.11
FVC, % predicted	76.4±20.2	80.9±24.2	0.36
FEV_1/FVC	45.0±12.8	54.7±35.0	0.03

Values are presented as means ± SD.

Table 3. Comparison of nocturnal home oximetry results

	Nocturnal desaturation without sleep apnea (n = 45)	Nocturnal desaturation with sleep apnea (n = 41)	p value
Recording time, min	480.7±95.0	515.9±160.8	0.23
Desaturation index	28.4±13.4	28.6±13.9	0.94
Average saturation, %	89.5±1.6[a]	87.4±10.6	0.33
Recording time with saturation <90%, %	63.7±22.0	65.7±62.6	0.67

Values are presented as means ± SD. [a] n = 44.

Table 4. Comparison of polysomnographic features

	Nocturnal desaturation without sleep apnea (n = 45)	Nocturnal desaturation with sleep apnea (n = 41)	p value
Recording time, min	442.6±74.1	464.0±51.0	0.12
Total sleep time, min	292.7±82.6	311.2±78.3	0.29
Sleep efficiency, %	66.4±15.9	68.0±16.9	0.66
Saturation	89.7±2.4	89.3±2.6	0.46
Time with saturation <90% (% sleep time)	51.0±33.4	46.6±32.1	0.53
Apnea-hypopnea index, events/h	5.5±3.8	32.6±19.9	<0.001
Obstructive apnea index, events/h	1.2±2.0	6.4±8.8	<0.001
Oxygen desaturation index, events/h	8.6±16.0	23.2±20.8	<0.001
REM sleep, %	14.0±6.7	14.7±6.3	0.63

Values are presented as means ± SD.

Polysomnography

Oxygen desaturation indices obtained with nocturnal oximetry and during PSG were not correlated (r = –0.27; p = 0.1). With the exception of the apnea-hypopnea index that defined the presence or absence of sleep apnea, no difference was observed in any of the sleep characteristics (Table 4).

Discussion

This study evaluates the role of nocturnal oximetry as a diagnostic tool for sleep apnea in patients with COPD. It was limited to the subgroup of patients with significant desaturation associated with cyclical changes in saturation on oximetry tracing. Our results show that the diagnosis of sleep apnea in COPD should not be based solely

on the result of a nocturnal oximetry because sleep apnea was confirmed in only 50% of patients with oximetry tracings highly suggestive of sleep apnea.

None of the baseline clinical characteristic that we measured could differentiate patients without sleep apnea from those with sleep apnea. However, slight differences between the 2 groups were observed (Table 2). Patients without obstructive sleep apnea had more severe airway obstruction, although the difference in FEV_1 was not statistically significant. The clinical significance of this finding is uncertain. Of note, the difference in AHI between both groups was large (5.5 vs. 32.6/h). Most of the events in those with sleep apnea were hypopneas and only 6.4 were real obstructive events. We hypothesize that hypopneas may only represent sleep-related hypoventilation in COPD patients, so that the generalization of the current definition of sleep apnea based on the apnea-hypopnea index to patients with COPD could be questioned.

Screening for sleep apnea in COPD may be important, as it is associated with increased adverse events and mortality compared with either COPD or sleep apnea alone [1, 8, 9, 20, 21]. Marin et al. [4] prospectively evaluated the relation between overlap syndrome and hospitalization for COPD exacerbations and mortality in patients without cardiovascular comorbidities who had overlap syndrome. They found an increased risk of death and hospitalization for COPD exacerbations in patients with untreated overlap syndrome compared to patients treated by continuous positive airway pressure (CPAP) and COPD patients without obstructive sleep apnea [4]. In another observational study of 1,112 patients with COPD and 2,284 patients with obstructive sleep apnea where 227 had overlap syndrome, multivariate analysis revealed that a better adherence to CPAP was associated with reduced mortality [16]. A Brazilian prospective study also observed higher survival rates in CPAP-treated patients compared to untreated patients with overlap syndrome [22]. Increased mortality is thought to be due, at least in part, to the increased depth of nocturnal hypoxemia in this population, which predisposes to cardiovascular events and pulmonary hypertension [1, 3, 23].

