Sleep Disordered Breathing in Group 1 Pulmonary Arterial Hypertension

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Study Objectives: To determine the prevalence and clinical predictors of sleep disordered breathing (SDB) and impact on outcomes in a cohort of patients with WHO group 1 pulmonary arterial hypertension (PAH).

Methods: A retrospective, cross-sectional review of 52 consecutive subjects with known WHO group 1 PAH referred for assessment of possible SDB. Subjects had overnight polysomnography within 6 months of right heart catheterization performed as part of a routine clinical protocol.

Results: SDB was present in 71% of the PAH patients: 56% had OSA and 44% CSA. Older age and subjective sleepiness as assessed by the Epworth Sleepiness Scale score > 10 were predictive of SDB. A high prevalence of OSA occurred

in both male (50%) and female (60%) subjects. No differences in cardiopulmonary hemodynamics or survival between those with and without SDB were observed.

Conclusions: This high prevalence of SDB in the PAH population suggests that systematic screening and testing is important in this group. Further studies are necessary to determine the pathophysiological effect of SDB and potential impact of SDB treatment in this population.

Keywords: Obstructive sleep apnea, central sleep apnea, sleep disordered breathing, pulmonary arterial hypertension, apnea-hypopnea index

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Pulmonary hypertension (PH) is a chronic cardiopulmonary condition defined by an elevated pulmonary artery pressure. It may be a consequence of various etiologies and has diverse pathobiological mechanisms. Sleep disordered breathing (SDB) is a group of ventilatory disorders during sleep which includes obstructive sleep apnea (OSA), central sleep apnea (CSA), and sleep related hypoventilation. SDB is included as one of the potential etiologies of PH.¹ In patients with SDB, the prevalence of pulmonary hypertension (PH) ranges from 17% to 52%.²⁻⁴ The etiology of this PH is considered to occur through mechanisms such as hypoxic vasoconstriction with subsequent vascular remodeling, systemic inflammation, and hypercoagulable states.⁵ However PH in this group of patients is typically not severe.⁶ In patients with pulmonary arterial hypertension (PAH), right ventricular overload, hypertrophy, and dilatation eventually lead to right ventricular failure occurring as a result of increasing pulmonary vascular resistance. While SDB is prevalent in the general population with recent estimates of 20% to 30%, in those with cardiovascular disease, particularly left ventricular failure, there is a higher reported prevalence of 47%.^{7,8} Despite a high prevalence of right ventricular failure in PAH, few studies have evaluated the prevalence of SDB in this condition. Similar to left ventricular failure, SDB could be secondary to the low cardiac output that characterizes patients with PAH. Alternately, SDB may not be causally related, but simply occur as a comorbidity in these patients—many of whom are obese or have other risk factors for SDB.⁶ However in this context, the extent to which SDB contributes to the patient's symptoms, disease progression, or right ventricular failure is

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disordered breathing (SDB) is prevalent in the general and cardiac populations, but there are few studies on those with WHO Group 1 pulmonary arterial hypertension (PAH). The prevalence, clinical determinants, and impact of SDB on this patient cohort are uncertain.

Study Impact: A high prevalence of sleep disordered breathing, in particular obstructive sleep apnea in WHO Group 1 PAH was observed. This study underscores the need for further research in this patient population.

unclear. The objectives of this study were to determine the prevalence and clinical correlates of SDB (both OSA and CSA) in a cohort of patients with known WHO Group 1 PAH and to determine if there was an influence on short-term outcome. These observations will help determine whether prospective or randomized studies should be undertaken to more clearly evaluate the role of SDB in PAH.

