Ambulatory Rehabilitation Improves Exercise Capacity in Patients With Pulmonary Hypertension

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ABSTRACT

Background: Rehabilitation is a central treatment modality for patients with chronic cardiopulmonary disease. Physical exertion for patients with pulmonary arterial hypertension (PAH) has typically been discouraged. Inpatient pulmonary rehabilitation has been shown to improve exercise capacity in patients with PAH. The present study aimed to evaluate outpatient pulmonary rehabilitation for patients with PAH.

Methods and Results: Twenty-two patients with PAH or chronic pulmonary thromboembolic disease were allocated to ambulatory rehabilitation (n = 11) or to the control group (n = 11). All patients were stable on PAH-specific medication. The rehabilitation group underwent 24 1-hour sessions of exercise training/rehabilitation over 12 weeks. Primary end points were change in 6-minute walking distance (6MWD) and peak oxygen uptake (VO_2) on cardiopulmonary exercise testing. All of the patients assigned to rehabilitation and 9 control subjects completed the study. In the rehabilitation group, 6MWD increased by 32 m, and in the control group 6MWD decreased by 26 meters ($P = .003$). Peak VO_2 increased in the rehabilitation group by 1.1 mL kg^{-1} min^{-1} and decreased by 0.5 mL kg^{-1} min^{-1} in the control group ($P < .05$). Peak work rate during cardiopulmonary exercise test also increased in the rehabilitation group, with borderline significance ($P = .051$). Echocardiography and blood N-terminal pro−brain natriuretic peptide levels were unchanged. No adverse events occurred due to the rehabilitation program.

Conclusions: Ambulatory rehabilitation is a safe and efficacious treatment for patients with pulmonary hypertension already on medical therapy.

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Key Words: Exercise, heart failure, oxygen uptake, pulmonary hypertension, rehabilitation.

Pulmonary arterial hypertension (PAH) refers to a group of diseases characterized by increased pulmonary vascular resistance leading to right ventricular failure.[1] A similar clinical presentation may be seen with chronic pulmonary thromboembolic disease (CTE). Over the past 15 years, there have been significant advances in the pharmacologic treatment of PAH.[1] However, patients with PAH continue to suffer from dyspnea, physical limitation, decreased quality of life, and premature death.

Cardiopulmonary rehabilitation aims to maximize the patient's ability to function despite their disease.[2,3] Patients are rehabilitated through an individualized program of aerobic and resistance exercise training. In addition, rehabilitation should include patient education, risk-factor management, and optimization of medical therapy.[2] Rehabilitation is now considered to be a standard of care for patients with cardiac failure and ischemic heart disease as well as chronic obstructive pulmonary disease and other chronic lung diseases.[2−4]

The role of exercise training/rehabilitation is evolving in the treatment of PAH. Traditionally, PAH patients have been advised to limit their physical activity and maintain a sedentary lifestyle to avoid provoking PAH symptoms, notably exercise-induced syncope.[5] Mereles et al[6] published a landmark article in which 30 PAH patients were randomized to normal physical activity or intensive inpatient rehabilitation for 3 weeks followed by a home exercise program for 12 weeks. In the rehabilitation group, there were dramatic improvements in 6-minute walk distance

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(6MWD), oxygen uptake (VO_2), and quality of life compared with the control group. No adverse events occurred due to the training program. The practical application of that study is hampered by the limited availability and high cost of inpatient rehabilitation. Recently in an uncontrolled study, de Man et al[7] described improved exercise endurance after exercise training in PAH patients. Exercise training has recently been recommended as part of the comprehensive care of the PAH patient.[1]

The aim of the present study was to evaluate conventional outpatient rehabilitation for PAH/CTE patients. Our hypothesis was that ambulatory rehabilitation would improve exercise capacity.

Methods

The study was prospective. Patients were allocated nonrandomly into treatment groups according to their willingness and ability to attend the rehabilitation course. The study was monitored by the Institutional Review Board. Each of the patients signed a written informed consent. The trial was registered at clinicaltrials.gov (ID: NCT00544726).

