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Prevalence of pulmonary embolism in patients with obstructive sleep apnea and chronic obstructive pulmonary disease: The overlap syndrome

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ABSTRACT

Objective: Growing evidence indicates that both obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) may be closely associated with the prevalence of pulmonary embolism (PE). However, the relationship of overlap syndrome (OS) (coexistence of OSA and COPD) with PE is unclear. The purpose of this study was to investigate whether OS were associated with increased PE prevalence.
Methods: We performed a retrospective chart review of patients who underwent sleep study at Beijing An Zhen Hospital from 2011 to 2014. The association of OS with PE prevalence was estimated by using logistic regression models.
Results: In contrast to control patients (neither OSA nor COPD), those subjects with OS had higher odds of PE (OR9.61; 95%CI 4.02–21.31, $p < 0.001$) with significance persisting after adjusting for covariates (OR 5.66; 95%CI 1.80–16.18, $p = 0.004$). Meanwhile, patients with OS compared with those with isolated OSA also had significantly higher odds of PE in univariate (OR 4.79; 95%CI 2.04–10.33, $p = 0.0007$) and adjusted models (OR 3.89; 95%CI 1.27–10.68, $p = 0.019$). In subgroup analysis, patients with OS had higher odds of PE than control group among male subjects (OR 8.12, 95%CI1.86–31.87, $p = 0.007$) and patients ≥ 58 years (OR 5.50, 95%CI 1.51–18.14, $p = 0.012$) in multivariable models. Percentage of total sleep time with saturation lower than 90% (T90) ≥ 2.6% was significantly associated with prevalence of PE (OR 4.72, 95%CI1.34–19.83, $p = 0.015$) in subgroup of patients older than 58.
Conclusions: OS is independently associated with PE prevalence. Longitudinal studies are needed to better understand the relationship with incident PE.

Introduction

Obstructive sleep apnea (OSA), characteristic of repeated breath cessation with intermittent hypoxemia, has been proved to increase the risk of incident cardiovascular diseases.[1] Our research and previous studies showed the potential association between OSA and pulmonary embolism (PE) prevalence.[2-6] Hypercoagulable state is always found in patients with OSA,[3,7] and might link to the incidence of thrombogenesis. Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation. Hypoxemia and hypercapnia occur due to the decreased ventilation from airway obstruction, hyperinflation and ventilator muscle impairment.[8,9] Noticeably, not only does COPD increase the risk of cardiovascular diseases significantly,[10] but also was proved to be closely related with deep vein thrombosis (DVT) and PE.[11,12]

While the association of OSA and COPD with PE is well established respectively, to the best of our knowledge, the potential contribution of overlap syndrome (OS) (pathologic state with concomitant OSA and COPD) to PE prevalence has not been previously investigated. Obviously, patients with OS may experience even more severe pathological injury, especially hypoxemia/ischemia, than those with isolated COPD or OSA. The aim of this study was to test whether OS is associated with PE prevalence, and compare the odds of PE in patients with OS to those with aforementioned isolated pathological states.

Materials and methods

Study population

The study included retrospectively subjects referred to the Center for Sleep Medicine in Beijing An Zhen Hospital, who completed sleep

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; FEV_1, forced expiratory volume at first second; FVC, ratio of FEV_1 and forced vital capacity; HST, home sleep test; PSG, polysomnography; $MeanS_aO_2$, average oxygen saturation during sleep; $MinS_aO_2$, minimum oxygen saturation during sleep; OS, overlap syndrome; OSA, obstructive sleep apnea; PAP, positive airway pressure; PE, pulmonary embolism; T90, saturation lower than 90%

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study, either by polysomnography (PSG) or home sleep test (HST), from January 2011 to December 2014. Patients < 18 years ($n = 17$) at the date of sleep study were excluded from the analysis (Fig. 1). Seventy-eight subjects were also excluded because of the prior treatment toward OSA, i.e. positive airway pressure (PAP), surgery and oral appliance, etc. Patients ($n = 7$) with cyanotic congenital heart diseases or pneumonia were not included in the study for their significant interference with saturation. The final cohort of study participants included 1,939 patients. This study was approved by the An Zhen Hospital Institutional Review Board.

