

Individually tailored home-based physiotherapy program makes sustainable improvement in exercise capacity and daily physical activity in patients with pulmonary arterial hypertension

Līna Butāne , Liene Spilva-Ekerte, Matīss Šablinskis, Andris Skride and Daina Šmite

Abstract

Background: Pulmonary arterial hypertension (PAH) is a rare, chronic, progressive, and life-threatening cardiopulmonary disease. This study investigated the impact of an individually tailored 12 weeks home-based physiotherapy program in PAH patients, with the aim to evaluate change in exercise capacity and daily physical activity level.

Methods: This was an analysis of secondary outcomes from a prospective, randomized, controlled intervention study. Twenty-one participants were recruited from the Latvian PH registry based on inclusion criteria and randomized in a training group (TG) and control group (CG). Both groups continued a medical target therapy, but for TG, the individually tailored home-based physiotherapy program was added including physical exercises, relaxation, self-control, education, and supervision with telehealth elements. Outcomes included a 6-min walk test (6MWT) (m) and daily physical activity based on accelerometry results assessed at baseline, after 12 weeks, and at follow-up 6 months after commencement of intervention.

Results: 6MWT distance significantly ($p < 0.05$) and clinically (>33 m) increased within TG after 12 weeks (51.8 m, 95% CI = 25.7–77.9 m, Cohen's $d = 1.7$) and at follow-up (75.5 m, 95% CI = 46.1–104.8 m, Cohen's $d = 2.1$). A significant difference in 6MWT results between the groups at 12 weeks and follow-up was approved. In TG, low-intensity activities significantly ($p < 0.05$) increased both after 12 weeks (Cohen's $d = 1.6$) and at follow-up (Cohen's $d = 1.2$), moderate-intensity activities significantly ($p < 0.05$) increased at follow-up (Cohen's $d = 1.3$), and no significant improvements were present in CG.

Conclusion: The individually tailored 12 weeks home-based physiotherapy program comprising comprehensive physical exercise training, relaxation, self-control skills training, and education, added to stable medical target therapy and supervised by physiotherapist through telehealth elements, is effective in improving exercise capacity and increasing daily time in low or moderate physical activities 6 months after commencement of the intervention in patients with PAH.

Keywords: daily physical activity, exercise, home-based, individually tailored, physiotherapy, pulmonary arterial hypertension, rehabilitation, self-control skills

Received: 10 December 2021; revised manuscript accepted: 27 September 2022.

Introduction

Pulmonary arterial hypertension (PAH) is a rare disease affecting 15 to 50 persons per million within the United States and Europe.¹ It is a

chronic, progressive, and life-threatening cardiopulmonary pathology, characterized by elevated pulmonary arterial pressures leading to right ventricular failure.²

Ther Adv Respir Dis

2022, Vol. 16: 1–16

DOI: 10.1177/
17534666221132477

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The increased pulmonary vascular resistance and pulmonary arterial pressure impair adequate gas exchange in alveoli, resulting in decreased oxygen saturation in blood, and subsequently lower exercise tolerance. Symptoms of the disease include shortness of breath, fatigue, chest pain, vertigo, and episodes of syncope.³⁻⁵

Various factors, including limited exercise tolerance in combination with muscle weakness, as well as sleep disorders, depression, and inability to adapt to the persistent anxiety caused by severe, chronic, and life-threatening disease, lead to poor quality of life and contribute to social isolation.⁶

Due to recent advances in the target therapies, patient survival, clinical stability, and quality of life have notably improved, even though the persistence of symptoms and low exercise tolerance are often seen.^{1,7}

The 2019 European Respiratory Society statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension (PH) concludes that individually tailored, supervised exercise programs are likely to be safe for patients with PH who are stable on medical therapy. This will lead to significant improvements in exercise capacity, muscular function, and quality of life and even facilitate right ventricular function and pulmonary hemodynamics. Nevertheless, more studies are necessary to make enhancements and solidify exercise program methodology and form in patients with PAH.^{5,8,9}

In the setting of any chronic disease, improving long-term rehabilitation interventions that promote the adaptation process and sense of living a meaningful life is crucial. Most recent evidence supports the effectiveness and safety of home-based exercise programs.^{10,11} Data are lacking in exercise programs that are integrated into patient's daily life, done in a familiar setting with preexisting activities. This could be a promising tool to stimulate self-efficacy and self-control abilities, significant for this patient group as it leads to improvements in the daily level of activity.

