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Sleep Disturbance, Symptoms, Psychological Distress, and Health-Related Quality of Life in Pulmonary Arterial Hypertension

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Sleep Disturbance, Symptoms, Psychological Distress, and Health-Related Quality of Life in Pulmonary Arterial Hypertension

Abstract

Background:

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by elevated pulmonary pressures that lead to right heart failure and premature mortality. Patients experience multiple symptoms including dyspnea, fatigue and chest pain, but little is known about sleep disturbance, PAH symptoms, psychological distress and health-related quality of life (HRQOL) in PAH.

Aim:

The purpose of this study was to describe the occurrence of sleep disturbance and compare PAH symptoms, psychological distress, and HRQOL across severity of sleep disturbance.

Methods:

One hundred and ninety-one participants completed a socio-demographic and clinical data form, PAH Symptom Severity Scale, Profile of Mood States (POMS) short form and the Medical Outcomes Short Form-36 (SF-36). Descriptive statistics were used to describe sleep disturbances; analysis of variance models were used to quantify differences in PAH symptoms, psychological distress and HRQOL by sleep disturbance groups.

Results:

The majority of participants (n=162, 85%) were women with a mean age of 53 years. Sixty-five (34%) reported no sleep disturbance; 54 (28%) mild sleep disturbance; 41 (22%) moderate sleep disturbance; and 31 (16%) severe sleep disturbance. Those reporting higher sleep disturbance severity reported worse PAH symptoms, psychological distress, and HRQOL.

Conclusions:

Sleep disturbance is a significant finding in PAH. Increasing levels of sleep disturbance are associated with worse PAH symptoms, psychological states, and health-related quality of life. Interventions that decrease sleep disturbances may improve symptoms and HRQOL.

Keywords

sleep, sleep disorders, health-related quality of life, psychological states

Disciplines

Cardiology | Cardiovascular Diseases | Circulatory and Respiratory Physiology | Medical Humanities | Medicine and Health Sciences | Nursing | Sleep Medicine

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Title Page

Sleep disturbance, symptoms, psychological distress and health-related quality of life in pulmonary arterial hypertension

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a devastating disease characterized by elevated pulmonary pressures that lead to right heart failure and premature mortality. Patients experience multiple symptoms including dyspnea, fatigue and chest pain, but little is known about sleep disturbance, PAH symptoms, psychological distress and health-related quality of life (HRQOL) in PAH.

Aim: To describe the occurrence of sleep disturbance and compare PAH symptoms, psychological distress and HRQOL across severity of sleep disturbance.

Methods: One-hundred ninety one participants completed a socio-demographic and clinical data form, PAH Symptom Severity Scale, Profile of Mood States short form (POMS) and the Medical Outcomes Short From-36 (SF-36). Descriptive statistics were used to describe sleep disturbances; analysis of variance models were used to quantify differences in PAH symptoms, psychological distress and HRQOL by sleep disturbance groups.

Results: The majority of participants (n=162, 85%) were women with a mean age of 53 years. Sixty-five (34%) reported no sleep disturbance; 54 (28%) mild sleep disturbance; 41 (22%) moderate sleep disturbance; and 31 (16%) severe sleep disturbance. Those with reporting higher sleep disturbance severity reported worse PAH symptoms, psychological distress and health-related quality of life.

Conclusions: Sleep disturbance is a significant finding in PAH. Increasing levels of sleep disturbance are associated with worse PAH symptoms, psychological states, and health-related quality of life. Interventions that decrease sleep disturbances may improve symptoms and HRQOL.
Key Words

Sleep, sleep disorders, health-related quality of life, psychological states
Introduction

Pulmonary arterial hypertension (PAH), one type of pulmonary hypertension, is a devastating illness affecting primarily young to middle-aged women. PAH is defined hemodynamically as a mean pulmonary arterial pressure $\geq 25$ mmHg and a pulmonary capillary wedge pressure $< 15$ mmHg. Over time, these elevated pulmonary pressures lead to right heart failure. The etiology of PAH includes idiopathic, familial, connective tissue disease, portopulmonary hypertension, sickle cell disease and congenital heart disease. Approximately 80% of those diagnosed with PAH are women. The mean age at diagnosis is 50 years, although there is typically a delay of 2 years from symptom onset to diagnosis. Estimated prevalence of PAH is 7.6 to 15 cases per million. Symptoms of PAH include fatigue and dyspnea on exertion that may be attributed to other cardiopulmonary disorders. Mortality remains high; 61% at 5 years.

