Original article

Is obstructive sleep apnea syndrome a risk factor for pulmonary thromboembolism?

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Keywords: *pulmonary embolism; obstructive sleep apnea syndrome; sleep apnea; venous thromboembolism*

Background In many studies, obstructive sleep apnea (OSA) has been shown to be an independent risk factor for cardiovascular disease. Conversely, there are few reports establishing possible relation between OSA and venous thromboembolism (VTE). In this study, the aim is to evaluate OSA via polysomnography in patients with pulmonary embolism and drawing the attention of clinicians to the presence of obstructive sleep apnea syndrome (OSAS) may be a risk factor for pulmonary embolism.

Methods Fifty consecutive patients who were diagnosed with pulmonary embolism (PE) were evaluated prospectively for OSAS. Polysomnographic examination was conducted on 30 volunteer patients. The frequency of OSAS in PE was determined and PE cases were compared to each other after being divided into two groups based on the presence of a major risk factor.

Results The study consisted of a total of 30 patients (14 females and 16 males). In 56.7% of the patients (17/30), OSAS was determined. The percent of cases with moderate and severe OSAS (apnea hipoapnea index >15) was 26.7% (8/30). Patients who had pulmonary thromboembolism (PTE) without any known major VTE risk (*n*=20), were compared to patients with VTE risk factors (*n*=10), and significantly higher rates of OSAS were seen (70% and 30% respectively; *P*=0.045). The mean age of the group with major PE risk factors was lower than the group without major PE risk factors (52 years old and 66 years old, respectively; *P*=0.015), however, weight was greater in the group with major PE risk factors (88 kg and 81 kg, respectively; *P*=0.025). By multivariate Logistic regression analysis, in the group without any visible major risk factors, the only independent risk factor for PE was OSAS (*P*=0.049).

Conclusions In patients with PTE, OSA rates were much higher than in the general population. Moreover, the rate for patients with clinically significant moderate and severe OSA was quite high. PTE patients with OSA symptoms (not syndromes) and without known major risk factor should be examined for OSA. There seems to be a relationship between OSA and PTE. However, whether this relationship is a causal relationship or a relationship due to common risk factors or long-term complications of OSA is not clear. Further comprehensive studies on those special topics are needed to clarify these points.

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Obstructive sleep apnea (OSA), which is the most frequent disorder among sleep breathing disorders, is characterized by recurrent, partial or complete collapses in the upper airway during sleep.[1] The overall prevalence in the population is between 1.2%–4.5% in females and 3.1%–7.5% in males.[2]

OSA is known to be associated with cerebrovascular and cardiovascular morbidity and mortality.[3,4] The link between OSA and cardiovascular diseases like hypertension, ischemic heart disease, congestive heart failure (CHF), cerebrovascular accidents (CVAs) has been shown in many reports.[5-8] Conversely, there are few reports establishing a possible relation between OSA and venous thromboembolism (VTE).

Pulmonary thromboembolism (PTE) is a frequently diagnosed cardiopulmonary disease; its annual incidence in the United States is over 0.01% and within three months following diagnosis, the mortality rate reaches 15%.[9] In each age group, the incidence is higher in males and the mortality rates are higher in males, elderly and in African Americans.[10,11] There are some common risk factors like obesity, age and male gender in OSA and PTE. VTE is an increasingly common and challenging complications of CHF and CVAs which are also complications of OSA.

In the light of this information, in patients with PTE, OSA prevalence was thought to be higher than in the normal population. In this study, the objective is to investigate whether the prevalence of OSA is high in patients with pulmonary embolism (PE) and if such a relationship exists, to draw the attention of clinicians to the presence of OSA as a possible risk factor for PTE.

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METHODS

Study group

In this cross-sectional study, 50 consecutive patients who were diagnosed as PTE at Düzce University Faculty of Medicine Chest Diseases Service, between November 2009 and December 2010, were evaluated, in terms of OSA. The approval was obtained from Düzce University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (approval number: 2010-90).

The exclusion criteria were unconscious patient, a worse general status after one month of treatment, and refusing the polysomnographic examination. Inclusion criteria were patients with confirmed VTE and agreeing to participate in the study. Thirty PTE patients who received polysomnography constituted the study group. The flow chart of the study is summarized in Figure 1.

