Nocturnal hypoxia in patients with idiopathic pulmonary arterial hypertension

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Abstract
Background: Sleep-disordered breathing causes a variety of cardiovascular complications and increases the risk of a poor prognosis in patients. There is still some controversy regarding the clinical diagnosis and treatment of sleep-disordered breathing in patients with pulmonary hypertension. The aim of this study was to determine the incidence of desaturation in idiopathic pulmonary arterial hypertension (IPAH) patients, evaluate the effect of desaturation on the clinical status of patients with IPAH, and identify possible influencing factors.

Methods: Patients with IPAH diagnosed by right heart catheterization who underwent overnight cardiorespiratory monitoring from January 2018 to July 2019 were enrolled. Nocturnal hypoxic time was defined as the time that oxygen saturation remained below 90%. Desaturation was defined as a nocturnal oxygen saturation level less than 90% for more than 10% of the total recording time. Baseline clinical characteristics and parameters were collected to compare IPAH patients with and without desaturation. In addition, logistic regression was performed to identify possible factors associated with desaturation in IPAH patients.

Results: Fifty patients with IPAH were included. Among them, 17 patients presented desaturation. Patients with desaturation were older, had a shorter six-min walking distance (6MWD), had a higher mean right atrial pressure, and had a lower daytime arterial oxygen partial pressure than patients without desaturation, and there were significant differences in the VE/VCO2 and VE/VCO2 slope (P < 0.05). The multivariate logistic regression analysis indicated that the 6 MWD (OR = 0.971, 95% CI: 0.948–0.994, P = 0.013) and; VE/VCO2 slope (OR = 1.095, 95% CI: 1.010–1.307, P = 0.032) were independently associated with desaturation after adjusting for age, sex, and body mass index.

Conclusion: Nocturnal hypoxia is common in IPAH patients. Desaturation may aggravate the clinical situation of patients with IPAH. In IPAH patients, a poor exercise capacity (6 MWD) and the VE/VCO2 slope can predict desaturation after adjusting for age, sex, and body mass index.

Keywords
nocturnal hypoxia, desaturation, idiopathic pulmonary arterial hypertension

Study background
Pulmonary hypertension (PH) refers to a clinical syndrome of involving pulmonary vascular structural and functional changes caused by various etiologies, leading to a progressive increase in pulmonary vascular resistance, eventually causing right ventricle failure and even death. Its etiology is complex, and its clinical manifestations are diverse, with a high rate of misdiagnosis and mortality. The prognoses of patients with advanced severe pulmonary hypertension (PH) are generally very poor; once the condition advances, conventional cardiovascular treatment is ineffective, and can even aggravate the condition, which is a very significant problem in clinical practice.1 According to a French study,
the intensive care unit (ICU) admission mortality reached 41% in patients with pulmonary arterial hypertension (PAH). In recent decades, advances in targeted drug therapy have greatly improved the prognosis of PAH. Because of improved diagnosis methods, there has been a significant increase in the number of patients with PH. However, the United States Registry to Evaluate Early and Long-term pulmonary and Arterial Hypertension Disease Management (REVEAL registry) reported that: the 5-year survival rate of patients with PAH was still only 61.2%. Many studies have shown that nocturnal hypoxemia is very common in patients with PH and is associated with disease progression, but the mechanism remains unclear. Data on the relationship between IPAH and nocturnal hypoxemia are still lacking. To investigate whether nocturnal hypoxemia has an effect on patients with IPAH and its associated factors, we conducted a single-center study including patients with IPAH diagnosed by RHC and explored the mechanisms associated with nocturnal hypoxia in patients with IPAH.

Study methods

This single-center study was conducted at Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences. The study was conducted with the approval of the Ethics Committee of Fuwai Hospital. Written informed consent was obtained from all the participants.

