

# Nature of Disordered Sleep in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

Piyush P Gupta<sup>1</sup>, Amol B Fuladi<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Respiratory Medicine, Government Medical College and Hospital, Akola, Maharashtra, India, <sup>2</sup>Professor and Head, Department of Respiratory Medicine, Government Medical College and Hospital, Akola, Maharashtra, India

## Abstract

**Introduction:** Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world. Comorbidities occur frequently in COPD patients.

**Aim:** The present study was an observation based cross-sectional prospective study carried out with an aim to evaluate the breathing disorders during sleep in patients with COPD and to correlate this disorder with the stage of the disease.

**Materials and Methods:** A total of 50 patients were eligible for participation in our study. 18 patients had moderate COPD, 19 patients had severe COPD, and 13 patients had very severe COPD as per the global initiative for chronic obstructive lung disease guidelines.

**Results:** Mean sleep efficiency was low at  $53.25 \pm 18.15$ . Sleep latency was normal in three patients only. We found abnormal sleep architecture in all three groups with decreased duration of stage N3 and stage rapid eye movement. Obstructive sleep apnea (OSA) was present in 23 of 50 subjects of COPD (Overlap syndrome).

**Conclusion:** In present study, it was found that OSA is highly prevalent in patients with moderate to very severe COPD. Sleep quality is also poor among this selected group.

**Key words:** Apnea-hypopnea index, COPD, Sleep

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the world,<sup>[1]</sup> represents an important public health challenge that is both preventable and treatable. Globally, the COPD burden is projected to increase in the coming decades due to continuous exposure to COPD risk factors and aging of the population.<sup>[2]</sup>

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis.<sup>[3-7]</sup> Some of these arise independently of COPD whereas others

may be causally related, either with shared risk factors or by one disease increasing the risk of another.

Comorbidities that occur frequently in COPD patients include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, lung cancer, and sleep-related breathing disorder.<sup>[8]</sup>

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing (SDB) clinically recognized four decades ago and defined by the total or partial intermittent collapse of the upper airway resulting in nocturnal hypoxemia and arousals from sleep. Recent data indicate an increasing trend, with 26% of adults estimated to have mild-to-severe OSA (apnea-hypopnea index [AHI] >5/h).<sup>[9]</sup>

COPD and OSA syndrome (OSAS) are highly prevalent disorders, so the possibility of both occurring together in the same patient is relatively high by chance alone. Current estimates for the prevalence of COPD are in the region

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**Corresponding Author:** Dr. Amol B Fuladi, Damle Marg, Ramdaspath, Akola - 444 001, Maharashtra, India.

of 10% and the prevalence of OSAS is at least 10%. The coexistence of both disorders, termed the overlap syndrome, carries additional prognostic implications relating to worsening respiratory failure, cardiovascular, and other comorbidities, and ultimately survival.<sup>[10]</sup>

Early small studies showed a high prevalence of OSA in COPD and vice versa.<sup>[11,12]</sup> However, these studies may have had selection bias. The more recent Sleep Heart Health Study (SHHS), a large community-based cohort study, showed no increase in the prevalence of OSA in mostly mild obliterative airway disease patients compared to the general population.<sup>[13]</sup> Similar results were shown by Bednarek *et al.*<sup>[14]</sup> in a Polish cohort with predominantly mild COPD.

Little is known about the path physiological and clinical consequences of having concomitant COPD and OSA. Recent studies have demonstrated that patients with COPD-OSA have a high risk of death as well as increased risk of exacerbations if OSA remains untreated. Therefore, evaluating the presence of OSA in patients with advanced COPD seems logical.<sup>[9]</sup>

To that end, we investigated sleep characteristics of patients enrolling in a respiratory medicine department of a tertiary care center to determine the nature of disordered sleep in patients with advanced COPD.

## METHODS

The present study was an observation based cross-sectional prospective study carried out in a well-equipped sleep laboratory of the Department of Respiratory Medicine, R D Gardi Medical College, Ujjain, India. The aim of the study was to evaluate the breathing disorders during sleep in patients with COPD and to correlate this disorder with the stage of the disease.

The study cohort was constituted by patients of COPD registered into chest OPD or admitted in Indoor Units of the hospital from July 2012 to July 2014.

