Original Article

Obstructive sleep apnea in patients with chronic thromboembolic pulmonary hypertension

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Background: Due to its effects, like an exaggerated negative intrathoracic pressure, sympathetic activation, systemic inflammation, oxidative stress, and endothelial dysfunction, obstructive sleep apnea (OSA) has been involved as a cause in multiple cardiovascular diseases. These diseases include coronary artery disease, hypertension, heart failure, and pulmonary hypertension (PH). Furthermore, OSA often coexists with chronic thromboembolic pulmonary hypertension (CTEPH) in clinical practice. However, few studies focus on OSA and its relationship with CTEPH. This study aims to determine whether OSA has an influence on the clinic status of patients with CTEPH, and to identify what possible factors are associated with OSA in CTEPH.

Methods: Patients who were newly diagnosed with CTEPH and received overnight polysomnography (PSG) monitoring from September 2015 to December 2017 were enrolled. OSA was defined as apnea-hypopnea index (AHI) of ≥5/h and the obstructive events at ≥50%. Baseline clinical characteristics and parameters were collected and compared between CTEPH patients with and without OSA. In addition, logistic regression analysis was performed to identify possible factors associated with OSA in CTEPH.

Results: Fifty-seven patients with CTEPH were eventually enrolled. Among them, 32 patients were diagnosed with OSA by PSG. CTEPH patients with OSA showed an older age, a higher body mass index (BMI), a higher hemoglobin level, a lower oxygen saturation and a worse World Health Organization functional class (WHO FC) (all $P<0.05$) when compared to CTEPH patients without OSA. In addition, sleep data including AHI, oxygen desaturation index and minimum oxygen saturation were also statistically different between two groups (all $P<0.05$). Adjusted for age, sex and BMI, hemoglobin [odd ratio (OR) =1.057, 95% confidence interval (CI): 1.001–1.117, P=0.046], oxygen saturation (OR =0.718, 95% CI: 0.554–0.929, P=0.012), N-terminal pro-brain natriuretic peptide (OR =1.001, 95% CI: 1.000–1.002, P=0.016), mean right atrium pressure (OR =1.284, 95% CI: 1.030–1.600, P=0.026), mean pulmonary arterial pressure (mPAP) (OR =1.087, 95% CI: 1.001–1.180, P=0.048), cardiac index (CI) (OR =0.058, 95% CI: 0.008–0.433, P=0.037), pulmonary vascular resistance (OR =1.004, 95% CI: 1.001–1.007, P=0.014) and WHO FC III–IV (OR =18.550, 95% CI: 2.363–144.128, P=0.005) were associated with OSA in CTEPH. Multivariate logistic regression analysis demonstrated CI (OR =0.051, 95% CI: 0.003–0.868, P=0.040) was independently associated with OSA in CTEPH in addition to age, sex and BMI.

Conclusions: OSA may aggravate the clinical status of CTEPH patients to some degree. In turn, a worse hemodynamics, oxygenation state and cardiac function are associated with OSA in CTEPH after being adjusted for age, sex and BMI. Among them, CI is the most important parameter in indicating the coexistence of OSA and CTEPH.

Keywords: Obstructive sleep apnea (OSA); chronic thromboembolic pulmonary hypertension (CTEPH); polysomnography (PSG); hemodynamics

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Introduction

Sleep apnea syndrome (SAS), a highly prevalent public health problem, is characterized by a recurrent apnea and hypopnea during sleep. Obstructive sleep apnea (OSA) is the most frequent subtype of SAS, which is caused by a complete or partial obstruction of the upper airway during nocturnal sleep (1). Except for leading to a decline in sleep quality decline and daytime sleepiness, OSA is considered to be a risk factor for many cardiovascular diseases like, coronary artery disease, hypertension, heart failure, arrhythmia and pulmonary hypertension (PH). The underlying mechanism that causes this may be relevant to an exaggerated negative intrathoracic pressure, sympathetic activation, oxidative stress, systemic inflammation and endothelial dysfunction (2).