Study sample

Data were collected consecutively from hospitalized patients diagnosed with IPAH by RHC between January 2018 and July 2019. All enrolled patients underwent respiratory polygraphy and presented a stable clinical state. Respiratory polygraphy examinations were performed before or after RHC at intervals not exceeding seven days. Based on the respiratory polygraphy results, the participants were divided into two groups: the IPAH without desaturation and combined desaturation groups. The exclusion criteria were as follows: (1) patients with other types of PH; (2) patients aged less than 18 years; (3) patients with chronic liver or renal insufficiency, defined as liver enzymes more than three times the normal value and a creatinine clearance rate <30 ml/min; (4) patients with life-threatening arrhythmia; (5) patients with sleep times less than 2 h; (6) patients aged >75 years, or patients with the presence of FEV1 <60% of the predicted value for obstructive or restrictive pulmonary dysfunction; and (7) patients with a BMI ≥35 kg/m² or patients with a previous diagnosis of sleep-disordered breathing.

Patient assessment

The baseline clinical characteristics of each subject, including age, gender, BMI, smoking history, six-min walk distance (6 MWD), World Health Organization functional class (WHO FC), comorbid conditions, and medication history, were collected separately. In addition, fasting venous blood was collected on admission to evaluate N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP), and high-sensitivity C-reactive protein (hs-CRP) levels. Oxygen partial pressure (PaO₂), carbon dioxide partial pressure (PaCO₂), and peripheral capillary oxygen saturation (SpO₂) were determined by arterial blood gas tests. Echocardiography and pulmonary function testing was performed on each patient before RHC. The diastolic left ventricular diameter was measured in the left ventricular long-axis view, and the diastolic right ventricular diameter was measured in the apical four-chamber view. When there was no transvalvular gradient or right ventricular outflow tract gradient, the systolic pulmonary arterial pressure (SPAP) equaled right ventricular systolic pressure (RVSP). The systolic right ventricular pressure was reliably estimated from the peak tricuspid regurgitation velocity, combined with the right atrial pressure (RAP) level, using the simplified Bernoulli equation: RVSP = 4 (peak tricuspid regurgitation jet velocity) + RAP. In addition, the ejection fraction (EF) was assessed using the Simpson biplane method. All the subjects underwent RHC to obtain baseline hemodynamic parameters, i.e. mean right atrial pressure (MRAP), mean pulmonary artery pressure (MPAP), cardiac index (CI), and pulmonary vascular resistance (PVR).

Cardiorespiratory study

Each enrolled IPAH patient underwent overnight cardiorespiratory recording using an Embletta system (Medcare Flaga, Reykjavik, Ireland) at the sleep center of Fuwai Hospital. The device recorded nasal airflow, finger pulse oximetry, thoracoabdominal movements, body position, and snoring. According to the American Academy of Sleep Medicine (AASM) Manual for Scoring Sleep and Related Events, sleep apnea is defined as a complete cessation of oronasal respiratory airflow during sleep or a decrease of more than 90% from baseline and lasting for more than 10 s. Hypopnea is defined as a decrease in respiratory airflow intensity during sleep of more than 30% from baseline, accompanied by a decrease in oxygen saturation ≥3% from baseline. If the apnea-hypopnea index (AHI) was ≥5/h, sleep apnea was diagnosed. If the apnea event was accompanied by the cessation of respiratory movement in the chest and abdomen, it was considered central apnea; otherwise, it was considered obstructive sleep apnea (OSA). OSA was diagnosed if the obstructive AHI was ≥5/h and the central apnea event accounted for <50% of the apnea event; central sleep apnea (CSA) was diagnosed if the central apnea event was >50%. OSA-related PH belongs to WHO Group III PH. Nocturnal hypoxic time was defined as the total time that the patient’s fingertip SpO₂ remained below 90% during sleep respiratory monitoring.
Desaturation was considered to be present if oxygen saturation was <90% for more than 10% of the total recording time according to nocturnal oximetry.

