Obstructive sleep apnoea and venous thromboembolism: pathophysiological links and clinical implications

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There is growing pathophysiological and clinical evidence that obstructive sleep apnoea is associated with an increase in the incidence of, and poor health outcomes in, patients with pulmonary embolism
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ABSTRACT Obstructive sleep apnoea (OSA) and pulmonary embolism (PE) remain major health issues worldwide. Data from pathophysiological studies suggest that both intermittent hypoxia and sleep fragmentation are associated with increased blood coagulability, endothelial dysfunction and venous stasis. There is growing evidence that OSA is potentially prevalent in and a risk factor for PE. Conversely, patients with acute PE have two to four times greater risk of moderate-to-severe OSA. The role of continuous positive airway pressure (CPAP) treatment in improving clinically meaningful outcomes in PE patients remains unclear, although some authors have suggested that CPAP could improve the hypercoagulability state and normalise circadian alterations in some of the coagulation molecules, as observed in patients with OSA. Emerging research highlights the complex interdependent relationships between OSA and PE, emphasising the need for rigorous, well-powered trials that address the impact of OSA and its treatment on the prevention and management of PE. Undoubtedly, these will require closer collaboration between the sleep medicine and clinical/venous thromboembolism communities.

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Introduction

Obstructive sleep apnoea (OSA) is the most common form of sleep disordered breathing (SDB). It is mainly characterised by recurrent episodes of partial or complete upper airway closure leading to intermittent hypoxia and sleep fragmentation. OSA is considered a major public health issue, affecting 5–15% of the general population, increasing linearly with age up to 60–65 years. However, these estimates of prevalence are markedly affected by the methodology used to evaluate OSA, bias in the selection of subjects, the definition of hypopnoea and the selected apnoea/hypopnoea index (AHI) cut-off point [1–3]. OSA can potentially increase the risk of a wide range of cardiovascular comorbidities, such as arterial hypertension, stroke, ischaemic heart disease, arrhythmias and heart failure [4, 5]. The pathophysiological mechanisms underlying the association between OSA and cardiovascular disease (CVD) are still incompletely understood, but seem to involve both intermittent hypoxia and sleep fragmentation, which can induce sympathetic activation, inflammation, oxidative stress and blood hypercoagulability, all well-known cardiovascular risk factors [6–8].

Pulmonary embolism (PE) remains a major health issue worldwide [9]. PE is the most common cause of vascular death after myocardial infarction and stroke, and it is the leading preventable cause of death in hospital patients [10]. Despite advances in medical therapy, the mortality rates attributed to PE vary from 1.4% to 17.4% in the short term and rise to 30% in studies with long-term follow-up [11, 12]. Therefore, in addition to the usual management of PE, continued efforts have been made to identify additional factors and comorbidities that might contribute to the development and severity of PE.

Venous thromboembolism (VTE) and OSA share some risk factors (*i.e.* age, obesity and physical inactivity), and, although the evidence is still limited, there is growing evidence that OSA is a risk factor for PE, the most serious complication of VTE [13]. Furthermore, PE patients with OSA require higher warfarin doses to achieve therapeutic anticoagulation [14], and some data suggest that OSA might be associated with poor health outcomes in patients with acute PE [14, 15]. This article attempts to 1) review the potential pathogenic mechanisms underlying the occurrence of VTE in patients with OSA; 2) assess the prevalence of OSA in patients with acute PE, and the potential effect of PE on the number and severity of SDB events; 3) address the effect of OSA treatment on the response to anticoagulant therapy and VTE outcomes; and 4) provide some recommendations for future research aimed at filling in gaps in our existing knowledge.

OSA and venous thrombosis

The origin of VTE is described by Virchow's triad, which comprises blood hypercoagulability, vascular endothelial damage and venous stasis [16]. VTE risk factors reflect these underlying pathophysiological processes, which include age, malignancy, major surgery, multiple trauma, obesity, prolonged immobilisation, pregnancy and puerperium and inherited or acquired thrombophilia [16]. OSA could potentially influence all three mechanistic pathways of Virchow's triad.

OSA and hypercoagulability

Increased blood coagulability has emerged as a possible pathophysiological mediator of cardiovascular morbidity in OSA. Data suggest that the chronic intermittent hypoxia experienced by patients during SDB may be responsible for sympathetic hyperactivity, endothelial dysfunction, elevation of inflammatory and oxidative stress markers and subsequent alterations to the coagulation system (figure 1) [8, 17]. Although the exact mechanisms are not fully understood, it has been observed that intermittent hypoxia (and sustained hypoxia related to obesity in OSA patients) leads to the activation of the transcription factor hypoxia-inducible factor-1, with attendant downstream gene pathway regulation, as well as concurrent and preferential activation of inflammatory pathways regulated by the transcription factor nuclear (NF)-κB. NF-κB factor mediates the expression of genes encoding for inflammatory cytokines, tumour necrosis factor, chemokines, adhesion molecules and pro-coagulant factors, including plasminogen activator inhibitor (PAI)-1 and tissue factor pathway inhibitor [18–20]. Figure 2 presents an overview of studies suggesting the presence of a relationship between OSA and factors contributing to hypercoagulability [21–78]. Hypoxia affects platelet function by increasing platelet reactivity [79]. More specifically, some studies have suggested significant associations between OSA and whole-blood hypercoagulability [62, 63], increased haematocrit [21–26] and blood viscosity [24, 26, 27], increased concentrations of coagulation factors (including FXIIa [28], FVIIa [28], thrombin and antithrombin [28], fibrinogen [21, 24, 29–34] and von Willebrand factor [31, 35]), increased platelet activity [24, 29, 43–49, 51–61], impaired fibrinolytic activity [36–42] and an increase in tissue factor serum levels [35–38]. A major problem in assessing the association of OSA with increased coagulability is the coexistence of many confounding factors in OSA patients, such as obesity, hypertension, diabetes, dyslipidaemia, smoking and other chronic respiratory conditions, which can also directly alter the haemostasic system [17].

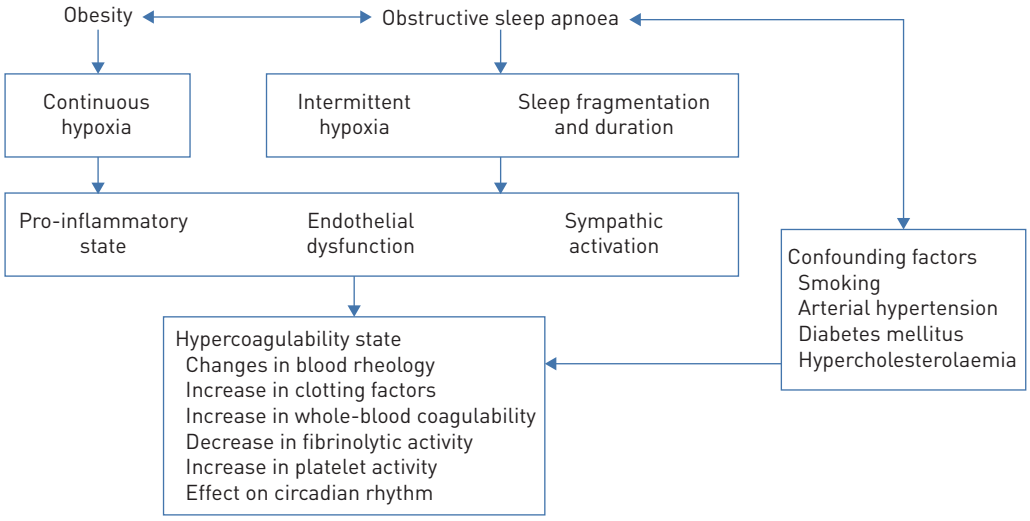

FIGURE 1 Potential pathophysiological links between obstructive sleep apnoea and a state of hypercoagulability, including the importance of obesity as a confounding factor.

