The Effects of a 10-wk Outpatient Pulmonary Rehabilitation Program on Exercise Performance, Muscle Strength, Soluble Biomarkers, and Quality of Life in Patients with Pulmonary Hypertension

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ABSTRACT

Purpose

Pulmonary arterial hypertension (PAH) is characterized by right ventricular failure, leading to exertional dyspnea, skeletal muscle weakness, and poor quality of life (QOL). Apart from treatment with PAH-specifi c drugs, guidelines recommend pulmonary rehabilitation (PR). Clinical PR programs have shown improvement in functional capacity and QOL. However, little is known about the effectiveness of an outpatient PR program. The aim of our study was to assess effectiveness of a multidisciplinary outpatient PR program.

Methods

Patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH), who were in a stable condition on optimized drug therapy, followed a 10-wk outpatient program in a rehabilitation center. The PR program was designed to improve exercise capacity and health status by means of low load cycling, walking, and muscle training twice a week combined with psychological counseling. QOL was measured by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire.

Results

Twenty-one patients (13 women) with PAH (n = 16) or CTEPH (n = 5) completed the study. All patients were in New York Heart Association (NYHA) functional class III, and their mean age was 45 ±16 yr. After PR, the mean cycling endurance time increased by 4.4 min ($P < .001$), 6-min walk distance by 12.2 m ($P < .05$), and maximum inspiratory pressure by 5.8 cm H_2O ($P = .01$). Skeletal muscle function increased significantly. The CAMPHOR questionnaire demonstrated significant decrease in symptoms and improvement in QOL. Soluble biomarkers did not show any change before and after PR.

Conclusions

Outpatient PR could be an effective instrument to improve exercise capacity and health status in patients with PAH or CTEPH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and incurable condition of the pulmonary vasculature, characterized by increased pulmonary vascular resistance and elevated pulmonary arterial pressure leading to progressive right ventricular (RV) failure. Despite improvement in specific medical treatment of PAH over the last years, patients with PAH still suffer from significant dyspnea, fatigue and skeletal muscle weakness, resulting in exercise limitation/intolerance and poor quality of life (QOL).[1] Exercise intolerance is a key feature in PAH for which the underlying hemodynamic impairment is primarily responsible.[2] Several studies however demonstrated that beside hemodynamic impairment and ventilatory - perfusion mismatches, respiratory and skeletal muscle dysfunction plays an important role in exercise limitation in PAH patients[3-8] and therefore is an important determinant for exercise limitation.[9-12]

Since muscle impairment limits PAH patients in their daily life activities it has a strong negative influence on QOL.[4,13,14] Reduction in muscle dysfunction and exercise intolerance are therefore recognized to be important goals in the treatment of PAH patients. Exercise programs have been shown to improve muscle function by increasing type 1 fiber surfaces.[6,15] Moreover, previous studies have shown both a shift from type IIx to type IIa fibers and a total increase in type II fibers. Furthermore, exercise programs have been demonstrated to improve muscle capillarization,[6,15] muscle strength and exercise capacity in PAH patients.[5,16,17] This not only results in a higher physical activity level but also results in improvement in health-related QoL measured by the 36- item Short Form Survey (SF-36).[18-20]

Historically, patients with PAH were recommended to restrain from physical activity, including pulmonary rehabilitation (PR) because of poor prognosis and risk of sudden cardiac death. In 2006, Mereles et al.[18] were the first to demonstrate in a small randomized controlled trial that exercise training is safe and has beneficial effects on functional capacity and QOL.

Little is known so far about the effect of exercise training on RV function. Most studies did not show a significant effect, while some showed a minor decrease in systolic RV pressure measured by echocardiography.[18,20-22] The underlying mechanism has not yet been elucidated, although in a rat model it was shown that exercise training may lead to less pronounced pulmonary vascular remodeling, and only high intensive training lowered RV systolic pressure and RV hypertrophy.[23,24] Biomarkers such as N-terminal pro B-type natriuretic peptide (NT-pro BNP) and high sensitive troponin-T (HsTnT), are recognized as markers of RV function and are negatively associated with outcomes in

patients with Pulmonary Hypertension (PH).[1] We therefore investigated these markers in our patient group before and after PR program as a marker of RV function.

