

COPD sleep phenotypes: Genesis of respiratory failure in COPD

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Abstract

The chronic obstructive pulmonary disease (COPD) patients could have respiratory failure during sleep without daytime overt arterial blood gas (ABG) abnormality. We undertook a study first of its kind to attempt in distinguishing the underlying pathophysiological mechanisms. It was a prospective observational study in stable COPD patients. The inclusion criterion was presence of day time $\text{PaO}_2 > 60$ mmHg and $\text{PaCO}_2 < 45$ mmHg. Twenty five out of 110 patients were excluded because of the ABG abnormality. The remaining 85 patients were subjected to overnight pulse oximetry and end-tidal (ET)- CO_2 monitoring. The nocturnal oxygen desaturation was defined as per Fletcher's criteria. The nocturnal hypoventilation was defined as per American academy of sleep medicine (AASM) guidelines. Patients having saw-tooth pattern

on pulse oximetry and/or snoring were subjected to polysomnography. Thirty-eight patients out of 85 (44.8%) had nocturnal gas exchange abnormality in absence of daytime respiratory failure and were identified into 3 different phenotypes: obstructive sleep apnea (OSA), nocturnal hypoventilation and nocturnal oxygen desaturation. The isolated abnormality was seen in 24 patients: 10 patients had OSA, 9 had nocturnal hypoventilation and 5 had nocturnal oxygen desaturation. Overlap of two or more phenotypes was seen in 14 patients. As compared to the nocturnal hypoventilation and desaturation phenotypes, the OSA phenotype had a significantly higher BMI and FEV_1 . The nocturnal hypoventilation and the desaturation phenotypes did not have significant difference in FEV_1 and BMI, but the daytime SpO_2 and PaO_2 differed significantly. Such parameters could help in identifying the three distinct COPD-sleep phenotypes (OSA, nocturnal hypoventilation and nocturnal oxygen desaturation). A phenotype based nocturnal management may help in delaying the process of overt respiratory failure in COPD.

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Ethics approval and consent to participate: The study was carried out after obtaining ethical clearance in adherence to the guidelines of the declaration of Helsinki from the institutional ethical committee (IEC PGIMSR Basai Darapur, New Delhi, No. DM (A) H-19/14/17/IEC/2012-PGIMSR dated 27/11/2017). Written and informed consent was obtained from all the participants.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with a high global morbidity and mortality burden. The high morbidity and mortality are primarily related to chronic respiratory failure. The COPD patients have impaired nocturnal respiratory disturbance prior to developing overt chronic respiratory failure [1,2]. There have been no studies so far which have evaluated nocturnal gas exchange abnormality in absence of overt respiratory failure in COPD with an attempt to distinguish the underlying pathophysiological mechanisms. The COPD patients may develop nocturnal hypoxemia and/or nocturnal hypoventilation. The hypoxia is caused by the ventilation perfusion mismatch and hyperinflation of the lung [3]. The hypoventilation is caused by pump failure because of the impaired central drive and the blunted chemoreceptor response [4]. Furthermore, COPD patients could have co-occurrence of obstructive sleep apnea (OSA) that can also cause nocturnal gas exchange abnormality [5]. So far, no study has segregated these respiratory abnormalities and differentiated the clinical characteristics. We undertook this study to classify COPD patients into distinct sleep phenotypes in order to identify the clinical characteristics for its early recognition and appropriate management.

Aims and objectives

To find out the prevalence of respiratory disturbance at night in absence of daytime respiratory failure and to identify and characterize "COPD sleep phenotypes".

Materials and Methods

This was a prospective observational study, carried out in a tertiary care center. The study was carried out after obtaining ethical clearance in adherence to the guidelines of the declaration of Helsinki from the Institutional Ethical Committee (IEC PGIMSR Basai Darapur, New Delhi, No. DM (A) H-19/14/17/IEC/2012-PGIMSR dated 27/11/2017) and written informed consent from the patients. 110 stable COPD patients coming to the outpatient department from December 2017 to July 2018 were enrolled in the study. As per the department protocol spirometry was performed for all the subjects with Medisoft/Morgan Scientific Spiro Airin® and was interpreted as per the American Thoracic Society (ATS) guidelines [6]. The forced vital capacity (FVC), forced expiratory volume at 1 second (FEV₁), FEV₁/FVC ratio were recorded. The patients were diagnosed COPD according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition [7]. The daytime arterial blood gas (ABG) analysis was performed at the outset. The patients who had abnormal day time ABG i.e., PaO₂ <60 mmHg and PaCO₂ >45 mmHg were excluded from study. Patients with cardiac failure or ejection fraction <50% were also excluded.