OSA most often occurs in men, the obese, and those who are aged more than 65 years (3). Recently, several studies have revealed that OSA is closely linked to a thromboembolic phenomenon, due to the increased platelet activation and hypercoagulability (4). Deflandre *et al.* (5) found that OSA was an independent risk factor for venous thromboembolism (VTE) events. Arzt *et al.* (6) also demonstrated that OSA occurred more frequently in patients with deep vein thrombosis (DVT) and/or acute pulmonary embolism (PE) than in the control group. Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by a chronic obstruction of the major pulmonary arteries and microvascular disease, and is regarded as a long-term complication of PE event. CTEPH is classified as a group 4 PH by the World Health Organization (WHO). It has been reported that the incidence of CTEPH within the first 2 years after suffering from a PE event is about 0.1–9.1% (7,8). Furthermore, specific risk factors for VTE have been identified as risk factors for CTEPH (9). This is in line with the high prevalence of OSA in CTEPH patients. Dumitrascu *et al.* (10) found that approximately 20% of the CTEPH patients were accompanied by OSA. However, the data about the relationship between CTEPH and OSA is still lacking. To investigate whether OSA has an effect on CTEPH patients, we performed a single-center, retrospective study in CTEPH patients whose diagnosis had been established by a right heart catheterization (RHC). In addition, factors associated with OSA in CTEPH were also investigated.

Methods

This single center study was conducted in Fuwai Hospital, National Center for Cardiovascular Diseases in Beijing, China. The study was performed with the approval of the Fuwai Hospital Ethics Committee. Written informed consent of all participants was obtained.

Study sample

We retrospectively reviewed the data of the hospitalized patients who had been newly diagnosed with CTEPH between August 2015 and December 2017. Before diagnosis, each patient received at least three months of effective anticoagulation therapy and underwent routine screening of CTEPH which included echocardiography, ventilation/perfusion scan and computed tomography (CT) angiography. Finally, patients whose RHC results showed a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg with a pulmonary artery wedge pressure (PAWP) of ≤15 mmHg, together with mismatched perfusion defects by image inspecting, were confirmed with CTEPH (11). Hospitalized patients in our center who had snoring at night, daytime sleepiness, neck circumference enlargement or micrognathia were advised to receive overnight polysomnography (PSG). Patients who agreed to receive the PSG, and had finally been diagnosed with CTEPH were enrolled. All enrolled CTEPH patients were in stable clinical status. PSG was performed before or after RHC in hospital; the time interval was no more than 7 days. According to the results of the PSG, all participants were then divided into two patient categories: CTEPH patients with and without OSA. Patients having one of the following conditions were excluded: (I) other forms of PH; (II) age less than eighteen years old; (III) chronic heart failure with ejection fraction <30%; (IV) chronic liver or kidney dysfunction, defined as having three times higher liver enzymes than normal and a creatinine clearance rate of less than 30 milliliter/minute respectively; (V) life-threatening cardiac arrhythmias; (VI) a sleep period of less than two hours.

Patients assessment

The baseline clinical characteristics of each participant was collected, including the age, sex, body mass index (BMI), smoking history, six-minute walking distance (6-MWD), WHO functional class (WHO FC), comorbidity, drug therapy and PE, or VTE history. In addition to this, hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), red blood cell width (RDW), N-terminal pro-brain natriuretic peptide (NT-proBNP), uric acid, creatinine and high sensitive C reactive protein (hs-CRP) were measured using fasting venous blood samples on the first day of admission. Partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and oxygen saturation (SPO_2) were measured by arterial blood gas. Transthoracic echocardiography and pulmonary function testing were performed on each patient before RHC. Diastolic left ventricle diameter was measured in the left ventricular long axis view and diastolic right ventricle diameter was measured in the apical four chamber view. SPAP is equal to right ventricular systolic pressure (RVSP) in the absence of a gradient of across the pulmonic valve or right ventricular outflow tract. RVSP can be reliably estimated from a peak tricuspid regurgitation jet velocity, using the simplified Bernoulli equation, combined with the right atrium pressure (RAP) level: RVSP=4 (peak tricuspid regurgitation jet velocity)^2 + RAP (12). In addition, the Simpson biplane method was used to assess EF. To confirm the diagnosis of CTEPH, RHC was conducted. The baseline hemodynamic parameters, i.e., mean RAP (mRAP), mPAP, cardiac index (CI) and pulmonary vascular resistance (PVR) were obtained in all patients.