In recent years, evidence for the beneficial effects of PR is increasing.[25-27] The European Respiratory Society (ERS) and the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PH recommend supervised rehabilitation programs in expert centers for PAH patients in stable condition on optimized PH specific drug therapy.[1] However, most programs so far have been carried out in a hospital setting or were at least started in a hospital setting. Unfortunately, programs in a hospital setting are not always feasible for patients.

We know that PAH as a disease that has great impact on the QOL of these patients.[28] This has also been shown by a QOL questionnaire specifically designed for patients with PAH, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[29,30] We therefore decided to offer a PR program with a multidisciplinary approach including: educational sessions, psychological counseling, advice by an occupational therapist, dietary advice, and group sessions with fellow patients.

Since knowledge about the safety and effectiveness of a PR program in an exclusively outpatient setting is still lacking, our goal was to develop an achievable multidisciplinary outpatient PR program.

We considered withholding PAH patients from a PR program at this stage not to be ethical. This study has therefore specifically been designed as a prospective cohort study.

The aim of our study was to assess the effectiveness of such an outpatient PR program on exercise capacity, muscle strength, soluble biomarkers and QOL.

METHODS

Study design

This prospective cohort study was conducted from January 2016 until December 2017 as a collaboration between the Erasmus University Medical Centre (Rotterdam, The Netherlands) and the Revant Rehabilitation Centre (Breda, the Netherlands). Patients underwent an evaluation at the rehabilitation center before entering the program. They followed an outpatient PR program for 10 wk consisting of 2 sessions per week. Immediately after the PR program an assessment was performed for the effectiveness of the program.

Study procedure

All patients were diagnosed according to the ERS/ESC guidelines.[1] Patients in World Health Organization (WHO) groups I and IV were eligible for the study. Patients had to be in a clinically stable condition under optimized PH drug therapy for ≥3 mo before entering the study (see Supplemental Digital Content 1, available at: http://links.lww.com/JCRP/A119). No changes in PH specific medication were made during the PR program. Patients were excluded if they had participated in a rehabilitation program previously, if they were not able to give informed consent, or if they were younger than 18 y. This protocol was approved by the medical ethical committee, Erasmus MC Rotterdam, the Netherlands (protocol MEC-2011-392). All participating patients signed an informed consent form before commencing the program.

Outcome measures

Patients were evaluated at baseline and week 10, immediately after the PR program. Primary outcome measures were changes at week 10 compared to baseline in exercise capacity, determined by cycling endurance time (CET), and change in QOL as measured by the CAMPHOR.

The PR program was designed to focus on both muscle strength and endurance for cycling and walking. Therefore, we chose the measured CET (min) as primary endpoint to investigate the effect of PR on endurance and exercise capacity. The CET was measured by a sub-maximal constant work rate exercise test at a constant load 75% of the baseline peak workload.

The CAMPHOR is a self-administered PH-specific health status questionnaire with 3 scales to assess symptoms, activity and quality of life. It also contains three symptom-subscales for energy, breathlessness and mood. Scores for symptoms and QOL range from 0-25, higher scores indicating worse QOL. Activity scores range from 0-30, higher scores indicating more physical limitations. Prior research validated the CAMPHOR questionnaire and the correlation between 6MWD and NYHA classification.[30] The CAMPHOR questionnaire was taken at baseline and after 10 weeks of PR.