Fostering participation in daily physical activities is an essential goal both in health promotion and a fundamental part of successful functional recovery during rehabilitation. Currently, the most frequently monitored data about the level of physical

activities are the number of steps and covered distance, but the necessity to use more specific instruments and the ability to detect different motions/movements, for example, in persons with severe functional limitations and chronic disease, are growing.¹²

This article presents the analysis of secondary outcomes from a recently completed randomized trial that investigated the effectiveness of the individually tailored home-based physiotherapy program added to stable target medical therapy in a sample of patients with PAH from the Latvian PH registry with a defined primary outcome of perceived autonomy and participation in activities of everyday life in the context of one's health condition. The presented analysis was done to evaluate change in exercise capacity and daily physical activity level immediately after the 12-week individually tailored home-based physiotherapy program and 6 months after commencement.

Methods

Study population and design

This is an analysis of secondary outcomes from a prospective, randomized, controlled intervention study conducted from February 2020 to September 2020. The participants were evaluated three times in total: at the beginning of the study, after 12 weeks, and 6 months after the start of the study (follow-up).

The participants with PAH diagnosed by right heart catheterization were enrolled in the Latvian PH registry in two steps. After the screening of the registry data, all relevant PAH patients were selected, and afterward, the study selection criteria were applied by a cardiologist specialized in PH. The inclusion criteria for this study were: PAH (idiopathic or connective tissue disease), NYHA functional class II–III, age > 18 years, clinically stable, and on optimized medical target therapy for at least 3 months before entering the study. In the second stage, the initially selected patients were contacted via phone and inclusion criteria such as consent to participate in the study and ability to visit the university clinic for onsite assessments were applied. Any noncompliance with the inclusion criteria, which were defined in detail, served as exclusion criteria. During the study, the failure to attend the intended evaluation at one site was established as an exclusion criterion.

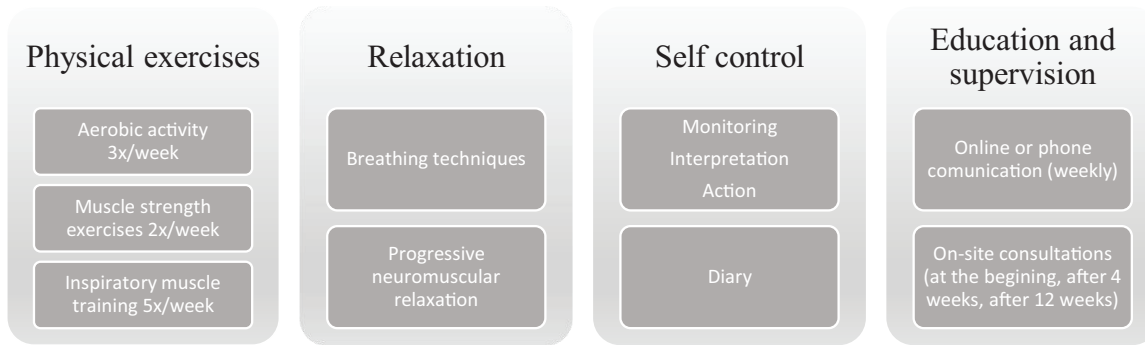


Figure 1. The physiotherapy training program content.

Riga Stradins University Ethics Committee approved the study (Nr 3/08.09.2018), and all of the patients signed written informed consent form prior to inclusion in the study. An independent researcher ensured a blinded assessment.

Intervention – individually tailored home-based physiotherapy program as add-on to medical target therapy

The patients from both the experimental group [further in article named as training group (TG)] and control group (CG) continued medical target therapy under the care of a cardiologist and their primary care doctor. Patients in the TG underwent a complex physiotherapy training program developed specifically for PAH patients, consisting of 12-week individually adjusted home-based exercise training, education, self-control measures, and telehealth elements. Our pilot study results confirmed that the individually adjusted home exercise program with close self-control and telehealth elements is safe and feasible in PAH patients.¹³ The overview of the program is shown in Figure 1.

A specialized physiotherapist led the program. The exercises were adapted individually and clearly explained for each patient, and included the following modalities:

1. **Aerobic activity:** 20- to 40-min cyclic activity, three times a week. The type of activity was selected individually (e.g. walking, bicycle ergometer). Intensity: perceived exertion as 5–6 on 10 points Borg scale and sustained SpO₂ or decrease of no more than 5% from the baseline. Progression was based on individual tolerability, provided by an increase in

training duration, and limited by ‘alarm signs’: peak heart rate (HR) of more than 120 bpm, decrease in SpO₂ to 85%; perceived exertion as very hard (>6 on Borg scale) and subjective symptoms of exercise intolerance (severe dyspnea or fatigue, dizziness, pain, etc.). The first increase in the intensity of aerobic activity was made after 4 weeks during the adjustment of the program, considering the results of the re-evaluated 6-min walk test (6MWT) and the analysis of the diary. Intensity was increased: by increasing the total time of the aerobic activity performance period on the day of performance and/or by increasing the number of repetitions for intervals with higher intensity. The next increase in intensity could occur every 4 weeks, according to diary data. In cases where HR was also used in exercise dosing, the progression could also be made by increasing the target HR by another 10 bpm, but not exceeding 120 bpm, and maintaining adequate recovery within 5 min.

