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CLINICAL REVIEW

Obstructive sleep apnea and venous thromboembolism: Overview of an emerging relationship

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SUMMARY

Obstructive sleep apnea (OSA) is a risk factor for cardiovascular syndromes. Venous thromboembolism (VTE) is a chronic disease, and pulmonary embolism (PE) is the major expression of VTE and the third most frequent cardiovascular disease. An increasing and emerging number of cross-sectional and longitudinal studies have linked OSA to VTE, and have postulated different putative pathways to explain how OSA might increase the risk of PE.

We aim to provide a critical overview of the existing evidence about the complex relationship between these two conditions, with some factors and confounding variables still to be clarified. A global interpretation of the studies shows OSA is highly prevalent in VTE patients. This association represents a major public health burden, given the high prevalence and the mortality rates of both disorders. Although still not proven, OSA may induce a persistent hypercoagulable state that may contribute to increase VTE rate and its recurrence. Coagulant activity, platelet function and fibrinolytic system may improve after continuous positive airway pressure (CPAP) in OSA. However, there is a still a lack of randomized controlled trials to evaluate the potential of CPAP and/or extend oral anticoagulation to reduce PE incidence, recurrence and mortality by PE in patients with OSA.

Introduction

Venous thromboembolism (VTE) is a frequent, chronic and potentially fatal disease. Pulmonary embolism (PE) is a major manifestation of VTE and is the third most frequent cardiovascular disease. The overall annual incidence rate of VTE ranges between 75 and 269 cases per 100,000 persons, as it has been shown by studies performed in Western Europe, North America, Australia, and southern Latin America. Importantly, there is a dramatic increase in the risk of VTE with increasing age (particularly in women). The risk of VTE approximately doubles with each decade after the age of 40 years, with subjects 70 years of age or older having an incidence of up to 700 per 100,000 [1,2].

PE is a major public health burden. It has been reported as having a 30-day and one year mortality at 4 and 13 percent, respectively, and this case-fatality rate increases with age. PE accounts for 370,000 related deaths every year in six European countries [1], and mortality is likely to increase as the population ages due to the global epidemic of obesity in developing and emerging countries [3]. Anticoagulation is recommended in patients with acute PE because it is highly effective in reducing both early death and the PE recurrence rate.

PE is the result of the interaction between patient-related (usually permanent) and setting-related risk factors (e.g., surgery for hip fracture or total hip and knee replacement, major surgery, or trauma and spinal cord injury). Numerous studies have identified patient-related risk factors for PE, including age, active cancer, congenital or acquired thrombophilia, hormone replacement and oral contraceptive therapy, previous PE, and obesity [1].

Obstructive sleep apnea (OSA) is characterized by repetitive partial or complete closure of the upper airway during sleep despite increased respiratory effort. It is a common disorder, and prevalence surveys estimate that 17% of women and 34% of men in middle age are affected by this syndrome [4]. Cardiovascular disturbances are the most important complications of OSA and may

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Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
CT90%	Percentage of total time study spent with $nSaO_2$<90%
DVT	Deep vein thrombosis
$nSaO_2$	Nocturnal oxygen saturation
OSA	Obstructive sleep apnea
PAI-1	Plasminogen activator inhibitor type-1
PE	Pulmonary embolism
TPA	Tissue-type plasminogen activator
VTE	Venous thromboembolism

cause severe morbidity and mortality [5]. Some risk factors for OSA, including obesity, increasing age, and sedentary lifestyle are the same as those for PE [1,6]. In addition, there is increasing evidence of a hypercoagulable state in OSA [7–11]. Several studies have reported that fibrinogen [7], D-dimer [8], platelet activity and aggregability [12], and hematocrit [9] are elevated and that the fibrinolytic capacity [10] was reduced in OSA patients compared with healthy controls. On the other hand, short and medium-term continuous positive airway pressure (CPAP) therapy may reduce exaggerated coagulant activity [7,8], platelet function [11], and improve fibrinolytic capacity [10] in OSA patients, which might possibly provide an explanatory link for the high prevalence of vascular diseases and PE in these patients.

There is growing evidence from cross-sectional, retrospective and longitudinal studies that OSA could be a risk factor for PE [13–30]. This association represents a major public health burden, given the high prevalence and mortality rates of both disorders.

The aim of this review is to identify and critically evaluate the current evidence that supports the existence of a possible relationship between OSA and thromboembolic disease. To perform a systematic review on the most relevant aspects of this relationship, we conducted a bibliographic search with no time restrictions in the PubMed databases and the complete databases of the Web of Science, focused on the identification of clinical series about the OSA-VTE association, descriptions of coagulation alterations induced by sleep apnea or by its main components, and evaluations of the effect of apnea suppression on the embolic profile. The studies were required to have a precise methodology, while clearly presenting the importance and limitations of their results in the interpretation of the evaluated association. The keywords sleep-apnea, intermittent hypoxia, sleep fragmentation, venous thromboembolism, pulmonary embolism, coagulation, platelet, D-dimer and anticoagulation were used, and the search was limited to the English language. The initial searches identified a total of 558 studies. After excluding duplicates, there were 546 and 435 were subsequently removed after title and abstract screening. 111 full-text articles were assessed for eligibility, of which 48 were excluded: 26 studies did not include information about VTE or coagulation, 17 did not include participants/models with OSA, and five studies included patients with hypoxemia secondary to other respiratory disorders (Fig. 1). Finally, 63 studies were included in our narrative synthesis.

Next, we describe our contemporary understanding of the emerging relationships between OSA and VTE. We also provide the available evidence of mechanisms by which OSA might contribute to the pathogenesis of VTE, and we assess clinical and epidemiological data of such association. Finally, in order to better understand unresolved questions, we consider directions for future research.

OSA and venous thromboembolism

Obesity and age are the main OSA risks factors. Therefore, its prevalence is rising as the population ages and obesity rates increase in developing and emerging countries. Each episode of airway obstruction starts a sequence of adverse hemodynamic, inflammatory, and autonomic events. Exaggerated negative intrathoracic pressure, intermittent hypoxia and hypercapnia, and arousal from sleep that elicits sleep fragmentation repeated with every apnea/hypopnea episode, minute after minute, over the course of the night and over time have been recognized as the main factors that may elicit increases of inflammatory mediators and oxidative stress status. These changes could generate endothelial dysfunction, and arterial stiffness, leading to atherosclerosis, ventricular hypertrophy and cardiac chambers remodelling. As a result, OSA has been recognized as a cause of systemic hypertension, based on the increased prevalence and incidence of hypertension among patients with OSA, an observed dose–response effect between the severity of OSA and the likelihood of hypertension, and the fact that CPAP, although modestly, can decrease systemic blood pressure but by levels that are clinically significant [31]. In addition, observational studies have demonstrated a consistent association between OSA and coronary heart disease, cardiac arrhythmias, heart failure, stroke, and pulmonary hypertension [5]. PE is the third most frequent cardiovascular disease but its relationship with OSA has not been studied until recently.

We identified 18 studies exploring the association between OSA and VTE (Table 1). Overall, the risk of deep vein thrombosis (DVT) or PE was found to be two to four-fold higher in OSA patients compared to those without.

