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# Obstructive sleep apnea is prevalent in patients with pulmonary embolism

## Abstract

**Purpose:** Obstructive sleep apnea (OSA) syndrome causes systemic consequences due to hypoxia and endothelial dysfunction. The purpose of this study was to investigate whether OSA is more common in subjects with pulmonary embolism (PE).

**Methods:** This prospective study was conducted between November 2009 and December 2010 in the Department of Pulmonary Medicine of Gaziantep University. Twenty-eight patients with PE were included in the study group along with forty-five subjects with OSA as the control group. The control group was selected from among subjects who were referred to the sleep clinic. Full night polysomnography was performed for each subject.

**Results:** Mean apnea-hypopnea index (AHI) was found to be higher in the PE group compared with the control group ( $p=0.010$ ). Severe obstructive sleep apnea (OSA) was detected in 21.4% of the PE group but in no controls ( $p=0.015$ ). Sleep stage 2 was longer in control group whereas stage 1 and rapid eye movement (REM) sleep was longer in the PE group. Snoring and excessive daytime sleepiness were more common in the control group compared with the study group. AHI severity and thrombus localization were not significantly different between the groups ( $p=0.350$ ).

**Conclusion:** Our study findings suggest that OSA is more prevalent and severe in subjects with PE compared with control subjects. The clinical significance of less prevalent excessive daytime sleepiness and snoring in subjects with PE should be evaluated in further studies.

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TABLE 1. Demographic and clinic characteristics of the study population

	PE group	Control group	P
Male n (%)	14 (50)	30 (67)	0.115
Age (mean±SD)	54.93±17.2	50.42±12.7	0.243
BMI (mean±SD)	30.5±6.6	28.7±6.5	0.274
Waist circumference (cm) (mean±SD)	106.9±12.5	104.0±13.1	0.481
Neck circumference (cm) (mean±SD)	39.68±3.6	40.12±3.2	0.701
Snoring, n (%)	17 (60.7)	37 (82.2)	0.042
EDS, n (%)	12 (42.9)	0 (0)	<0.001
Witnessed apnea, n (%)	3 (10)	0 (0)	0.083

EDS: Excessive daytime sleepiness

The main mechanism in the thromboembolic process is hypercoagulability due to defects in anticoagulant and fibrinolytic systems [1]. It has been suggested that hypercoagulability in subjects with obstructive sleep apnea (OSA) might be related to increases in factor XIIa, factor VIIa, thrombin-antithrombin complex, tissue factor, plasma fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and platelet activity [1, 2]. OSA may cause hemodynamic disturbances due to decreased venous return or to chronic venous stasis or to damage to the vascular endothelial structure [3]. A relationship was found among AHI, low SpO<sub>2</sub> and high PAI concentrations in moderate to severe OSA [2]. Endothelin-1 levels were higher in OSA, and these high levels caused vasoconstriction and a decrease in the level of nitric oxide - a potent vasodilator [3]. OSA activates the sympathetic nervous system and causes an increase in inflammatory mediators, catecholamines, cellular and vascular adhesion molecules, which have prothrombotic properties in circulation [4]. All of these pathophysiologic changes in OSA may predispose patients to the development of pulmonary embolism (PE); however, there are limited data about the role of thromboembolic events in OSA.

The aim of the study was to investigate whether frequency and severity of OSA is different in subjects with PE compared with those with OSA alone. This prospective controlled study is the first study evaluating OSA in PE patients with polysomnography (PSG).

## Methods

This prospective study was conducted between November 2009 and December 2010. All subjects admitted to the Department of Pulmonary Medicine of Gaziantep University who were diagnosed with PE were included in the study group. The control group consisted of age- and sex-matched subjects, without a clinic history consistent with PE, who were referred

to the Sleep Clinic. PE was diagnosed when compatible physical examination findings and thrombus in multislice CT angiography were present. Subjects with any restrictive/obstructive lung pathology, or who were younger than 18 years of age, were excluded from the study. The results of a physical examination, as well as neck and waist circumference and body mass index (BMI; calculated as kg/m<sup>2</sup>), were recorded for each patient. Lower extremity venous Doppler USG were performed in the PE group. Sleep studies were performed a minimum of one week after the diagnosis when clinical stabilization of the acute PE episode was achieved. PSG recordings were obtained via Viasys Sleep Screen.

Sleep studies were scored manually by the same author (MU) according to AASM 2007 criteria. OSA was classified as mild, moderate and severe by AHI scores of 5-15, 15-30 and ≥30, respectively [5]. Total number of arousals and periodic leg movements (PLM) per hour were defined as arousal and PLM index, respectively [5]. Epworth sleepiness scale score of each patient were calculated [6].

Statistical analysis was performed with Statistical Package for Social Sciences for Windows 13 program. Results are shown as mean and standard deviation. Mann Whitney-U test, T Test, X<sup>2</sup> and Fisher's Exact Test were used for statistical evaluation and p<0.05 was accepted for statistical significance. Ethics Committee approval was obtained.

## Results

A total of 73 subjects were included in this study, with 28 in the PE group (50% male) and 45 in the control group (67% male). Mean age, body mass index, neck and waist circumference were not statistically different between groups (p>0.05). Demographic and clinical characteristics of study groups are presented in Table 1.

