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Research Article

The Possibility of Overlap Syndrome in Advanced Stage COPD Patients

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Abstract

Objective: We studied the frequency of obstructive sleep apnea syndrome (OSAS) in patients with COPD and the relationship between COPD stage and OSAS frequency to identify OSAS risk group among patients with COPD.

Methods: A portable sleep monitoring device was used regardless of presence of OSAS symptoms in COPD inpatients. Spirometry, arterial blood gas analysis, Epworth sleepiness scale (ESS) scores were compared between the group with overlap syndrome (OS) and COPD alone.

Results: OSAS frequency was 42% in 50 patients. No difference was observed between the group consisting of GOLD grade B and C patients and the group of grade D patients in terms of OSAS frequency. NREM3, min. oxygen saturation and average oxygen saturation levels were found to be significantly lower while mass index, ESS scores, FEV1 and FEV1/FVC were significantly higher in the OS group compared with single COPD group.

Conclusion: OSAS frequency was found to be relatively higher in COPD patients than the overall population. Moreover, OS patients had deeper nocturnal oxygen desaturation, higher ESS scores and daytime sleepiness levels than the patients with COPD alone group. The possibility of OSAS comorbidity should be considered particularly in end-stage COPD patients. Besides the other cardinal symptoms of OSAS, patients with excessive daytime sleepiness must be examined in this respect.

Keywords: *Chronic Obstructive Pulmonary Disease; Obstructive Sleep Apnea Syndrome; Overlap Syndrome; Watch-PAT*

Introduction

Obstructive sleep apnea syndrome (OSAS) is a frequent disease in the society. Chronic obstructive pulmonary disease (COPD) is one of the lung diseases with a frequent incidence and high mortality. Since both diseases are quite common, it is possible that these diseases accompany each other in some individuals. The term "Overlap Syndrome" (OS) came out to address patients who have findings of both COPD and OSAS [1,2]. When the two diseases occur together, the oximetry tracing conducted during polysomnography (PSG) shows a different desaturation tracing. Particularly in the REM (rapid eye movements) period, the "saw-tooth desaturation pattern" defining an intermittent and short term desaturation is accompanied by a deeper and longer desaturation pattern called "concavity in tracing" [1,3,4].

The presence of nocturnal oxygen desaturation is a well-known fact in COPD patients; however, hypoxemia is more explicit in OS and leads to more serious cardiopulmonary function failures. What is more, even in patients with mild or moderate levels of airway obstruction and mild hypoxemia, coexistence of OSAS refers to poor prognosis and the disease shows a rapid progression. Especially in COPD patients with diurnal hypercapnia and polycythemia findings and who have exacerbations requiring frequent hospitalization, findings of OSAS must be questioned. If major symptoms of OSAS are present, a PSG is a must because individuals having both diseases together are more likely to have pulmonary hypertension, right-sided heart failure and carbon dioxide increase [5-7].

It has been revealed that the destruction in pulmonary hemodynamics and blood gas is much higher in the coexistence of COPD and OSAS in comparison with the presence of only one of these diseases. Cardiovascular mortality and morbidity are increased in OSAS and especially in its coexistence with COPD, this increase occurs at higher levels [2,8,9].

As an alternative to the polysomnography which is carried out under laboratory conditions and require technicians and equipment, the necessity for portable devices has come out which are more practical, require less effort and cost, can be used without technician attendance at home or any hospital room. The Watch-PAT (peripheral arterial tonometry) we used in our study is a portable monitoring device and detects respiratory movements based on peripheral arterial tonus using an algorithm automatically. It can measure peripheral arterial tone, oximetry, snoring and body position [10-12].

This technology uses a finger-mounted sensor that eliminates venous pulsations and measures continuous arterial volume changes. Changes in the arterial volume are regulated by alpha adrenergic innervation and reflect sympathetic activity. Episodes of apnea and hypopnea may result in arousals, sympathetic nervous system activation and therefore peripheral vasoconstriction, which in turn cause PAT signal to weaken. Thus, when apneas are detected, hypopneas may be detected as well with the 4% falls in oxygen saturation. The period in which the size of PAT signals decrease free from respiratory events and REM specific beats occur is determined as the REM period [10-12].

