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Slow-Paced Respiration Therapy to Treat Symptoms in Pulmonary Arterial Hypertension

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Abstract

Objective—To determine the feasibility of using slow-paced respiration therapy to treat symptoms in women with pulmonary arterial hypertension (PAH).

Background—People with PAH report increased dyspnea, fatigue and sleep disturbance that can impair health-related quality of life (HRQOL).

Methods—Ten women with PAH received 8-weeks of daily, 15 minute sessions using slow-paced respiration therapy via the RESPeRATE™ device. Participants had baseline and follow up assessments including plasma norepinephrine and interleukin-6 (IL-6), self-report questionnaires to measure dyspnea, fatigue, depressive symptoms, sleep and HRQOL along with 7-day actigraphy and sleep diaries.

Results—The mean age was 50 years. Adherence to the intervention was 92%. There was decrease in median IL-6 levels [1.3 ± 0.5 to 1.1 ± 0.4 , 95% CI (0.03–0.43)] over the study period. Sleep disturbance decreased, depressive symptoms decreased and HRQOL scores decreased (higher scores indicate worse HRQOL).

Conclusions—In this pilot study, slow-paced respiration therapy is feasible in patients with PAH and may improve symptoms and lower IL-6.

Keywords

pulmonary arterial hypertension; respiration therapy; actigraphy; sleep disturbance

Introduction

Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease affecting primarily young to middle age women (80%).¹ PAH is characterized by elevated pulmonary pressures leading to right heart failure and ultimately premature death.² Treatment regimens can be complex and may not alleviate all symptoms experienced by people with PAH.³ Common symptoms that can be severe, interfere with patients' lives and negatively affect health-related quality of life (HRQOL) include dyspnea, fatigue and sleep disturbance.^{4,5} Sleep disturbance is prevalent in PAH (66%)⁴ and 26% of patients report daytime sleepiness.⁵ In PAH, increasing levels of sleep disturbance are associated with worse PAH symptoms (e.g. dyspnea), psychological distress, diminished HRQOL and reduced physical ability.^{6,7}

The pathobiology of PAH involves activation of the sympathetic nervous system (SNS),^{8,9} proliferation and remodeling of the pulmonary vessels, inflammation¹⁰ and thrombosis. Activation of the SNS is associated with clinical deterioration¹¹ and elevated cytokine levels predict mortality in PAH.¹² Activation of the SNS (elevated norepinephrine; NE levels) is present in people with short sleep.¹³ Interleukin-6 (IL-6) mediates excessive daytime sleepiness and insomnia.¹⁴ Short (< 6 hours) and long (> 8 hours) sleep durations are associated with increased mortality and those associations are partially explained by inflammatory markers (IL-6).¹⁵

One novel, biobehavioral treatment for sleep disturbance is slow-paced respiration therapy using a US Food and Drug Administration-approved device for hypertension. The device

contains headphones and a sensor that attaches to the chest to detect inhalation and exhalation. The musical tones synchronize with the respiratory cycle to slowly guide the user to decrease respirations. RESPeRATE™ moderates effects of the SNS; lowers blood pressure; improves functional capacity and ejection fraction; and significantly decreases pulmonary pressures in left heart failure by decreasing respirations.¹⁶ Interventions such as RESPeRATE™ have the potential to improve sleep disturbance in PAH without negative interactions with other therapies used for PAH. In this pilot study we aimed to: 1) determine the feasibility (adherence and retention) of slow-paced respiration therapy using the RESPeRATE™ device for 8 weeks and 2) estimate the efficacy of slow-paced respiration therapy using the RESPeRATE™ device to decrease sleep disturbance, catecholamine levels (plasma NE) and proinflammatory biomarker levels (plasma IL-6).

