Sleep apnea and venous thromboembolism

A systematic review

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Summary

Recent evidence suggests that obstructive sleep apnea is a significant and independent risk factor for a number of cardiovascular disorders. Since the association between obstructive sleep apnea and cardiovascular disease is mediated by endothelial dysfunction, hypercoagulability and platelet abnormalities, we sought to investigate whether sleep apnea may also be considered a risk factor for venous thromboembolism (VTE). We carried out an electronic search in Medline and Scopus using the keywords "apnea" OR "apnoea" AND "venous thromboembolism" OR "deep vein thrombosis" OR "pulmonary embolism" in "Title/Abstract/Keywords", with no language or date restriction. Fifteen studies (8 case-control, 4 retrospective observational, 2 prospective case-control and 1 prospective observational) were finally selected for this systematic review. In all studies except one (14/15; 93 %), obstructive sleep apnea was found to be an independent risk factor for VTE, either deep-vein thrombosis (DVT) or pulmonary embolism (PE). In the two prospective case-control studies the risk of DVT or PE was found to be two- to three-fold higher in patients with obstructive sleep apnea than in those without. In conclusion, the current epidemiological evidence supports the hypothesis that obstructive sleep apnea may be an independent risk factor for VTE.

Keywords

Venous thromboembolism, thrombosis, sleep apnea, risk

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Introduction

Obstructive sleep apnea is a common form of sleep-disordered breathing (SDB), typically characterised by recurrent episodes of partial or complete upper airway closure associated with apnea, hypopnea and intermittent hypoxia (1). The burden of this condition is generally comprised between 9–15 % in middle-aged adults, with a marginally higher prevalence in men than in women (2–4).

Untreated obstructive sleep apnea is currently considered an important risk factor for vascular morbidity and mortality, being implicated in the pathogenesis of several cardiovascular diseases (5, 6). A number of pathogenic mechanisms have been suggested to promote the onset of cardiovascular complications in patients with sleep apnea, including haemodynamic alterations, sympathetic nervous system activation, oxidative stress, systemic inflammation and vascular endothelial dysfunction (7–11). Importantly, a hypercoagulable state has also been associated with obstructive sleep apnea (12, 13).

Venous thromboembolism (VTE), which conventionally includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent pathology worldwide, with a prevalence approximating 0.1–0.2 % in the general population (14). Besides the convincing association with cardiovascular events of arterial origin, the evidence that patients with obstructive sleep apnea exhibit a vast number of haemostatic abnormalities that are also well-established risk factors for venous thrombosis (15) is suggestive for the existence of a possible role of this sleeping disorder in the pathogenesis of VTE. Therefore, we performed a systematic review of published clinical studies that investigated the association between obstructive sleep apnea and VTE.

Search methodology

An electronic search was carried out in Medline (with PubMed interface) and Scopus using the keywords "apnea" OR "apnoea" AND "venous thromboembolism" OR "deep vein thrombosis" OR "pulmonary embolism" in "Title/Abstract/Keywords", with no language or date restriction. All articles identified according to the search criteria were systematically reviewed and assessed for quality by two authors (G. L. and M. F.), according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist criteria. The references of selected articles were also hand-searched to identify other pertinent documents.