Sleep study

All patients had full night polysomnography (SomnoMedics: Model: Somnoscreen PSG, Germany) at the sleep laboratory. Two-channel electro-enchephalography (EEG), 2-channel electrooculography (EOG), 2-channel chin electromyography (EMG), oral and nasal air flow (thermistor and nasal cannula), thorax and abdomen movements, body position, snoring, electrocardiography (ECG) and pulse oxymeter records were obtained (> 6 hours). All records were scored manually. Apnea was defined as the complete cessation of airflow through the mouth and nose for 10 seconds or more. Hypopnea was defined as the decrease of more than 30% in the oral and nasal air flow for 10 seconds or more, accompanied by 4% desaturation. Apnea-hypopnea index (AHI) is the total number of apnea and hypopnea incidence occurring per hour of sleep. Patients with apnea-hypopnea index ≥5 were diagnosed as OSA.

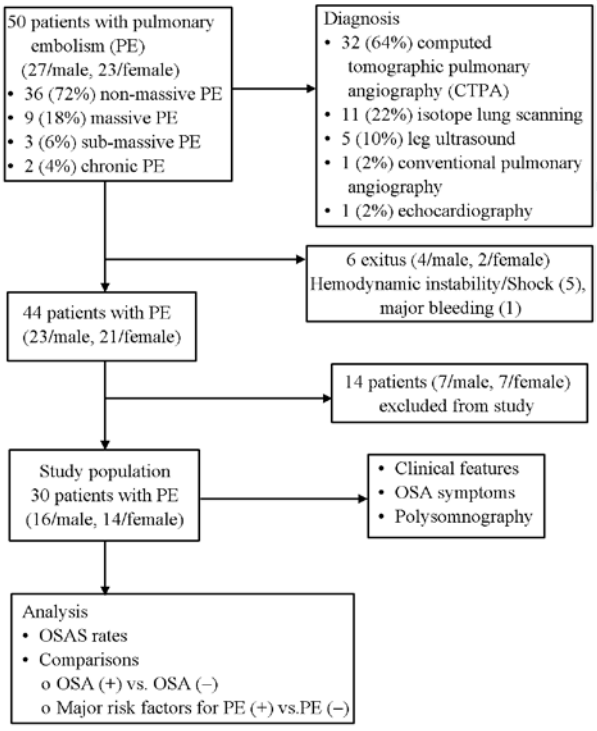


Figure 1. The flow chart of the study.

Assessment of patients

Snoring and witnessed apnea symptoms in the patients were assessed. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale. Based on their AHI, the patients were divided into the following groups; no OSA (AHI <5), mild OSA (AHI 5–15), moderate OSA (AHI 16–30), and severe OSA (AHI >30). Again, PTE patients were divided into two groups depending on whether they had a major risk factor or not. Surgery (major abdominal and pelvic surgery, hip, knee replacement, postoperative intensive care), obstetrics (pregnancy, caesarian section, puerperium), lower limb problems (fracture, trauma, stroke, spinal cord injury), malignancy (abdominal, pelvic, advanced, metastatic, chemotherapy), immobility (>3 days), and previous proven VTE were considered as major risk factors for PE.

Statistical analysis

Values are expressed as mean ± standard error (SE). Data were entered into the SPSS 16.0 Program (Statistical Package for Social Sciences for Windows, Chicago, IL, USA). For the paired comparison numerical data, the Student's *t* test was used. Chi-square was used in the comparison of categorical data. For parameters that were significant based on univariant analyses of the groups with and without PE as a major risk factor, multivariant (Logistic regression) analysis was conducted. A *P* value less than 0.05 was considered to be the statistically significant.