Methods

Study Design and Participants

This was a prospective single arm clinical trial. This study was approved by the University of Pennsylvania Institutional Review Board and registered with [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02080533) (NCT02080533) prior to recruitment of participants. We enrolled 10 participants between August 2014 and April 2015. We included women ≥ 21 years of age with a diagnosis of World Health Organization (WHO) Group I PAH (idiopathic, heritable, drug or toxin-induced, or associated with connective tissue disease, congenital heart disease, or HIV). Participants were on targeted PAH therapy at stable doses for at least 3 months. Exclusion criteria included pregnancy, hypotension (systolic blood pressure less than 90 mmHg or diastolic blood pressure less than 60 mmHg), chronic fatigue syndrome, obstructive sleep apnea, restless leg syndrome, narcolepsy, major depression, hospitalized or acutely ill or a lung transplant recipient. Thirty-five females were screened over 6 months (Figure 1). Twenty-two were eligible; 13 patients were ineligible (3 under 21 years old; 10 patients had a medication change in the past 3 months). Six patients declined to participate (4 due to travel to clinic; 2 were traveling during the study period). We enrolled 10 participants of the 16 who were interested in participating. There were 6 patients who were not enrolled because we met our target enrollment of 10 participants. The refusal rate was 27%.

Procedures

The RESPeRATE™ device is a US Food and Drug Administration-approved portable computerized device to lower systemic blood pressure by guiding the person through sessions of therapeutic breathing. The device contains headphones and a sensor that attaches to the chest to detect inhalation and exhalation. The goal of the therapy is to guide the user to the slowest breathing rate that is comfortable for them. Breathing is synchronized with different tones for inhalation and exhalation. The device records and saves the initial breath rate and final breath rate per minute along with how many minutes the device was used for each session.

Participants were asked to use the device for 15 minutes daily for 8 weeks within 2 hours of their usual bedtime. Participants were trained how to use the RESPeRATE™ device by the principal investigator (PI). The PI demonstrated how to wear the device (sensor belt and

headphones) and the participant then provided a return demonstration. Participants then went through the auditory tutorial provided by the RESPeRATE™ device. Participants demonstrated slow-paced respirations and how to use the device to the PI. Participants were also provided a written booklet with instructions on how to use the device. They were also reminded that they could replay the tutorial on the RESPeRATE™ device at any time and/or call the PI for any difficulty using the device. All participants were all able to return-demonstrate the required elements of the device to the PI.

The research coordinator screened potential participants for eligibility; the PI confirmed eligibility. The research coordinator approached patients about their interest in the study at their clinic visit or via the telephone. The PI would approach patients who were interested to explain the study, answer any questions and obtain informed consent. After a 12-hour fast, a urine pregnancy test was performed and the participant's vital signs, height and weight were obtained in the morning of the enrollment day. Phlebotomy for plasma levels of NE and IL-6 was performed after resting in a chair quietly for 15 minutes. Participants then completed a baseline questionnaire including a sociodemographic and medical history interview along with the Multidimensional Dyspnea Profile (MDP),¹⁷ the Multidimensional Fatigue Inventory (MFI),²⁰ the Pittsburgh Sleep Quality Index (PSQI),²¹ the Patient Health Questionnaire (PHQ-8)²³ and the emPHasis-10.²⁵ Participants were instructed how to use the 7-day wrist actigraph and complete the sleep diary, which was to begin on day one. On day 7 (Week 1) participants were called and reminded to stop wearing the actigraph and to return the device along with the 7-day sleep diary in the self-addressed stamped envelope provided. Participants were reminded to begin using the RESPeRATE™ device at the beginning of Week 2, daily for 15 minutes per day. Participants were sent another actigraph to wear the last week of the intervention (Week 8) along with the 7-day sleep diary. After the 9 week study period (one week of baseline actigraphy and eight weeks of slow-paced respiration therapy), participants returned while fasting to repeat vital signs, phlebotomy, and completion of the MDP, MFI, PSQI, PHQ-8 and the emPHasis-10.