TABLE 2. Polysomnography findings of study groups

	PE group	Control group	P
Stage 1 (%)	8.4	5.6	0.018
Stage 2 (%)	46.7	56.6	0.002
Stage 3 (%)	21.6	19.2	0.226
REM (%)	23.3	18	<0.001
AHI (mean±SD)	17.57±18.1	9.53±6.7	0.010
ESS score (mean±SD)	4.96±3.2	5.50±5.2	0.510
PLM index (mean±SD)	0.14±0.5	3.00±10.4	0.181
Arousal index (mean±SD)	11.75±6.6	9.53±6.0	0.074

AHI: Apnea hypopnea index

ESS: Epworth sleepiness scale

PLM: Periodic leg movement

Mean AHI in PE and control group were 17.57 and 9.53, respectively ( $p=0.010$ ). Mean Epworth sleepiness scale was not different between the groups ( $p=0.510$ ). Twenty-eight PE patients underwent lower extremity venous Doppler USG in order to search for deep vein thrombosis (DVT). DVT was detected in 10 out of 28 (36%) patients. Ten patients with DVT exhibited pulmonary thrombus in CT angiographic evaluation. Snoring and excessive daytime sleepiness (EDS) were more common in the control group ( $p<0.05$ ). Witnessed apnea was not different between the groups ( $p>0.05$ ). PSG findings of study subjects were demonstrated in Table 2. Duration of Stage 1, 2 and rapid eye movement (REM) sleep differed significantly between the groups ( $p<0.05$ ). Arousal and PLM indexes were not different between the groups ( $p>0.05$ ).

Severity of OSA in PE group was classified as follows: eight (28.5%) normal, eight (28.5%) mild, six (21.4%) moderate, six (21.4%) severe. Severity of OSA in control group was classified as follows: 16 (35.6%) normal, 20 (44.4%) mild, nine (20%) moderate. Severe OSA was not detected in any subjects in the control group which differed from the PE group ( $p=0.015$ ).

PE was verified with CT pulmonary angiography in all patients. Thrombus localizations were as follows: main pulmonary artery in 19 subjects (67.85%) and segmental or subsegmental arteries in nine subjects (32.14%). Table 3 shows thrombus localizations with respect to OSA severity. Thrombus localization did not significantly differ with severity of OSA ( $p=0.350$ ).

The groups were assessed for OSA risk factors. Age and BMI were found to be higher among sleep apneic PE patients than sleep apneic controls, while male gender was more common in OSA+ controls. The frequency of risk factors and symptoms in patients with OSA were presented in Table 4.

## Discussion

The results of this study showed that the prevalence of OSA in subjects with PE is higher than a group of subjects referred to sleep clinic and without a clinic relevant with PE. Hasegawa *et al.* detected OSA in two of seven patients with PE [7]. Arnulf *et al.* also demonstrated that 63% of patients with DVT or PE had AHI>15 and that AHI severity is related to hypertension and advanced age [8].

TABLE 3. Thrombus localization and OSA severity in PE patients

Site of embolus	Main+segmental+subsegmental PA (n)	Main PA (n)	Segmental+subsegmental PA (n)
AHI <5	3	3	3
Mild OSA	5	-	2
Moderate OSA	4	1	1
Severe OSA	1	2	3

PA: Pulmonary artery

AHI: apnea-hypopnea index

TABLE 4. The frequency of risk factors and symptoms in patients with OSA

	PE Group n=20	Control Group n=29	P
Male gender	10	25	p=0.01
Age (years)	57.8	49.8	p=0.025
BMI (kg/m <sup>2</sup> )	32.2	25.7	p=0.14
Neck circumference (cm)	40.7	36.7	p=0.46
Waist circumference (cm)	107.2	85.1	p=0.031
Epworth Sleepiness Scale Score	5.2	4.8	p=0.52
Snoring (n)	17	26	p=0.26
Excessive daytime sleepiness (n)	11	0	P<0.01
Witnessed apnea (n)	3	0	p=0.09

In our study, forty-three percent (n=13) of patients in the PE group had AHI $\geq$ 15. Ambrosetti *et al.* investigated PE and OSA in their prospective follow-up study [9] and showed that patients had increased incidence of venous thromboembolism in the three consecutive years after the diagnosis of OSA. A recent study by Berghaus *et al.* demonstrated that severity of sleep disordered breathing was unchanged with treatment in patients with acute PE [10].

Snoring was more common in control group whereas witnessed apnea was not different among PE and control groups. In contrary to this finding Epstein et al demonstrated more snoring complaint in their study as more common in PE subjects with OSA risk [11]. Our study group consisted of patients admitted to sleep clinic which might explain snoring as more common complaint. Our study has priority to this study is to show OSA presence and severity with performing objective test "PSG" in both PE and control group.

Another interesting finding of our study is that EDS was more common in the control group. Although 60% of patients with PE did not have this complaint there was higher frequency of respiratory events in the PE group in comparison with the control group. Although snoring and EDS were no more frequent in the PE group than in the control group and there was no difference in the number of complaints of witnessed apnea, OSA was more common in the PE group, which also had higher mean AHI and more severe OSA. Thus, PSG may be necessary for patients with PE despite the absence of OSA symptoms. The clinical significance of this finding - whether patients with PE must undergo PSG for detecting possible OSA - should be evaluated in further studies.

Although some parameters were found to be different between genders in our recent study, no differences were found between study and control groups with respect to gender [12].

The duration of stage 2 sleep was longer in the control group compared with the PE group. Sleep structure was better preserved, although AHI was more severe, and there was a higher incidence of OSA in the PE group. In addition, although REM stage is expected to decrease in OSA, our PE subjects had higher REM stage although they had more frequent and severe OSA [13]. More patients would be necessary to determine whether these findings are unique to PE or not. Arousal index may have been slightly higher in PE group but the difference was not statistically significant.

The present study had two limitations: spiral CT angiography was not done in the control group and the control group was selected from the patients admitted to the sleep clinic and may not reflect healthy control subjects.

In conclusion, the results of this study suggest that PE might be a risk factor for OSA. Further studies are necessary in order to investigate extent, causality and triggering factors in this relationship between PE and OSA.

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