Secondary outcome measures were changes at week 10 compared with baseline in 6MWD, respiratory muscle strength maximal inspiratory mouth pressure and skeletal muscle strength (quadriceps force and biceps force). The 6-min walking test (6MWT) was carried out according the ERS/American Thoracic Society (ATS) technical standards.[31] The maximal inspiratory mouth pressure was measured during a forced inspiratory effort from residual volume, using a respiratory pressure meter (MicroRPM).[32] Quadriceps

force and biceps force were assessed using a handheld dynamometer (MicroFET2) during maximal isometric knee extension and elbow flexion, respectively.[33]

The maximal peak cycling workload was measured during a maximal incremental symptom-limited cardiopulmonary exercise test (CPX) carried out in semi-supine position. The CPX was performed according to ATS guidelines,[34] with 3 min of rest, 3 min of unloaded cycling, followed by a progressive increase of the workload (5-25 W/minute). Ventilation oxygen-uptake and carbon dioxide output were measured breath-by-breath using a Jaeger CPX metabolic cart. Ventilatory efficiency was derived from the measured ventilation and carbon dioxide output).

Pulmonary rehabilitation program

The 10-wk PR program with 2 group training sessions/wk was especially developed for PH patients. The program included program endurance training (walking and cycling), lower- and upper-limb strength training, individualized psychological counseling, dietary advice, advice by an occupational therapist, educational group sessions, and interaction sessions with fellow patients. Once a week, the group would go out- doors during a physical training session to train activities in a real-life setting, for example, going to a supermarket or walking. The duration of the different activities of both weekly training sessions is shown in Supplemental Digital Content 2 (available at: http://links.lww.com/JCRP/A120). During educational sessions, information was provided by various members of the multidisciplinary team on pathophysiological changes in PH, the importance of dietary advice on the intake of proteins and vitamins, acceptance and coping of the disease, and how to manage energy distribution (breathing techniques etc). Specific PH questions from the patients were collected and answered by the PH special- ized pulmonologist and PH specialized nurse.

To individualize the training program and determine the training intensity at the start, patients performed exercise tolerance tests during the 2 to 3 d of baseline assessments. A symptom-limited maximal incremental CPX was performed to assess the maximal workload (Wmax) and two 6MWTs to evaluate distance walked and speed.

The training program contained the following components: bicycle *occupational training* by a stepwise schedule. Steps 1 and 2 started with exercise-rest interval training at 40% of the maximal workload achieved during the incremental CPX at baseline (Wmax). Steps 3 to 10 comprised continuous cycling for 15 to 20 min at 40% to 80% of Wmax. Training intensity progressed to the next step if perceived exertion during exercise remained <5 on the Borg dyspnea scale, if fatigue did not last >24 hr after the previous training session, and if existing physical complaints did not increase.

Walking training was performed on a treadmill ac- cording to a protocol with the same stepwise approach as mentioned earlier. Steps 1 to 3 comprised interval training at 60% to 75% of the speed achieved during the 6MWT at baseline. Steps 4 to 10 comprised continuous walking during 10 to15 min at 60%-75% to 75%-100% of the baseline 6MWT-speed.

Resistance training consisted of training leg-, arm and abdominal muscles on weight training equipment (Technogym). During the baseline assessment, the1 repetition maximum (1RM) training weight that could correctly be moved with appropriate breathing was determined for each exercise. During subsequent sessions, the training was intensified by gradually increasing repetitions of movements and weight/load to improve muscle strength and endurance respectively, according to ATS/ERS statement on PR.[25]

Once weekly the training sessions included a 60-min outdoor group activity, such as walking or cycling. Physiotherapists supervised all training sessions and, if needed, educated the patients in perceiving their physical limits and optimal breathing technique. Symptoms, heart rate and oxygen saturation to exercise, were closely monitored following specific PH rehabilitation guidelines.[1,25]

Blood samples were collected on the first and last days of the PR program. Biomarker assessment was performed for C-reactive protein, cystatin C, hemoglobin, red cell distribution width, NT-pro BNP, HsTnT, iron, and uric acid. Biomarkers were measured in peripheral blood samples within <1 hr after venous puncture at the clinical chemistry department at the Erasmus MC (Rotterdam, the Netherlands).