2. **Strength training:** five to six resistance exercises (involving upper or lower limbs) with 5 to 10 repetition in each set, two times a week; accomplished using person’s own body weight or low weights [dumbbells or water bottles (0.5–1 kg)]. Initially, the resistance consisted of overcoming the force of gravity, the progression was made by increasing the number of repetitions (up to 10 times), and the duration of holding its final position (up to 5 s). The second step of progression was performed after 4 weeks, when the type of exercises was changed, increasing their degree of difficulty, and if the maximum progression with the resistance created by gravity was reached, then additional

weight was added using dumbbells or water bottles, and accordingly the already mentioned progressions in the number of repetitions and retention. The third step of progression was achieved in cases where maximum progression was achieved in all parameters; then upper and lower extremity exercises were included in the 1-day training, maintaining two training days per week.

3. Inspiratory muscle training: with PHILIPS breathing trainer *Threshold IMT*, five times a week. Before training, the submaximal strength of the inspiratory muscle was assessed using a Philips Threshold IMT device (Manufacturer Philips Respironics, Pennsylvania, United States). The device maintains a constant set pressure (cm H₂O) regardless of the smoothness and speed of inhalation, creating a target resistance to the inspiratory muscles. Device graduation: 9–41 cm H₂O. The patient sits upright, comfortable position with relaxed shoulders and slightly elevated chin, puts a special nose clip on, covers the mouthpiece of the device with his mouth, and is asked to perform an uninterrupted, maximal deep inhalation through the mouth. Initially, three attempts are made so that the patient understands the operation of the test, and the maximum objective indicators are obtained. The best result of the pressure reached (cm H₂O) is recorded. The particular IMT device with a threshold pressure of 41 cm H₂O was optimal, as the initial inspiratory muscle strength scores of the participants in our study were relatively low. The training was started with 30% of the submaximal test results obtained and three breaths in three sets with a 1-min break between them (3 × 3). The number of repetitions gradually increased to seven (3 × 7), when the resistance increased by 5 cm H₂O. With this resistance, the number of repetitions gradually increased, then increased the resistance accordingly, progressing to 65–70% of the submaximal test result obtained.

The relaxation included breathing techniques (diaphragmatic breathing; slow breathing; pursed lip breathing; breathing pattern perception; and awareness) and elements of progressive neuromuscular relaxation and body awareness five times a week.

Self-control included monitoring of heart rate, SpO₂, perceived exertion on the Borg scale, subjective clinical symptoms, recognition of alarm, and warning signs with appropriate action that were initially discussed. To enhance compliance, patients were required to fill a daily study diary. Paper or online format diary and pulse oximeter (*Beurer PO 60; Manufactured Beurer GmbH, Soefflinger Str. 218, 89077 Ulm, Germany*) to ensure self-control measures for each participant of the TG was provided.

The educational and motivational elements provided by a physiotherapist (both in verbal and visual handout materials) were a part of the program. Education included information about the benefits of exercises, relaxation and optimal self-control, possible adverse events of exercise, options of managing daily life activities, as well as self-management strategies for coping with exacerbation of disease symptoms or stress situations.

The program was led by a specialized physiotherapist in PH and was carried completely home-based, including supervision through telehealth elements, that is, telephone conversations at least once a week, and monitoring and analysis of the online diary in Google Docs or for the photographs of the paper diary sent each week, as participants could choose the type of diary at the beginning based on intervention. The program included three face-to-face outpatient sessions (consultations) with the physiotherapist in the University Clinic – at the beginning with the aim of individually adjusting the program, preparing and training to use equipment, as well as trying your hand at each element of the program. To promote sufficient adherence and develop sustained behavior changes, an individualized approach was highlighted. Both intensity and mode of exercise were individually adapted for each participant to integrate them into their daily life (e.g. a particular day regime or recreational activities), home environment, and individual preferences and possibilities were discussed. Education and support for the improvement of self-control was adapted for particular baseline comprehension and skills. A second onsite visit was arranged for re-evaluation and program adjustment at the University Clinic for each participant in the TG 4 weeks after starting the program, to maximize clinical safety. A third face-to-face session was conducted after the 12-week program to provide individually tailored further recommendations. Support and encouragement were important aspects of communication throughout the program. Furthermore, to recognize adverse

events, BNP and CRO levels were evaluated during the intervention period. The program was led by the specialized physiotherapist in close collaboration with the specialized cardiologist. The investigated physiotherapy program included monitoring of performance safety which included monitoring/analysis of self-control data on SpO₂, HR, symptoms/perceived exertion, biomarkers B-type natriuretic peptide (BNP) and high-sensitivity C-reactive protein (CRP). Both biomarkers were detected in the peripheral blood serum in collaboration with E. Gulbja Laboratory at the beginning and after competition (12 weeks) of the program. Absolute value analysis included baseline evaluation based on high-risk reference values (BNP > 300 ng/l; high sensitivity CRP > 5 mg/l) and a significant increase in these indicators, which could indicate the inadequacy of the intensity of the exercise applied as well as the progression of the disease.