Inclusion/Exclusion Criteria

Patients >18 years old were eligible for inclusion if they met the following criteria: PAH as defined by the standard hemodynamic criteria at right-heart catheterization (mean pulmonary artery pressure >25 mm Hg at rest, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance >3 Wood units)[1]; diagnosis of idiopathic-PAH, PAH-associated conditions, or CTE; clinically stable on PAH-specific medication (prostanoids, phosphodiesterase-5 inhibitors, endothelin receptor antagonists, or calcium-channel blockers) for ≥3 months before enrollment; and New York Heart Association (NYHA) functional class II-III.

Patient were excluded for the following reasons: NYHA functional class I or IV (safety concerns); PAH due to congenital heart disease with a right-to-left shunt, left heart disease, chronic hypoxemia, or chronic lung diseases (defined as total lung capacity or forced exhaled volume in 1 second <60% of predicted); acute intercurrent illness requiring hospital admission in the month proceeding screening; any non-PAH medical condition likely to interfere with participation in or completion of the program, eg, musculoskeletal disorders, terminal malignancy; participation in another rehabilitation scheme within 6 months of enrollment in the study.

Patient Assessment

All patients underwent a clinical assessment including full history and physical examination. Six-minute walk (6MW) tests were performed by a technician unaware of the patient's study allocation, in accordance with published guidelines.[8] Cardiopulmonary exercise testing (CPET) was performed on a cycle ergometer/metabolic cart device ($CardiO_2Max$; Medical Graphics, St. Paul, Minnesota). The CPET protocol was 2 minutes sitting at rest on the ergometer, 2 minutes of unloaded pedaling followed by a 15 W/min ramp to the subjects' self-perceived maximal exertion. Electrocardiograms, oxygen saturation (SpO_2), and Borg scores were recorded at 2-minute intervals. The anaerobic threshold was determined from the V-slope method. For each CPET examination, we calculated the VE/VCO_2 slope (VE, minute ventilation; VCO_2, carbon dioxide production) and the oxygen uptake efficiency slope (OUES, the slope of logVE vs VO_2). These parameters reflect ventilatory efficiency and oxygen uptake, respectively, throughout the entire exercise test rather than just peak values. Both are useful prognostic indicators for patients with heart failure.[9] Echocardiography was performed by a cardiologist unaware of the subject's study allocation to estimate systolic pulmonary artery pressure (SPAP) and cardiac output. N-terminal fragment of pro−brain natriuretic peptide (NT-proBNP) levels were measured in whole blood samples (Cardiac Reader; Roche Diagnostics, Indianapolis, Indiana). Historical data from diagnostic right-heart catheterization were extracted from the patients' files, and invasive hemodynamics were not measured specifically for the study.

Rehabilitation Protocol

Subjects in both study groups were advised to continue their normal routine daily activities. No changes were permitted in PAH-specific medication during the study. Subjects in the rehabilitation group underwent 24 biweekly 1-hour sessions of exercise training in the pulmonary rehabilitation center of our institution. The subjects attended sessions together at fixed times to encourage camaraderie and mutual support. Sessions were led by a physiotherapist experienced in rehabilitation and were supervised by a study physician. Patients were monitored with pulse oximetry. Exercise intensity was titrated according to patient tolerance, heart rate (HR) (to achieve 60%−80% of CPET maximal HR), and oxygen saturation, and rest on a chair was permitted as required. Supplemental oxygen was provided for subjects with oxygen desaturation during exercise (SpO_2 <90%).

The training program consisted of two 6-week blocks. In the first block, subjects did interval training with treadmill walking, cycling, and step climbing. In the second block, subjects performed longer periods of continuous aerobic exercise, with resistance training by step climbing, unsupported arm/leg exercises with and without dumbbells (0.5−1 kg), and supporting body weight over a chair. We also recommended to patients in the exercise group to add daily home-based exercise with stair-climbing and brisk walking, after establishing patient-awareness of safe levels of physical activity. Patients were supported medically and psychologically as required and were given encouragement throughout the program.

Outcome Measures

The primary outcome was change in the patient's 6MWD and VO_2 during the CPET after 12 weeks. The secondary outcome measures were changes in cardiac function (SPAP, cardiac output, and NT-proBNP levels), other parameters derived from the CPET, and adverse events.