Recent studies show patients with PAH experience multiple symptoms that interfere with their lives and negatively affect their quality of life. Sleep disturbance is increasingly recognized as a factor interfering with the ability to cope with symptoms and maintain health-related quality of life (HRQOL). Only two studies investigating sleep disturbance in pulmonary hypertension have been conducted and these studies illustrate that sleep disturbances may be a factor greatly interfering with the HRQOL of these patients. Sleep disturbance in PAH can be caused by insomnia and restless leg syndrome. Seventy-three percent of patients (N=40) with pulmonary hypertension had poor sleep quality that was associated with depression, dyspnea and decreased HRQOL. Fifty percent had insomnia, 26% reported excessive daytime sleepiness (EDS) and 30% were found to have restless leg syndrome. Prostanoid therapy was associated with improved HRQOL but not sleep quality. In another study 46% (N=55)
of those with pulmonary hypertension had restless leg syndrome. Those with a history of hypothyroidism and opioid use for leg pain were most likely to have restless leg syndrome. Limitations of these studies included small sample sizes and inclusion of various etiologies of pulmonary hypertension, making it difficult to generalize to those with PAH only.

These preliminary studies suggest sleep disturbance is present in pulmonary hypertension, but the prevalence of sleep disturbance in those with PAH only remains unknown. Understanding the effects of sleep disturbance in patients with PAH may have implications for interventions and patient outcomes such as morbidity, psychological distress and HRQOL. The aims of this study were to:

(1) describe the occurrence of sleep disturbance and
(2) compare PAH symptom, psychological distress and HRQOL across severity of sleep disturbance.

Methods

Study Design

A cross-sectional study design was used.

Sample

The convenience sample included 191 participants recruited from United States PAH support groups, an on-line Pulmonary Hypertension Association (PHA) discussion board, and at Northeast United States and international Pulmonary Hypertension conferences. The PHA sponsors a biennial conference where investigators can recruit and enroll study participants. At a monthly support meeting the principal investigator (PI) was introduced and allowed to briefly
discuss the purpose of this study and invite participants to approach the PI after the meeting if they wished to participate. An advertisement was posted by the PHA website administrator; participants contacted the PI via email if they were interested in participating. Only those patients self-reporting PAH who were able to read and speak English were included. Patients were enrolled over an 18 month period.

Measures

Participants completed the following questionnaires: a socio-demographic and clinical data form, the PAH Symptom Severity Scale, the Profile of Mood States (POMS) short form the Medical Outcomes Study Short Form- 36 (SF-36).

Socio-demographic and Clinical Data Form: Socio-demographic and clinical variables were collected via a tool developed by the research team. Socio-demographic information included gender, age, ethnicity, education, occupation and employment status. Self-reported clinical variables included date of PAH diagnosis, PAH etiology, initial symptoms of PAH, oxygen and medication use. World Health Organization (WHO) functional class(1) was assigned by the PI (LAM) using assessment data from self-reported symptoms. WHO functional class I includes those with PAH who do not have symptoms such as shortness of breath (SOB) with exertion. Those with WHO functional class II have mild SOB with exertion while WHO functional class III patients have moderate to severe symptoms of SOB with exertion. WHO functional class IV patients have symptoms at rest.(12)

Sleep Disturbance: Sleep disturbance was measured by a single item on the PAH Symptom Severity Scale labeled “sleep difficulty”. Sleep difficulty is measured on a 0 to 10 scale with zero indicating absence of sleep difficulty and 10 representing the worst possible sleep difficulty.
**PAH Symptom Severity Scale:** The PAH Symptom Severity Scale is a symptom scale developed by the research team that contains 17 symptoms: SOB with exertion, SOB lying down, SOB at rest, awakening at night SOB, fatigue, sleep disturbance, chest pain, abdominal swelling, swelling of ankles and feet, syncope, palpitations, dizziness, cough, nausea, loss of appetite, hoarseness, Raynaud’s phenomenon (cold, numbness of extremities). Symptoms were selected based on the literature, (13-15) input from the research team, experts caring for patients with PAH and patients with PAH. Symptoms are rated on a 0-10 scale, with zero indicating an absence of the symptom and 10 indicating “extremely intense”. Participants are asked to rate their symptoms over the past month. The Cronbach alpha for the scale is typically .90-.91; (7) in the current study alpha was .90. Validity testing is on-going.

