Polysomnography findings of patients with overlap syndrome according to severity of lower airway obstruction

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Background: The concurrence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) is known as overlap syndrome (OS). The obstruction of the upper airway leads to OSA and the obstruction of the lower airway leads to COPD. The aim of this study was to compare polysomnographic findings of patients with OS according to severity of lower airway obstruction. **Materials and Methods:** Seventy-two patients were included in this cross-sectional study. Patients with COPD referred to a sleep clinic with suspicion of OSA were evaluated by polysomnography (PSG). PSG findings were interpreted based on the American Academy of Sleep Association criteria (2012). COPD severity was categorized into four groups based on GOLD criteria using forced expiratory volume in the first second (FEV $_1$). PSG findings also were compared between patients regarding severity of lower airway obstruction (FEV $_1$ \geq 50% and FEV $_1$ \leq 50%. **Results:** Sixty-eight of the patients had OS. Twenty-nine (42.6%) were male. The mean age was 62.3 \pm 6.88 years. Thirty-two (54.4%) of the patients were in GOLD 2. The mean apnea/hypopnea index was 57.41 \pm 36.16. Seventy-two percent of patients had severe OSA. Severe OSA was more prevalent in patients of GOLD 2 and 3 groups compared to the other groups. Among PSG findings, only N2 sleep stage was significantly longer in patients with FEV1 \leq 50% than in patients with FEV $_1$ \leq 50% (61.5 \pm 11.2, 55.3 \pm 13.4, P = 0.039). **Conclusion:** Polysomnographic findings (except N2 stage) are not different in patients with OS with respect to severity of lower airway obstruction.

Key words: Chronic obstructive pulmonary disease, overlap syndrome, polysomnography, sleep apnea

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is often induced by smoking, causes respiratory symptoms such as shortness of breath, cough, and sputum, which can lead to poor quality of life in patients. COPD imposes a significant economic burden on the health system.^[1,2] The mortality rate of COPD is increasing worldwide and will be the third leading cause of death by 2020.^[1] Due to the increasing prevalence of COPD, it is important to control symptoms, improve quality of life, and treat comorbid diseases.^[1]

The concurrence of COPD and OSA is introduced as overlap syndrome (OS).^[3] Obstructive sleep apnea (OSA) is a disease caused by the intermittent and repetitive obstruction of upper airways during sleep. Breathing during sleep is interrupted in OSA. It leads to frequent awakening, periodic hypoxia, and release of mediators such as adrenaline.^[4] In patients with COPD, respiratory muscle strength decreases and upper airway resistance increases due to hypoxia and hypercapnia compared to healthy controls.^[5] Previous studies have reported that 27%–70% of patients with COPD who have the



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mean awake oxygen saturation of over 90% can experience substantial desaturation at night, especially during rapid eye movement (REM) sleep.^[6-8] These events lead to overnight symptoms, poor sleep quality, and systemic complications. ^[9-11] Different prevalence rates have been reported for OS in patients with COPD. Although OS prevalence has been reported as much as 10%,^[12] this was not confirmed in a more recent study.^[13] Almost half of patients with COPD suffer from poor sleep quality,^[14] and their sleep quality has a direct impact on their quality of life.^[15]

Since COPD and OSA are caused by obstruction of lower^[16] and upper airways, respectively, it appears that they affect each other. According to the results of previous studies, the effect of COPD severity can be evaluated on sleep architecture and respiratory events during sleep in OS patients.^[17,18] In this study, we evaluated the PSG findings of OS patients based on the severity of lower airway obstruction.

MATERIALS AND METHODS

This cross-sectional study was conducted on patients with COPD referred to a sleep clinic from March 2016 to September 2017. The ethics committee of the Qazvin University of Medical Sciences approved the study protocol. The patients gave written informed consent form.

