Sleep-disordered breathing in adults with precapillary pulmonary hypertension: Prevalence and predictors of nocturnal hypoxemia

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Research Article

Keywords: Sleep-disordered breathing, Polysomnography, Pulmonary hypertension, Nocturnal hypoxemia

Posted Date: April 19th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1564273/v1

Abstract

Purpose

To evaluate the frequency of sleep-disordered breathing (SDB) and predictors of the presence of nocturnal desaturation in adults with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

Methods

Outpatients with a hemodynamic diagnosis of precapillary pulmonary hypertension who underwent portable polysomnography were evaluated. Diagnosis and severity of SDB were assessed using three well-established respiratory disturbance index (RDI) thresholds: 5.0/h, 15.0/h, and 30.0/h, while nocturnal hypoxemia was defined by the average oxygen saturation (SpO_2) < 90%. Multiple linear regression analysis evaluated the potential relationships among explanatory variables with the dependent variable (average SpO_2 values), with comparisons based on the standardized regression coefficient (β). The R-squared (R^2; coefficient of determination) was used to evaluate the goodness-of-fit measure for the linear regression model.

Results

Thirty-six adults were evaluated (69.4% females). The majority of the participants (75.0%) had SDB (26 with obstructive sleep apnea [OSA] and one with central sleep apnea [CSA]); while 50% of them had nocturnal hypoxemia. In the linear regression model (R^2 = 0.391), the mean pulmonary artery pressure [mPAP] (β: -0.668; p = 0.030) emerged as the only independent parameter of the average SpO_2.

Conclusion

Our study found that the majority of the participants had some type of SDB with a marked predominance of OSA over CSA, while half of them had nocturnal desaturation. Neither clinical and hemodynamic parameters nor the RDI was a predictor of nocturnal desaturation, except for mPAP measured during a right heart catheterization, which emerged as the only independent and significant predictor of average SpO_2.

Introduction

Pulmonary hypertension (PH) is a serious hemodynamic condition that can co-develop in several diseases or can be idiopathic and is associated with high morbidity and mortality [1, 2]. The presence of PH is usually confirmed by performing right heart catheterization (RHC), with a mean pulmonary artery

pressure (mPAP) > 20 mmHg having been recently adopted as the diagnostic criterion [3]. According to the pathophysiological mechanism, PH is currently classified according to the World Health Organization into 5 sub-groups: Group 1: Pulmonary arterial hypertension (PAH); Group 2: PH associated with left heart disease; Group 3: PH associated with pulmonary and/or hypoxemic diseases; Group 4: PH associated with pulmonary artery obstruction, and Group 5: PH due to an unknown or multifactorial mechanism [3]. PAH and chronic thromboembolic pulmonary hypertension (CTEPH) reflect the overall vascular responses aiming to overcome the underlying high resistance within the pulmonary circulation and maintain right ventricular cardiac output [3].

Obstructive sleep apnea (OSA) is the most frequent presentation of sleep-disordered breathing (SDB) and is characterized by the collapse of the upper airway during sleep, resulting in intermittent hypoxemia, increased respiratory effort, and sleep fragmentation [4]. There is growing evidence that OSA plays an important role in the pathogenesis of cardiovascular and metabolic diseases [5, 6], and of increased overall and cardiovascular mortality [7, 8], along with increased healthcare costs [9, 10]. A Brazilian study conducted in the city of São Paulo that included 1,042 volunteers who were representative of the city population showed that 32.8% suffered from OSA [11]. More recent estimates suggest that nearly one billion people may be affected worldwide, with around 425 million individuals aged between 30 and 69 years suffering from moderate-to-severe OSA [12]. The gold standard for the diagnosis of OSA consists of an in-laboratory polysomnographic test (PSG); however, PSGs are not widely available for a large number of individuals with suspected OSA in countries with limited financial resources, such as Brazil [4].