METHODS

We conducted a retrospective, single-center review of 52 consecutive patients referred from the PH clinic at our institution for assessment of possible SDB between February 2006 and September 2011. Referral for polysomnography was routine for all patients in whom a prior polysomnogram had not been performed in another institution. PAH was defined and classified according to the WHO guideline¹ prior to the initiation of therapy. Only those subjects with WHO Group 1 disease were

included in the analysis. Group 1 PAH disease includes those with PAH of idiopathic, unknown, or heritable etiology, drug and toxin induced, or associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, chronic hemolytic anemia, or schistosomiasis. It also includes those with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. All eligible subjects had right heart catheterization and clinical assessments including: determination of New York Heart Association (NYHA) functional class, body mass index (BMI), six-minute walk distance (6MWD), 2D-echocardiogram, pulmonary function tests, and brain natriuretic peptide (BNP) performed within 6 months of the polysomnography. These tests were part of the standard clinical evaluation of PH in our institution. Subjects previously treated for or diagnosed with SDB were excluded from the study.

PSG was performed using standard techniques and scoring criteria for sleep stages and arousals from sleep.^{9,10} Thoracoabdominal motion was monitored by respiratory inductance plethysmography and nasal airflow by nasal pressure cannulae (Binaps model 550; Salter Labs, Arvin, CA). Both arterial oxyhemoglobin saturation (SpO_2) and transcutaneous carbon dioxide (SenTec Digital Monitor) (reported as PtcCO_2) were monitored. Signals were recorded on a computerized sleep recording system (Sandman; Nellcor Puritan Bennett Ltd, Ottawa, Canada) and scored by a technician. Obstructive and central apneas were scored as $> 90\%$ reduction of tidal volume for ≥ 10 sec with and without thoracoabdominal motion, respectively. Hypopneas were scored as 50% to 90% reduction in tidal volume from baseline for ≥ 10 sec on nasal pressure signal with an arousal or oxygen desaturation $\geq 3\%$. Obstructive hypopneas were scored if there was out-of-phase thoracoabdominal motion.^{9,11} Central hypopneas were scored if there was an absence of thoracoabdominal paradox. Cheyne-Stokes breathing was scored as per the recent guidelines.⁹ The oxygen desaturation index (ODI) was defined as the number of oxygen desaturations per hour $\geq 3\%$ below baseline. The severity of sleep apnea was assessed by the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]). For the purposes of this study, subjects were divided into no SDB (AHI < 5 events/h of sleep), OSA (AHI ≥ 5 and $\geq 50\%$ of the events obstructive), and CSA (AHI ≥ 5 and $> 50\%$ of the events central). The Epworth Sleepiness Scale (ESS), a subjective measure of daytime sleepiness, was completed on the night of polysomnography. Subjective sleepiness was defined as a score > 10 .

Right heart catheterization was performed following overnight fast. The hemodynamic variables measured at end-expiration included right atrial pressure, pulmonary capillary wedge pressure (PCWP), and mean pulmonary artery pressure (mPAP). Cardiac output was determined by the indirect Fick method. Pulmonary vascular resistance was calculated by dividing (mPAP - PCWP) by cardiac output (unit dynes/cm⁵). Pulmonary function testing and 6MWD testing were performed in all subjects using recommended protocols and techniques.^{12,13} A BNP value > 100 pg/mL is considered elevated. Survival status was obtained through the medical health records with a censor date of January 2013.

The study was approved by the University Health Network, Toronto General Hospital research ethics board (08-1051-BE).

Data Analysis

Differences between groups were assessed using Student t-test for normally distributed continuous variables and the Mann-Whitney-U test for abnormally distributed variables. The χ^2 or Fisher exact test was used to compare nominal variables and one-way analysis of variance with Tukey correction as appropriate. Relationships between single variables were examined by Pearson correlation coefficient. Multivariable relationships between SDB and independent variables were examined by linear regression (enter method), with $p < 0.05$ to enter and $p > 0.1$ to remove. Data were expressed as means $\pm$ SD or No. (%). A p-value of < 0.05 was considered statistically significant. Analyses were performed with the use of SPSS 20.0.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Subjects

During the study period, 152 patients were diagnosed with WHO Group 1 PAH; 52 of these met inclusion criteria and were included in the analyses. There were no significant differences between the mean age (49.4 ± 16 , 48 ± 15 years), BMI (29.6 ± 9.5 , 29.4 ± 9.2 kg/m²), and male to female ratio (1: 1.45, 1:1.5) of the entire cohort of subjects ($n = 152$) and those not included ($n = 100$), respectively. Polysomnography had been performed at other institutions in 60 patients in whom OSA was diagnosed in 42 (70%).