Multidimensional Dyspnea Profile (MDP)—The MDP was developed to assess the overall breathing discomfort, sensory qualities and emotional responses to the sensation of dyspnea in research and clinical settings.¹⁷ Participants self-administered the MDP that includes 11 items related to dyspnea (allows for an ‘other’ item designated by the participant) over the past 7 days. Cronbach alpha was 0.82 and the intraclass correlation coefficient was 0.91.¹⁸ and there was a high correlation between the MDP ratings and the modified Borg scale ($r^2=0.64$, $p<0.001$).¹⁷ Higher scores indicate increased dyspnea.

Multidimensional Fatigue Inventory (MFI)—The MFI was self-administered and includes five subscales measuring general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue.¹⁹ There are four items for each subscale and all responses are on a likert scale that range from “yes, that is true” to “no, that is not true”. The response time is “how you have been feeling lately.” Subscale scores range from 1–5 and those scores indicative of fatigue are reversed scored. Each subscale score ranges from 4–20 with higher scores indicating increased fatigue levels. Construct validity was established after comparisons between and within groups, Convergent validity was established by correlating

the MFI-scales with a Visual Analogue Scale measuring fatigue ($r=.22-.78$). Cronbach alpha= 0.84.²⁰

Pittsburgh Sleep Quality Index (PSQI)—The PSQI was self-administered and measures subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction on most nights over the past month.²¹ There are 19 self-rated questions and 5 questions rated by the bed partner or roommate if available. The 19 items form seven component scores that range from 0–3. Zero indicates no sleep difficulty while 3 indicates severe sleep difficulty. The seven component scores are summed to form a global score (0–21). A score greater than 5 indicates poor sleep quality. Sensitivity is 89.6% and 86.5% specificity to distinguish good and poor sleepers. Cronbach alpha=0.83.²¹

Patient Health Questionnaire-8 (PHQ-8)—The PHQ-8 contains eight items to measure depression. Scores range 0–24 where scores 0–3 indicated no-to-minimal depressive symptoms; scores 4–9 indicated mild-to-moderate depressive symptoms; scores 10 is considered major depression, and scores 20 indicated severe major depression.^{22–24} Participants are asked, for example, sleep and energy levels and if they have been “feeling down, depressed, or hopeless.” A score of 10 has an 88% sensitivity and 88% specificity for major depression.²²

emPHasis-10—The emPHasis-10 is a 10-item questionnaire to measure HRQOL in patients with PAH. Questions regarding symptoms such as breathlessness and fatigue are asked along with questions regarding how PAH affects their ability to live and function. Intraclass correlation coefficient=0.95 and internal consistency Cronbach alpha=0.90. EmPHasis-10 scores correlated consistently with WHO functional class (ANOVA $F=1.73$; $p<0.001$). Scores range 0–50 and higher scores indicate greater impairment in HRQOL.²⁵

Assessment of Sleep—The actigraph is a wristwatch-like accelerometer worn on the non-dominant wrist to provide data regarding duration of sleep and daytime naps and sleep disturbance.^{26, 27} Variables derived from actigraphy are: sleep onset latency (SOL), sleep efficiency (SE), total time in bed, total sleep time, wake after sleep onset (WASO), number of awakenings and average awakenings. SOL is the time from trying to initiate sleep to sleep onset. WASO is the time spent awake from sleep onset to final awakening. SE is the ratio of total sleep time to the time in bed.²⁸ The current study used the Actigraph Sleep™ (Pensacola, FL) monitor and sleep diaries were used to reconcile the actigraphy data with self-report. All participants completed a 7-day sleep diary that recorded time in bed, time out of bed, and how many awakenings. In comparison to polysomnography, actigraphy is valid and reliable in assessing sleep-wake patterns $r=0.92$, $p<0.01$.^{29–31} Previously reported agreement between subjective sleep diaries and polysomnographic data was kappa=0.87, with a sensitivity of 92.3% and specificity of 95.6%.³²