Despite limited evidence to date, SDB is probably more prevalent in patients with PAH and CTEPH than in the general population [13–19]. Interestingly, patients with idiopathic PAH (Group 1) are usually women and are not necessarily obese [20], and such demographic characteristics fundamentally differ from the usual patients being referred to a sleep laboratory with suspected OSA [21]. Such discrepancies may therefore hamper the clinical recognition of PAH patients at risk of SDB, and reduce the screening of SDB among PAH patients [22]. Since SDB (including OSA) leads to intermittent nocturnal hypoxemia, increased intrathoracic pressure swings with associated hemodynamic changes, and increased sympathetic activity, the presence of SDB can further compromise cardiovascular function in PAH patients [23]. A previous study showed that the presence of nocturnal hypoxemia, but not the occurrence of SDB, was associated with poorer survival in patients with PAH [20]. In addition, routine treatment with continuous positive airway pressure (CPAP) among PH patients suffering from SDB resulted in a beneficial, albeit modest reduction in pulmonary arterial pressure levels [23–25].

Considering that studies evaluating the prevalence of SDB in adults with PAH and CTEPH are surprisingly scarce, in addition to the fact that, to date, there are no studies in Brazil evaluating the prevalence of SDB in these patients, our main objectives were to estimate the prevalence of SDB in adult outpatients with precapillary PH diagnosis (World Health Organization Groups 1 or 4) and to evaluate predictors of nocturnal hypoxemia in this population.

Methods

A cross-sectional study was carried out at the *Instituto de Doenças do Tórax* of the *Universidade Federal do Rio de Janeiro* from June 2021 to December 2021. Inclusion criteria were adult individuals (age ≥ 18 years) with a hemodynamic diagnosis of precapillary PH (World Health Organization Groups 1 or 4) who underwent a home sleep apnea test [HSAT] in a single night. Subjects were excluded for any of the following reasons: previously diagnosed OSA receiving CPAP treatment, technically inadequate HSAT (total recording time < 240 minutes), nocturnal use of supplemental oxygen, and any individual who did not sign the informed consent form. In addition, eligible patients who were clinically unstable (New York Heart Association class IV) or had been hospitalized in the month preceding the HSAT were also excluded.

Clinical, demographic, and anthropometric data were systematically collected by one researcher (M.S.M.) using a standardized form on the same day of the HSAT. Subject characteristics included clinical data and self-reported comorbidities (hypertension and excessive daytime sleepiness [EDS]). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). Neck circumference (NC) was measured using a 150-cm tape measure, with all participants in the sitting position, with the upper edge of the measuring tape positioned below the laryngeal prominence and applied perpendicularly to the long axis of the neck. Epworth Sleepiness Scale (ESS), an 8-item questionnaire that assesses the subjective likelihood of falling asleep in various settings was completed: a score ≥ 11 (from 0 to 24 points) was considered indicative of the presence of EDS [26]. The ESS has already been validated for use in the Brazilian population [27].

The research project was conducted in accordance with the Declaration of Helsinki and was previously approved by the Ethics Committee of the *Universidade Federal do Rio de Janeiro* (CAAE:44429421.5.0000.5257). All study participants gave written informed consent before study enrollment, and the anonymity of each participant was strictly preserved.

Right heart catheterization

A hemodynamic evaluation was performed on all study participants using a Swan-Ganz catheter. The hemodynamic variables collected and used in data analysis included pulmonary capillary wedge pressure (PCWP), mPAP, cardiac output, and pulmonary vascular resistance (PVR). The diagnosis of precapillary PH was based on the finding of mPAP > 20 mm Hg measured directly, in absence of elevated PCWP (PCWP ≤ 15 mm Hg), and with PVR ≥ 3 Wood units [3].