Statistical Analysis

Data were analyzed by a professional statistician using SPSS 15.0 (SPSS Corp, Chicago, IL). Analysis was by intention to treat. Categoric data were analyzed with Fisher exact test or chi-square as appropriate. For continuous data, nonparametric tests were used owing to the nonnormal distribution of the data. The change (delta) in the various parameters was calculated for each subject, and the 2 patient groups were compared with the Mann-Whitney U test on the delta. A P value of <.05 was considered to be a statistically significant result.

Results

Patients

Eleven patients were enrolled into each group. The groups were similar regarding demographic data, disease subtype, and treatment (Table 1). At baseline, the rehabilitation group had significantly lower 6MWD ($P = .048$) and a trend toward lower peak VO_2 ($P = .095$) (Table 1). Attendance at exercise sessions was high (250/264, 95%). Owing to intercurrent adverse events (see below) only 9 control patients could be retested at the end of the study period.

Primary End Points

Patients in the rehabilitation group showed a significant improvement in both primary endpoints (Table 2). 6MWD increased 32 m in the rehabilitation group compared with a deterioration of −26 m in the control group ($P = .003$). The change in 6MWD for each subject is shown in Figure 1. Peak VO_2 increased in the rehabilitation group by 1.1 mL kg^{-1} min^{-1} versus a slight decrease (−0.51 mL kg^{-1} min^{-1}) in the control group ($P = .02$). In a within-groups analysis, control patients' 6MWD decreased significantly (paired Mann-Whitney test: $P = .01$), whereas there was a significant increase in 6MWD in the rehabilitation group (paired Mann-Whitney test: $P = .026$).

Secondary End Points

In the secondary exercise endpoints there was a significant increase in VE ($P = .02$) in the rehabilitation group. Peak work rate also increased in the rehabilitation group with a borderline significance ($P = .051$). Peak HR was unchanged in both groups. Oxygen pulse (VO_2/HR) and peak Borg score showed nonsignificant trends to increase in the rehabilitation group ($P = .08$ for both). No significant changes were seen in VE/VCO_2 slope or OUES. No significant changes were observed in resting echocardiographic parameters or NT-proBNP levels (Table 2).

Table 1. Baseline Characteristics of the Patients

	Control	Rehabilitation	*P* Value
Patients (n)	11 (6M/5F)	11 (1M/10F)	.063
Age (y)	46 ± 4.5	57 ± 3.7	.14
Weight (kg)	65 ± 9.4	74 ± 6.5	.49
Systolic BP (mm Hg)	115 ± 4	111 ± 4	.59
Diastolic BP (mm Hg)	75 ± 4	68 ± 3	.36
Hemoglobin (g/dL)	13.0 ± 0.9	12.5 ± 0.7	.65
PAH diagnosis (n)			.167
Idiopathic	7	3	
Connective tissue disease	4	5	
Congenital heart disease	0	1	
Chronic thromboembolic	0	2	
Treatment			
PDE5 inhibitor	6	4	.67
Endothelin antagonists	7	7	1.0
Prostanoids	5	3	.65
Monotherapy	4	8	.11
Combination therapy	7	3	
Historic cardiac catheterization			
mPAP (mm Hg)	45 ± 5	57 ± 6	.6522
PVR (Wood units)	11.8 ± 3.1	13.5 ± 1.7	.33
CI (L min^{-1} m^{-2})	3.4 ± 0.9	2.03 ± 0.25	.09
RAP (mm Hg)	8 ± 2	8 ± 1	.702

Continuous variables are given as mean ± SE unless otherwise stated. Note that right heart catherization data were at the time of diagnosis and not related to the present study. BP, blood pressure; CI, cardiac index; mPAP, mean pulmonary artery pressure; PDE5 phosphodiesterase-5; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

Adverse Events

No adverse events occurred during the exercise training sessions. In the rehabilitation group, 1 patient was admitted for anemia which recovered by the end of the study. In the control group, there were 3 serious adverse events resulting in 2 study drop-outs. One patient in the control group experienced a clinical worsening of PAH and died despite hospital admission and treatment with intravenous epoprostenol. Another control group patient was diagnosed with lung cancer requiring pulmonary resection and he was therefore not retested. One patient in the control group was admitted for community-acquired pneumonia and recovered fully by the end of the study and was retested.