Statistics

Values are reported as mean (standard deviation) unless otherwise indicated. Changes in exercise capacity, muscle strength and QOL from baseline to 10 weeks were assessed using paired t-test or Wilcoxon signed rank test. P-values <.05 were considered statistically significant. All statistical analyses were performed using Prism (GraphPad Software, La Jolla, CA, USA) or SPSS version 24.

RESULTS

In this study, 21 patients were included with either PAH (n = 16) or inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (n = 5). The demographics of the study group, which consisted of 8 men and 13 women, are provided in Table 1. All study

Table 1. Demographic and Patient Characteristics[a]

Characteristic	Patients with pulmonary hypertension (*n* = 21)
Gender, female	13 (62)
Age, yr	45.1 ± 15.5
Height, cm	166.7 ± 9.4
Weight, kg	79.9 ± 23
BMI, kg/m^2	28.5 ± 7.1
WHO functional class III	21 (100)
Cause of pulmonary hypertension	
CTEPH	5 (24)
PAH	16 (76)
IPAH	7 (33)
CHD	5 (24)
SLE/SSc	3 (14)
PVOD	1 (5)
PH-specific drugs	
PDE-5 inhibitor	18 (86)
ERA	19 (90)
Prostacyclins	4 (19)
Selexipag	4 (19)
Drug combination therapy	
Monotherapy	3 (14)
Dual therapy	10 (48)
Triple therapy	7 (33)
Echocardiography (<6 mo prior to PR)	
RV pressure, mm Hg	55.8 ± 22.9
RA pressure, mm Hg	5.4 ± 3.3
RVSP, mm Hg	61.2 ± 23.4
6MWT, m	465 ± 98
6MWT, % predicted	84 (73, 79)
6MWT Borg fatigue/dyspnea scores (end of test)	4.4 ± 2.3/ 5.4 ± 2.8
CPX	
Peak workload, W	70.8 ± 37.9
Peak V'O_2, % of predicted	55.3 ± 18.3
Peak V'O_2, mL/kg/min	13.7 ± 3.4
RER	1.13 ± 0.13
V'E,max, L/min	50.2 ± 16.1
HRmax, % of predicted	73.1 ± 12.6
Peak V'E/V'CO2	43.1 ± 10.8

Abbreviations: BMI, body mass index; CHD, congenital heart disease; CPX, cardiopulmonary exercise test; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PDE-5, phosphodiesterase-5 inhibitor; RA, right atrial; RER, respiratory exchange ratio; RV, right ventricular; RVSP, right ventricular systolic pressure; 6MWT, 6-min walk test; SLE/SSc, systemic lupus erythematosus or systemic sclerosis–associated PH patient; V'CO2, carbon dioxide output; V'E , ventilation; V'O_2, oxygen uptake; WHO, World Health Organization.

[a]Data are reported as mean ± standard deviation, median (interquartile range), or n (%).

subjects tolerated the exercise testing and training well. No adverse events, defined as an increase in symptoms, progression of PH, or need for hospital admission, took place during the program.There was no withdrawal or loss to follow-up of patients during the PR program.

Mean CET increased significantly by 4.4 min (+92%) after 10 wk of PR (Figure 1, Table 2).

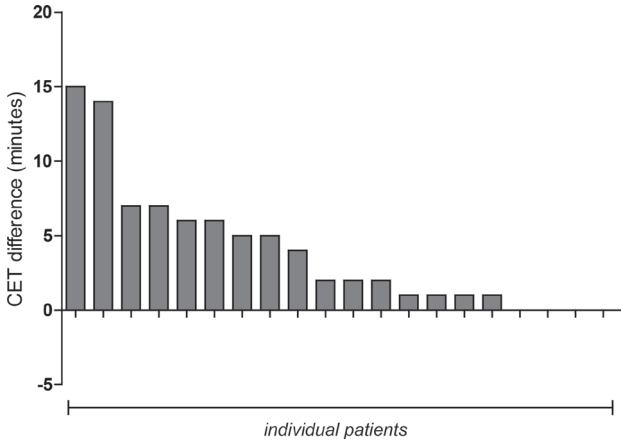

Figure 1. Change in CET for individual patients at baseline and after a 10-wk outpatient pulmonary rehabilitation program. CET indicates cycling endurance time.