Sleep test

All participants underwent an HSAT (ApneaLink^{TM}AIR, ResMed, San Diego, California, USA) after careful instructions regarding the application of the portable monitor. The HSAT consists of continuous monitoring of airflow through a nasal cannula, thoracic impedance belt, and pulse oximeter. All recording data were manually scored by a board-certified sleep physician (R.L.M.D.) - who was blinded to all clinical data collected by another researcher (M.S.M) - according to a previously published guideline by the American Academy of Sleep Medicine [28]. Obstructive apneas were classified from a drop of ≥ 90%

from baseline in airflow with a persistent respiratory effort lasting at least 10 seconds. Hypopneas were classified from a drop of ≥ 30% from baseline in airflow for ≥ 10 seconds, which were associated with an oxygen desaturation of ≥ 4% [28]. The severity stratification of SDB was defined by three well-established respiratory disturbance index (RDI) thresholds, namely ≥ 5.0/h (any SDB), ≥ 15.0/h (moderate-to-severe SDB), or 30.0/h (severe SDB). In turn, each SDB was classified as OSA, i.e., the predominance of obstructive events over central ones, or as central sleep apnea (CSA) when there was a predominance of central respiratory events in relation to obstructive events [28]. Nocturnal hypoxemia was defined by average oxygen saturation (SpO_2) of less than 90% [20, 31]obtained from continuous records of the pulse oximetry existing in the HSAT.

Statistical analysis

Data analysis was conducted using the SPSS for Windows statistical software package (version 21.0; Chicago, IL, USA). Results were summarized as median and interquartile range (IQR) for continuous variables and as frequencies (n) and respective percentages (%) for categorical variables. Comparisons were performed using the chi-square test or Fisher's exact tests for categorical variables and the nonparametric Mann-Whitney or *Kruskal-Wallis* tests for continuous variables. The correlation among continuous variables was evaluated by Spearman's rank correlation coefficient (r). The presence of collinearity among the continuous variables was excluded if the variance inflation factor (VIF) > 10.0 with tolerance < 0.1. After excluding collinearity, continuous variables that were not normally distributed were log-transformed before being evaluated in the linear regression model. Multiple linear regression analysis evaluated the relationship among possible explanatory variables and the dependent variable (average SpO_2), with comparisons based on the standardized regression coefficient (β). The R-squared (R^2; coefficient of determination) was employed as a goodness-of-fit measure for the linear regression model. All two-tailed tests were considered statistically significant if the p-value < 0.05.

Results

Thirty-six adult subjects were consecutively recruited and included in the final analysis (the flowchart of the study is illustrated in Figure 1). Among the study participants, 31 (86.1%) were classified as Group 1, while the remaining 5 patients (13.9%) had Group 4. Of the 31 patients classified as Group 1 PAH, idiopathic (n = 21), congenital (n = 6), portal hypertension (n = 2), human immunodeficiency virus infection (n = 1), and connective tissue disease (n = 1) accounted for the putative etiologies. All 5 patients in Group 4 had CTEPH. The characteristics of the study participants are summarized in Table 1. Overall, 25 subjects were females (69.4%), with a median age: 49.0 years (IQR: 38.2-57.0) and median BMI: 25.5 kg/m^2 (IQR: 20.7-28.9). Half of the study participants (n = 18; 50%; Table 1) had nocturnal desaturation. Clinical and hemodynamic parameters were similar in patients with or without nocturnal desaturation. Similarly, both RDI and oxygen desaturation index (ODI) values were also similar to those with or without nocturnal hypoxemia (p-values: 0.504 and 0.317; respectively).

Twenty-seven participants fulfilled the criteria for SDB: 26 suffered from OSA and one participant fulfilled the diagnostic criteria of CSA with no evidence of Cheyne-Stokes respiration (male, RDI: 20.7 events/h, and average SpO_2: 89.0%). Overall, the severity of SDB was distributed as follows: mild (n = 19), moderate (n = 4), and severe (n = 4). As illustrated in the Figure 2, the values of the average SpO_2 were not statistically different in no-SDB (n = 9) or SDB subjects (n = 27); p = 0.124. In addition, the average SpO_2 was similar across the three severity levels of SDB (p = 0.185; Figure 2).