The effect of continuous positive airway pressure (CPAP) treatment on OSA-associated hypercoagulability has been evaluated in several observational, case–control, uncontrolled and nonrandomised studies, with disparate results. However, very few randomised clinical trials have tackled this issue (table 1). Robinson *et al.* [28] randomised 220 patients with OSA (defined as >10 dips of >4% oxygen desaturation per hour due to obstructed respiration) to receive either subtherapeutic CPAP (n=112) or therapeutic CPAP (n=108) for 1 month. The mean±SD compliance with CPAP in the group assigned to therapeutic CPAP was 5.0±1.9 h. The levels of activated coagulation factors XIIa, VIIa, thrombin–antithrombin complex and soluble P-selectin were higher in OSA patients at baseline than in unmatched controls, but did not fall after 1 month of therapeutic CPAP treatment.

Von Känel *et al.* [41] randomised 44 patients with OSA to receive 2 weeks of either therapeutic CPAP (n=18), 3 $L \cdot min^{-1}$ supplemental nocturnal oxygen (n=16) or placebo-CPAP (<1 cmH_20) (n=10). CPAP treatment reduced PAI-1 (p=0.039), but there were no changes in von Willebrand factor, soluble tissue factor or D-dimer levels.

In a prospective crossover study, Toukh *et al.* [80] randomised 12 patients with severe OSA to either CPAP or no CPAP for 2 weeks, a 1-week washout period and then another testing period of 2 weeks. Investigators used thromboelastography to assess coagulability at the beginning and at the end of each period. At baseline, 10 patients had shorter clotting times, a six-fold increase in the rate of clot formation, a 12-fold increase in clot strength and a 10-fold increase in the clotting index, compared to reference values. CPAP significantly reduced AHI (p=0.0003), clot strength (p=0.019) and the clotting index (p=0.014).

It is now well established that various molecules linked to the coagulation system exhibit circadian oscillatory patterns. Haus [81] found an increase in coagulability in the early morning, a time when a peak incidence of major cardiovascular events such as stroke, myocardial infarction and sudden cardiac death has been reported in the general population. Moreover, some authors found that coagulation activity increases during the night in OSA patients, suggesting a time-related correlation between increased coagulability and cardiovascular events in these patients [82]. These findings might explain why CPAP treatment could decrease the cardiovascular risk through improvements in the coagulation system. In a placebo-controlled crossover study, Phillips *et al.* [70] randomised 28 patients with moderate–severe OSA to receive therapeutic or placebo CPAP, for 2 months each, with a 2-month washout between treatments, and then a further 2-month crossover treatment period. The concentration of various coagulation factors such as PAI-1, D-dimer, fibrinogen, von Willebrand factor, FVIII, FVII and FV were monitored (seven measurements over the course of 24 h). The levels of von Willebrand factor in the early morning, and those of FVII and FV at night were significantly lower in the CPAP group, compared with the control group, although the circadian effect of CPAP has yet to be confirmed [39]. Treatment of OSA with CPAP resulted in lower 24-h levels of von Willebrand factor (−3.9%, p=0.013), FVIII (−6.2%, p=0.007) and FV (−4.2%, p<0001), compared with placebo. The greatest difference occurred during the night-time and early-morning periods. However, D-dimer, FVII and PAI-1 did not differ between treatments [70, 78].

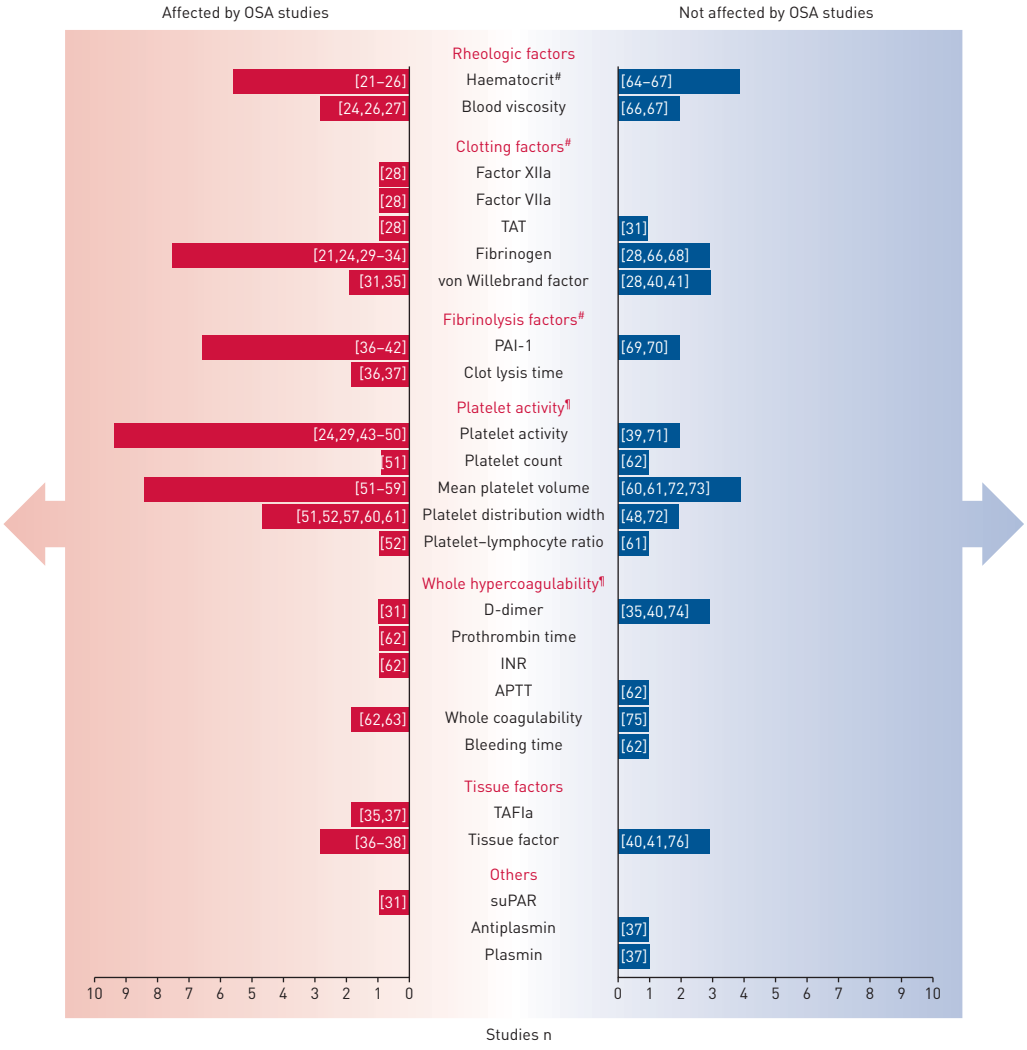

FIGURE 2 Coagulability factors and their association with obstructive sleep apnoea (OSA), including reference citation numbers of studies supporting or discrediting the association. The length of the horizontal bars is proportional to the number of studies, according to the graduated scale. TAT: thrombin–antithrombin; PAI: plasminogen activator inhibitor; INR: international normalised ratio; APTT: activated partial thromboplastin time; TAFIa: thrombin activatable fibrinolysis inhibitor a; suPAR: soluble urokinase-type plasminogen activator receptor. #: coagulation factors affected by OSA more consistently in the current publications: haematocrit, clotting factors (mainly fibrinogen), fibrinolysis factors and platelet activity; ¶: platelet activity includes PMAs, sCD40, P-selectin, B-thromboglobulin, platelet factor-4, adrenaline/ADP-induced platelet activating, PAC1 concentrations and platelet aggregation.