RESULTS

The study consisted of a total of 30 patients (14 females) between the ages of 28–85 years old (mean±SE (61±2.8) years old). There were 24 non-massive PTE patients (80%), two sub-massive PTE patients (10%), two patients with chronic PTE (6.7%) and one patient with massive PE (3.3%) (Figure 2). In 56.7% of patients (17/30) we determined to have OSA. The percentage of patients with moderate and severe OSA (AHI >15) was 26.7% (8/30) (Figure 3). The mean age of the group with major PE risk factors was lower than the group without major PE risk factors (52 years old and 66 years old, respectively; *P*=0.015), however, weight was greater in the group with major PE risk factors (88 kg and 81 kg, respectively; *P*=0.025). In the group without a major risk factor, blood urea nitrogen (BUN) levels were significantly higher. Between the groups with and without a PTE major risk factor, no significant difference was determined based on body mass index, hematocrit level, AHI and other polysomnographic findings (Table 1).

Between the groups with and without PTE major risk factor, there was no significant difference based on gender, cigarette and alcohol use, OSA symptoms,

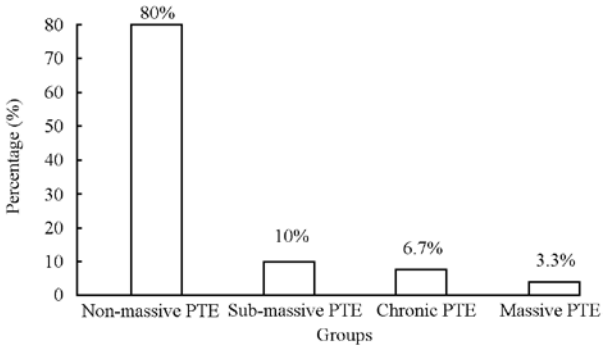


Figure 2. Clinical presentation of pulmonary embolism cases.

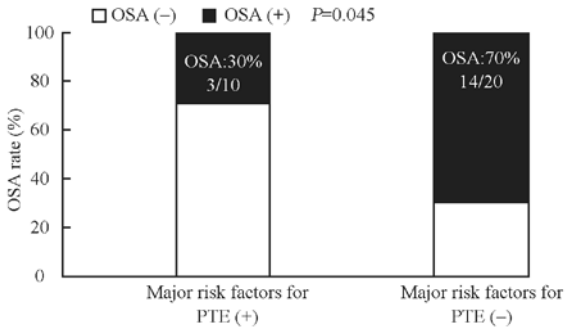


Figure 4. OSA rates according to presence of major risk factor for PTE.

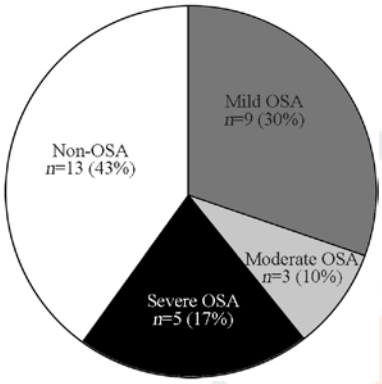


Figure 3. The frequency and severity of OSA in patients with PTE.

accompanying diseases (diabetes mellitus, hypertension, hypercholesterolemia, heart failure, chronic obstructive pulmonary disease, asthma, and hypothyroidism), and drug use (angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, diuretics and aspirin) (Table 2).

In patients who have PTE without any known major VTE risk factors, compared to those patients with VTE risk factors, significantly higher OSA levels were observed; 70% (14/20) vs. 30% (3/10) *P*=0.045, respectively (Figure 4).

Based on the multivariant Logistic regression analysis conducted, among the group without any visible major risk factors, the only independent risk factor for PTE was OSA (*P*=0.049, Table 3). In patients without PE risk factors, who had snoring and aspirin use, a statistically significant higher rate of OSA was determined. Between the groups with and without OSA, no significant difference was present based on gender, cigarette and alcohol use, accompanying diseases (diabetes mellitus, hypertension, hypercholesterolemia, heart failure, chronic obstructive pulmonary disease (COPD), asthma, and hypothyroidism), and ACE inhibitor, beta blocker, calcium-channel blocker and diuretic use (Table 4). OSA was found in 72.2% of patients with snoring, and in all patients with witnessed apnea and daytime sleepiness symptoms. As the snoring severity increased, the likelihood of OSA was also significantly increased. Among those without any symptoms, OSA was observed in 33.3% of patients. OSA was found in 64.3% of patients with a single major symptom, and in all patients with two or more symptoms (Table 5).