Data from cross-sectional studies

Arnulf et al. [14] reported this relationship for the first time. They found that 63% of 72 patients with PE or DVT had an AHI greater than 15 h^{-1} and concluded that these findings suggest a possible association between OSA and PE because previous studies had shown a lower OSA prevalence (around 15%) in the general population between 60 and 65 years. OSA patients were older (66 vs. 54 years), therefore, age could be a confounding factor. In order to study this fact better, Epstein et al. performed a case–control study, where they found that 71 patients with PE had a higher prevalence of snoring and risk of having OSA than 199 control subjects (in whom PE was suspected but ruled out by computed tomography pulmonary angiography) [15]. Moreover, multivariate analysis revealed a significant and independent association between PE and the risk of OSA (OR = 2.78, p = 0.001). However, there was a higher prevalence of men and a lower prevalence of heart failure in the PE group than in control subjects, and controls were patients with suspected PE and probably additional heart or lung syndromes. Nevertheless, the main limitation of this study was that the patients underwent no sleep study to confirm the presence and severity of associated OSA, which was defined by questionnaire. In a more precise approach, three case–control studies were published with sleep studies in all participants. Kosovali et al. [25] performed a small case–control study including 28 patients with PE and 45 controls (selected from the sleep clinic). Mean AHI was found to be higher in the PE group compared with the control group. Twenty PE subjects had OSA (72.5%), and severe OSA was only identified in the PE group (21.4%). Arzt et al. completed a larger case–control, in which controls were selected from the hospitalised patients without VTE, in the same institution [22]. The frequency of

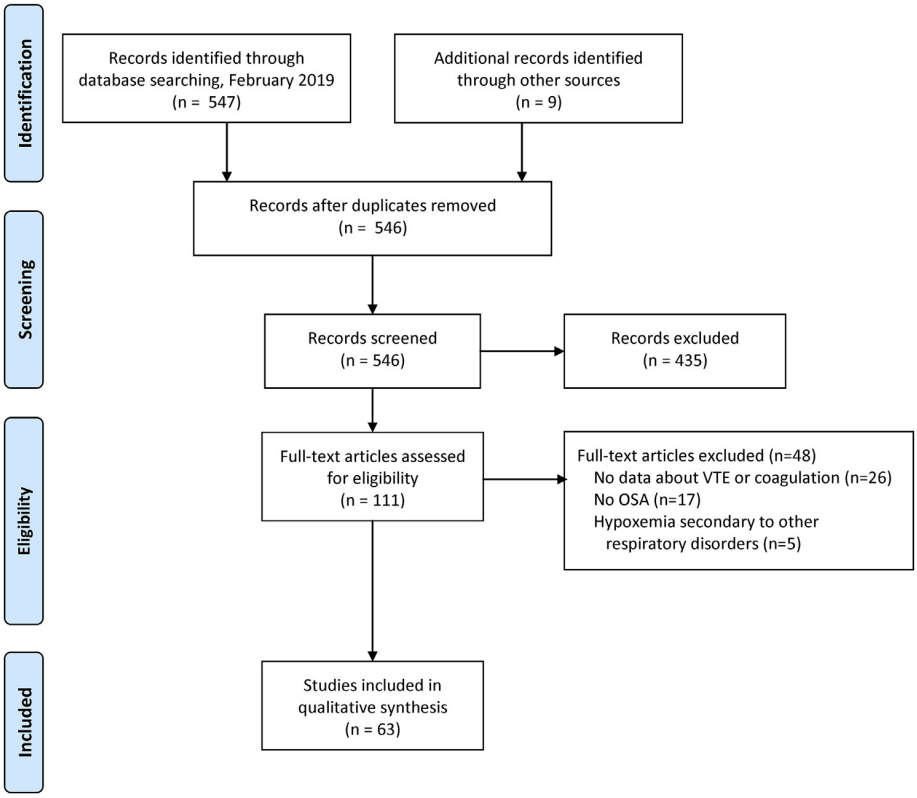

Fig. 1. Flow of information through the different phases of the selection process of the papers included in this review.

OSA with at least a moderate severity degree was found to be higher in VTE cases than in controls (40 versus 26%). OSA was found to be significantly associated with the risk of VTE (OR, 2.28; 95% CI, 1.08–4.85). Remarkably, this association was found to be stronger in women than in men. Nevertheless, the non-significantly increased odds ratio in men may reflect a lack of study power (due to the lower sample size in the sex-specific subanalyses) rather than a real lack of association, as this result has not been reproduced in other studies. Similarly, we have shown a significantly higher PE prevalence in all OSA severity groups when compared with controls in a larger study of 107 PE patients from two different hospitals. We also found a significant association between AHI and PE after adjustment for the main confounding factors. Using AHI as a continuous variable, the adjusted OR was 1.038, which indicated that for every 10-unit rise in AHI, PE risk increased by 45% [32].

The most recent data comes from a single-center that establishes fairly comparable OSA prevalence in PE patients. The authors selected 106 consecutive PE patients who were prospectively evaluated by a portable sleep study device [33]. Nocturnal polysomnography was performed in all subjects who had an AHI>15 h^{-1} or evidence of increased daytime sleepiness. OSA prevalence was 58.5%, and 10.4% were severe. Interestingly, the same group selected 206 acute PE patients who were able to specify the precise time of PE symptom onset. In addition to finding a high OSA prevalence (66% had AHI≥5 h^{-1}), they showed that symptom onset of PE was significantly more frequent during sleep time in patients with moderate or severe OSA compared to patients with an AHI<15 h^{-1}. Moreover, the probability of sleep-related PE manifestation increased with the severity of OSA [29].

Together, these findings suggest that OSA prevalence is higher in PE patients than in those subjects without.

Data from provoked VTE patients

Even more importantly, the risk of a provoked DVT or PE episode was found to be two-to four-fold higher in the populations of patients with OSA than in those without. A retrospective observational analysis of 5554 severe obese patients after bariatric surgery identified 12 patients dying from PE [16]. The prevalence of OSA was found to be high in these patients (4/12; 33%); more than two-fold higher than that reported in the general population. On the other hand, in only one retrospective case–control investigation including 7282 patients who underwent arthroplasty, the OSA prevalence was found to be slightly, but not significantly higher in patients who had PE than in those who did not (6.5% vs. 5.4%; $p = 0.593$). OSA was not found to be significantly associated with the risk of VTE [17]. Conversely, D'Apuzzo and Browne retrospectively reviewed data from the US Nationwide Inpatient Sample. They included 258,455 patients who underwent arthroplasty, with 16,608 (6.4%) being diagnosed with OSA and 511 with PE. Patients with OSA had a two-fold higher rate of a provoked PE episode compared to those without (0.4 vs. 0.2%). Accordingly, OSA remained an independent post-operative PE risk factor after adjustment for age, body mass index (BMI), gender and comorbidities (OR, 2.02; 95% CI, 1.3–2.9) [23]. Similarly, Memtsoudis et al. [18] performed a population-based sample retrospective US study that aimed to analyse perioperative demographics and pulmonary outcomes of patients with OSA after orthopaedic ($n = 2,610,441$) and general surgical procedures ($n = 3,441,262$). Patients with OSA had more frequent pulmonary complications (most significantly perioperative tracheal intubation and mechanical ventilation) than their matched controls. In addition, PE was slightly more frequent in orthopedic OSA patients (0.51 vs. 0.42%), but PE incidence was not influenced by OSA in the group of general surgery patients (0.45

Table 1
Summary of the major studies investigating the association between obstructive sleep apnea and venous thromboembolism disease.

