CHEST

OSA Is a Risk Factor for Recurrent VTE

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BACKGROUND: OSA is a risk factor for a first episode of pulmonary embolism (PE), although its impact on the risk of thromboembolism recurring is uncertain. Our objective was to explore the prognostic value of OSA after the discontinuation of oral anticoagulation (OAC) in patients with a first episode of PE.

METHODS: In 120 consecutive patients who had stopped OAC for a first episode of PE, we performed home respiratory polygraphy and recorded sleep characteristics, classic risk factors for PE, blood pressure measurements, spirometric parameters, physical activity, and levels of D-dimer and prothrombin fragment 1+2 (F1+2). Patients were followed for 5 to 8 years, and the main end point was PE recurrence. Restarting OAC for any thromboembolic event was evaluated as a secondary end point.

RESULTS: During the follow-up period, 19 patients had a PE recurrence, and 16 of them had an apnea-hypopnea index (AHI) $\geq$ 10 h^{-1}. In a multivariate Cox regression model, an AHI $\geq$ 10 h^{-1} (hazard ratio [HR], 20.73; 95% CI, 1.71-251.28), mean nocturnal oxygen saturation ($nSaO_2$) (HR, 0.39; 95% CI, 0.20-0.78), time with SaO_2 < 90% (CT90%) (HR, 0.90; 95% CI, 0.82-0.98), and D-dimer level (HR, 1.001; 95% CI, 1.00-1.002) were identified as independent risk factors for recurrent PE. Twenty-four patients resumed OAC, and AHI $\geq$ 10 h^{-1} (HR, 20.66; 95% CI, 2.27-188.35), mean $nSaO_2$ (HR, 0.54; 95% CI, 0.32-0.94), and Epworth Sleepiness Scale (ESS) (HR, 0.73; 95% CI, 0.56-0.97) were retained as independent risk factors for the resumption of OAC.

CONCLUSIONS: After a first episode of PE, OSA is an independent risk factor for PE recurrence or restarting OAC for a new thromboembolic event.

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KEY WORDS: D-dimer; pulmonary embolism; recurrent pulmonary embolism VTE; sleep apnea

ABBREVIATIONS: AHI = apnea-hypopnea index; AUC-ROC = area under the receiver operating characteristic curve; CT90% = percentage of total time study spent with SaO_2 < 90%; DASH = D-dimer, age, sex, and hormonal therapy; ESS = Epworth Sleepiness Scale; F1+2 = prothrombin fragment 1+2; IDI = integrated discrimination improvement; NRI = net reclassification index; $nSaO_2$ = nocturnal oxygen saturation; OAC = oral anticoagulation; PE = pulmonary embolism; SaO_2 = arterial oxygen saturation

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VTE is a frequent, chronic, and potentially fatal disease. Pulmonary embolism (PE) is a major manifestation of VTE, with an annual incidence of one to two cases per 1,000 person-years; it is strongly age dependent. PE and OSA share some risk factors (advanced age, physical inactivity, and obesity),[1,2] and there is growing evidence from cross-sectional and longitudinal studies that OSA is a risk factor for PE.[3-8] This association represents a major public health burden, given the high prevalence of both disorders and the mortality rates from PE.[2,9]

Patients with a first episode of PE have a cumulative recurrence rate of approximately 30% at 10 years.[10] Recurrent PE is associated with mortality rates of 9%, and it is also a risk factor for chronic pulmonary hypertension. Anticoagulants are highly effective in reducing the PE recurrence rate, but their administration must be carefully weighed against the risk of bleeding complications. The risk of recurrence depends on the number and severity of risk factors in an individual patient. Significant risk factors for the recurrence of PE include a previous unprovoked episode, cancer, continued estrogen use, vena cava filters, high post-anticoagulation plasma D-dimer levels, male sex, and obesity.[10-21] The last two factors are well known clinical features associated with OSA.[1] Moreover, there is evidence that OSA is a hypercoagulation state.[22-25] In fact, patients with PE and OSA require higher warfarin doses to achieve a therapeutic international normalized ratio than do subjects without OSA.[26] Recently, we found that patients with PE and OSA had higher rates of elevated D-dimer levels after discontinuation of oral anticoagulation than did patients without OSA.[27] However, to our knowledge, no longitudinal studies to date have explored the role of OSA as a risk factor for recurrent thromboembolic events.

Based on the aforementioned features, we sought to investigate whether OSA was associated with an increased risk of recurrent PE after discontinuation of OAC for a first PE episode. Accordingly, we examined (secondary outcome) the prognostic value of OSA to assess the risk for restarting OAC for any thromboembolic event.