Sleep study

During all PSGs ($n = 597$) completed by E-Series system for Sleep/EEG (Compumedics Ltd, Abbotsford, Victoria, Australia), airflow was monitored by nasal pressure transducer and oronasal thermocouple. Surface electrodes were applied to record electroencephalogram, electrooculogram, and submental electromyogram. Breath-sensing plethysmography of thoraco-abdominal movement was adopted to measure respiratory effort. For home sleep study ($n = 1,342$), portable Embletta equipment with nasal pressure transducer and orinasal thermocouple, percutaneous pulse saturation and plethysmography were used. Experienced registered polysomnographic technologists who were irrelevant to the study scored the sleep study digitally. Apneas were scored if a ≥ 90% decrease of airflow lasted for ≥ 10 s (viewed on the thermal airflow channel), and hypopneas were scored if a ≥ 30% decline in airflow lasted for ≥ 10 s (viewed on the nasal pressure channel) with a ≥ 3% oxygen desaturation. Apnea-hypopnea index (AHI) is the number of breathing events of apneas and hypopneas per hour of sleep, and OSA was diagnosed if patients had AHI ≥ 15/h. Nocturnal oxygen saturation, including average oxygen saturation during sleep

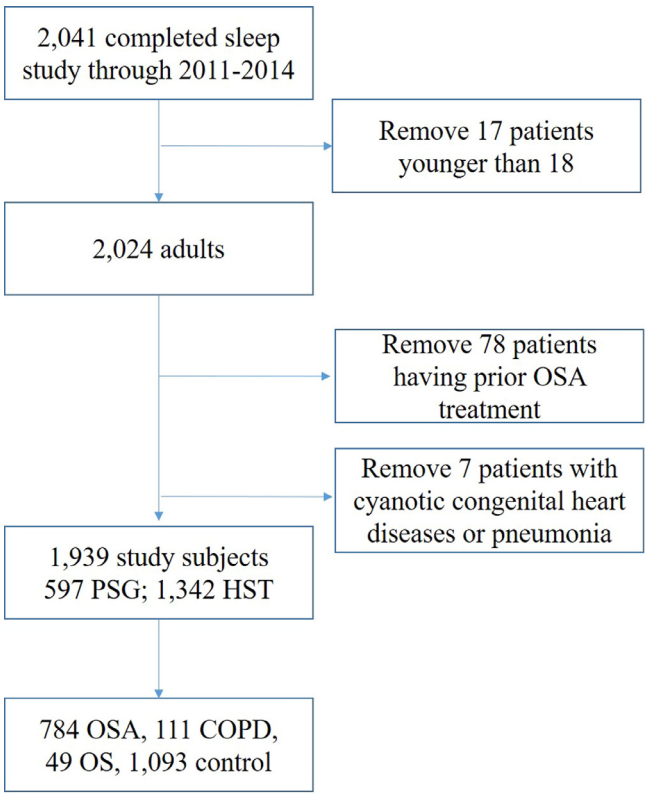

Fig. 1. Flow chart of sample selection. COPD: chronic obstructive pulmonary disease; HST: home sleep test; OSA: obstructive sleep apnea; OS: overlap syndrome; PSG: polysomnography.

($meanSaO_2$), minimum oxygen saturation during sleep ($minSaO_2$) and percentage of total sleep time with saturation < 90% (T90) were calculated automatically. Patients diagnosed with OSA were referred to visit a sleep specialist for further consults and intervention.