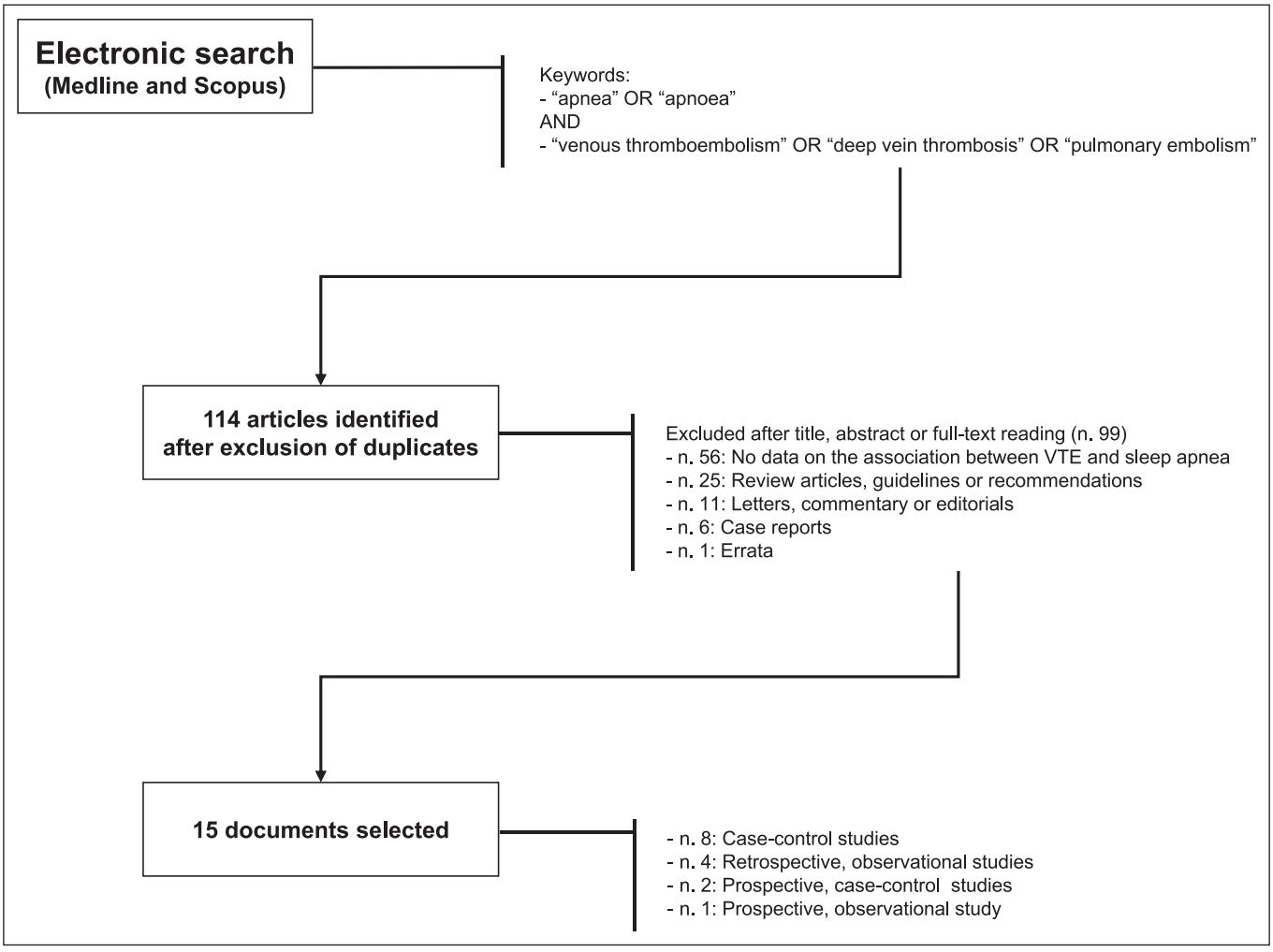

Figure 1: Description of the search methodology.

Results

After elimination of duplicate documents across the scientific databases, a total number of 114 publications could be identified. Ninety-nine documents were excluded after accurate reading of title, abstract and full text (when available) (▶Figure 1). Therefore, 15 studies (8 case-control, 4 retrospective observational, 2 prospective case-control and 1 prospective observational) were finally selected for this systematic review (median QUADAS score, 10; range 7–13) (16–30) (▶Table 1). Inter-rater agreement was excellent (kappa statistics, 0.96; $p<0.001$).

The first study that investigated the potential association between VTE and obstructive sleep apnea was published by Arnulf et al. in 2002 (16). The authors studied 68 patients with VTE (10 with DVT and 58 with PE), and observed that the overall prevalence of obstructive sleep apnea was 63% (43/68) in their study population, which is up to four-fold higher than that observed in the general population (i.e. 9–15%) (2).

Sapala et al. conducted a retrospective observational analysis of 5,554 operations of bariatric surgery for clinically severe obesity, to identify relevant risk factors associated with fatal post-surgery VTE (17). A total number of 12 (0.21%) subjects died from fatal PE. The prevalence of obstructive sleep apnea was found to be considerably high in these patients (4/12; 33%), more than two-fold higher than that reported in the general population (i.e. 9–15%) (2).

