Impact of obstructive sleep apnea on pulmonary hypertension in patients with chronic obstructive pulmonary disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) syndrome are highly prevalent respiratory conditions. Their coexistence is referred to as the overlap syndrome. They are both related to pulmonary hypertension (PH) development. This study investigated the effects of OSA on PH in patients with COPD and the associated factors.

Methods: Consecutive patients with stable COPD were recruited for an observational cross-sectional study from September 2016 to May 2018 at Peking University Third Hospital. In total, 106 patients with COPD were enrolled and performed home portable monitoring and echocardiography. OSA was defined by an apnea hypopnea index (AHI) ≥10 events/h. Based on OSA absence or presence, patients were divided into the COPD with OSA and COPD without OSA groups. Factors affecting pulmonary artery pressure (PAP) and PH were identified using univariate analysis and logistic regression models.

Results: In the 106 patients with COPD, the mean age was 69.52 years, 91.5% were men, and the mean forced expiratory volume in 1 s (FEV_1) percentage of predicted was 56.15%. Fifty-six (52.8%) patients with COPD were diagnosed with OSA, and 24 (22.6%) patients with COPD were diagnosed as PH. Compared with COPD without OSA group, the median PAP in COPD with severe OSA group increased by 5 mmHg (36.00 [26.00–50.00] mmHg *vs.* 31.00 [24.00–34.00] mmHg, $P = 0.036$). COPD with percent of night-time spent with oxygen saturation below 90% (T90) > 10% group had higher PAP than COPD with T90 ≤ 1% group (36.00 [29.00–50.00)] mmHg *vs.* 29.00 [25.50–34.00] mmHg, $F = 7.889$, $P = 0.007$). Univariate analysis revealed age, FEV_1% predicted, T90, and Charlson index had statistically significant effects on PH. Multiple regression analysis showed a significant and independent effect of both FEV_1% predicted (odds ratio [OR] = 3.46; 95% confidence interval [CI]: 1.15–10.46; $P = 0.028$) and AHI (OR = 3.20; 95% CI: 1.09–19.35; $P = 0.034$) on PH.

Conclusions: Patients with COPD with OSA are more susceptible to PH, which is associated with declining lung function and increased severity of OSA. Thus, nocturnal hypoxemia and OSA in elderly patients with COPD should be identified and treated.

Keywords: Chronic obstructive pulmonary disease; Echocardiography; Obstructive sleep apnea; Pulmonary hypertension

Introduction

Chronic obstructive pulmonary disease (COPD) occurs in 13.7% of adults in people aged 40 years or older in China.[1,2] Owing to the development of an aging population worldwide, the prevalence and mortality rate of COPD are increasing year by year. Obstructive sleep apnea (OSA) accounts for approximately 4.1% of the Chinese population.[3,4] OSA could cause daytime sleepiness, affect the quality of life and increase mortality of the individuals. The coexistence of both disorders is often referred to as the overlap syndrome, which occurs in approximately 1% of adults.[5]

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Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAP) >25 mmHg at rest as assessed by right heart catheterization.[6] Right heart failure is fatal in patients with COPD, and PH secondary to COPD is the primary cause of right heart failure. The prevalence of PH and cor pulmonale in COPD cases varies from 20.0% to 62.4%. PH is mainly due to chronic hypoxic pulmonary vasoconstriction of the small pulmonary arteries, eventually resulting in vascular remodeling.[7] In the recent 20 years, limited epidemiologic data have suggested that the prevalence of PH in OSA ranges from 17% to 53%.[8–12] Intermittent hypoxia, negative pleural pressure, and endothelial dysfunction have been shown to play an important role in the pathogenesis of PH in OSA.[13]

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OSA can cause severe hypoxemia and hypercapnia at night. Hence, it is speculated that patients with OSA have a higher prevalence of PH, but few studies have investigated this relationship. Thus, the purpose of the current study was to investigate the effects of OSA on PH in patients with COPD and the associated factors by comparing the PAP and proportion of PH in patients with COPD with OSA and without OSA.

Methods

Ethical approval

The study was approved by the Ethics Committee of Third Hospital of Peking University (No. IRB00006761-M2016164). All patients gave their informed consent.

Patient recruitment

This cross-sectional study was performed from September 2016 to May 2018 at Peking University Third Hospital. Patients with stable COPD were invited to participate in study. Participants were allocated into either the group with OSA or into the group without OSA based on whether home portable monitoring evaluation revealed an apnea hypopnea index (AHI) of ≥10 events/h or <10 events/h, respectively. Inclusion criteria were as follows: (1) patients age >40 years; (2) outpatients diagnosed with COPD according to the criteria recommended by China Guidelines of COPD (revised version 2013)[14]; and (3) patients with stable COPD with no acute exacerbation of symptoms and upper respiratory tract infection in the 6 weeks preceding the study. Exclusion criteria were as follows: (1) patients with an active medical, neurologic or psychiatric disorder that could impact the results of the questionnaire; (2) patients with comorbidities that affected PH (such as acute heart failure, congenital cardiovascular disease, pulmonary embolism, obesity hypoventilation syndrome, central sleep apnea, neuromuscular disease, pulmonary arteritis caused by autoimmune diseases, and other chronic pulmonary diseases such as fibrosis); and (3) patients with near-terminal illness. During a clinical examination, height, weight, and neck circumference were measured. Exposure history of noxious particles, exacerbations in the past 12 months, therapy information, and comorbidities were recorded during a physician-led interview. Participants completed questionnaires related to the assessments of COPD and OSA. Pulmonary function data of patients in the last 6 months were recorded. Patients were asked to perform echocardiography and home portable monitoring.

Pulmonary function tests

A diagnosis of COPD was confirmed by reviewing the medical records for a clinical diagnosis of COPD[14] and spirometric data meeting the diagnostic criteria of global initiative for obstructive lung disease (GOLD) 2017.[15] Pulmonary function tests were performed with a spirometer (Medgraphics, Elite Series DL, St. Paul, MN, USA).

Home portable monitoring

All participants underwent nocturnal sleep monitoring using the ApneaLink™ (ResMed, MAP Medicine Technology, Martinsried, Germany) device at home. The device recorded the patient's nasal respiratory pressure signal, thoracoabdominal movement, and oxygen saturation during sleep.[16] All physiologically important respiratory events were identified using the 2017 American Academy of Sleep Medicine (AASM) definition.[17] Apnea was diagnosed when the peak signal excursion dropped by ≥90% of pre-event baseline levels as determined using a nasal pressure sensor for ≥10 s. Hypopnea was diagnosed when the peak signal excursion dropped by ≥30% of pre-event baseline levels as determined using a nasal pressure sensor for ≥10 s in association with ≥4% arterial oxygen desaturation. The OSA severity was categorized based on the AHI as normal (<5), mild (≥5 to 15), moderate (≥15 to 30), and severe (≥30). Considering that OSA was more common in the elderly, we categorized OSA using an AHI of ≥10 events/h.