Confirmation of COPD and PE

The diagnosis of COPD and PE, made by the attending physician on the basis of medical history, post-bronchodilator spirometry and imaging was identified by chart review by investigators and rechecked to confirm that the diagnosis was in accordance with temporal guidelines.[13,14] Spirometric data were not available for 34 patients with COPD, because prior spirometries were completed before the current admission and patients had been treated appropriately i.e.by bronchodilators. Most patients ($n = 63$) with PE were diagnosed by CTPA while others ($n = 9$) were diagnosed by lung scintigraphy for the concerns regarding renal dysfunction. Demographic data including age, sex and body mass index (BMI), smoking history, previous medical history of diabetes, hypertension, coronary artery disease, cerebrovascular disease, renal disease, heart failure and deep vein thrombosis were also extracted. A modified Charlson comorbidity index (CCI) was created to assess patient's mortality risk. The algorithm included age (1 point for age ≤ 40; 2 for 41–50; 3 for 51–60; 4 for 61–70; 5 for ≥ 71), coronary diseases (1 point), heart failure (1 point), diabetes (1 point), cerebrovascular disease (1 point), renal dysfunction (2 points) and cancer (6 points).

Statistical analysis

Continuous variables were expressed in median and interquartile range, and categorical variables were described as frequency and percentage. Pearson's chi-squared tests were used for comparison of categorical variables, while Kruskal-Wallis/ Wilcoxon tests were used for comparison of continuous variables. Multivariable logistic regression was used to explore the factors associated with PE prevalence. Age, sex, BMI and modified CCI were adjusted for in multivariable models because of their clinical value and significant differences among analyzed groups. Analyses were performed by using JMP, version 11 (SAS Institute; Cary, North Carolina), and a $P < 0.05$ was considered statistically significant.

Results

Among all investigated subjects referred for over-night sleep tests, more females than males were diagnosed with OSA (586[70.4%] vs. 569[51.4%], $p < 0.001$), although median values of AHI were lower in females vs. males in general (14[6,35] events/h vs. 7[2,17] events/h, $P < 0.001$) and in OSA subgroup (35[22, 58] events/h vs. 27[19, 44] events/h, $P < 0.001$). Totally, 784 patients were diagnosed with OSA, and 111 were diagnosed with COPD, among whom 49 patients met the criteria of OS. Seventy-two patients were confirmed to have PE diagnosed medianly 11 days (IQR: 4–28 days) before sleep study. Patients with OS had higher median values of BMI than subjects in other groups, while patients with isolated OSA had the highest proportion of male gender (Table 1). Chronic diseases of hypertension, diabetes and heart failure were more prevalent in patients with OS than others. Prevalence of smoking history and coronary disease was very high in patients with isolated COPD. As to 111 patients diagnosed with COPD before sleep study (Table 2), no difference existed between subjects with isolated COPD and OS in terms of spirometric data of FEV_1/FVC ratio and FEV_1.

Fig. 2 demonstrates that OS patients, compared to those with isolated OSA and isolated COPD, had lower $meanSaO_2$ (91[87, 92] % vs 92[91, 94] %, $p < 0.001$, and 91[87, 92] % vs 91[89, 92] %, $p = 0.484$) and $minSaO_2$ (78 [71, 84] % vs 81 [76, 85] %, $p = 0.003$, and 78 [71, 84] % vs 84 [81, 86] %, $p < 0.001$) and higher T90 (21.6[10.1, 79.3] % vs 9.1