**Psychological states** The POMS short form comprised 30 items that measure fluctuating mood states. These items form six subscales anger, anxiety, depression, confusion, fatigue and vigor. Each item is rated on a 5 point Likert scale, 0 (not at all) to 4 (extremely) for each mood state. Higher scores indicate more negative moods, except vigor which is reversed scored. Concurrent validity was established using the modified Hopkins Symptom Distress Scales and Minnesota Multiphasic Personality Inventory-2. (16) Internal consistency ranges from 0.84 to 0.95. (16, 17) The Cronbach alpha for the current study was .70.

**SF-36** The SF-36 is a widely used instrument that measures generic HRQOL. The SF-36 measures physical and mental health by assessing eight subscales. The subscales (general health, physical functioning, role physical, pain, fatigue, social functioning, mental health, role emotional) and each composite summary score (mental and physical) are reported on a scale of 0-100 with higher scores indicating better HRQOL. Validity (18) and reliability have been
established with Cronbach alpha ranges between .73-.96. The Cronbach alpha for the current study was .84.

Procedure

This investigation conformed with the principles outlined in the Declaration of Helsinki. This study was approved by the hospital and University Institutional Review Boards. Participants were given paper and pencil forms and questionnaires to complete along with a self-addressed stamped envelope. Participants were given unique identification numbers. Return of completed surveys was considered consent to participate.

Statistical Analysis

The primary outcome measure of sleep disturbance was assessed using the PAH Symptom Severity Scale. Participants were categorized into four groups on the basis of self-reported sleep disturbance: no (0) mild (1-3), moderate (4-7), and severe (8-10). These categories were established using existing literature and investigator input. Descriptive statistics are used to characterize the population to which inferences may be made. Specifically, means and standard deviations are provided for continuous socio-demographic and clinical characteristics overall, and by sleep disturbance groups, while frequencies and percents are provided for categorical variables. Comparisons of continuous and categorical socio-demographic and clinical characteristics across groups are made using one-way Analysis of Variance (ANOVA) models and chi-square statistics, respectively. Medications are compared across groups using indicator variables for each specific medication. The total number of PAH symptoms among the sixteen symptoms examined is compared across sleep disturbance groups using a one-way ANOVA model and the F statistic, with post-hoc pair-wise comparisons.
accomplished on the basis of Dunnett's tests. Similarly, PAH symptom intensity, as well as POMS and SF-36 subscales, are described overall and within sleep disturbance groups using means and standard deviations, and compared using one-way ANOVA models and Dunnett's pair-wise post-hoc tests. No adjustment was made for multiplicity. All statistical analyses were accomplished using SPSS version 20. Statistical significance was taken at the 0.05 level.

Results

Of the 191 participants, 126 (66%) reported some level of sleep disturbance, Table 1. For the sleep disturbance categories, 65 (34%) had no sleep disturbance, 54 (28%) mild, 41 (22%) moderate, and 31 (16%) severe sleep disturbance. There were significant differences among the sleep disturbance groups with regards to PAH symptoms, psychological distress and HRQOL.

Table 2 provides estimates (mean ± SD) for symptom intensity for 16 PAH symptoms. The symptoms with the highest mean scores for the total sample were SOB with exertion and fatigue. All symptoms differed significantly between the no sleep disturbance and the severe sleep disturbance groups. Syncope did not differ among the groups. Pair-wise post-hoc differences are also indicated in Table 2. Figure 1 provides a visual display of the distribution for the total number of symptoms by each sleep disturbance group.

With regards to psychological distress, the sleep disturbance groups differed significantly on all the POMS subscales (anxiety, depression, anger, vigor, fatigue, confusion) and total score, with results for pair-wise post-hoc differences displayed in Table 3. Confusion was the only psychological state that differed between no and moderate sleep disturbance.

Similarly, the sleep disturbance groups differed significantly on all SF-36 subscales and composite summary scores (Table 4). The role emotional subscale differed only between the no
disturbance and mild sleep disturbance and the no disturbance and severe sleep disturbance groups.

Discussion

This study demonstrates that sleep disturbance is common in PAH and associated with other PAH symptoms, psychological distress and HRQOL. As sleep disturbance severity increases, so does the occurrence of PAH symptoms and there is greater PAH symptom severity. The linear increase in symptom distress in relation to increasing sleep disturbance suggests that sleep disturbance increases with symptom severity, creating an escalating cycle of sleep disturbance and symptoms severity. Higher WHO functional classes and increased oxygen use were more common as sleep disturbance severity increased.