In our studied cohort, the prevalence of SDB (OSA and CSA) in patients with PAH was 71% ($n = 37$), of whom 60% ($n = 31$) had an AHI ≥ 10 and 42% ($n = 22$) had an AHI ≥ 15 . SDB was of moderate severity. Sixty percent ($n = 31$) of subjects had nocturnal oxygen desaturation, defined as $> 10\%$ total sleep time at $< 90\%$ oxyhemoglobin saturation.

The population had a mean age of 53 ± 15 years with a preponderance of females (58%, $n = 30$). They were overweight with a body mass index of 29.6 ± 9.2 kg/m² and had a lack of subjective daytime sleepiness as assessed by ESS (7.3 ± 5.3). Subjects had a mean pulmonary artery pressure of 46.3 ± 20.6 mm Hg and walked a mean of 388.3 ± 133.8 meters on the 6MWT. The majority of subjects had NYHA functional class II ($n = 26$, 50%) or III ($n = 13$, 25%).

At the time of polysomnography, 40% ($n = 21$) of subjects were on treatment for PAH, of whom 16 were treated with an endothelial receptor antagonist, 7 with a phosphodiesterase inhibitor, and 2 with prostacyclin therapy. Four patients were on dual therapy. The median time on medications was 5 months. The majority (46%) of subjects had idiopathic PAH, followed by 25% with congenital heart disease and 21% with connective tissue disease (Table 1). Seven patients were on supplemental oxygen during polysomnography, of whom 5 were diagnosed with OSA with AHI ≥ 10 events per hour.

Of those with SDB, the majority had OSA (56%, $n = 29$). Seventy-six percent ($n = 22$) of subjects with OSA subsequently underwent treatment with positive airway pressure; however, compliance data were not collected on these subjects. Subjects with OSA were significantly older than those with no SDB ($p < 0.05$). Polysomnographic data are presented in Table 2. There were no significant differences in

Table 1—Baseline characteristics

	Total Group (n = 52)	OSA (n = 29)	CSA (n = 8)	NSA (n = 15)
Age (years)	53 ± 15	55 ± 15*	59 ± 13	44 ± 15
Gender				
Male	22 (42.3%)	11 (50.0%)	4 (18.2%)	7 (31.8%)
Female	30 (57.7%)	18 (60.0%)	4 (13.3%)	8 (26.7%)
Body mass index (kg/m ²)	29.6 ± 9.2	30.9 ± 7.6	26.7 ± 6.4	28.4 ± 12.8
Group 1 PH				
IPAH	24 (46.2%)	11 (45.8%)	4 (16.7%)	9 (37.5%)
CTD	11 (21.2%)	8 (72.7%)	1 (9.1%)	2 (18.2%)
HIV	3 (5.8%)	2 (66.7%)	1 (33.3%)	0 (0.0%)
CHD	13 (25.0%)	8 (61.5%)	1 (7.7%)	4 (30.8%)
Group 1' PH				
PVOD	1 (1.9%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

Values are mean ± SD or number (%) as indicated. *p < 0.05 between OSA and NSA group difference by ANOVA. OSA, obstructive sleep apnea; CSA, central sleep apnea; NSA, no sleep apnea; PH, pulmonary hypertension; IPAH, idiopathic pulmonary hypertension; CTD, connective tissue disease; HIV, human immunodeficiency virus; CHD, congenital heart disease; PVOD, pulmonary veno-occlusive disease.