Table 1
Demographic and clinical characteristics of 1,939 study subjects

	Control (n = 1,093)	Isolated COPD (n = 62)	Isolated OSA (n = 735)	OS (n = 49)	P value
Age, years	56(45, 66)	69(59, 77)	64(54, 73)	69(63, 76)	<0.001
Male, n(%)	531(48.6)	38(61.3)	507(69.0)	31(63.3)	<0.001
Body mass index, kg/m^2	25.9(22.3, 30.6)	28.0(23.5, 33.2)	28.2(24.4, 32.3)	29.0(26.2, 34.6)	<0.001
History of smoking, n(%)	711(65.1)	51(82.3)	462(62.9)	36(73.5)	0.011
Diabetes, n(%)	166 (15.2)	22 (35.5)	142 (19.3)	25 (51.0)	<0.001
Hypertension, n(%)	394 (36.1)	37 (59.7)	377 (51.3)	35 (71.4)	<0.001
Coronary artery disease, n(%)	176 (16.1)	32 (51.6)	174 (23.7)	22 (44.9)	<0.001
Cerebrovascular disease, n(%)	26(2.4)	1(1.6)	40(5.4)	2(4.1)	0.005
Renal disease, n(%)	23(2.1)	2(3.2)	19(2.6)	0	0.602
Heart failure, n(%)	46(4.2)	8(12.9)	62(8.4)	13(26.5)	<0.001
Deep vein thrombosis, n(%)	58(5.3)	13(21.0)	63(8.6)	8(16.3)	<0.001
Modified CCI, points	2(1,3)	4(3, 5)	3(2, 4)	4(3, 5)	<0.001

CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; OS: overlap syndrome; OSA: obstructive sleep apnea;

[3.2, 23.4] %, $p < 0.001$, and 21.6[10.1, 79.3] % vs 15.4[4.1, 64.0] %, $p = 0.063$) and AHI (52 [25, 85] event/h vs 32 [21, 53] event/h, $p = 0.003$, and 52 [25, 85] event/h vs 6 [2, 9] event/h, $p < 0.001$). Compared with patients completed HST, subjects who underwent PSG reported slightly higher median values of AHI (9[3, 23] event/h vs. 10 [5, 28] event/h, $p = 0.009$) and T90(2.1[0.2, 11.2] % vs. 2.7[0.3, 2.7] %, $p = 0.033$), while other sleep data were not significantly different (supplement Table 1).

In contrast to control patients, those subjects with OS had higher odds of PE (OR9.61; 95%CI 4.02–21.31, $p < 0.001$) with significance persisting after adjusting for age, sex, BMI and modified CCI (OR 5.66; 95%CI 1.80–16.18, $p = 0.004$) (Fig. 3). Meanwhile, patients with OS compared with those with isolated OSA also had significantly higher odds of PE in univariate (OR 4.79; 95%CI 2.04–10.33, $p = 0.0007$) and adjusted models (OR 3.89; 95%CI 1.27–10.68, $p = 0.019$). Patients with OS did not have significantly higher odds of PE than isolated COPD subjects in unadjusted (OR 2.57; 95%CI 0.82–8.88, $p = 0.105$) and adjusted models (OR 2.61; 95%CI 0.65–11.53, $p = 0.177$).

Table 2
Spirometric data of 111 patients diagnosed with COPD

	Isolated COPD (n = 62)	OS(n = 49)	P value
Age, years	69 (59, 77)	69 (63, 76)	0.645
Male, n (%)	38 (61.3)	31 (63.3)	*0.831*
FEV_1/FVC ratio, %	64(43, 67)	58(44, 67)	0.755
FEV_1, % predicted	56(35, 77)	54(33, 65)	0.341
Long-acting beta$_2$-agonist, n (%)	41(66.1)	39(79.6)	0.116
Inhaled corticosteroids, n (%)	43(69.4)	41(83.7)	0.681
Long acting muscarinic antagonist, n (%)	35(56.5)	33(67.3)	0.242

FEV_1: forced expiratory volume at first second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; OS: overlap syndrome.