Sleep study

Each enrolled CTEPH patients undertook an overnight PSG test in the Sleep Center of Fuwai Hospital using the Embletta (Medcare Flaga, Reykjavik, Iceland). The device recorded nasal airflow, finger pulse oximetry, thoracic and abdominal movement, body position, and snoring. Based on the American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events (13), the definition of a sleep apnea event must satisfy a decrease of nasal airflow by more than 90%, lasting at least 10 seconds. If the airflow absence is accompanied by a persistent or enhanced inspiratory effort, the apnea event is considered as obstructive. The definition of a hypopnea event must meet a decrease of nasal airflow by more than 30%, lasting at least 10 seconds along with a drop of more than 4% oxygen desaturation. If there is snoring or increased inspiratory flattening of the nasal pressure or associated thoracoabdominal paradox, the hypopnea event is considered as obstructive. The total number of apnea and hypopnea events is divided by the number of sleeping hours to calculate the apnea-hypopnea index (AHI). AHI ≥5/h and the obstructive events ≥50% are diagnostic criteria of SAS.

Statistical analysis

Continuous variables are presented as a mean ± SD or median (interquartile range). Categorical variables are given as counts or percentages. In order to compare the baseline parameters between two groups, an unpaired *t*-test was used for normally distributed, continuous variables and a nonparametric Kruskal-Wallis test was used for the non-normally distributed continuous variables. Categorical variables were compared using an χ^2 test. To explore possible factors that were associated with OSA in CTEPH, logistic regression analysis was also used. P value <0.05 was considered as statistically significant. Data analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients characteristics

A total of 78 patients were newly confirmed with CTEPH and in a stable clinical status. Among them, 62 patients received an overnight PSG monitoring before or after RHC. Five CTEPH patients without available sleep data were excluded. Finally, 57 CTEPH patients who received PSG were enrolled. Baseline clinical characteristics of CTEPH patients with and without OSA were compared, and are displayed in *Table 1*. CTEPH patients with OSA showed an older age (57±9 versus 50±12 years, P=0.020), a higher BMI (24.98±3.06 versus 23.32±2.95 kg·m^{-2}, P=0.044) and a worse WHO FC (P=0.033). Other characteristics did not make a difference between the two groups.

Laboratory, hemodynamic and echocardiographic tests

Table 2 compared laboratory, hemodynamic and echocardiographic parameters between the two groups. CTEPH patients with OSA have a higher hemoglobin level (163.47±15.81 versus 155.24±14.10 g/L, P=0.046) than those without. There was no difference in other parameters.

Table 1 Baseline clinical characteristics of all participants

Variable	CTEPH without OSA (n=25)	CTEPH with OSA (n=32)	P value
Clinical parameters			
Age (years)	50±12	57±9	0.020
Males/females	10/15	21/11	0.054
BMI ($kg·m^{-2}$)	23.32±2.95	24.98±3.06	0.044
Smoking	6	14	0.121
6-MWD (m)	395.52±91.86	373.67±76.28	0.363
WHO FC I–II/III–IV	14/11	9/23	0.033
PE or VTE history	13	21	0.176
Comorbidities			
Coronary heart disease	1	3	0.431
Diabetes mellitus	3	5	0.696
Systemic hypertension	4	10	0.184
Dyslipidemia	3	9	0.138
Drug therapy			
Targeting medication (none/single/combination)	6/15/4	9/17/6	0.874
Positive inotropes	19	19	0.186
Diuretics	24	29	0.431

Continuous variables are presented as mean ± SD. Categorical variables are given as counts. CTEPH, chronic thromboembolic pulmonary hypertension; OSA, obstructive sleep apnea; WHO FC, World Health Organization functional class; BMI, body mass index; 6-MWD, six minutes walking distance.