Table 2—Polysomnographic data

	Total Group (n = 52)	OSA (n = 29)	CSA (n = 8)	NSA (n = 15)	p-value*
Epworth sleepiness scale	7.3 ± 5.3	11.3 ± 7.9	5.6 ± 4.1	8.5 ± 4.9	0.013
Sleep efficiency (%)	69.8 ± 19.8	70.5 ± 16.2	59.7 ± 21.3	73.8 ± 24.8	0.258
Sleep onset latency (min)	31.2 ± 54.8	25.3 ± 24.8	24.5 ± 43.1	46.2 ± 91.8	0.459
Stage N1 (%)	12.2 ± 15.8	11.5 ± 12.0	10.9 ± 3.6	14.0 ± 26.6	0.863
Stage N2 (%)	60.7 ± 14.7	63.2 ± 11.3	58.8 ± 13.5	56.9 ± 20.3	0.377
Stage N3 (%)	14.0 ± 10.8	12.9 ± 10.7	15.6 ± 9.8	15.3 ± 11.9	0.721
Stage REM (%)	13.1 ± 8.0	12.3 ± 7.7	14.6 ± 7.9	13.8 ± 8.8	0.711
Arousal index (n/h)	21.5 ± 17.0	23.2 ± 16.2	24.7 ± 3.0	16.8 ± 22.8	0.433
AHI (n/h)	16.5 ± 15.8	21.2 ± 15.8	25.9 ± 13.8	2.4 ± 1.5	< 0.001
Central event index (n/h)	3.5 ± 8.8	0.71 ± 1.6	19.4 ± 14.7†	0.3 ± 0.4	< 0.001
Obstructive event index (n/h)	12.0 ± 14.3	20.5 ± 15.3‡	6.4 ± 3.4	2.0 ± 1.5	< 0.001
Oxygen desaturation index (n/h)	14.6 ± 14.4	19.6 ± 15.9	16.3 ± 11.0	4.1 ± 4.5*	0.003
% TST < 90% O ₂ Sat	37.5 ± 38.8	45.3 ± 39.6	29.4 ± 36.4	26.9 ± 37.2	0.271
Wake SpO ₂ (%)	91.8 ± 4.8	90.9 ± 5.0	92.6 ± 4.1	93.2 ± 4.4	0.275
Mean SpO ₂ (%)	90.3 ± 5.3	89.2 ± 5.7	91.6 ± 4.7	91.8 ± 4.5	0.244
Minimum SpO ₂ (%)	80.6 ± 10.9	77.5 ± 11.9	83.7 ± 10.3	85.4 ± 6.5	0.051
PtcCO ₂ (mm Hg)	40.4 ± 13.4	42 ± 8.7	38.3 ± 18.6	40.9 ± 11.7	0.798
Periodic leg movement index (n/h)	20.1 ± 40.6	17.3 ± 36.2	22.8 ± 41.8	24.1 ± 49.8	0.856

Values are expressed as mean ± SD. *Between group differences (NSA, OSA, CSA); †p < 0.05 vs OSA & CSA; ‡p < 0.05 vs NSA & OSA; §p < 0.05 vs NSA & CSA. OSA, obstructive sleep apnea; CSA, central sleep apnea; NSA, no sleep apnea; AHI, apnea-hypopnea index; TST, total sleep time; SpO₂, oxygen saturation; PtcCO₂, transcutaneous carbon dioxide.

sleep architecture or arousal index between SDB groups. The ODI was significantly lower in the no SDB compared with both the OSA and CSA groups. The CSA was in a Cheyne-Stokes pattern of respiration with a mean total cycle length of 46.6 ± 5.3 seconds. Cardiac and pulmonary function data (**Table 3**) demonstrated no significant between group differences.

The prevalence of SDB did not vary significantly between genders, with OSA rather than CSA more prevalent in both males and females. The mean pulmonary artery pressure and six-minute walk distance were, however, significantly different between males and females (**Table 4**).