Echocardiography

All patients underwent transthoracic echocardiography examinations at rest with a two-dimensional, color-flow Doppler apparatus (Vivid E9, GE Vingmed Ultrasound A/S, Strandpromenaden 45, N-3191 Horten, Norway). Subjects were placed in the left lateral position by an experienced ultrasound physician for examination and image acquisition. The right side of the heart (right atrium, tricuspid valve, right ventricle) was investigated to evaluate the right heart performance and to calculate the PAP. When tricuspid regurgitation was recorded using the color-flow Doppler, the maximum velocity (V) of tricuspid incompetence was calculated with a continuous Doppler study of at least four consecutive beats. Right ventricular pressure (RVP) was derived using the equation $RVP = 4V^2$ + right atrial pressure (RAP). For standardization, a RAP of 5 mmHg was assumed for all patients unless clear features were present such as an inferior vena cava diameter of >2.1 cm with <50% collapsibility. The estimated RVP is considered to represent the PAP, if there is no evidence of pulmonary valvular dysfunction. Tricuspid regurgitation velocity (TRV) >2.8 m/s and systolic PAP >36 mmHg on the echocardiographic examination were regarded as PH.[18]

Questionnaires

Daytime sleepiness was assessed using the Epworth sleepiness scale (ESS). The patient was diagnosed with daytime sleepiness when the ESS score was ≥9 points.[19] Dyspnea was quantified using the modified Medical Research Council Dyspnea scale (mMRC).[20] Symptoms were also quantified by use of COPD assessment test (CAT).[21] Hospital anxiety depression scale (HADS) was a self-reported, 14-item depression, and anxiety screening instrument assessing the severity of symptoms in medically ill patients.[22] Quality of life in patients with COPD was evaluated using St. George respiratory questionnaire (SGRQ).[23] Significant comorbidities were recorded and quantified according to the well-established Charlson index.[24,25]

Exacerbation frequency

An acute exacerbation (AE) of COPD was defined as an acute worsening of respiratory symptoms that resulted in additional therapy. The definition of severe exacerbation

was that patient required hospitalization or visits the emergency room. Patients were asked about the number of exacerbations in the most recent 12 months.[15]

Primary outcomes and secondary outcomes

Primary outcomes were the PAP and proportion of PH. Secondary outcomes were exacerbation frequency, depression, anxiety, quality of life, and comorbidities.

Statistical analysis

Descriptive data with normal distribution were expressed as mean ± standard deviation (SD). Descriptive data without normal distribution were expressed as medians (interquartile range [IQR]) and frequencies were expressed as percentages. Comparisons were made between the COPD without OSA group and COPD with OSA group using Chi-squared tests for categorical variables, and *t* tests or Wilcoxon rank-sum tests for continuous variables depending on distribution. To compare patient characteristics among different groups, statistical analyses were performed using Chi-squared tests for categorical variables, and one-way analysis of variance for continuous variables. The relationship between two continuous variables was determined by measuring the Pearson correlation coefficient. Univariate analysis and a logistic regression model were used to obtain determinants of PAP and PH. A value of $P < 0.05$ was considered significant for all analyses. All statistical analyses were performed with SPSS version 17.0 (SPSS, Chicago, IL, USA).

Results

Of the 159 screened individuals with COPD, 106 participated in the study and completed home portable monitoring and echocardiography. The mean age was 69.52 years, 91.5% were men, and the median body mass index (BMI) was 23.77 kg/m^2 [Table 1]. In total, 56 individuals were allocated to the COPD with OSA group and 50 were allocated to COPD without OSA group [Figure 1].

Baseline characteristics of COPD without OSA group and COPD with OSA group

In 106 patients with COPD, 56 patients (52.8%) had an AHI ≥10 events/h and were considered to have COPD with OSA. Individuals in the COPD without OSA and COPD with OSA groups did not differ by sex, age, BMI, neck circumference, or exposure history of noxious particles. The proportion of patients undergoing drug therapy for stable COPD in the COPD without OSA and COPD with OSA groups was 84.0% and 73.2%, respectively ($\chi^2 = 0.501$, $P = 0.639$). However, the use of theophylline in the COPD without OSA group was 20.4% higher than that in COPD with OSA group (5.4% *vs.* 26.0%, $\chi^2 = 8.783$, $P = 0.005$). Spirometry demonstrated on an average, moderate and severe COPD. The post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio and FEV_1% predicted of the two groups were similar (56.54% *vs.* 56.70%, $t = -0.061$, $P = 0.951$; 54.19% *vs.* 57.98%, $t = -0.897$, $P = 0.372$, respectively) [Table 1].

Sleep measures in COPD without OSA group and COPD with OSA group

Eighty-four participants (79.2%) with COPD snored and 37 participants (34.9%) with COPD were daytime sleepiness. The prevalence of snoring in the COPD without OSA group was similar to that in the COPD with OSA group (82.1% *vs.* 76.0%, $\chi^2 = 0.606$, $P = 0.479$). The prevalence of sleepiness between the COPD with and without OSA groups did not show statistical differences (42.9% *vs.* 26.0%, $\chi^2 = 1.231$, $P = 0.102$). Compared with COPD individuals without OSA, individuals with OSA had elevated AHI (20.00 [13.13–34.50] events/h *vs.* 5.05 [3.00–6.83] events/h, $Z = -0.861$, $P < 0.001$), more severe minimal oxygen desaturation (minimal SpO_2) (83.50 [76.00–87.00]% *vs.* 88.50 [86.00–91.00] %, $Z = -5.429$, $P < 0.001$), and greater percentage of night-time spent with oxygen saturation below 90% (T90) (3.10 [0.50–26.25] % *vs.* 0 [0–1.00] %, $Z = -5.054$, $P < 0.001$) [Table 2].

Echocardiography in the COPD without OSA group and COPD with OSA group

The left ventricular ejection fraction (LVEF) did not show significant difference between the two study groups (70.00 [67.50–72.00] % *vs.* 70.00 [66.00–73.00] %, $Z = -0.203$, $P = 0.839$). The mean peak TRV (2.61 ± 0.52 m/s *vs.* 2.58 ± 0.40 m/s, $t = -0.066$, $P = 0.947$) and median PAP (31.00 [26.00–38.00] mmHg *vs.* 32.00 [25.00–36.50] mmHg, $Z = -0.172$, $P = 0.846$) were similar in the COPD with OSA group and the COPD without OSA group. In total, 10 of 50 (20.0%) COPD without OSA participants and 14 of 56 (25.0%) COPD with OSA participants had PH ($\chi^2 = 0.377$, $P = 0.644$) [Table 3].

