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 $\pm$ 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.

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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; O₂ = oxygen; PETCO₂ = end-tidal partial pressure of CO₂; 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; $\dot{V}$ CO₂ = CO₂ expired; $\dot{V}$ E = ventilation; $\dot{V}$ O₂ = oxygen uptake; WHO = World Health Organization

Pulmonary hypertension (PH) is mediated through severe microvascular dysfunction, which restricts pulmonary circulation¹ 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 function²⁰ and overall HRQoL²¹ 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.

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 FEV₁/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 (O₂) at the baseline visit performed the CPET breathing a hyperoxic gas

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mixture (fraction of inspired O_2 of 40%). During the subsequent 6MWT, the O_2 flow rate was set at 6 L/min. Follow-up visits for these patients were performed using the same concentration of supplemental O_2 . Patients were then randomized to either an aerobic exercise training (AET) plus education intervention (education/exercise combined [EXE]) group or an education-only (EDU) control group. Identical educational lectures were given to both groups over 10 weeks. The education sessions consisted of weekly 1-hour lectures on anatomy and physiology, lung disease processes, medication use, oxygen therapy, sleep disorders, preventing infection, airway clearance, interpreting pulmonary function tests, energy conservation, panic control, relaxation techniques, breathing retraining, community resources, advance directives, social well being, nutrition, and benefits of exercise. Only patients in the EXE group participated in 24-30 additional sessions of medically supervised treadmill walking for 30-45 min per session over the same 10-week period. A target exercise intensity of 70% to 80% of each patient's heart rate (HR) reserve obtained from the baseline CPET was used to guide each exercise session. Target HR range was calculated as: $0.7 \text{ and } 0.8 \times (\text{peak HR} - \text{resting HR}) + (\text{resting HR})$, in accordance with the method of Karvonen.⁴¹ Treadmill speed and/or grade were continuously adjusted to keep each patient within or as close as possible to their target HR range. Perceived dyspnea, and exertion, O_2 saturation, and HR were continuously monitored throughout the sessions. The CPET, 6MWT, and HRQoL questionnaires were repeated following the 10-week intervention period in both groups.

Outcome Measures

The primary outcome for this study was the change in 6MWT distance. Secondary outcomes included measures obtained from CPET, such as time to exercise intolerance, $\dot{V}O_{2s}$, time at anaerobic threshold (AT), peak work rate (WR), peak MET as calculated from the speed and grade of the final CPET stage achieved, peak ventilatory efficiency for CO_2 ($\dot{V}E/\dot{V}CO_{2s}$), and peak end-tidal CO_2 (PETCO₂). Gas exchange data were obtained using the MedGraphics Cardio2 Ultima CPET system (Medical Graphics Corp). Peak $\dot{V}O_2$ was determined as an average of the last eight breaths during the last completed stage of the modified Naughton, or the patients' point of maximal exertion, whichever was higher. The AT was identified by V-slope⁴² of continuous breath-by-breath $\dot{V}O_2$ and expired minute volume measurements. Other secondary outcome measures included changes in patients' stroke volume (SV), cardiac output (Qt), and cardiac index (QI), as measured by bioimpedance cardiography (PhysioFlow PF-05; Manatec Biomedical). Arteriovenous O_2 difference was calculated in volume-percent units as the quotient of $\dot{V}O_2$ and Qt. General HRQoL was assessed quantitatively using the Short Form 36 Health Survey, version 2 (SF-36v2), and disease-specific HRQoL was assessed by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), which has been validated in the United States.⁴³

Statistical Analysis

Baseline characteristics of EXE and EDU groups were compared using two-sample *t* tests; categorical variables were examined by χ^2 tests. Paired *t* tests were used to compare within-group differences, and two-sample *t* tests were used for determination of between-group differences. If the test for normality (Shapiro-Wilke) was not met, a Wilcoxon signed-rank test and Mann-Whitney rank sum test was performed instead. A subsequent intention-to-treat analysis was conducted in which the preintervention scores were imputed as the postintervention scores when data were missing at follow-up. Values of $P \leq .05$ (one-tailed) were accepted as statistically significant. All analyses were performed using SigmaPlot, version 12 (Systat Software, Inc). Central tendencies are presented as mean $\pm$ SD.

