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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 min 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.



## 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, inflammation[10] and thrombosis. Activation of the SNS is associated with clinical deterioration[11] 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 h) and long (>8 h) sleep durations are

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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 (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 (Fig. 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

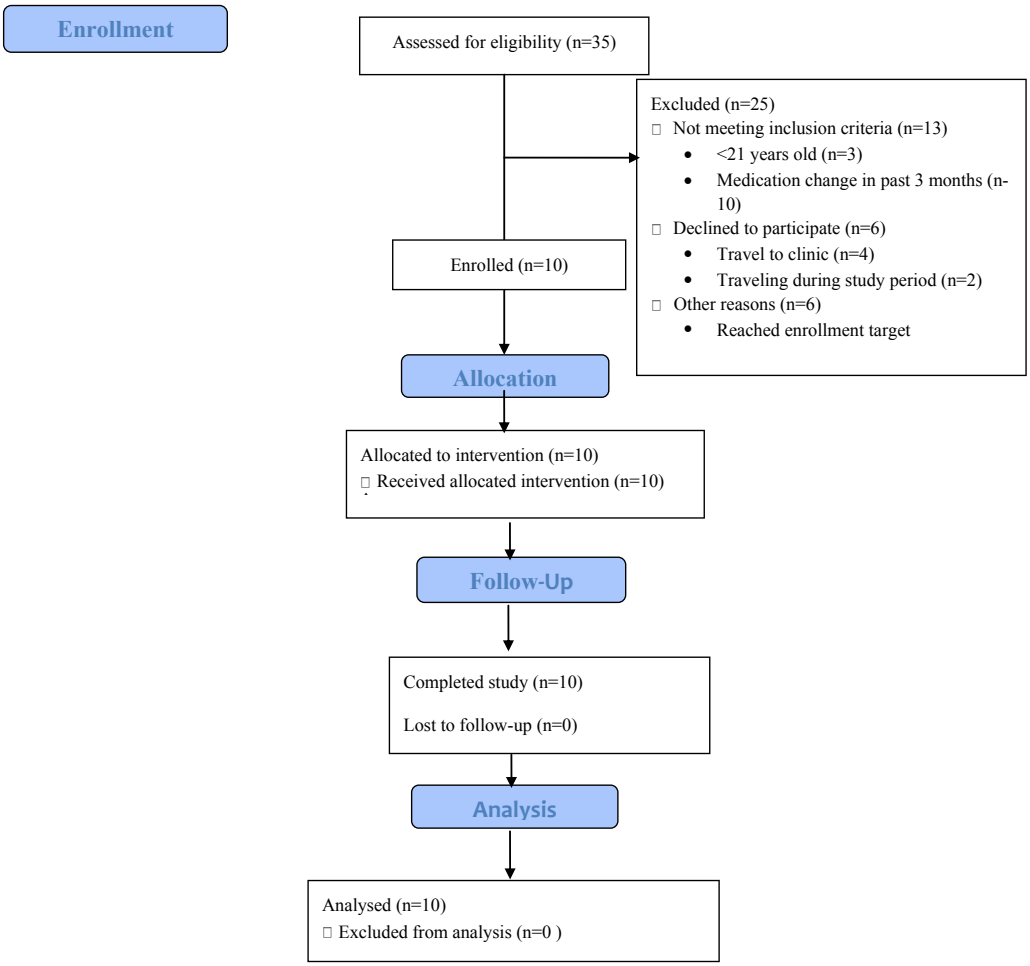


**Fig. 1.** Flow diagram of the progress through the phases.