The demographic features like age, sex and body mass index (BMI) of remaining 85 patients were noted down. Detailed clinical history and examination findings were noted. All the patients were thoroughly evaluated with respect to their sleep. This included the total duration of sleep, quality of sleep and day time symptoms. Snoring history was elicited from the patient as well as close relatives.

All the patients were subjected to unsupervised overnight pulse oximetry and overnight end tidal CO₂ (ET-CO₂) monitoring in the sleep laboratory. The sleep laboratory was maintained as per the American academy of sleep medicine (AASM) criteria [8]. The pulse oximetry was done using a finger probe. The ET-CO₂ was measured using a nasal cannula. The finger probe and nasal cannula were attached to the polysomnography machine. All the patients were subjected to a second daytime ABG analysis at the start of the study. The values of ABG were correlated with the SpO₂ and the ET-CO₂.

Those patients who gave history of snoring and/or saw tooth pattern on overnight pulse oximetry [9] were subjected to level 1 polysomnography (PSG) as per the AASM guidelines [8]. Philips Respirex Alice 5 Diagnostic Sleep System® was used. The scoring of sleep stage and the respiratory events were done as per the AASM guidelines [8]. 20 patients were subjected to overnight polysomnography based on history of snoring and saw tooth pattern on nocturnal pulse oximetry.

The data was tabulated on MS-Excel® (2010). Statistical analysis for mean, standard deviation, sensitivity and specificity was done using open EPI software® (OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01). The *p*-value was calculated using *t*-test for the continuous variables and Kruskal Wallis test for non-parametric variables.

Definitions

OSA: Five or more scoreable respiratory events (apnea or hypopneas) per hour of sleep along with daytime or nocturnal symptoms or rather fifteen or more scoreable respiratory events (apneas or hypopneas) per hour of sleep [9].

Nocturnal hypoventilation: An increase in the ET-CO₂ to >55

mm Hg for ≥10 min, or an increase in the ET-CO₂ by ≥10 mm Hg above the awake supine value to a value over 50 mm Hg for ≥10 min [10].

Nocturnal oxygen desaturation: A drop in SpO₂ to <90% for >30% of total sleep time without nocturnal ET-CO₂ increase [11].

Results

Among the 110 COPD, 25 patients were found to have deranged day-time blood gases i.e., PaO₂ <60 mmHg and PaCO₂ >45 mmHg. The remaining 85 patients were included in the study. The average age was 59.6±7.69 years. 82/85 patients had COPD secondary to cigarette/bidi smoking and 3 had exposure to environmental smoke. 38/85 (44.8%) patients were found to have nocturnal gas exchange abnormality. These patients could be identified into 3 different phenotypes. These phenotypes were seen either in isolation or as overlap of two or more. The isolated abnormality was seen in 24 patients: 10 patients had OSA, 9 had nocturnal hypoventilation and 5 had nocturnal oxygen desaturation. An overlap of two or more phenotype was seen in 14 patients (Figure 1). 7 patients had nocturnal oxygen desaturation and nocturnal hypoventilation. 2 patients had OSA and nocturnal hypoventilation. Another 2 had OSA and nocturnal oxygen desaturation. Three patients had all 3 disorders simultaneously, i.e., OSA with nocturnal oxygen desaturation and nocturnal hypoventilation. The mean nocturnal SpO₂, mean nocturnal ET-CO₂, mean night-time T90 (% time in bed with SpO₂<90%), mean daytime SpO₂, mean day-time PaO₂, mean FEV₁ (in ml and % predicted), and mean BMI values in the isolated phenotypes are given in Table 1. Table 2 shows the statistical significance of the differences in above parameters in the three COPD-sleep phenotypes and their interpretation.