Discussion

We performed a controlled trial of ambulatory rehabilitation for PAH and CTPE patients on medical therapy. We demonstrated a significant improvement in 6MWD and VO_2 in the rehabilitation group compared with the control group. No adverse events occurred during the exercise training. The improvement in 6MWD distance is broadly similar to those achieved in pharmaceutical trials of PAH-specific medications.[1]

The present results are consistent with earlier studies of rehabilitation in PAH.[6,7] The improvement in exercise capacity in our cohort was more modest than in Mereles' group. Exercise training seems to have a dose-response relationship in other patient groups undergoing pulmonary rehabilitation, and Mereles et al noted that patients who exercised more hours showed better improvement.[3,6]

This study is important, because it is the first controlled study to show the safety and efficacy of exercise training in PAH patients in the context of an ambulatory ''real-world'' setting. Indeed, the nonrandomized design also reflects ''real-world'' practice where not all patients are prepared or logistically able to commit to an exercise program, and those who do derive, benefit. Our exercise program should be replicable and reimbursable in most modern health care systems that offer cardiopulmonary rehabilitation. An important limitation in our study was the nonrandomized design. This was due to difficulty in recruiting subjects into a randomized study and resulted in some differences between the groups at baseline. The rehabilitation group had lower exercise capacity at baseline, with lower 6MWD ($P = .048$) and a trend toward lower VO_2 ($P = .09$). We speculate that this may be a result of lower utilization of combination therapy in this group. Nevertheless, these

Table 2. Exercise Capacity and Cardiac Function in the 2 Groups

	Control Baseline	Rehabilitation Baseline	Control Delta	Rehabilitation Delta	*P* Value
6MWD (m)	425 ± 24	353 ± 18*	−26 ± 6	32 ± 11	.0033
NT-proBNP (ng/L), median (IQR)	480 (130 to 1,360)	177 (127 to 1,710)	51 (0 to 221)	214 (−240 to 645)	.59
NYHA functional class					
II	9	4	0	0	0.6
III	2	7	−1	−1	
CPET results					
Peak VO_2 (mL kg^{-1} min^{-1})	11.6 ± 1.65	8.2 ± 0.56	−0.5 ± 0.3	1.1 ± 0.3	.020
Peak work rate (W)	57 ± 7	37 ± 6	−5 ± 6	14 ± 5.5	.051
Peak HR (beats/min)	130 ± 4	122 ± 4	−8 ± 2	−7 ± 3	.75
Peak VE (L/min)	45 ± 4	38 ± 5	−1.4 ± 1.4	6 ± 2	.026
O_2/HR (mL $min^{-1}beat^{-1}$)	5.6 ± 0.4	4.8 ± 0.4	0 ± 0	1 ± 0.4	.08
RER	1.11 ± 0.02	1.06 ± 0.02	−0.01 ± 0.01	0.03 ± 0.01	.09
Borg score	16 ± 0.3	15 ± 0.35	−0.2 ± 0.7	2 ± .4	.08
SpO_2 at peak	92 ± 1	85 ± 3	−1 ± 0.8	−2 ± 2	.61
AT (% predicted VO_2 peak)	27 ± 2	30 ± 2	2 ± 0.8	7 ± 0.8	.10
VE/VCO_2 slope	52.1 ± 8.1	60.0 ± 5.7	0.43 ± 1.53	0.84 ± 3.79	.93
OUES	0.86 ± 0.11	0.75 ± 0.08	0.06 ± 0.04	0.1 ± 0.08	.86
Echocardiography					
sPAP (mm Hg)	69 ± 7	62 ± 9	−1 ± 3	3 ± 7	1.0
Cardiac output	4.6 ± 0.3	4.7 ± 0.3	−0.4 ± 0.3	−0.6 ± 0.2	.77

Data are shown as mean ± SE unless otherwise stated. In the control group, only 9 subjects were analyzed at the end of the study. 6MWD, 6-minute walking distance.

AT, anaerobic threshold; NT-proBNP, N-terminal fragment of pro−brain natriuretic peptide; HR, heart rate; IQR, interquartile range; NYHA, New York Heart Association; RER, respiratory exchange ratio; SpO_2, oxygen saturation; sPAP, systolic pulmonary artery pressure; VO_2, oxygen uptake; VE, minute ventilation; VCO_2, carbon dioxide production; OUES, oxygen uptake efficiency slope.

