Nocturnal Hypoxemia, But Not Sleep Apnea, Is Associated With a Poor Prognosis in Patients With Pulmonary Arterial Hypertension

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Background: Sleep apnea (SA) can cause repeated nocturnal arterial oxygen desaturation and result in acute increase in pulmonary arterial pressure (PAP). The presence of SA is associated with a poor prognosis in patients with chronic left-sided heart failure, but little is known for patients with pulmonary arterial hypertension (PAH).

Methods and Results: We enrolled 151 patients with PAH (44±16 years old, male/female=37/114). They were all in the Nice Classification group 1 (idiopathic PAH/associated PAH=52/48%, mean PAP of 46±16 mmHg). They underwent right-heart catheterization and a sleep study with simplified polysomnography. Averaged percutaneous oxygen saturation (SpO₂) during sleep was measured and an apnea-hypopnea index >5 was defined as SA. SA was noted in 58 patients (obstructive SA/central SA: 29/29). Over an average follow-up of 1,170±763 days, 32 patients died. By Kaplan-Meier analysis, there was no significant difference in deaths of patients with and without SA (χ²=2.82, P=0.093). On the other hand, the mortality in patients with lower averaged SpO₂ was significantly higher than in those with higher averaged SpO₂ (χ²=14.7, P<0.001) and that was the only independent variable related to death in multivariate Cox proportional hazards analysis.

Conclusions: SA in patients with PAH was not associated with worse prognosis, unlike left ventricular heart failure, but nocturnal hypoxemia was related to poor prognosis.

Key Words: Nocturnal hypoxemia; Pulmonary arterial hypertension; Sleep apnea

Sleep apnea (SA) can cause repeated nocturnal arterial oxygen desaturation, sleep fragmentation, increased sympathetic activity, oxidative stress, inflammation and endothelial dysfunction, negative swings in intrathoracic pressure, and acute increase in pulmonary arterial pressure (PAP). Pulmonary vasoconstriction occurs in response to alveolar hypoxia, then increased pulmonary vascular resistance (PVR), contributing to an increase in PAP and resulting in pulmonary vascular remodeling. Sleep-disordered breathing (SDB) in patients with pulmonary arterial hypertension (PAH), which comprises not only SA, but also periodic breathing and nocturnal hypoxemia, is common. Many studies show that the presence of SA is associated with a poor prognosis in patients with left-sided heart failure, but the effect of nocturnal hypoxemia and SA on the outcome of patients with PAH is unknown.

The objective of the present study, therefore, was to determine whether nocturnal hypoxemia and/or SA is associated with prognosis in PAH patients.

Methods

Study Subjects
The retrospectively enrolled subjects were 151 patients with PAH in the Nice Classification group 1 who were admitted for routine hemodynamic follow-up and were screened for SDB from April 2008 through February 2010 (37 males, 114 females; 44±16 years old). The mean PAP (mPAP) was 46±16 mmHg, and PVR was 12±9 Wood units. Patients with a total sleep time <3 h in the sleep studies were excluded.

PAH was defined by right-heart catheterization (RHC) as mPAP ≥25 mmHg with a pulmonary artery wedge pressure (PAWP) <15 mmHg. They were classified, on the basis of the Nice Classification; into idiopathic PAH (IPAH; n=78) and associated PAH (n=73) (52% and 48%, respectively). There were 6 patients with Eisenmenger syndrome in the associated PAH group.

Assessments
Serum hemoglobin (Hb) and B-type natriuretic peptide...
(BNP) concentration, height and weight were measured and the body mass index (BMI) was calculated according to the following equation: BMI=weight (kg)/height^{2}(m^{2}).

**Right-Heart Catheterization**

RHC was performed with a 6F double-lumen, balloon-tipped flow-directed catheter (Harmac Medical Products, Inc., Buffalo, NY, USA) via a transjugular approach. Baseline hemodynamics were recorded; the zero reference level (the midstich between the precordium and back) was checked at the beginning of pressure measurement, and the PAWP was obtained as the mean value of the occlusion artery trace. Measurements were obtained at the end of a normal expiration with the patient supine in order to assess pulmonary artery pressures (mean PAP, systolic PAP and diastolic PAP) and PAWP in addition to pressures in the right chambers.