Predictors of SDB

Univariate analysis demonstrated a relationship between age ($r^2 = 0.123$, $p = 0.011$), and an Epworth score > 10 ($r^2 = 0.118$, $p = 0.012$) and the presence of SDB. Multiple regression analysis showed that age ($\beta = -0.393$, $p = 0.002$) and ESS > 10 ($\beta = -0.388$, $p = 0.003$) remained independently associated with the presence of SDB and accounted for 24% of the variability of SDB in patients with PH. The Epworth Sleepiness Scale score > 10 had 19.4% sensitivity and 50% specificity when predicting SDB (AHI ≥ 5) in patients with PH.

In those subjects with OSA, there was a significant relationship between age, BMI > 30 kg/m², and Epworth score > 10

Table 3—Cardiopulmonary data

	Total Group (n = 52)	OSA (n = 29)	CSA (n = 8)	NSA (n = 15)	p-value [‡]
Serum brain natriuretic peptide (pg/mL)	281.3 ± 351.0	286.0 ± 331.0	347.4 ± 363.8	236.8 ± 400.8	0.802
Pulmonary vascular resistance (dyn·s/cm ⁵)	788.8 ± 583.1	765.5 ± 566.5	825.9 ± 553.0	808.3 ± 667.0	0.964
Cardiac output (L/min)	4.3 ± 1.5	4.4 ± 1.6	3.7 ± 1.3	4.5 ± 1.5	0.554
Right atrial pressure (mm Hg)	8.6 ± 4.8	9.1 ± 5.4	7.3 ± 3.8	8.5 ± 4.6	0.669
Pulmonary capillary wedge pressure (mm Hg)	10.2 ± 6.0	10.0 ± 6.4	10.1 ± 5.4	10.7 ± 5.8	0.953
Mean pulmonary arterial pressure (mm Hg)	46.3 ± 20.6	49.2 ± 23.5	39.8 ± 13.0	44.4 ± 18.1	0.496
Systolic pulmonary arterial pressure (mm Hg)	73.0 ± 30.4	74.9 ± 34.6	71.4 ± 23.6	70.0 ± 26.5	0.890
Diastolic pulmonary arterial pressure (mm Hg)	27.9 ± 17.1	28.6 ± 20.3	24.0 ± 6.7	28.6 ± 13.9	0.811
Left ventricular end diastolic pressure (mm Hg)	11.8 ± 7.8	10.8 ± 7.9	13.0 ± 4.2	13.8 ± 10.1	0.812
Right ventricular end diastolic pressure (mm Hg)	9.9 ± 4.8	8.3 ± 4.2	9.0 ± 1.4	10.2 ± 6.9	0.769
Forced expiratory volume in 1 s (% pred)	72.1 ± 21.6	69.5 ± 18.3	71.7 ± 35.3	76.5 ± 20.1	0.610
Left ventricular ejection fraction, %	64.2 ± 7.2	64.2 ± 6.7	64.0 ± 8.4	64.2 ± 7.2	0.998
Forced vital capacity (% pred)	79.4 ± 23.6	76.0 ± 22.7	79.2 ± 33.3	85.1 ± 21.3	0.514
Forced expiratory volume/Forced vital capacity (% pred)	70.1 ± 8.8	70.4 ± 8.4	67.6 ± 10.0	70.6 ± 9.4	0.727
Total Lung Capacity (% pred)	91.5 ± 18.3	89.8 ± 18.2	91.6 ± 20.0	94.6 ± 18.5	0.754
Diffusion capacity for carbon monoxide (% pred)	67.3 ± 18.8	70.0 ± 18.3	75.8 ± 26.0	58.6 ± 13.6	0.104
6-Minute walk distance (m)	388.3 ± 133.8	378.0 ± 110.2	353.9 ± 160.2	428.5 ± 160.4	0.384

Values are expressed as mean ± SD. [‡]Between group differences (NSA, OSA, CSA). OSA, obstructive sleep apnea; CSA, central sleep apnea; NSA, no sleep apnea.