In our study those with worse sleep disturbance had higher PAH symptom severity and psychological distress. This is consistent with the results from a small study of patients with pulmonary hypertension where sleep quality was associated with symptoms (breathlessness, mood and energy), depression and dyspnea. In patients with heart failure (HF), depression and fatigue have been associated with insomnia. Additionally our study expands current knowledge of PAH symptom severity by the use of a comprehensive symptom profile. These are new findings that may provide a direction for future intervention. Perhaps screening and treating symptoms in PAH may improve sleep, but more research is necessary to test this hypothesis.

Psychological distress may be another factor explaining the occurrence of sleep disturbance. Our study shows that sleep disturbance severity was associated with anger, anxiety, depression, confusion and fatigue. Other studies have shown that depression is associated with sleep disturbance in PAH(10) and depression and anxiety have been found to be prevalent in
patients with PAH.\textsuperscript{(14, 15, 26)} While we do not know if sleep disturbance is the outcome of patients experiencing exacerbated symptoms and psychological distress, these findings provide us with possible directions for further investigation. For example, future research could target optimal symptom control (e.g. SOB), which could improve sleep. Conversely, improving sleep in the patient with PAH may improve their other symptoms.

Our study showed an association with PAH symptom severity and HRQOL. Similar to our findings, sleep disturbance is common in HF and impairs HRQOL.\textsuperscript{(27, 28)} Impaired sleep and EDS affect cognition, physical functioning and treatment adherence in patients with HF.\textsuperscript{(25, 29-32)} Our study showed those with worse self-reported sleep disturbance had poorer physical functioning. Insomnia symptoms are also associated with increased depression, fatigue, EDS and functional performance in HF \textsuperscript{(25)} and affects global perceived health in sleep-disordered breathing.\textsuperscript{(33)} Self-reported sleep quality is also associated with functional performance and mental health in HF.\textsuperscript{(34)} We found those with PAH who had sleep disturbances reported higher levels of fatigue and depression.

Those with worse sleep also had lower HRQOL in our study. Physically, those with sleep disturbance also experienced fatigue and limitations in performing physical activities. Psychologically, those with sleep disturbance had psychological distress, social disability and emotional problems. A study of patients with pulmonary hypertension found sleep disturbance was associated with activity and HRQOL.\textsuperscript{(10)} Those with sleep disturbance had worse physical functioning and lower mental health HRQOL. Studies have shown that insomnia \textsuperscript{(25)} and sleep quality \textsuperscript{(35)} are associated with functional performance in HF. More investigation is needed to determine possible underlying mechanisms of sleep disturbance than influence HRQOL in PAH.
Sixty percent of our sample reported oxygen use and those patients tended to also have more sleep disturbance than those not reporting oxygen use. Patients with obstructive sleep apnea and EDS were also found to have impaired HRQOL. Nocturnal oxygen desaturation was associated with HRQOL. In patients with stable HF nocturnal brain (B-type) natriuretic peptide (BNP) changes were related to the severity of nighttime hypoxemia but not to the type of sleep-discorded breathing episodes or arousals. No relationship was found between BNP and the frequency of sleep-disordered events. Nocturnal, intermittent hypoxemia in HF was associated with the outflow of cardiac natriuretic peptides from cardiac myocytes, suggesting that nocturnal hypoxia can increase cardiac wall stress and worsen cardiac function. The severity of hypoxemia did not correlate with increased BNP levels. Sleep-disordered breathing in patients with HF may have a negative impact due to hypoxia. Similar to these studies, hypoxemia may be a contributor to sleep disturbance in PAH but more investigation is needed. We did not collect data on how patients were using their oxygen therapy (continuous, as needed, or at night only). There could be an undiagnosed sleep disorder or nocturnal hypoxemia contributing to the perception of disturbed sleep in PAH, but more investigation is needed to clarify the relationship between oxygen use and sleep disturbance.

While our study demonstrates the prevalence of sleep disturbance in patients with PAH is common, the reason for this problem remains unclear. Medications such as beta blockers have been implicated in sleep problems but were not associated with sleep disturbance in PAH, nor were angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor agonists (ARB) in the current study. This may be due to the relatively few people taking beta blockers, ACEI and ARB in this study.