Assessment

Six-min walk test. 6MWT is a submaximal exercise test, widely used in assessing exercise capacity in patients with heart failure and pulmonary hypertension, and it is also recommended for risk stratification and follow-up assessments.^{14,15} 6MWT was performed according to guidelines,¹⁶ with SpO₂, HR, and blood pressure monitoring. Distance (m) covered during the test was recorded, and minimal clinically significant difference (>33 m) was determined based on previous studies.¹⁷ In addition, desaturation during 6MWT was recorded based on the threshold level of decrease of 3 or more SpO₂ % from baseline (rest) level or reaching 88%.¹⁸

Accelerometry. To evaluate daily physical activities, data from the accelerometer were obtained. We established cooperation with Maastricht University and used their developed instrument *MOX Physical Activity Monitor* (MOX1) (Maastricht Instruments; www.accelerometry.eu; Maastricht Instruments BV, Universiteitssingel 50, 6229 ER Maastricht, Netherlands). The accuracy of this instrument has been confirmed by comparing the results to the 'gold standard' of activity monitoring *ActiGraph*.¹⁹ The MOX is a smart monitoring platform. The sensor was worn on thigh²⁰ to measure accurately the level of physical activity as postures and movements during daily living activities. The small, lightweight device records the measured movement signals and transmit them wirelessly to a user interface. The sensor was applied and worn for 7

consecutive days continuously, including during sleep, bathing, or showering. Participants were encouraged to participate in their routine activities while completing the assessment. None of the patients were participating in a structured exercise program during the assessment. On completion, the data were downloaded using *MOX software* to analyze daily time in each of physical activity level (sedentary, standing, low-, moderate-, and high-intensity activities) as calculated by software taking into account the registered time unit of acceleration measurement, filter (including the lowest sensed frequency), and sensor position based on validated algorithms.²⁰ As a result, time spent in each physical activity level expressed as percentage of the total awake time is presented.

At 12 weeks and follow-up, adverse events were evaluated, which were defined as: exacerbation of the primary disease with or without hospitalization, episode of syncope, death, and a significant increase in BNP.

Statistical analyses. Data were analyzed using IBM SPSS Statistics (v. 23.0). We choose mathematical methods of statistics stepwise, based on small group recommendations.²¹ Both data to be processed [i.e. walked distance (m) in 6MWT and % from awaked time spent at a particular level of activity obtained from accelerometry] were continuous data. First, the normality assumption in all measures was justified by probability plots (*Quantil-Quantil*) that are recommended to use in small sample sizes.^{21,22} Thus, we proceeded to evaluate the equal variance assumption by examining the ratio of the largest and smallest variances. Common recommendation is to assume that group variances are equal if the ratio of the largest to the smallest variance is ≤ 3 , but in our study, sample sizes were unbalanced and so we used less cutoff value, that is, 1.5. Based on this rule of thumb, we concluded that the equal variance assumption is reasonable for data of 6MWT results; thus, the two-sample t-test was used to compare the means in both, that is, TG and CG at each assessment. In turn, the equal variance assumption was not reasonable for data from accelerometry results; thus, Welch's extensions to t-test assuming unequal variances (heteroscedastic) were performed respectively.²¹ To analyze changes of the means within each group between baseline, after 12 weeks and follow-up assessments, the paired two-sample t-test was performed. The α level 0.05 was chosen; thus, the results statistically significant were determined if $p < 0.05$. The measure effect size for t-test results

Cohen's d (d) was calculated and its thresholds interpreted as small (0.2), medium (0.5), and large (0.8) effects.²³ For statistically significant ($p < 0.05$) results, *post hoc* statistical power was calculated by using G-Power software according to the values and a power at least 80% ($1 - \beta \geq 0.8$) was assumed as appropriate to control $1 - \beta$ error probability.²³ Data are presented as mean \pm standard deviation (SD) unless specified otherwise.

Results

Participant characteristics

Twenty-one patients diagnosed with PAH were included and randomly assigned to either TG or CG (Figure 2). There were no significant differences in baseline demographic and clinical characteristics between the groups. Detailed participant characteristics are shown in Table 1.

Adherence

All patients in the TG showed high adherence throughout the program, achieving satisfactory performance. Analysis of the diary data confirmed that none of the participants had completely interrupted the program in any of the weeks, but some participants had not fulfilled some elements of the program (muscle strength or aerobic exercise) on certain days (less than 10% of total scheduled days), and the most common reasons were planned outdoors activities (e.g. doctor's appointment) or an exacerbation of comorbidities (e.g. acute lumbago).