Author	Type of Study	Subjects	Mean age, y	Mean BMI, kg/m^2	OSA diagnosed by	Main limitations	Conclusions
Arnulf et al., 2002 [14]	Cross-sectional	68 patients with VTE (10 with DVT and 58 with PE)	–	–	Polysomnography	No comparative group. OSA patients were older (66 vs 54 years)	High prevalence of moderate-severe OSA (63%) in patients with VTE
Sapala et al., 2003 [16]	Retrospective, observational	5554 operations of bariatric surgery (12 fatal PE)	39	59.2 ± 4.8	Not specified	No comparative group. Retrospective single centre study	High prevalence of OSA (33%) in patients with fatal PE
Ambrosetti et al., 2004 [13]	Prospective, observational	89 patients with OSA followed for 3 years	62 ± 11	34.4 ± 6.8	Polysomnography	No comparative group. Very small sample size	Incidence of VTE in patients with OSA higher that in historical general population (DVT: 0.8 vs 0.05 per 100/year; PE: 0.4 vs 0.1 per 100/year)
Epstein et al., 2010 [15]	Case-control	270 consecutive patients with suspected PE (71 with established PE)	60 ± 16	28.7 ± 7.0	Berlin Questionnaire	No objective OSA diagnosis. Gender and clinical differences between groups	Higher prevalence of snoring and risk of having OSA (65%) than control subjects
Mraovic et al., 2010 [17]	Retrospective case–control study	7282 patients (107 with PE) undergoing total hip or total knee arthroplasty	–	–	Medical records	PE patients were older and had a higher obesity rate. Possibility of coding inaccuracy	OSA prevalence was found not significantly higher in patients who had PE than in those who had not (6.5% vs 5.4%; p = 0.593).
Memtsoudis et al., 2011 [18]	Population-based sample, retrospective	2,610,441 orthopedic patients and 3,441,262 general surgical patients (OSA 2.52% and 1.40%, respectively)	Orthopedic OSA: 63, general surgical OSA: 53	–	National Inpatient Sample	Readmissions and events after discharge were not registered. Obesity rate was unexpectedly low in both non OSA groups. Possibility of coding inaccuracy	PE was slightly more frequent in orthopedic OSA patients (0.51 vs. 0.42%, P = 0.0038) but not in general surgical patients (0.45 vs. 0.49%, P = 0.22).
Bosanquet et al., 2011 [19]	Retrospective, observational	840 patients with VTE (130 with OSA)	55	31.5	Polysomnography	Inherent weakness of a retrospective study. It could not be ascertained whether OSA preceded VTE or vice versa	OSA prevalence (AHI≥5 h^{-1}) was 15.5% in those patients with DVT and/or PE. OSA patients had higher prevalence of PE (71.7% vs 61.9%; p = 0.047) but similar rates of DVT
Kezban et al., 2012 [20]	Retrospective, observational	30 patients with PE (10 with major risk factor for VTE and 20 without)	61 ± 3	–	Polysomnography	No comparative group. Small sample size	High prevalence of OSA (AHI ≥ 5 h^{-1} 57%), in patients with PE
Chou et al., 2012 [21]	Prospective, case–control	5680 patients with OSA and 4505 without followed up for 3.6 years	45 ± 18	–	National Health Insurance Research Database	No data on OSA severity, BMI, smoking status or proportion of OSA patients on CPAP. PE not evaluated. Possibility of coding inaccuracy	OSA independent risk factor for DVT (HR, 3.11; 95% CI, 1.52–6.39). No data on PE Incidence
Arzt et al., 2012 [22]	Case-control	82 patients with VTE and 82 matched controls	VTE: 57 ± 17 Controls: 56 ± 17	27.6 ± 4.5	Type 3 portable sleep monitoring system	Single centre study	OSA prevalence (AHI≥5 h^{-1}) was found to be higher in VTE cases than in controls (76 versus 57%, p = 0.013). OSA was found to be significantly associated with the risk of VTE (OR, 2.28; 95% CI, 1.08–4.85). Remarkably, this association was found to be stronger in women
D'Apuzzo et al., 2012 [23]	Case-control	258,455 patients (16,608 with OSA) undergoing total hip arthroplasty or total knee arthroplasty	67	–	US Nationwide Inpatient Sample	Incomplete data collection, uncertain accuracy of coding related to diagnosis and procedures	OSA independent risk factor for PE (OR, 2.02; 95% CI, 1.3–2.9) OSA patients had a two-fold higher rate of provoked PE compared to those without (0.4% vs 0.2%; p = 0.001). OSA remained an independent post-operative PE risk factor after adjustment for age, BMI, gender and comorbidities (OR, 2.02; 95% CI, 1.3–2.9).
Lin et al., 2013 [24]	Prospective, case–control	15,664 subjects (1424 with OSA) followed up for five years	56 ± 12	–	Longitudinal Health Insurance Database	No data on OSA severity, BMI, or proportion of OSA patients on CPAP. Possibility of coding inaccuracy	2-fold higher VTE incidence in patients with OSA than in those without (1.3% versus 0.5%). OSA independent risk factor for VTE (HR, 2.07; 95% CI, 1.21–3.52) and DVT (HR, 1.88; 95% CI, 1.08–3.29)

Table 1 (*continued*)

Author	Type of Study	Subjects	Mean age, y	Mean BMI, kg/m^2	OSA diagnosed by	Main limitations	Conclusions
Kosovali et al., 2013 [25]	Case-control	28 patients with PE and 45 controls	PE: 55 ± 17 Controls: 50 ± 13	30.5 ± 6.6	Polysomnography	Single centre and small sample size. Control group were subjects who were referred to the sleep clinic	Mean apnea-hypopnea index (AHI) was found to be higher in the PE group compared with the control group (p = 0.010). 20 PE subjects had OSA (72.5%). Severe OSA was identified in 21.4% of the PE group but in no controls (p = 0.015).
Alonso-Fernández et al., 2013 [26]	Case-control	107 patients with PE and 102 controls	PE: 57 ± 15 Controls: 54 ± 15	27.6 ± 4.9	Type 3 portable sleep monitoring system	Controls were not evaluated by CT. DVT was not routinely determined.	OSA was more frequent in patients with PE than in a population without previous history of PE (75 versus 45%, p = 0.00003) OSA independent risk factor for PE (OR for every 10-unit rise of apnea-hypopnea index, 1.04; 95% CI, 1.01 −1.07)
Louis et al., 2014 [27]	Retrospective, cross-sectional analysis.	55,781,965 pregnancy-related inpatient hospital discharges	–	–	Nationwide Inpatient Sample database	Possible mistakes in coding. Exceptionally low obesity prevalence (1.5%)	OSA independent risk factor for PE (OR, 4.47; 95% CI,2.25 −8.88)
Peng et al., 2014 [28]	Population retrospective cohort study	3511 patients with OSA and 35,110 matched controls	42 ± 17	–	Taiwan National Health Insurance Research Database	No data on BMI/obesity prevalence and proportion of OSA patients on CPAP. Possibility of coding inaccuracy	OSA was found to be independent risk factor for both DVT (HR, 3.50; 95% CI, 1.83−6.69) and PE (HR, 3.97; 95% CI, 1.85−8.51).
Berghaus et al., 2016 [29]	Cross-sectional	106 PE patients	63.3 ± 1.4	28.8 ± 0.5	Type 4 portable sleep study device + polysomnography	No comparative group. OSA patients were older (69 vs 62 years)	OSA prevalence was 58.5%, and 10.4% were severe (AHI>30/h^{-1})
Berghaus et al., 2016 [30]	Cross-sectional	206 PE patients	60.4 ± 1.2	29.9 ± 0.5	Type 4 portable sleep study device + polysomnography	No comparative group. OSA patients were older (31 vs 30 years)	OSA (AHI≥5 h^{-1}) prevalence was 66%. Symptom onset was significantly more often sleep-related in subjects with an AHI>15 h^{-1}compared to patients with an AHI<15 h^{-1}.