Methods

Subjects, Design, and Ethics

We performed a prospective study (University Hospital Son Espases, Palma de Mallorca and University Hospital La Paz, Madrid, Spain). Eligible cases were all consecutive patients with a previous (6-12 months) PE episode diagnosed by CT pulmonary angiography who had completed at least 3 months of OAC with a vitamin K antagonist. All subjects were included when they stopped OAC, the withdrawal of which was decided by physicians not involved in the study. They were included in the study from October 1, 2006 to November 30, 2009. Patients were excluded if they had severe daytime hypoxemia (Pao_2< 60 mm Hg), very serious illness with an estimated survival of less than 12 months, or disabling cognitive problems. The study was approved by the Institutional Ethics Committee ("Comité de ética de investigación clínica de las Islas Baleares," project approval No. IB 743/06 PI), and all subjects gave their written informed consent.

Measurements

A validated portable recording sleep monitoring system was used to perform a sleep study. Every patient was classified as having OSA when the obstructive component was dominant and the apnea-hypopnea index (AHI) was ≥ 10 per hour (10 h^{-1}). Office blood pressure, spirometric readings, and physical activity were measured as previously described (e-Appendix 1).

In all subjects, anthropometric, clinical, and sleep data were collected. As potential confounders, we recorded sex, age, BMI, neck circumference, and classic risk factors for PE (prolonged immobilization, major surgery, trauma, cancer, major medical disease, hormone replacement therapy, oral contraceptive therapy, or cerebrovascular disease). One month after oral anticoagulation was stopped, a venous blood sample was collected and D-dimer and prothrombin fragment 1+2 (F1+2) levels were measured as previously described.[27]

Follow-Up and Outcome Measurements

Patients were treated by their general practitioners or pulmonologists according to the current guidelines,[2] and they were checked every 12 months during the follow-up period of 5 to 8 years until May 19, 2015. In patients with OSA, CPAP treatment was prescribed according to the national guidelines,[28] and in such cases, pressure level was established by either full standard polysomnography or autotitrating the CPAP device.[29] We recorded the changes in comorbidity and current treatment.

The main end point of the present study was the recurrence of PE, confirmed by CT. As a secondary end point, we assessed the reinstitution of anticoagulation therapy because of a new episode of PE or deep venous thrombosis confirmed by venography or color duplex ultrasonography.

Vital status and study outcomes were ascertained through follow-up visits, ED or general practitioner reports, telephone contacts, and clinical records. A participant was considered lost to follow-up if we could not contact the patient or if he or she had moved to another place or died. Results were reported for patients within a minimum follow-up of 6 months.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (interquartile range), depending on their distribution. Categorical variables are reported as absolute numbers and percentages.

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Comparisons between groups were performed using the Student t test or Mann-Whitney U test for continuous variables and the χ^2 test (or Fisher exact test if the expected frequencies were < 5) for categorical variables.

Kaplan-Meier curves and log-rank tests of both recurrence of PE and reintroduction of anticoagulant therapy were performed after stratifying by AHI. On multivariate Cox regression analysis, variables were included if they were independently associated with both the outcome and the exposure ($P < .05$) or if they modified the risk ratio estimate for any of the remaining covariates ($> 0.5\%$ change). Survival models were always adjusted for sex, age, BMI, neck circumference, presence of classic risk factors for PE, blood pressure, FEV_1/FVC ratio, and physical activity level.

To assess whether the addition of the new survival models to the classic D-dimer, age, sex, and hormonal therapy (DASH) score[30] and the Vienna Prediction Model[13] improved the predictive power for recurrent PE or resuming anticoagulation, we calculated the area under the receiver operating characteristic curve (AUC-ROC) for the classic models with and without inclusion of the new risk factors. AUC-ROC equality was assessed by the method of DeLong et al.[31] Net reclassification index (NRI) and integrated discrimination improvement (IDI) were applied to quantify the improvement contributed by the new risk factors.[32]

All effects were considered significant at $P < .05$. Statistical analyses were performed using SPSS, version 13.0 (SPSS Inc).

Results

General Characteristics and Sleep Study Variables

One hundred twenty patients with a first episode of PE who had received at least 3 months of OAC were included in the study. The description of demographic characteristics, comorbidities, classic risk factors for thromboembolic disease, physical activity level, D-dimer and F1+2 levels, as well as sleep parameters are summarized in Table 1. Overall, 71 patients with PE (59.2%) had OSA (AHI $> 10\ h^{-1}$), and 33 (27.5%) of these cases were severe (AHI $> 30\ h^{-1}$). In contrast, daytime sleepiness was present in only 20 subjects (16.7%).

During the follow-up period of 78 $\pm$ 16 months, nine patients died, none because of thromboembolic events. OSA was no more frequent in those patients who died, and we did not find any significant mortality risk factor.