RESULTS

Of 302 potential patients screened, 26 patients performed baseline testing and were randomly assigned to EXE or EDU (Fig 1). Two of the 26 patients enrolled were subsequently excluded due to medication changes that occurred during participation in the study, and one patient failed to complete the minimum number of training sessions. Therefore, data from the 23 patients in the EXE and EDU groups (Table 1) were included in the analyses. By chance, all study participants were women: 48% were black, and 39% were white. The most common etiology was PH associated with connective tissue diseases (74%), followed by idiopathic PH (22%). Almost all patients were treated with PH medications prescribed as triple- (39%), dual- (26%), or monotherapy (30%). The majority of patients were classified as WHO/NYHA functional class II and III (91%). Baseline cardiac hemodynamics and lung function (as measured in the most recent cardiac catheterization and pulmonary function test before enrollment) were not statistically different between groups. Groups were also similar in terms of 6MWT distance and cardiorespiratory function at baseline.

Patients' level of activity was determined from the self-reported International Physical Activity Questionnaire that records the amount of physical activity performed within 7 days of pretesting and posttesting visits. Analysis of the questionnaire confirmed that patients in the EDU group did not engage in extra activity during the 10-week period, with similar total MET-min/wk being reported at baseline and 10 weeks in this group ($1,335 \pm 1,297$ vs $1,633 \pm 1,418$ MET-min, $P = .247$). In contrast, the EXE group reported significantly more activity being performed after AET ($1,137 \pm 1,226$ vs $3,009 \pm 1,799$ MET-min, $P = .002$). A summary of the training intensity achieved by EXE during 10 weeks of treadmill AET is shown in Table 2. Patients attended 28 ± 2 sessions and exercised for $1,081 \pm 92$ min over the course of 10 weeks. Seven of the 10 patients in the EXE group achieved and maintained their target HR in each of the AET sessions. The three remaining patients achieved 52% to 63% of their HR reserve, approximating 63% to 74% of their peak $\dot{V}O_2$ at baseline. There were no serious adverse events related to the AET sessions.

Outcome Measures

Ninety percent of patients in the EXE group demonstrated an increase in 6MWT distance. Sixty percent increased their distance by ≥ 40 m (Fig 2). Overall, exercise training resulted in a significant ($P = .002$) improvement in 6MWT distance in EXE, whereas no significant change in 6MWT was observed for EDU (Table 3). Large postintervention increases in

FIGURE 1. Participant flow through the stages of the randomized trial.

CPET time to exercise intolerance ($P = .001$), time to AT ($P = .053$), peak WR ($P = .004$), peak METs ($P = .004$), and peak PETCO₂ ($P = .020$) were also observed in the EXE group. No significant changes in peak HR, SV, Qt, arteriovenous O₂ difference, and QI were observed in either group (Table 3). Three patients in the EXE group were excluded, resulting in an uneven comparison between the EXE and EDU groups (Fig 1). However, the intention-to-treat analysis revealed that increases in 6MWT distance (43 ± 46 m), time to exercise intolerance (1.5 ± 1.4 min), and peak WR (20 ± 23 W) remained significant in the EXE group.

Figure 3 displays the results from the SF-36v2 and CAMPHOR, where higher scores on SF-36v2 are indicative of better HRQoL and lower scores on CAMPHOR signify better HRQoL. Significant improvements in physical functioning, role limitations due to physical problems, general health perception, vitality, social functioning, and mental health categories of the SF-36v2 were observed in the EXE group. Significant changes in the SF-36v2 domains were not observed in the EDU group. CAMPHOR scores also improved following AET, when patients reported

better HRQoL and reduction in symptoms experienced in all subdomains, including improved mood, increased energy, and less breathlessness. Only the function domain was unchanged in the EXE group; significant changes were not observed in the CAMPHOR for any domains in the EDU group. An intention-to-treat analysis in the EXE group still revealed significant improvements in the same domains of SF-36v2 and CAMPHOR as the per-protocol analysis.