Table 2 reports the Spearman rank-order correlation coefficients between oximetry data and RDI values. Baseline SpO_2, nadir SpO_2, and time spent with oxygen saturation under 90% (T90) were significantly correlated with the average SpO_2: r: 0.062 ($p < 0.001$); r: 0.794 ($p < 0.001$), and r: -0.945 ($p < 0.001$); respectively. On the other hand, neither ODI nor RDI were statistically correlated with the average SpO_2: p-values: 0.087 and 0.164; respectively.

Table 3 shows the findings from the multiple linear regression analysis containing nine possible relevant parameters regarding the dependent variable (average SpO_2). In the linear regression model (coefficient of determination [R^2] = 0.391), the mPAP (β: -0.668; 95% CI: -0.259 to -0.015; p = 0.030) emerged as the only significant and independent predictor of the average SpO_2 values. Interestingly, the RDI did not significantly influence the SpO_2 measurements (β: -0.001; 95% CI: -0.149 to 0.049; p = 0.998); Table 3.

Discussion

In the present study of 36 clinically stable patients with precapillary PH, 75.0% were found to suffer from a degree of SDB, with the vast majority of SDB fulfilling the criteria of OSA. Furthermore, 50% of the subjects had evidence of nocturnal hypoxemia. Despite the high prevalence of OSA in the cohort, most patients were classified as having mild OSA, but the prevalence of nocturnal hypoxemia was elevated, regardless of the presence of SDB. Moreover, mPAP values were the only significant and independent predictor of the average SpO_2 values, suggesting that the severity of PH (estimated by mPAP) can infer the presence of sleep hypoxemia. Our findings concur with those of previous studies and show that PH severity is associated with the degree of hypoxemia during sleep [15, 29].

The frequency of SDB in patients with precapillary PH is generally high, with some studies reporting a high prevalence of both OSA and CSA [17, 20, 30], and another suggesting a marked predominance of OSA over CSA [31]. In one cross-sectional study that evaluated 52 subjects with Group 1 PAH, SDB was present in 71% (56% had OSA and 44% CSA) [30]. Similarly, among 38 outpatients with idiopathic PAH (n = 23) or CTEPH (n = 15), a high SDB prevalence was found, with CSA being clearly predominant [17]. However, in another recent study that evaluated 71 patients with precapillary PH (41% males) and 35 matched controls, OSA was detected in 68% of the precapillary PH patients as compared to 5% among controls [31]. Moreover, only 1 PAH patient had CSA (AHI: 12 events/h) without Cheyne-Stokes respiration [31]. Similar to our findings, nocturnal hypoxemia was present in 48% of patients with PAH, and the presence of nocturnal hypoxemia was unrelated to the presence of OSA [31].

We should emphasize that sleep-related hypoxemia is a prevalent disturbance among precapillary PH patients with a widely variable percentage of subjects displaying sleep-related hypoxemia depending on the oximetry-derived criterion used to assess nocturnal desaturation [32, 33]. All such studies, albeit only a few in number, suggest that the presence of nocturnal hypoxemia occurs regardless of the presence of SDB, and when present is frequently associated with a worse prognosis in patients suffering from PAH [20, 32, 33]. In a small cohort of 13 PAH individuals, nocturnal hypoxemia was reported in 10/13 patients [32]. Another study found that 30 of 43 PAH patients exhibited nocturnal desaturation, with those patients with desaturations during sleep also suffering from higher mPAP values and lower cardiac index [34]. In a cohort of 63 individuals with PAH or CTEPH, 63% had nocturnal hypoxemia [35], while in another previous study that included 15 PAH patients, only 2 had sleep apnea, but 8 patients had sleep-related hypoxemia without the presence of sleep apnea [36].

