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Original Research

PULMONARY VASCULAR DISEASE

Benefits of Intensive Treadmill Exercise Training on Cardiorespiratory Function and Quality of Life in Patients With Pulmonary Hypertension

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Background: **Pulmonary hypertension (PH) restricts the ability to engage in physical activity and decreases longevity. We examined the impact of aerobic exercise training on function and quality of life in patients with World Health Organization group 1 PH.**

Methods: **Patients were randomized to a 10-week education only (EDU) or education/exercise combined (EXE) group. The exercise program consisted of 24-30 sessions of treadmill walking for 30-45 min per session at 70% to 80% of heart rate reserve. Outcome variables included changes in 6-min walk test (6MWT) distance, time to exercise intolerance, peak work rate (WR) from a cardiopulmonary treadmill test, and quality-of-life measures, including the Short Form Health Survey, version 2 (SF-36v2) and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).**

Results: **Data are presented as mean ± SD. Twenty-three women (age, 54 ± 11 years; BMI, 31 ± 7 kg/m²) were randomized to the EDU (n = 13) or EXE (n = 10) groups. Following 10 weeks of intervention, patients in the EXE group demonstrated an improvement in 6MWT distance (56 ± 45 m; *P* = .002), increased time to exercise intolerance (1.9 ± 1.3 min; *P* = .001), and peak WR (26 ± 23 W; *P* = .004). Additionally, the EXE group scored significantly (*P* < .050) better on six of the eight scales on SF-36v2, and five of the six scales on CAMPHOR. In contrast, no significant improvement was observed for any of the outcome measures following EDU. No adverse events were noted in either group.**

Conclusion: **Ten weeks of brisk treadmill walking improved 6MWT distance, cardiorespiratory function, and patient-reported quality of life in female patients with group 1 PH.**

Trial registry: **ClinicalTrials.gov; No.: NCT00678821; URL: clinicaltrials.gov**

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Abbreviations: 6MWT = 6-min walk test; AET = aerobic exercise training; AT = anaerobic threshold; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CPET = cardiopulmonary exercise test; EDU = education only; EXE = education/exercise combined; HR = heart rate; HRQoL = health-related quality of life; IPAQ = International Physical Activity Questionnaire; MET = metabolic equivalent; NYHA = New York Heart Association; O_2 = oxygen; $P_{ET}CO_2$ = end-tidal partial pressure of CO_2; PH = pulmonary hypertension; QI = cardiac index; Qt = cardiac output; RPE = Modified Borg Rating of Perceived Exertion; SF-36v2 = Short Form 36 Health Survey, version 2; SV = stroke volume; $\dot{V}CO_2$ = CO_2 expired; $\dot{V}E$ = ventilation; $\dot{V}O_2$ = oxygen uptake; WHO = World Health Organization

Pulmonary hypertension (PH) is mediated through severe microvascular dysfunction, which restricts pulmonary circulation[1] and attenuates cardiorespiratory function,[2,3] ultimately resulting in right-sided heart failure and decreased longevity.[4-6] Patients with PH frequently experience poor health-related quality of life (HRQoL)[7-9] and limitations in their ability to engage in physical activity.[10,11] There are currently nine US Food and Drug Administration-approved medications available for the treatment of PH. While PH-specific therapies have improved longevity,[12-15] prognosis is still poor,[16] and the impact of these therapies on HRQoL is still not well characterized.[6,17,18] All but one of these medications were approved for

use based, at least in part, on moderate improvements on the 6-min walk test (6MWT), which is often used as a surrogate measure of exercise capacity,[11,19] HRQoL,[18] and longevity.[11,19]