OSA and endothelial dysfunction

Several studies have analysed the association between OSA, CPAP treatment and endothelial dysfunction. Recently, Wang *et al.* [83] reported on a meta-analysis of the association between flow-mediated dilation of the brachial artery (FMD) and OSA. The authors evaluated 28 studies involving 1496 OSA patients and 1135 controls. Overall, OSA was associated with a significant reduction in FMD (−3.07, 95% CI −3.71– −2.43; p<0.00001) that was independent of known confounders such as body mass index (BMI), age, sex, smoking status, Epworth sleepiness scale (ESS) and other cardiovascular risk factors. These findings suggest a relationship between OSA and endothelial dysfunction. The latter does not seem to depend on altered vascular smooth muscle function, as the aforementioned meta-analysis showed that the nitroglycerin induced dilation test elicited similar responses in OSA patients and controls. The mechanisms underlying OSA's impairment of endothelial function are unclear, but they probably involve intermittent hypoxia, intrapleural pressure swings and recurrent arousals. Of these, intermittent hypoxia is considered the most important factor promoting the production of reactive oxygen species, thereby increasing oxidative stress and decreasing nitric oxide synthetase activity. This causes an attenuation of nitric oxide production and release and an impairment of endothelial function. Another meta-analysis

TABLE 1 Effect of continuous positive airway pressure (CPAP) on coagulation status in sleep apnoea patients

First author, year [reference]	Study design	Subjects and randomisation	Inclusion/exclusion criteria	Baseline characteristics (control group *versus* CPAP group)	Sleep study and OSA definition	CPAP compliance (control group *versus* CPAP group)	Follow-up	Main results
Robinson, 2004 [28]	Randomised clinical trial	n=220 n=112 subtherapeutic CPAP and n=108 therapeutic CPAP	Male, aged 30–75 years, EES >9	Age 49.1±10.3 years *versus* 49.7±10.3 years BMI 35.9±6.3 kg·m^{-2} *versus* 35.6±7.6 kg·m^{-2} DI4% 38.5±20.3 events·h^{-1} *versus* 38.9±21.1 events·h^{-1} ESS 16.2:3.3 *versus* 16.3±3.3	PSG (>10 dips of <4% oxygen desaturation per hour)	4.1±2.4 h per night *versus* 5±1.9 h per night p<0.005	4 weeks	Decrease in FVIIa and FXII concentrations No effect on FXIIa, sP-sel, TAT, vWF, fibrinogen, FVII, FVIII and homocysteine concentrations
Phillips, 2012 [70]	Randomised crossover clinical trial	n=28 therapeutic or placebo CPAP; 1-month washout	AHI >25 events·h^{-1} with ODI >20 events·h^{-1} Age >21 years Exclusion criteria: BMI >35 kg·m^{-2}; liver disease; uncontrolled type 2 diabetes	Age 49±14 years Male/female 25/3 BMI 31.7±4.1 kg·m^{-2} AHI 37.9±23.9 events·h^{-1} ODI 31.3 (22.4) events·h^{-1} ESS 10.3±4.9	PSG	3.4±2.3 h per night *versus* 4.4±2.2 h per night	2 months with CPAP and 2 months sham CPAP in all patients	Decrease in early-morning level of vWF, and nocturnal levels of FVIII and FV. No effect on PAI-1, D-dimer, fibrinogen and FVII
Von Känel[#], 2006 [41]	Randomised clinical trial	n=44 n=18 therapeutic CPAP; n=16 nocturnal oxygen; n=10 placebo-CPAP	AHI >15 events·h^{-1} (unattended home sleep study) PSG confirming the diagnosis <15 periodic limb movements per hour of sleep	Age 46.1±2.3–48.4±3.4 years Male/female 34/9 BMI 30.4±1.1–31.1 ±1.4 kg·m^{-2} AHI 59.1±10–66.6 ±6.9 events·h^{-1}	PSG (AHI >15 events·h^{-1})	6.28±0.38 h per night *versus* 6.63 ±0.3 h per night	2 weeks	Decrease in PAI-1 concentration. No effect on vWF, sTF and D-dimer. AHI was an independent (age and BMI) predictor of PAI-1 levels, explaining 22% of the variance
Toukh, 2012 [80]	Randomised crossover clinical trial	n=12 CPAP or no-CPAP; 1 week washout	Severe OSA (AHI >30 events·h^{-1}) Age 33–61 years Exclusion criteria: COPD; anticoagulant or antiplatelet treatment	Age 46±9 years Male/female 8/4 BMI 36±8 kg·m^{-2} AHI 34±19 events·h^{-1}	PSG (7 patients) Split-night protocol (5 patients)		2 weeks on CPAP or placebo, 1 week washout and 2 weeks crossover	CPAP induced decrease in clot strength and clotting index (hypercoagulability markers) assessed by thromboelastography
McEwen, 2012 [78]	Randomised crossover clinical trial	n=28 therapeutic CPAP or placebo CPAP; 1 month washout	AHI >25 events·h^{-1} with ODI >20 events·h^{-1} Age >21 years Exclusion criteria: BMI >35 kg·m^{-2}; liver disease; uncontrolled type 2 diabetes	Age 49±14 years Male/female 25/3 BMI 31.7± 4.1 kg·m^{-2} AHI 37.9±23.9 events·h^{-1} ODI 31.3±22.4 events·h^{-1} ESS 10.3±4.9	PSG	3.4±2.3 h per night *versus* 4.4±2.2 h per night	2 months with CPAP and 2 months sham CPAP in all patients	No difference between CPAP and placebo in fibrin generation
El Solh, 2008 [77]	Case–control study	n=35 OSA and n=12 controls	Male patients referred to sleep unit due to suspicion of OSA	Age 49±7.2 years *versus* 47±7.5 years BMI 31.6±4.4 kg·m^{-2} *versus* 29.8±3.1 AHI 27.7±11.3 events·h^{-1} *versus* 3.1±1.4 events·h^{-1} ESS 12.9±3.19 *versus* 3.7±1.8	PSG	5.1±1.1 h per night	8 weeks	Decreased level of tissue factor

Continued

TABLE 1 Continued

First author, year [reference]	Study design	Subjects and randomisation	Inclusion/exclusion criteria	Baseline characteristics (control group *versus* CPAP group)	Sleep study and OSA definition	CPAP compliance (control group *versus* CPAP group)	Follow-up	Main results
Guardiola, 2001 [63]	Case–control study	n=11 therapeutic CPAP, n=22 OSA without CPAP (n=16 with 1-night CPAP)	Patients referred to sleep unit due to suspicion of OSA	Age 51±9 years *versus* 44±2 years Male/female 23/10 BMI 39±11 kg·m^{-2} *versus* 41±2 AHI 47±15 events·h^{-1} *versus* 51±87 events·h^{-1}	PSG (AHI >5 events·h^{-1})	5.6±0.4 h per night	10.5±1.3 months	Untreated OSA had significantly shortened clotting times in evening and morning whole-blood samples compared to treated patients. One night of CPAP treatment did not produce changes in morning whole-blood coagulation
Saarelainen, 1996 [25]	Observational study	n=12 patients with AHI >20 events·h^{-1}, lowest S_{a0_2} <85% and hypertension with good compliance with CPAP	AHI >20 events·h^{-1} Hypertension Exclusion criteria: any other chronic illness, high alcohol intake or current smokers	Age range 37–55 years BMI range 29.6–42.9 kg·m^{-2}	RP	<4 h·day^{-1} were excluded from the study	3 months	Decreased haematocrit
Reinhart, 2002 [24]	Case–control study	n=13 patients with CPAP and n=8 controls	Patients referred to sleep unit due to suspicion of OSA	Age 57.4± 13.2 years *versus* 54.3±10.4 years BMI 29.8±3.1 kg·m^{-2} *versus*25.9±3.2 kg·m^{-2} ESS 8.8±4.2 *versus* 5.1±2.1			Long term	No change in plasma viscosity and fibrinogen and haematocrit
Tazbirek, 2009 [26]	Case–control group	n=31 OSA patients and n=19 healthy controls	Male patients referred to sleep unit due to suspicion of OSA	Age 47.1±6.9 years *versus* 49.4±8.6 years BMI 33.1 kg·m^{-2} *versus* 35.7 kg·m^{-2} AHI 2.1 events·h^{-1} *versus* 45±16.2 events·h^{-1}	PSG		5 nights	Improvement in blood rheological properties (whole-blood viscosity, plasma viscosity and aggregation index and increase in aggregation half-time)
Hui, 2004 [45]	Case–control study	n=42 patients with OSA and n=23 controls without OSA (AHI <10 events·h^{-1})	Patients referred to sleep unit due to suspicion of OSA	Age 49.1±12.4 years *versus* 47.7±9.4 years BMI 28.8±3 kg·m^{-2} *versus* 30.7± 4.8 kg·m^{-2} AHI 6±3 events·h^{-1} *versus* 47±25 events·h^{-1} ESS 9.8±5.2 *versus* 11.7±5.9	PSG	3.9±1.9 h per night	3 months	Decrease in IPA+
Bokinsky, 1995 [44]	Observational study	n=6 patients with OSA and n=5 patients without OSA	Patients referred to sleep unit due to suspicion of OSA	BMI range 34–46 kg·m^{-2} AHI 87.2±23.2 events·h^{-1} *versus* 5.3±5.3 events·h^{-1}	PSG		1 night	Reduced platelet aggregation