Recurrent PE

Comparisons of characteristics between patients with and those without PE recurrence are shown in Table 2. Nineteen patients presented with a PE recurrence during the follow-up period (10.7 events/100 patients-year), and 16 of them had OSA. The prevalence of at least mild OSA (AHI $> 10\ h^{-1}$) was significantly higher in patients with PE recurrence compared with those who did not have relapses (84% vs 54%; $P = .012$). In addition, patients with PE recurrence had worse mean nocturnal oxygen saturation ($nSaO_2$) than those without recurrence, but no differences were found in daytime somnolence (Table 2). Kaplan-Meier analysis showed that those patients with a previous PE episode and OSA had a higher risk of recurrent PE than did those without OSA (crude hazard ratio [HR], 4.05; 95% CI, 1,18-13,91; $P = .026$) (Fig 1). Adjusted HRs for PE recurrence are shown in Table 3. The presence of an AHI $> 10\ h^{-1}$ as well as mean $nSaO_2$, the percentage of total time study spent with $Sao_2 < 90\%$ (CT90%), and D-dimer levels after oral anticoagulation is discontinued were identified as independent risk factors for recurrent PE.

The addition of the new sleep risk factors significantly improved the predictive capacity of the DASH score and Vienna Prediction Model. The new multivariate model was significantly better in predicting recurrent PE than were the clinical models alone (Fig 2), supported by both the net reclassification index (NRI) and the integrated discrimination improvement (IDI) index (Table 4). We repeated the risk prediction analyses after eliminating D-dimer level from the multivariate model, since D-dimer is a component of the DASH score and the Vienna Prediction Model. In this case, the addition of AHI, mean nocturnal Sao_2 ($nSao_2$), and CT90% to the classic predictive models achieved a significant improvement in risk prediction (Fig 2, Table 4).

Resumption of Anticoagulation Therapy

Twenty-four patients restarted anticoagulation therapy during the follow-up period (12.8 events/100 patient-years): PE was the cause in 19 cases and deep venous thrombosis was the cause in five cases. Table 5 shows the comparison between patients who resumed anticoagulation therapy and those who did not. The prevalence of OSA was significantly higher among patients who restarted anticoagulation therapy than among those who discontinued it (83% vs 53%; $P = .005$), but no differences in mean $nSao_2$ and daytime somnolence were found between the two groups. Patients with a previous PE episode and OSA had a higher risk of restarting anticoagulation therapy than did patients with no apnea (crude HR, 3.33; 95% CI, 1.12-9.90; $P = .031$) (Fig 3). Additionally, the multivariate Cox regression model showed that AHI $\geq 10\ h^{-1}$, mean $nSaO_2$, and Epworth Sleepiness Scale (ESS) are independent risk factors for restarting OAC in patients with PE (Table 6).

TABLE 1] General Baseline Characteristics of the Study Subjects

Sex	
Female, No. (%)	45 (37.5)
Male, No. (%)	75 (62.5)
Age, y	57 ± 15
BMI, kg/m^2	28.1 ± 5.3
Neck circumference, cm	39.4 ± 3.9
Current smoker, No. (%)	21 (17.5)
Pack-years	30 ± 23
Alcohol intake, g/d	6.2 ± 17
Comorbidities	
Obesity, No. (%)	30 (25.0)
Hypertension, No. (%)	48 (40.0)
Diabetes mellitus, No. (%)	16 (13.3)
Dyslipidemia, No. (%)	37 (30.8)
Heart failure, No. (%)	15 (12.5)
COPD, No. (%)	20 (16.7)
Cancer, No. (%)	17 (14.2)
Depression/anxiety, No. (%)	20 (16.7)
Cerebrovascular disease, No. (%)	6 (5.0)
Previous embolic risk factors	
Immobilization, No. (%)	24 (20.0)
Major surgery, No. (%)	9 (7.5)
Trauma, No. (%)	8 (6.7)
Longer airplane travel, No. (%)	2 (1.7)
Major medical diseases, No. (%)	21 (17.5)
Hormonal contraceptive use, No. (%)	4 (3.3)
Antipsychotic drugs, No. (%)	8 (6.7)
Physical activity level	
Low, No. (%)	26 (22.0)
Moderate, No. (%)	53 (43.9)
High, No. (%)	41 (34.1)
Baseline lung function	
FVC, % predicted	101 ± 16
FEV_1, % predicted	99 ± 16
FEV_1/FVC ratio	0.78 ± 0.09
Baseline Sao_2, %	95 ± 3
D-dimer, ng/mL	502 ± 494
F1+2, pmol/L	438 ± 566
Sleep characteristics	
ESS	6.8 ± 4.0
Daytime sleepiness (ESS > 11), No. (%)	20 (16.7)
AHI, h^{-1}	21.1 ± 20.5
AHI ≥ 10 h^{-1}, No. (%)	71 (59.2)
AHI ≥ 30 h^{-1}, No. (%)	33 (27.5)
Mean $nSao_2$, %	93 ± 2
Low $nSao_2$, %	79 ± 10
CT90%	27.2 ± 58.7
Desaturation index, h^{-1}	18.3 ± 19.7

Values represent mean ± SD, median (interquartile range) or percentage, depending on their distribution. AHI = apnea-hypopnea index; CT90% = percentage of total time study spent with Sao_2 < 90%; ESS = Epworth Sleepiness Scale; F1+2 = prothrombin fragment 1+2; $nSao_2$ = nocturnal oxygen saturation.