Laboratory analysis—For baseline and follow up assessments, blood was centrifuged and plasma samples were immediately stored at -80°C until analysis. IL-6 was analyzed by the MESO Scale proinflammatory IL-6 singleplex # K151QXD (MESO Scale Discovery [MSD], Rockville, MD, USA) in duplicate. Standard curve ranges 0.05 – 203.25 pg/mL and

0.06 pg/mL is the manufacturer defined minimum detectible concentration. Coefficient of variation (CV) inter-assays range 1.1–4.8%. NE was measured using reversed phase high-performance liquid chromatography (HPLC) with electrochemical detection after extraction with activated alumina. Intra-assay coefficient of variability for norepinephrine is 0.7% and 0.63% at 293 and 1234 pg/mL and the inter-assay CV 3.2% and 3.9% at 291 and 1223 pg/mL.

Data Analysis

All data were cleaned and analyzed for potential outliers. All available data were analyzed. Continuous variables are shown as means $\pm$ standard deviation or median and intraquartile range (IQR) and categorical variables as n (percentage). Effect size estimates for change since baseline (Cohen's *d*), were also calculated for all outcome variables. Confidence intervals were also calculated. We analyzed the actigraph data using the Actilife Sleep Software™ v6.12 using the Cole Kripke algorithm³³ in 60 second epochs. We did not have any missing data. Questionnaires were all checked for completeness before participants left the clinic. Participants were all compliant in using and returning the actigraph devices and returning to the clinic for follow up. We calculated that a sample size of 10 participants would result in a two-sided 95% confidence interval with a width equal to .442 (56% to 99%) when the estimated sample proportion for adherence or retention is .90. Adherence was calculated as the number of days the participant used the RESPeRATE™ device by the number of intervention days (56 days). Therefore a sample of 10 was enrolled to show feasibility and to generate preliminary data for effect estimates for use in planning a larger clinical trial.

Results

Ten women were enrolled for this pilot study (Table 1). All participants completed the study baseline and follow up assessments and there was a 92.2% adherence for those completing the 8 weeks of therapy (daily for 15 minutes for 8 weeks) via the RESPeRATE™ device and 100% study retention over the 9-week study period. The mean age was 50.1 ± 13.5 and the racial/ethnic categories were: 60% White (non-Hispanic), 30% Black and 10% Asian, Table 1. Fifty percent of the sample was classified as idiopathic/heritable PAH and 80% of the sample was World Health Organization (WHO) Group functional class II. Seventy percent were taking phosphodiesterase type-5 inhibitors, 40% were taking endothelin receptor antagonists, 40% were using anticoagulants, 30% diuretics and 20% intravenous prostacyclin analogues. No serious adverse events were reported and there were no changes in baseline and follow up blood pressures or hypotension over the study period. Over the study period, the average initial breath rate per minute was 16.6 ± 4.8 at the beginning of the session and the average final breath rate per minute 8.3 ± 4.3 at the end of the session. The average number of minutes for each session that participants used the RESPeRATE™ device over the study period was 10.8 ± 2.5 minutes (each session is a maximum of 15 minutes).

Table 2 presents the results of comparisons between baseline and follow-up measurements of sleep character outcomes (confidence intervals (CI) and effect size estimates). There was a 3.7 unit decrease from baseline to follow-up in WASO after using the RESPeRATE™

device ($d = 0.63$, 95% CI $-9.34-44.59$). There was a small effect for SOL, which decreased by about three minutes ($d = 0.18$, 95% CI $-6.69-7.47$) and a moderate effect for Duration of an Awakening, which decreased by one minute ($d = 0.50$, 95% CI $-0.34-2.23$). There was a small effect for both SE, which increased by 5% ($d = 0.14$, $-9.45-22.67$ 95% CI), and Total Sleep Time, which increased by 19 minutes ($d = 0.20$, 95% CI $-72.54-30.43$). There was also a small effect for Sleep Quality (PSQI) ($d = 0.11$, 95% CI $-0.10-0.50$), which decreased by 3 points (median) at follow-up (lower scores indicate better sleep quality).