Exacerbation frequency, HADS, SGRQ, and Charlson Index in COPD without OSA group and COPD with OSA group

There were no differences in exacerbation frequency (1.00 [0–1.50] *vs.* 1.00 [0–1.00], $Z = -0.260$, $P = 0.795$), HADS score (8.00 [3.00–14.00] *vs.* 6.50 [3.00–12.25], $Z = -0.912$, $P < 0.362$), total SGRQ score (33.04 [23.42–46.23] *vs.* 35.09 [19.14–45.65], $Z = -0.176$, $P = 0.860$) and Charlson index (1.00 [0–2.00] *vs.* 1.00 [0–1.75], $Z = -0.217$, $P = 0.829$) between groups. The prevalence of coronary heart disease (23.2% *vs.* 14.0%, $\chi^2 = 1.465$, $P = 0.320$), congestive heart failure (16.1% *vs.* 12.0%, $\chi^2 = 2.669$, $P = 0.131$), cerebrovascular disease (10.7% *vs.* 6.0%, $\chi^2 = 0.756$, $P = 0.495$), diabetes mellitus (16.1% *vs.* 16.0%, $\chi^2 < 0.001$, $P = 0.992$), and arterial hypertension (42.9% *vs.* 46.0%, $\chi^2 = 0.106$, $P = 0.845$) was not significantly increased in the COPD with OSA group compared with the COPD without OSA group [Table 4].

Table 1: Baseline characteristics of COPD without OSA group and COPD with OSA group.

Variables	All ($N = 106$)	COPD without OSA ($n = 50$)	COPD with OSA ($n = 56$)	Statistics	P
Men	97 (91.5)	45 (90.0)	52 (92.9)	0.278*	0.732
Age (years)	69.5 ± 10.1	69.1 ± 9.2	69.9 ± 10.9	0.387†	0.700
Height (m)	1.69 ± 0.06	1.69 ± 0.06	1.69 ± 0.07	0.597†	0.552
Weight (kg)	67.00 (60.00–75.00)	66.00 (61.00–72.00)	68.50 (60.00–75.38)	0.352‡	0.726
BMI (kg/m^2)	23.77 (21.11–25.75)	23.37 (21.39–25.70)	24.14 (21.04–25.96)	–0.275‡	0.783
Neck circumference (cm)	39.29 ± 3.43	38.46 ± 2.57	39.90 ± 3.86	1.712†	0.092
Smoking history				3.554*	0.190
Current smoker	27 (25.5)	16 (32.0)	11 (19.6)	2.125*	0.182
Former smoker	65 (61.3)	30 (60.0)	35 (62.5)	0.070*	0.843
Never smoker	14 (13.2)	4 (8.0)	10 (17.9)	1.462*	0.160
Smoking exposure (Pack-years)	30.00 (20.00,48.50)	37.50 (20.00, 43.50)	30.00 (15.00, 50.00)	0.138†	0.890
Indoor pollution exposure	40 (37.7)	16 (32.0)	24 (42.9)	1.325*	0.316
Occupational exposure	57 (53.8)	30 (60.0)	27 (48.2)	1.476*	0.247
Drug therapy	83 (78.3)	42 (84.0)	41 (73.2)	0.501*	0.639
LAMA	14 (13.2)	7 (14.0)	7 (12.5)	0.052*	0.820
LABA+ICS	18 (17.0)	11 (22.0)	7 (12.5)	1.691*	0.208
LAMA+LABA+ICS	34 (32.1)	17 (34.0)	17 (30.4)	0.161*	0.835
Theophylline	16 (15.2)	13 (26.0)	3 (5.4)	8.783*	0.005
mMRC (score)	2.00 (1.00–2.00)	1.00 (1.00–2.00)	2.00 (1.00–2.00)	–1.003‡	0.316
CAT (score)	10.50 (6.00–15.25)	9.00 (6.00–15.50)	11.00 (7.00–15.50)	–0.842‡	0.400
FVC (L)	2.78 ± 0.74	2.88 ± 0.72	2.64 ± 0.76	–1.283†	0.204
FVC predicted (%)	76.58 ± 16.20	79.43 ± 14.76	72.93 ± 17.44	–1.641†	0.106
FEV_1 (L)	1.60 ± 0.65	1.68 ± 0.61	1.50 ± 0.70	–1.112†	0.270
FEV_1% predicted (%)	56.15 ± 19.46	57.98 ± 17.78	54.19 ± 21.17	–0.897†	0.372
FEV_1/FVC (%)	56.62 ± 11.91	56.70 ± 10.84	56.54 ± 13.10	–0.061†	0.951
FEV_1/FVC predicted (%)	69.55 ± 15.39	71.10 ± 14.80	67.57 ± 16.15	–0.924†	0.359
GOLD stage				2.876*	0.417
1	8 (7.5)	5 (10.0)	3 (5.4)	0.286*	0.471
2	49 (46.2)	26 (52.0)	23 (41.1)	1.269*	0.330
3	37 (34.9)	14 (28.0)	23 (41.1)	1.986*	0.221
4	12 (11.3)	5 (10.0)	7 (12.5)	0.010*	0.766
RV/TLC (%)	55.68 ± 13.32	54.87 ± 12.61	56.50 ± 14.12	0.547†	0.586
RV/TLC predicted (%)	140.15 ± 37.33	138.49 ± 36.41	141.90 ± 38.67	0.406†	0.686
DLCO (mL·min^{-1}·mmHg^{-1})	20.26 (14.47, 27.19)	22.53 (15.11, 27.55)	17.66 (11.09, 25.46)	–1.293‡	0.196
DLCO predicted (%)	63.72 ± 20.30	67.04 ± 18.90	60.61 ± 21.36	–1.253†	0.215
DL/VA (mL·min^{-1}·mmHg^{-1})	3.73 ± 1.10	3.85 ± 1.25	3.62 ± 0.96	–0.712†	0.480

Data are presented as n (%), mean ± standard deviation or medians (interquartile range). * χ^2 value. † t value. ‡ Z value. BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; Current smoker: Individuals who have smoked more than 100 cigarettes in one's lifetime and currently smoking cigarettes; Former smoker: Individuals who have smoked more than 100 cigarettes in one's lifetime and quit smoking at least 1 year; Never smoker: Individuals who have smoked less than 100 cigarettes in one's lifetime; CAT: COPD assessment test; FVC: Forced vital capacity; DL/VA: Diffusing capacity per liter of lung volume; DLCO: Carbon monoxide diffusing capacity; FEV_1: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroids; LABA: Long-acting beta 2 agonists; LAMA: Long-acting antimuscarinic antagonists; mMRC: Modified Medical Research Council Dyspnea scale; OSA: Obstructive sleep apnea; RV: Residual volume; TLC: Total lung capacity.