6MWT results

There were no significant differences in baseline 6MWT results between the groups. 6MWT distance significantly ($p < 0.05$) and clinically (> 33 m)¹⁸ increased within TG after 12 weeks (51.8 m, 95% CI = 25.7–77.9 m, Cohen's $d = 1.7$, large) and at follow-up (75.5 m, 95% CI = 46.1–104.8 m, Cohen's $d = 2.1$, large). In contrast, no significant improvements were present in CG. Significant difference in 6MWT results between the groups at 12 weeks and follow-up were approved. Detailed 6MWT outcomes are shown in Table 2. The individual changes in 6MWT for each participant are shown in Figure 3.

At baseline, 16 (76.2%) of all participants: 8 TG and 5 CG, showed clinically important

desaturation (decrease $\geq 3\%$ from baseline) during 6MWT: mean 7.1 ± 2.4 (median 7) TG and 6.2 ± 6.1 (median 3) CG. After 12 weeks, only two participants in TG had desaturation and in both was less severe, and none of the participants demonstrated desaturation at the follow-up evaluation. In the CG, no uniform trend was found for the dynamics of the desaturation characteristics, as for two participants, who initially did not demonstrate desaturation, it was shown in the evaluations after 12 weeks and follow-up, while for three participants with initially small desaturation, it was no longer found in the repeated evaluations.

Accelerometry results

The results on *sedentary time* during awake time revealed that at baseline *less than 8 h/day sedentary spent* only $n = 1$ (4.8%) of the sample who was from TG. Furthermore, after 12 weeks, 5 (25%) participants: 4 (36.4%) TG and 1 (11.1%) CG, but at follow-up 4 (21.1%): 3 (27.3%) TG and 1 (12.5%) CG, respectively.

On the other hand, 81% of all the studied participants at baseline spent *10 or more h/day sedentary*: 7 (63.6%) TG and all participants in CG. After 12 weeks, this proportion decreased to 45% of all samples: 3 (27.3%) TG and 6 (66.7%) CG participants; at follow-up 52.6% of all participants: 4 (36.4%) TG and 6 (75%) CG showed 10 or more sedentary hours/day.

The mean proportion of *sedentary time* significantly ($p < 0.05$) reduced within both TG (6.7%, 95% CI = 2.2–11.1%, Cohen's $d = 0.9$, large) and CG (12.4%, 95% CI = 2.3–22.6%, Cohen's $d = 1.4$, large) after 12 weeks and at follow-up (TG: 9.4%, 95% CI = 3.6–15.1%, Cohen's $d = 1.0$, large; CG: 13.1%, 95% CI = 1.9–24.3%, Cohen's $d = 0.9$, large). There were no significant differences in daily sedentary time (%) results between the groups in either assessment. Detailed accelerometry outcomes are shown in Table 3. The individual changes in sedentary time (%) for each participant are shown in Figure 4.

Daily time at *low- or moderate-intensity activities* increased within TG: low-intensity activities significantly ($p < 0.05$) increased both after 12 weeks (Cohen's $d = 1.6$, large) and at follow-up (Cohen's $d = 1.2$, large) and moderate-intensity activities significantly ($p < 0.05$) increased only at follow-up (Cohen's $d = 1.3$, large). In contrast, no