The inclusion criterion was lack of disease exacerbation for at least 1 month. Patients with comorbid diseases were excluded from the study. Demographics and sleep data were collected for all the patients. Among the clinical symptoms, snoring, morning headache, and witnessed apnea were investigated. The Epworth Sleepiness Scale (ESS) was used to evaluate sleepiness during the day. ESS is a self-administered questionnaire with eight questions to measure daytime sleepiness. The questionnaire has a four-point Likert response format (0–3), and the total score ranges from 0 to 24, with a higher ESS score showing a person's higher average sleep propensity in daily life. The ESS score ≥11 indicates excessive daytime sleepiness and high risk for OSA. [19,20] We used a valid Persian version of the questionnaire. [21]

Polysomnography (PSG) was performed and recorded on a full PSG system (Respironics, USA). PSG findings were manually scored and interpreted by a sleep subspecialist based on the American Academy of Sleep Association (AASM, 2012) criteria. [22] PSG included electroencephalography, electrooculography, chin electromyography, leg electromyography, nasal/oral airflow, plethysmography for respiratory effort (chest and abdomen), arterial oxygen saturation, body position, and audio–video recording of sleep. A standard atmosphere

with proper temperature and a suitable bed was provided in the test room. The patients attended the sleep clinic 3 h before bedtime. Gold electrodes were connected to them by an experienced nurse according to the AASM latest recommendation. The patients went to bed in their habitual sleep time. After the lights were turned off, the test was started, lasting for an average of 400 min (7 h) for each case. We considered the following sleep measures: time in bed (time in minutes, between Light Off and Sleep End); total sleep time (the sum, in minutes, of all sleep epochs between Sleep Onset and Sleep End); sleep-onset latency (the interval, in minutes, between Light Off and Sleep Start); wake after sleep onset (the sum, in minutes, of all wake epochs between Sleep Onset and Sleep End); and sleep efficiency percentage (the ratio of the total sleep time to time in bed multiplied by 100). Sleep is a cyclical process. Typically, a sleeper experiences five main sleep stages during their sleep time: wake, non-REM (NREM) (including N1, N2, and N3), and REM. Oxygen saturation is the percentage of fully saturated hemoglobin molecules with oxygen and is considered normal in ≥95%. The total number and frequency of arousals and awakenings per hour of sleep is referred to as arousal index. Apnea was defined as ≥90% reduction in nasal airflow compared to the baseline for at least 10 s. It was considered as obstructive apnea (OA) if respiratory effort was found in chest and abdomen. There was no respiratory effort in central apnea (CA). Decreased oronasal airflow over 30% for at least 10 s, with arterial oxygen loss ≥4% and/or arousal or awakening, was considered as hypopnea. The apnea-hypopnea index (AHI) was calculated as the number of apneic and hyponic events per hour of sleep. If the patient experienced both OA and CA, it is referred to as mixed apnea. [17] Patients with AHI above 5 were considered as OSA patients. The OSA severity was divided into three categories (AHI 5-14: mild, AHI 15–29: moderate, and AHI≥30: severe). Since all the patients were known to have COPD, those with an AHI >5 were included in the study with the definition of OS.

A two-stage spirometry was performed with a Jaeger spirometry device (Jaeger Ltd Hochberg, Germany) and interpreted by a pulmonologist based on the ATS guideline. According to the GOLD criteria, [1] the patients were divided into four groups as Gold 1: $\text{FEV}_1 \ge 80\%$, Gold 2: $50\% \le \text{FEV}_1 < 80\%$, GOLD 3: $35\% \le \text{FEV}_1 < 50\%$, and GOLD 4: $\text{FEV}_1 < 35\%$. Since the number of patients in the groups 1 and 4 was low, the patients were divided into two groups to compare sleep characteristics based on airway obstruction: patients with $\text{FEV}_1 \ge 50\%$ and those with $\text{FEV}_1 < 50\%$.

At first, the q-q plot and Kolmogorov–Smirnov test were carried out for data normality test, which confirmed data normality. Moreover, *t*-test and the Pearson correlation test were used for quantitative variables whereas the Chi-square

test was used for qualitative variables. Data were analyzed using SPSS software version 20 (IBM Corp., Armonk, NY, USA). P < 0.05 was considered as statistically significant.

RESULTS

Patient characteristics

Of the eighty-two patients referred to the clinic, 10 patients were excluded due to having comorbid disease. Of the 72 patients who were evaluated, 68 (95%) had OS. 29 (42.4%) of the patients with OS were male. The mean age was 62.3 ± 6.88 years and mean body mass index (BMI) was 33.6 ± 6.8 kg/m². Among the clinical signs, snoring was the most common sign (86.8%), followed by witnessed apnea (67.6%) and morning headache (60.3%). The mean FEV₁ was 56.99 ± 16.93 %. Thirty-two patients (54.4%) were in Gold 2. The demographic characteristics and findings of spirometry are presented in Table 1. There was no significant difference between the two groups (FEV₁ below and above 50%) in terms of age, sex, BMI, clinical symptoms, smoking rate, and ESS score.