Echocardiography and secondary outcomes grouped according to AHI, minimal SpO_2, and T90

Patients with COPD were divided into four categories based on their AHI: COPD without OSA group (AHI < 5), COPD with mild OSA group (5 ≤ AHI < 15), COPD with moderate OSA group (15 ≤ AHI < 30), and COPD with severe OSA group (AHI ≥ 30). Compared with COPD without OSA group, the median PAP in COPD with severe OSA group increased by 5 mmHg (36.00 [26.00–50.00] mmHg *vs.* 31.00 [24.00–34.00] mmHg, $P = 0.036$). The mean peak TRV (2.88 ± 0.63 m/s *vs.* 2.53 ± 0.39 m/s, $P = 0.047$), median PAP (36.00 [26.00–50.00] mmHg *vs.* 30.50 [26.00–35.75] mmHg, $P = 0.024$), and Charlson index (1.00 [0.25–2.75] *vs.* 0 (0–1.75), $P = 0.022$) in the COPD with severe OSA group were higher than those in the COPD with mild OSA group [Table 5].

According to the degree of nocturnal hypoxemia, patients with COPD were divided into COPD without hypoxemia group (minimal $SpO_2 \geq 90\%$), COPD with mild hypoxemia group (85% ≤ minimal $SpO_2 < 90\%$), COPD with moderate hypoxemia group (80% ≤ minimal $SpO_2 < 85\%$), and COPD with severe hypoxemia group (minimal $SpO_2 < 80\%$). There were no statistical differences in the

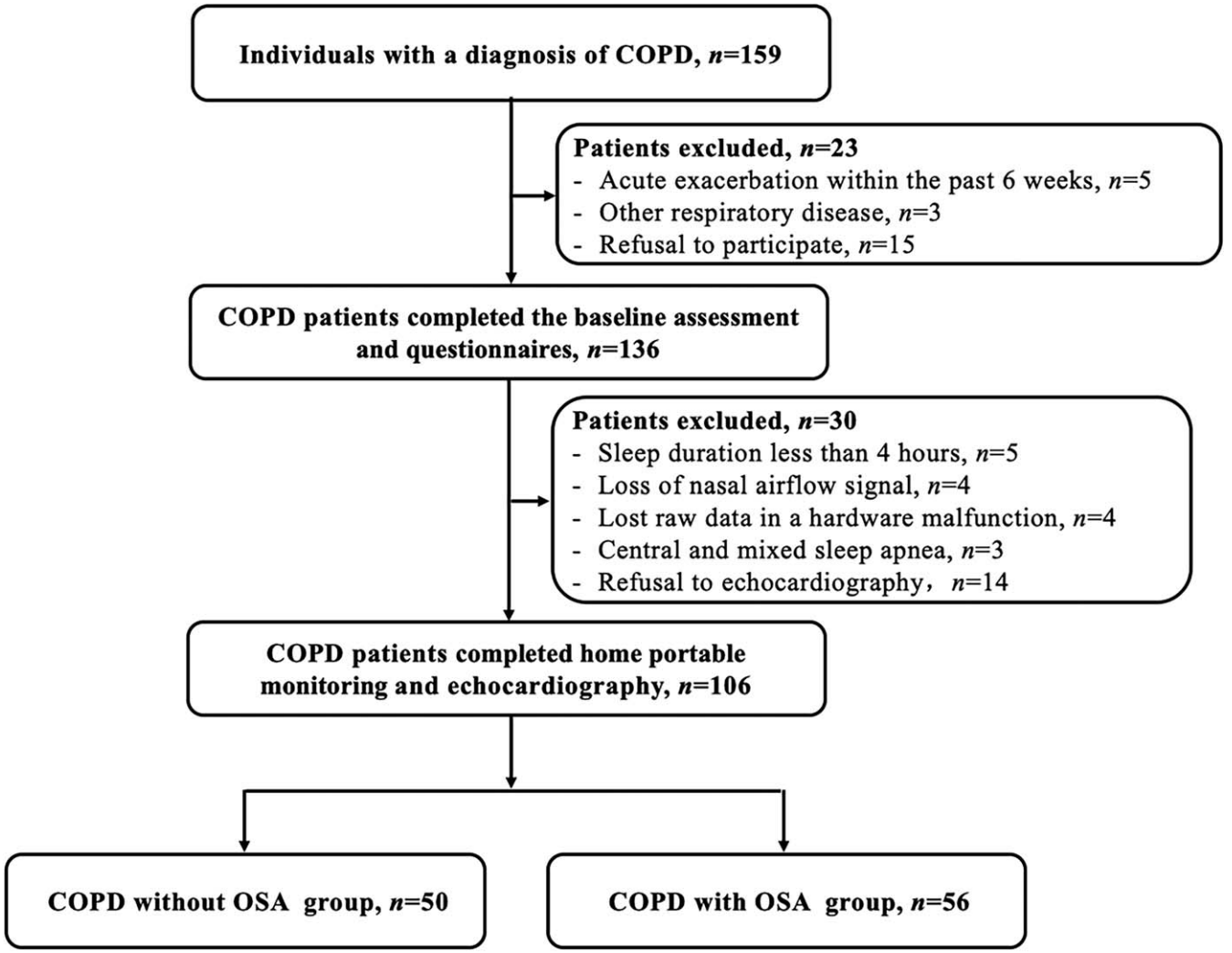

Figure 1: Study workflow for individuals enrolled in the study. COPD: Chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea (apnea hypopnea index ≥10 events/h).

Table 2: Sleep measures in the COPD without OSA group and COPD with OSA group.