The addition of this new risk model also significantly improved the predictive capacity of the DASH score and Vienna Prediction Model (e-Fig, 1, e-Table 1).

Sensitivity Analysis

We repeated the risk prediction analyses after excluding patients with obesity. For both the DASH score and the Vienna Prediction Model, the addition of the new risk models improved prediction of recurrence of embolism or reinstitution of anticoagulation therapy on the likelihood ratio test ($P < .001$), the NRI test, and the IDI test (e-Figs 2, 3, e-Tables 2, 3).

CPAP Effect on Recurrent PE and Resumption of Anticoagulation Therapy

CPAP was prescribed in 31 patients with OSA. CPAP compliance (CPAP use > 4 h/night) tended to be lower among patients with PE recurrence than among those without recurrence (17% vs 64%; $P = .051$).

To minimize any potential CPAP treatment effect, a further analysis was completed in only untreated patients or those with CPAP adherence < 4 h/night. In the multivariate Cox regression model, we found that the association of AHI ≥ 10 h^{-1} and risk of recurrent PE was slightly stronger than those shown in Table 3 and e-Table 4. Finally, OSA, $nSao_2$, and ESS remained independent risk factors for the resumption of anticoagulation therapy (e-Table 5).

Finally, to assess the effect of CPAP treatment on the risk of PE recurrence or the resumption of anticoagulation therapy, we compared the patients with OSA and adequate CPAP compliance and the patients with OSA without CPAP or with poor CPAP compliance. No significant risk differences between groups were found, probably due to the small sample size (e-Fig 4). However, when patients with OSA without CPAP or with poor CPAP compliance, were compared with subjects with no OSA or patients with OSA with adequate CPAP compliance, a higher risk of PE recurrence or resumption

TABLE 2] Characteristics of Patients With and Those Without Recurrence of PE

Variable	Patients with PE Recurrence (n = 19)	Patients Without PE Recurrence (n = 101)	*P* Value
Male sex, No. (%)	11 (58)	64 (63)	.418
Age, y	61 ± 12	57 ± 15	.239
BMI, kg/m^2	27.4 ± 7.2	28.3 ± 4.9	.634
Neck circumference, cm	38 ± 4	40 ± 4	.247
Current smoker, No. (%)	2 (11)	19 (19)	.308
Bronchial artery occlusion index, %	38.3 ± 21.3	30.5 ± 23.4	.218
Previous evidence of a classic risk factor for PE, No. (%)	18 (95)	79 (78)	.078
Hypertension, No. (%)	10 (53)	38 (38)	.166
Diabetes mellitus, No. (%)	0	16 (16)	.050
Dyslipidemia, No. (%)	5 (26)	32 (32)	.433
Heart failure, No. (%)	2 (11)	19 (19)	.600
COPD, No. (%)	1 (5)	27 (27)	.403
Cancer, No. (%)	2 (11)	15 (15)	.470
Depression/anxiety, No. (%)	4 (21)	16 (16)	.400
Cerebrovascular disease, No. (%)	1 (5)	5 (5)	.653
Daily physical activity, total METs	4,866 ± 7,389	3,753 ± 5,497	.626
FVC, % predicted	105 ± 19	101 ± 15	.401
FEV_1, % predicted	101 ± 16	97 ± 17	.390
FEV_1/FVC ratio	0.80 ± 0.06	0.78 ± 0.09	.211
Baseline Sao_2, %	95 ± 4	95 ± 3	.758
D-dimer, ng/mL	667 ± 770	469 ± 421	.366
F1+2, pmol/L	437 ± 237	438 ± 613	.990
EES	6.9 ± 4.5	6.8 ± 3.9	.927
Daytime sleepiness (ESS > 11), No. (%)	2 (11)	18 (18)	.344
AHI, h^{-1}	28.9 ± 23.3	19.7 ± 19.6	.120
AHI ≥10 h^{-1}, No. (%)	16 (84)	55 (54)	.012
AHI ≥30 h^{-1}, No. (%)	6 (32)	27 (27)	.428
Mean $nSao_2$, %	92 ± 2	94 ± 2	.035
Low $nSao_2$, %	77 ± 9	79 ± 10	.335
CT90%, median (IQR)	13 (1.7-28.0)	3.4 (0.5-33.1)	.630
Desaturation index, h^{-1}	25.6 ± 22.6	16.9 ± 18.9	.140

Values represent mean ± SD, median (interquartile range), or percentage, depending on their distribution. IQR = interquartile range; METs = metabolic equivalents; PE = pulmonary embolism. See Table 1 legend for expansion of other abbreviations.

of anticoagulation therapy was found in the untreated patients with apnea (e-Fig 5).