Continued

TABLE 1 Continued

First author, year [reference]	Study design	Subjects and randomisation	Inclusion/exclusion criteria	Baseline characteristics (control group *versus* CPAP group)	Sleep study and OSA definition	CPAP compliance (control group *versus* CPAP group)	Follow-up	Main results
Maruyama, 2012 [49]	Observational study	n=7 patients with CPAP	Patients referred to sleep unit due to OSA suspicion (OSA) with AHI >5 events·h^{-1}	Pre-CPAP *versus* post-CPAP Age Male/female BMI 22.7±3.3 *versus* 22.9±3 AHI 36.7±16.5 events·h^{-1} *versus* 5.2±4.6 events·h^{-1}	PSG		6±1.4 months	Decreased levels of PDMPs. No changes in PAI-1 and SF
Steffanina, 2015 [38]	Case–control study	14 healthy controls and 17 CPAP	Patients referred to sleep unit due to suspicion of OSA and subjects from the general population	Age 52±13.4 years *versus* 55.3±7.8 years Male/female 9/5 *versus* 10/7 BMI 26.5±5.6 kg·m^{-2} *versus* 36.9±7.8 AHI 1.5±0.8 events·h^{-1} *versus* 30.3±16.5 events·h^{-1} ODI 1.9±0.8 events·h^{-1} *versus* 39±16.1 events·h^{-1}	Portable sleep apnoea monitoring device	>4 h·day^{-1} (patients with <4 h·day^{-1} were excluded)		CPAP decreased PAI-1 and TGF-β levels (failed to normalise), but not uPA and tPA levels
Akinnusi, 2009 [43]	Case–control study	n=12 healthy controls and n=12 CPAP adjusted by age, sex and BMI	Patients referred to sleep unit due to suspicion of OSA and subjects from the general population	Age 47.8±7.7 years *versus* 51.9±14.3 years Male/female 10/2 *versus* 10/2 BMI 31.7±3.3 kg·m^{-2} *versus* 33.9±4.9 kg·m^{-2} AHI 3.7±1.3 events·h^{-1} *versus* 42.1±31.5 events·h^{-1} ESS 3.9±1.7 *versus* 13.6±2.3	PSG	5.3±1.1 h per night	8 weeks	CPAP reduced sP-sel, CD40L and platelet-monocyte aggregates, but failed to normalise the values

Data are presented as mean±SD, unless otherwise stated. OSA: obstructive sleep apnoea; ESS: Epworth sleepiness scale; BMI: body mass index; DI4%: dips of <4% oxygen desaturation; PSG: polysomnography; sP-sel: soluble P-selectin; TAT: thrombin–antithrombin; vWF: von Willebrand factor; AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; PAI-1: plasminogen activator inhibitor-1; sTF: soluble tissue factor; COPD: chronic obstructive pulmonary disease; Sa_{O_2}: arterial oxygen saturation; RP: respiratory polygraphy; IPA+: index of platelet activation; TGF: transforming growth factor; uPA: urokinase-type plasminogen activator; tPA: tissue-type plasminogen activator. #: data are presented as mean±SEM.

[84] that included four randomised clinical trials with a total of 75 OSA patients who received CPAP therapy and 75 controls who received subtherapeutic CPAP concluded that CPAP therapy significantly improved endothelial function by increasing the FMD response by 3.9% (95% CI 1.93–5.80%). This difference is clinically meaningful, as the improvements observed in the FMD after statin treatment only amounted to 1.5%, while those found after angiotensin-converting enzyme inhibitor treatment [85] and exercise activity [86] were 1.3% and 2.1%, respectively. In addition, this meta-analysis showed that CPAP improved other markers of endothelial dysfunction, such as forearm venous occlusion plethysmography and the plasma concentration of total nitric oxide.

OSA and venous stasis

Apart from the pro-coagulant state associated with obesity, which increased the risk of VTE [87–89], obesity itself is thought to predispose a patient to venous stasis, which is a trigger of deep vein thrombosis (DVT). Since >80% of OSA patients are overweight (BMI 25–29 $kg \cdot m^{-2}$) and >60% present with obesity (BMI $\geqslant 30$ $kg \cdot m^{-2}$) [90], future research should examine the differential effects of obesity and OSA on the risk of VTE.

In summary, OSA could provoke VTE through the three classic mechanistic pathways of Virchow's triad: hypercoagulability, endothelial dysfunction and venous stasis. CPAP therapy might play a beneficial role in coagulation disorders in OSA, and this effect might be more pronounced during the night or in the early morning, when there is a greater pro-coagulant activity and a greater cardiovascular risk, especially in OSA patients. Secondly, OSA increases the inflammatory state and induces increased oxidative stress, mainly through intermittent hypoxaemia and sleep fragmentation, which have been related to endothelial dysfunction, the latter improving with CPAP therapy. Venous stasis is associated with obesity, a comorbidity present in most OSA patients. Additionally, obesity could contribute to a state of hypercoagulability through the presence of sustained tissue hypoxia. Future large randomised clinical trials on the effect of CPAP on the coagulation system are needed to assess the relationship between OSA and a hypercoagulability state, taking into account the various potential confounding factors.

Risk of acute PE in OSA

Two case–control studies (OSA *versus* non-OSA) found a higher risk of VTE (OR 2.1–3.1) in OSA patients (figure 3). Chou *et al.* [97] used a nationwide Taiwanese database to analyse the incidence of VTE in a cohort of 5680 subjects with recently diagnosed OSA and 4505 controls without OSA matched for age, sex, comorbidities, major operations and fractures, excluding subjects with previous VTE. 30 (0.53%) OSA patients and 10 (0.22%) controls developed DVT during a mean follow-up of 3.6 years (hazard ratio (HR) 3.11, p=0.002), and the association was even higher in OSA patients who needed CPAP (HR 9.58, p=0.007). Lin *et al.* [98] employed the same Taiwanese national database to assess the increased risk of VTE among patients with OSA during the first 5 years after the diagnosis, including 1424 OSA patients and 14 240 control subjects without OSA matched for age and sex (10 control subjects per study subject). They found that the incidence of VTE was 2.67% in OSA patients and 0.96% in the control group (HR 2.1, p<0.05). It is important to mention that the main limitation of the national Taiwan database is that this database was not specifically designed to address the relationship between OSA and other comorbidities or complications (including PE), so there is a lack of important information in this respect. Therefore, these studies should only be considered as hypothesis-generating. Finally, another retrospective study found that subjects with OSA developed VTE more frequently with an OR range 2.02–4.5 [96, 99, 100]. Although these associations do not necessarily imply a causal relationship, they support the hypothesis that patients with OSA may present an increased risk of VTE.