Variables	All ($n = 106$)	COPD without OSA ($n = 50$)	COPD with OSA ($n = 56$)	Statistics	*P*
Snore	84 (79.2)	38 (76.0)	46 (82.1)	0.606*	0.479
ESS (score)	7.00 (5.00, 10.00)	7.00 (4.00, 10.00)	8.00 (5.00, 11.00)	−1.238‡	0.216
ESS≥10	37 (34.9)	13 (26.0)	24 (42.9)	3.304*	0.102
AHI (events/h)	10.35 (5.18–20.85)	5.05 (3.00–6.83)	20.00 (13.13–34.50)	−8.861‡	<0.001
<5	25 (23.6)	25 (50.0)	–	–	–
≥5 to 15	45 (42.5)	25 (50.0)	20 (35.7)	1.010*	0.422
≥15 to 30	20 (18.9)	–	20 (35.7)	–	–
≥30	16 (15.1)	–	16 (28.6)	–	–
ODI (events/h)	10.00 (5.15–19.50)	5.20 (3.00–6.90)	18.60 (12.60–36.15)	−8.034‡	<0.001
Mean SpO_2 (%)	94.00 (93.00–95.43)	94.95 (94.00–96.00)	93.85 (92.00–94.98)	−3.380‡	0.001
Minimal SpO_2 (%)	86.00 (80.00–89.25)	88.50 (86.00–91.00)	83.50 (76.00–87.00)	−5.429‡	<0.001
T90 (%)	1.00 (0–7.00)	0 (0–1.00)	3.10 (0.50–26.25)	−5.054‡	<0.001
T85 (%)	0 (0–0.01)	0	0 (0–3.00)	−3.165‡	0.002
T80 (%)	0	0	0 (0–1.00)	−3.617‡	<0.001

Data are presented as *n* (%), or medians (interquartile range). *χ^2 value. †*t* value. ‡*Z* value. AHI: Apnea hypopnea index; COPD: Chronic obstructive pulmonary disease; ESS: Epworth sleepiness scale; ODI: Oxygen desaturation index; OSA: Obstructive sleep apnea; T80: Percent of night-time spent with time SpO_2 < 80%; T85: Percent of night-time spent with SpO_2 < 85%; T90: Percent of night-time spent with oxygen saturation below 90%; –: No data.

Table 3: Echocardiography in the COPD without OSA group and COPD with OSA group.

Variables	All ($n = 106$)	COPD without OSA group ($n = 50$)	COPD with OSA group ($n = 56$)	Statistics	P
LVEF (%)	70.00 (67.00–72.00)	70.00 (66.00–73.00)	70.00 (67.50–72.00)	–0.203*	0.839
RA end-systolic area (mm^2)	15.00 (12.80–16.00)	14.25 (13.00–16.00)	15.00 (12.00–16.50)	–0.090*	0.928
RV end-diastolic dimension (mm)	21.00 (18.30–23.00)	20.65 (18.30–22.73)	21.50 (18.50–23.00)	–0.460*	0.646
Peak TRV (m/s)	2.60 ± 0.46	2.58 ± 0.40	2.61 ± 0.52	–0.066†	0.947
Not measurable	33 (31.1)	15 (30.0)	18 (32.1)	0.057‡	0.837
<2.8 m/s	49 (46.2)	25 (50.0)	24 (42.9)	0.017‡	0.897
2.8–3.4 m/s	19 (17.9)	8 (16.0)	11 (19.6)	0.238‡	0.800
>3.4 m/s	5 (4.7)	2 (4.0)	3 (5.4)	0.288‡	0.671
PAP (mmHg)	31.50 (26.00–37.75)	32.00 (25.00–36.50)	31.00 (26.00–38.00)	–0.172*	0.846
PH	24 (22.6)	10 (20.0)	14 (25.0)	0.377‡	0.644

Data are presented as *n* (%), the mean ± standard deviation or medians (interquartile range). *Z value. †t value. ‡χ^2 value. COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction; OSA: Obstructive sleep apnea; PAP: Mean pulmonary arterial pressure; PH: Pulmonary hypertension; RA: Right atrium; RV: Right ventricular; TRV: Tricuspid regurgitation velocity. 1 mmHg = 0.133 kPa.

Table 4: Exacerbation frequency, HADS, SGRQ, and Charlson index in the COPD without OSA group and COPD with OSA group.

Variables	All ($N = 106$)	COPD without OSA ($n = 50$)	COPD with OSA ($n = 56$)	Statistics	P
AE (times)	1.00 (0–1.00)	1.00 (0–1.00)	1.00 (0–1.50)	–0.260*	0.795
Severe AE (times)	0 (0–1.00)	0.50 (0–1.00)	0 (0–1.00)	–0.479*	0.632
HADS (score)	7.00 (3.00–13.00)	6.50 (3.00–12.25)	8.00 (3.00–14.00)	–0.912*	0.362
Anxiety	20 (18.9)	7 (14.0)	13 (23.2)	1.465†	0.320
Depression	22 (20.8)	10 (20.0)	12 (21.4)	0.033†	0.854
SGRQ total score	34.58 (20.22–46.11)	35.09 (19.14–45.65)	33.04 (23.42–46.23)	–0.176*	0.860
Symptoms score	44.72 (31.00–62.76)	50.32 (30.60–66.56)	43.20 (29.98–57.98)	–0.780*	0.436
Activity score	41.39 (26.80–59.46)	35.71 (29.28–59.56)	41.39 (23.72–59.46)	–0.408*	0.683
Impacts score	27.47 (11.09–37.83)	25.27 (11.22–38.45)	30.31 (10.82–37.75)	–0.273*	0.785
Charlson index	1.00 (0–2.00)	1.00 (0–1.75)	1.00 (0–2.00)	–0.217*	0.829
CHD	20 (18.9)	7 (14.0)	13 (23.2)	1.465†	0.320
CHF	12 (11.3)	6 (12.0)	9 (16.1)	2.669†	0.131
Cerebrovascular disease	9 (8.5)	3 (6.0)	6 (10.7)	0.756†	0.495
DM	17 (16.0)	8 (16.0)	9 (16.1)	<0.001†	0.992
Arterial hypertension	47 (44.3)	23 (46.0)	24 (42.9)	0.106†	0.845

Data are presented as *n* (%), or medians (interquartile range). *Z value. †χ^2 value. AE: Acute exacerbation; CHD: Coronary heart disease; CHF: Congestive heart failure; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; HADS: Hospital anxiety depression scale; OSA: Obstructive sleep apnea; SGRQ: St. George respiratory questionnaire.

median PAP, proportion of PH, and secondary outcomes between the four groups [Table 6].

Based on T90, the patients were also divided into three groups, including COPD with T90 ≤ 1%, 1% < T90 ≤ 10% and T90 > 10%. We found that the mean peak TRV (2.87 ± 0.54 m/s *vs.* 2.51 ± 0.40 m/s, $P = 0.008$), median PAP (36.00 [29.00–50.00] mmHg *vs.* 29.00 [25.50–34.00] mmHg, $P = 0.007$), and Charlson index (1.00 [0–3.00] *vs.* 0 [0–1.00], $P = 0.019$) in the COPD with T90 > 10% group were significantly higher than those in COPD with T90 ≤ 1% group [Table 7].