Ambrosetti et al. performed a small prospective study to assess the incidence of clinically evident VTE in a series of 89 patients with obstructive sleep apnea referred to a sleep clinic, and who were followed up for three years (18). Overall, two episodes of VTE were recorded during follow-up (1 patient with DVT and another one with both DVT and PE; incidence rate: 2.2%). Compared to the general population, a considerably 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 obstructive sleep apnea (14).

Epstein et al. carried out a case-control study including 270 consecutive patients undergoing computed tomographic angiogram for suspected PE (19). A final diagnosis of PE could be made in 71 patients (26%), whereas PE was ruled out in the remaining

Table 1: Description of epidemiological studies investigating the association between obstructive sleep apnea, venous thromboembolism (VTE), deep-vein thrombosis (DVT) or pulmonary embolism (PE).

Author	Study design	Study population	Prevalence of sleep apnea	Outcome	Reference
Arnulf et al, 2002	Retrospective, observational	68 patients with VTE (10 with DVT and 58 with PE; no demographical data reported)	63 %	Remarkably high prevalence of obstructive sleep apnea (i. e. 63 %) in patients with VTE	[16]
Sapala et al, 2003	Retrospective, observational	5,554 operations of bariatric surgery for clinically severe obesity (no demographical data reported; 12 fatal PE)	33 %	Remarkably high prevalence of obstructive sleep apnea (i. e. 33 %) in patients with fatal PE	[17]
Ambrosetti et al, 2004	Prospective, observational	89 patients with obstructive sleep apnea (13 women and 76 men, mean age 62 ± 11 years) followed for 3 years	100 %	Prevalence of VTE in patients with obstructive sleep apnea higher that in the general population (DVT: 0.8 vs 0.05 per 100/year; PE: 0.4 vs 0.1 per 100/year)	[18]
Epstein et al, 2010	Case-control	270 consecutive patients undergoing computed tomographic angiogram for suspected PE (154 women and 116 men; mean age 61 ± 17 years; 71 with PE)	65 % in PE cases versus 36 % in controls	Obstructive sleep apnea independent risk factor for PE (OR, 2.78; 95 % CI, 1.54–5.03)	[19]
Mraovic et al, 2010	Case-control	7,282 patients (4,090 women and 3,192 men; 107 with PE) undergoing total hip or total knee arthroplasty	6.5 % in PE cases versus 5.4 % in controls	Obstructive sleep apnea non-significantly associated with PE (OR, 1.23; 95 % CI, 0.57–2.67)	[20]
Bosanquet et al, 2011	Retrospective, observational	840 patients with VTE (453 women and 387 men; median age 55 years and range 18–94 years; 130 with obstructive sleep apnea)	15.5 %	Increased prevalence of obstructive sleep apnea (i. e., 15–17 %) in patients with VTE than in the general population	[21]
Kezban et al, 2012	Case-control	30 patients with PE (14 women and 16 men; mean age 61 ± 3 years; 10 with major risk factor for VTE and 20 without)	70 % in PE cases versus 30 % in controls	Obstructive sleep apnea independent risk factor for PE (beta coefficient, 3.93; p=0.049)	[22]
Chou et al, 2012	Prospective, case-control	5,680 patients with obstructive sleep apnea (2,153 women and 3,527 men; mean age 45 ± 18 years) and 4,505 without (1,689 women and 2,816 men; mean age 45 ± 18 years), followed up for 3.6 years	100 %	Obstructive sleep apnea independent risk factor for DVT (HR, 3.11; 95 % CI, 1.52–6.39)	[23]
Arzt et al, 2012	Case-control	82 patients with VTE (40 women and 42 men; mean age 57 ± 17 years) and 82 matched controls (40 women and 42 men; mean age 56 ± 17 years)	Frequency of moderate degree of sleep apnea 18 events/hour in cases versus 12 events/hour in controls	Central sleep apnea independent risk factor for VTE (OR, 2.28; 95 % CI, 1.08–4.85)	[24]
D'Apuzzo et al, 2012	Case-control	258,455 patients (150,162 women and 108,292 men; mean age 66 years; 16,608 with obstructive sleep apnea) undergoing total hip arthroplasty or total knee arthroplasty	6.4 %	Obstructive sleep apnea independent risk factor for PE (OR, 2.02; 95 % CI, 1.3–2.9)	[25]
Lin et al, 2013	Prospective, case-control	15,664 subjects (6380 women and 9284 men; mean age 56 ± 12 years; 1,424 with obstructive sleep apnea) followed up for 5 years	9.1 %	Obstructive sleep apnea 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)	[26]
Kosovali et al, 2013	Case-control	28 patients with PE (14 women and 14 men; mean age 55 ± 17 years) and 45 controls (15 women and 30 men; mean age 55 ± 17 years)	21 % in PE cases versus 0 % in controls	Obstructive sleep apnea independent risk factor for PE (OR, 26.3; 95 % CI, 1.42–487.7)	[27]
Alonso-Fernández et al, 2013	Case-control	107 patients with PE (41 women and 66 men; mean age 57 ± 15 years) and 102 controls (48 women and 54 men; mean age 54 ± 15 years)	9.8 % in PE cases versus 4.1 % in controls	Obstructive sleep apnea independent risk factor for PE (OR for every 10-unit rise of apnea-hypopnea index, 1.04; 95 % CI, 1.01–1.07)	[28]
Louis et al, 2014	Case-control	55,781,965 pregnancy-related inpatient hospital discharges (no demographical data reported)	3.0 %	Obstructive sleep apnea independent risk factor for PE (OR, 4.47; 95 % CI,2.25–8.88)	[29]
Peng et al, 2014	Case-control	3,511 patients with obstructive sleep apnea (896 women and 2,615 men, mean age 42 ± 17 years) and 35,110 matched controls (8,960 women and 26,150 men; mean age 42 ± 17 years)	10 %	Obstructive sleep apnea independent risk factor for DVT (HR, 3.50; 95 % CI, 1.83–6.69) and PE (HR, 3.97; 95 % CI, 1.85–8.51)	[30]

CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

199 subjects. The frequency of obstructive sleep apnea was found to be nearly double in PE cases than in controls (65% vs 36%; p<0.001). In multivariate logistic regression analysis with multiple adjustment for age, gender and comorbidities, obstructive sleep apnea was found to be an independent risk factor for PE (odds ratio [OR], 2.78; 95% confidence interval [CI], 1.54–5.03).

Mraovic et al. performed a retrospective case-control study, reviewing medical records of 7,282 patients who underwent total hip or total knee arthroplasty, 107 of whom (1.5%) were diagnosed with PE (20). The prevalence of obstructive sleep apnea was found to be marginally but not significantly higher in patients who developed PE than in those who did not (6.5% vs 5.4%; p=0.593). Accordingly, sleep apnea was not found to be significantly associated with the risk of VTE in univariate analysis (OR, 1.23; 95% CI, 0.57–2.67).

Bosanquet et al. performed a retrospective observational study including 840 patients with VTE (619 with DVT and 530 with PE), 130 of whom diagnosed with obstructive sleep apnea (21). The prevalence of obstructive sleep apnea was found to be marginally higher in the whole cohort of patients with VTE (i.e. 15.5%), as well as in patients with DVT (15.3%) or PE (17.1%) compared to the general population (i.e. 9–15%) (2).

Kezban et al. conducted a small case-control study including 30 patients with PE who were studied by means of polysomnographic examination to establish the frequency of obstructive sleep apnea (22). Patients without any major risk factor for VTE (n = 20) were found to have significantly higher rates of obstructive sleep apnea compared to those with major risk factors for VTE (n = 10; 70% vs 30%; p=0.045). Accordingly, obstructive sleep apnea was found to be an independent risk factor for PE in multivariate regression analysis (beta coefficient, 3.93; p=0.049).

In a following investigation, Chou et al. performed a prospective, case-control study including 5,680 patients with obstructive sleep apnea and 4,505 without, who were selected from the Taiwan National Health Insurance Research Database and followed up for a mean period of 3.6 years (23). A total number of 40 patients (0.39%) developed DVT on follow up, with an incidence that was more than double in patients with obstructive sleep apnea than in those without (0.53% vs 0.22%; p=0.001). In Cox proportional hazards regression analysis, obstructive sleep apnea was found to be a significant and independent predictor of DVT (hazard ratio [HR], 3.11; 95% CI, 1.52–6.39). Interestingly, this association was found to be even stronger in patients with severe obstructive sleep apnea needing treatment with continuous positive airway pressure (CPAP) (HR, 9.57; 95% CI, 3.18–28.82).