A total of 50 consecutive COPD patients who consented to be enrolled into the study were classified into moderate, severe, and very severe stages based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the management of COPD, i.e., Mild COPD: Forced expiratory volume in 1 s (FEV1)/Forced vital capacity (FVC) <70%, FEV1 >80% predicted; Moderate COPD: FEV1/FVC <70%, FEV1 50–80% predicted; and Severe COPD: FEV1/FVC <70%, FEV1 30–50% predicted; very severe COPD: FEV1/FVC <70%, FEV1 <30% predicted.

The inclusion criteria followed for enrolling the patients in the study were age >40 years; clinical history consistent with COPD; irreversible airflow obstruction, i.e., FEV1/FVC <70% and post-bronchodilator change in FEV1 <15% (or) if FEV1 <1.5 L, change in FEV1 <200 ml.

Patients with active tuberculosis, congestive heart failure, chronic renal failure, morbid obesity (Body mass index [BMI] >40), pregnant women, age <40 years and >80 years were excluded from the study.

All COPD patients were subjected to detailed clinical history, thorough physical examination, ear, nose and throat examination, Mallampati grading to rule out upper airway obstruction. All patients were asked to fill up the Epworth Sleepiness questionnaire. BMI was recorded (BMI = weight in kg/height in m<sup>2</sup>). Neck circumference (cm) was measured at the level of the cricothyroid membrane.

For each enrolled subject, spirometry was done using international protocols by Computerized Spirometry Machine (MIR-Spiro lab III) for confirmation and staging of COPD.

All patients underwent polysomnography (Level 1 using Alice 5 Respirationics) to diagnose OSA along with sleep quality (include total sleep time, sleep efficiency, sleep latency, percentage of sleep stage N<sub>1</sub>, N<sub>2</sub>, N<sub>3</sub>, and rapid eye movement [REM]), arousal index (AI) (i.e., average number of arousal per hour of sleep), periodic leg movement index (PLMI) (i.e., the average number of periodic limb movement in an hour of sleep), desaturation index, and AHI (The average number of apneas and hypopneas in an hour of sleep). The AHI grading was done according to the American Academy of Sleep Medicine guidelines. Patients were classified according to the severity of OSA as mild (AHI 5–15), moderate (AHI 15–30), and severe (AHI >30). Correlation of all outcomes with the severity of COPD was studied.

Qualitative data were collected, and results were arranged into tables, and statistical test-Chi-square test, regression correlation, and Mann–Whitney non-parametric test were applied for the tables. *P* value for significance was taken out for all the tables. Test was considered significant when *P* < 0.05.

Microsoft Excel 2010 software and SPSS version-20 was used for data entry and analysis.

## RESULTS

A total of 58 patients were eligible for participation in our study. Eight studies (13.7%) were not suitable for analysis:

sleep duration <4 h ( $n = 2$ ), loss of EEG signal ( $n = 2$ ), and lost raw data in a hardware malfunction ( $n = 4$ ). A final sample of 50 subjects was included in the analysis.

Eighteen (36%) patients had moderate COPD, 19 (38%) patients had severe COPD, and 13 (26%) patients had very severe COPD as per GOLD guidelines. Majority of the patients 44 (88%) were in the age group of 55 years and above (range 45–80 years, mean 61.12 years). 49 (98%) males and one (2%) female participated in the study.

On physical examination, there were no risk factors for OSA such as deviated nasal septum, high arched palate, macroglossia, and retrognathia. The mean BMI was  $18.12 \pm 3.92$ . The mean neck circumference was  $34.64 \pm 3.71$  cm. However, both BMI and neck circumference were not significantly different in the compared groups ( $P = 0.72$  and  $P = 0.97$ , respectively). All the patients had mallampati score of <3, signifying no additional risk factor for OSA.

Most of the patients enrolled in the study were heavy smokers with a mean pack year of 33.9. Smoking history was not significantly different across the three groups ( $P = 0.56$ ).

Baseline demographic, anthropometric, and spirometric data are presented in Table 1 for all subjects who completed the study. There were no significant demographic differences in patients of all the three study groups [Table 1].