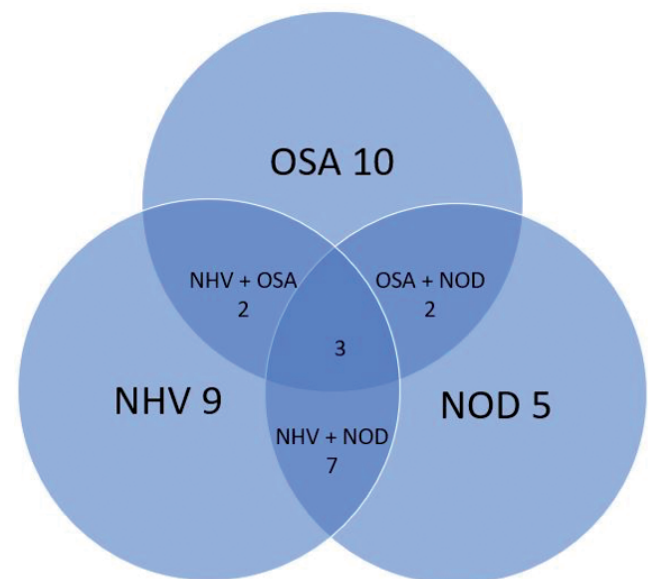


Figure 1. Venn diagram showing COPD sleep phenotypes. OSA, obstructive sleep apnea; NOD, nocturnal oxygen desaturation; NHV, nocturnal hypoventilation.

The nocturnal oxygen desaturation phenotype was characterized by lower nocturnal SpO₂ and higher night time T90. The nocturnal hypoventilation phenotype had higher nocturnal ET-CO₂. The nocturnal oxygen desaturation and OSA phenotypes had significantly lower daytime SpO₂ and PaO₂ compared to nocturnal hypoventilation phenotype. The lung functions and BMI were significantly higher in OSA phenotype compared to other phenotypes. The distinguishing characteristics of the three COPD-sleep phenotypes are shown in Figure 2.

Discussion

McNicholas *et al.* stated in 2013 that sleep is a forgotten dimension in COPD [1], it still remains so. The COPD patients are not routinely evaluated in terms of nocturnal gas exchange abnormality. We found that 44.8 % patients had nocturnal gas exchange abnormality when there was no daytime chronic respiratory failure. The nocturnal hypoxemia was shown in a study by Fletcher *et al.* [12] where

Table 1. Mean nocturnal SpO₂, mean nocturnal ET-CO₂, mean night-time T90 (% TIB), mean day-time SpO₂, mean day-time PaO₂, mean FEV₁ (in ml and % predicted), and mean BMI values in the various COPD-sleep phenotypes.

COPD-sleep phenotype	OSA (10)	Nocturnal hypoventilation (9)	Nocturnal oxygen desaturation (5)
Mean nocturnal SpO ₂	93.2±2.01	95.12±2.47	90.4±2.96
Mean nocturnal ET-CO ₂	42.3±1.82	45.25±1.28	40.6±1.51
Mean night-time T90 (% TIB)	14.4±3.77	3.17±4.82	42.33±16.93
Mean daytime SpO ₂ (%)	93.9±2.5	97.22±0.66	95.4±1.14
Mean daytime PaO ₂ (mmHg)	65.64±4.17	80.65±6.66	71.1±3.73
Mean daytime PaCO ₂ (mmHg)	39.78±2.77	38.37±3.13	37.42±5.16
Mean FEV ₁ (ml)	1609±371.7	1028±301	1180±245.7
Mean FEV ₁ (% predicted)	54.36±15.37	40.22±12.5	38.8±10.6
Mean BMI (kg/m ²)	27.9±3.12	21.04±1.52	21.26±2.6

OSA, obstructive sleep apnea; ET-CO₂, end tidal CO₂; T90, % of time in bed with SpO₂<90%; FEV₁, forced expiratory volume in 1st second; BMI, body mass index.

Table 2. Statistical significance (p-values) of the differences in various parameters in the COPD-sleep phenotypes.

COPD-sleep phenotype	Nocturnal hypoventilation vs nocturnal oxygen desaturation	Nocturnal hypoventilation vs OSA	Nocturnal oxygen desaturation vs OSA	Interpretation
Mean nocturnal SpO ₂	0.007	0.07	0.04	The mean nocturnal SpO ₂ was significantly lower in nocturnal oxygen desaturation compared to nocturnal hypoventilation and OSA
Mean nocturnal ET-CO ₂	0.001	0.001	0.09	The mean nocturnal ET-CO ₂ was significantly higher in nocturnal hypoventilation compared to OSA and nocturnal oxygen desaturation
Mean night-time T90 (% TIB)	0.001	0.001	0.001	The mean night time T90 was significantly higher in nocturnal oxygen desaturation compared to nocturnal hypoventilation and OSA
Mean daytime SpO ₂ (%)	0.002	0.001	0.22	The mean daytime SpO ₂ was significantly lower in nocturnal oxygen desaturation and OSA compared to nocturnal hypoventilation
Mean daytime PaO ₂ (mmHg)	0.01	0.001	0.2	The mean daytime PaO ₂ was significantly lower in nocturnal oxygen desaturation and OSA compared to nocturnal hypoventilation
Mean daytime PaCO ₂ (mmHg)	0.67	0.29	0.24	There was no significant difference in mean daytime PaCO ₂ between the three phenotypes
Mean FEV ₁ (ml)	0.35	0.001	0.03	The mean FEV ₁ (ml) was significantly higher in OSA compared to nocturnal hypoventilation and nocturnal oxygen desaturation
Mean FEV ₁ (% predicted)	0.83	0.001	0.04	The mean FEV ₁ (% predicted) was significantly higher in OSA compared to nocturnal hypoventilation and nocturnal oxygen desaturation
Mean BMI (kg/m ²)	0.84	0.001	0.001	The mean BMI was significantly higher in OSA compared to nocturnal hypoventilation and nocturnal oxygen desaturation