Comparing results of the CAMPHOR questionnaire before and after PR, our study group showed an improvement in scores for symptoms and QOL (Figure 2).

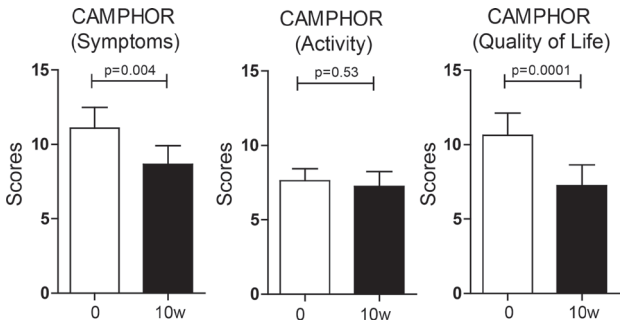

Figure 2. Health-related quality-of-life scores (CAMPHOR) at baseline (white bars) and after a 10-wk outpatient pulmonary rehabilitation program (black bars). Values are mean ± standard error of mean. CAMPHOR indicates Cambridge Pulmonary Hypertension Outcome Review.

Table 2. Test results at baseline and after a 10-wk outpatient pulmonary rehabilitation program[a]

Characteristic	Baseline (N=21)	Post-rehabilitation Therapy (N = 21)	*P* Value
CET, min	4.8 ± 2.1	9.2 ± 5.5	<.001
6MWT, m	465.2 ± 97	477.4 ± 92	.01
6MWT Borg fatigue score	4.4 ± 2.3	4.8 ± 2.0	.38
6MWT Borg dyspnea score	5.4 ± 2.8	5.3 ± 2.1	.89
MIP, cm H_2O	97.6 ± 17.5	103.40 ± 20.1	.01
MIP, % of predicted	102.95 ± 17.9	109.45 ± 22.3	.01
Soluble biomarkers			
Hemoglobin, mmol/L	8.1 ± 1.3	7.9 ± 1.3	.06
RDW, %	15.2 ± 2.9	14.9 ± 2.2	.36
Uric acid, mmol/L	0.3 ± 0.1	0.3 ± 0.1	.78
Iron, micromol/L	15.2 ± 2.8	14.9 ± 2.2	.36
Cystatin C, mg/L	1.2 ± 0.5	1.2 ± 0.3	.98
CRP, mg/L	6.1 ± 7.2	5.2 ± 6.7	.43
Hs-TnT, ng/L	11.2 ± 9.5	12.1 ± 11.0	.46
NT-pro BNP, pmol/L	86.8 ± 173.8	88.7 ± 155.4	.87

Abbreviations: CET, cycling endurance time; CRP, C-reactive protein; Hs-TnT, high sensitive troponin-T; MIP, maximal inspiratory pressure; NT-pro BNP, N-terminal pro B-type natriuretic peptide; RDW, red cell distribution width; 6MWT, 6-min walk test.

[a]Data are given as mean ± standard deviation. 6MWT Borg score values were end-of-test scores.

Secondary endpoints

After 10 wk of PR, the 6MWD increased by 3% (12.2 ±20.4 m; Table 2). After PR therapy, mean muscle function of the dominant quadriceps side increased by 78 N (+ 23%). In the nondominant quadriceps, mean muscle function increased by 62 N (+ 18%) after PR therapy (Figure 3A). Similarly, biceps dominant muscle function increased by 11 N (+ 6%) after PR therapy. In the nondominant biceps, muscle function increased by 16 N (+ 9%) after PR therapy (Figure 3B). Changes in the percentage of predicted values of the muscle function tests are shown in Figure 3. After10 wk of PR, maximal inspiratory mouth pressure increased significantly compared with baseline (Table 2).