DISCUSSION

In this study, among patients with PTE diagnosis, prevalence of OSA was higher (57%) than the general population (1%–5%).[12-14] Moderate and severe OSA (AHI >15) prevalence (27%) were also higher than general population. At the same time, the study revealed that OSA could be a possible risk factor for PTE, independent of age, weight and other accompanying conditions.

Table 1. Comparison of clinical and polysomnographic findings between the groups with and without major risk factors for PTE (mean±SE)

Characteristics	Major risk factors for PTE (–) (*n*=20)	Major risk factors for PTE (+) (*n*=10)	*P* values
Age (years)	66.0±2.9	52.0±4.8	0.015
Weight (kg)	81±3	88±5	0.025
Body mass index (kg/m^2)	29.4±1.2	30.8±2.1	0.542
BUN (mg/dl)	21.2±1.7	14.1±2.4	0.023
Hemoglobin (g/dl)	12.7±0.3	11.8±0.5	0.109
Hematocrit (%)	38.6±0.9	36.0±1.1	0.108
Polysomnographic features			
Apnea hypopnea index	14.8±3.7	21.3±12.4	0.525
Desaturation index	12.2±3.1	13.7±6.8	0.829
Saturation <90%	10±3	8±4	0.664
Sleep efficiency (%)	79.6±3.0	74.9±3.7	0.351
Snoring in polysomnography (%)	52.0±22.6	28.0±7.1	0.472
Heart rate index	25.0±9.3	34.6±21.6	0.640
Arrhythmia index	120.6 ±50.8	40.4 ±26.7	0.294
Longest oxygen desaturation* (seconds)	86.0 ±7.1	76.0 ±9.3	0.414

* The time of oxygen desaturation >4% during sleep time.

Table 2. Comparison of clinical and demographic findings between the groups with and without major risk factor for PTE

Characteristics	Major risk factors for PTE (–) (*n*=20)	Major risk factors for PTE (+) (*n*=10)	*P* values
Gender (female/male)	9/11	5/5	0.796
Smoking (*n* (%))	5 (25)	1 (10)	0.663
Alcohol (*n* (%))	1 (5)	–	0.667
OSA rate (*n* (%))	14 (70)	3 (30)	0.045
OSA symptoms (*n* (%))			
Snoring*	10 (50)	7 (70)	0.297
Witnessed apnea	2 (10)	2 (20)	0.584
Daytime sleepiness†	2 (10)	2 (20)	0.584
Drug used (*n* (%))			
ACE inhibitory	5 (25)	1 (10)	0.663
Beta blocker	–	–	–
Ca-canal blocker	2 (10)	–	0.540
Diuretic	3 (16)	1 (10)	0.704
ASA (aspirin)	5 (25)	1 (10)	0.633
Comorbid diseases (*n* (%))			
Diabetes mellitus	2 (10)	3 (30)	0.300
Hypercholesterolemia	1 (5)	–	0.567
Hypertension	7 (35)	4 (40)	0.548
Heart failure	4 (20)	1 (10)	0.640
COPD	5 (25)	1 (10)	0.633
Asthma	1 (5)	–	0.667
Hypothyroid	1 (5)	–	0.667

*Habitual snoring: presence of snoring for at least 5 nights per week. †Daytime sleepiness: epworth sleepiness scale >10. ACE: angiotensin converting enzyme.

Table 3. Multivariant analysis of significant parameters in univariant analysis of the cases with and without major risk factor for PTE

Characteristics	Major risk factors for PTE			Logistic regression	
	No (*n*=20)	Yes (*n*=10)	*P* values	*B*	*P* values
Age (mean±SE, years)	65.0±2.9	52.0±4.8	0.015*	0.025	0.634
Weight (mean±SE, kg)	81.1±3.1	87.9±5.3	0.025*	0.160	0.056
BUN (mean±SE, mg/dl)	21.2±1.7	14.10±2.4	0.023*	–0.319	0.070
OSA rate (*n* (%))	14 (70)	3 (30)	0.045†	3.934	0.049‡

*Student's *t* test; †Chi-square test. ‡Logistic regression analysis.