Regular participation in an aerobic exercise training program is well recognized to improve both cardiorespiratory function[20] and overall HRQoL[21] in the general population. This includes subsets of patients with illnesses that severely impair cardiorespiratory function.[21,22] The importance of improving cardiorespiratory function through physical activity is further highlighted by the negative association between exercise capacity and mortality in patients with cardiovascular disease.[23,24] In fact, medically supervised aerobic exercise is often encouraged for patients with cardiovascular diseases,[22,25] chronic heart failure,[26,27] COPD,[28] and asthma,[29] with very few adverse events.[25,30-32] Conversely, patients with PH are often advised to limit their participation in exercise and strenuous activities due to concerns over precipitous rises in the pulmonary pressures and the possibility of right-sided heart failure.[10] There is also some uncertainty regarding the ability of patients who have PH to actually obtain clinically important cardiorespiratory benefits from participation in aerobic exercise. Several recent studies, however, have provided evidence that exercise training may be safe for many of these patients.[9,33-37] Two of these studies[9,33] reported clinically important improvements in 6MWT distance, peak oxygen uptake ($\dot{V}O_2$) during supine cardiopulmonary exercise tests, and patient-reported HRQoL following intensive, inpatient, aerobic exercise programs. Despite the encouraging findings of these studies, uncertainty persists regarding the applicability of their interventional methods to current outpatient pulmonary and cardiac rehabilitation standards of care.

We have undertaken a phase 2b, randomized clinical trial aimed at examining safety, clinical outcomes, and mechanisms of adaptation associated with participation in vigorous, medically supervised, aerobic exercise training in patients with PH. We hypothesized that vigorous treadmill walking as a rehabilitation program would be safe and beneficial in this population. The outcomes were achieved using an outpatient, treadmill exercise training protocol that can be easily adopted by most pulmonary and cardiac rehabilitation programs.

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Materials and Methods

Patients

Patients with World Health Organization (WHO) group 1 PH were recruited from local outpatient clinics and enrolled between September 2009 and October 2011. Men and women were eligible if they were between 21 and 82 years of age, had PH diagnosed by a resting mean pulmonary arterial pressure ≥ 25 mm Hg as measured by right-sided heart catheterization, were on stable PH therapies for at least 3 months, were sedentary, and had no pulmonary rehabilitation for 6 months prior to enrollment. To avoid "ceiling" or "floor" effects, patients were excluded if they were classified as WHO and New York Heart Association (NYHA) functional class I and could walk >400 m during a 6MWT, or classified as functional class IV and could not walk >50 m during a 6MWT. Additional exclusion criteria included FEV_1/FVC ratio $\leq 65\%$; history of ischemic heart disease; ejection fraction $<40\%$; documented pulmonary capillary wedge pressure ≥ 18 mm Hg; significant hepatic, renal, or mitochondrial dysfunctions; severe psychiatric disease; use of medications that may limit exercise capacity or ability to adapt to exercise training; antiretroviral therapies; illicit drugs; tobacco use; or pregnancy. Signed informed consent was obtained from the patients prior to any study procedures and data collection. Patients were also told to refrain from engaging in additional exercise not related to the protocol and/or activities that deviated from their regular routine. This protocol was approved by the respective institutional review boards (US National Institutes of Health: number 08-CC-0133; Inova Fairfax Hospital: number 08.129; and George Mason University: number 6057) before recruitment of patients or implementation of procedures.

Study Design

Patients' study eligibility was determined through medical history and physical examination. Afterward, patients completed a symptom-limited, baseline cardiopulmonary exercise test (CPET) on a treadmill; the 6MWT; and HRQoL questionnaires to determine their cardiorespiratory function, functional capacity, and patient-reported HRQoL, respectively. The CPET was a modified Naughton protocol that increased the speed or grade of the treadmill every 2 min (e-Table 1). The first three stages were increased gradually so that the metabolic equivalent (MET) requirements would be small.[38] This allowed patients with severe exercise intolerance to complete at least two to three stages prior to the introduction of a grade component. The rest of the protocol increased speed or grade to approximate one MET increment per stage. This protocol is similar to previous studies[38,39]; however, walking at 2 miles per h was extended (stage 6) by increasing grade rather than speed. A standardized 6MWT was conducted around a circular "course" measuring 80 m, rather than a hallway, as described in the American Thoracic Society Guidelines.[40] Investigators administering the CPET, 6MWT, and questionnaires were blind to randomization at baseline. Patients using supplemental oxygen (O_2) at the baseline visit performed the CPET breathing a hyperoxic gas