The Pearson correlations between the three factors (AHI, minimal SpO_2, and T90) and PAP are shown in Figure 2. AHI and minimal SpO_2 were not linearly correlated with PAP ($r = 0.180$, $P = 0.121$; $r = -0.189$, $P = 0.103$); only T90 was positively correlated with PAP ($r = 0.252$, $P = 0.028$).

Univariate and logistic regression analysis for the variables associated with PH in subjects with COPD

Univariate analysis performed on data in patients with COPD revealed significant effects of age, FEV_1% predicted, T90, and Charlson index on PH. According to the regression model, FEV_1% predicted <50% increased the risk of PH by 3.46 times (odds ratio [OR] = 3.46; 95% confidence interval [CI]: 1.15–10.46; $P = 0.028$) and AHI ≥15 events/h increased the risk of PH by 3.20 times (OR = 3.20; 95% CI: 1.09–19.35; $P = 0.034$). Moderate to severe OSA and GOLD stage 2 or higher were independent factors contributing to PH in subjects with COPD [Table 8].

Table 5: Echocardiography and secondary outcomes grouped according to AHI.

Variables	COPD without OSA ($n = 25$)	COPD with mild OSA ($n = 45$)	COPD with moderate OSA ($n = 20$)	COPD with severe OSA ($n = 16$)	Statistics	P
Peak TRV (m/s)	2.54 ± 0.40	2.53 ± 0.39	2.61 ± 0.52	2.88 ± 0.63*	1.517†	0.218
PAP (mmHg)	31.00 (24.00–34.00)	30.50 (26.00–35.75)	31.00 (26.00–42.50)	36.00 (26.00–50.00)* ‡	1.959†	0.128
PH	4 (16.0)	6 (13.3)	6 (30.0)	5 (31.3)	5.680§	0.130
AE (times)	1.00 (0–1.00)	1.00 (0–1.00)	1.00 (0–1.88)	1.00 (0–1.00)	0.126†	0.945
Severe AE (times)	0 (0–1.00)	1.00 (0–1.00)	0 (0–1.00)	1.00 (0–1.00)	0.285†	0.836
HADS (score)	6.00 (2.50–12.00)	7.00 (3.00–12.75)	8.50 (5.00–14.50)	8.50 (3.00–13.25)	0.768†	0.768
Anxiety	3 (12.0)	9 (20.0)	5 (25.0)	3 (18.8)	1.299§	0.744
Depression	5 (20.0)	10 (22.2)	4 (20.0)	3 (18.8)	0.114§	0.990
SGRQ total score	35.59 (19.25–48.62)	34.14 (18.69–47.32)	36.52 (20.58–47.25)	31.88 (24.46–43.58)	0.008†	0.999
Symptoms score	51.68 (35.23–67.46)	44.37 (27.08–65.49)	44.38 (33.63–53.89)	38.21 (25.66–61.11)	0.730†	0.536
Activity score	35.63 (17.88–61.95)	35.47 (23.44–60.15)	41.58 (35.47–60.07)	42.18 (30.99–53.24)	0.085†	0.968
Impacts score	24.69 (11.09–41.62)	27.82 (11.07–38.12)	26.14 (9.72–38.11)	33.22 (10.31–36.64)	0.098†	0.961
Charlson index	1.00 (0–1.50)	0 (0–1.75)	0 (0–3.00)	1.00 (0.25–2.75)†	1.931†	0.129

Data are presented as *n* (%), the mean ± standard deviation or medians (interquartile range). *$P < 0.05$ *vs.* COPD with mild OSA group. †*F* value. ‡$P < 0.05$ *vs.* COPD without OSA group. §χ^2 value. AE: Acute exacerbation; AHI: Apnea hypopnea index; COPD: Chronic obstructive pulmonary disease; HADS: Hospital anxiety depression scale; OSA: Obstructive sleep apnea; PAP: Mean pulmonary arterial pressure; PH: Pulmonary hypertension; SGRQ: St. George respiratory questionnaire; TRV: Tricuspid regurgitation velocity. 1 mmHg = 0.133 kPa.

Table 6: Echocardiography and secondary outcomes grouped according to minimal SpO2.

Variables	COPD without hypoxemia ($n = 26$)	COPD with mild hypoxemia ($n = 41$)	COPD with moderate hypoxemia ($n = 16$)	COPD with severe hypoxemia ($n = 23$)	Statistics	P
Peak TRV (m/s)	2.58±0.44	2.55 ± 0.35	2.55 ± 0.54	2.76 ± 0.63	0.651*	0.585
PAP (mmHg)	31.00 (24.00–38.00)	30.00 (26.00–34.25)	32.00 (23.00–40.50)	35.10 (25.50–50.00)	1.066*	0.369
PH	5 (19.2)	6 (14.6)	4 (25.1)	6 (26.1)	4.488†	0.224
AE (times)	0.50 (0–1.00)	1.00 (0–2.00)	1.00 (0–1.00)	1.00 (0–1.00)	0.293*	0.830
Severe AE (times)	0.50 (0–1.00)	0.50 (0–1.00)	0 (0–1.00)	0 (0–1.00)	0.630*	0.597
HADS score	9.00 (3.00–15.00)	6.00 (3.00–10.25)	5.00 (3.00–13.00)	9.50 (3.25–15.50)	0.858*	0.466
Anxiety	6 (23.1)	5 (12.2)	3 (18.8)	6 (26.1)	2.277†	0.534
Depression	8 (30.8)	5 (12.2)	3 (18.8)	6 (26.1)	3.849†	0.280
SGRQ total score	34.64 (20.32–48.48)	36.86 (18.47–48.48)	29.94 (18.07–44.23)	31.88 (24.86–44.39)	0.329*	0.804
Symptoms score	50.32 (25.76–69.92)	44.02 (34.74–62.20)	43.96 (26.47–59.55)	44.87 (26.59–68.62)	0.133*	0.940
Activity score	35.47 (27.72–64.42)	41.77 (17.88–60.32)	41.40 (23.43–59.46)	41.39 (35.47–55.98)	0.214*	0.887
Impacts score	25.27 (12.61–47.10)	28.00 (11.09–38.21)	22.39 (4.59–37.57)	31.77 (14.24–38.11)	0.585*	0.626
Charlson index	1.00 (0–2.00)	0 (0–1.00)	0.50 (0–2.75)	1.00 (0–2.00)	0.946*	0.421

Data are presented as *n* (%), the mean ± standard deviation or medians (interquartile range). *F value. †χ^2 value. AE: Acute exacerbation; COPD: Chronic obstructive pulmonary disease; HADS: Hospital anxiety depression scale; PAP: Mean pulmonary arterial pressure; PH: Pulmonary hypertension; SGRQ: St. George respiratory questionnaire; TRV: Tricuspid regurgitation velocity. 1 mmHg = 0.133 kPa.