Soluble biomarker levels were measured in all study subjects at baseline and after the PR program. However, no significant changes were seen in the soluble biomarker profiles (Table 2).

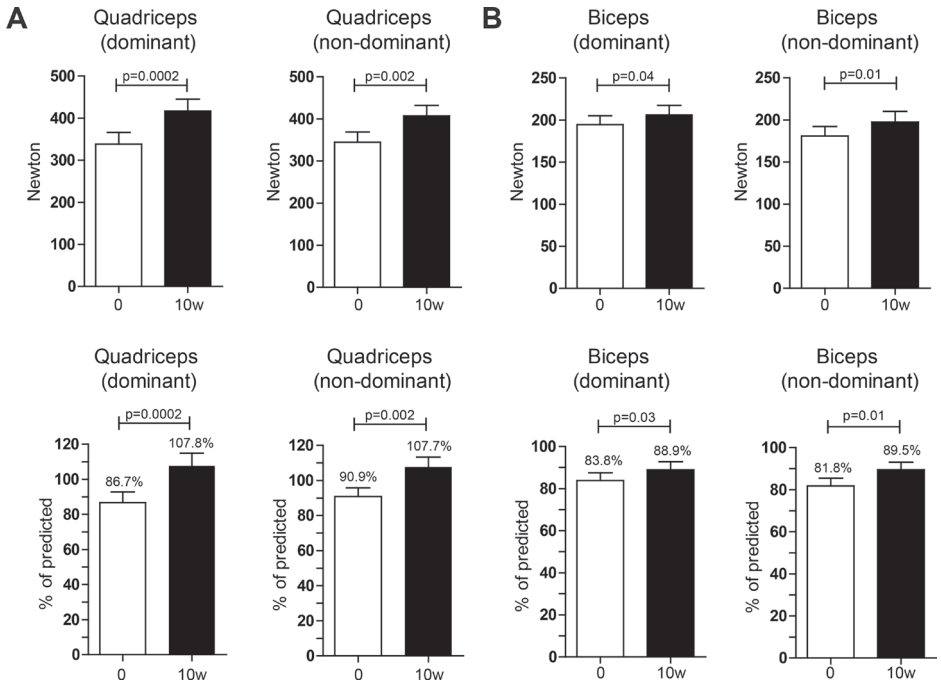

Figure 3. Skeletal muscle function of quadriceps (A) and biceps (B) (dominant and nondominant) at baseline (white bars) and after a 10-wk outpatient pulmonary rehabilitation program (black bars). Values are shown as mean percentage of predicted ± standard error of mean.

DISCUSSION

In this study we demonstrated that our multidisciplinary outpatient PR program is safe for PH patients, since no adverse events occurred during the 10-wk training period. Moreover, there was a positive effect on primary outcome parameters, including exercise capacity and endurance measured by the CET, as well as QOL in 2 out of 3 scales measured by the CAMPHOR questionnaire. In addition, all secondary outcome measures improved, including 6MWD, respiratory muscle strength and skeletal muscle strength.

While several studies have shown effectiveness of PR in an inpatient setting,[18,19,35] our study also shows beneficial effects for PR in an exclusively outpatient setting. The most beneficial effect was found in functional endurance measured by bicycle endurance (increase in the CET of 288 seconds). This result can be considered as a clinical meaningful effect since in a study by Laviolette et al.[36] in patients with chronic obstructive pulmonary disease (COPD), a difference of 100 to 200 sec in the CET was regarded as a clinical significant result. A significant, however small increase in the 6MWD was demonstrated as well. This relatively limited effect compared with the larger effect shown in

other rehabilitation studies,[18,22] could be due to a "ceiling" effect in the 6MWT as shown by Frost et a.l[37] The mean 6MWD at baseline in our cohort was 465 m. Since all other outcome parameters (CET, skeletal muscle function, QOL) changed significantly with a larger improvement and considering the findings by Frost et al., we assume that a ceiling effect in the 6MWT is a more logical explanation of our data than different exercise volumes.