Pulmonary function, arterial blood gas and sleep study

Data about the pulmonary function, arterial blood gas and sleep study of the two groups are shown in *Table 3*. CTEPH patients with and without OSA had a similar pulmonary function. However, OSA patients had a lower PaO_2 (60.13%±13.48% versus 68.22%±13.27%, P=0.008) and SPO_2 (90.32%±4.16% versus 93.26%±2.25%, P=0.004). In terms of the sleep data, the OSA group had a higher AHI (16.74±12.21 versus 2.43±1.69, P<0.001) and oxygen desaturation index [(13.35 (8.40, 31.45) versus 3.50 (1.75, 6.05), P<0.001] but a lower minimum SPO_2 (77.25%±7.82% versus 80.28%±8.75%, P=0.041).

Possible factors associated with OSA in CTEPH

Logistic regression analysis which was adjusted for age, sex and BMI demonstrated that hemoglobin [odd ratio (OR) =1.057, 95% confidence interval (CI): 1.001–1.117, P=0.046], SPO_2 (OR =0.718, 95% CI: 0.554–0.929, P=0.012), NT-proBNP (OR =1.001, 95% CI: 1.000–1.002, P=0.016) and WHO FC III–IV (OR =18.550, 95% CI: 2.363–144.128, P=0.005) were associated with OSA in CTEPH. In addition, hemodynamic parameters including mRAP (OR =1.284, 95% CI: 1.030–1.600, P=0.026), mPAP (OR =1.087, 95% CI: 1.001–1.180, P=0.048), CI (OR =0.058, 95% CI: 0.008–0.433, P=0.037), PVR (OR =1.004, 95% CI: 1.001–1.007, P=0.014) were also associated with OSA in CTEPH. These details are shown in *Table 4*. To further identify which factor was more important in indicating the coexistence of OSA and CTEPH, a multivariate logistic regression analysis including SPO_2, NT-proBNP, WHO FC, mRAP, mPAP, CI in addition to age, sex and BMI was performed, which is detailed in *Table 5*.

Discussion

Since the early 1970s, there has been an increasing amount of studies demonstrating how OSA can increase

Table 2 Laboratory, hemodynamic and echocardiographic parameters of all participants

Variable	CTEPH without OSA (n=25)	CTEPH with OSA (n=32)	P value
Laboratory parameters			
NT-pro BNP (pg·mL^{-1})	1,103.00 (158.80–1,965.00)	1,457.00 (324.78–2,075.50)	0.254
Uric acid (μmol·L^{-1})	441.98±106.54	465.50±117.65	0.748
Creatinine (μmol·L^{-1})	81.80±17.75	86.58±15.11	0.277
Hs-CRP (mg·L^{-1})	1.82 (1.11–4.40)	3.08 (1.64–4.65)	0.113
Hb (g·L^{-1})	155.24±14.10	163.47±15.81	0.046
Ht (L/L)	0.46±0.04	0.48±0.05	0.275
MCV (fL)	90.06±3.67	91.60±4.07	0.145
RDW (%)	13.64±1.31	13.57±0.87	0.525
RHC parameters			
MRAP (mmHg)	4±3	6 ±4	0.098
MPAP (mmHg)	46±9	48±12	0.443
CI (L·min^{-1}·m^{-2})	3.09±0.69	2.83±0.60	0.141
PVR (dyn·s·cm^{-5})	829.31±263.37	947.10±381.35	0.247
Echocardiographic parameters			
Left ventricular ejection fraction	64±4	65±6	0.543
Diastolic left ventricle diameter (mm)	40±6	41±8	0.572
Diastolic right ventricle diameter (mm)	33±7	33±7	0.912
Diastolic right ventricle/left ventricle diameter ratio	0.85±0.24	0.87±0.38	0.73
SPAP (mmHg)	89±20	89±22	0.961