AHI, apnea hypopnea index; BMI, body mass index; DVT, deep vein thrombosis; OSA, obstructive sleep apnea; PE, pulmonary embolism; VTE, venous thromboembolism.

vs. 0.49%, p = 0.22). This study is limited by the normal analysis of large administrative databases as clinical information and complications, readmissions and events after discharge were not registered. Furthermore, the obesity rate was unexpectedly low in both non OSA groups (6 and 4.3%), when the prevalence of obesity in the USA in that period was equal to or greater than 20% [3]. Finally, a US study included 55 million pregnancy-related inpatient hospital discharges. The whole rate of OSA was 3.0 per 10,000; however, the rate increased extensively from 0.7 in 1998 to 7.3 in 2009, with an average annual upsurge of 24%, which was paralleled by an average 20% annual increase in obesity rates. Women with OSA were older and used more tobacco, alcohol and illegal drugs during pregnancy than other women. After adjusting for known/suspected socio-demographic and clinical confounders accessible in the database, OSA during pregnancy was more probably associated to experiencing adverse clinical conditions and pregnancy-related complications. PE was found to be markedly more frequent in pregnant women with OSA than in those without, and it was found to be a significant and independent risk factor for PE (OR, 4.47; 95% CI, 2.25−8.88). The main limitation is that the source of data is subject to errors in coding, which increase false-positive and false-negative diagnoses. It is important to highlight the extremely low obesity prevalence (1.5%) reported in this study population in comparison with the published literature that defines obesity using pre-pregnancy BMI [27].

While almost all these studies suggest an association between OSA and provoked VTE, the fact that a substantial variation was observed in the prevalence of OSA (7%−33%) in these samples stands out and this association needs to be confirmed in other cohort studies.

Data from retrospective studies and population-based samples

Bosanquet et al. performed a retrospective observational study including 840 patients who were diagnosed of VTE for 10 years in a single hospital. One hundred and thirty had concomitant OSA (defined with AHI>5 h^{-1} or the presence of OSA in the patient's medical history confirmed by a sleep study in an outside laboratory); OSA prevalence was 15.5% [19]. However, the largest population retrospective cohort study included 3511 patients with OSA and 35,110 matched controls recruited from a Taiwan database [28]. Twenty-six VTE cases were identified in OSA patients (15 DVT and 11 PE) and 51 in those without (30 DVT and 21 PE) during the follow up period (12 years). OSA was found to be an independent risk factor for VTE. In multivariable Cox proportional hazard regression, adjusted for age and the main comorbidities, OSA was found to be

an independent risk factor for both DVT (HR, 3.50; 95% CI, 1.83–6.69) and PE (HR, 3.97; 95% CI, 1.85–8.51). The risk was slightly higher during the first two years, but increased throughout the study period. The main problems were that the investigators did not collect weight and BMI data, and therefore they could not rule out the influence of obesity on the results. Furthermore, they did not report how many OSA patients were on CPAP during the follow up.

Based on these findings, OSA appears to be highly prevalent in patients with PE. However, more rigorous investigations systematically employing sleep studies in all subjects, with attention to important confounding factors such as body habitus, age and cardiovascular risk, are needed.

Data from prospective studies

Some other prospective and longitudinal studies have also suggested an association between OSA and PE. Ambrosetti et al. evaluated the incidence of VTE in 89 patients with OSA, who were followed up for three years. Overall, two episodes of VTE were found during follow-up. Compared to the general population, a substantially higher incidence of first episode of both DVT (0.8 vs. 0.05 per 100/year) and PE (0.4 vs. 0.1 per 100/year) was found in patients with OSA [13]. This first prospective study offered preliminary findings, but the lack of a control group, and the very small sample size limited the evidence and generalization of the results. Consequently, a large cohort study was conducted to better understand the association between OSA and VTE, including 1424 newly diagnosed OSA patients, and a group of 14,240 subjects selected from insurance records who were prospectively followed up for five years [24]. The rates of incident VTE (1.3% versus 0.5%) and DVT (1.2% versus 0.5%) were more than 2-fold higher in OSA patients than in those without. As expected, OSA patients had a higher prevalence of several comorbidities associated with VTE and OSA, including cancer, inflammatory bowel disease, heart failure, hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, renal disease, and obesity. Conversely, regression analysis revealed that OSA remained a significant and independent risk factor for both VTE (HR, 2.07; 95% CI, 1.21–3.52) and DVT (HR, 1.88; 95% CI, 1.08–3.29) after adjusting for the aforementioned comorbidities. In addition, the authors stratified the subjects by gender, and found that the adjusted HR of VTE during the 5-year follow-up period was statistically significant both in males and females. No data related to how many OSA patients were on CPAP treatment or their compliance was reported. Moreover, BMI was not available and the authors could only adjust for the presence of confounding through the use of ICD-9 coding for obesity (BMI>27), leaving, as in the previous works, substantial room for residual confounding. With a similar approach, Chou et al. completed the largest prospective study of the relationship between OSA and DVT. They selected 5680 OSA patients and 4505 without (matched for age, sex, comorbidities, major operation, and fractures), who were followed up for a mean period of 3.6 years. Forty patients (0.39%) had DVT on follow-up, and cumulative incidence was more than double in patients with OSA than in those without (0.53 vs 0.22%) [21]. In regression analysis, OSA was found to be a significant and independent predictor of DVT (HR, 3.11; 95% CI, 1.52–6.39). This association was found to be even stronger in patients with OSA needing CPAP treatment, which could suggest that more severe OSA patients probably have a higher risk of DVT. However, factors associated with increasing severity of OSA, such as sedentariness, obesity, and underlying comorbidities, may also lead to an augmented risk for DVT. Nevertheless, this study has some limitations. The most important one is that the diagnoses of OSA and DVT were collected from physician registered data. Consequently, there are no data on real OSA severity, nor on CPAP recommendation or compliance rates. Additionally, some personal information, such as BMI and smoking status was not available, so it was impossible to assess the contributory and confounding effect of these factors.

A limited number of studies have examined whether OSA increases the incidence of VTE. Based on these findings, OSA appears to be a risk factor for new VTE episodes, but it could also be possible that the increased risk may be related to some associated comorbidities, such as obesity or other comorbidities than to OSA per se.