Table 4. Comparison of clinical and demographic findings of PTE cases according to presence of OSA

Characteristics	OSA(–) (*n*=13)	OSA(+) (*n*=17)	*P* values
Gender (female/male)	7/6	7/10	0.491
Smoking (*n* (%))	1 (7.7)	5 (29.4)	0.154
Alcohol (*n* (%))	1 (7.7)	–	0.433
Major risk factors for PTE (*n* (%))	7 (53.8)	3 (17.6)	0.045
OSA symptoms (*n* (%))			
Snoring*	5 (38.5)	13 (76.4)	0.035
Witnessed apnea	–	4 (23.5)	0.113
Daytime sleepiness†	–	4 (23.5)	0.113
Drug used (*n* (%))			
ACE inhibitory	2 (15.4)	4 (23.5)	0.672
Beta blocker	–	–	–
Ca-canal blocker	1 (7.7)	1 (5.9)	0.687
Diuretic	1 (7.7)	3 (18.8)	0.606
ASA (aspirin)	–	6 (35.3)	0.024
Comorbid diseases (*n* (%))			
Diabetes mellitus	2 (46.2)	2 (11.8)	0.491
Hypercholesterolemia	–	1 (5.9)	0.567
Hypertension	3 (23.1)	8 (47.1)	0.259
Heart failure	1 (7.7)	4 (23.5)	0.355
COPD	1 (7.7)	5 (29.4)	0.196
Asthma	1 (7.7)	–	0.433
Hypothyroid	–	1 (5.9)	0.567

*Habitual snoring: presence of snoring for at least 5 nights per week. †Daytime sleepiness: epworth sleepiness scale >10. ACE: angiotensin converting enzyme.

Table 5. The rates of OSA confirmed in PSG regarding to the presence of OSA symptoms in PTE cases

OSA symptoms	*n*	Rate of OSA (%)	*P* values
Snoring*	18	13 (72.2)	0.035
Witnessed apnea	4	4 (100.0)	0.113
Daytime sleepiness†	4	4 (100.0)	0.113
Severity of snoring			
No	12	4 (33.3)	
Mild	12	7 (54.5)	0.042
Severe	6	6 (100.0)	
Major Symptoms			
No major symptom	12	4 (33.3)	
1 major symptom	14	9 (64.3)	0.049
≥2 major symptoms	4	4 (100.0)	

*Habitual snoring: presence of snoring for at least 5 nights per week. †Daytime sleepiness: epworth sleepiness scale >10.

In other studies,[12,13] the prevalence of OSA was reported to be between 0.3% and 15.0%. This difference between results is, to a great extent, due to the different study methods and diagnosis criteria. When these differences are taken into consideration, OSA is observed in approximately 1%–5% of adults.[12-14] An epidemiological study conducted in our country reported the OSA prevalence to be 1.8%.[15]

In a study conducted by Hasegawa et al[16] in 2000, the results of polysomnographic examinations conducted on seven PTE patients found a moderate and severe OSA frequency of 28.6%. In another study from 2002,[17] published as a letter to the editor in JAMA, using polysomnographic examination conducted on 68 VTE (58 PTE, 10 deep vein thrombosis (DVT)) patients, the OSA prevalence was much higher (84%) than the results from our study (57%). Moreover, in 63% of cases, AHI was higher than 15. Based on snoring, morning fatigue,

daytime sleepiness, and cognitive impairment, no significant difference could be found between the patients with OSAS and the patients without OSAS. The average age of patients with OSA was higher; however, no relationship was found between age and AHI severity. Similarly, no relationship was found between AHI, and gender, BMI and Epworth sleepiness score. Due to this very high OSA prevalence in their results, the authors suggested that there might be a relationship between VTE and sleep related respiratory disorders.[17]

In a study by Ambrosetti et al,[18] during the 3-year follow-up, 89 patients, who were diagnosed by polysomnographically with OSA, received CPAP treatment and did not have any permanent or temporary risk factors, the DVT rate was 0.8% and the PTE rate was 0.4%, which are higher than in the general population.