**Cardiopulmonary exercise test**

All the consecutively enrolled patients with newly diagnosed IPAH underwent cardiopulmonary exercise testing (CPET) (Cosmed S.R.L., Rome, Italy). The operational criteria for cardiopulmonary exercise were as follows: 3 min of rest, then 3 min of idling, followed by increments of 5–20 W (depending on the patient’s exercise capacity) until the patient reached a symptom-limited maximal exercise state. Respiratory gas exchange, including oxygen uptake, carbon dioxide output and minute ventilation, was continuously measured throughout the trial. The patient’s heart rate, ECG output, and oxygen saturation were also continuously monitored. Blood pressure was measured every 3 min and at the end of exercise. Peak oxygen uptake (peak VO2) was defined as the maximal oxygen uptake over a 30-s period at maximal exertion during the continuous incremental power test. Minute ventilation/carbon dioxide output at the anaerobic threshold (VE/VCO2) was defined as the ratio of required ventilation (VE) per 1 L of CO2 expelled at the anaerobic threshold.

**Statistical analysis**

The continuous variables are presented as means ± standard deviations or percentages, and the categorical variables are presented as counts or percentages. For the continuous variables, the mean comparisons of two independent samples conforming to normal distributions were analyzed by two independent samples t-tests, and categorical variables were analyzed by Chi-square tests; a P-value <0.05 was considered significantly. A logistic regression analysis was also used to explore the factors associated with prolonged nocturnal hypoxia in IPAH patients. All data were analyzed by SPSS 22.0 software.

**Patient characteristics**

A total of 82 patients were newly diagnosed with IPAH and presented a stable clinical status. At the time of this study, they were in stable condition and had been on the same therapy for at least one month. Among them, 70 patients underwent overnight cardiorespiratory monitoring before or after RHC. Finally, a total of 50 patients with complete sleep data were enrolled. The baseline clinical characteristics of IPAH patients with and without desaturation were compared, as shown in Table 1; IPAH patients with desaturation were older (39.71 ± 7.43 years vs 29.09 ± 8.13 years, P = 0.003) and had a shorter 6MWD (329.43 ± 52.20 m vs. 463.39 ± 97.81 m, P = 0.001) than IPAH patients without desaturation. The other characteristics did not differ between the two groups.

| Variable                  | IPAH with desaturation (n = 17) | IPAH without desaturation (n = 33) | P value |
|---------------------------|---------------------------------|-----------------------------------|---------|
| Clinical parameters       |                                 |                                   |         |
| Age(years)                | 39.71 ± 7.43                    | 29.09 ± 8.13                      | 0.003   |
| Females                   | 12(70.59%)                      | 26 (78.79%)                       | 0.681   |
| BMI (kg·m⁻²)              | 22.82 ± 3.36                    | 22.53 ± 3.18                      | 0.827   |
| 6-MWD (m)                 | 329.43 ± 52.20                  | 463.39 ± 97.81                    | 0.001   |
| WHO FC I/II/III/IV        | 2/5/10/0                        | 2/11/20/0                         | 0.502   |
| HR (beats/min)            | 84.57 ± 11.62                   | 79.76 ± 13.82                     | 0.397   |
| SBP (mmHg)                | 116.14 ± 17.30                  | 109.82 ± 11.98                    | 0.248   |
| DBP (mmHg)                | 75.14 ± 10.38                   | 71.27 ± 8.78                      | 0.248   |
| Comorbidities             |                                 |                                   |         |
| Coronary heart disease    | 0                               | 0                                 | 1       |
| Diabetes mellitus         | 1                               | 3                                 | 0.65    |
| Systemic hypertension     | 1                               | 6                                 | 0.196   |
| Dyslipidemia              | 1                               | 3                                 | 0.144   |
| Drug therapy              |                                 |                                   |         |
| Targeting medication      | 0/7/10                          | 0/11/22                           | 0.871   |
| (none/single/combination) |                                 |                                   |         |
| Positive inotropes        | 3                               | 5                                 | 0.44    |
| Diuretics                 | 10                              | 13                                | 0.216   |

Note: Continuous variables are presented as mean ± SD. Categorical variables are given as counts.

**Laboratory, hemodynamic, and echocardiographic examinations**

Table 2 compares laboratory, hemodynamic, and echocardiographic parameters between the two groups. The MRAP was higher in IPAH patients with desaturation (10.00 ± 6.81 mmHg vs. 5.06 ± 3.18 mmHg, P = 0.007). There were no significant differences in other parameters.