*Significant difference between the groups at baseline.

sicker patients showed significant improvement without adverse effects.

There was a decrease in exercise capacity in the control group. This has typically been described in the placebo arm of PAH-specific drug trials. Patients on long-term monotherapy or on placebo in combination therapy trials are usually more stable.[10,11] In Mereles et al's study also, 6MWD decreased in the control group. We speculate that the absence of placebo effect in nonpharmaceutical trials may explain this phenomenon.[6] It should be noted, however, that the statistical significance of the improvement in the rehabilitation group was not dependent on the decrease in the control group (P = .026). Investigator bias in our data should be minimal, because most of the outcome measures were both objective and quantitative and were measured by technicians/physicians uninvolved with the study. The exercise-group subjects may have performed better in post-rehabilitation exercise testing owing to motivational factors. In the CPET, however, there were no significant changes in respiratory exchange ratio or Borg scores in either group, suggesting that changes in peak VO_2 and work rate were not motivational. Despite the methodologic issues, we believe that ambulatory rehabilitation has a demonstrable positive effect on exercise capacity in the PAH/CTE population, although the exact magnitude of the effect remains unclear. The questions raised by this study can only be resolved in a large multicenter randomized trial.

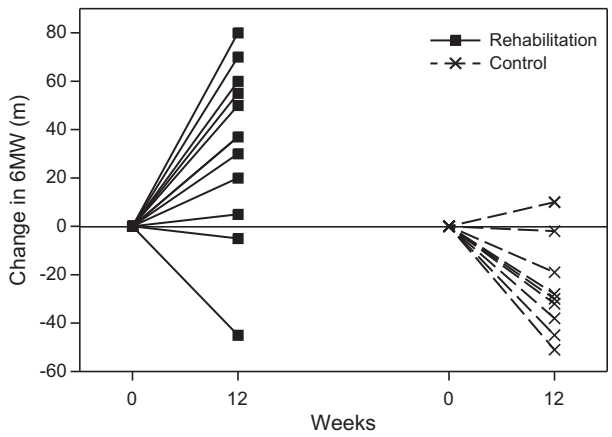

Fig. 1. Individual changes in 6-minute walking (6MW) distance for patients with pulmonary hypertension.

The mechanism by which rehabilitation improves exercise capacity in these patients is not entirely clear. Earlier studies by Sun et al[12] have shown that exercise intolerance in PAH patients is multifactorial, including ventilation-perfusion mismatching, right-to-left shunting, and decreased cardiac output. There is also evidence of impaired skeletal muscle function in PAH patients, leading to reduced peripheral oxygen extraction and respiratory muscle weakness.[13,14] Patients with chronic heart failure may also have impaired exercise tolerance owing to activity of muscle metaboreceptors, and it is reasonable to presume that a similar mechanism exists for patients with PAH.[15] As many as one-third of patients with PAH have symptoms of depression and/or anxiety which can also affect physical function.[16] Patients with chronic disease frequently enter a vicious cycle of dyspnea, physical inactivity, muscle loss, and deconditioning, and it is fair to assume that PAH patients are no different.[17] Work by de Man et al[7] demonstrated changes in quadriceps muscle function after

exercise training in PAH patients, including increased oxidative capacity and muscle fiber diameter. Of note in the present work, there was no change in OUES or VE/VCO_2 slope, NT-proBNP, and echocardiography, suggesting that cardiac performance and gas exchange were not affected by rehabilitation, although our study lacks power to confirm this definitively. Similarly, Mereles et al[6] deduced that improved exercise capacity in the rehabilitation group resulted from changes in skeletal muscle function, because cardiac output on exercise echocardiography was unchanged, as was minute ventilation during the CPET. To summarize, the present literature suggests that rehabilitation benefits PAH patients by improving skeletal muscle function rather than by changing pulmonary hemodynamics or gas exchange, emphasizing that this treatment modality is complementary to conventional medical therapy.

Conclusions

In conclusion, we performed a controlled study of ambulatory rehabilitation for patients with medically treated PAH or CTE. Rehabilitation was safe and effective in increasing exercise capacity, and should be considered an adjunct to medical therapy. There is much work to be done to determine how best to rehabilitate patients with this devastating disease.

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Disclosures

None.

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