In a study conducted by Zhang et al,[19] in elderly Chinese OSA patients, nCPAP treatment of OSA eliminated the tendency towards hypercoagulation and thrombosis for patients also diagnosed to be in a prethrombotic state. Recently, a study by Epstein et al,[20] investigated the relationship between OSA and PTE. In this study, among 270 patients pre-diagnosed with PTE, 71 patients were designated as the study group and 199 patients without PTE, made up the control group. The demographic and clinical features of all patients were analyzed. Similar to our study, based on the univariate analysis, weight and OSA risk was significantly higher in patients with PTE. Additionally, a relationship between PTE, and male gender, hereditary risk factors and heart failure was determined. In the multivariant analysis conducted, male gender, the presence of hereditary risk factors and OSA risk factors were found to be independent risk factors for PTE. However, polysomnographic examination was only conducted on 32% of patients in this study, and in a majority of them OSA risk was evaluated using the Berlin questionnaire. Again, in this study, familial risk factors and family history of PTE and VTE were evaluated by questioning, while the laboratory evaluation for thrombophilia was conducted for patients receiving treatment. In our study, laboratory evaluation for thrombophilia was not conducted, and in PTE patients without any visible major risk factor, OSA was the only independent risk factor.

A recent retrospective study by Basenquet et al[21] with 840 patients with VTE suggested a possible link between OSA and VTE due to the high prevalence of OSA (15.5%) among patients with VTE. Furthermore, compared to the control group (without OSA), those who had OSA were more obese and had significantly higher rates of diabetes, coronary artery disease, and chronic heart failure.

It is well known that the main PTE risk factors are based on "Virchow's triad" consisting of endothelial dysfunction, hypercoagulability and lower extremity stasis. Our study was based on the hypothesis that OSA may be an independent risk factor for VTE. Until now, there has been significant evidence presented indicating OSA leads to endothelial dysfunction, hypercoagulability and stasis. In OSA, vascular endothelial function was shown to be impaired and directly influenced by an increase in endothelin-1 levels causing vasoconstriction and a decrease in NO levels.[22] In OSA, hypercoagulability (measured by increased thrombin/anti-thrombin 3 complex, fibrin D-dimer, von Willebrand factor) levels were shown to increase, independent of gender, age, body mass index, mean oxygen saturation and hematocrit levels. Again, in OSA, platelet aggregability was suggested to increase secondarily to increased nocturnal catecholamine levels.[23-25] During sleep in patients with OSA, an increase in platelet activation and aggregation was shown, which could be treated with nasal CPAP therapy.[26] In patients with severe OSA, as a result of increased platelet activation, it is suggested that mean platelet volume (MPV) is significantly increased and there is a correlation between MPV and AHI.[27,28]

It is suggested that the relationship between OSA and VTE can be explained by hypercoagulability, increased plasma fibrinogen levels, platelet activation and decreased fibrinolytic capacity.[6] In OSA, hemodynamic changes were shown to cause a decrease in acute venous cycle and chronic venous stasis.[29] Again, in patients with OSA, CHF was shown to be frequent. Respiration disorders were investigated in two large studies, among patients with congestive heart failure with systolic dysfunction, and OSA was observed in 11% of 81 patients and 37% of 450 patients.[30,31] CHF may play a role in PTE etiology by causing venous stasis. Studies designed to explain the relationship between OSA and VTE are limited. The studies are generally aimed at explaining the relationship between OSA and cardiovascular diseases.[3,32-39]

OSA prevalence peaks at age 45–65 years in the general population. Based on some publications, after the age of 65 OSA prevalence decreases.[40,41] In our study, among PTE cases with OSA, the mean age was 65 years. This is associated with our patients being an advanced age group. In our study, in the group without a major risk factor for PTE, the mean age was significantly higher. This situation suggests that the real risk factor for PTE may be advanced age. However, as a result of multivariate analysis, the real effective factor was OSA. Obesity is among the most important factors defined for OSA. In those with a BMI above 29, the OSA risk is 8–12 times more compared to those who are not obese.[42] Obesity is also a known factor for PTE. In our study, in the group without a known major risk factor for PTE in which OSA is seen more frequently, the mean weight was lower. This supports the idea that OSA may be a risk factor for PTE, independent of weight. However, in patients included in our study, in both groups with and without PTE risk

factors, the BMI was above 29. Thus, the group included in this study consisted of relatively obese patients.