Discussion

This study demonstrated that patients with COPD with OSA were more susceptible to PH, which might be associated with declining lung function and increased OSA severity. The main findings of this study are: (1) 56 patients (52.8%) with COPD were diagnosed as OSA, and 24 patients (22.6%) with COPD had PH; (2) COPD with severe OSA group and COPD with T90 >10% group had higher PAP; (3) multiple regression analysis revealed significant and independent effects of both FEV_1% predicted and AHI on PH. These findings were consistent with our hypothesis that OSA is an aggravating factor of PAP and PH in patients with COPD.

In our study, we showed a high prevalence of OSA in patients with COPD, which was similar to the high prevalence reported in other studies.[26–28] This might be related to the fact that most of the subjects were elderly and had moderate to severe lung injury. Previous studies have found that the prevalence of OSA increased with age.[29,30] Considering the average age was 70 years in our study, we used AHI ≥10 events/h as a diagnostic criterion. Moreover, we found that the use of theophylline in COPD with OSA group was higher than that in COPD without OSA group. Previous studies have shown that theophylline could improve AHI, nocturnal hypoxia and sleep-related gas exchange in OSA.[31,32] Theophylline may have a stimulant effect on central respiratory drive and the upper airway muscles. It is unclear if theophylline is a more suitable drug for patients with COPD with OSA. In addition, 79.2% of patients with COPD snored and 34.9% of patients with COPD were daytime sleepiness. However, snoring and daytime sleepiness were not

Table 7: Echocardiography and secondary outcomes grouped according to T90.

Variables	COPD with T90 ≤ 1% (*n* = 52)	COPD with 1% < T90 ≤ 10% (*n* = 31)	COPD with T90 > 10% (*n* = 23)	Statistics	*P*
Peak TRV (m/s)	2.51 ± 0.40	2.54 ± 0.47	2.87 ± 0.54* †	3.877‡	0.025
PAP (mmHg)	29.00 (25.50–34.00)	31.50 (20.50–36.25)	36.00 (29.00–50.00)* †	4.323‡	0.017
PH	9 (17.3)	4 (12.9)	8 (34.8)	7.297§	0.028
AE (times)	1.00 (0–1.00)	1.00 (0–1.00)	1.00 (0–1.50)	0.078‡	0.925
Severe AE (times)	0 (0–1.00)	0 (0–1.00)	1.00 (0–1.00)	0.047‡	0.954
HADS (score)	6.00 (3.00–13.00)	7.00 (3.00–11.50)	10.00 (4.00–16.00)	0.959‡	0.387
Anxiety	9 (17.3)	5 (16.1)	6 (26.1)	1.018§	0.650
Depression	11 (21.2)	5 (16.1)	6 (26.1)	0.806§	0.704
SGRQ total score	34.64 (20.12–47.32)	35.38 (19.15–44.91)	33.04 (24.41–47.85)	0.628‡	0.536
Symptoms score	49.98 (32.56–62.82)	43.60 (32.57–65.55)	45.84 (25.43–62.16)	0.280‡	0.756
Activity score	35.47 (23.30–60.17)	38.59 (28.22–59.46)	47.20 (35.47–59.46)	1.168‡	0.315
Impacts score	26.75 (11.48–37.61)	25.71 (11.22–37.81)	33.43 (9.74–41.94)	0.793‡	0.455
Charlson index	0 (0–1.00)	0 (0–2.00)	1.00 (0–3.00)* †	2.897‡	0.046

Data are presented as *n* (%), the mean ± standard deviation or medians (interquartile range). *$P < 0.05$ *vs.* COPD group with T90 ≤ 1% group. †$P < 0.05$ *vs.* COPD group with 1% < T90 ≤ 10% group. ‡*F* value. §χ^2 value. AE: Acute exacerbation; COPD: Chronic obstructive pulmonary disease; HADS: Hospital anxiety depression scale; PAP: Mean pulmonary arterial pressure; PH: Pulmonary hypertension; SGRQ: St. George respiratory questionnaire; T90: Percent of night-time spent with oxygen saturation below 90%; TRV: Tricuspid regurgitation velocity. 1 mmHg = 0.133 kPa.

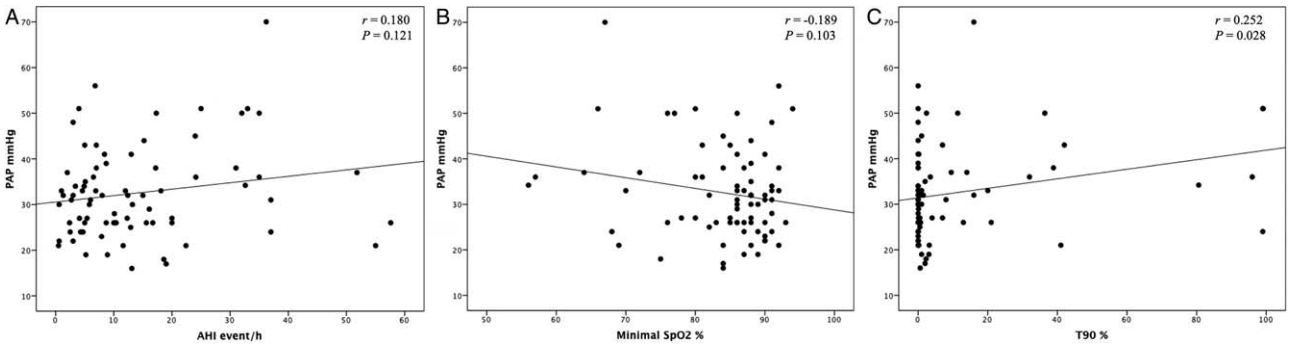

Figure 2: Correlation between (A) Apnea hypopnea index (AHI), (B) minimal oxygen desaturation (minimal SpO_2), and (C) percent of night-time spent with oxygen saturation below 90% (T90) and pulmonary artery pressure (PAP) in COPD subjects. COPD: Chronic obstructive pulmonary disease.

significant clinical features for identifying OSA in patients with COPD. At present, there is no recognized tool for screening OSA in patients with COPD. For patients with COPD, we need to further explore simpler identifiable features and screening methods for OSA. Sleep monitoring is needed to diagnose OSA for patients with COPD.