DISCUSSION

Our results revealed significant improvements in functional capacity, cardiorespiratory function, and HRQoL following 10 weeks of medically supervised, outpatient, treadmill walking in patients with group 1 PH. The control group failed to demonstrate any improvements across these outcome variables. Our study confirms the finding of a clinically relevant improvement in 6MWT distance following AET. Further, the expression of METs based on the last stage attained in the CPET³⁹ suggest that the higher METs attained by the EXE group following AET may be an indicator of improved hemodynamic parameters

Table 1—Baseline Characteristics of Study Patients

Characteristics	Randomized Group		P Value
	EXE Group (n = 10)	EDU Group (n = 13)	
Age, y	53.0 (13.0)	55.5 (8.5)	.295
Female patient, No. (%)	10 (100.0)	13 (100.0)	1.00
Race/ethnicity, No. (%)			.195
White	6 (60.0)	3 (23.1)	
Black	3 (30.0)	8 (61.5)	
Other	1 (10.0)	2 (15.4)	
BMI, kg/m ²	30.2 (7.0)	31.8 (7.4)	.307
Supplemental O ₂ , No. (%)	4 (40.0)	4 (30.8)	.685
WHO group 1 PH etiology, No. (%)			.643
Idiopathic	2 (20.0)	3 (23.1)	
Drug-induced	0	1 (7.7)	
Associated with connective tissue diseases			
Scleroderma	5 (50.0)	5 (38.5)	
Lupus	1 (10.0)	1 (7.7)	
Sjögren syndrome	1 (10.0)	1 (7.7)	
Rheumatoid arthritis	0	1 (7.7)	
Mixed connective tissue disorder	1 (10.0)	1 (7.7)	
NYHA/WHO functional classification, No. (%)			.376
Class I	1 (10.0)	0	
Class II	4 (40.0)	8 (61.5)	
Class III	4 (40.0)	5 (38.5)	
Class IV	1 (10.0)	0	
Drug combination therapy, No. (%)			.191
None	0	1 (7.7)	
Monotherapy	5 (50.0)	2 (15.4)	
Dual therapy	1 (10.0)	5 (38.5)	
Triple therapy	4 (40.0)	5 (38.5)	
Cardiac catheterization			
Mean pulmonary artery pressure, mm Hg	40.3 (13.8)	43.8 (14.2)	.281
Right atrial pressure, mm Hg	8.6 (7.2)	9.0 (6.4)	.298
Pulmonary capillary wedge pressure, mm Hg	9.9 (2.8)	9.4 (2.9)	.348
Pulmonary vascular resistance, dynes/s/cm ⁵	508 (293)	583 (409)	.299
Cardiac index, L/min/m ²	3.3 (1.6)	2.9 (0.7)	.402
Pulmonary function test			
FVC, % predicted	74.3 (17.4)	65.6 (11.3)	.080
FEV ₁ , % predicted	72.4 (15.8)	63.5 (13.1)	.050
Ratio FEV ₁ /FVC, %	81.5 (13.6)	75.8 (7.7)	.107
Performance measures			
6MWT distance, m	411 (73)	377 (97)	.183
CPET variables			
Time to exercise intolerance, min	11.1 (3.1)	9.7 (3.3)	.151
Peak $\dot{V}O_2$, mL/kg/min	17.6 (5.7)	14.7 (5.1)	.111
Peak WR, W	102 (41)	87 (50)	.229
Peak MET	5.3 (1.3)	4.8 (1.6)	.247
Time at AT, min	4.4 (2.2)	4.2 (2.3)	.396

Data given as mean (SD) unless otherwise indicated. 6MWT = 6-min walk test; AT = anaerobic threshold; CPET = cardiopulmonary exercise test; EDU = education only; EXE = education/exercise combined; MET = metabolic equivalent calculated from speed and grade at peak exercise; NYHA = New York Heart Association; $\dot{V}O_2$ = oxygen uptake; WHO = World Health Organization; WR = work rate.

and lower mortality rate⁴⁴ in these patients. A mean improvement of one MET following AET suggests that the risk of death for patients in the EXE group may have been reduced by as much as 17%.⁴⁵ Findings of the current study suggest that supervised AET of relatively high intensity is safe and effective as a therapeutic adjunct for improving functional capacity, cardiorespiratory function, HRQoL, and possibly survival in patients with PH. One factor that differentiates

this study from prior work^{9,33} is that the improvement was achieved in the context of a readily available and accessible outpatient pulmonary rehabilitation program.