Discussion

The main finding in this study is that after a first episode of PE, patients with OSA had a higher risk of recurrent PE than did those without OSA. Moreover, AHI and nocturnal hypoxemia, assessed by the mean $nSao_2$ and CT90%, are independent risk factors for PE recurrence and for resuming anticoagulation because of a new thromboembolic event.

We have previously found a significant association between OSA and PE. In fact, for every 10-unit rise in AHI, the PE risk increased by 45%.[3] Some other cross-sectional and longitudinal studies have also suggested an association between OSA and PE.[4-8] PE is the result of Virchow's classic risk triad, namely, vascular endothelial impairment, stasis of blood flow, and increased coagulability, or a combination of these factors.[33] OSA could hypothetically affect all three mechanistic pathways. Intermittent hypoxia increases oxidative stress[34] and an inflammatory response that impairs endothelial

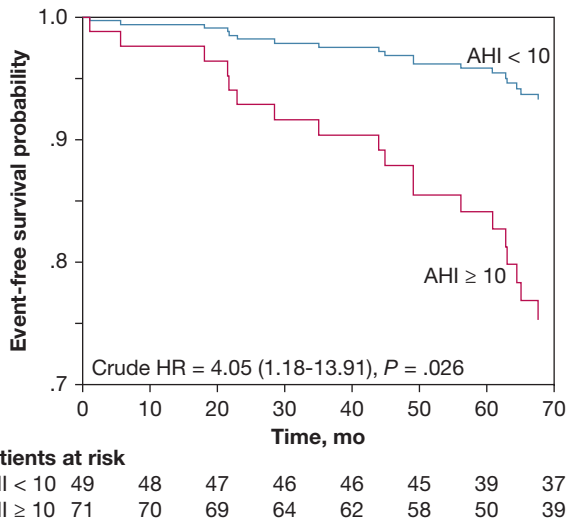

Figure 1 – *Time until first recurrent pulmonary embolism (PE) in patients classified according the apnea-hypopnea index (AHI). Crude hazard ratio (HR) is presented. AUC-ROC = area under the operating characteristic curve; DASH = D-dimer, age, sex, and hormonal therapy.*

function.[35] OSA-related hemodynamic alterations and sedentarism[36] may slow IV flow.[37] Also, increased coagulability, platelet activity, and decreased fibrinolytic capacity in OSA may be improved after CPAP.[22-25]

VTE recurs frequently, and nearly 30% of patients experience recurrence within 10 years.[38] Although numerous risk factors for a first VTE have been recognized, only a few are known to play a role in the prediction of a recurrent event; they include cancer, continued estrogen use, vena cava filters, high post-anticoagulation D-dimer levels, male sex, and obesity.[10-21]

Increased BMI seems to predict a recurrence of venous embolism. Eichinger et al[12] showed that compared with patients of normal weight, the risk of recurrence was 60% higher among obese patients.[12] Other groups have also reported that obesity is a risk factor for recurrent VTE in prospective studies,[10,14,39] and an algorithm developed to predict recurrent venous thromboembolism includes obesity.[40] To our knowledge, the potential impact of OSA as a risk factor for PE recurrence has never been explored. In the present study, we found that OSA is related to an increased risk of recurrent PE and other thromboembolic events. After adjusting for several confounding factors, including BMI, OSA remained an independent risk factor for recurrent PE and reintroduction of anticoagulation. Considering the high prevalence of unsuspected OSA among obese patients, the risk of recurrent PE that is commonly attributed to obesity might be partially related to OSA.

TABLE 3] Risk Factors for PE Recurrence

Risk Factor	Adjusted HR[a]	95% CI	*P* Value
D-dimer, ng/mL	1.001	1.000-1.002	.014
ESS	0.74	0.54-1.02	.65
AHI ≥ 10 h^{-1}	20.73	1.71-251.28	.017
Mean $nSao_2$, %	0.39	0.20-0.78	.008
Low $nSao_2$, %	1.01	0.90-1.14	.832
CT90%	0.90	0.82-0.98	.012

See Table 1 legend for expansion of abbreviations.
[a]Adjusted for sex, age, BMI, neck diameter, and presence of classic risk factors for PE, BP, FEV_1/FVC ratio, physical activity level, and all variables in table by multivariate Cox regression model.