Although hypoxemia during sleep is frequent in precapillary PH, the underlying mechanism still remains unclear. It is usually advanced that ventilation-perfusion mismatch and narrowing of the distal airways, increasing the pulmonary physiologic dead space underlie the higher frequency of hypoxemic events in PAH [36–38]. Of note, the presence of continuous nocturnal hypoxemia, rather than the presence of SDB-related intermittent hypoxemia has been implicated in a poor prognosis among PAH patients [20], possibly because chronic hypoxemia promotes hypoxic pulmonary vasoconstriction and pulmonary vascular remodeling [39]. Notwithstanding, pulse oximetry has been proposed as part of the routine assessment of patients with PAH to detect the presence of nocturnal hypoxemia [34]. However, oximetry alone may not be a sufficiently accurate diagnostic test for identifying SDB in precapillary PH patients [40] because of inadequate discriminatory power when compared to PSG [17].

Our study is not without limitations. First, it was conducted in a single institution, which may limit its generalizability and therefore requires external validation. Second, the sample size was relatively small, which could lead to type 2 beta errors, such that our findings must be considered with caution. Third, all study participants were evaluated with a sleep test on a single night and the possibility of night-to-night variability must be considered. Fourth, the diagnosis of OSA was based on the RDI obtained from an HSAT, which may underestimate the actual prevalence and severity of SDB. Finally, as the hemodynamic parameters were not evaluated in close temporal proximity or concurrently with the HSAT, inferences from the associations between these two sets of measures require caution.

Conclusion

In summary, the majority of precapillary PH patients exhibited the presence of some type of SDB, and more particularly of OSA, the latter not being associated with nocturnal desaturation. The mPAP emerged as the only independent and significant predictor of the average SpO_2 assessed from the HSAT, suggesting that the nocturnal desaturation documented in these patients is likely influenced by the severity of precapillary PH than by the presence of SDB.

Declarations

Funding: *The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.*

Competing Interests: *The authors have no relevant financial or non-financial interests to disclose.*

Author Contributions: *The study conception and design were performed by MSM, RLMD, DW, APC, and FCQM. Material preparation, data collection, and analysis were performed by MSM, RLMD, and DG. The first draft of the manuscript was written by MSM, RLMD, and DG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.*

Ethics approval: *This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Universidade Federal do Rio de Janeiro* (CAAE: 44429421.5.0000.5257).

Consent to participate: All patients provided informed consent.

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Tables

Table 1 Summary of patient characteristics

Parameter	Total (n = 36)	Without nocturnal hypoxemia (n = 18)	With nocturnal hypoxemia (n = 18)	p-value
Clinical data				
Female sex	25 (69.4)	12 (66.7)	13 (72.2)	> 0.999
Age, years	49.0 (38.2-57.0)	47.0 (37.7-54.5)	49.0 (37.7-58.2)	0.739
BMI, kg/m^2	25.5 (20.7-28.9)	25.5 (21.0-28.4)	25.5 (20.4-30.1)	0.739
NC, cm	35.0 (33.0-41.0)	35.0 (33.0-41.5)	35.0 (33.0-41.0)	0.897
EDS	5 (13.9)	2 (11.1)	3 (16.7)	> 0.999
Hypertension	7 (19.4)	4 (22.2)	3 (16.7)	> 0.999
Hemodynamic data				
mPAP, mmHg	52.0 (45.0-69.0)	50.0 (42.5-68.0)	56.5 (49.5-72.7)	0.716
PCWP, mm Hg	10.0 (7.0-13.0)	11.0 (10.0-14.0)	8.5 (5.2-12.2)	0.239
CO, L/min	4.1 (3.0-5.5)	4.1 (2.7-5.2)	4.0 (3.0-5.5)	> 0.999
PVR, Wood units	9.9 (8.0-14.7)	9.0 (7.7-11.4)	12.6 (8.5-17.1)	0.449
HSAT data				
TRT, min	398.0 (341.5-461.0)	399.0 (319.7-474.2)	398.0 (342.5-450.7)	0.739
RDI, n/h	7.1 (4.8-14.4)	6.4 (4.3-8.3)	9.3 (6.1-17.6)	0.504
Baseline SpO_2, %	93.0 (91.0-95.0)	94.0 (93.0-96.0)	92.0 (89.0-94.0)	0.028
Average SpO_2, %	89.5 (88.0-91.0)	91.0 (90.0-92.2)	88.0 (87.0-89.0)	< 0.001
Nadir SpO_2, %	79.5 (76.0-85.0)	85.0 (79.0-87.2)	78.0 (73.7-80.0)	0.020
T90, %	63.0 (32.0-	33.0 (6.0-49.0)	85.0 (69.7-94.0)	<