In our study, in the group without PTE risk factors, the BUN levels were significantly higher, compared to the group with risk factors. However, the mean BUN value was within the upper normal limit, and was not at a clinically significant level. This may be related to the mean age of the group being high. Studies are present indicating that PTE risk does not increase in case of renal dysfunction.[43,44] In our multivariate analysis, in the group without PTE risk factor, BUN value was shown not to be an independent risk factor for PTE, which is consistent with the literature.

In our study, between groups with and without PTE risk factors, no difference was determined based on cigarette and alcohol use, concomitant disease, and drug use. Among the study group, there was no one with a history of oral contraceptive use.

The most commonly known symptoms of OSA are sleepiness during day time and witnessed apnea. Snoring is the most frequently seen symptom in OSA. In patients with OSA, habitual snoring is present and irregular snoring is typical due to disruptions by frequently recurring apnea.

Despite the high OSA prevalence in individuals with snoring, the positive predictive value is 63% and negative predictive value is 56%.[45] In our study, OSA was observed in 72.2% of patients with snoring, similar to the literature.

Our study has three major limitations. First, there were the lack of any laboratory tests regarding hereditary PTE risk factors. In our patients, hereditary PE risk evaluation was conducted only by recovering the family history in anamnesis. However, none of our patients carried the features of the special group that is recommended for PTE risk factor investigation. Second, it is high mean age in patients without known major risk factor for PTE. Interaction of age, OSA and PTE with each other was a conflicting factor. Even though OSA and age were independent risk factors for PTE by univariant analysis, the only independent risk factor was OSA in multivariant analysis. Third, it is the relatively small number of cases. One of the major reasons for this was that a large majority of clinical patients were not appropriate for polysomnographic assessment.

In patients with PTE, OSA rates were much higher than in the general population. Moreover, the rate for patients with clinically significant moderate and severe OSA was quite high. PTE patients with OSA symptoms and with no known major risk factors should be examined for OSA. There seems to be a relationship between OSA and PTE. However, whether this relationship is a causal relationship or a relationship due to common risk factors or long-term complications of OSA is not clear. Further comprehensive studies on those topics are needed.

REFERENCES

1. Dorasamy P. Obstructive sleep apnea and cardiovascular risk. Ther Clin Risk Manag 2007; 3: 1105-1111.
2. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008; 5: 136-143.
3. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163: 19-25.
4. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353: 2034-2041.
5. Minoguchi K, Yokoe T, Tazaki T, Minoguchi T, Oda N, Tanaka A, et al. Silent brain infarction and platelet activation in obstructive sleep apnea. Am J Respir Crit Care Med 2007; 175: 612-617.
6. Von Kanel R, Dimsdale JE. Hemostatic alterations in patients with obstructive sleep apnea and implications for cardiovascular disease. Chest 2003; 124: 1956-1967.
7. Lattimore JL, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003; 41: 1429-1437.
8. Shamsuzzam AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003; 290: 1906-1914.
9. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353: 1386-1389.
10. Giuntini C, Di Ricco G, Marini C, Malillo E, Palla A. Pulmonary embolism: epidemiology. Chest 1995; 107 (1 Suppl): 3S-9S.
11. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple cause mortality data. Ann Intern Med 2003; 20: 21-24.
12. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep disordered breathing among middle aged adults. N Engl J Med 1993; 328: 1230-1235.
13. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001; 163: 608-613.
14. Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 2004; 79: 1036-1046.
15. Kokturk O. Obstructive sleep apnea syndrome: epidemiology. Tuberk Toraks 1998; 46: 193-201.
16. Hasegawa R, Shiomi T, Sasanabe R, Otake K, Banno K, Oki Y, et al. Sleep apnea syndrome in patients with pulmonary thromboembolism. Psychiatry Clin Neurosci 2000; 54: 342-343.
17. Arnulf I, Merino-Andreu M, Perrier A, Birolleau S, Similowski T, Derenne JP. Obstructive sleep apnea and venous thromboembolism. JAMA 2002; 287: 2655-2656.