Obesity is associated with sedentarism and venous stasis, and it has also been related to impaired fibrinolysis and high concentrations of clotting factors, which might lead to a prothrombotic state,[41] which can further increase because obesity is associated with high estrogen levels and chronic low-grade inflammation.[42] It is tempting to speculate that OSA and obesity may additively or synergistically lead to upregulation of procoagulant activity, which may intensify the risk of PE recurrence.

An elevated D-dimer level after the discontinuation of anticoagulation is recognized as a risk factor for recurrent PE.[43] Recently, we reported that the D-dimer levels of patients who discontinued anticoagulation after a first episode of PE are directly related to OSA severity.[27] In keeping with these data, we found that D-dimer levels were an independent risk factor for recurrence of PE. These results might be considered in balancing risks and benefits of extending anticoagulation, particularly in patients with PE with associated OSA.

Besides the AHI, we identified nocturnal hypoxia as an independent risk factor for the recurrence of PE. This finding is concordant with several pieces of evidence suggesting that intermittent hypoxia plays an important role in the procoagulant state of patients with OSA.[25,27] VTE frequently starts at the venous valves, where stasis and hypoxia may occur, which can induce endothelial injury, initiating a potentially hypercoagulable microenvironment.[44] Besides, OSA is associated with a sedentary lifestyle and obesity,[36] which may induce a procoagulant state and venous stasis; therefore, it might be hypothesized that nocturnal hypoxemia in patients with OSA may lead to upregulation of procoagulant activity in valvular sinuses.

The DASH score[30] and Vienna Prediction Model[13] are emergent useful tools for estimating PE recurrence.

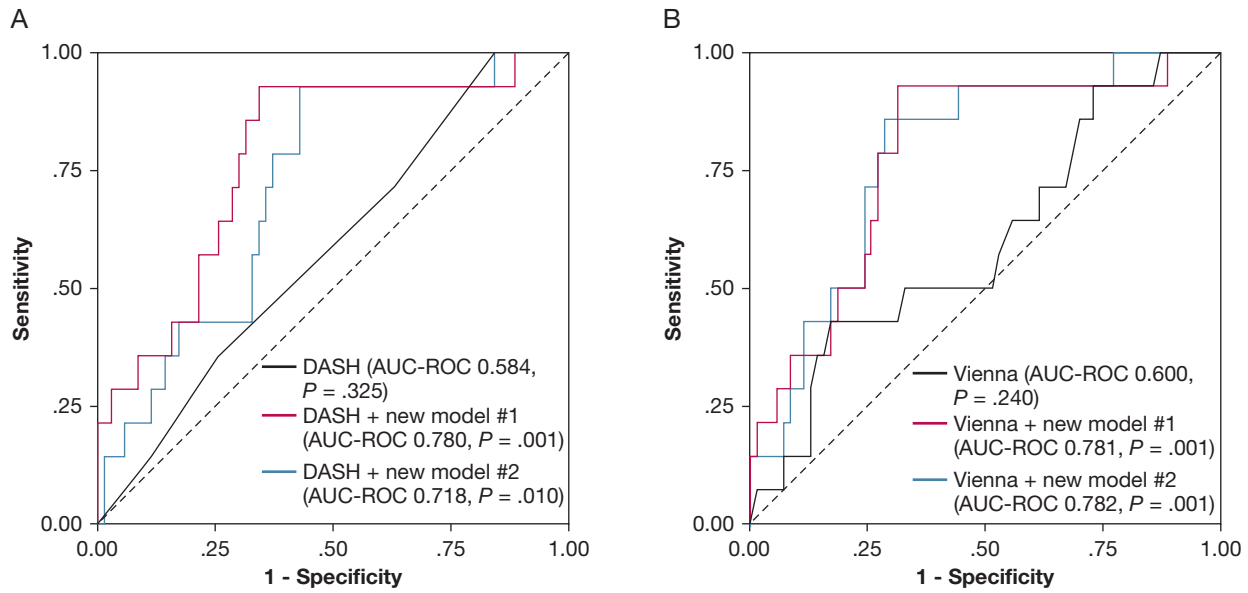

Figure 2 – *Receiver operating characteristics curves for prediction of pulmonary embolism recurrence after the follow-up period using the DASH or Vienna classic models alone (black lines in A and B, respectively) or together with the new risk model No. 1 (which includes apnea-hypopnea index (AHI) ≥ 10 h^{-1}, mean nocturnal oxygen saturation ($nSaO_2$), percentage of total time study spent with oxygen saturation < 90% (CT90%), and D-dimer level (red line) and the alternative risk model without D-dimer level (new model No. 2, blue line). See Figure 1 legend for expansion of abbreviations.*

Adding the new sleep risk factors identified in this study (AHI, mean $nSaO_2$, and CT90%) significantly improved the risk assessment of both the DASH score and Vienna Prediction Model, and although these new models with added value of OSA are promising, they must be externally validated in large prospective studies before generalization.