	85.0)			0.001
ODI, n/h	4.5 (2.2-12.4)	4.1 (1.0-7.0)	8.8 (2.9-15.7)	0.317

Numeric and categorical variables were reported as median (interquartile range) and n (%), respectively. BMI: body mass index; NC: neck circumference; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance; HSAT: home sleep apnea test; TRT: total recording time; RDI: respiratory disturbance index; SpO_2: oxygen saturation; T90: time spent with oxygen saturation under 90%; ODI: oxygen desaturation index at 4%. Excessive daytime sleepiness (EDS) was assessed by the Epworth Sleepiness Scale ≥ 11 points. Nocturnal hypoxemia was assessed by the presence of average oxygen saturation < 90%

Table 2 Correlation between respiratory parameters and average SpO_2 obtained from HSAT (n = 36)

Parameters	Average SpO_2, %	
	Spearman's coefficient (r)	p-value
RDI, n/h	-0.237	0.164
Baseline SpO_2, %	0.662	< 0.001
Nadir SpO_2, %	0.794	< 0.001
T90, %	-0.945	< 0.001
ODI, n/h	-0.289	0.087

HSAT: home sleep apnea test; RDI: respiratory disturbance index; SpO_2: oxygen saturation; T90: time spent with oxygen saturation under 90%; ODI: oxygen desaturation index at 4%

Table 3 Linear regression according to the average SpO_2 as dependent variable (n = 36)

Parameters	Average $SpO_{2,}$ %				
	β	95% CI		t-test	p-value
		Lower	Upper		
Sex	-0.276	-4.806	1.270	-1.234	0.235
Age, years (Log)	-0.103	-0.136	0.090	-0.434	0.670
BMI, kg/m^2 (Log)	-0.273	-0.522	0.241	-0.780	0.447
EDS	-0.078	-5.643	4.253	-0.298	0.770
Hypertension	-0.019	-4.540	4.288	-0.061	0.953
mPAP, mmHg (Log)	-0.668	-0.259	-0.015	-2.376	0.030
PCWP, mm Hg (Log)	0.567	-0.001	0.779	2.132	0.051
CO, L/min (Log)	0.029	-0.871	0.968	0.112	0.912
RDI, n/h (Log)	-0.001	-0.149	0.149	-0.002	0.998

RDI: respiratory disturbance index; SpO_2: oxygen saturation BMI: body mass index; EDS: excessive daytime sleepiness (Epworth Sleepiness Scale ≥ 11 points); mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CO: cardiac output; β: standardized regression coefficient; CI: confidence interval. The neck circumference (NC) and pulmonary vascular resistance (PVR) were excluded from analysis due to collinearity: NC (tolerance: 0.081 and variance inflation factor [VIF]: 12.296) and PVR (tolerance: 0.090 and VIF: 11.132). Logarithmic transformation (Log) was performed on continuous variables with a non-normal distribution. Coefficient of determination (R^2): 0.391