Since assessment of daily activity may be more clinically meaningful to a patient than the 6MWD,[38] accelerometry may be an even better indicator of physical activity in daily life.[39] Therefore, accelerometry could be considered for all PR programs as an instrument for quantifying physical activity.

Consistent with other PR programs, [19,21,35] we observed no changes in soluble biomarkers levels before and after the PR program. A small decrease in RV systolic pressure has been seen in just a few, but not all studies. More studies investigating the effects of exercise training on pulmonary vascular remodeling, RV function and RV remodeling are needed, as well as studies assessing possible underlying mechanisms.

QOL, as measured by the CAMPHOR questionnaire, also improved significantly in our study group for the categories "symptoms" and "quality of life". The "activity" category, however, did not show a significant change. Individual patient evaluations on the contrary showed an increased capacity for activity. This observed difference by the CAMPHOR questionnaire might be due to a lack of discriminative power in a relatively small patient group. In a PR study by Chan and colleagues,[40] the "functioning" category from the CAMPHOR questionnaire did not show a significant improvement either. This study group however, was even smaller .

At the end of this PR program, all patients received a personalized training program to continue physical training under supervision of a first line physiotherapist to enhance the duration of the beneficial effect. Future studies are needed to evaluate the duration and clinical implications of our PR program.

Our study however also has several limitations. First, the study group consisted of PAH patients WHO class 1 with different underlying causes and WHO class 4, CTEPH patients. Analysis of the data of solely the PAH/WHO group I showed similar results. The study unfortunately lacks power to draw conclusions for specific PAH sub-groups. Second, only NYHA class III patients were included, which was not our initial intention. However, NYHA class III patients are undoubtedly clinically impaired in their functioning in daily life, more so than NYHA class I and II patients. They might therefore be more motivated

to participate in an extensive PR program. Moreover, NYHA class III patients are still able to participate in an intensive outpatient PR program, which might not be possible in the case of NYHA class IV patients. This possible explanation was also shown by Hayton et al.[41] in a study where COPD patients showed decreased PR attendance when either their disease was too mild or the COPD too severe to benefit from PR.

Finally, in a paper by Spruit and colleagues,[25] training 3 times/wk was regarded to be even more effective. However, our aim was to maximize training efficiency and to minimize the impact of the PR program on daily life activities of the participating PH patients.

CONCLUSION

This study demonstrates that a 10-wk multidisciplinary PR program has considerable beneficial effects on functional capacity, functional endurance, skeletal muscle function and health-related QOL. While many studies have shown effectiveness for inpatient rehabilitation programs for PH patients, our study demonstrated that an exclusively outpatient PR programme for PH patients is effective and safe. Long-term durability of these improvements and implications must be further evaluated in future studies.

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The authors declare no conflicts of interest .

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Supplementary Digital Content 1. Patient characteristics; right heart catheterization values at diagnosis.

Characteristic	Patients with pulmonary hypertension (n = 21)
Right heart catheterization (at diagnosis)	
Mean pulmonary artery pressure, mmHg	46.0 ± 15.6
Right atrial pressure, mmHg	8.4 ± 4.4
Pulmonary capillary wedge pressure, mmHg	8.7 ± 4.3

Data reported as mean ± standard deviation

Supplementary Digital Content 2. Group training session schedule.

Group training - Session 1		*Group training - Session 2*	
45 min	Treadmill walking Cycling Fitness training	45 minutes	Treadmill walking Cycling Fitness training
15 min	Rest	15 minutes	Rest
60 min	Outdoor walking or cycling	60 minutes	PH specific education on health
15 min	Rest		
45 min	Treadmill walking Cycling Fitness training	45 minutes	Treadmill walking Cycling Fitness training
15 min	Rest	15 minutes	Rest