Data are presented as mean ± SD or median (interquartile range). CTEPH, chronic thromboembolic pulmonary hypertension; OSA, obstructive sleep apnea; NT-pro BNP, N-terminal pro-brain natriuretic peptide; Hs-CRP, high sensitive C reactive protein; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; RDW, red blood cell width; RHC, right heart catheterization; MRAP, mean right atrium pressure; MPAP, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SPAP, systolic pulmonary artery pressure.

the mortality rate of various cardiovascular diseases (14). Intermittent hypoxia and an inflammation condition which had resulted from OSA may contribute to pulmonary vasoconstriction and pulmonary vascular remodeling, leading to a temporary or persistent PH (15). However, few studies have investigated the relationship between OSA and CTEPH. In this study, we demonstrated that the clinical status of CTEPH patients with OSA might be exacerbated when compared to those patients without OSA, which was supported by a higher Hb, lower SPO_2 and worse WHO FC. Adjusted for age, sex and BMI, a worse hemodynamics, oxygenation state and cardiac function were associated with OSA in CTEPH. Multivariate regression analysis has further demonstrated CI was independently associated with OSA in CTEPH, among multiple other factors in addition to age, sex and BMI. However, we did not observe a linear relationship between CI and AHI as Orr *et al.* Established on a previous study that demonstrated the relationship between OSA and cardiovascular diseases (2), the influence of OSA on CTEPH was mainly discussed.

OSA itself can be a cause of PH which is categorized as WHO group 3 PH. Through hypoxic pulmonary vasoconstriction and left heart damage, OSA can lead to pre-capillary and post-capillary PH (11). Sajkov *et al.* (16) separately investigated the prevalence of PH in 27 and 32 OSA patients without cardiopulmonary diseases in 1994 and 1999. About 41% and 34% of these OSA patients were screened as PH, respectively using echocardiography. OSA

Table 3 Parameters including pulmonary function, arterial blood gas and sleep study of all participants

Variable	CTEPH without OSA (n=25)	CTEPH with OSA (n=32)	P value
Pulmonary function (% pred)			
FEV1	76.95±13.09	73.92 ±14.55	0.671
FVC	84.00±11.07	84.38±16.06	0.786
FEV1/FVC	95.81±8.61	92.50±9.14	0.431
TLC	81.67±7.78	79.38±13.05	0.618
DLCO	68.57±14.54	67.96±9.46	0.943
Arterial blood gas			
PaO_2 (mmHg)	68.22±13.27	60.13±13.48	0.008
$PaCO_2$ (mmHg)	36.78±5.27	34.45±4.79	0.104
SPO_2 (%)	93.26±2.25	90.32±4.16	0.004
Sleep study			
AHI	2.43 (0.85–4.20)	16.74 (7.65–23.65)	<0.001
ODI	3.50 (1.75–6.05)	13.35 (8.40–31.45)	<0.001
SPO_2-min (%)	80.28±8.75	77.25±7.82	0.041
SPO_2 <90% (%)	43.15±33.08	49.20±32.88	0.495

Data are presented as mean ± SD or median (interquartile range). CTEPH, chronic thromboembolic pulmonary hypertension; OSA, obstructive sleep apnea; FEV1, forced expiratory volume at first second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusion capacity for carbon monoxide of the lung; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; SPO_2, oxygen saturation; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SPO_2-min, minimum oxygen saturation; SPO_2 <90%, time spent lower than 90% of oxygen saturation.