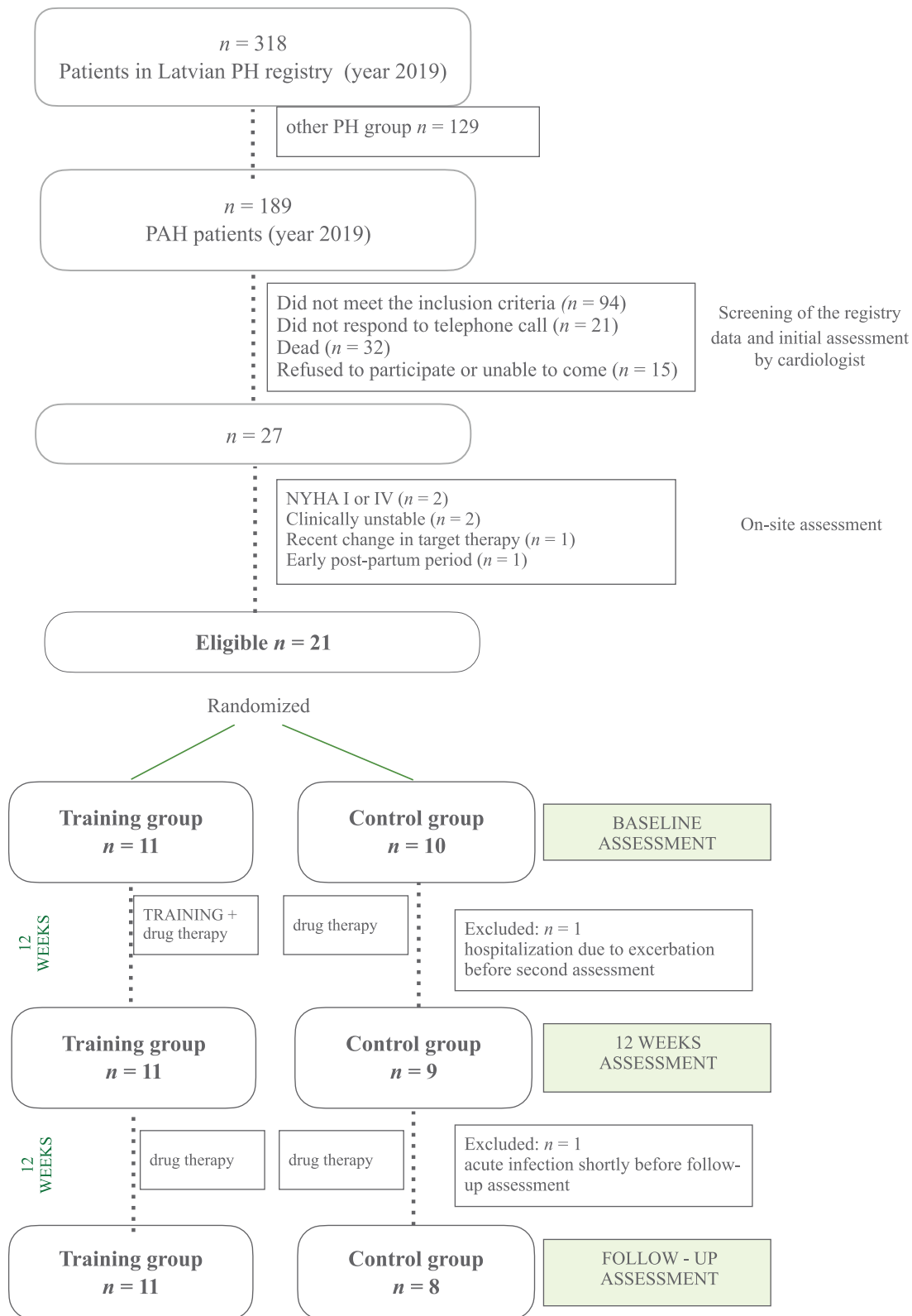


Figure 2. The study flow chart.

Table 1. Characteristics of participants.

Variables	TG (n = 11)	CG (n = 10)
Age (years)	63.2 ± 16.9	66.8 ± 14.2
Gender (n)		
Women/men	10/1	9/1
BMI (kg/m ²)	26.7 ± 5.1	31.1 ± 9.9
PAH etiology (n)		
Idiopathic	9	7
Connective tissue disease	2	3
PAH target therapy (n)		
PDE5 inhibitor	11	10
ERA	4	5
Ventavis	1	-
Spirolactonum	11	9
Oxygen therapy	-	2
Comorbidities (n)		
Hypertension	6	5
Dislipidemia	5	7
CHF	9	7
AF	7	5
Time since diagnosis (years)	2.6 ± 2.9	2.2 ± 1.2
Cardiac catheterization		
mPAP (mmHg)	44.3 ± 16.2	50.6 ± 13.7
PAWP (mmHg)	12.5 ± 5.4	16.4 ± 8.6
PVR (WU)	8.4 ± 5.1	9.4 ± 6.4

AF, atrial fibrillation; BMI, body mass index; CHF, chronic heart failure; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PAH, pulmonar arterial hypertension; PAWP, pulmonary arterial wedge pressure; PDE, phosphodiesterase; PVR, pulmonary vascular resistance.

Data are presented as n (the number of participants/patients) or mean ± SD (standard deviation).

We found no significant difference between the groups in mean age, BMI, time since diagnosis or cardiac catheterization results based on performed t-test for independent samples.

significant improvements were present in CG. A significant difference in daily time at low- or moderate-intensity activities (%) results between the groups at 12 weeks and follow-up were approved,

but only follow-up results reached appropriate power ($1-\beta \geq 0.8$) (Table 3). The individual changes in time (%) of low- or moderate-intensity activities for each participant at follow-up assessment are shown in Figure 5.

The results on the total time of moderate to vigorous (high) physical activity per week revealed that almost all (20/21) participants accumulated 150 min or more in the observed period of 7 consecutive days at the baseline. Only one participant from CG revealed a little less accumulated time (123 min).

At follow-up assessments, TG demonstrated a significant improvement as described above, in addition, if at baseline 5 (45.5%) TG participants completed moderate to vigorous activities 60 min or more per day, then at follow-up 9 (81.8%), respectively. Instead, only 2 (25%) participants in CG reach 60 min/day in moderate to vigorous activities, with no change compared to baseline [2 (20%)].