Taken together, the available epidemiological data supports the hypothesis that patients with OSA may have an increased risk of VTE. In all studies, with the exception of one that could be identified in our literature search (17/18; Table 1), OSA was found to be a potential independent risk factor for either DVT and/or PE. The prevalence was wide-ranging depending on the study design, the sleep monitoring system used, OSA definition and the population characteristics of each study, but it was much higher than non VTE populations (Table 1 and Fig. 2). It seems that it is even higher in those patients with recurrent VTE, which may suggest that OSA leads to a persistent hypercoagulable state. On the other hand, the OSA prevalence in patients with provoked VTE (after surgery or gestation-related) was found to be lower compared with those patients of studies which included different proportions of provoked and unprovoked VTE episodes, although statistically higher than the comparative control groups in most studies. This finding may be explained by the fact that hip and knee surgery or gestation are usually considered strong prothrombotic states, which may overwhelm any other risk factor and, therefore, decrease the potential impact of OSA in the pathogenesis of VTE.

When VTE triggering factors are combined with non-triggering factors, there is a greater increase in the risk of VTE than that corresponding to each factor separately [34]. In the same manner, a recent retrospective study found that OSA with concomitant chronic obstructive pulmonary disease patients had significantly higher risk of PE compared with those with isolated OSA, and this risk remained significant after adjusting for age, sex, BMI and modified Charlson Comorbidity Index [35]. Therefore, OSA also appears to be a contributing non-triggering factor that, combined with other non-triggering factors, may further increase the risk of VTE.

The OSA and VTE relationship is very complex with many factors and confounding variables still to be clarified. Observational studies

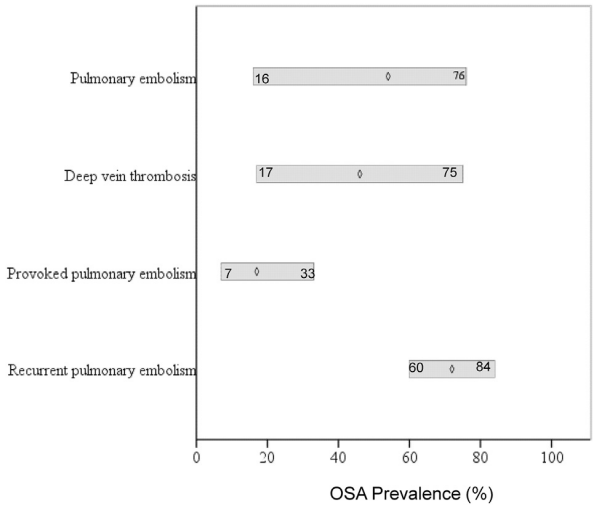

Fig. 2. Obstructive sleep apnea (OSA) prevalence in venous thromboembolism disease (VTE).

have found a consistent association between OSA and VTE. Even though most studies have shown that this association was independent of the confounding influence of obesity, it is not clear in any given patient whether OSA lies directly along the pathway or is linked through common comorbidities (also associated with OSA) such as metabolic syndrome or diabetes mellitus. In addition, aging could be an important confounding factor as it is closely related to both OSA and VTE. However, several cross-sectional studies found that OSA was an age-independent PE risk factor (when compared to a control group matched for age) [21,22,24,32] and a prospective study found a high incidence of first VTE in OSA patients with no differences in age when comparing OSA patients with randomly selected comparison subjects [24].

Discussion

Potential mechanisms of the relationship between obstructive sleep apnea and venous thromboembolism

OSA effect on Virchow triad

PE is the result of Virchow's classic risk triad, namely vascular endothelial impairment, stasis of blood flow, and/or increased coagulability or a combination of these factors [36]. The pathophysiological mechanisms linking OSA and VTE are far from being clearly determined, but OSA could hypothetically affect all three mechanistic pathways (Fig. 3). Intermittent hypoxia increases oxidative stress [37], and inflammatory response that impairs endothelial function [38]. OSA-related hemodynamic alterations and sedentariness [6] may slow intravenous flow [5]. There is also evidence of a hypercoagulability status in patients with OSA, which might contribute to an increased risk of VTE. Hong et al. [39] found that prothrombin time in moderate to severe OSA patients was shorter when compared with controls. Mehra and colleagues [40] studied thrombotic parameters in 507 subjects from individuals with a wide spectrum of OSA. They found that both fibrinogen and plasminogen activator inhibitor type-1 (PAI-1) increase with increasing AHI even after adjustment for confounders. These indicate less fibrinolytic capacity and a hypercoagulable state. There are some further cross-sectional studies that support increased coagulability, platelet activity and aggregability [12] and decreased fibrinolytic capacity in OSA. It has also been shown that coagulant activity, platelet function and fibrinolytic system improve after treating OSA (both CPAP and mandibular advancement splint) [7,10–12,41,42]. However, the associations with OSA and the hematological changes after CPAP treatment have not been uniformly established for all biomarkers [10,41,43]. One recent study showed that hypertensive OSA patients were characterized by faster blood clot development, denser fibrin links, lower clot permeability and longer clot lysis time (in part resulting from increased PAI-1 levels). Even though the sample size was very small and the design was non-randomized, this study also reported that 3-month CPAP treatment reversed the aforementioned altered clot properties, independently of other factors and comorbidities, including systemic hypertension [44]. An elevated D-dimer level after stopping anticoagulation is recognized as a risk factor for recurrent PE [45]. We have also recently reported that the D-dimer levels of patients who discontinued anticoagulation after a first episode of PE are related to OSA severity [46]. A single abnormality factor is seldom enough to cause venous thrombosis, as it may require a synergy of several factors. Toukh et al. [47] used thromboelastography to assess coagulability, which provides information about the full spectrum of the hemostatic process (from the initial formation of fibrin until lysis of the clot) and found that OSA patients had a procoagulant state that was reduced after two weeks of CPAP. As a result, there may be a thrombosis threshold where the trend to cause thrombin is not effectively regulated by antithrombotic mechanisms. Taken together, these observations suggest that increased platelet activation/aggregability and hypercoagulability could play a role in the increased susceptibility of OSA patients to thromboembolic phenomena such as VTE.

Hypoxia as a procoagulant state

OSA includes several pathophysiological triggers. Besides sleep fragmentation, intrathoracic pressure swings and recurrent hypercapnia, OSA is characterized by an exclusive form of hypoxia, with

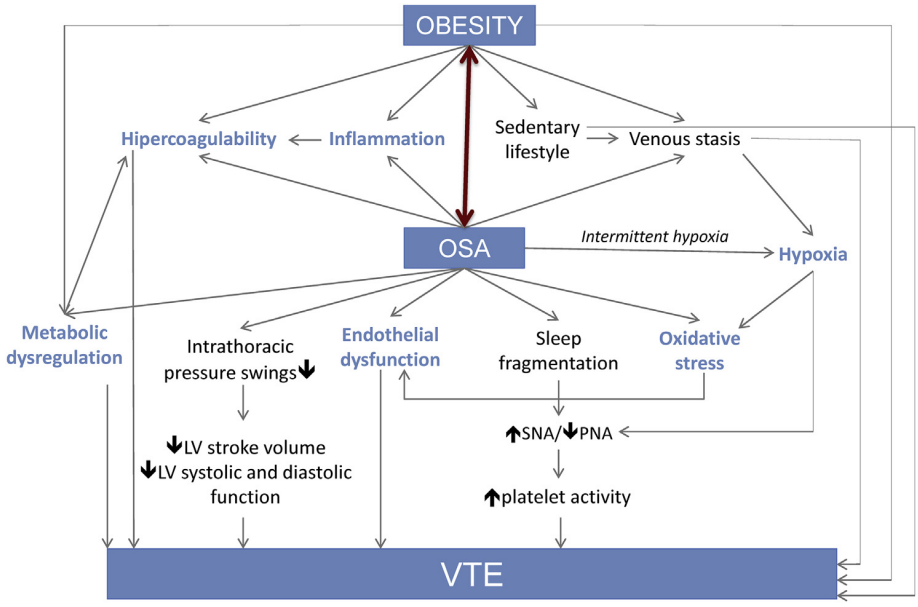

Fig. 3. Pathogenic mechanism implicated in the development of: venous thromboembolism disease (VTE) in obstructive sleep apnea (OSA) LV:left Ventricle; SNA: sympathetic activity; PNA: Parasympathetic nerve activity.