In the present study, we analyzed the whole cohort irrespective of CPAP treatment, because OSA is a

TABLE 4] Values for Prediction of Recurrent PE After Follow-Up Period

Statistic	Estimate	95% CI	*P* Value[a]
AUC-ROC DASH score alone	0.584	0.431-0.737	.325
AUC-ROC Vienna Prediction Model alone	0.600	0.437-0.763	.240
AUC-ROC new model No. 1 alone	0.787	0.662-0.912	.001
AUC-ROC new model No. 2 alone	0.724	0.605-0.842	.002
AUC-ROC DASH + new model No. 1	0.780	0.649-0.910	.001
AUC-ROC Vienna + new model No. 1	0.781	0.651-0.910	.001
IDI DASH + new model No. 1	0.1527	0.0314-0.2740	.017
IDI Vienna + new model No. 1	0.1443	0.0313-0.2573	.016
NRI DASH + new model No. 1	0.285	0.255-0.314	.029
NRI Vienna + new model No. 1	0.271	0.244-0.299	.001
AUC-ROC DASH + new model No. 2	0.718	0.586-0.851	.010
AUC-ROC Vienna + new model No. 2	0.782	0.661-0.902	.001
IDI DASH + new model No. 2	0.0768	0.0257-0.1279	.004
IDI Vienna + new model No. 2	0.1102	0.0385-0.1819	.003
NRI DASH + new model No. 2	0.215	0.196-0.235	.001
NRI Vienna + new model No. 2	0.529	0.497-0.560	.001

New model No. 1 includes all independent risk factors for PE recurrence identified in the previous multivariate model (AHI ≥ 10 h^{-1}, mean $nSaO_2$, CT90%, and D-dimer level). New model No. 2 includes the variables of model No. 1 without the D-dimer level. DASH = D-dimer, age, sex, and hormonal therapy; IDI = integrated discrimination improvement; NRI = net reclassification improvement. See Table 1 legend for expansion of other abbreviations.
[a]*P* values for AUC-ROC assess the difference from 0.5.

TABLE 5] Comparison of Patients Depending on Whether They Needed to Restart Anticoagulation

Variable	Patients Who Resumed Anticoagulation (n = 24)	Patients Who Discontinued Anticoagulation (n = 96)	*P* Value
Male sex, No. (%)	14 (58)	61 (64)	.403
Age, y	59 ± 13	57 ± 15	.539
BMI, kg/m^2	26.8 ± 6.6	28.5 ± 5.0	.297
Neck circumference, cm	38 ± 4	40 ± 4	.176
Current smoker, No. (%)	5 (21)	16 (17)	.414
Bronchial artery occlusion index, %	33.7 ± 21.4	31.2 ± 23.7	.644
Previous evidence of some classic risk factor for PE, No. (%)	19 (79)	78 (81)	.508
Hypertension, No. (%)	10 (42)	38 (40)	.515
Diabetes mellitus, No. (%)	0	16 (17)	.021
Dyslipidemia, No. (%)	6 (25)	31 (32)	.334
Heart failure, No. (%)	3 (25)	12 (18)	.398
COPD, No. (%)	2 (25)	18 (27)	.648
Cancer, No. (%)	3 (13)	14 (15)	.545
Depression/anxiety, No. (%)	4 (17)	16 (17)	.626
Cerebrovascular disease, No. (%)	1 (4)	5 (5)	.655
Daily physical activity, total METs	4,296 ± 6,765	3,814 ± 5,537	.788
FVC, % predicted	106 ± 18	100 ± 15	.142
FEV_1, % predicted	101 ± 15	97 ± 17	.250
FEV_1/FVC	0.80 ± 0.05	0.78 ± 0.09	.249
Baseline Sao_2, %	95 ± 3	95 ± 3	.755
D-dimer, ng/mL	489 ± 271	505 ± 537	.863
F1+2, pmol/L	693 ± 516	378 ± 567	.155
EES	6.5 ± 4.1	6.9 ± 4.0	.643
Daytime sleepiness (ESS > 11), No. (%)	2 (8)	18 (19)	.181
AHI, h^{-1}	25.8 ± 21.5	20.0 ± 20.1	.243
AHI ≥ 10 h^{-1}, No. (%)	20 (83)	51 (53)	.005
AHI ≥ 30 h^{-1}, No. (%)	6 (25)	27 (28)	.489
Mean $nSao_2$, %	92 ± 3	93 ± 2	.090
Lowest $nSao_2$, %	77 ± 10	79 ± 10	.268
CT90%, median (IQR)	31 ± 52	26 ± 61	.715
Desaturation index, h^{-1}	24.0 ± 21.3	16.9 ± 19.1	.163