The 6MWT distance is commonly used to assess functional capacity in patients with PH because it correlates with peak $\dot{V}O_2$ achieved during CPET⁴⁶ and may predict mortality.^{15,46,47} Some have suggested that achieving a 6MWT improvement ≥ 41 m may be

Table 2—Training Summary of Patients in the EXE Group

Patient	Total Sessions	Total Time, min	Target Training HR (70%-80% HR Reserve)		Training HR				Maximum RPE
			Lower	Upper	Lower	Upper	Mean	% HR Reserve	
1	30	1,030	122	127	108	139	127	80	3
2	24	931	135	141	132	144	137	73	5
3	30	1,155	116	122	114	125	120	77	4
4	28	1,109	124	129	120	135	125	72	3
5	28	1,118	139	146	133	152	144	77	4
6	30	1,200	137	144	126	159	140	74	8
7	27	1,065	115	120	110	124	118	76	5
8	30	1,200	111	116	79	120	102	52	3
9	26	1,023	126	133	95	135	121	63	3
10	25	977	143	151	99	151	130	54	7
Mean	27.8	1,080.8	126.8	132.9	111.6	138.4	126.4	69.8	4.5
SD	2.3	91.6	11.2	12.1	17.2	13.1	12.3	10.0	1.8

HR = heart rate (beats/min); RPE = Modified Borg rating of perceived exertion. See Table 1 legend for expansion of other abbreviation.

an appropriate estimate of the minimally important improvement in distance for clinical significance.⁴⁸ However, others have suggested that the 6MWT alone may not be robust enough to detect differences in treatment outcomes in certain conditions, for example, chronic heart failure.⁴⁹ It is important to note that the present study also used CPET measurements. Indeed, CPET has been recommended over 6MWT for assessing cardiorespiratory changes in response to exercise training.⁵⁰ The results from CPET in the present study mirrors that of the 6MWT findings in that the patients in the EXE group demonstrated significant improvements in both 6MWT

distance and indices of cardiorespiratory function following AET, whereas the patients in the EDU group showed no significant difference in either assessment.

Patients with PH experience elevated $\dot{V}_E/\dot{V}_{CO_2}$ ratios and lower $PETCO_2$ at rest and at peak exercise compared with normal adults.⁵¹⁻⁵³ While this may be a result of ventilation/perfusion inequalities at the lung,² this may also be reflective of increased ventilatory drives in these individuals.⁵⁴ We did not observe a change in $\dot{V}_E/\dot{V}_{CO_2}$ in the EXE group following AET; however, $PETCO_2$ was significantly increased. This likely reflects the higher anaerobic cost and CO_2 produced at the higher workloads attained following AET.

FIGURE 2. Distribution of the improvement observed in the 6MWT distance for both groups. Black bars represent patients in the education/exercise combined (EXE) group and gray bars represent patients in the education only (EDU) group. Dashed black line represents the minimally important difference for 6MWT distance in patients with pulmonary hypertension.⁴⁸ 6MWT = 6-min walk test.

Table 3—Outcome Measures Across Intervention Groups

Outcome Measures	EXE Group			EDU Group			Between-Group Difference, Mean (95% CI)	P Value
	Preintervention	Postintervention	P Value	Preintervention	Postintervention	P Value		
6MWT distance, m	411 (73)	467 (86)	.002	377 (97)	389 (107)	.134	45 (9-80)	.008
Time to exercise intolerance, min	11.1 (2.0)	13.0 (3.1)	<.001	9.7 (3.3)	10.1 (3.7)	.132	1.5 (0.4-2.6)	.004
Peak $\dot{V}O_2$, mL/kg/min	17.5 (5.7)	18.9 (10.3)	.348	14.7 (5.1)	15.1 (5.7)	.318	0.9 (−3.2 to 5.0)	.463
Time at AT, min	4.4 (2.2)	5.6 (2.3)	.053	4.2 (2.3)	4.4 (2.6)	.301	0.9 (−0.5 to 2.4)	.097
Peak WR, W	102 (41)	127 (54)	.004	87 (50)	97 (56)	.084	16 (−6 to 37)	.071
Peak MET	5.3 (1.3)	6.3 (1.8)	.004	4.8 (1.6)	5.2 (1.8)	.110	0.7 (0.0-1.5)	.027
$\dot{V}E/\dot{V}CO_2$ slope at peak $\dot{V}O_2$	40.7 (8.8)	40.6 (9.5)	.462	35.9 (6.5)	35.2 (6.1)	.218	0.6 (−1.9 to 2.1)	.315
PETCO ₂ at peak $\dot{V}O_2$, mm Hg	31.7 (6.5)	33.4 (7.0)	.020	36.8 (6.8)	37.6 (6.6)	.170	0.8 (−1.5 to 3.2)	.230
HR at peak $\dot{V}O_2$, bpm	140 (13)	139 (24)	.467	133 (17)	135 (12)	.191	−3.1 (−13.8 to 7.7)	.279
SV at peak $\dot{V}O_2$, mL ^{a,b}	108 (28)	98 (24)	.134	98 (28)	98 (26)	.464	11 (−11 to 32)	.151
Qt at peak $\dot{V}O_2$, L/min ^{a,b}	15.6 (4.7)	14.4 (4.4)	.238	13.2 (3.9)	13.7 (2.8)	.251	1.7 (−1.9 to 5.3)	.162
a- $\dot{V}O_2$ Diff at peak $\dot{V}O_2$ ^{a,b}	8.7 (3.9)	9.3 (2.4)	.274	10.2 (3.8)	9.9 (2.9)	.367	1.0 (−4.7 to 6.6)	.361
Qt at peak $\dot{V}O_2$, L/min/m ^{2,a,b}	8.3 (2.0)	7.8 (2.0)	.282	6.8 (1.5)	7.0 (1.0)	.233	0.8 (−1.1 to 2.6)	.191