Polysomnography characteristics

The mean AHI was 57.41 \pm 36.16. Seventy-two percent of the patients had an AHI above 30. Severe OSA was more prevalent in GOLD 2 and 3 groups compared to the other groups [Figure 1]. There was no significant difference in AHI between the groups with FEV₁ below and above 50%. Among the studied clinical symptoms, only witnessed apnea had a significant association with AHI levels (P < 0.05).

Comparison of the PSG findings in patients with OS by FEV, category is shown in Table 2. In the sleep architecture,

Table 1: Characteristics of the study participants based on forced expiratory volume in 1 s category

Variables	Total	FEV,	FEV,	P
	(<i>n</i> =68)	<50%	≥50%	
Age (years), mean±SD	62.3±6.88	61±12.01	63.1±12.1	0.484
Gender (male), n (%)	29 (42.6)	9 (36)	20 (46.5)	0.398
BMI (kg/m²)	33.6±6.8	35.2±6.18	32.7±17.7	0.154
Smoking, n (%)	31 (48.4)	11 (47.8)	20 (48.8)	0.942
ESS score*, mean±SD	12.51±5.10	11.9±5.1	12.8±5.1	0.502
Witnessed apnea, n (%)	46 (67.6)	19 (76)	27 (62.8)	0.262
Snoring, n (%)	59 (86.8)	21 (84)	38 (88.4)	0.608
Morning headache, n (%)	41 (60.3)	16 (66.7)	25 (59.5)	0.565
FEV ₁ , mean±SD	56.99±16.9	39.04±8.9	67.4±10.4	< 0.001
GOLD, n (%)				
1	6 (8.8)	-	6 (14)	< 0.001
2	37 (54.4)	-	37 (86)	
3	19 (27.9)	19 (76)	-	
4	6 (8.8)	6 (24)	-	

BMI=Body mass index; ESS=Epworth sleepiness scale; FEV_1 =Forced expiratory volume in the 1 s; SD=Standard deviation; GOLD=Global initiative for chronic obstructive lung disease

the maximum sleep time was related to the non-REM sleep (239.50 \pm 82.04 min), and N2 stage had the maximum percentage of total sleep time (58.52 \pm 12.65%). The average oxygen saturation of the patients during sleep was low (83.60 \pm 8.32%). Only N2 sleep stage was significantly longer in patients with FEV₁ <50% than in patients with FEV₁ <50% (P = 0.039).

PSG findings were not significantly different between men and women with OS. Based on the PSG findings, smoker and nonsmoker patients were only different in terms of sleep-onset latency. The average sleep-onset latency in the smokers was higher than that in the nonsmokers (P = 0.03).

The findings related to the correlation of AHI with age and PSG are presented in Table 3. AHI had significantly negative correlation with factors of age, REM sleep, mean arterial oxygen saturation, minimum oxygen saturation, total sleep time, and arousal index so that with increasing each factor, AHI decreased. Among the studied clinical symptoms, only witnessed apnea had a significant association with AHI (P < 0.05).

DISCUSSION

Ninety-five percent of the COPD patients referred for PSG had OS in the present study. We obtained four major findings in this study: (1) there was no significant difference in AHI between the groups with FEV_1 below and above 50%; (2) according to the PSG findings, only N2 sleep stage in patients with FEV_1 <50% was significantly higher compared to the other groups; (3) AHI in the OS patients had negative correlation with age, REM sleep, arterial oxygen saturation, and total sleep time; and (4) in the OS patients, the mean arterial oxygen saturation and minimum oxygen saturation during sleep were not related to FEV_1 . Patients in the groups did not differ statistically in terms of sex, age, BMI, and smoking. Therefore, we expect that if there is a

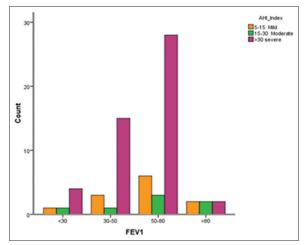


Figure 1: Obstructive sleep apnea severity at different stages of GOLD

Table 2: Comparison of the polysomnographic findings in patients with overlap syndrome based on forced expiratory volume in the 1 s category