Potential effect of acute PE on OSA risk and severity

Four prospective cohort studies have suggested that patients with acute PE have a two to four times greater risk, compared to patients with no PE, of moderate-to-severe OSA, and a 26 times greater risk of severe OSA [91–95] (figure 3). Epstein *et al.* [91] evaluated the risk of OSA in 71 consecutive acute PE patients in comparison with 199 patients without PE. They found a higher rate of positive Berlin questionnaire responses suggesting an OSA in those patients with confirmed PE (OR 2.78, p=0.001), notwithstanding any differences in sex, age and BMI. In another small prospective case–control study of 28 patients with PE and 45 matched controls, Kosovali *et al.* [94] found severe OSA (AHI >30 $events \cdot h^{-1}$) diagnosed by polysomnography in six (21.4%) patients in the PE group, but did not find severe OSA in the control group (OR 26.3, p=0.015). Arzt *et al.* [93] assessed the increased risk of OSA in 82 consecutive acute patients with VTE compared to 82 matched controls by performing respiratory polygraphy 1 month after the thromboembolic event. OSA was found to be significantly associated with the risk of VTE (OR 2.28, p<0.05). Alonso-Fernández *et al.* [95] performed a similar matched control study including 107 patients with acute PE and 102 control subjects without PE matched for age, sex and BMI, and they found a

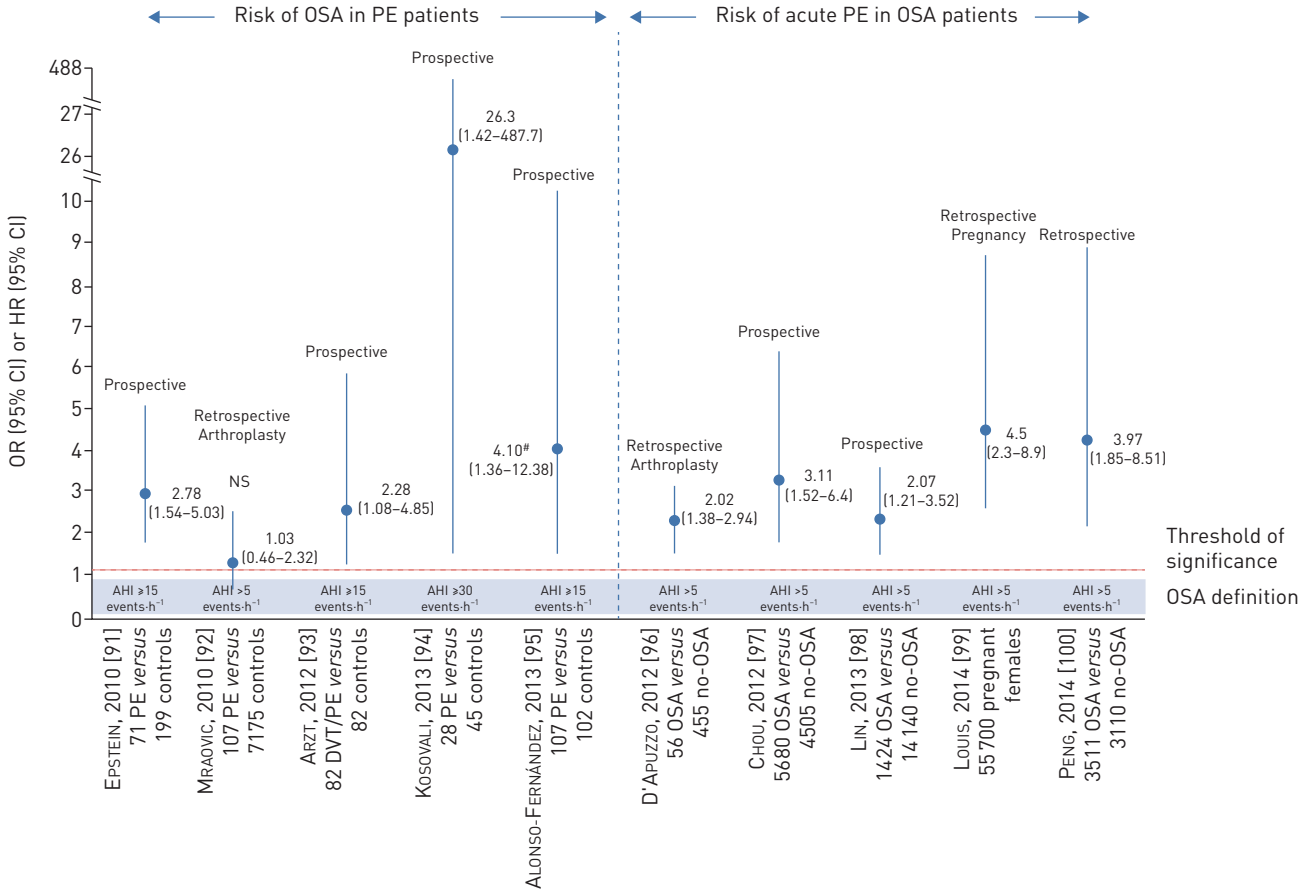

FIGURE 3 Case–control studies investigating the association between obstructive sleep apnoea (OSA) and pulmonary embolism (PE). HR: hazard ratio; AHI: apnoea/hypopnoea index; DVT: deep vein thrombosis; NS: nonsignificant. #: adjusted for age, sex, body mass index, neck circumference, smoking habit, daily physical activity, lung function and classic risk factors for PE.

significantly increased risk of moderate OSA (AHI >15 events·h^{-1}) diagnosed using home respiratory polygraphy (OR 4.1, p=0.01).

In addition, there is increasing evidence that some cardiovascular diseases may affect the severity of OSA. Patients with heart failure, systemic hypertension (particularly drug-resistant hypertension) or renal failure may present a rostral fluid shift from the legs when supine, resulting in excess fluid in the pharyngeal area contributing to its collapse [4, 101, 102].

This pathogenic mechanism has been demonstrated in both healthy subjects and OSA patients with chronic venous insufficiency (CVI) [103–106]. Shiota *et al.* [103] performed a prospective study in 27 healthy subjects to evaluate the effects of fluid redistribution from the lower to the upper body on the collapse of the upper airway in a recumbent position. Compared with controls, subjects who received positive lower body pressure at 40 mmHg *via* anti-shock trousers significantly increased their neck circumference and reduced the cross-sectional area of the upper airway, which could contribute to pharyngeal narrowing and airflow obstruction during sleep. Subsequently, Redolfi *et al.* [106] assessed the impact of wearing compression stockings during the day in 12 nonobese subjects with OSA and CVI. They found that redistribution of fluid from the legs to the neck overnight contributes to the pathogenesis of OSA in subjects with CVI, and that prevention of fluid in the legs during the day, and of its nocturnal movement towards the neck, attenuates OSA in such cases.

More than one-quarter of patients with acute PE have right ventricular (RV) dysfunction detected by echocardiography, which might cause a retrograde increase in central venous pressure [107–109]. Therefore, it is biologically plausible that patients with acute PE and associated RV dysfunction could present fluid accumulation and greater collapsibility of the upper airway, thereby increasing the number of respiratory events during sleep. However, this increase in the number of respiratory events during sleep is likely to be transient and disappears when the function of the RV normalises after administration of