18. Ambrosetti M, Lucioni A, Ageno W, Conti S, Neri M. Is venous thromboembolism more frequent in patients with obstructive sleep apnea syndrome? J Thromb Haemost 2004; 2: 1858-1860.
19. Zhang X, Yin K, Wang H, Su M, Yang Y. Effect of continuous positive airway pressure treatment on elderly Chinese patients with obstructive sleep apnea in the prethrombotic state**.** Chin Med J 2003; 116: 1426-1428.
20. Epstein MD, Segal LN, Ibrahim SM, Friedman N, Bustami R. Snoring and the risk of obstructive sleep apnea in patients with pulmonary embolism. Sleep 2010; 33: 1069-1074.
21. Bosanquet JP, Bade BC, Zia MF, Karo A, Hassan O, Hess BT, et al. Patients with venous thromboembolism appear to have higher prevalence of obstructive sleep apnea than general population. Clin Appl Thromb Hemost 2011; 17: E119-E124.
22. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. J Clin Sleep Med 2007; 3: 409-415.
23. Von Kanel R, Le DT, Nelesen RA, Mills PJ, Ancoli-Israel S, Dimsdale JE. The hypercoagulable state in sleep apnea is related to comorbid hypertension. J Hypertens 2001; 19: 1445-1451.
24. Sanner BM, Konermann M, Tepel M, Groetz J, Mummenhoff C, Zidek W. Platelet function in patients with obstructive sleep apnoea syndrome. Eur Respir J 2000; 16: 648-652.
25. Eisensehr I, Ehrenberg BL, Noachtar S, Korbett K, Byrne A, McAuley A, et al. Platelet activation, epinephrine, and blood pressure in obstructive sleep apnea syndrome. Neurology 1998; 51: 188-195.
26. Bokinsky G, Miller M, Ault K, Husband P, Mitchell J. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure. A preliminary investigation. Chest 1995; 108: 625-630.
27. Varol E, Ozturk O, Gonca T, Has M, Ozaydin M, Erdogan D, et al. Mean platelet volume is increased in patients with severe obstructive sleep apnea. Scand J Clin Lab Invest 2010; 70: 497-502.
28. Brækken SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Mean plaelet volume is a risk factor for venous thromboembolism: the Tromso study. J Thromb Haemost 2009; 8: 157-162.
29. Marrone O, Bonsignore MR. Pulmonary haemodynamics in obstructive sleep apnoea. Sleep Med Rev 2002; 6: 175-193.
30. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998; 97: 2154-2159.
31. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999; 160: 1101-1106.
32. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000; 283: 1829-1836.
33. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. Lancet 1988; 2: 397.
34. Franklin KA, Nilsson JB, Sahlin C, Naslund U. Sleep apnoea and nocturnal angina. Lancet 1995; 345: 1085-1087.
35. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. Chest 2000; 118: 591-595.
36. Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. Hypertension 1998; 32: 293-297.
37. Koehler U, Glaremin T, Cassel W, Feuring M, Pomykaj T, Schafer H, et al. Nocturnal ventricular arrhythmia in patients with sleep apnea and suspected coronary heart disease. Med Klin (Munich) 1993; 88: 684-690.
38. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996; 275: 1557-1562.
39. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. Sleep-disordered breathing and poor functional outcome after stroke. Stroke 1996; 27: 252-259.
40. McNamara SG, Grunstein RR, Sullivan CE. Obstructive sleep apnea. Thorax 1993; 48: 754-763.
41. Stradling JR. Obstructive sleep apnea. Definitions, epidemiology and natural history. Thorax 1995; 50: 683-689.
42. Kokturk O. Obstructive sleep apnea syndrome: clinical features. Tuberk Toraks 1999; 47: 117-126.
43. Mossey RT, Kasabian AA, Wilkes BM, Mailloux LU, Susin M, Bluestone PA. Pulmonary embolism: low incidence inchronic renal failure. Arch Intern Med 1982; 142: 1646-1648.
44. Rotter W, Roettger P. Comparative pathologic anatomic study of cases of chronic global renal insufficiency with and without preceding hemodialysis. Clin Nephrol 1973; 1: 257-265.
45. Deegan PC, Nolan P, Carey M, McNicholas WT. Effects of positive airway pressure on upper airway dilator muscle activity and ventilatory timing. J Appl Physiol 1996; 81: 470-479.

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