repetitive short sequences of desaturation followed by re-oxygenation, called intermittent hypoxia. This phenomenon seems to play an important role in the procoagulant state [8–10,44,46]. In addition to AHI, nocturnal hypoxemia (assessed by the mean nocturnal oxygen saturation (nSaO2)) and the percentage of total time study spent with nSaO2<90% (CT90%) were independent risk factors for PE recurrence and for resuming anticoagulation because of a new thromboembolic event [26]. VTE frequently starts at the venous valves sinuses, where stasis, inflammatory stimuli and hypoxia may occur. These circumstances could activate endothelial cells that would lead to the surface expression of adhesion receptors (P-selectin, E-selectin, and von Willebrand factor), and may facilitate the binding of circulating leukocytes and microvesicles. Subsequent activation of the leukocytes induces expression of the potent procoagulant protein tissue factor that triggers thrombosis if protective anticoagulant pathways are overwhelmed [48]. Interestingly, OSA has been shown to increase P-selectin [11], E-selectin [49], von Willebrand factor [50], microvesicles [51] tissue factor [50] levels, that fall significantly after CPAP therapy. What is more, OSA is associated to a sedentary way of life and obesity [6], and consequently to a further procoagulant state and venous stasis. Therefore, it might be speculated that nocturnal hypoxemia in OSA patients may lead to an up-regulation of procoagulant activity in valvular sinuses that could build a potentially hypercoagulable microenvironment.

Obesity, sedentary lifestyle, OSA and PE

Obesity has a high prevalence in Western Countries [3]. A meta-analysis included 15 studies and found that the BMI≥30 kg/m^2 increases the risk of VTE (OR 2.33 95% CI, 1.68 to 3.24), [52]. The association of obesity with VTE becomes stronger as the BMI increases. The morbidly obese (BMI≥40 kg/m^2) patients are at an even higher risk than those with BMI 30–40 kg/m^2 [53]. Eichinger et al. showed that risk of recurrence was 60% higher among obese patients compared with patients of normal weight [54]. Other groups have also reported that obesity is a risk factor for recurrent VTE in prospective studies [45], and an algorithm developed to predict recurrent venous thromboembolism includes obesity [55]. Considering the high prevalence of unsuspected OSA among obese patients, the risk of PE that is commonly attributed to obesity could be partially related to OSA. Case-control studies have shown an association between OSA and VTE, independent of obesity [23,24,32]. Moreover, we found no differences in BMI between patients with or without PE recurrence in a study that followed up 120 consecutive patients, who had stopped oral anticoagulation for a first episode of PE. After adjusting for several confounding factors, including BMI, OSA remained as an independent risk factor for recurrent PE [26].

There are also several lifestyle factors that might influence the relationship between OSA and VTE. OSA is associated to a sedentary lifestyle and obesity [6] that may induce a procoagulant state and venous stasis, which have also been associated with an increased risk of PE. In contrast, moderate intensity of regular aerobic exercise has been shown to improve endothelial release of tissue-type plasminogen activator (TPA) in overweight and obese adults. Besides, obesity is associated with sedentary way of life and venous stasis, and it has also been related to impaired fibrinolysis and high concentrations of clotting factors leading to a prothrombotic state [56]. Moreover, this state can further increase because obesity is associated with high estrogen levels and chronic low-grade inflammation. It is tempting to speculate that OSA and obesity may additively or synergistically lead to up-regulation of procoagulant activity that may intensify (in addition to concomitant sedentary lifestyle) the risk of VTE, although this hypothesis has not been proven.

OSA metabolic disorders and PE

The relationships between OSA and VTE may be confounded by several additional factors. Metabolic syndrome is associated with VTE and individual components that define the syndrome have also demonstrated associations with OSA [57]. Higher concentrations of triglycerides in VTE and OSA have been reported, which have also been proposed as a possible PE risk factor. Furthermore, both chronic and acute hyperglycemia may cause coagulation activation and hypofibrinolysis by mechanisms independent of obesity. What is more, hyperglycemia is often accompanied by hyperinsulinemia and their combined effects may result in an even stronger hypercoagulable state [58].

The relationship between OSA and VTE is very complex and the precise pathogenic mechanisms are still unclear. In addition, it may be likely that respiratory events in OSA have a long-term cumulative burden, and, depending on the length and severity of OSA in each patient, could lead to different effects on the pathogenesis of VTE. On the other hand, apart from maladaptive processes, OSA could also elicit a cascade of adaptive homeostatic processes, termed preconditioning. Therefore, patients who were previously exposed for a long time to mild sleep apneas near or below the threshold of damage may acquire homeostatic and anticoagulant compensatory mechanisms and consequently reduce the risk of venous thrombosis. Nevertheless, this is still unproven.

The existing data suggest that OSA is associated to a procoagulant state, but the interactions between OSA and single clotting factors are unclear. Moreover, more rigorous investigations and randomized controlled trials with sufficient statistical power are needed to determine the relationship between individual procoagulant factors, OSA, and other confounded factors, such us obesity, a sedentary lifestyle and metabolic comorbidities.

Obstructive sleep apnea and venous thromboembolism: clinical considerations

OSA in unprovoked VTE

All evidence of the relationship between OSA and VTE comes from groups of patients with provoked VTE or mixed groups with different proportions of provoked and unprovoked VTE episodes. However, it is still not clear whether the association between OSA and VTE remains significant in the subgroup of unprovoked VTE, which represents 20–30% of them. We performed a sub-analysis in the group with idiopathic PE (36 patients), defined as a PE in the absence of the classical major VTE risk factors. In this subgroup, the association between OSA and PE was even higher. Consequently, PE risk increased by 51% in patients with no other risk factors, for every 10-point increase in AHI [32]. Similarly, a small study with 30 PE found that mean weight was lower in PE patients without major risk factors for VTE than in those with provoked PE, and, conversely the study showed that OSA prevalence was markedly higher in the non-provoked PE group compared to those patients with provoked PE (70 vs. 30%, P = 0.045, respectively) [20]. Even though these data come from one small study, and as a secondary analysis in the other one, they could support the idea that OSA may be a risk factor per se, independently of obesity, especially in non-provoked VTE episodes, but further studies are needed to answer this question more definitively.