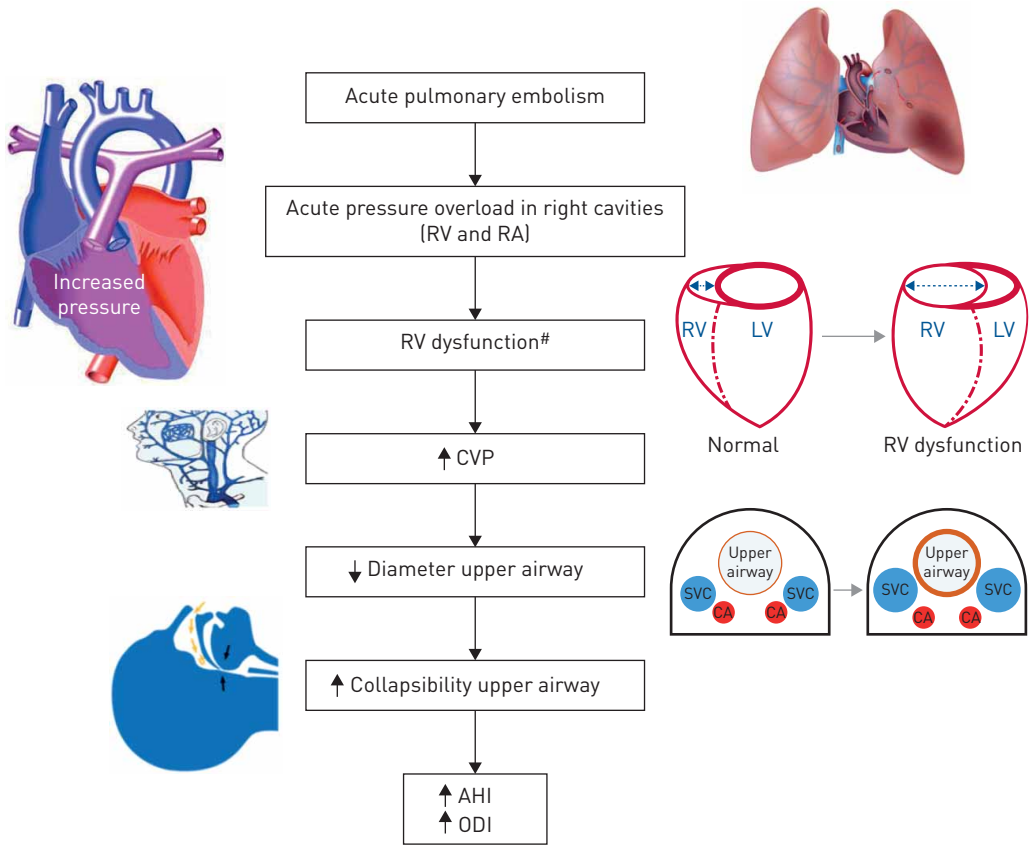

FIGURE 4 Pathophysiological hypothesis of the impact of acute pulmonary embolism on sleep-disordered breathing. RV: right ventricle; RA: right auricle; CVP: central venous pressure; SVC: superior vena cava; CA: carotid artery; AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index. #: according to cardiac reserve.

PE-specific therapy (figure 4). Nevertheless, the effect of acute PE on the prevalence and severity of SDB has not been evaluated comprehensively.

BERGHAUS *et al.* [110] conducted a prospective study to evaluate the impact of acute PE on the severity of SDB in OSA patients. 76 consecutive patients with acute PE underwent diagnostic nocturnal polysomnography during their hospital admission. Patients with an AHI >15 events·h^{-1} were re-evaluated after 3 months. Compared to the initial PSG, the mean oxygen saturation while asleep was significantly lower shortly after acute PE ($p<0.03$), but there were no significant changes in the mean oxygen desaturation index (ODI) or the mean AHI after the 3 months of anticoagulation therapy. Patients with significant inferior vena cava contrast backflow had a higher mean ODI and AHI, but it did not significantly influence the changes observed during the follow-up period.

The question as to whether OSA severity is modified in accordance with the time point of the PE event (acute or stable/chronic) is vitally important, to improve our knowledge about both the ideal time to perform a sleep study intended to diagnose a pre-existing OSA and the therapeutic implications.

In summary, prospective studies of patients with confirmed acute PE suggest an increased risk of coexisting moderate and severe OSA when compared with similar control groups. In addition, PE could produce or worsen SDB, especially during the acute phase and in those patients with right ventricular dysfunction, and thus modify the prevalence and severity of OSA in the different stages of PE. However, this is still a hypothesis, and further research is required to prove it.

Prevalence of OSA in patients with PE

Several studies have evaluated the prevalence of undiagnosed OSA in patients with acute PE (table 2). Although most studies included consecutive patients with acute symptomatic PE, the demographic features of the study populations (age, sex) were different across the different studies. Furthermore, the scheduling of the sleep test varied from one study to another, from 24 to 72 h to >3 months after the diagnosis of acute PE. The vast majority of studies used full polysomnography to diagnose OSA, which was defined as an AHI ⩾5 events·h^{-1}. Overall, the prevalence of OSA ranged from 6.4% to 74.4% [14, 15, 91–96, 99, 111–122].

TABLE 2 Prevalence of obstructive sleep apnoea (OSA) in patients with pulmonary embolism and study characteristics

First author, year [reference]	Subjects n (% male)	Study population	Mean age years	BMI kg·m^{-2}	Mean ESS score	Sleep study	Prevalence of OSA in patients with PE	Mean/median AHI events·h^{-1}
Prospectively enrolled patients, single-centre								
Konnerth, 2018 [111]	253 (50.2)	Consecutive acute VTE, excluding treated OSA	64	NA	NA	RP (during hospitalisation when there is clinical stabilisation) PSG (30 days after if AHI >15 events·h^{-1} or AHI ⩽15 events·h^{-1} but ESS score >10)	PSG-AHI >15 events·h^{-1} 35.2%	NA
Berghaus, 2016 [112]	206 (48.1)	Consecutive acute VTE, excluding treated OSA and severe neurological impairments	60.4±1.2	29.9±0.5	5 (range 0–15)	RP PSG (30 days after if AHI >15 events·h^{-1} or AHI ⩽15 events·h^{-1} but ESS score >10)	AHI 5–15 events·h^{-1} 41.3% AHI 16–30 events·h^{-1} 11.2% AHI >30 events·h^{-1} 13.6%	8 (range 0–83)
Berghaus, 2016 [113]	106 (48.1)	Consecutive acute PE patients, no exclusion criteria	63.3±1.4	28.8±0.5	6.3±0.5	RP PSG (3 days after if AHI >15 events·h^{-1} or AHI ⩽15 events·h^{-1} but ESS score >10)	AHI 5–15 events·h^{-1} 35.8% AHI 16–30 events·h^{-1} 12.3% AHI >30 events·h^{-1} 10.4%	10.9±1.3
Ghiasi, 2015 [114]	137 (57.7)	Consecutive acute PE patients, excluding preliminary haemodynamically unstable patients and impossibility of 1-month follow-up	Low risk OSA 48.6±18.4 High risk OSA 63.3±10.3	Low risk OSA 23.8±2.4 High risk OSA 33.6±3.9	NA	STOP-Bang questionnaire	High risk OSA 69.3%	NA
Jiang, 2014 [115] and Xie, 2015 [14]#	97 (46.4)	Consecutive acute PE patients excluding patients with severe comorbidities (malignancies, CTD, thrombolytic therapy, *etc*.)	OSA 60±12.9 Non-OSA 63±12.7	OSA 30.7±5.4 Non-OSA 26±4.1	NA	PSG (during hospitalisation when there is clinical stabilisation)	AHI >15 events·h^{-1} and AHI 5–15 events·h^{-1} + daytime symptoms 33.0% AHI 5–15 events·h^{-1} 14.4% AHI >15 events·h^{-1} 18.6%	NA
Kosovali, 2013 [94]	73 (50)	Consecutive acute PE patients and matched controls without history of PE referred to the sleep clinic	PE group 54.93±17.2 Control group 50.42±12.7	PE group 30.5±6.6 Control group 28.7±6.5	PE group 5±3.2 Control group 5.5±5.2	PSG (⩾1 week after PE diagnosis when there is clinical stabilisation)	AHI >30 events·h^{-1} 21.4% (0% in control group)	PE group 17.6±18.1 Control group 9.5±6.7
Kezban, 2012 [116]	30 (53.3)	Consecutive acute PE patients	61±2.8	29.4±1.2	NA	PSG	AHI >5 events·h^{-1} 56.7% AHI >15 events·h^{-1} 26.7% AHI >30 events·h^{-1} 16.7%	Non-major risk factor for PE group 14.8±3.7 Major risk factor for PE group 21.3±12.4
Berghaus, 2012 [110]	76 (46.6)	Consecutive acute PE patients	63.6±12.5	33.1±5.2	7.0±3.1	PSG (in acute phase)	AHI >15 events·h^{-1} 19.7%	IVC reflux group 34±10.0 Without IVC reflux group 28.0±17.0