PSG index	Total	FEV ₁ <50%	FEV ₁ ≥50%	Pa
TST (min)	409.58±77.18	399.8±81.6	419.9±71.9	0.285
NREM (%)	95.03±4.96	95.8±4.2	94.1±5.6	0.139
N1	23.87±10.50	21.8±8.2	26.1±12.2	0.097
N2	58.52±12.65	61.5±11.2	55.3±13.4	0.039
N3	12.38±7.41	12.2±7.1	12.5±7.8	0.873
REM (%)	4.97±4.96	4.21±4.1	5.8±5.5	0.139
OA (/h)	139.62±127.51	142.5±131.2	136.5±125.3	0.848
CA (/h), median	34.3	36.6	32.2	0.334
MA (/h), median	35.1	36.3	33.5	0.407
WASO	277.8±88.3	270.11±84.5	286.1±92.7	0.462
SE (%)	56.67±16.11	59.6±16.3	59.7±16.1	0.982
SOL (min), median	22.5	38.03	30.7	0.130
Al (/h)	12.62±10.35	13.5±12.3	11.5±7.6	0.452
SO ₂ (%)	83.60±8.32	82.7±8.6	84.4±8	0.394
Min SO ₂ (%)	59.85±19.12	57.8±20.03	61.9±18.2	0.386
AHI (/h)	57.41±36.16	62.1±36.3	52.5±35.9	0.279
AHI, n (%)				
Mild	12 (17.6)	4 (16)	8 (18.6)	0.841
Moderate	7 (10.3)	2 (8)	5 (11.6)	
Severe	49 (72.1)	19 (76)	30 (69.8)	

"Significant at level of 0.05 using t-test. Data are presented as mean±SD. PSG=Polysomnography; TST=Total sleep time; NREM=Nonrapid eyes movement; REM=Rapid eyes movement; OA=Obstructive apnea; CA=Central apnea; MA=Mixed apnea; WASO=Waking after sleep onset; SE=Sleep efficiency; SOL=Sleep-onset latency; Al=Arousal index; SO₂=Mean arterial oxygen saturation; Min SO₂=Minimum Oxygen saturation; AHI=Apnea-hypopnea index, FEV₁=Forced expiratory volume in the 1 s

Table 3: The correlation between apnea-hypopnea index and polysomnography findings

Variables	r	P
REM (%)	-0.383	0.001
SaO ₂ (%) (mean)	-0.285	0.001
Min SO ₂ (%)	-0.302	0.012
TST (min)	-0.241	0.047
Al	-0.388	0.001

TST=Total sleep time; REM=Rapid eyes movement; SaO_2 =Arterial oxygen saturation; Min SO_2 =Minimum Oxygen saturation; Al=Arousal index

difference between the groups in terms of the PSG findings, it is due to the difference in FEV,.

The results of studies on the association between the severity of airway obstruction and occurrence of sleep apnea are different. In a study by Sharma *et al.*, it was shown that in patients with obstructive pulmonary disease (Asthma and COPD), FEV₁ was not a prognostic factor in the possibility of sleep apnea, and also, the severity of the obstruction was not a reason for the higher probability of sleep apnea. [17] However, Krachman *et al.* showed that air trapping rates in COPD patients had an inverse relationship with sleep apnea, [23] and Biselli *et al.* demonstrated that hyperinflation in COPD could result in more stable upper airway. [24] Different results may be due to various mechanisms involved in

the development of sleep apnea in addition to the usual predisposing factors in COPD.^[25] In COPD, decreased sleep duration, malnutrition, smoking, and increased central respiratory drive potentials due to hypercapnia and hypoxia are involved in the development of sleep apnea in addition to the usual predisposing factors.^[25] In a study by He *et al.*, it was shown that reducing night ventilation was due to increased airway resistance in OS patients, but due to reduced respiratory drive in COPD patients.^[25] COPD is linked with skeletal muscle myopathy, and it may affect upper airway dilator muscles or reflexes.^[7]