OSA, obstructive sleep apnea; ET-CO₂, end tidal CO₂; T90, % of time in bed with SpO₂<90%; FEV₁, forced expiratory volume in 1st second; BMI, body mass index.

they found that 22% COPD patients having a daytime $\text{PaO}_2 \geq 60$ mmHg, desaturated below a baseline of 90% for $\geq 30\%$ of their sleep time. Some other studies have found that 27-70% of COPD patients with the daytime saturations between 90% and 95% have nocturnal oxygen desaturation [13-16]. But in these studies, the contribution of nocturnal hypoventilation leading to hypoxemia have not been evaluated. We found that though nocturnal hypoxemia was seen in 17 (20%) patients with daytime $\text{PaO}_2 > 60$ mm of Hg, the majority 70% (12/17) had nocturnal hypoventilation.

We also found that 21 (24.7%) patients with normal day time CO_2 had a presence of sleep hypoventilation. There has been no study, which has evaluated nocturnal hypoventilation in presence of normal daytime CO_2 . Though a study by O'Donoghue *et al.* [17] has shown that 43% of stable hypercapnic COPD patients had nocturnal hypoventilation.

Another significant finding in our study was that 17/85 (20%) patient had OSA but, 10 of them did not have either nocturnal hypoventilation or nocturnal oxygen desaturation. The association between COPD and OSA in the same patient, known as overlap syndrome is common. The prevalence of overlap syndrome varies

from 2.9% to 65.9% in COPD patients [18]. Our study clearly brings out the different characteristics of patients having nocturnal gas exchange abnormality, which can be termed as "COPD sleep phenotypes". Differentiating OSA, nocturnal hypoventilation and nocturnal oxygen desaturation into 3 different phenotypes is a novel thing. We compared the three phenotypes among themselves in terms of mean BMI, mean SpO_2 , mean PaO_2 , mean PaCO_2 , and mean FEV_1 . In the patients who had nocturnal oxygen desaturation, their day time PaO_2 and SpO_2 was significantly lower than those who had nocturnal hypoventilation. The BMI and FEV_1 , however were similar. This means that the patients with nocturnal hypoventilation and nocturnal oxygen desaturation may have different ability to respond to hypercapnia at night. Those with nocturnal hypoventilation have poor response to elevation of nocturnal CO_2 compared to nocturnal oxygen desaturation phenotype. The patients who have nocturnal hypoventilation would be unable to maintain their normal daytime CO_2 levels soon. There is evidence regarding the fact that increased CO_2 levels cause blunting of the chemoreceptor response [19]. This blunted response to increased nocturnal CO_2 subsequently causes day time hypercapnia and