Table 3 presents the results of comparisons between baseline and follow-up measurements of MDP and MFI outcomes (CI and effect size estimates). For the fatigue subscales there were decreases in several areas, including General Fatigue ($d = 0.02$, 95% CI $-1.67-1.89$), Reduced Activity ($d = 0.21$, 95% CI $-0.05-0.89$), and Reduced Motivation ($d = 0.10$, 95% CI $-1.53-0.73$). On the Dyspnea subscale there was a decrease in the Anxious subscale ($d = 0.26$, 95% CI $-0.41-2.01$). Depression (PHQ) ($d = 0.26$, 95% CI $-0.13-2.73$) and HRQOL scores ($d = 0.40$, 95% CI $-2.03-12.83$) decreased (higher scores indicate worse HRQOL). IL-6 levels decreased following the intervention [baseline: $M=1.3$ (IQR= $1.1-1.7$); follow-up $M=1.2$ (IQR= $0.8-1.4$); $d = 0.45$, 95% CI $0.03-0.43$], while there was no difference in NE levels.

Discussion

This is the first study to our knowledge to determine the feasibility of using the RESPeRATE™ device to improve symptoms in PAH. Slow paced respiration therapy using the RESPeRATE™ showed a trend in decreasing IL-6 levels and a possible trend in reducing WASO, SOL, and the amount of time when awakened. This study shows the feasibility of using slow-paced respiration therapy via the RESPeRATE™ device in a sample of women with PAH. There was a high rate of adherence. All the participants completed the follow up assessments so that there were no missing data in this small, short-term study.

While a pilot feasibility study, there was a decrease in WASO from baseline to follow up. The baseline WASO ranged between 69–121 minutes and follow up WASO was between 41–92 minutes (normal WASO <30 minutes). The effect size was also in the medium to large range, $d=0.63$. Total sleep time increased by 19 minutes and SE also increased to near normal (normal $\approx 85\%$) with a medium effect. SOL, the number of awakenings and the average time of each awakening decreased. These results are similar to a study of an 8-week yoga intervention for insomnia³⁴ and Qigong, an ancient Chinese practice, which includes slow, rhythmic breathing in healthy individuals.³⁵ Qigong was also found to improve sleep in perimenopausal women³⁶ and women with fibromyalgia.^{37,38,39} Similar to these studies, we also found a decrease in depressive symptoms and self-reported sleep duration (PSQI). Controlled breathing exercises also improved anxiety and depression in a sample of patients with chronic obstructive pulmonary disease.⁴⁰ Our study showed similar trends in improvement in anxiousness (MDP), sleep quality (PSQI), depressive symptoms and HRQOL.

Investigators have shown that PAH is characterized by increased circulating IL-6 levels.⁴¹ We have shown that IL-6 levels are not elevated in a small treated sample of PAH patients in

a clinical trial at baseline.⁴² However, higher IL-6 levels in this population were linked to increased fatigue, anxiety and depression.⁴³ Our pilot data provide preliminary evidence that slow-paced respiration may decrease IL-6 levels leading to improved depressive symptoms and fatigue. Sleep loss can result in increased proinflammatory cytokines (IL-6) and poor sleep quality.⁴⁴ Short (≤ 6 hours) and long (> 8 hours) sleep durations were associated with increased mortality and those associations were partially explained by inflammatory markers (IL-6).¹⁵ Therefore, interventions that improve sleep may decrease inflammation. IL-6 levels decreased after 8 weeks of slow-paced respiration therapy and some sleep variables also showed less sleep disturbance such as WASO.