Oxygen saturation in arterial blood (SaO_{2}), the partial pressure of the arterial O_{2} (PaO_{2}), arterial CO_{2} (PaCO_{2}) in the radial artery and O_{2} saturation in the pulmonary artery (SvO_{2}) were measured. Cardiac output (CO) was determined by the Fick method using the following formula: CO (L/min)=Oxygen consumption (VO_{2});1.34×Hb×{(SaO_{2}−SvO_{2})}. PVR was calculated as: PVR (Wood unit)=(mPAP−PAWP)/CO. Estimated VO_{2} was determined as follows: body surface area (BSA)×125 (for individuals >60 years old), and BSA×110 (for individuals <60 years old).

**Sleep Study**

The overnight sleep study was performed in room air on the day of RHC using a cardiopulmonary polygraphy (LS-300, Fukuda denshi, Tokyo, Japan) consisting of a pressure sensor for nasal airflow, 2 stress-sensitive belts for the ribcage and abdomen, respectively, a continuous pulse oximeter, and body position sensor.

Oronasal signals detected with a thermistor were used as respiratory sensors, and thoracic and abdominal effort was measured with the 2 belt sensors. Percutaneous oxygen saturation (SpO_{2}) was recorded with digital pulse oximetry (sampling frequency, 1 s), and average SpO_{2} during sleep was measured. Nocturnal hypoxemia was defined as an average SpO_{2}<90%.

Apnea was defined as a cessation of airflow for at least 10s. Hypopnea was defined as a reduction in airflow of more than 50% from baseline for more than 10s, accompanied by at least a 3% decrease in SpO_{2}. The number of episodes per hour of apnea plus hypopnea was defined as the AHI. An AHI >5 was considered to indicate SA. An episode of obstructive SA was defined as cessation of airflow in the presence of thoracic and abdominal wall motion. An episode of central SA was defined as the cessation of both airflow and thoracic and abdominal wall motion. Determination of the type of SA is majority of obstructive or central.

Detection of respiratory events and an analysis of oxygenation were performed manually by investigators without knowledge of the clinical characteristics of the patient (T.T.).

**Statistical Analysis**

Clinical variables for patients who did or did not die were compared through χ^{2} tests (for categorical variables) and non-paired t-tests (for continuous variables). The relationships between SA, nocturnal hypoxemia and death were evaluated by Kaplan-Meier analysis. Cutoff value

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**Table 1. Patients' Characteristics**

<table>
<thead>
<tr>
<th>Total (n=151)</th>
<th>Sleep apnea (+) (n=58)</th>
<th>Sleep apnea (−) (n=93)</th>
<th>P value</th>
<th>Nocturnal hypoxemia (+) (n=31)</th>
<th>Nocturnal hypoxemia (−) (n=120)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44±16</td>
<td>45±15</td>
<td>44±16</td>
<td>0.517</td>
<td>52±15</td>
<td>42±16</td>
</tr>
<tr>
<td>Male/Female, n</td>
<td>37/114</td>
<td>16/42</td>
<td>21/72</td>
<td>0.561</td>
<td>8/23</td>
<td>29/91</td>
</tr>
<tr>
<td>IPAH/associated PAH, n</td>
<td>78/73</td>
<td>56/37</td>
<td>22/36</td>
<td>0.012</td>
<td>12/19</td>
<td>66/54</td>
</tr>
<tr>
<td>BMI (kg/m^{2})</td>
<td>21.7±4.5</td>
<td>20.8±4.2</td>
<td>22.0±4.2</td>
<td>0.119</td>
<td>20.7±3.8</td>
<td>21.4±4.3</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>13.4±2.1</td>
<td>13.6±2.4</td>
<td>13.2±1.9</td>
<td>0.264</td>
<td>13.7±2.0</td>
<td>13.3±2.2</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>202±302</td>
<td>207±275</td>
<td>195±316</td>
<td>0.812</td>
<td>245±255</td>
<td>171±267</td>
</tr>
<tr>
<td>RA (mmHg)</td>
<td>6.2±4.1</td>
<td>6.5±3.7</td>
<td>6.0±4.3</td>
<td>0.433</td>
<td>7.6±4.9</td>
<td>5.9±3.8</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>46.1±15.6</td>
<td>49.1±15.8</td>
<td>42.4±15.3</td>
<td>0.061</td>
<td>44.1±15.8</td>
<td>46.6±16.6</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>7.4±3.0</td>
<td>7.4±3.1</td>
<td>7.3±3.1</td>
<td>0.865</td>
<td>7.1±4.0</td>
<td>7.5±2.8</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.8±1.6</td>
<td>3.6±1.4</td>
<td>3.8±1.5</td>
<td>0.508</td>
<td>3.3±1.3</td>
<td>4.0±1.8</td>
</tr>
<tr>
<td>PVR (wood unit)</td>
<td>12.4±8.7</td>
<td>14.2±10.2</td>
<td>11.3±7.5</td>
<td>0.055</td>
<td>12.1±6.0</td>
<td>12.4±9.3</td>
</tr>
<tr>
<td>PaO_{2} (mmHg)</td>
<td>73.8±16.6</td>
<td>72.4±11.3</td>
<td>74.6±19.1</td>
<td>0.452</td>
<td>67.0±21.4</td>
<td>75.0±15.4</td>
</tr>
<tr>
<td>PaCO_{2} (mmHg)</td>
<td>34.7±5.4</td>
<td>33.4±5.1</td>
<td>35.5±5.4</td>
<td>0.032</td>
<td>36.2±6.1</td>
<td>34.4±5.3</td>
</tr>
<tr>
<td>AHI (h)</td>
<td>6.0±7.6</td>
<td>13.7±8.5</td>
<td>1.8±1.5</td>
<td>&lt;0.001</td>
<td>7.6±11.0</td>
<td>5.6±6.5</td>
</tr>
<tr>
<td>Averaged SpO_{2} (%)</td>
<td>93.8±0.03</td>
<td>93.6±0.04</td>
<td>94.0±0.03</td>
<td>0.556</td>
<td>88.2±0.02</td>
<td>95.1±0.02</td>
</tr>
<tr>
<td>OSA/CSA, n</td>
<td>29/29</td>
<td>23 (25%)</td>
<td>23 (25%)</td>
<td>0.221</td>
<td>13 (42%)</td>
<td>19 (16%)</td>
</tr>
</tbody>
</table>