Data given as mean (SD). a- $\dot{V}O_2$ Diff = arteriovenous oxygen difference; PETCO₂ = expired end-tidal CO₂; Qt = cardiac index; $\dot{V}CO_2$ = expired CO₂; $\dot{V}E/\dot{V}CO_2$ = ventilatory efficiency for CO₂; SV = stroke volume. See Table 1 and 2 legends for expansion of other abbreviations.

^aDue to equipment malfunction, n = 8 for EXE.

^bDue to equipment malfunction, n = 9 for EDU.

PH patients are perhaps “used” to high ventilatory drives, and it is possible that AET may have improved their ability to expel CO₂, thereby prolonging their time on the treadmill.

Findings of the current study were in agreement with previous studies, which specifically reported improvements in 6MWT distance,^{9,33,35-37} peak WR,^{9,33} and patient-reported HRQoL.^{9,33,35} In a seminal study by Mereles et al,⁹ inpatients were randomized to either a nonexercising control group, or a 3-week intervention regimen of high-intensity interval training on a cycle ergometer (10-25 min/d, 7 d/wk) combined with flat or uphill walking (60 min/d; 5 d/wk). Patients in the exercise intervention group achieved clinically important increases in 6MWT distance and improvements in HRQoL, as well as small but significant increases in peak $\dot{V}O_2$, peak WR, and WR at AT. However, CPETs were conducted in the supine position and peak HR was significantly higher after AET,⁹ making interpretation of the CPET findings difficult. A more recent, uncontrolled study by the same group with a larger sample size corroborated these findings and expanded the ability to generalize results across several WHO groups.³³ In both studies, an additional 12-week regimen of cycling and walking appeared to result only in a maintenance effect of the initial intervention. Most patients with PH in the United States cannot be hospitalized for rehabilitation, creating uncertainty regarding the relevance of the findings to current clinical practice.

The approach used in the current study was different from the cited studies.^{9,33} Aerobic exercise training and education sessions were carried out in existing clinical pulmonary rehabilitation programs. The regimen provided 90-135 min/wk of AET over 10 weeks at an intensity commonly used in outpatient pulmonary and cardiac rehabilitation programs. Overall, patients in the EXE group completed approximately 1,080 min of AET at their training intensity over the 10 weeks compared with 1,110-1,425 min completed over the 3-week, inpatient, AET regimens in the previous reports.^{9,33} The majority of our patients had an increase in the 6MWT above what has previously been shown to be the minimal important distance.⁴⁸ Additionally, there were significant improvements in HRQoL, CPET time to exercise intolerance, peak WR, and peak METs following AET. Although not statistically significant, the 1.4 mL/kg/min increase in peak $\dot{V}O_2$ obtained by upright treadmill CPET in the current study was nearly identical to the significant increases in peak $\dot{V}O_2$ obtained during supine CPET in previous reports.^{9,33} These results were obtained using only treadmill exercise to perform all CPET and AET sessions. Use of this single mode highlights the ease with which training and testing procedures similar to those used in this study can be implemented.