Table 4—Gender differences

	Male (n = 22)	Female (n = 30)	p-value [‡]
OSA prevalence	50.0%	60.0%	0.576
Age (years)	49 ± 15	55 ± 15	0.197
Body mass index (kg/m ²)	27 ± 6	31 ± 11	0.160
NYHA Class	2	2	0.643
Epworth Sleepiness Scale	7 ± 5	8 ± 6	0.535
AHI (n/h)	16.3 ± 14.3	16.6 ± 17.0	0.956
Oxygen desaturation index (n/h)	11.5 ± 13.4	17.0 ± 15.5	0.190
% TST < 90% O ₂ Sat	38.4 ± 40.6	36.9 ± 38.0	0.892
Periodic leg movement index (n/h)	23.3 ± 52.4	17.8 ± 30.0	0.633
Pulmonary vascular resistance (dyn·s/cm ⁵)	908.6 ± 599.1	689.8 ± 563.3	0.230
Mean pulmonary artery pressure (mm Hg)	53.0 ± 19.3	41.2 ± 20.4	0.046
6-minute walk distance (m)	435.7 ± 113.1	351.1 ± 128.8	0.025
FEV1/FVC (% pred)	69.7 ± 9.8	70.3 ± 8.2	0.821

Values are mean ± SD or number (%) as indicated. [‡]Between group differences (male, female). OSA, obstructive sleep apnea; NYHA, New York Heart Association.

Table 5—Independent predictors of OSA in PAH

Variables	Beta	p-value
ESS > 10	-0.401	0.003
Age	-0.329	0.011
BMI > 30	-0.266	0.042

Variables included in analysis were ESS, age, and BMI > 30 kg/m². Adjusted R² for model 0.345, p < 0.0005.

Table 6—Independent predictors of OSA in females with PAH

Variables	Beta	p-value
Age	-0.430	0.013
BMI > 30	-0.262	0.143
ESS > 10	-0.321	0.077

Variables included in analysis were ESS, age, and BMI > 30 kg/m². Adjusted R² for model 0.375, p < 0.004.

(r² = 0.113, p = 0.026; r² = 0.119, p = 0.022; r² = 0.221, p = 0.001, respectively). Multiple regression analysis showed that all of these variables remained independently associated with the presence of OSA and accounted for 34% of the variability of

OSA in patients with PAH (**Table 5**). In female subjects, only age was independently associated with the presence of OSA, accounting for 37.5% of the variability in female PAH patients with comorbid OSA (**Table 6**).

The median (range) duration of follow-up was 1,719 (92 to 2,504) days. At the time of this study, 62% of subjects ($n = 32$) were alive, 38% ($n = 18$) were deceased, and 2 had lung transplantation. The presence of SDB, treatment with CPAP, or treatment for PAH at the time of the initial polysomnography, was not significantly associated with survival. However, when audited in January 2013, of those OSA subjects alive and initially prescribed CPAP, only 50% of subjects continued to use CPAP. Survival outcome was associated with NYHA class, BNP, percent-predicted FEV1, and 6MWD. On multiple regression analysis, only BNP remained independently associated with survival outcome ($\beta = 0.402$, $p = 0.014$).

DISCUSSION

This cross-sectional cohort study of PAH patients has demonstrated a very high prevalence of SDB (71%) in a cohort of PAH patients from the Toronto pulmonary hypertension program. Moreover, the majority of the subjects (56%) had OSA with an older age, and $ESS > 10$ predictive of SDB. There were no differences in cardiopulmonary hemodynamics or survival between those with OSA, CSA, and no SDB. There was however, a high prevalence of OSA in female subjects, with age being the most important predictor in this group.