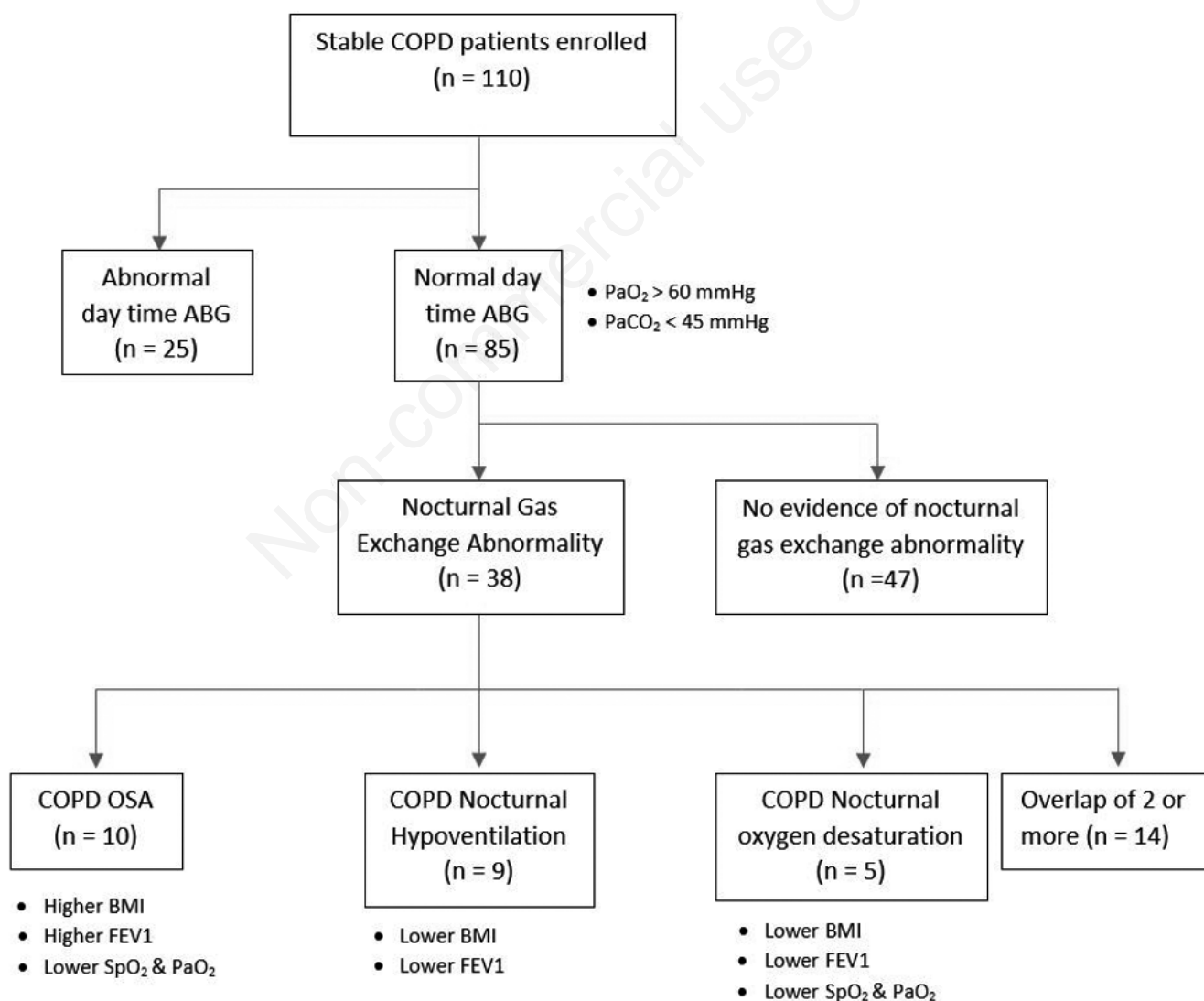


Figure 2. Flow diagram showing classification of COPD phenotypes.

hence overt respiratory failure. This process of daytime hypercapnia can be delayed if they are treated early with bilevel positive airway pressure (BPAP). We found a striking difference in the spirometry and blood gas profile of patients having OSA compared to those having nocturnal oxygen desaturation or nocturnal hypoventilation. The patients with OSA had a statistically significant higher mean BMI and mean FEV₁ as compared to those who had nocturnal hypoventilation or nocturnal oxygen desaturation. This indicates that patients having OSA have a preserved lung functions and higher BMI. In a study by Schreiber *et al.* [20] patients having OSA were found to have less severe airway obstruction which is also seen in our study. The presence of low BMI is protective for OSA [21]. Since 10/17 OSA patients did not have hypoxia or hypoventilation they can be treated with continuous positive airway pressure therapy (CPAP). Those with desaturation persisting on CPAP may require additional oxygen. Those with overlap of hypoventilation will require BPAP if their nocturnal CO₂ did not improve with CPAP alone.

To conclude the COPD patients going into respiratory failure pose a huge burden on health care system. The various clinical characteristics can help in early detection of the different phenotypes of COPD patients and subject them to appropriate nocturnal investigation (O₂ and/or CO₂ monitoring or PSG). These investigations can define the treatment options for different diseases in terms of CPAP, BPAP or nocturnal oxygen therapy [9]. Thus, it is important to perform the sleep evaluation at the time of diagnosis of COPD and then annually. A treatment as per the respective phenotypes is likely to prevent the progression of disease and development of respiratory failure. Further research with case-control study and follow up is needed to see the response to treatment.

Limitation of the study

Our study is the first of its kind and brings out a new perspective, but it has a few shortcomings. The logistics issues prevented us from performing level 1 polysomnography on all the patients. It is an observational study with a small sample size. The patients need to be followed up for seeing the progression of disease.

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