We did not find a decrease in plasma NE levels. Although we provided a detailed protocol detailing the need to fast and rest for 15 minutes in a comfortable sitting position prior to phlebotomy, these measurements are known to be highly variable and sensitive to a variety of stimuli, including treatments.⁴⁵ Some participants were taking beta blockers and/or diuretics possibly influencing the norepinephrine levels. Although dyspnea did not decrease in this pilot study, the participants' self-reported dyspnea scores were either "no dyspnea" or in the mild range at baseline allowing little room for improvement. Similarly, the fatigue scores were in the mild to moderate range. There were some decreases in general fatigue, reduced activity and reduced motivation.

There are several limitations to this study. This was a pilot feasibility study in a small convenience sample of women without blinding or randomization, making causal inference difficult. A larger randomized controlled trial that is appropriately powered to test the effectiveness of slow-paced respiration therapy to improve sleep disturbance and other PAH-related symptoms is necessary. The sample included mostly WHO functional class II participants (80%). A larger sample with more diversity in WHO functional class would be important. To avoid heterogeneity in this small study we only included women, a larger sample should include men. We also demonstrated the ability to recruit and retain participants in the study with a well-tolerated intervention without any serious adverse events.

Conclusions

In conclusion, in a pilot study of 10 women there was 100% retention and high adherence to the 9-week study period. Slow-paced respiration therapy was associated with reduced plasma IL-6 levels and no serious adverse events occurred. Preliminary results suggest improved sleep including actigraphy (e. g. WASO, sleep efficiency, total sleep time) along with self-reported global sleep quality. Depressive symptoms decreased along with HRQOL scores (lower scores indicated better HRQOL). The subscales on the dyspnea subscales (MDP) decreased (higher scores indicate worse dyspnea) along with the fatigue subscales for general fatigue, reduced activity and mental fatigue (MFI).

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Highlights

- A pilot study of 10 women there was 100% retention and high adherence to the 8-week slow-paced respiration therapy intervention.
- Slow-paced respiration therapy was associated with reduced plasma IL-6 levels and no serious adverse events occurred.
- Preliminary results suggest decreased wake after sleep onset, increased sleep efficiency and increased total sleep time.
- Depressive symptoms decreased and HRQOL scores decreased (higher HRQOL scores indicate worse HRQOL).

Figure 1.
Flow diagram of the progress through the phases

Table 1

Characteristics of Sample of Patients with Pulmonary Arterial Hypertension

Characteristics N=10	Value
Age, years	50.1 ± 13.5
Female	10 (100%)
Race/ethnicity	
White (non-Hispanic)	6 (60%)
Black	3 (30%)
Asian	1 (10%)
WHO Group 1 PAH etiology	
Heritable	3 (30%)
Idiopathic	2 (20%)
Connective tissue disease	3 (30%)
Congenital heart disease	1 (10%)
HIV	1 (10%)
Medications	
Intravenous prostacyclin analogue	2 (20%)
Inhaled prostacyclin analogue	1 (10%)
Endothelin receptor antagonists	4 (40%)
PDE-5 inhibitors	7 (70%)
Combination therapy	4 (40%)
Diuretics	3 (30%)
Anticoagulants	4 (40%)
WHO functional class	
Class II	8 (80%)
Class III	2 (20%)
Body mass index kg/m ²	28.0 ± 4.1