**Pulmonary function, arterial blood gas and sleep studies**

Table 3 compares the pulmonary function, arterial blood gas, and sleep study data between the two groups and shows that the pulmonary function of IPAH patients with and without desaturation was similar. However, IPAH patients with desaturation had a lower PaO2 (61.95 ± 10.51 mmHg vs. 77.92 ± 12.10 mmHg, P = 0.005), a lower mean SpO2 (89.23 ± 1.76 % vs. 94.25 ± 1.90 %, P < 0.001), a higher VE/VCO₂ (49.74 ± 14.31 vs. 40.68 ± 7.73, P = 0.023), and a higher VE/VCO₂ slope (59.15 ± 29.30 vs. 41.08 ± 10.99, P = 0.014) than IPAH patients without desaturation.

Table 1. Baseline clinical characteristics of all participants.
Possible factors associated with prolonged nocturnal hypoxia in IPAH patients

After adjustments for age, sex, and BMI in the logistic regression analysis, the 6-MWD (OR: 0.985, 95% CI: 0.973-0.996, \( P = 0.009 \)), MRAP (OR: 1.286, 95% CI: 1.040-1.590, \( P = 0.020 \)), \( \text{PaO}_2 \) (OR: 0.904, 95% CI: 0.830-0.984, \( P = 0.019 \)), \( \text{VE/VCO}_2 \) (OR: 1.010-1.307, \( P = 0.032 \)) and \( \text{VE/VCO}_2 \) slope (OR: 1.065, 95% CI: 1.003-1.142, \( P = 0.028 \)) were associated with desaturation in IPAH patients (Table 4). To further determine which factors were the most important in IPAH combined with desaturation, a multivariate logistic regression analysis was performed; it showed that the 6-MWD (OR: 0.971, 95% CI: 0.984-0.994, \( P = 0.013 \)) and \( \text{VE/VCO}_2 \) (OR: 1.095, 95% CI: 1.010-1.307, \( P = 0.032 \)) had the strongest associations (Table 5).

Discussion

Our study demonstrated a high incidence of desaturation in patients with IPAH, as desaturation was present in 34% (17/50) of the patients. Desaturation was defined as a nocturnal \( \text{SpO}_2 \) level below 90% for more than 10% of the sleep duration. Earlier studies reported that sleep-disordered breathing was an important risk factor for a variety of cardiovascular and metabolic diseases, with a high prevalence in patients with PH.

Silvia et al. analyzed 38 patients with PH (mainly IPAH), congenital heart disease, and chronic thromboembolic pulmonary hypertension (CTEPH). When an AHI/21 ≥10/h was defined as the cut-off value, 11% of the patients with PH presented OSA and 68% of the patients presented nocturnal hypoxemia. Minai et al. performed nocturnal oximetry tests on 43 patients with IPAH and PAH associated with connective tissue diseases and found that nocturnal hypoxemia was present in 69.8% of the patients; and that the nocturnal hypoxia group had a higher BNP, higher mean RAP, higher mean PAP, higher PVR, and lower CI than the no hypoxia group, suggesting that nocturnal hypoxemia is associated with the progression of PH and the dysregulation of right ventricular function.4 Florian et al.5 showed that nocturnal hypoxemia is common in PAH and CTEPH patients and