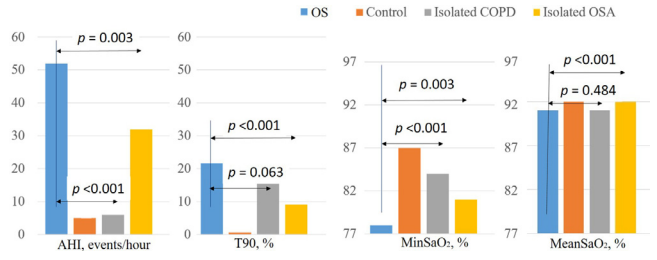

Fig. 2. Sleep parameters of 1939 study subjects. AHI: apnea-hypopnea index; meanSaO_2: average oxygen saturation during sleep; minSaO_2, minimum oxygen saturation during sleep; T90: percentage of total sleep time with saturation < 90%; OS: overlap syndrome.

Comparisons of PE odds between patients with OS and control subjects were investigated in subgroups divided by gender and median value of age respectively (Table 3). After adjusting for covariates of age, sex, BMI and modified CCI, patients with OS had higher odds of PE than the control group among male subjects (OR 8.12, 95%CI1.86–31.87, $p = 0.007$) and patients ≥ 58 years (OR 5.50, 95%CI 1.51–18.14, $p = 0.012$).

To investigate the association between sleep data and PE prevalence, meanSaO_2, minSaO_2 and T90 were stratified by their median values. Table 4 shows in female subjects and patients older than 58 years, meanSaO_2 < 93%, minSaO_2 ≤ 85%, T90 ≥ 2.6% and AHI ≥ 15 events/h were all associated with PE prevalence. However, in the adjusted model, only T90 ≥ 2.6% had significant association with prevalence of PE (OR 4.72, 95%CI1.34–19.83, $p = 0.015$) in the subgroup of patients older than 58. Similarly, patients with T90 ≥ 2.6% reported by HST had higher odds of PE prevalence than

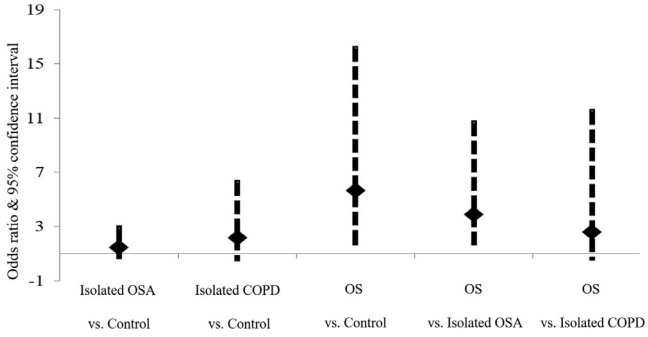

Fig. 3. Independent association of OS with PE (n = 1,939). Adjust for age, sex, BMI and modified CCI. CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; OS: overlap syndrome; PE: pulmonary embolism.

Table 3
Comparison of PE odds between patients with OS (n = 49) and control (n = 1,093) in subgroup analysis

	Unadjusted			Adjusted*		
	OR	95%CI	P value	OR	95%CI	P value
Age < 58*	7.50	0.39–46.96	0.144	7.52	0.30–74.73	0.178
Age ≥ 58*	7.80	2.95–19.41	0.0001	5.50	1.51–18.14	0.012
Male#	13.79	4.72–38.32	<0.0001	8.12	1.86–31.87	0.007
Female#	4.89	0.73–19.57	0.091	3.39	0.45–17.40	0.208

BMI: body mass index; CCI: Charlson Comorbidity Index; OS: overlap syndrome; PE: pulmonary embolism.
* Adjust for age, sex, BMI and modified CCI.
# Adjust for age, BMI and modified CCI.

Table 4
Sleep parameters associated with PE prevalence (**n = 1,939**) .