Values represent mean ± SD, median (interquartile range), or percentage, depending on their distribution. See Table 1 and 2 legends for expansion of abbreviations.

chronic syndrome and, therefore, patients would have been exposed to intermittent hypoxia and other OSA-related consequences for many years before starting treatment. However, because a treatment effect may have hidden a possible association between OSA and risk of recurrence, we conducted a further analysis excluding treated patients with OSA and adequate CPAP adherence (> 4 h/night) and found similar results. This finding should not be interpreted as a lack of efficacy of CPAP in preventing PE recurrence. In fact, although nonsignificant, CPAP compliance tended to be lower among patients with PE recurrence than among those without recurrence (64% vs 17%; $P = .051$). Interestingly, in our study, the AHI cutoff that identified an increased risk of PE recurrence was 10 and not 30. In addition to the small number of subjects with AHI > 30, it is possible that the CPAP prescription in patients with severe OSA justifies its lack of predictive ability. In any case, we acknowledge that our study was not designed to address this issue, and a large randomized controlled trial is needed to clarify if CPAP decreases the risk of recurrent PE.

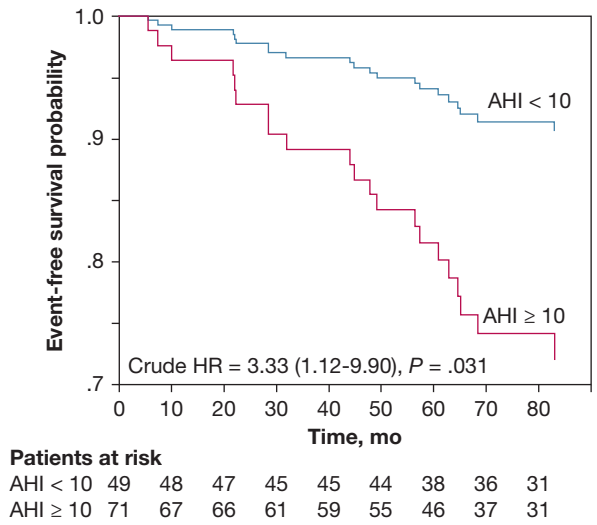

Figure 3 – *Time until resumption of anticoagulation in patients with a first episode of pulmonary embolism classified according to the AHI. Crude HR is presented. See Figure 1 legend for expansion of abbreviations.*

TABLE 6] Risk Factors for Resumption of Anticoagulation Therapy in a Multivariate Model

Variable	Adjusted HR[a]	95% CI	*P* Value
D-dimer, ng/mL	1.000	0.999-1.001	.599
ESS	0.73	0.56-0.97	.028
AHI ≥ 10 h^{-1}	20.66	2.27-188.35	.007
Mean $nSaO_2$, %	0.54	0.32-0.94	.028
Low $nSaO_2$, %	1.00	0.91-1.11	.939
CT90%	0.93	0.87-1.003	.060

See Table 1 legend for expansion of abbreviations.
[a]Adjusted for sex, age, BMI, neck diameter, presence of classic risk factors for PE, BP, FEV_1/FVC ratio, physical activity level, and all variables in this table by multivariate Cox regression model.

The main strength of the present study is the long-term follow-up of our patients, but there are also a number of limitations that should be considered. First, the status of pulmonary and upper limb vessels was not routinely investigated, so we could not rule out asymptomatic events. Second, although OSA diagnosis was based on a type 3 portable sleep monitoring system without electroencephalographic signals, it has been previously validated, and all patients were studied with the same device. Third, there is strong evidence that the risk of recurrence after stopping anticoagulation therapy is higher among unprovoked patients with PE than in those ones with provoked PE. We included only 38 unprovoked patients with PE, which precluded any further analysis; therefore, we do not know the impact of OSA on the risk of PE recurrence in the subgroup of unprovoked patients with PE. Finally, this was an observational study with few patients receiving CPAP and without random assignation, which limits any supplementary subanalyses on CPAP influence.

To conclude, we have found that OSA is an independent risk factor for recurrent PE and the reinstitution of anticoagulation treatment, indicating that these patients have a persistent hypercoagulable state. Despite identification of classic PE recurrence risk factors and the development of new prophylaxis regimens, the occurrence of PE is growing, so recognizing OSA as a risk factor for PE recurrence might enhance our ability to predict new thromboembolic events. Given the high prevalence of OSA in patients with PE, the procoagulability state induced by intermittent hypoxia, and the risk for PE recurrence, the potential for CPAP and the extension of oral anticoagulation (or both) to reduce PE recurrence and mortality in patients with PE and OSA clearly warrants further study.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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