Limitations
This study has several limitations. First, a non-random sample was used for this study. Self-report instruments can lead to recall bias among participants. The sleep measure was only a single item measure from the PAH Symptom Severity Scale. Single item measures have been shown to be valid and reliable in measuring other concepts such as stress, (39) and quality of life.(40) Sleep quality(41) and sleepiness(42) also have been measured using single items. This single item gives a broad but vague description of the type of sleep disturbance in PAH. We also did not measure sleep objectively using polysomnography. PAH has several etiologies, some of the subgroups have very small sample sizes, so there may be differences in how they experience symptoms, psychological distress and HRQOL. The Cronbach alpha of the POMS was borderline in this sample suggesting this may not be the best measure of psychological distress in PAH. Participants self-reported their PAH status, so we do not have verification of their diagnostic hemodynamics to verify the PAH diagnosis. Although PAH primarily affects women, men are underrepresented in this sample. Other clinical variables such as current hemodynamics were not collected and may play an important role in sleep disturbance.

Conclusions

We have established a link between difficulty sleeping and PAH symptoms, psychological distress and HRQOL in PAH. Now a follow up study is necessary to define the nature of the sleep disturbance. This study demonstrates the pervasiveness of sleep disturbance and the interplay among symptoms, psychological distress and HRQOL in patients with PAH. As we continue to describe the symptom experience in PAH, the need for comprehensive symptom assessment is needed in the clinical setting. Assessment of symptoms and sleep disturbance in PAH and implementation of interventions could improve outcomes important to patients such as symptom control, functional status and HRQOL. In addition, improvement in
sleep and other symptoms may have an impact on hospital readmissions, morbidity and mortality outcomes but further research is needed to explore these issues.

In summary, we have demonstrated that those patients with PAH have sleep disturbance and those with increased sleep disturbance have worse PAH symptoms, psychological distress and HRQOL. Future research will need to further define sleep disturbance and underlying mechanisms along with designing and testing interventions to target sleep and symptoms. Working to improve sleep and symptoms may have an important impact on HRQOL.
Implications for Practice

- Sleep disturbance is common in pulmonary arterial hypertension (PAH).
- Those with increasing difficulty sleeping have worse PAH symptoms and health-related quality of life.
- Screening for sleep difficulty in PAH is needed and interventions to improve sleep need to be developed and tested.

Acknowledgements

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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References


Table 1. Socio-demographic and clinical characteristics for the total sample of adults with Pulmonary Arterial Hypertension and separated by sleep disturbance category

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<th>Variable (N=191)</th>
<th>Total N=191</th>
<th>No Sleep Disturbance n=65</th>
<th>Mild Sleep Disturbance (score 1-3) n=54</th>
<th>Moderate Sleep Disturbance (score 4-7) n=41</th>
<th>Severe Sleep Disturbance (8-10) n=31</th>
<th>p-value</th>
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<td>Age (years) Mean ± SD</td>
<td>53.2 ± 15.1</td>
<td>53.2 ± 16.4</td>
<td>54.5 ± 15.2</td>
<td>52.7 ± 51.2</td>
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<td>36 (67%)</td>
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<td>Retired</td>
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<td>79 (41%)</td>
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<tr>
<td>Oxygen Use</td>
<td>115 (60%)</td>
<td>29 (49%)</td>
<td>46 (24%)</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>37 (73%)</td>
<td>14 (24%)</td>
<td>14 (30%)</td>
<td></td>
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<tr>
<td></td>
<td>25 (69%)</td>
<td>14 (30%)</td>
<td>11 (30%)</td>
<td></td>
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<tr>
<td></td>
<td>24 (77%)</td>
<td>7 (24%)</td>
<td>7 (24%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>.858</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CCB</td>
<td>46 (24%)</td>
<td>115 (60%)</td>
<td>46 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERA</td>
<td>95 (50%)</td>
<td>29 (49%)</td>
<td>14 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE-5</td>
<td>110 (58%)</td>
<td>37 (73%)</td>
<td>14 (30%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostanoids</td>
<td>75 (39%)</td>
<td>25 (69%)</td>
<td>11 (30%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>117 (61%)</td>
<td>29 (49%)</td>
<td>14 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>29 (15%)</td>
<td>31 (65%)</td>
<td>14 (30%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>25 (13%)</td>
<td>31 (65%)</td>
<td>14 (30%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>23 (62%)</td>
<td>7 (24%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>.858</td>
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<tr>
<td></td>
<td></td>
<td>23 (79%)</td>
<td>23 (79%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>.473</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>6 (21%)</td>
<td>6 (21%)</td>
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<td></td>
<td></td>
<td></td>
<td>.808</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>3 (10%)</td>
<td>3 (10%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>.828</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>23 (12%)</td>
<td>12 (18%)</td>
<td>7 (13%)</td>
<td>4 (10%)</td>
<td>0 (0%)</td>
<td>.071</td>
</tr>
<tr>
<td>---------</td>
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</tr>
</tbody>
</table>