		Unadjusted			Adjusted*		
	Compared with	OR	95%CI	*P* value	OR	95%CI	*P* value
In male subjects							
$MeanSaO_2 < 93\%$	$MeanSaO_2 \geq 93\%$	1.98	0.96–4.48	0.065	2.03	0.79–6.26	0.147
$MinSaO_2 \leq 85\%$	$MinSaO_2 > 85\%$	1.56	0.78–3.33	0.209	1.06	0.45–2.67	0.905
$T90 \geq 2.6\%$	$T90 < 2.6\%$	2.04	1.02–4.35	0.042	1.44	0.61–3.67	0.407
AHI < 15/h	AHI ≥ 15/h	1.57	0.81–3.13	0.178	1.05	0.45–2.47	0.913
In female subjects							
$MeanSaO_2 < 93\%$	$MeanSaO_2 \geq 93\%$	2.23	1.09–4.93	0.028	1.42	0.59–3.73	0.442
$MinSaO_2 \leq 85\%$	$MinSaO_2 > 85\%$	2.14	1.06–4.61	0.033	1.13	0.50–2.67	0.772
$T90 \geq 2.6\%$	$T90 < 2.6\%$	2.56	1.28–5.39	0.008	1.77	0.75–4.35	0.1933
AHI < 15/h	AHI ≥ 15/h	3.37	1.70–6.81	<0.001	2.31	1.02–5.27	0.050
Subjects ≥ 58 years old							
$MeanSaO_2 < 93\%$	$MeanSaO_2 \geq 93\%$	3.99	1.56–12.21	0.003	3.05	0.87–12.92	0.082
$MinSaO_2 \leq 85\%$	$MinSaO_2 > 85\%$	3.01	1.23–8.46	0.015	3.11	0.91–12.54	0.070
$T90 \geq 2.6\%$	$T90 < 2.6\%$	4.57	1.86–12.84	0.0007	4.72	1.34–19.83	0.015
AHI < 15/h	AHI ≥ 15/h	1.72	0.97–3.13	0.065	1.51	0.77–3.01	0.229
Subjects < 58 years old							
$MeanSaO_2 < 93\%$	$MeanSaO_2 \geq 93\%$	1.23	0.67–2.38	0.518	1.37	0.64–3.16	0.419
$MinSaO_2 \leq 85\%$	$MinSaO_2 > 85\%$	1.20	0.66–2.26	0.557	0.76	0.39–1.54	0.443
$T90 \geq 2.6\%$	$T90 < 2.6\%$	1.31	0.73–2.44	0.366	1.12	0.57–2.31	0.743
AHI < 15/h	AHI ≥ 15/h	2.39	1.01–5.65	0.047	1.67	0.45–5.73	0.427

AHI: apnea-hypopnea index; $meanSaO_2$: average oxygen saturation during sleep; BMI: body mass index; CCI: Charlson Comorbidity Index; $minSaO_2$: minimum oxygen saturation during sleep; PE: pulmonary embolism; T90: percentage of total sleep time with saturation < 90%.
* Adjust for age, sex, BMI and modified CCI.

counterparts with T90 < 2.6% in the multivariable models (supplement Table 2). Other sleep data collected were not significantly associated with PE prevalence in the adjusted models of all subgroups.

Discussion

Our retrospective data suggested that OS, a pathologic state with concomitant COPD and OSA, is associated with PE prevalence among patients referred for sleep tests, mostly for suspicion of nocturnal disordered breathing. The current finding is consistent with previous studies demonstrating contribution of OSA[2-6] and COPD[11,12] to thrombogenesis respectively, and proves that OS is more closely associated with PE prevalence than isolated OSA. As a common clinical syndrome, OS needs medical concerns not only from traditional cardiovascular profile but also from the aspect of pulmonary circulation.