Continued

TABLE 2 Continued

First author, year [reference]	Subjects n (% male)	Study population	Mean age years	BMI kg·m^{-2}	Mean ESS score	Sleep study	Prevalence of OSA in patients with PE	Mean/median AHI events·h^{-1}
Epstein, 2010 [91]	270 (61)	Patients who underwent CTA for suspected PE: 71 patients with acute PE and 199 controls	60±15.7	PE group 28.7±7 Control group 27.9±6.7	NA	Berlin questionnaire	OSA in PE group 65% (36% in control group)	NA
Arnulf, 2002 [117]	68 (NA)	Consecutive acute PE and DVT patients	NA	BMI >30 kg·m^{-2} 16%	NA	PSG	AHI >15 events·h^{-1} 63%	NA
Prospectively enrolled patients, more than one centre								
Mañas, 2017 [118]	62 (45)	Consecutive acute symptomatic PE patients Exclusion criteria: known OSA on treatment; treatment with thrombolytics at the time of PE diagnosis; life expectancy <3 months; pregnancy; haemodynamic instability at presentation; and geographic inaccessibility that precluded follow-up	68.3±14.3	29.4±4.5	ESS >10 34%	RP (within 7 days after PE diagnosis, preferably within the first 48 h)	AHI ⩾5 and <15 events·h^{-1} 27% AHI ⩾15 and <30 events·h^{-1} 19% AHI ⩾30 events·h^{-1} 19%	18.1±21.0
Alonso-Fernández, 2016 [15]	120 (62.5)	Patients who stopped for ⩾3 months with OAC due to a first episode of PE	57±15	28.1±5.3	EES >11 16.7%	RP	AHI >10 events·h^{-1} 59.2% AHI >30 events·h^{-1} 27.5%	NA
García-Suquía, 2015 [119]	175 (48.6)	Patients who stopped for ⩾3 months with OAC due to a first episode of PE	PE group OSA 60±14; non-OSA 50±16 Control group OSA 61±12; non-OSA 49±14	PE group OSA 27.8; non-OSA 26.8 Control group OSA 27.5; non-OSA 25.7	PE group OSA 7.1±3.9; non-OSA 5.8±3.5 Control group OSA 6.0±3.9; non-OSA 6.5±2.5	RP	AHI >5 events·h^{-1} 74.4% (46.1% in control group)	PE group OSA 22; non-OSA 3.4 Control group OSA 12.9; non-OSA 2.4
Alonso-Fernández, 2013 [95]	209 (62)	107 patients with acute PE and 102 matched controls, excluding patients with severe hypoxaemia or estimated survival <12 months	PE group 57±15 Control group 54±15	PE group 27.6±4.9 Control group 26.4±3.9	PE group 7±4 Control group 6±3	RP	PE group AHI >5 events·h^{-1} + EES >11: 14.0% (*versus* control group 4.9%)	PE group 21.2±20.6 Control group 12.4±23
Arzt, 2012 [93]	164 (51)	82 consecutive DVT/PE patients and 82 matched controls	VTE group 57±17 Control group 56±17	VTE group 27.6±4.5 Control group 27.5±4.4	VTE group 4.9±3.2 Control group 6.0±4.5	RP (during first month after PE)	AHI >15 events·h^{-1} 40% (*versus* 26% control group)	DVT/PE group 17.8±17.9 Control group 12.4±15.2

Continued

TABLE 2 Continued

First author, year [reference]	Subjects n (% male)	Study population	Mean age years	BMI kg·m^{-2}	Mean ESS score	Sleep study	Prevalence of OSA in patients with PE	Mean/median AHI events·h^{-1}
Retrospective, single-centre								
Bosanquet, 2011 [120]	840 (46.1)	Patients with VTE diagnosis	55	31.5	NA	Data obtained from single-centre medical records	AHI >15 events·h^{-1} 15.5%	NA
Mraovic, 2010 [92]	7282 (43.8)	Patients who underwent hip or knee arthroplasty: 107 patients with PE and 7175 controls	NA	NA	NA	Data obtained from single-centre medical records	OSA in PE group 6.5% (*versus* 5.4% in control group)	NA
Sapala, 2003 [121]	12 (33)	Patients who died after a gastric bypass surgery	NA	59.2±4.8	NA	Not specified	33%	NA
Retrospective, more than one centre								
Louis, 2014 [99]	55 781 965 (0)	Pregnancy-related hospital discharges	NA	NA	NA	Data obtained from USA database of NIS	OSA code 0.03%	NA
D'Apuzzo, 2012 [96]	285 455 (49.1)	Patients who underwent total hip or knee arthroplasty	66.5	NA	NA	Data obtained from USA database of NIS	OSA code 6.4%	NA

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; ESS: Epworth sleepiness scale; PE: pulmonary embolism; AHI: apnoea/hypopnoea index; VTE: venous thromboembolism; NA: not available; RP: respiratory polygraphy; PSG: polysomnography; CTD: connective tissue disease; IVC: inferior vena cava; CTA: computed tomography angiogram; DVT: deep vein thrombosis; OAC: oral anticoagulant; NIS: Nationwide Inpatient Sample. #: both studies used the same sample; ¶: by NA data.

When analyses were restricted to prospective cohort studies (16 studies; n=1888 patients) [14, 15, 91, 93–95, 111–119], the prevalence of OSA ranged from 54.4% to 74.4%, the prevalence of moderate-to-severe OSA (AHI ⩾15 events·h^{-1}) from 19.7% to 63% and the prevalence of severe OSA (AHI ⩾30 events·h^{-1}) from 10.4% to 27.5%. Moreover, 14–33% of patients presented with OSA syndrome (AHI ⩾5 events·h^{-1} plus ESS ⩾10). Three case–control studies found that the prevalence of moderate-to-severe OSA, severe OSA and OSA syndrome in the PE population were significantly higher compared to those in matched controls without PE after adjustment for age and BMI (21.4% *versus* 0%, 14% *versus* 4.9% and 40% *versus* 26%, respectively; p<0.05 for all comparisons) [93–95]. All these findings suggest that the prevalence and severity of OSA and OSA syndrome are higher in acute PE patients than in the general population [2, 123].

In summary, the high prevalence of OSA in PE patients emphasises the value of establishing a good clinical history of sleep-related symptoms in these patients and of performing sleep studies based on prospective registries of PE patients to confirm the real prevalence of both OSA and OSA syndrome in these cohorts.

OSA and PE prognosis

Concomitant OSA might play a major role in the early phase after PE, when the heart might be in a vulnerable state and therefore sensitive to the consequences of SDB (increased cardiac workload, endothelial dysfunction, excessive desaturations) and, ultimately, to a mismatch of myocardial oxygen demand and supply.

In a prospective single-centre cohort study of 106 patients diagnosed with acute symptomatic PE, investigators assessed the prevalence of undiagnosed SBD during the first month of follow-up after PE diagnosis [113]. In this study, eight (7.6%, 95% CI 3.3–14.3%) of the 106 patients had high-risk (*i.e.* haemodynamically unstable) PE. Of the 23% (24 out of 106) that had an AHI >15 events·h^{-1}, five patients (21%, 95% CI 7.1–42%) had high-risk PE, compared to 3.7% of patients with an AHI <15 events·h^{-1}. Significantly, none of these high-risk PE patients died within 30 days of their PE diagnosis [113]. Ghiasi *et al.* [114] prospectively assessed the prognostic value of a high risk of OSA, according to the STOP-Bang questionnaire, in 137 stable patients with acute symptomatic PE. This study did not find any relationship between a high-risk (*i.e.* >6 points) STOP-Bang questionnaire and 30-day all-cause mortality (OR 1.58, 95% CI 0.56–4.49; p=0.39). However, the lack of association between OSA and prognosis in this study might have been due to the absence of a confirmatory testing for the diagnosis of sleep apnoea, and a lack of statistical power. More recently, Konnerth *et al.* [111] prospectively evaluated the influence of OSA on disease severity among survivors of acute PE, in 253 stable patients with acute PE. They found that moderate-to-severe OSA was significantly more frequent among intermediate- and high-risk PE patients (81%) compared to the low-risk PE cohort (16.3%, p=0.006). In addition, moderate or severe OSA patients were hospitalised significantly longer for PE. However, the cohort of patients with relevant OSA were significantly older in comparison to the nonrelevant OSA cohort (73 *versus* 59 years, p<0.001) [109].