Screening COPD patients for potential sleep apnea can be challenging as usual risk factors, such as male gender and increased BMI and neck circumference are inconsistently associated with sleep apnea in COPD [24]. Even though we could not identify any clinical characteristics to be associated with a higher probability of an overlap syndrome in our study, other studies suggest that patients with a predominant emphysema, a lower BMI, and lung hyperinflation may have a lower likelihood of concomitant obstructive sleep apnea [25, 26]. Furthermore, sleep quality is often poor in COPD [6, 7, 27]. As a consequence, fatigue and tiredness are common symptoms and they should not be considered as indicative of the presence of sleep apnea [7, 27]. A prospective, observational study also suggested that the Epworth Sleepiness Scale, a well-validated questionnaire commonly used as a screening tool for obstructive sleep apnea, is a poor predictor of alertness disturbances in patients with sleep apnea associated with moderate COPD [24]. To further complicate the screening of sleep apnea in COPD, these patients rarely have typical symptoms such as excessive daytime sleepiness, snoring, gasping, or choking [24, 28].

Although many experts agree that the diagnosis of overlap syndrome should be supported by a complete (type-1) PSG study in mild to moderate COPD, this has not been well studied [20]. Also, the validity of portable (type 3) sleep studies is uncertain [29]. Nocturnal oximetry has the benefit of being readily available. However, because it does not monitor sleep duration and arousals, it underestimates the frequency of breathing events such as hypopnea, which is defined as a reduction of flow associated with oxygen desaturation and/or arousal [30]. The current state of knowledge suggests that a more comprehensive study, such as full overnight PSG, should be conducted in order to better qualify the type of nocturnal breathing events, the presence of CO_2 retention and the magnitude and depth of oxygen desaturation, as well as to decide on the most appropriate treatment in this population prone to hypoventilation and hypercapnia [31]. We would concur with this recommendation.

Our study has several limitations. First, we excluded patients with significant desaturation whose oximetry tracing demonstrated only nonperiodic variation in saturation throughout sleep. However, it is noteworthy that, because of the shape of the oxygen-hemoglobin dissociation curve, episodes of apnea superimposed to hypoventilation-induced hypoxemia should translate into cyclical changes on the oximetry tracing. Similarly, we excluded patients who did not desaturate significantly during sleep but whose oximetry tracing was nevertheless suggestive of sleep apnea. These patients were not considered for inclusion in the INOX trial. For this reason, we could not determine the prevalence of overlap syndrome among patients with moderate to severe COPD. Second, because full sleep studies were performed off-protocol, only 90 of the 170 patients with an oximetry tracing suggestive of sleep apnea during INOX screening finally underwent full PSG. Also, because they were performed off protocol, PSG exams could not be

standardized across centers, although they all met international standards in all centers. Third, our study has a small sample size and focuses on a very specific population. Finally, the significant apnea-hypopnea threshold for overlap syndrome is unknown and whether the apnea-hypopnea index correctly predicts clinical outcomes in COPD patients remains to be determined [20].

Conclusion

Our study demonstrated that the diagnosis of sleep apnea in patients with moderate to severe COPD cannot rely on nocturnal home oximetry alone, even when typical cyclical changes in saturation are seen on oximetry tracing. When overlap syndrome is suspected, a full-night in laboratory PSG should be performed.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

F.M. has received honoraria for giving a lecture or attending an advisory board for Boehringer, GSK, Novartis, and Grifols. He has also received research grants for participating in multicenter trials for AstraZeneca, Boehringer Ingelheim, GSK, Sanofi, and Novartis and unrestricted research grants and personal fees from Boehringer Ingelheim, Grifols, and Novartis. The remaining authors do not declare any conflict of interests with this study.

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Author Contributions

A.-C.L., F.S., C.J.E.S., A.A.F., and Y.L. participated in the design of the protocol. A.-C.L., S.B., E.B., and Y.L. participated in the data extraction. A.-C.L., F.S., C.J.E.S., A.A.F., F.M., and Y.L. participated in the interpretation of the results and the final revision of this paper. A.-C.L. and Y.L. drafted this paper. All of the authors (A.-C.L., F.S., S.B., E.B., C.J.E.S., A.A.F., F.M., and Y.L.) read and approved the final version of this paper.

Appendix

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