Adverse events

No predefined adverse events were observed in participants in TG during the 6-month study period. In CG, one participant has an exacerbation of PAH and needs hospitalization.

Details of the *post hoc* power analysis for outcome results are given in the supplementary material.

Discussion

The study results confirm that an individually tailored home-based physiotherapy program significantly improves exercise capacity for patients with PAH, who are on stable medical target therapy, not only immediately after completing the program but also long-term, as indicated by an increase in 6MWT distance. At the same time, the largest improvement of daily time in low- or moderate-intensity physical activities was observed 6 months after the commencement of the intervention.

The mean increase in 6MWT distance from baseline to 12 weeks was 51.8 and 75.5 m on follow-up. Based on a systematic review and meta-analysis by Zeng *et al.*⁷ on the effectiveness of physical exercise and rehabilitation interventions in PAH patients, with 17 individual studies included, the

Table 2. 6MWT results (distance) in training and control groups.

6MWT results (distance, m)	Baseline (Mean ± SD)	12 weeks (Mean ± SD)	Estimated means difference (95% CI)	Change within group <i>p</i> value (Cohen's <i>d</i> value)	Follow-up (Mean ± SD)	Estimated means difference (95% CI)	Change within group <i>p</i> value (Cohen's <i>d</i> value)
TG	378.3 ± 124.3	450 ± 114	51.8 [25.7 to 77.9]	0.001 (1.7)+	473.6 ± 118.8	75.5 [46.1 to 104.8]	<0.001 (2.1)+
CG	296.1 ± 110.1	290.6 ± 112.2	2.2 [-22.3 to 26.8]	0.84 (0.2)	302.5 ± 139.7	13.8 [-5.0 to 32.5]	0.13 (0.2)
Difference between the groups <i>p</i> value (Cohen's <i>d</i> value)	0.12 (0.7)	0.01 (1.4)+			0.01 (1.3)+		

6MWT, 6-min walk test; CI, confidence interval; SD, standard deviation.

To explore the difference between the groups, we used t-test for independent samples, but for detecting the change in mean values within each group between baseline and after 12 weeks or baseline and follow-up assessments, we performed paired two-sample t-test.

+Results are statistically significant and achieved appropriate power as both $p < 0.05$ and $1 - \beta \geq 0.8$ were observed.