Figures

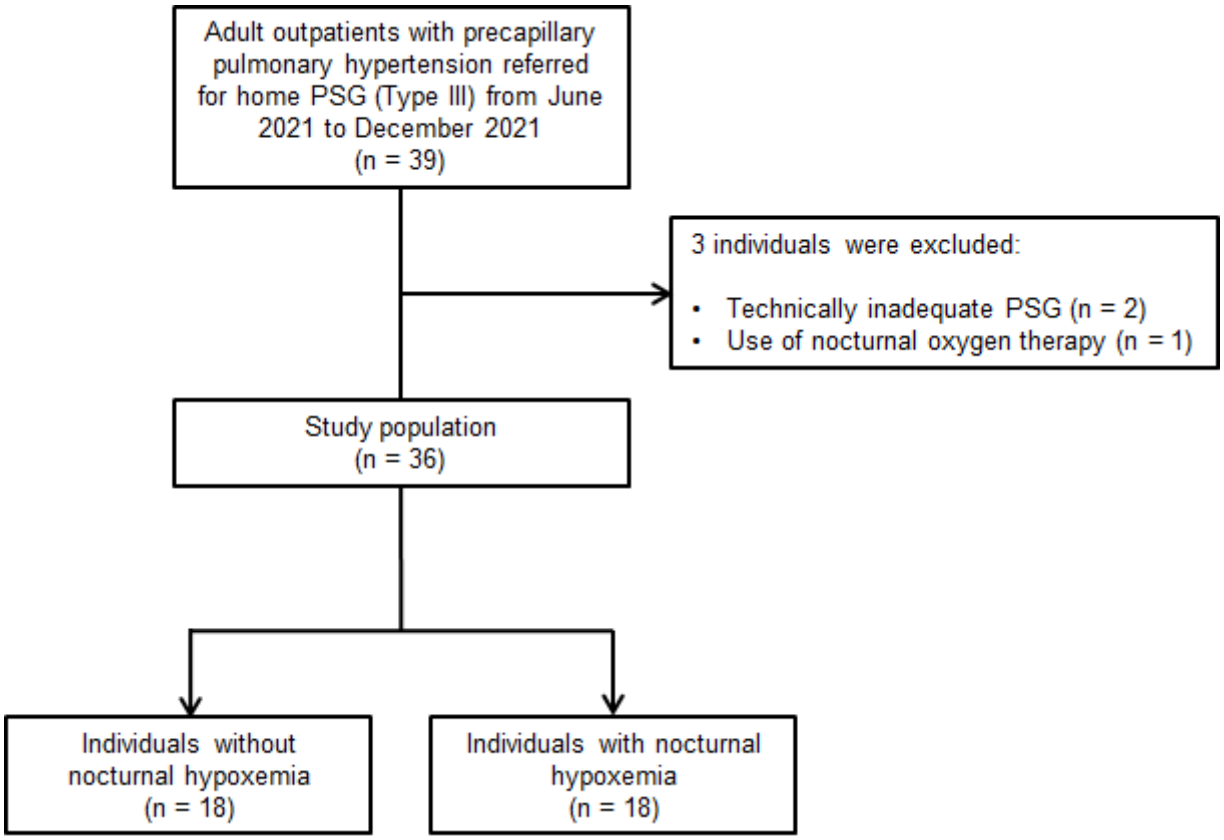

Figure 1

Patient recruitment flowchart. PSG: polysomnography

Figure 2

Boxplot diagram showing the distribution of the average oxygen saturation (SpO_2) according to the presence or absence of sleep-disordered breathing (SDB) [**A**] or based on severity levels of SDB [**B**] on 36 adult patients with precapillary pulmonary hypertension. Diagnosis of SDB was assessed by respiratory disturbance index (RDI) ≥ 5.0/h, while the severity of SDB was categorized by three well-defined RDI thresholds: 5.0/h, 15.0/h, and 30.0/h. The bottom and top of the box represent the lower (25^{th} percentile) and upper (75^{th} percentile) quartiles, respectively, while the horizontal bars indicate the median (50^{th} percentile). The upper and lower bounds of the error bars denote the range. The average SpO_2 was similar in patients with or without SDB (p = 0.124); [**A**]. Similarly, the average SpO_2 was also not statistically different across different severity levels of SDB (p = 0.185) [**B**].