Aim of the Study

The aim of the present study is to determine OSAS frequency in COPD patients receiving hospital treatment due to acute exacerbation, examine the relationship between COPD severity classes and OSAS frequency and to identify the OSAS risk group among COPD patients.

Methods

Patient Selection

The study was carried out between September 2013 and December 2014 by conducting a sleep test with the portable sleep monitoring device Watch-PAT 200 on patients who were hospitalized with acute COPD exacerbation, treated and planned for discharge, regardless of whether they had symptoms and findings of OSAS or not.

Diagnosis and classification of COPD was performed according to the GOLD diagnosis and staging criteria. Diagnosis and stating of OSAS, on the other hand, was based on International Classification of Sleep Disorders-3 (ICSD-3) [13]. Patients whose sleep activity was under 50% during sleep records and those who had previously been diagnosed with OSAS were excluded from the study.

Permission was taken from the ethics committee of the hospital prior to the study. Each patient was informed about the study and their informed consent was obtained.

Watch-PAT

Sleep monitoring was performed with Watch-PAT 200 (Itamar Medical Ltd. Israel) device on the patient's bed. Watch-PAT was conducted on patients whose exacerbation treatments were completed during their stay in the chest diseases clinic prior to discharge. The findings were evaluated and scored by a specialist researched trained in this field.

Other measurements

Pulmonary function test measurements were taken using ZAN 100, Flow handy, Germany device at standing position with nose clips. Until three acceptable tests were obtained, minimum three and maximum five performances were applied. The highest forced vital capacity and the first second forced expiratory volume were recorded. Changes in ESS subjective daily sleepiness were employed in the study and an ESS score over 10 was accepted as excessive daytime sleepiness [14].

Statistical analysis

Data distribution was evaluated with Kolmogorov-Smirnov test. Normally distributed data were tested with T-test for difference. On the other hand, Mann Whitney U test was employed for the data that did not follow a normal distribution. $P < 0,05$ was accepted as the value of significance.

Results

A total of 50 COPD patients, 41 male and 6 female, participated in the present study and 21 (43%) of the patients were found to have OSAS. No difference was found between the OSAS and non-OSAS groups in terms of age and amount of smoking; their BMIs were different (Table 1).

	All patients	Overlap syndrome	COPD	p
Number of patients (n)	50	21	29	-
Smoking (package/year)	39,6 ± 27,15	35 ± 26,6	42,95 ± 27,5	0,445
Age (Year)	64,84 ± 9,73	66,71 ± 10,24	63,48 ± 9,29	0,292
Body mass index (kg/m^2)	26,5 ± 9,38	32,9 ± 10,83	21,86 ± 4,16	< 0,001

Table 1: *Comparisons in terms of demographic data and body mass indices.*
COPD: Chronic Obstructive Pulmonary Disease.

In the COPD severity grades of the patients according to GOLD, 43 patients were in GOLD grade D, 6 were grade C and 1 patient was in grade B and none of the patients were in grade A. Due to the low number of patients and in order to allow for comparisons, grades B and C were brought together and no significant difference was found between this group and grade D group in terms of OSAS frequency (42,85% and 41,86% respectively) ($p < 0.05$). A statistically significant difference was found between OSAS and non-OSAS groups in terms of FEV1 and FEV1/FVC values (Table 2).

	All patients	Overlap syndrome	COPD	p
FEV1 (%)	28,52 ± 13,36	33,86 ± 12,95	24,66 ± 12,48	0,015
FEV1/FVC (%)	51,86 ± 9,5	57,62 ± 8,06	47,69 ± 8,3	< 0,001
PaO_2 (mmHg)	93,18 ± 114,24	78,1 ± 30,64	104,1 ± 147,9	0,36
$PaCO_2$ (mmHg)	65,1 ± 12,63	61,67 ± 11,75	67,59 ± 12,86	0,40

Table 2: *Comparisons of spirometry and arterial blood gas parameters.*
FEV1: First Second Forced Expiratory Volume; FVC: Forced Vital Capacity; PaO_2: Partial Arterial Oxygen Pressure; $PaCO_2$: Partial Arterial Carbon Dioxide Pressure; COPD: Chronic Obstructive Pulmonary Disease.