Arzt et al. performed a case-control study including 82 patients with VTE and 82 matched controls (24). The frequency of sleep apnea with an at least moderate degree was found to be higher in VTE cases than in controls (18 ± 18 events/hour vs 12±15 events/hour; p=0.039). Accordingly, sleep apnea was found to be significantly associated with the risk of VTE (OR, 2.28; 95% CI, 1.08–4.85). Interestingly, this association was found to be stronger in women (OR, 15.2; 95% CI, 1.67–138.3) than in men (OR, 2.78, 95% CI, 0.89–8.72).

D'Apuzzo and Browne retrospectively reviewed data from the US Nationwide Inpatient Sample, and identified 258,455 patients who underwent revision total hip arthroplasty or revision total knee arthroplasty, 16,608 of whom (6.4%) diagnosed with obstructive sleep apnea and 511 (0.2%) with PE (25). Patients with obstructive sleep apnea had a two-fold higher rate of PE compared to those without (0.4% vs 0.2%; p=0.001). Accordingly, obstructive sleep apnea was found to be a significant and independent risk factor for post-operative PE after multiple adjustment for age, gender and comorbidities (OR, 2.02; 95% CI, 1.3–2.9).

Lin et al. performed a case-control study including 15,664 subjects, who were prospectively followed for five years (26). Overall, 87 cases of VTE (0.6%) and 83 cases of DVT (0.5%) were diagnosed on follow-up. The rates of incident VTE (1.3% versus 0.5%) and DVT (1.2% versus 0.5%) were more than 2-fold higher in patients with obstructive sleep apnea than in those without. Moreover, Cox proportional hazards regression analysis revealed that obstructive sleep apnea was 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).

Kosovali et al. carried out a small case-control study including 28 patients with PE and 45 controls, who were subjected to full-night polysomnography (27). The presence of severe sleep apnea was found to be significantly higher in patients with PE than in controls (21% vs 0%; p=0.015). Accordingly, severe sleep apnea was found to be a significant risk factor for PE (OR, 26.3; 95% CI, 1.42–487.7).

Alonso-Fernández et al. also performed a case-control study including 107 patients with PE and 102 controls (28). The apnea-hypopnea index was found to be nearly double in PE cases than in controls (21.2 per hour vs 11.5 per hour; p<0.001). Moreover, a significantly higher frequency of obstructive sleep apnea was found in patients with PE compared to controls (p=0.02). Accordingly, obstructive sleep apnea was found to be a significant risk factor for PE after adjustment for the main covariates (OR for every 10-unit rise of apnea-hypopnea index, 1.04; 95% CI, 1.01–1.07).

Louis et al. designed a retrospective investigation including 55,781,965 pregnancy-related inpatient hospital discharges from the US Nationwide Inpatient Sample (NIS) database (29), which were divided according to the presence of sleep apnea. The rate of PE was found to be substantially higher in pregnant women with obstructive sleep apnea than in those without (2.66 vs 0.11 per 1,000 pregnancy-related discharges; p<0.001). In the fully-adjusted multivariable model, obstructive sleep apnea was found to be a significant and independent risk factor for PE (OR, 4.47; 95% CI, 2.25–8.88).

Finally, Peng et al. carried out a large population cohort study including 3,511 patients with obstructive sleep apnea and 35,110 matched controls recruited from the Taiwan National Health Insurance Research Database (NHIRD) (30). A total number of 26 VTE cases were identified in patients with obstructive sleep apnea (15 DVT and 11 PE) and 51 in those without (30 DVT and 21 PE). In multivariable Cox proportional hazard regression, obstructive sleep apnea was found to be an independent risk factors for both DVT (HR, 3.50; 95% CI, 1.83–6.69) and PE (HR, 3.97; 95% CI,

1.85–8.51) after multiple adjustment for age, gender and comorbidities.

Discussion

Several lines of evidence now attest that obstructive sleep apnea should be regarded as a significant and independent risk factor for a number of cardiovascular disorders, such as hypertension, coronary heart disease, stroke, arrhythmias and heart failure. Some plausible biological links have also been uncovered to support this association, which mainly involve hypoxia, enhanced sympathetic hyperactivity, oxidative stress, metabolic and hormonal deregulations, inflammation, as well as endothelial dysfunction, hypercoagulability and platelet abnormalities (31). The evidence that a variety of haemostatic abnormalities are present in patients with obstructive sleep apnea was hence suggestive enough for conducting a systematical review of the current scientific literature aimed to establish whether or not a similar association may also exist with VTE.