The present study revealed the prevalence of PH in 22.6% patients with COPD. Previous studies showed 38.7% to 62.4% cases of PH in patients with COPD.[33–35] In patients with COPD, increased PAP is an independent predictor of future exacerbations and life expectancy reduction. Decrease in the pulmonary vascular bed and chronic hypoxia are two main mechanisms of increased pulmonary vascular resistance and subsequent PH COPD.[7,36] In the present study, with increasing duration of hypoxemia, a significant increase in PAP was observed. However, we did not directly observe a significant increase in PAP with increasing severity of OSA and hypoxemia. Compared with AHI, the duration of hypoxemia may be more relevant to PH. Therefore, further studies involving larger sample size are needed to understand better clinical and biochemical profile of patients with OSA.

The prevalence of OSA-related PH varies from 17% to 53% in studies using right heart catheterization.[10,13,37] In general, older age, high BMI, worse nocturnal desaturations, and poor lung function are closely related to PH in OSA.[10,38] The occurrence of PH was mainly related to BMI and nocturnal hypoxia, and AHI was not an independent risk factor for PH. However, those studies were not limited to patients with OSA alone and subjects might have chronic cardiopulmonary disease, such as COPD. It is difficult to determine whether PH is due to intermittent hypoxemia caused by sleep apnea or persistent hypoxemia associated with chronic cardiopulmonary disease. Some studies have attempted to control the effect of cardiopulmonary disease as a confounding factor. Small sample studies have shown that the prevalence of PH in OSA without lung or heart disease was 20.7% to 41.0%.[39] Most studies have found that OSA-induced PH was mild to moderate, and some studies have challenged the effect of AHI on PH.[11,12,37,40] Few studies have focused on PH in patients with COPD with OSA. The coexistence of OSA may have a synergistic adverse effect on pulmonary hemodynamics leading to right ventricular dysfunction in patients with COPD. Chaouat *et al*[41] have

Table 8: Univariate and logistic regression analysis for the variables associated with PH in subjects with COPD.

	Univariate analysis				Multivariable model		
Variables	**OR**	**95% CI**	***P***	**Variables**	**OR**	**95% CI**	***P***
Sex	1.81	0.42–7.83	0.428	Sex, male			0.709
Age	1.06	1.02–1.12	0.011	Age >70 years			0.056
BMI	0.98	0.87–1.11	0.778	BMI > 25 kg/m^2			0.913
Smoking exposures	1.54	0.72–3.27	0.265	Smoking exposures			0.650
Charlson index	1.48	1.10–2.00	0.009	Charlson index			0.524
FEV_1% predicted	0.96	0.93–0.99	0.015	FEV_1% predicted < 50%	3.46	1.15–10.46	0.028
AHI	1.02	0.99–1.06	0.137	AHI ≥ 15 events/h	3.20	1.09–9.35	0.034
T90	1.02	1.00–1.04	0.034	T90 > 10%			0.578
Minimal SpO_2 (%)	0.97	0.93–1.02	0.220	Minimal SpO_2 (%)			0.702

AHI: Apnea hypopnea index; BMI: Body mass index; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in one second; OR: Odds ratio; PH: Pulmonary hypertension; T90: Percent of night-time spent with oxygen saturation below 90%.

reported that the prevalence of PH in patients with overlap syndrome is 29% higher than that in patients with OSA alone. Hawrylkiewicz *et al*[42] have suggested that PH was very common (14/17, 82.4%) in patients with OS, but did not correlate with the severity of nocturnal desaturation in OS patients. Consistent with other research reports, we also found that patients with COPD with OSA developed more severe hypoxemia at night. In a study by Kendzerska *et al*,[43] the degree of hypoxemia had a better ability to predict PH than did AHI in individuals with COPD and OSA. In addition, they demonstrated that co-occurrence of COPD and severe OSA has a synergistic effect on cardiovascular events and mortality.

Although our results suggested that apnea-hypopnea was an independent risk factor for PH in patients with COPD, this observation is still controversial. In this present study, we found that AHI and oxygen desaturation index (ODI) did not differ between the groups. This might be explained by the fact that patients with COPD were more likely to experience hypoxemia at night. An increase in upper respiratory resistance during night sleep in patients with COPD is almost always accompanied by hypoxemia. Therefore, hypoxemia occurs with apnea-hypopnea in COPD. Previous studies found the primary determinant of oxygen desaturation during repetitive airway obstruction was the duration of obstruction rather than the number of obstructions, and that hypoxemia was a main factor in elevating PAP.[44] However, repetitive airway obstruction can cause repeated negative changes in intrathoracic pressure, which can lead to increased intrathoracic venous reflux, resulting in right ventricular hypertrophy and PH. A systematic review and meta-analysis showed that patients with OSA exhibited right ventricular dilatation, increased wall thickening, and altered RV function. [45] Repetitive airway obstruction can also cause microarousal and changes in sleep structure. The average PAP during rapid eye movement (REM) sleep is higher than that during non-REM sleep.[46,47] The increase in sympathetic nerve excitation and catecholamine secretion caused by apnea-hypopnea, as well as inflammation, oxidative stress, and endothelial dysfunction caused by intermittent hypoxia have been suggested to play a role in the pathogenesis of PH in OSA.

Our study has a few limitations. This study was cross-sectional, and we did not observe the compliance and efficacy of positive pressure ventilation therapy in patients with COPD with OSA. We failed to diagnose OSA using polysomnography, and could not assess the quality and stage of sleep in patients with COPD. Compared with polysomnography, the ApneaLink device is a simple, easy-to-use and reliable device with high sensitivity and specificity in calculating AHI. Apnea Link has been shown to underestimate and overestimate the AHI of OSA patients;[16,48] however, we used AHI ≥10 events/h as a criterion for diagnosing OSA to reduce errors. In recent years, echocardiography has been recommended as a first non-invasive screening and diagnostic technique for PH.[18] The accuracy of Doppler echocardiography in evaluating PAP has been verified using right heart catheterization. Patients with TRV-estimated elevated PAP have an intermediate or high risk of PH. This study can help in diagnosis and treatment of these patients with COPD in a timely manner.

In conclusion, we observe that patients with COPD have a high prevalence of OSA. COPD with OSA patients are more susceptible to PH, which is associated with declining lung function and increased OSA severity. The severity of airflow obstruction, apnea-hypopnea and nocturnal hypoxia play important roles in the pathogenesis of PH in patients with COPD. Our observations can help understand the clinical and physiologic characteristics of individuals with COPD, with and without OSA and to identify suspected PH in COPD. Moreover, OSA and nocturnal hypoxemia deserve attention in elderly patients with COPD. The effect of the interaction between COPD and OSA on PH needs further confirmation. Furthermore, whether sleep apnea can promote PAP, or whether this interaction is bidirectional needs further study.

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Conflicts of interest

None.

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