Data are mean value±SD. AHI, apnea-hypopnea index; BMI, body mass index; BNP, B-type natriuretic peptide; CO, cardiac output; CSA, central sleep apnea; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; OSA, obstructive sleep apnea; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, mean right atrial pressure; SpO_{2}, percutaneous oxygen saturation.
Nocturnal Hypoxemia in PAH

Results

Characteristics of the Subjects
Among the total 151 patients, SA was noted in 58 patients (obstructive SA/central SA: 29/29 patients), seen in approximately one-third of the patients. Table 1 shows a comparison of the clinical characteristics of patients with SA (n=58) and without SA (n=93) and between the patients with nocturnal hypoxemia (n=31) and without nocturnal hypoxemia (n=120). Patients with and without SA were comparable in terms of age, sex, BMI, Hb, BNP, mPAP, CO, and averaged SpO2 during sleep. However, PVR in the SA group tended to be higher than in the non-SA group (14.2 ± 10.2 vs. 11.3 ± 7.5 Wood unit, P=0.055). PaCO2 was lower, meaning hyperventilation during waking in the SA group. On the other hand, patients with nocturnal hypoxemia were significant older (52 ± 15 vs. 45 ± 16 years old, P=0.003) and had daytime hypoxemia (67.0±21.4 vs. 75.0±15.4 mmHg, P=0.049) than those without nocturnal hypoxemia. The rate of death was significantly higher in the nocturnal hypoxemia group (42% vs. 16%, P=0.004).

Outcome
Over an average follow-up period of 1,170±763 days, 32 patients died. The causes of death included progressive heart failure in 29 patients, catheter-related infection in 2,
variate Cox proportional hazards analysis, only lower averaged SpO₂ was identified as an independent prognostic marker (HR: 0.001, 95% CI 0.001–0.036, P=0.008) (Table 4).

In addition, by Kaplan-Meier analysis, there was no significant difference between patients with and without SA with regard to death (χ²=2.82, P=0.093) (Figure 1). However, the mortality in patients with nocturnal hypoxemia was significantly higher than in those without nocturnal hypoxemia (χ²=14.7, P<0.001) (Figure 2).