Table 4 Logistic regression analysis corrected for age, sex and BMI

Variable	Odd ratio	95% confidence interval	P value
SPO_2 (%)	0.718	0.554–0.929	0.012
NT-pro BNP ($pg·mL^{-1}$)	1.001	1.000–1.002	0.016
Hb ($g·L^{-1}$)	1.057	1.001–1.117	0.046
MRAP (mmHg)	1.284	1.030–1.600	0.026
MPAP (mmHg)	1.087	1.001–1.180	0.048
CI ($L·min^{-1}·m^{-2}$)	0.058	0.008–0.433	0.037
PVR ($dyn·s·cm^{-5}$)	1.004	1.001–1.007	0.014
WHO FC III–IV *vs.* I–II	18.550	2.363–144.128	0.005

BMI, body mass index; SPO_2, oxygen saturation; NT-pro BNP, N-terminal pro-brain natriuretic peptide; Hb, hemoglobin; MRAP, mean right atrium pressure; MPAP, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class.

Table 5 Multivariate logistic regression analysis in addition to age, sex and BMI

Variable	Odd ratio	95% confidence interval	P value
SPO_2 (%)	0.759	0.536–1.074	0.119
NT-pro BNP ($pg·mL^{-1}$)	1.001	1.000–1.002	0.116
MRAP (mmHg)	0.933	0.565–1.542	0.787
MPAP (mmHg)	1.005	0.876–1.154	0.942
CI ($L·min^{-1}·m^{-2}$)	0.051	0.003–0.868	0.040
WHO FC III–IV *vs.* I–II	4.464	0.185–107.522	0.357

BMI, body mass index; SPO_2, oxygen saturation; NT-pro BNP, N-terminal pro-brain natriuretic peptide; Hb, hemoglobin; MRAP, mean right atrium pressure; MPAP, mean pulmonary arterial pressure; CI, cardiac index; WHO FC, World Health Organization functional class.

often occurs in male, the obese and older individuals (17-19). This was proved by our results, which showed that CTEPH patients with OSA had an older age, a higher BMI and a larger proportion of male sex. In addition, OSA is prevalent in the population with cardiovascular diseases, particularly left heart failure. There is also a high prevalence of OSA in PH patients. Minic *et al.* (20) demonstrated that 56% of the 72 patients with WHO group 1 PH had OSA. In our study, we found that 32 of the 57 CTEPH patients had OSA. This high prevalence of OSA in CTEPH accorded with the findings of Orr *et al.* (21), whose study revealed that sleep disordered breathing was found in 57% of the 49 CTEPH patients.

Intermittent hypoxia and apnea bring about an enhanced inspiratory effort, as well as a large negative intrathoracic pressure swing. Increased venous return leads to a right ventricular enlargement, and thus impedes the left ventricular filling (16). Additionally, increasing amounts of studies have revealed that OSA possibly has negative effects on the right ventricular function and structure. Guidry *et al.* (22) revealed that the right ventricular wall measured by echocardiography was much thicker in severe OSA patients, when compared with mild OSA patients. Other studies also revealed a decrease of the right ventricular contraction in patients with severe OSA (23,24). The detrimental influences of OSA on the left and right ventricles were consistent with the worse WHO FC in CTEPH patients with OSA in our study. This theory was also confirmed by our multivariate logistic regression results, which demonstrated that CI was independently associated with OSA in CTEPH in addition to age, sex and BMI. However, there was not a linear relationship between CI and AHI (data not shown). We speculated that a lower CI was associated with the coexistence of OSA, rather than associated with the severity of OSA in CTEPH. The chronic effects of OSA on pulmonary circulation and right ventricle also lead to a deteriorated hemodynamic (25); however, due to the limited sample size, hemodynamic parameters in this study did not reach a statistical difference in CTEPH patients with and without OSA.