Moreover, several studies have evaluated the recurrence of thromboembolic disease and its relationship with the presence of sleep apnoea. Xie *et al.* [14] studied PE patients, 32 of them with OSA. Warfarin was administered for 6 months and all the patients were followed for 18 months. OSA patients had more recurrence of PE than non-OSA patients after successful treatment for 6 months. Other studies have assessed the risk of recurrence of PE in terms of a greater pro-coagulation state. A higher risk of PE recurrence has also been reported in patients with unprovoked PE who had a high post-anticoagulation D-dimer (>500 ng·mL^{-1}) than in patients with normal D-dimer levels. García-Suquia *et al.* [119] evaluated 101 OSA patients; 64 (74.4%) with PE and 41 (46.11%) without PE. Plasma D-dimer levels were higher in PE patients with OSA than in those with no OSA. D-dimer levels significantly correlated with the AHI and nocturnal hypoxia. More patients with PE and OSA had high D-dimer levels after stopping anticoagulants than those with PE with no OSA (35.4% *versus* 19.0%, p=0.003), indicating that there is a persistent hypercoagulable state in OSA, which could increase the risk of a recurrence of pulmonary embolism. Alonso-Fernández *et al.* [15] followed a population of 120 patients for 5–8 years after a first episode of PE, and identified OSA as an independent risk factor for PE recurrence. In this study, 19 patients presented a PE recurrence during the follow-up period (10.7 events per 100 patient-years) and 16 of them had OSA. The prevalence of patients with AHI >10 events·h^{-1} was significantly higher in patients with PE recurrence than in those who did not have any relapses (84% *versus* 54%, p=0.012). The presence of an AHI >10 events·h^{-1} was identified as an independent risk factor for recurrent PE. The analysis showed that those patients with a previous PE episode and OSA had a higher risk of recurrent PE than those with no OSA (crude HR 4.05, 95% CI 1.18–13.91; p=0.026).

In summary, studies of patients with proven acute PE have shown conflicting data regarding the association between OSA and the severity and recurrence of PE presentation and short-term outcomes.

Implications of OSA in the treatment of PE

The goals of anticoagulation, the mainstay of VTE treatment, are to prevent VTE extension, embolism, recurrence and death.

Vitamin K antagonists (*e.g.* warfarin) are the most widely used oral anticoagulant agents worldwide [124]. The appropriate dose of warfarin is difficult to establish because it can vary by a factor of 10 from one patient to another, with clinical variables (*e.g.* age, sex, body weight) and genetic variations contributing significantly to these discrepancies [115, 125, 126]. A prospective study of 97 patients with acute PE demonstrated that 33% had OSA and that the severity of OSA had a significant independent correlation with warfarin dosage (r=0.415, p=0.018) [115]. This analysis did not address the issue of whether a need for higher doses translates into increased clinical end-points (*i.e.* recurrent VTE while on anticoagulation).

The most common and difficult decision about stopping anticoagulants after a time-limited course or using extended therapy arises in patients with a first unprovoked proximal PE and absence of an increased risk of bleeding. In this subgroup of patients, patient sex and D-dimer level measured ~1 month after stopping anticoagulant therapy can help to further stratify the risk of recurrent VTE [127–129]. Studies of patients with PE have demonstrated an association between OSA and a risk of recurrent VTE after discontinuation of anticoagulant therapy, as previously commented. In a cohort of 97 patients with PE who had received 6 months of warfarin, Xie *et al.* [14] prospectively evaluated the risk of recurrent PE during the first 12 months after discontinuation of anticoagulant therapy. Univariate analysis showed that an AHI $\geqslant$15 events·h^{-1} was significantly associated with the risk of recurrent PE (21% *versus* 6.8%, p=0.047). Similarly, a prospective study of 120 patients who had stopped oral anticoagulants for a first episode of PE found that an AHI >10 events·h^{-1} was an independent predictor of PE recurrence (HR 20.73, 95% CI 1.71–251.28) [15].

In summary, there is increasing evidence that, after discontinuation of anticoagulation, patients with OSA have a higher risk of recurrent PE than those without OSA. Prospective management studies and randomised trials should address whether CPAP treatment reduces this risk and whether OSA patients might benefit from extended anticoagulant therapy for their VTE.

Future challenges

The relationship between VTE and OSA is one of the least studied aspects of the epidemiological connections between CVD and OSA, even though both diseases are highly. Accordingly, the major studies of the relationship between OSA and increased cardiovascular risk do not usually include the presence of VTE among their single or composite end-points, and therefore the information available on this subject is very limited. Table 3 shows some of the studies that would be required in the future to more fully elucidate the putative relationship between VTE and OSA.

The ongoing POPE study (Prognostic Significance of Obstructive Sleep Apnoea in Patients with Acute Symptomatic Pulmonary Embolism) is a well-powered, multicentre, observational study designed to prospectively assess the prognostic significance of concomitant OSA in haemodynamically stable outpatients with acute symptomatic PE [118]. Recruited patients undergo an overnight sleep study within

TABLE 3 Future challenges for the study of the relationship between obstructive sleep apnoea (OSA) and venous thromboembolism (VTE)

Epidemiology of the OSA–VTE relationship	Inclusion of VTE as an end-point within CVD in relevant studies Follow-up studies of international registers of OSA patients to evaluate their risk of VTE Analysis of the impact of confounding variables (especially obesity)
Pathophysiology	Studies with sufficient statistical power to evaluate which elements of coagulation and other biomarkers are associated with the presence of OSA and its treatment, as well as the factors that modulate this relationship
Evolution of VTE in OSA patients	Studies on the short- and long-term effect of OSA on relapses, cardiovascular outcomes and other variables of interest in patients with VTE
Impact of VTE on OSA	Studies of the effect of PE with RV dysfunction on the diameter and collapsibility of the upper airway
Treatment of OSA	Effect of CPAP on different elements of coagulation Clinical trials with sufficient statistical power on the effect of CPAP in the short- and long-term on relapses, major cardiovascular events and other variables of interest
Treatment of VTE	Effect of OSA and its treatment on the effect of anticoagulant treatment in VTE patients

CVD: cardiovascular disease; RV: right ventricle; CPAP: continuous positive airway pressure.

7 days (and preferably within 48 h) of the diagnosis of PE, using a level-3 portable diagnostic device. The study uses a composite of PE-related death, cardiovascular death, clinical deterioration requiring an escalation of treatment or nonfatal cardiovascular events (recurrent venous thromboembolism, acute myocardial infarction or stroke) within 30 days of the diagnosis of PE as the primary outcome. The results of this trial should significantly deepen our understanding of the burden and cardiovascular effects of OSA in PE patients.

Conclusions

Emerging research highlights the complex interrelationships between OSA and VTE, presenting clinical and research opportunities as well as challenges. Epidemiological research indicates that OSA is associated with increases in the incidence of PE. Data from small trials provide evidence that, after discontinuation of anticoagulation, patients with OSA are at a higher risk of recurrent PE than those without OSA. While CPAP treatment improves patient-reported outcomes such as sleepiness, quality of life and mood, its effectiveness in reducing significant clinical end-points (*i.e.* recurrent VTE and PE-related mortality) is still unclear. According to the results available in the literature, the authors of the present study think that there is not enough scientific evidence to systematically perform a sleep study in all PE patients or establish the best time to perform a sleep study (acute phase *versus* stable phase of the PE). The most important concern is probably an insistence that a good clinical sleep history should be introduced for all patients with acute PE in order to rule out a symptomatic or severe OSA and decide whether a sleep study should be performed.

There is a critical need for rigorous, well-powered trials that address the impact of OSA treatment on the primary and secondary prevention of VTE. Future studies could benefit from the careful identification of subgroups most likely to respond to the intervention, a larger sample size (allowing detection of clinically relevant effects across strata) and the incorporation of methods for improving adherence to treatment over long periods of observation. These goals may best be addressed through strengthening collaboration between the pneumology, sleep medicine and clinical trial communities.

Conflict of interest: None declared.

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