### Table 2. Laboratory, hemodynamic, and echocardiographic parameters of all participants.

| Variable                      | IPAH with desaturation (n = 17) | IPAH without desaturation (n = 33) | \( P \) value |
|-------------------------------|---------------------------------|-----------------------------------|---------------|
| Laboratory parameters         |                                 |                                   |               |
| NT-pro BNP (pg·mL\(^{-1}\))   | 1244.29 ± 2298.35               | 987.86 ± 1182.94                  | 0.466         |
| CRP (mg·L\(^{-1}\))           | 4.42 ± 2.93                     | 3.84 ± 4.79                       | 0.762         |
| Hs-CRP (mg·L\(^{-1}\))        | 3.13 ± 3.38                     | 2.40 ± 3.03                       | 0.57          |
| MRAP (mmHg)                   | 10.00 ± 6.81                    | 5.06 ± 3.18                       | 0.007         |
| MRVP (mmHg)                   | 12.29 ± 5.47                    | 9.15 ± 5.50                       | 0.179         |
| SPAP (mmHg)                   | 98.43 ± 24.17                   | 121.42 ± 180.87                   | 0.741         |
| DPAP (mmHg)                   | 45.29 ± 7.65                    | 39.55 ± 15.85                     | 0.359         |
| MPAP (mmHg)                   | 62.14 ± 14.24                   | 56.57 ± 20.99                     | 0.509         |
| PCWP (mmHg)                   | 9.17 ± 3.66                     | 7.80 ± 3.88                       | 0.433         |
| \( Q_p \) (L/min)             | 3.63 ± 1.06                     | 4.25 ± 0.98                       | 0.144         |
| \( Q_s \) (L/min)             | 3.77 ± 1.06                     | 4.82 ± 1.34                       | 0.063         |
| CI (L·min\(^{-1}·m^2\))      | 1537.87 ± 691.27                | 1144.02 ± 508.97                  | 0.09          |
| Echocardiographic parameters  |                                 |                                   |               |
| Left ventricular ejection fraction | 66.00 ± 4.93                 | 62.53 ± 4.41                      | 0.071         |
| Diastolic left auricle diameter (mm) | 30.29 ± 3.86              | 28.64 ± 3.00                      | 0.216         |
| Diastolic left ventricle diameter (mm) | 35.29 ± 5.38             | 36.21 ± 6.17                      | 0.715         |
| Diastolic right ventricle diameter (mm) | 32.57 ± 8.44            | 31.70 ± 5.59                      | 0.734         |
| VTR (m/s)                     | 3.92 ± 0.75                     | 17.07 ± 73.87                     | 0.669         |
| PTR (mmHg)                    | 58.07 ± 32.44                   | 71.81 ± 28.90                     | 0.299         |

Note: Data are presented as mean ± SD or median (interquartile range).

IPAH: idiopathic pulmonary arterial hypertension; NT-pro BNP: N-terminal pro-brain natriuretic peptide; CRP: C reactive protein; Hs-CRP: high sensitive C reactive protein; MRAP: mean right atrium pressure; MPAP: mean pulmonary arterial pressure; SPAP: systolic pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; VTR: the speed of tricuspid regurgitation; PTR: the pressure difference of tricuspid regurgitation.
reflects disease severity, even when their daytime SpO2 is normal.

Fadia et al. also showed that nocturnal hypoxemia and sleep apnea were very common in patients with PH. A multivariate logistic regression analysis suggested that symptoms did not predict the occurrence of nocturnal hypoxemia, while FEV1 25%–75% (OR: 0.9519, 95% CI: 0.9089–0.9968, \( P = 0.036 \)) and MPAP (OR: 1.1068, 95% CI: 1.0062–1.2175, \( P = 0.037 \)) indicated the condition of nocturnal hypoxemia, although the related mechanism remains unclear.6 Minai et al.7 showed that nocturnal hypoxia was
prevalent in patients with PH, and patients in the nocturnal hypoxia group tended to have higher NT-proBNP concentrations, total pulmonary resistance and mean PAPs, and lower CIs than patients in the no hypoxia group.

The different studied patient populations may account for the differences in the results. Considering that the leading causes of nocturnal hypoxia associated with different types of PH may very considerably, our study included only patients with IPAH; patients with this type of PH are usually young and female, so the incidence of nocturnal hypoxia was relatively low in IPAH patients.

Nocturnal hypoxia stimuli include pulmonary vasoconstriction, symptomatic activation, inflammation and oxidative stress secondary to OSA, and hypoxia promotes pulmonary vascular remodeling.8

When we compared patients with and without desaturation, after adjusting for age, sex, and BMI, we found that the condition of desaturation was a risk factor for a decreased 6MWD, increased MRAP, and decreased carbon dioxide ventilatory efficiency during CPET in patients with IPAH.