PDE-5=Phosphodiesterase type 5; WHO= World Health Organization

Table 2

Sleep Characteristics from Actigraphy and Pittsburgh Sleep Quality Index

N=10	Baseline Median (IQR)	Follow Up Median (IQR)	Baseline Mean $\pm$ SD	Follow Up Mean $\pm$ SD	Effect Size <i>d</i>	95% CI
Actigraphy Sleep						
Wake after sleep onset (minutes)	90.4 (68.6–121.3)	86.7 (40.5–92.2)	94.4 $\pm$ 27.6	76.8 $\pm$ 28.2	.63	–9.34–44.59
Sleep onset latency (minutes)	7.8 (3.6–12.1)	4.7 (1.5–15.5)	8.7 $\pm$ 6.2	8.3 $\pm$ 9.2	.05	–6.69–7.47
Sleep efficiency	80.0 (76.5–83.0)	85.4 (79.2–88.8)	79.6 $\pm$ 5.4	83.0 $\pm$ 9.2	.43	–9.45–22.67
Total time in bed (minutes)	496.8 (441.4–496.8)	526.5 (449.0–601.1)	515.1 $\pm$ 106.3	518.1 $\pm$ 104.5	.03	–53.45–47.48
Total sleep time (minutes)	413.5 (349.4–510.0)	432.4 (347.9–548.8)	412.0 $\pm$ 99.5	433.1 $\pm$ 112.5	.20	–72.54–30.43
Number of awakenings	17.7 (13.6–21.6)	17.4 (13.3–21.0)	18.1 $\pm$ 4.2	17.2 $\pm$ 6.1	.17	–4.13–5.91
Awakening time (minutes)	5.6 (3.5–6.6)	4.7 (3.2–5.6)	5.5 $\pm$ 2.1	4.5 $\pm$ 1.2	.50	–0.34–2.23
Pittsburgh Sleep Quality Index (PSQI)						
Sleep onset latency*	1.5 (1.0–3.0)	2.0 (1.0–3.0)	1.8 $\pm$ 1.1	2.0 $\pm$ 1.1	.18	–0.86–0.46
Sleep efficiency*	0 (0–3.0)	1.0 (0.8–2.3)	1.2 $\pm$ 1.5	1.4 $\pm$ 1.1	.14	–1.01–0.61
Sleep duration*	1.0 (0–3.0)	0 (0–2.0)	1.3 $\pm$ 1.4	0.7 $\pm$ 0.9	.47	–0.24–1.44
Sleep disturbance*	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 $\pm$ 0.9	2.0 $\pm$ 0.8	.00	–0.34–0.34
Sleep quality*	1.0 (0.8–2.0)	1.0 (0.8–1.3)	1.3 $\pm$ 0.9	1.1 $\pm$ 0.9	.22	–0.10–0.50
Sleep medications*	0 (0–2.3)	0 (0–1.0)	0.8 $\pm$ 1.3	0.5 $\pm$ 1.0	.23	–0.18–0.78
Daytime dysfunction*	0.5 (0–1.3)	0.5 (0–2.0)	0.8 $\pm$ 1.0	0.8 $\pm$ 0.9	.00	–0.58–0.58

N=10	Baseline Median (IQR)	Follow Up Median (IQR)	Baseline Mean ± SD	Follow Up Mean ± SD	Effect Size <i>d</i>	95% CI
PSQI Total **	11.5 (2.8–14.3)	8.5 (4.5–11.8)	9.2 ± 6.1	8.5 ± 4.6	.11	–1.09–2.49

Sleep onset latency: (abnormal > 30mins) Time from the decision to sleep to the onset of sleep.
Wake after sleep onset: (abnormal > 30mins) Time spent awake from sleep onset to final awakening.
Total sleep time: (abnormal <6 hours or >9 hours)
Sleep efficiency: (abnormal <85%) Ratio of total sleep time to nocturnal time in bed

PSQI:

* Minimum Score = 0 (better); Maximum Score = 3 (worse);
** Minimum Score = 0 (better); Maximum Score = 21 (worse) Total PSQI 5 associated with good sleep quality Total PSQI > 5 associated with poor sleep quality

Table 3
Multidimensional Dyspnea Profile (MDP) and Multidimensional Fatigue Inventory (MFI) Scores