OSA has been universally recognized as an important risk factor for cardiovascular disease.[1] Few studies have investigated the potential contribution of OSA to PE incidence.[4,5,15] The underlying mechanism linking OSA and thrombogenisis is not clear yet, but hypercoagulation induced by hypoxemia in OSA drew attentions.[3,16] In our previous study among patients with PE, patients with OSA needed a comparatively higher dose of anticoagulant agent (partly due to hypercoagulation) to achieve therapeutic target than control subjects. The higher the AHI was, the higher the dose of anticoagulation that was needed.[3] Moreover, quite a few OSA subjects experienced reboundance of hypercoagulation and even reoccurrence of PE after warfarin cessation.[2]

The hypercoagulant state in OSA may be a physiological response to hypoxia during breathing events. In contrast to those with isolated OSA, patients with OS suffer even more severe hypoxia. They may have decreased pulmonary ventilation due to both upper and lower airway obstruction, as well as reduced respiratory drive due to breathing muscular fatigue and intrathoracic overinflation,[17] both leading to high possibility of hypoxemia and hypercarbia. Noticeably, OSA and COPD have similarities but also have differences in pathogenesis. I.e., OSA leads to intermittent hypoxemia during sleep, while COPD causes continuous hypoxemia. Therefore, patients with OS may experience overlapping injury from both OSA and COPD. As shown in our current study, compared with patients with OSA, OS patients may experience more severe desaturation during sleep, although further study is needed to prove the hypothesis that OS patients might have more severe hypercoagulation induced by desaturation.

Women are considered to have high prevalence of PE or DVT, partly due to improper use of contraceptives,[18] pregnancy[19] and high incidence of autoimmune rheumatic diseases,[20] but the association of OS with PE was significant only in the male subgroup rather than its female counterpart. The current research cannot explain the reason for this phenomenon. However, considering the high prevalence of OS (or COPD and OSA respectively) in males, the aforementioned association between OS and PE deserves attention.

Although a potential cardioprotective role of repeated ischemia from intermittent episodes of apneas via preconditioning has been anticipated,[21] and even possible survival advantage from OSA has been reported in older patients,[22] in the circumstance with concomitant OSA and COPD, severe hypoxemia can hardly be recognized as protective. Conversely, our results revealed that high hypoxic burden (evaluated by T90) was independently associated with PE prevalence in older subgroups.

Patients with OS have poorer prognosis than those with only COPD, and PAP was proved to reduce long-term risk.[23] Although the effect of PAP on cardiovascular prognosis was questioned in the Sleep Apnea Vascular Endpoints (SAVE) study,[24] this study excluded patients with severe hypoxemia, which is very common in subjects with OS. Further study is needed to prove whether or not PAP therapy in OS patients may correct hypercoagulation induced by hypoxic state, and thus reduce the risk of incidence and recurrence of thrombotic diseases. Interestingly, OSA patients tend to need a higher dose of anticoagulant agent to maintain INR to target range.[3] If hypercoagulant state in patients with OS were corrected thanks to remission of hypoxemia, warfarin dose might be modified in order to reduce the risk of bleeding. Meanwhile, compared with isolated OSA subjects, patients with OS may present hypercapnia frequently; bi-level ventilation might be considered when necessary.

The strength of the study is that we included a large population of patients who completed overnight sleep study scored by technicians who were not part of the study team. The consistency between different technicians were achieved by internal validation measures. There are limitations inherent to the retrospective study design. First, the

control patients without OS were not healthy subjects, since they were referred for sleep tests for suspected sleep issues. Meanwhile asymptomatic patients with COPD were not likely to be prescribed of spirometry, which may increase the risk to ignore COPD and thus OS. Second, many patients accepted HST instead of PSG, the most potent technique to diagnose OSA. Therefore, the inconsistent strategies may undermine the accuracy to diagnose OSA.

Conclusion

Patients with OS had a lower degree of oxygen saturation during sleep and higher odds of PE than control subjects and those with isolated OSA. High hypoxic burden may be related to PE prevalence. Longitudinal studies are needed to investigate the relationship between OS and PE incidence, and whether PAP treatment may reduce hypoxemia and even hypercoagulation in patients with OS and thus the risk of thrombotic events is also to be determined.

Acknowledgement

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Financial Disclosure and Conflicts of Interest

Dr. Xie has served as a consultant for ResMed and Philips. He has spoken at meetings sponsored by Philips and ResMed. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2018.11.001.

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