It is still unclear whether any pathophysiological link exists between OSA and severe COPD. Bednarek *et al.* in a study on MONICA-II observed sleep-disordered breathing in 11% of individuals with OSA. [13] It has been reported that a patient with either COPD or OSA has a >10% risk of having the other disorder. [8] Thus, in a patient with either COPD or OSA, it would be helpful to screen for the other, based on clinical history, physical examination, and review of systems. [8]

In the present study, neither AHI and sleep characteristics nor the mean arterial oxygen saturation and minimum oxygen saturation during sleep were related to FEV, in the OS patients. In Sharma et al.'s study, similar to the present study, there was no correlation between the level of oxygen overnight and FEV₁ in OS patients.^[17] In a previous study, the level of oxygen overnight in patients with OS was lower than that in patients with COPD or OSA alone. [26] However, a recent study on 524 patients with OSA did not follow this result.[27] While it was expected that more obstruction in COPD patients would produce greater oxygen desaturation, nocturnal hypoxemia was not exaggerated in individuals with FEV₁ < 50%, in our study. One of the possible reasons for this discrepancy might be that most of our patients had severe OSA, and that upper airway obstruction had more impact on the overnight oxygen desaturation compared to lower airway obstruction.

In the present study, OSA and COPD were not directly associated with each other in terms of severity, which is similar to Choi *et al.*'s study.^[15] Other factors such as obesity may be more important. The prevalence of obesity is lower in COPD patients than in patients with moderate to severe OSA and also is variable between different categories of COPD severity. Using systemic glucocorticoids can lead to weight gain and therefore increased risk of OSA. On the other hand, dynamic hyperinflation and nocturnal oxygenation may be improved by glucocorticoids in these patients.^[28]

In our study, AHI had negative significant correlation with total sleep time, arousal index, and oxygen saturation. Some studies showed that age, gender, smoking history, COPD

GOLD stage, dyspnea, comorbidities, and FEV₁ (% predicted) were correlated with AHI or arousal index in patients with COPD.^[29-31] In the present study, AHI had also negative correlation with age. This finding was previously found by some studies.^[32-34] In Bixler *et al.*'s study, OSA severity decreased with age but was not related to BMI.^[32] In a study conducted to compare the mechanisms of apnea in young people and the elderly, AHI was lower in the elderly, but duration of events was longer.^[34] Most of respiratory events recorded in the present study were OA. Upper airway obstruction due to anatomical collapsibility has a greater role in older adults whereas ventilatory chemoreceptors play a more prominent role in younger patients with OSA.^[34]

Among sleep complaints and sleep architecture, only N2 was different between the two groups in the present study. In a multicenter study recently performed on 377 patients with COPD, the rate of airway obstruction was not related to sleep quality.[35] COPD patients have poor sleep quality and increased sleep fragmentation. Although over 50% of patients with COPD report sleep symptoms, these complaints are often underreported by patients. [28] In a previous study, ventilation in stage 2 sleep was lower than wakefulness in patients with COPD alone and with OS. In patients with OS, neural respiratory drive was similar between NREM sleep and wakefulness.[25] Neural respiratory drive increased from wakefulness to stage 2 sleep in patients with OSA while decreased in patients with COPD alone. It can be suggested that mild to moderate OSA can somewhat compensate the reduced neural respiratory drive of COPD.[25] In Shiina et al.'s study, total sleep time, sleep efficiency, and N3/N4 sleep stages were statistically lower in patients with OS than in patients with OSA alone.[27] Nevertheless, we did not find any study comparing different stages of sleep in different levels of GOLD, and further investigation in this area is required.

Limitation

We had two limitations: (1) our patients were clinically at high risk for OSA and thus they were not good representatives of total OS population and (2) most of our patients were in GOLD 2 and 3, and insufficient patients in GOLD 1 and 4 may have affected the outcome.

CONCLUSION

Different characteristics of sleep in the patients with OS (except sleep stages) were not affected by decrease in FEV₁. FEV₁ alone is not an appropriate indicator for referring patients with COPD to sleep laboratories. Clinicians should be aware of the high prevalence of sleep abnormalities in COPD. We recommend PSG studies on patients with COPD to evaluate OSA regardless of disease severity. More

research is definitely needed to determine causes of OSA in patients with COPD.

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Conflicts of interest

There are no conflicts of interest.

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