N=10	Baseline	Follow Up	Baseline Mean $\pm$ SD	Follow Up Mean $\pm$ SD	Effect Size <i>d</i>	95% CI
MDP						
My breathing requires muscle work <i>or</i> effort.	0 (0–2.8)	1.0 (0–4.3)	1.3 $\pm$ 0.5	1.4 $\pm$ 0.5	.22	–0.33–0.13
I am not getting enough air <i>or</i> I am smothering <i>or</i> I feel hunger for air.	0 (0–2.8)	0 (0–2.8)	1.3 $\pm$ 0.5	1.3 $\pm$ 0.5	.13	–0.78–0.18
My chest and lungs feel tight <i>or</i> constricted.	0 (0–4.3)	1.0 (0–3.5)	1.4 $\pm$ 0.5	1.4 $\pm$ 0.5	.04	–0.81–0.61
My breathing requires mental effort <i>or</i> concentration.	0 (0–5.0)	0 (0–1.3)	1.3 $\pm$ 0.5	1.0 $\pm$ 0.3	.23	–0.10–0.50
I am breathing a lot.	0 (0–3.5)	0.5 (0–2.0)	1.3 $\pm$ 0.5	1.3 $\pm$ 0.5	.05	–1.27–1.47
Depressed	0.5 (0–4.0)	0.5 (0–3.3)	1.9 $\pm$ 2.5	1.8 $\pm$ 2.9	.04	–0.76–0.96
Anxious	1.5 (0–5.8)	0.5 (0–4.3)	2.9 $\pm$ 3.2	2.1 $\pm$ 3.0	.26	–0.41–2.01
Frustrated	0.5 (0–4.3)	0 (0–2.8)	2.0 $\pm$ 2.6	1.8 $\pm$ 3.0	.07	–0.91–1.31
Angry	0 (0–3.0)	0 (0–1.3)	1.4 $\pm$ 2.3	1.2 $\pm$ 2.8	.07	–0.54–0.94
Afraid	0.5 (0–3.0)	0 (0–2.5)	1.7 $\pm$ 2.8	1.6 $\pm$ 2.9	.05	–0.31–0.51
MFI						
General Fatigue	11.5 (8.5–14.3)	10.5 (8.0–13.5)	11.4 $\pm$ 4.4	11.3 $\pm$ 4.1	.02	–1.67–1.89
Physical Fatigue	10.0 (8.5–11.8)	11.5 (7.8–13.3)	10.7 $\pm$ 4.1	11.3 $\pm$ 4.1	.15	–2.12–0.92
Reduced Activity	11.0 (4.8–16.3)	9.5 (4.8–15.0)	11.0 $\pm$ 4.1	9.9 $\pm$ 4.9	.21	–0.46–2.66
Reduced Motivation	7.5 (4.0–10.0)	6.5 (4.0–11.5)	7.6 $\pm$ 3.6	8.0 $\pm$ 4.1	.10	–1.53–0.73

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N=10	Baseline	Follow Up	Baseline Mean ± SD	Follow Up Mean ± SD	Effect Size <i>d</i>	95% CI
Mental Fatigue	4.0 (4.0–11.0)	8.0 (4.0–10.3)	6.5 ± 3.5	7.3 ± 3.0	.25	–2.73–1.13

MDP: Scores range 0–10; 0=none; 10=“the most I can imagine”
MFT: Scores range 4–20; higher scores indicate increased fatigue

Personal Health Questionnaire Depression Scale 8 (PHQ) and emPHasis-10 (Health-Related Quality of Life)

Table 4

N=10	Baseline	Follow Up	Baseline Mean ± SD	Follow Up Mean ± SD	Effect Size <i>d</i>	95% CI
PHQ-8	2.5 (0–8.0)	1.0 (0–6.5)	4.2 ± 4.8	2.9 ± 3.8	.26	−0.13–2.73
emPHasis-10	20.0 (8.5–31.8)	12.0 (5.0–20.0)	21.0 ± 13.1	15.6 ± 13.8	.40	−2.03–12.83

PHQ: Scores range 0–24; scores 0–3 is no-to-minimal depressive symptoms; scores 4–9 mild-to-moderate depressive symptoms; score 10 is considered major depression, 20 is severe major depression.

emPHasis-10: Scores range 0–50; higher scores indicate greater impairment