OSA in recurrent VTE

VTE relapses frequently, and nearby 30% of patients have a new episode within 10 years. Recurrent PE is associated with mortality rates of 9%, and is also a risk factor for chronic pulmonary hypertension. Although numerous risk factors for first VTE have been documented, only a few of these are known to play a role in the prediction of a recurrent event, such as cancer, continued oestrogen

use, vena cava filters, high post-anticoagulation D-dimer, male gender, and obesity [54,59–63]. The last two factors are well-known clinical features associated with OSA. Besides, as previously discussed, there is evidence that OSA is associated with a hypercoagulation state [10,12,64,65]. As a matter of fact, patients with PE and OSA required higher warfarin doses to achieve a therapeutic international normalized ratio than subjects without OSA [66], and patients with PE and OSA had higher rates of elevated D-dimer levels after discontinuing oral anticoagulation than patients without OSA [46]. There are two longitudinal studies that investigated whether OSA was associated with an increased risk of recurrent PE after discontinuation of oral anticoagulation [26,67]. Xie et al. [67] followed up 97 PE patients (32 with OSA) for 18 mo. They found that OSA patients had higher recurrence rates of PE than non-OSA (21% vs. 6%). CPAP treatment was recommended for most OSA patients, but only four patients had appropriate compliance during the follow-up, which limited any further analysis. We followed up 120 consecutive patients, who had stopped oral anticoagulation for 5–8 years. Nineteen patients had a PE recurrence, and 16 of them had AHI$\geq$10 h^{-1}. Patients with OSA had a higher risk of recurrent PE than those without. Moreover, AHI and nocturnal hypoxemia, assessed by $nSaO_2$ and CT90, were independent risk factors for PE recurrence and for resuming anticoagulation because of a new thromboembolic event [26]. DASH score and Vienna Prediction Model are useful emergent tools for estimating PE recurrence. Adding the new sleep risk factors identified in this study (AHI, mean nSaO2 and CT90%) significantly improved the risk assessment of both prediction models. But, although these new models with the added OSA value are promising, they must be externally validated in large prospective studies before generalization.

OSA screening in VTE

One single study has reported that symptom onset of PE is significantly more often sleep-related in patients with moderate-severe OSA compared to patients with an AHI<15 h^{-1} [29]. Acute nocturnal hypoxia induced by PE during sleep was proposed as a potential trigger for sleep disruption. On the other hand, nocturnal blood coagulability seems to be increased in OSA syndrome as prior studies have demonstrated an elevation of coagulation markers in the early morning hours, possibly resulting in an increased nocturnal occurrence of VTE diseases [65,68,69].

Even though real OSA prevalence in VTE is not clear enough and there is a wide range of frequencies, it seems that OSA is widespread and circa to 50% (Fig. 2) in VTE patients. Nevertheless, it remains largely under-recognized, and consequently its identification and diagnosis constitute a great clinical challenge. Snoring is a common symptom in OSA patients and questions related to its existence and severity are common in clinical practice. A case–control study found that snoring was more frequent in PE patients than a control group of patients in whom PE was suspected and then ruled out [15]. Kezban et al. conducted a small study including 30 patients with previous PE. Snoring was quite a lot more frequent in OSA patients compared to those PE patients without sleeping breathing problems (76% vs 39%) [20]. Similarly, Berghaus et al. [33] found that snoring was more common among PE subjects with an AHI>15 h^{-1}. Even though PE patients were not sleepy during daytime, OSA patients with moderate-severe OSA showed a significantly increased mean ESS score than study participants with an AHI$\leq$15 h^{-1}. On the other hand, sleep-related breathing pauses reported by the patients' bed partners were more frequent in PE patients with an AHI>15 h^{-1} than those with AHI$\leq$15 h^{-1}, but we found no differences in snoring and the remaining subjective daytime or nighttime symptoms [32]. Similarly, Arnulf et al. [14] found that 26% of those VTE patients with moderate-severe OSA had breathing pauses while asleep (8% in those without OSA), but there were no differences in snoring, morning fatigue, nocturia, daytime sleepiness or cognitive impairment between the groups. As a result, clinical symptoms of OSA may be unhelpful to exclude this syndrome. Easy-to-use screening questionnaires, such as the Berlin and STOP-Bang, have been widely used for detecting OSA. Nevertheless, the presence of comorbidities can affect the performance of diagnostic tests because they may produce changes in symptoms that are similar to OSA ones, which in turn might produce false-positive test results. Therefore, OSA screening based on the questionnaires has been found to be suboptimal in both type 2 diabetes mellitus and chronic ischemic heart disease patients. Epstein et al. [15] used the Berlin questionnaire to defined OSA, but it was neither validated nor compared with polysomnography. As far as we know, OSA screening questionnaires performance in VTE populations has not yet been evaluated, and it cannot be recommended as a diagnostic tool. As a consequence, OSA screening should be performed using polysomnography, type 3 or 4 portable sleep monitoring system, like the methods that have been used in the above-mentioned studies (Table 1). They performed the sleep studies in subjects while admitted to hospital for PE [14,20,29,67], within one month [22], and between 3 and 6 mo after VTE diagnosis [32]. It seems that the diagnosis of OSA is representative in acute PE, as Berghaus et al. demonstrated with polysomnography performed in OSA stable patients after acute PE and again three months later, when AHI remained high. Consequently, in hemodynamically stable PE patients, sleep studies to rule out OSA can be performed with equivalent accuracy shortly after acute PE, or within the first 3–6 mo, as the transient increase of central venous pressure do not seem to affect the AHI once the patients are clinically stable [30].

VTE severity and OSA

PE prognosis varies widely. We may face different situations ranging from a potentially massive fatal PE to a peripheral PE with few clinical consequences. Clinicians focus their efforts on risk stratification as the prognosis depends on the timely delivery of optimal treatment. Hemodynamic assessment at presentation is a key element for risk stratification, with a higher mortality rate reported in those presenting circulatory collapse requiring vasopressor therapy. The acute right-sided heart failure is the main cause of death.

As far as we know, and despite considerable progress in the knowledge of the emerging relationship between OSA and VTE, very few studies to date have explored the role of OSA as a severity factor in PE. We have found that PE patients with moderate-severe OSA presented more severity evaluated in radiological terms (greater pulmonary artery obstruction), and by clinical prognostic scales such as simplified Geneva prognostic score and pulmonary embolism severity index (PESI). In addition, AHI was an independent risk factor for pulmonary artery obstruction and PESI [70]. Similarly, another cross-sectional study that included 207 patients found significantly more subjects with a high risk PE (simplified version of PESI$\geq$1) in the group with AHI>15 h^{-1} [29]. Moreover, the same group found that moderate-severe OSA was significantly more frequent among intermediate and high-risk PE patients (81.0%) compared to the low-risk PE cohort (16.3%). However, these data are limited because there were significant differences in age and other clinical parameters in different subgroups of the study [71].