The exact mechanism of desaturation in patients with IPAH is not clear. A low CI, and high RAP may confer a worse prognosis; this result has been confirmed by several studies.9–11 Peak oxygen consumption primarily reflects the amount of oxygen available to the body and can independently predict clinical deterioration but no death in patients with IPAH.12 Our study suggests that desaturation may also be a factor in predicting a worse prognosis in patients with PH. More precise mechanisms need to be confirmed in future studies.

Sleep apnea disturbs normal autonomic function, hemodynamic regulation and sleep architecture during sleep, and neuroendocrine changes, such as sympathetic stimulation and activation of the renin-angiotensin-aldosterone system, causes pathophysiological changes such as oxidative stress, an inflammatory response, impaired vascular endothelial function, insulin resistance, reduced heart rate variability and increased blood pressure variability, and promotes the development of cardiovascular diseases. Chronic hypoxia promotes the proliferation and remodeling of the pulmonary arteries, which in turn leads to a series of pathophysiological changes associated with PH.13–15 A variety of causes, such as hypopnea during sleep, changes in pulmonary ventilation and blood perfusion, and partial alveolar hypoventilation, can lead to the development of nocturnal hypoxia. Fadia et al.6 demonstrated that in IPAH and CTEPH patients, 76% presented ventilation/perfusion (VA/VQ) mismatch, and the occurrence of nocturnal hypoxia was most likely related to VA/VQ mismatch and could be associated with or independent of apnea events.6

Studies have suggested that long-term oxygen therapy may partially delay the progression of PH in patients with COPD. However, the pulmonary arterial pressure rarely returns to complete normality, and often leaves irreversible structural abnormalities.16 Calcium channel blockers (CCBs) are not recommended in patients with interstitial lung disease. On the one hand, CCB inhibits the constriction of blood vessels caused by low oxygen, which in turn damages gas exchange, on the other hand, there is no evidence of long-term application.17 However, our study did not investigate whether IPAH could be alleviated after the correction of nocturnal hypoxemia. Large, prospective cohort studies are needed to further explore these issues.

Nocturnal hypoxia is difficult to detect with a routine blood gas analysis on admission due to patients’ possible lack of typical complaints, such as snoring, daytime drowsiness, etc. Chronic hypoxia may aggravate a patient’s cardiac impairment. Most clinicians do not perform polysomnography or respiratory polygraphy if the patient does not have the typical complaint of daytime sleepiness, which may result in a significant underestimation of nocturnal hypoxia. According to our study, a correlation between nocturnal hypoxia and the severity of PH cannot be identified at present. However, our study indicates that chronic oximetry monitoring should be routinely performed in patients with IPAH. As in previous studies,4,18 we suggest that patients with advanced age and a high BMI, especially men with PH, should undergo polysomnography to determine the presence of OSA and nocturnal hypoxia.

Limitation
Due to the low incidence of IPAH, the sample size in our study was small, and selection bias is inevitable in prospective studies. In addition, we did not follow the patients, so we could not determine the effect of desaturation on the long-term survival of patients with IPAH. It was also not possible to determine whether the presence of nocturnal hypoxia had an effect on the therapeutic efficacy of targeted drugs. Furthermore, our study did not investigate whether IPAH could be alleviated after the correction of nocturnal hypoxemia. Large, prospective cohort studies are needed to further explore these issues.

Conclusion
In conclusion, nocturnal hypoxemia has a high incidence in patients with IPAH. Desaturation may aggravate IPAH to some extent, and a decreased 6MWD and reduced efficiency in carbon dioxide ventilation predicted the presence of nocturnal hypoxemia. It may be important to identify and treat patients with IPAH with nocturnal hypoxemia. The clinical significance of IPAH with nocturnal hypoxia still requires further investigation.

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Authors’ contributions
Lu Yan designed the overall project, drafted, and revised the manuscript, Zhihong Liu critically reviewed and revised the
Conflict of interest
The author(s) declare that there is no conflict of interest.

Consent to publish
All authors have approved to publish this manuscript on the journal: Pulmonary Circulation.

Ethical statement
The study was performed with the approval of Fuwai Hospital Ethics Committee (No.2009215). Written Informed Conferences of all participants were obtained.

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