**Table 1: Demographic, anthropometric, and spirometric data in COPD**

Parameters	Moderate COPD (n=18)	Severe COPD (n=19)	Very severe COPD (n=13)	P value
Age, year	59.8±16.5	60.5±0.0	63.8±10.0	0.16
Male/Female, %	94.4/5.6	100/0	100/0	0.0001
BMI, kg/m <sup>2</sup>	18.6±3.4	18.3±0.8	17.15±1.2	0.72
Smoking, pack-years	31.6±10.0	31.15±15.0	41.0±17.5	0.56
Neck circumference	35.2±1.2	34.5±0.7	34.1±0.0	0.97
FVC%	72.3±1.0	60.4±4.5	51±3.5	0.001
FEV1%	61.3±0.5	37.3±0.0	23.8±0	0.0001
FEV1/FVC%	64.45±10.0	56.6±8.3	48.2±13.5	0.004

COPD: Chronic obstructive pulmonary disease, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 s, BMI: Body mass index

**Table 2: Polysomnography data in COPD patients**

Sleep quality	Moderate COPD (n=18)	Severe COPD (n=19)	Very severe COPD (n=13)	P value
Sleep efficiency	74.1±2.9	81.2±11.5	68.27±18.9	0.09
Sleep latency	28.5±3.2	52.65±3.0	65.86±17.5	0.2
Sleep stage N1%	21.9±3.8	21.5±0.0	21.5±9.9	0.50
Sleep stage N2%	58.7±5.1	55.6±1.8	58.9±3.9	0.39
Sleep stage N3%	6.8±0.7	11.1±1.3	9.6±8.6	0.08
Sleep stage REM%	12.5±0.6	12.0±0.6	9.8±5.3	0.45

COPD: Chronic obstructive pulmonary disease, REM: Rapid eye movement

The average FEV1/FVC of the cohort was  $57.23 \pm 19.5$ . Subjects with very severe COPD had a mean FEV1/FVC of  $48.2 \pm 13.5$ . There was a significant difference in FEV1, FVC, and FEV1/FVC across all the three groups [Table 1].

Epworth Sleepiness Scale was in the normal range in 34 (68%) patients. Ten (20%) patients had score between 8 and 9 suggesting the average amount of daytime sleepiness and only 6 (12%) had score ranging from 10 to 15 suggesting excessive sleepiness depending on the situation. Not a single patient had scored higher than 16 suggesting excessive daytime sleepiness.

Mean sleep efficiency was low at  $53.25 \pm 18.15$ . Sleep efficiency differed significantly between severe and very severe COPD groups ( $P = 0.01$ ).

Sleep latency was normal in three patients only, 47 (94%) patients had sleep latency above normal (range 5–209 min).

Furthermore, we found abnormal sleep architecture in all three groups with decreased duration of stage N3 and stage REM, with no significant difference across the three groups ( $P = 0.08$  and  $P = 0.45$ , respectively) [Table 2].

OSA was present in 23 of 50 subjects (46%) of COPD (Overlap syndrome). Mild OSA was seen in 7 (14%) patients, moderate in 13 (26%) patients, and severe OSA in 3 (6%) patients. There was a significant correlation between OSA and FEV1, FVC ( $P = 0.01$  and  $P = 0.01$ , respectively). The severity of OSA increased with the severity of airflow obstruction.

Thirty (60%) patients had high AI. The severity of AI increased with the severity of disease ( $P \leq 0.0001$ ).

Forty (80%) patients had high (>5) desaturation index. 26 (52%) patients had mild desaturation index,<sup>[5-15]</sup> 10 (20%) patients had moderate desaturation index,<sup>[15-20]</sup> and 4 (8%) patients had severe desaturation index (>30). Desaturation index increased with the severity of COPD with a significant difference in moderate and severe, very severe COPD. On comparing desaturation index with

**Table 3: AHI, AI, desaturation index, and PLMI in moderate to very severe COPD**

Sleep study findings	Moderate COPD (n=18)	Severe COPD (n=19)	Very severe COPD (n=13)	P value
AHI	7.9±10.6	15.9±0.9	19.4±6.7	0.003
AI	3.6±5.2	9.6±1.9	14.1±7.1	0.001
Desaturation index	7.3±3.8	15.1±5.9	15.4±5.8	0.005
PLMI	2.8±1.6	8.5±0.9	15.5±3.5	0.0001

AHI: Apnea-hypopnea index, AI: Arousal index, PLMI: Periodic leg movement index, COPD: Chronic obstructive pulmonary disease

severity of COPD, the data were significant ( $P = 0.04$ ,  $P = 0.0008$ , respectively).