FIGURE 3. Health-related quality-of-life scores (SF-36v2 and CAMPHOR) for patients in the EXE group (left side) and EDU group (right side). White bars represent preintervention scores and black bars represent postintervention scores. Upright triangle symbols represent scores of SF-36v2 for the United States population.⁵⁷ *P* values are given for all domains and * denotes significant difference ($P < .05$) from preintervention scores. CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; Gen Health = general health; Phys Func = physical functioning; SF-36v2 = Short Form 36 Health Survey, version 2; Social Func = social functioning. See Figure 2 legend for expansion of other abbreviations.

Moreover, results of this study further demonstrate that METs calculated from treadmill speed and grade may be used to estimate cardiorespiratory fitness when measures of gas exchange are not available. The finding of neither a decrease in cardiac output nor the occurrence of a serious adverse event provides further evidence supporting the safety of AET for patients who have PH.

Based on significant improvements in the majority of the SF-36v2 domains, the current study suggests that overall HRQoL may be improved following 10 weeks of AET in patients with PH. This finding was again in agreement with previous reports.^{9,33} The current study expands the existing HRQoL information through a comparison of PH-specific, patient-reported HRQoL based on changes in the CAMPHOR. Patients in the EXE group showed improvements in PH-specific HRQoL, with patients reporting increased energy, improved mood, and less breathlessness following AET. These findings suggest that improved perception of HRQoL in domains specific to PH may accompany the enhanced physical capacity that follows AET.

This study had several limitations. First, our report was limited to patients with WHO group 1 PH of heterogeneous PH etiology, making extension of these results across various WHO clinical classifications difficult. Second, results of this study cannot be generalized across all WHO/NYHA functional classes due to the small sample size and delimitation to patients with functional classes II and III. In addition, by chance, only women met the criteria for inclusion and, thus, our results cannot be generalized to men. Some patients may develop a right-to-left shunt during exercise if a patent foramen ovale is present with greater pressure in the right vs left atrium.⁵⁵ A persistent exercise-induced right-to-left shunt was recently suggested to predict poorer prognosis among patients with PH.⁵⁶ The presence of exercise-induced right-to-left shunt could not be determined in this study and patients did not undergo follow-up right-sided heart catheterization. Inclusion of these measurements would provide additional information regarding right-sided heart function and hemodynamic changes that may occur following AET. Last, the current analysis may be underpowered with respect to the ability to observe

significant increases in cardiorespiratory variables such as peak $\dot{V}O_2$ and AT.

CONCLUSIONS

A vigorous, medically supervised, outpatient, treadmill walking program appears to be sufficient for improving functional capacity, cardiorespiratory function, and general medical and PH specific HRQoL in patients with group 1 PH. It appears that these improvements can be safely achieved at the training intensities, durations, and weekly frequencies that are standard in most pulmonary or cardiac rehabilitation programs. The long-term implications and durability of these improvements are yet to be determined.

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Dr Chan: contributed to the initial conceptualization of the protocol, the research design, data analysis, interpretation of the results, and writing in all sections of the manuscript.

Dr Chin: contributed to data collection, analysis, and interpretation; writing and preparation of the results and discussion section of the manuscript; and overall production of the manuscript.

Ms Kennedy: contributed to subject recruitment, management of institutional review board documents, data collection, and writing and preparation of the method section of the manuscript.

Dr Woolstenhulme: contributed to subject recruitment, data collection and analysis, and writing and preparation of the introduction and methods sections of the manuscript.

Dr Nathan: contributed to the initial conceptualization of the protocol, the research design, data interpretation, and critically revised the manuscript.

Dr Weinstein: contributed to design of the health-related quality of life assessment methods, data analysis and interpretation, and critically revised the manuscript.

Ms Connors: contributed to the intervention oversight, data collection, and general feedback on the manuscript.

Dr Weir: contributed to subject recruitment and general feedback on the manuscript.

Mr Drinkard: contributed to data collection, laboratory operations oversight, and general feedback on the manuscript.

Dr Lamberti: contributed to medical oversight of the pulmonary rehabilitation program at Inova Fairfax Hospital and general feedback on the manuscript.

Dr Keyser: contributed to the initial conceptualization of the protocol, study design, data interpretation and analysis, oversight of study operations, and writing in all sections of the manuscript.

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Additional information: The e-Table can be found in the "Supplemental Materials" area of the online article.

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