WHO = World Health Organization; CCB = Calcium channel blockers; ERA = Endothelin receptor antagonists; PDE-5 = Phosphodiesterase 5-inhibitors; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker
Figure 1. Pulmonary Arterial Hypertension total number of symptoms by sleep disturbance groups

a = Post hoc pairwise difference p < .05 between no and mild sleep disturbance
\( ^b \) = Post hoc pairwise difference \( p < .05 \) between no and moderate sleep disturbance

\( ^c \) = Post hoc pairwise difference \( p < .05 \) between no and severe sleep disturbance

\( ^d \) = Post hoc pairwise difference \( p < .05 \) between mild and severe sleep disturbance
Table 2 Pulmonary Arterial Hypertension symptom intensity (mean ± SD) for the full sample and by sleep disturbance groups

<table>
<thead>
<tr>
<th>Symptom Intensity</th>
<th>Total sample N=191</th>
<th>No Sleep Disturbance n=65</th>
<th>Mild Sleep Disturbance (score 1-3) n=54</th>
<th>Moderate Sleep Disturbance (score 4-7) n=41</th>
<th>Severe Sleep Disturbance (score 8-10) n=31</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOB with exertion</td>
<td>6.2 ± 2.7</td>
<td>5.1 ± 2.8</td>
<td>6.1 ± 2.7</td>
<td>6.7 ± 2.3</td>
<td>8.1 ± 2.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0 ± 2.5</td>
<td>3.5 ± 2.4</td>
<td>5.0 ± 2.5</td>
<td>5.8 ± 1.9</td>
<td>6.9 ± 1.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Swelling of ankles/feet</td>
<td>2.9 ± 3.1</td>
<td>1.6 ± 2.5</td>
<td>2.4 ± 2.8</td>
<td>4.1 ± 3.0</td>
<td>5.0 ± 3.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2.9 ± 2.6</td>
<td>2.1 ± 2.2</td>
<td>2.7 ± 2.3</td>
<td>3.0 ± 2.4</td>
<td>4.7 ± 3.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>2.7 ± 3.4</td>
<td>1.5 ± 2.6</td>
<td>2.5 ± 3.1</td>
<td>3.0 ± 3.7</td>
<td>5.3 ± 3.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.6 ± 2.5</td>
<td>1.6 ± 2.0</td>
<td>2.2 ± 2.2</td>
<td>3.2 ± 2.4</td>
<td>5.0 ± 2.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abdominal swelling</td>
<td>2.3 ± 3.2</td>
<td>1.0 ± 2.2</td>
<td>1.9 ± 3.0</td>
<td>3.5 ± 3.6</td>
<td>4.1 ± 3.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cough</td>
<td>2.3 ± 2.4</td>
<td>1.7 ± 2.1</td>
<td>1.9 ± 2.2</td>
<td>2.8 ± 2.7</td>
<td>3.7 ± 3.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>2.2 ± 2.4</td>
<td>1.3 ± 1.7</td>
<td>2.0 ± 2.1</td>
<td>2.6 ± 2.3</td>
<td>3.8 ± 3.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>1.9 ± 2.5</td>
<td>1.0 ± 1.9</td>
<td>1.3 ± 1.7</td>
<td>2.4 ± 2.3</td>
<td>4.1 ± 3.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SOB at rest</td>
<td>1.8 ± 2.3</td>
<td>1.3 ± 1.9</td>
<td>1.5 ± 1.8</td>
<td>1.6 ± 1.8</td>
<td>3.6 ± 3.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SOB lying down</td>
<td>1.7 ± 2.2</td>
<td>0.7 ± 0.9</td>
<td>1.6 ± 2.0</td>
<td>1.9 ± 2.3</td>
<td>3.2 ± 3.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5 ± 2.4</td>
<td>0.7 ± 1.6</td>
<td>1.2 ± 1.8</td>
<td>1.7 ± 2.5</td>
<td>3.2 ± 3.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>1.5 ± 2.3</td>
<td>1.1 ± 2.1</td>
<td>1.0 ± 1.6</td>
<td>1.7 ± 2.5</td>
<td>3.1 ± 2.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Awaken at night SOB</td>
<td>0.9 ± 1.8</td>
<td>0.1 ± 0.4</td>
<td>0.7 ± 1.4</td>
<td>1.1 ± 2.0</td>
<td>2.5 ± 2.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.5 ± 1.5</td>
<td>0.4 ± 1.6</td>
<td>0.3 ± 1.1</td>
<td>0.3 ± 1.1</td>
<td>1.1 ± 2.3</td>
<td>.079</td>
</tr>
</tbody>
</table>