In spite of PE with associated OSA appearing to have worse severity levels according to previous validated clinical scales, no data have currently been published exploring OSA as a mortality risk factor in PE. As previously stated, heart failure is the main cause of death in PE, and it could be speculated that OSA may play a negative role because there are several clinical and epidemiological evidence that associate OSA with the development and progression of heart failure, and importantly, OSA has been shown to be a marker of

disease severity and predictor of increased mortality in heart failure [72]. Nevertheless, there are some potential underlying pathophysiologic mechanisms that support the plausibility of this interplay. We hypothesize that OSA, as a procoagulant disease, could confer a greater pulmonary arterial obstruction, and therefore lead to collapse and cardiogenic shock. RV failure due to pressure overload is considered the primary cause of death in severe PE. Anatomical obstruction and vasoconstriction in PE lead to an increase in pulmonary vascular resistance that triggers an upsurge in RV pressure and volume and leads to a rise in wall tension and cardiomyocyte stretch that increases RV oxygen demand. Each sleep obstructive apnea event is accompanied with exaggerated negative intrathoracic pressure, which could enhance venous return and RV dilatation. In addition, it is likely that nocturnal hypoxia in OSA patients plays a negative role, increasing the imbalance between oxygen supply and demand, resulting in RV ischemia and further reducing contractile forces and RV output. Additionally, several pathophysiological consequences of OSA, including intermittent hypoxia-induced oxidative stress, recurrent arousals and intrathoracic pressure swings may provoke cardiac arrhythmias, either directly or via effects on the autonomic nervous system. Finally, there is evidence that fluid overload in heart failure with consecutive overnight rostral fluid shift from the legs to the neck is associated with upper airway narrowing and the severity of OSA. Based on these data, we may speculate that the deterioration of heart function related to PE could induce a vicious circle that might increase pharyngeal collapsibility and decrease pharyngeal caliber contributing to the progress of OSA. This, then would lead to both circulation and gas exchange abnormalities and further contribute to hemodynamic instability, particularly in acute PE episodes. Currently, however, this is only a theory, and more rigorous investigations are needed to prove it.

Taken together, these findings suggest that clinical symptoms and questionnaires are not appropriate screening methods to diagnose OSA in VTE patients. There is not enough evidence to recommend ruling out OSA in all VTE patients, and, in our opinion, an objective sleep study with type 3 or 4 portable sleep monitoring system or polysomnography should be performed when OSA is suspected and is symptomatic. Furthermore, there are few findings that suggest that OSA could be associated with a greater PE severity and more risk of recurrences, although ongoing studies could clarify this hypothesis.

Obstructive sleep apnea and venous thromboembolism: treatment and management

CPAP effect on coagulability and cardiac function

CPAP therapy and the subsequent resolution of sleep apneas could hypothetically decrease the impact of the Virchow's classic risk triad for VTE in OSA. Coagulant activity, platelet function and fibrinolytic system improved after short and medium-term CPAP interventional studies in OSA patients [7,10–12,41,42], although not all coagulability markers were reduced after CPAP treatment [10,41,43]. Moreover, CPAP reverses inflammation, oxidative stress and endothelial dysfunction and enhances endothelial repair capacity [37,38]. Lastly, several randomized trials have shown a beneficial effect of CPAP on cardiac function, with improvements in left ventricular systolic and diastolic function and pulmonary artery systolic pressure which may improve cardiac output and increase venous flow [73,74].

PE prognosis varies widely, ranging from a potentially fatal massive PE to a peripheral PE with few clinical consequences. Acute right-sided heart failure is the main cause of death. Observational studies have found a consistent association between OSA and heart failure, apnea-hypopnea index (AHI) being a marker of disease severity and predictor of increased mortality in chronic and unstable heart failure [75]. In these patients a significant improvement in left ventricular ejection fraction, and a reduction in sympathetic activity during CPAP treatment has been demonstrated, and a non-randomized study with a small sample size found a significant reduction on mortality [75].

OSA treatment and VTE

It should be noted that there are no studies on whether OSA treatment (with CPAP, oral appliance, and/or weight reduction) reduces the risk of incident or recurrent VTE. In addition, no data have been published on the outcomes of acute PE and concomitant OSA on the severity, mortality and general clinical prognosis after early CPAP treatment.

There are very few data exploring the CPAP effect on VTE. No randomized controlled trial has been performed. In a non-controlled study, 120 PE patients were followed up for 5–8 years, as an exploratory objective of the study. We found a higher risk of PE recurrence when comparing OSA patients without CPAP or with poor CPAP compliance with non-OSA subjects or OSA patients with adequate CPAP compliance. In addition, we found a tendency, although not significant, that CPAP compliance (>4 h/night) tended to be lower among patients with PE recurrence than amongst those without recurrence (17% vs. 64%; $p = 0.051$). However, this study and the sample size were not designed to address CPAP effect on the risk of recurrent PE, and a large randomized controlled-trial is needed to clarify whether CPAP decreases the risk of recurrent PE [26].

Effects of diet and exercise in OSA and VTE

Intentional weight loss through diet control and physical activity may modify risk factors for VTE among the population with obesity. Regular physical activity following body-weight loss was shown to reduce the activity of PAI-1 and increase the endothelial release of TPA in obese patients [76]. However, there are conflicting results as to whether increasing intensity and frequency of exercises, or whether exercises combined with diet control to an extent that can result in weight loss may decrease risk of VTE among obese individuals.

Exercise training attenuate OSA and weight-loss programs may effectively reduce AHI and OSA symptoms in obese patients. There is also evidence that the combination of antihypertensive drugs [77], or weight loss [78] with CPAP, could have a synergistic effect in reducing blood pressure in OSA. In the same manner, it could be speculated that CPAP (in addition to anticoagulant treatment and/or general way of life recommendations, including exercise and weight loss) could have a synergistic effect in reducing VTE prevalence and recurrence in OSA patients, supporting the multidimensional pathophysiology of VTE in this population.

Together, these findings suggest that CPAP therapy could play a beneficial role in OSA coagulation associated disorders. Even so, there are no data addressing the comparative, additive or independent benefit of weight loss, lifestyle modification or CPAP on PE incidence, recurrence rates or mortality.

Conclusions

This review shows that OSA is highly prevalent in VTE patients. Even though more studies are clearly needed to clarify the complex interrelationships between OSA and VTE and the influence of important cofounding factors such as obesity, age and comorbidities, it seems that OSA could be independently associated with both first and recurrent VTE, indicating that these patients could have a persistent hypercoagulable state. In spite of the identification of classical PE recurrence risk factors and the development of new prophylaxis regimens, the occurrence of PE is growing, so recognizing OSA as a potential risk factor for PE recurrence might

enhance our ability to predict new thromboembolic events. Given the high prevalence of OSA in patients with PE, and the persistent hypercoagulable state shown in these patients, we believe it would be necessary to perform further large multicenter studies to evaluate both the risk of VTE in OSA and the impact of important confounding factors such as age, obesity and metabolic comorbidities, and also analyze the effect of CPAP and/or extend anticoagulant treatment on the incidence, recurrence and mortality by PE in patients with OSA.

Practice points

1. The association between OSA and VTE is supported by several epidemiological studies as well as possible pathogenic mechanisms that make it biologically plausible.
2. There is accumulating evidence that OSA is highly prevalent in VTE patients.
3. OSA may induce a persistent hypercoagulable state that could contribute to increase the recurring VTE rate, and it might be a PE severity risk factor.
4. Improving increased blood coagulability induced by OSA could be an important target for effective CPAP treatment in primary and secondary VTE prevention.

Research agenda

1. To clarify the influence of OSA as a risk factor for VTE and the impact of confounding variables (especially obesity and age) in large population studies.
2. Future investigations should seek possibilities to identify better and cheaper instruments for OSA screening in VTE patients by including updated validation studies.
3. Conduct large, randomized controlled trials with long follow-up periods (at least 12 mo) to generate solid evidence about the potential of CPAP and/or extend oral anticoagulation (with other interventions such as physical activity and weight loss programs) to reduce PE recurrence and mortality in patients with PE and OSA.
4. Categorize PE with concomitant OSA patient subgroups in which CPAP treatment obtains a greater effect on secondary prevention.
5. Find out whether OSA per se in PE patients is associated with increased morbi/mortality and identify the mechanisms by which OSA could potentially mediates poor outcomes.

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Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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