Taken together, the available epidemiological data strongly supports the hypothesis that patients with obstructive sleep apnea may exhibit an increased risk of VTE. In all studies except one that could be identified with our literature search (14/15; 93%), sleep apnea was found to be an independent risk factor for VTE, either DVT or PE. Even more importantly, the risk of DVT or PE was found to be two- to three-fold higher in the populations of patients with obstructive sleep apnea than in those without in the two prospective case-control studies. In only one retrospective case-control investigation including patients undergoing total hip or total knee arthroplasty, the association between obstructive sleep apnea and PE was found to be weak and overall non-statistically significant. Nevertheless, this negative finding may be explained by the fact that hip or knee surgery is conventionally considered an outmost prothrombotic condition, which may overwhelm any other risk factor and hence decrease the potential contribution of sleep disturbances in the pathogenesis of VTE in patients undergoing orthopaedic surgery (32, 33). Another large observational study has been published in form of an abstract in 2009, but not including specific data on obstructive sleep apnea (34). Interestingly, the authors extracted data from the US National Hospital Discharge Survey (NHDS) between the years 1979 and 2005 to establish the relationship between SDB and VTE, and also found a significant association between these two conditions (relative risk, 1.72; 95% CI, 1.70–1.74).

Despite the fact that the prevalence of sleep apnea was highly heterogeneous across the different clinical studies (i.e. from 3% to 100%) (▶Table 1), the epidemiological association between this condition and VTE is reinforced by a number of biological explanations, recently reviewed by Liak and Fitzpatrick (13). In brief, by means of an electronic search in Medline, Ovid and ISI Web of Science, the authors identified original studies, meta-analyses and systematic reviews regarding the association between obstructive sleep apnea and haemostatic abnormalities. Several evidences were found in support of the fact that a prothrombotic state may be present in patients with obstructive sleep apnea, including enhanced haematocrit and viscosity, increased activity and/or concentration of a number of clotting factors (i.e. tissue factor, fibrinogen, thrombin, von Willebrand factor, factor VII and XII), platelet hyperreactivity, and a reduced fibrinolytic potential mostly attributable to decreased activity of plasminogen activator inhibitor-1 (PAI-1). Even more importantly, a large number of these abnormalities were found to be reversible by treatment with CPAP, which is currently regarded as the treatment of choice in patients with obstructive sleep apnea (35). Interestingly, Toukh et al. recently performed a small prospective crossover study, including 12 patients with obstructive sleep apnea, who were randomised to either CPAP or no-CPAP for two weeks and monitored with thromboelastography (36). Patients at baseline exhibited shorter clotting times, enhanced rate of clot formation, increased clot strength and clotting indices compared to the relative reference values. Even more importantly, the two-week CPAP treatment was effective to significantly decrease the apnea-hypopnea index along with clot strength and clotting index. McEwen et al. also recently measured the thrombotic potential across the sleep-wake cycle in a randomised, placebo-controlled crossover study including 28 patients (25 men, 3 women) with severe obstructive sleep apnea (37), and reported that fibrin generation in these patients was significantly increased in the morning.

In conclusion, the current epidemiological evidence supports the hypothesis that obstructive sleep apnea may be an independent risk factor for both cardiovascular disorders and VTE. As regards to the latter association, the lack of large prospective studies represents indeed a major hurdle for drawing definitive conclusions. It is also noteworthy that the patient populations, the study designs as well as the prevalence of both obstructive sleep apnea and VTE appear rather heterogeneous in the selected studies, which make is impossible to pool data and even directly compared the outcomes. Therefore, although it seems hence premature to suggest the routine treatment of obstructive sleep apnea (e.g. by means of CPAP) in patients at risk of VTE, a reinforcement of anti-thrombotic prophylaxis in these patients may be precautionarily considered. This approach may be particularly valuable in subjects with obstructive sleep apnea undertaking long airplane flights, in whom hypoxia due to low ambient pressure may contribute to increase the thromboembolic risk (38). Other patients who may benefit include those undergoing bariatric surgery, in whom the probability of adverse outcomes is amplified up to three-fold when a personal history of both VTE and obstructive sleep apnea is present (39).

Conflicts of interest
None declared.

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