The very high prevalence of SDB in our PAH population and in particular the prevalence of OSA was unexpected. There have been four previous cohort studies that have utilized polysomnography in the evaluation of SDB in the PAH population.¹⁴⁻¹⁷ Their study populations were small and ranged from 13 to 28 subjects, and comparisons between those patients with OSA, CSA, and no sleep apnea were not possible. In two of the studies, only those subjects with idiopathic pulmonary hypertension were included.^{15,17} Significant nocturnal desaturation (77% of 13 subjects) but no SDB was reported in one study.¹⁵ In the second study of 20 subjects, 30% had SDB with a periodic pattern of respiration consistent with Cheyne-Stokes respiration.¹⁷ Although, our subjects also had a Cheyne-Stokes pattern of respiration, these subjects were younger and less obese than our cohort and had more severe hemodynamic impairment, with a mean PAP of 56 mm Hg and a mean pulmonary vascular resistance of 1369 dyn/s/cm⁵. A predominance of CSA was also demonstrated in a cohort of 38 patients with PH (WHO group 1 and 4 disease) with a cardiopulmonary profile similar to our patients.¹⁶ The major differentiating factor was that their patient group had a lower mean body mass index (25 vs 30.6 kg/m²). The greater predominance of OSA rather than CSA in our cohort may in part be as a result of the higher mean body mass index.¹⁸ Prisco et al. evaluated 28 consecutive patients with PAH for SDB and demonstrated a 50% prevalence of mild obstructive sleep apnea (defined as an AHI ≥ 5 /h). This is similar to our prevalence (56%). Analysis of data on 2,438 patients with PAH from the Reveal database registry in the United States reported comorbid OSA in 21% of patients.⁶ The prevalence of OSA in our group is almost triple (56%). This discrepancy may be due to potential underestimation of SDB prevalence in the registry database if routine screening was not performed on all subjects. The observed prevalence of OSA in our cohort is also significantly higher than that seen in the general population.^{7,19} A recent prospective study using

portable polygraphy included 169 subjects with precapillary pulmonary hypertension (59 had WHO Group 1 disease); 25% of their subjects had SDB.²⁰ This lower prevalence of SDB may be due to the underestimation of SDB because of the use of portable polygraphy and the calculation of the AHI from time in bed rather than total sleep time, and also because of the lower BMI of their population (27.2 vs 29.6 kg/m²). However, a marginally higher ESS in our group (7.3 vs 5.3) may suggest recruitment bias in our study.

The presence of Cheyne-Stokes respiration in our cohort is of interest, particularly in light of the documented normal left ventricular function. The cycle length of our cohort, although prolonged, was of shorter duration than that of patients with heart failure (59 seconds),²¹ but similar in duration to that of patients with heart failure and preserved ejection fraction.²² Similar to subjects with end-stage renal disease,²³ the possible pathophysiological mechanism may be fluid overload leading to pulmonary edema at night with activation of the pulmonary irritant receptors causing hyperventilation and a reduction in the CO₂ below the apneic threshold. The lower PtcCO₂ in those with CSA supports this theory. A second possible mechanism may be the impaired cardiac output from poor pulmonary blood flow (due to reduced right ventricular function) or impaired left ventricular diastolic function from adverse right-left ventricular interactions. Both the nonsignificant reduction in the cardiac output and BNP levels in this group are supportive of these theories.

Similar to the findings in the other cohort studies, there was a lack of subjective sleepiness as assessed by the Epworth Sleepiness Scale in our PAH population. Sensitivity of the ESS was also extremely poor, although we demonstrated that an Epworth score > 10 was an independent predictor of both SDB and OSA. This lack of subjective sleepiness may be explained by the known presence of elevated sympathetic nervous activity in PAH.^{24,25} As occurs in heart failure subjects, there may be an inverse relationship between sleepiness and muscle sympathetic activity.²⁶ Thus the lack of subjective sleepiness may be explained through this mechanism of centrally mediated adrenergic alerting mechanisms.

In addition to an $ESS > 10$, the other predictors of OSA were older age and BMI > 30 kg/m². These predictors do not differ from those of the general population.²⁷ No additional factors relating to PH were found to be significant predictors of SDB, including the severity of the PAH or the total sleep time spent with an oxygen saturation less than 90%.