In patients with overlap syndrome, total sleep NREM3 (the percentage ratio of Non REM 3 phase duration within the whole sleep duration), min. O_2sat, average O_2sat percentages and oxyhemoglobin desaturation index (ODI) are lower in comparison with non-OSAS COPD patients. Their ESS score is higher (Table 3).

	All patients	Overlap syndrome	COPD	p
NREM3 (%)	14,18 ± 12,32	9,65 ± 7,24	17,37 ± 14,17	0,035
ODI (n/hours)	8,17 ± 18,31	19,37 ± 24,38	0,066 ± 0,020	< 0,001
min. O_2 sat. (%)	82,10 ± 12,44	72,76 ± 12,66	88,86 ± 6,60	< 0,001
avr. O_2 sat. (%)	91,78 ± 5,41	88,24 ± 5,77	94,34 ± 3,36	< 0,001
ESS score	9,75 ± 3,70	13,33 ± 2,08	7,14 ± 2.04	< 0,001

Table 3: *Sleep related data and Epworth Sleepiness Scale Scores.*

**NREM3(%): percentage ration of Non REM 3 phase within the whole sleep duration.*

**ODI: Oxyhemoglobin desaturation index*

**min. O_2 sat. (%): minimum oxygen saturation recorded during sleep.*

**avr. O_2 sat. (%): Average oxygen saturation recorded during sleep.*

**ESS: Epworth Sleepiness Score.*

COPD: Chronic Obstructive Pulmonary Disease.

Discussion

In our study, of the 50 inpatients in the clinic, 21 (42%) were found to have OSAS, which is more frequent compared to the overall population. Moreover, it was found that OSAS patients had higher Epworth sleepiness scale scores, BMI, FEV1 and FEV1/FVC levels than the non-OSAS COPD patients. However, no difference was found between the OSAS frequencies of the two COPD groups in terms of GOLD grades.

Varying ratios have been reported concerning the frequency of OSAS in COPD patients. Some studies claim that OSAS frequency among mild COPD patients is not higher than that in the overall population [2,15]. Sanders., *et al*. [16] examined 5954 individuals 1132 of whom had COPD (a majority of them being in the mild group) and found the frequency of OSAS in the mild COPD group to be similar to the non-COPD group [17]. The fact that the COPD group included patients with mild COPD is likely to have affected these results. A great majority of our patients were end-stage patients. 86% of the patients were GOLD grade D and 12% were GOLD grade C. 80% of them were receiving continuous oxygen treatment. We consider that the OSAS ratio found in the present study (42%), which may be accepted as high according to some studies, resulted from the fact that most patients in the study had end-stage COPD. In addition, considering that advanced age and the male gender are among the acknowledged risk factors for OSAS, the fact that most patients in our study were males and the mean age was 64,8 years may have influenced this result.

In a recent study which is similar to ours in terms of patient profile as it included end-stage COPD patients given significant amounts of oxygen, 23 (52%) out of 44 COPD patients also had OSAS and it was highlighted that OSAS prevalence was high among end-stage COPD patients [18].

In our study, of the 50 patients, 43 were of GOLD grade D, 6 were GOLD C and 1 was GOLD B while no patient was of GOLD grade A. Since the number of patients was low and in order to allow for comparisons, a group was made up of the patients in GOLD grades B and C. In the comparison of this group with the GOLD D group in terms of OSAS frequency, no significant difference was found. We think this

result was influenced by the fact that the patients other than grade D were mainly of grade C and that the number of early stage COPD patients was not sufficient.