**Discussion**

The main finding of this study was that the presence of SA was not associated with a poor prognosis in patients with PAH but lower SpO₂ was.
Nocturnal Hypoxemia in PAH

Prognosis
The presence of SA in patients with left-sided heart failure is associated with poor prognosis\textsuperscript{15,16} and therapeutic intervention is recommended. Minai et al reported that obstructive SA patients with severe pulmonary hypertension (PH) had increased mortality compared with patients without PH.\textsuperscript{17} However, there is a lack of information about prognosis in PAH patients with neither SA nor nocturnal hypoxemia. Only one study of prognosis has been reported, by Mimic et al, in which similar survival rates between those with and without SDB were shown.\textsuperscript{11}

Our study included relatively many PAH patients compared with previous studies. Interestingly, continuous nocturnal hypoxemia was related to poor prognosis, but intermittent hypopnea, as reflected by the AHI, was not. Because chronic hypoxemia may promote pulmonary artery vasoconstriction and remodeling,\textsuperscript{8,5} it may contribute to the poor prognosis in PAH. Similar mechanisms might be also seen during sleep in patients with nocturnal hypoxemia.

Negative intrathoracic pressure leads to an abrupt increase in venous return, then an increase in the volume of the right-sided heart. Intermittent decrease of CO results from interference of left ventricular dilation and contraction by leftward interventricular septal shift.\textsuperscript{18} Generation of negative intrathoracic pressure during SA would cause more pronounced and sustained reductions in CO in patients with left-sided heart failure.\textsuperscript{3} Intermittent decrease of CO in patients with PAH might be less influenced because of preserved left ventricular function. It has been hypothesized that blood flow restrictions to the region of the carotid body could play a role in inducing augmented carotid body chemoreflex activation in left-sided heart failure.\textsuperscript{19,20} Different mechanisms from SA to chemoreceptors may exist in right-sided heart failure.

Evidence-based guidelines endorse assessment of SDB when evaluating patients with PAH and, if suspected, a sleep study is recommended.\textsuperscript{21} However, from our study, evaluation of nocturnal hypoxemia is more important and should be strongly considered for therapeutic intervention rather than SA. Nocturnal hypoxemia should be treated by oxygen supplementation to keep \textit{SpO}_2 >90%.

Prevalence
To date, the prevalence of SDB in PAH patients has been reported.\textsuperscript{8,9,22} The study populations of these reports, including etiologies and severity of PAH and their BMI, varied. Generally, the prevalence of SDB in PAH patients appears to be much higher than in the general population.

The high occurrence of nocturnal hypoxemia, measured by oximetry, in PAH patients is reported. Rafanan et al report a prevalence of nocturnal hypoxemia of 77% in 13 patients with IPAH,\textsuperscript{14} and Minai et al observed a prevalence of 69.7% in 43 patients with IPAH and associated PAH.\textsuperscript{10} Jilwan et al reported that approximately 83% had nocturnal hypoxemia and approximately 90% had SA among patients with IPAH and chronic thromboembolic PH.\textsuperscript{12} Prisco et al reported an increased prevalence of OSA, accounting for 50% of patients with IPAH and secondary PAH,\textsuperscript{23} but the severity of PAH and the phenotype of the patients were similar in our study. Dumitrascu et al found that over 25% of patients referred from a PAH clinic who were NYHA Class II or III had an AHI >10.\textsuperscript{13} Of these, approximately 60% had OSA and 40% had CSA. Recently, Mimic et al reported a high prevalence (=70%) of SA (AHI ≥5) in patients with group 1 PAH.\textsuperscript{11} In the REVEAL registry, SA was seen in approximately 20% of the total entry patients (599/2,959),\textsuperscript{24} similar to our prevalence. However, the diagnosis of SA was presumed to be inaccurate.

In our study, females accounted for approximately 75% of the study group, and BMI was extremely low, meaning a lot of the PAH patient were lean. This may be a characteristic of Asian group 1 PAH patients. In addition, the AHI in our data was calculated for the time in bed and not for the total sleep time. These reasons may explain why our prevalence of SA was lower than in other reports.

Study Limitations
This was a retrospective study. The effects of therapeutic intervention during the follow-up period were not considered. Cheyne-Stokes respiration was not evaluated. Arousal and respiratory effort could not be fully described because only a simplified sleep study was conducted.

Conclusions
SA in patients with PAH was not associated with worse prognosis, unlike left ventricular heart failure. However, nocturnal hypoxemia was related to poor prognosis.

Author Contributions
M.N. and A.G. contributed to the study protocol, data analysis, and writing of the manuscript. Takeo Tanaka performed the data analysis. T.S. reviewed the data, and edited the paper. K.T., H.K., M.F., K.S. and T.I. contributed to editing of the manuscript.

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