Symptoms rated on 0-10 scale; 0 represents absence of the symptom; 10 represents worse possible symptom intensity. SOB=shortness of breath; Raynaud’s phenomenon= numb, painful hands or feet with cold and stress; p<.05 after correction for significant results for multiple comparisons:

\[ a = \text{Post hoc pairwise difference } p<.05 \text{ between no and mild sleep disturbance} \]
b = Post hoc pairwise difference p<.05 between no and moderate sleep disturbance

c = Post hoc pairwise difference p<.05 between no and severe sleep disturbance

d = Post hoc pairwise difference p<.05 between mild and moderate sleep disturbance

e = Post hoc pairwise difference p<.05 between mild and severe sleep disturbance

f = Post hoc pairwise difference p<.05 between moderate and severe sleep disturbance
Table 3 Mood states in Pulmonary Arterial Hypertension (mean ± SD) for the full sample and by sleep disturbance groups

<table>
<thead>
<tr>
<th>POMS</th>
<th>Total sample N=191</th>
<th>No Sleep Disturbance n=65</th>
<th>Mild Sleep Disturbance (score 1-3) n=54</th>
<th>Moderate Sleep Disturbance (score 4-7) n=41</th>
<th>Severe Sleep Disturbance (score 8-10) n=31</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety⁵,⁶</td>
<td>4.2 ± 4.3</td>
<td>2.4 ± 2.8</td>
<td>4.1 ± 4.0</td>
<td>5.4 ± 5.1</td>
<td>6.4 ± 5.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression⁵,⁶</td>
<td>3.6 ± 4.1</td>
<td>2.0 ± 2.6</td>
<td>3.8 ± 4.3</td>
<td>4.3 ± 3.8</td>
<td>5.9 ± 5.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anger⁵,⁶</td>
<td>3.0 ± 3.4</td>
<td>1.9 ± 2.2</td>
<td>3.3 ± 3.6</td>
<td>3.7 ± 3.6</td>
<td>4.2 ± 4.1</td>
<td>.003</td>
</tr>
<tr>
<td>Vigor⁴,⁵,⁶</td>
<td>6.4 ± 4.5</td>
<td>8.9 ± 4.4</td>
<td>6.1 ± 4.0</td>
<td>4.5 ± 3.9</td>
<td>4.5 ± 3.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fatigue⁵,⁶,⁷</td>
<td>8.7 ± 5.3</td>
<td>6.0 ± 4.5</td>
<td>8.1 ± 4.5</td>
<td>10.2 ± 4.2</td>
<td>13.8 ± 5.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Confusion⁵</td>
<td>4.7 ± 3.2</td>
<td>3.6 ± 2.4</td>
<td>4.8 ± 3.0</td>
<td>5.2 ± 2.8</td>
<td>6.0 ± 4.7</td>
<td>.003</td>
</tr>
<tr>
<td>Total⁴,⁵,⁶,⁸</td>
<td>17.5 ± 18.8</td>
<td>7.0 ± 12.8</td>
<td>16.9 ± 16.5</td>
<td>24.2 ± 16.7</td>
<td>31.8 ± 22.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

POMS=Profile of Mood States; Higher scores indicate worse mood scores, except higher vigor represents increased vigor. Total scores range from -20-100, each subscale score ranges from 0-20.; p<.05 after correction for significant results for multiple comparisons:

⁴=Post hoc pairwise difference p<.05 between no and mild sleep disturbance

⁵= Post hoc pairwise difference p<.05 between no and moderate sleep disturbance
c = Post hoc pairwise difference p<.05 between no and severe sleep disturbance

d = Post hoc pairwise difference p<.05 between mild and moderate sleep disturbance

e = Post hoc pairwise difference p<.05 between mild and severe sleep disturbance

f = Post hoc pairwise difference p<.05 between moderate and severe sleep disturbance
Table 4. Health Status in Pulmonary Arterial Hypertension (mean ± SD) for the full sample and by sleep groups

<table>
<thead>
<tr>
<th>SF-36 Subscale Scores</th>
<th>Total sample N=191</th>
<th>No Sleep Disturbance n=65</th>
<th>Mild Sleep Disturbance (score 1-3) n=54</th>
<th>Moderate Sleep Disturbance (score 4-7) n=41</th>
<th>Severe Sleep Disturbance (score 8-10) n=31</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>37.1 ± 21.2</td>
<td>46.1 ± 22.8</td>
<td>35.9 ± 17.5</td>
<td>31.8 ± 19.1</td>
<td>27.3 ± 20.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical function&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>41.5 ± 25.9</td>
<td>52.6 ± 27.6</td>
<td>35.7 ± 22.8</td>
<td>40.1 ± 24.5</td>
<td>30.3 ± 20.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Role physical&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>36.4 ± 40.3</td>
<td>56.5 ± 41.8</td>
<td>34.7 ± 38.4</td>
<td>22.8 ± 34.0</td>
<td>15.3 ± 28.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain&lt;sup&gt;a,b,c,e&lt;/sup&gt;</td>
<td>66.3 ± 27.5</td>
<td>82.1 ± 21.7</td>
<td>63.7 ± 24.4</td>
<td>61.1 ± 26.0</td>
<td>45.2 ± 28.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitality&lt;sup&gt;b,c,e&lt;/sup&gt;</td>
<td>41.3 ± 22.7</td>
<td>51.3 ± 22.6</td>
<td>42.0 ± 22.7</td>
<td>34.6 ± 18.7</td>
<td>27.7 ± 18.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Social function&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>65.5 ± 26.4</td>
<td>78.7 ± 20.3</td>
<td>63.6 ± 24.9</td>
<td>54.3 ± 28.2</td>
<td>56.0 ± 27.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mental health&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>71.9 ± 19.3</td>
<td>80.9 ± 13.2</td>
<td>70.3 ± 20.2</td>
<td>65.0 ± 20.2</td>
<td>65.1 ± 20.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Role emotional&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>67.0 ± 41.5</td>
<td>81.5 ± 33.3</td>
<td>57.9 ± 42.1</td>
<td>65.1 ± 44.7</td>
<td>54.8 ± 44.4</td>
<td>.003</td>
</tr>
<tr>
<td>Composite Summary scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>61.5 ± 21.0</td>
<td>73.1 ± 15.3</td>
<td>58.6 ± 21.0</td>
<td>54.8 ± 20.0</td>
<td>50.9 ± 22.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical health&lt;sup&gt;a,b,c,e&lt;/sup&gt;</td>
<td>45.4 ± 22.7</td>
<td>59.4 ± 22.2</td>
<td>42.4 ± 18.2</td>
<td>39.0 ± 19.8</td>
<td>29.6 ± 18.4</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Higher scores indicate better health; score range 0-100; p<.05 after correction for significant results for multiple comparisons:

<sup>a</sup>=Post hoc pairwise difference p<.05 between no and mild sleep disturbance
\[ b = \text{Post hoc pairwise difference p}<.05 \text{ between no and moderate sleep disturbance} \]

\[ c = \text{Post hoc pairwise difference p}<.05 \text{ between no and severe sleep disturbance} \]

\[ d = \text{Post hoc pairwise difference p}<.05 \text{ between mild and moderate sleep disturbance} \]

\[ e = \text{Post hoc pairwise difference p}<.05 \text{ between mild and severe sleep disturbance} \]

\[ f = \text{Post hoc pairwise difference p}<.05 \text{ between moderate and severe sleep disturbance} \]
Figure 1. Pulmonary Arterial Hypertension total number of symptoms by sleep disturbance groups

\( ^a \)=Post hoc pairwise difference \( p<.05 \) between no and mild sleep disturbance

\( ^b \)= Post hoc pairwise difference \( p<.05 \) between no and moderate sleep disturbance

\( ^c \)= Post hoc pairwise difference \( p<.05 \) between no and severe sleep disturbance

\( ^d \)= Post hoc pairwise difference \( p<.05 \) between mild and severe sleep disturbance