Lacedonia., *et al*. [19] studied the data of 720 patients; 65% had OSAS only, 23% had OS and 12% had COPD alone. They found FEV1 and FEV1/FVC values to be significantly lower in the COPD group than those in the OS group. The evaluation of two groups included in our study in terms of COPD severity according to GOLD guides, both groups were determined to be at a similar severity level. Nevertheless, FEV1 and FEV1/FVC values were found to be significantly higher in the OS group than those in COPD group. This may have resulted from the fact that OS patients carry the load of two comorbidities, go under more medical treatment activity and apply to hospital m more frequently. Yet this assumption still needs to be confirmed. Another question that comes up at this point is whether OS patients have more frequent exacerbations or not. In addition, the fact that OSAS patients were more overweight than non-OSAS patients may have influenced FEV1/FVC by causing a certain degree of restrictive pattern. We found no difference in terms of daytime partial arterial oxygen and carbon dioxide pressures (PaO_2, $PaCO_2$) between the OSAS and non-OSAS COPD groups. Lacedonia., *et al*. [19] found no difference for daytime PaO_2 and $PaCO_2$ between OS and COPD groups; however, the comparison of these values of OSAS group with the values of COPD alone and OS groups showed that PaO_2 values were significantly higher whereas $PaCO_2$ values were significantly lower.

Sleep related hypoxemia observed in COPD patients has been revealed to be often associated with vigilance oxyhemoglobin desaturation and hypercapnia. Nocturnal desaturation has been observed in patients whose daytime oxyhemoglobin saturation is lower than 93% while none of the patients having oxyhemoglobin saturation of over 95% have been observed to have nocturnal desaturation. This relationship (between daytime oxygen levels and nocturnal desaturation) was not examined in our study, since daytime oxygen levels were not used to this end in 80% of the patients as they received continuous oxygen treatment and due to the quite low number of patients who did received no oxygen treatment. A high correlation has been reported between nocturnal hypoxemia and diurnal PaCO2 values of over 50 mmHg [2,20]. As some of the patients were chronically hypercapnic and received BIPAP treatment in the day, this correlation could not be examined in our study.

In the evaluations of the sleep data in our study, significant differences were determined between OS and single COPD groups in terms of NREM3, ODI, minutes O_2sat and average O_2sat parameters. Moreover, our study found significant difference between OS and single COPD groups in terms of ESS, an indicator of daytime sleepiness level, as well. There are studies showing that the negative effects on the amount and quality of sleep and daytime sleepiness levels are much greater in the coexistence of OSAS and COPD than the individual effects of these two diseases. Disturbance in the sleep quality and nocturnal oxygen desaturations are greater in comparison with patients who have only one of these diseases. FEV1/FVC under 65% has been found to be associated with a greater risk of nocturnal desaturation [16]. Even if both diseases are at mild stages, in the coexistence of COPD and OSAS, it is emphasized that nocturnal oxygen desaturation is more apparent; OS implies poor prognosis and that COPD patients who have fast progression clinically must be evaluated for OSAS [1,9].

In the evaluation of ESS values which indicate daytime sleepiness levels, the values of the OS are significantly higher than those of the COPD group. Likewise, it has been reported in the literature that OS patients have higher ESS scores than COPD groups [19].

The limitations of our study include the fact that it involved mostly end-stage patients since it was conducted on patients treated in hospital; the correlation between daytime blood gas values and nocturnal desaturation could not be examined as some patients used oxygen and/or BIPAP and that the number of patients was limited.

The possibility of a patient who has any one of the COPD or OSAS diagnoses to have the other one as well is over 10%. Therefore, in a patient having one of these diseases, the possibility of having the one as well must be kept in mind [21]. It has been revealed that besides the increased morbidity and mortality, quality of life is also significantly lower in OS patients than COPD patients. OSAS accompanying COPD is known to be associated with an increased mortality by increasing exacerbations in COPD and accelerating the loss in pulmonary functions [22].

Conclusion

OSAS frequency in end-stage COPD patients was found to be higher in the overall population and in mild COPD patients in comparison with previous studies. FEV1 and FEV1/FVC values are high in Overlap Syndrome patients compared with those COPD alone. In patients with Overlap Syndrome, nocturnal oxyhemoglobin desaturation, disturbances in the overall sleep structure and quality and ESS scores are higher than those of single COPD patients in the same stage. For these reasons, the possibility of coexistence of these two diseases, which possess many common risk factors, should be considered particularly in end-stage COPD patients and COPD patients having obvious excessive daytime sleepiness should be evaluated for OSAS.

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Volume 8 Issue 12 December 2019