As PAH is predominantly a disease of women, it is not unexpected that in our population, there was a preponderance of females to males with a ratio of 1.36:1. This ratio is lower than that reported in the Reveal registry for PAH (4.1:1)⁶ and by the French group (1.9:1).²⁸ We do not believe that this is due to sampling bias in our group, as the female-to-male ratio is similar to that of our total Group 1 PAH cohort at the time (1.45:1). Interestingly, there was a high prevalence of SDB (73%), predominantly OSA (60%), in the female patients. This is significantly higher than those prevalence rates reported for the general population. For a similar AHI cutoff ≥ 5 , Duran and colleagues reported a 28% prevalence rate of OSA in women,⁷ while Bixler et al. reported a prevalence of 0.6% in pre-menopausal women and 2.7% in post-menopausal women.²⁹ The

high female prevalence of both OSA and CSA is surprising and may be related to the higher BMI of these subjects compared to our male subjects and to those subjects in other registries.⁶ One may speculate that nocturnal rostral fluid shifts may be involved in predisposing to ventilatory instability and SDB in these subjects.³⁰ In the female cohort, the severity of SDB was similar to that in the men, but women had a lower mean pulmonary artery pressure and pulmonary vascular resistance but worse exercise capacity as assessed by the 6MWD. The gender differences with respect to severity of PH and distance walked are consistent with previous reports.³¹

The mechanisms through which OSA may contribute to the development or worsening of underlying PAH include the mechanical effects of negative intrathoracic pressures resulting in alterations in RV loading, with adverse modulation by intermittent hypoxia.³² Elevated sympathetic nervous activity may also contribute to right ventricular hypertrophy and dysfunction,³³ and oxidative stress may contribute to endothelial dysfunction.³⁴ One possible mechanism through which PAH could cause SDB is the rostral shift of fluid from the legs during the daytime to the neck at night, predisposing to upper airway obstruction. Studies in patients with left ventricular failure have demonstrated a relationship between overnight rostral fluid shift from the legs to the neck and the severity of OSA.³⁰ Obese patients with PAH could also develop SDB through the reductions in lung compliance and chest wall and subsequent increases in airway resistance.^{35,36}

The similar survival rates between those without and with SDB observed in this study may be attributable to small numbers, short follow-up time, and a lack of power. No other studies have evaluated survival in PAH patients with SDB. However, in a study of subjects with OSA both with and without PAH, severe OSA (AHI $\geq$ 54/h) was a predictor of mortality.³⁷

This study has several limitations. The performance of polysomnography occurred at varying time points following the diagnosis of PAH, often following the commencement of PAH targeted medications. Although consecutive patients were studied, because of the retrospective nature of this study, referral bias cannot be eliminated. However, the lack of subjective sleepiness suggests that this is not a significant issue. Furthermore, analysis of all patients diagnosed with Group 1 PAH during the study period demonstrates similar demographic characteristics and a high prevalence of sleep apnea, as in our study cohort. There was no rigorous follow-up of those prescribed CPAP therapy; therefore, it was not possible to determine accurately whether or not treatment of OSA had an impact on outcomes.

In conclusion, this study demonstrates that SDB, particularly OSA, is highly prevalent in the PAH population in both male and female subjects. Older age and ESS > 10 are the primary risk factors in this cohort. The presence of OSA is one of the known factors contributing to delays in the diagnosis of PAH³⁸; conversely, it may be as important to screen for the presence of OSA in those diagnosed with PAH. Whether or not SDB is a causal agent, mediator of PAH, or coincidental finding requires future elucidation. Due to the heterogenous nature and multiple etiologies of PAH, larger and longer studies are warranted to determine the pathophysiological effects of comorbid SDB, contributions to long-term outcomes and efficacy of treatment.

ABBREVIATIONS

6MWD, six-minute walk distance
 AHI, apnea-hypopnea index
 BMI, body mass index
 BNP, brain natriuretic peptide
 CSA, central sleep apnea
 ESS, Epworth Sleepiness Scale
 NYHA, New York Heart Association
 ODI, oxygen desaturation index
 OSA, obstructive sleep apnea
 PAH, pulmonary arterial hypertension
 PAP, pulmonary artery pressure
 SDB, sleep disordered breathing

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