Nocturnal hypoxia stimulates pulmonary vasoconstriction, sympathetic activation, inflammation and oxidative stress which are secondary to OSA to promote pulmonary vascular remodeling (26). These pulmonary vascular changes induced by the OSA could aggravate the mismatched ventilation and perfusion of CTEPH patients, which was supported by a lower PaO_2 and SPO_2 level in arterial blood gas, higher oxygen desaturation index and minimum SPO_2 during night sleep in CTEPH patients with OSA. This result was similar to the previous study by Bady *et al.* (27) which had revealed a lower daytime arterial oxygen tension and a more severe nocturnal hypoxemia in pulmonary arterial hypertension patients with OSA. Our study showed lower SPO_2 was a factor associated with OSA in patients with CTEPH in *Table 4*. This finding was in accordance with the research by Zhong *et al.* (28) that revealed SPO_2 in waking condition might play a role as a predictor for the evaluation and the diagnosis in the patients with OSA. Besides, SPO_2 and AHI had a negative linear correlation in our study (data not shown). Moreover, higher Hb was observed in CTEPH patients with OSA in this study. Carlson *et al.* (29) and Moore-Gillon *et al.* (30) also observed a portion of patients with unexplained polycythemia who suffered from sleep breathing disorders. Two mechanisms may explain the elevation of Hb in OSA patients: (I) erythropoiesis induced by oxygen desaturation; (II) hemoconcentration resulting from fluid shifts from the intravascular to the extravascular bed. Hb elevation contributes to an increased blood viscosity of OSA patients, which can promote the occurrence of VTE. VTE including DVT and PTE appear to be more prevalent in OSA patients than in normal people, and OSA is even an independent risk factor for recurrent VTE (31). This phenomenon may be ascribed to the hypercoagulability and low fibrinolysis state of OSA. Bokinsky *et al.* (32) measured blood platelet aggregation and activation of patients with suspected OSA. The results showed an increased platelet aggregation and activation in OSA patients, whose effect was reduced by the therapy of OSA. Although there is no study suggesting OSA is a risk factor for CTEPH, we presume OSA can perhaps exacerbate the preexisting CTEPH, or even originally cause CTEPH in this way. Fluid retention in decompensated CTEPH patients facilitates a peripharyngeal edema during sleep, inducing a more severe narrowing of the upper airway, than found in the general population (33). Thus, the severity of CTEPH may be associated with OSA in turn. However, data in this study could not explain whether CTEPH aggravated OSA.

Clinical implications

From this study, we noticed CTEPH patients with OSA might have a worse clinical condition, than the CTEPH patients without OSA, reflecting the potentially detrimental influence of OSA on CTEPH in some way. We speculate OSA may further increase the mortality

of patients with CTEPH who are receiving a long term follow up. Therefore, it is imperative to recognize the existence of OSA in CTEPH patients, and give appropriate therapy for it.

Study limitations

The first limitation of our study is small sample size, due to a relative low incidence of CTEPH. Selection bias is unavoidable in a retrospective study. As a pulmonary vascular disease center, it is more likely CTEPH patients with OSA combined will be admitted. Also, the above-mentioned inclusion criteria for PSG may lead to the high detection rate of OSA. Using bed time to calculate AHI, which may underdiagnose OSA, is another limitation. In fact, the actual sleeping time is less than bed time. Moreover, we did not follow up with these patients, so we cannot ensure the effect of OSA on the mortality of CTEPH patients and if OSA contributes to a persistent and recurrent PH after CTEPH patients undergoing pulmonary endarterectomy. Additionally, whether OSA treatment can alleviate CTEPH and whether CTEPH treatment can alleviate OSA is not investigated in our study. Larger, prospective cohort studies are needed to solve these problems.

Conclusions

In summary, OSA may aggravate CTEPH in some way. It may be of great significance to recognize and treat OSA in CTEPH patients. The clinical significance of the relationship between OSA and CTEPH warrants further studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was performed with the approval of Fuwai Hospital Ethics Committee (No. 2009215). Written informed consents of all participants were obtained.

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