Periodic limb movement index was above normal in 20 (40%) patients. It significantly increased with the severity of disease ( $P \leq 0.0001$ ) [Table 3].

## DISCUSSION

The literature regarding sleep in COPD is somewhat mixed. The SHHS, for example, found no major increase in OSA risk among patients with COPD compared with matched control subjects.<sup>[13]</sup> However, they studied a community sample of patients with mild subclinical disease, and thus the findings may not generalize to clinical cohorts. On the other hand, Sharma *et al.* found a high risk of OSA in patients with COPD, but the authors failed to use GOLD standard polysomnography, and thus the results may be biased by misclassification.<sup>[15]</sup>

In studies by Bradley *et al.*<sup>[16,17]</sup> and by Chaouat *et al.*,<sup>[12]</sup> in which consecutive patients with SAHS were investigated (n - 50 and 265, respectively) the prevalence of an associated COPD, was, respectively, of 14%<sup>[17]</sup> and 11%.<sup>[12]</sup> These figures were considered as high, suggesting that the prevalence of COPD in SAHS exceeded that observed in the general population.

Our study, which consisted of COPD in different stages of severity, observed a high prevalence of SDB in patients with moderate to very severe COPD referred to our OPD. OSA was present in 23 of 50 subjects (46%). There was a significant correlation between OSA and FEV1, FVC ( $P = 0.01$  and  $P = 0.01$ , respectively). Thus, the severity of OSA increased with the severity of airflow obstruction.

We found abnormal sleep architecture in all the groups with decreased duration of stage N3 and stage REM, with no significant difference across the three groups ( $P = 0.08$  and  $P = 0.45$ , respectively). We have further identified poor sleep quality and low sleep efficiency in full polysomnography in COPD patients. Other studies

confirmed that patients with COPD experience poor sleep quality with diminished amounts of slow-wave and REM sleep.<sup>[18,19]</sup>

Pathophysiologically sleep has a number of adverse effects on breathing that include negative effects on respiratory control, respiratory muscle function, and lung mechanics.<sup>[10]</sup> These effects produce negligible adverse consequences in normal subjects but may result in profound disturbances of gas exchange in patients with COPD and they may experience profound oxygen desaturation, particularly during REM sleep, in addition to carbon dioxide retention, and the oxygen desaturation encountered during sleep may exceed that during maximum exercise.<sup>[10]</sup> Therefore, people with COPD-OSA have more profound hypoxemia (both day and night) than patients having either condition alone and may be predisposed to pulmonary hypertension.<sup>[9]</sup> Our study confirmed a significant increase in desaturation index with increasing severity of COPD.

Thus, the study findings point toward the important causative risk factors among patients with COPD (e.g., increased cardiovascular events and reduced quality of life) in afflicted individuals increasing morbidity and mortality. Previous studies also showed that the presence of COPD with OSA increases the risk of death seven-fold.<sup>[9]</sup>

Furthermore, our study demonstrated that the majority of subjects were naive to the OSA diagnosis, which may be clinically important. Poor sleep has classically been reported among both COPD and asthma patients. Therefore, many practitioners may attribute sleep difficulties or sleep symptoms to these respiratory diseases rather than investigate for OSA. Patients, too, may have a tendency to under-report poor sleep symptoms (possibly attributing them to underlying lung disease), or there may be a tendency among pulmonologists not to pay close attention to sleep-related symptoms in general.<sup>[20]</sup>

Our study suggests that OSA is common in COPD patients in outpatient pulmonary clinics, and pulmonologists should consider screening for OSA symptoms in these patients.

We acknowledge some limitations of our study. The sample size was modest compared with some prior reports in more general COPD populations. We studied a relatively sick homogeneous cohort of moderate to very severe COPD patients and thus our findings cannot be generalized to all patients with COPD, specifically those having mild disease. Therefore, larger-scale studies are warranted in COPD patients.

## CONCLUSION

To summarize, in this study, we found that OSA is highly prevalent in patients with moderate to very severe COPD. Sleep quality is also poor among this selected group. These patients have greater-than-expected sleep-disordered breathing, which could be an important contributory factor to morbidity and mortality. There was a significant difference in both efficiency and quality of sleep according to the severity of COPD. Thus, sleep disorders as a comorbid condition need to be studied in COPD to reduce mortality and morbidity in these patients.

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