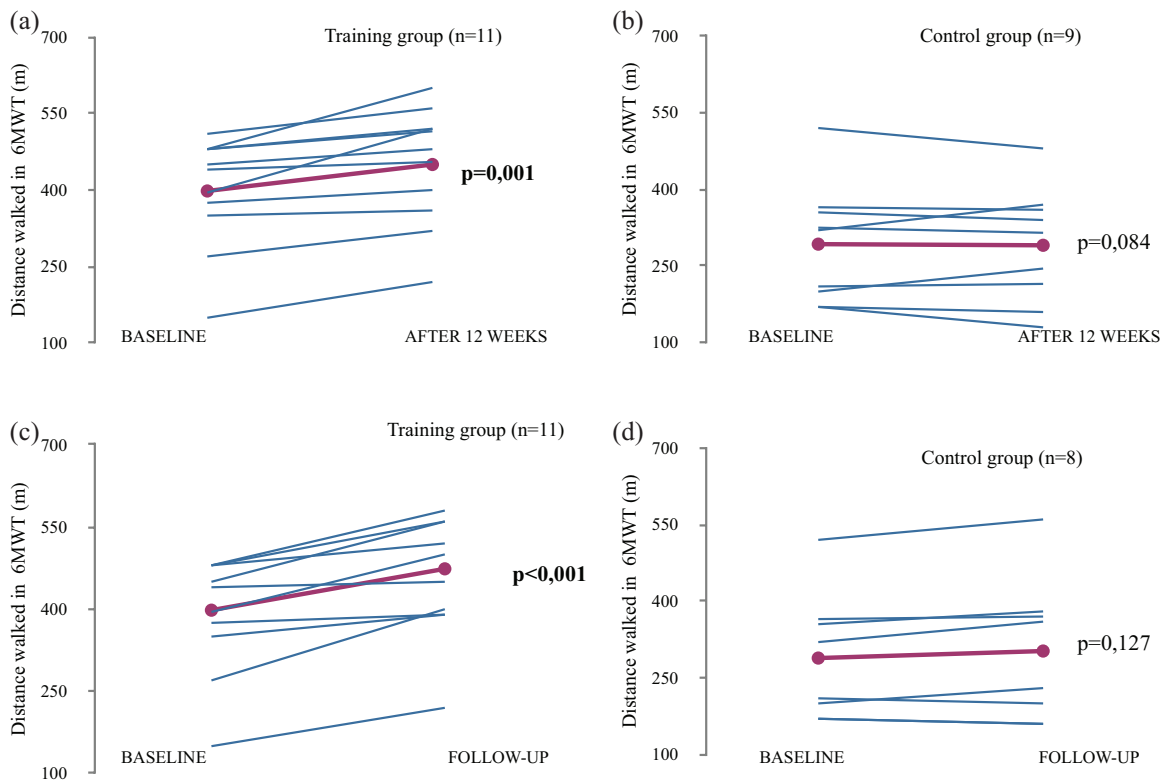


Figure 3. Paired profile of 6MWT results [distance (m)] at baseline and after 12 weeks or follow-up assessments in both groups. Distance walked in 6MWT at baseline and after 12 weeks for each participants (blue lines) and for group mean value (purple line) with levels of statistical significance (*p* values) is shown in (a) for training groups and in (b) for control group, respectively. Similarly, for training group and control group, 6MWT results at baseline and follow-up are shown in (c) and (d), respectively.

mean increase of 6MWT distance was 64.75 m (95% CI 53.19–76.31). Nevertheless, it should be noted that none of the studies investigated completely home-based programs supervised through

telehealth elements.⁷ However, the systematic review by Waller *et al.*⁵ on the effectiveness of various exercise programs in PAH patients revealed an increase in mean 6MWT distance 40–69 m in

Table 3. Accelerometry results presented as time (% from total awake time) spent sedentary or dynamic physical activities in training and control groups.

Accelerometry results (% from total awake time)	Baseline (Mean ± SD)	12 weeks (Mean ± SD)	Estimated means difference (95% CI)	Change within group p value (Cohen's d value)	Follow-up (Mean ± SD)	Estimated means difference (95% CI)	Change within group p value (Cohen's d value)
Sedentary							
Training group	67.2 ± 8.8	60.7 ± 10.1	-6.7 [2.2 to 11.1]	0.01 (0.9)+	58.1 ± 10.1	-9.4 [3.6 to 15.1]	0.005 (1.0)+
Control group	75.6 ± 3.6	63.4 ± 9.1	-12.4 [2.3 to 22.6]	0.003 (1.4)+	65.2 ± 11.2	-13.1 [1.9 to 24.3]	0.04 (0.9)
<i>Difference between the groups, p value (Cohen's d value)</i>	0.20 (0.9)	0.55 (0.2)			0.17 (0.6)		
Standing							
Training group	25.4 ± 6.4	28.7 ± 8.8	3.4 [0.4 to 6.3]	0.03 (0.8)	28.8 ± 8.9	3.4 [-0.1 to 6.97]	0.06 (0.7)
Control group	21.6 ± 5.7	29.8 ± 7.7	8.3 [0.9 to 15.7]	0.03 (0.9)	28.8 ± 9.7	8.9 [0.9 to 16.8]	0.03 (0.7)
<i>Difference between the groups, p value (Cohen's d value)</i>	0.18 (0.6)	0.72 (0.1)			0.97 (0)		
Low intensity							
Training group	1.31 ± 0.4	1.6 ± 0.5	0.2 [0.1 to 0.3]	<0.001 (1.6)+	1.8 ± 0.7	0.5 [0.2 to 0.7]	0.002 (1.2)+
Control group	1.0 ± 0.6	1.1 ± 0.4	0.04 [-0.3 to 0.4]	0.77 (0.3)	0.9 ± 0.4	0.1 [-0.3 to 0.4]	0.60 (0.2)
<i>Difference between the groups, p value (Cohen's d value)</i>	0.23 (0.6)	0.04 (1.1)			0.005 (1.6)+		
Moderate intensity							
Training group	7.1 ± 3.4	8.0 ± 2.4	0.8 [-0.6 to 2.2]	0.21 (0.4)	9.5 ± 3.5	2.3 [1.0 to 3.6]	0.002 (1.3)+
Control group	4.9 ± 2.8	5.4 ± 2.0	0.4 [-1.7 to 2.5]	0.67 (0.2)	4.8 ± 1.8	0.8 [-0.5 to 2.0]	0.19 (0.0)
<i>Difference between the groups, p value (Cohen's d value)</i>	0.11 (0.7)	0.02 (1.2)			0.002 (1.7)+		
High intensity							
Training group	1.4 ± 1.4	1.3 ± 0.8	-0.1 [-0.7 to 0.9]	0.78 (0.1)	1.7 ± 1.5	0.4 [-0.9 to 1.6]	0.50 (0.2)
Control group	0.3 ± 0.3	0.4 ± 0.6	0.2 [-0.2 to 0.5]	0.28 (0.2)	0.3 ± 0.3	0.1 [-0.04 to 0.2]	0.14 (0)
<i>Difference between the groups, p value (Cohen's d value)</i>	0.03 (0.8)	0.01 (1.1)			0.01 (0.9)		

CI, confidence interval; SD, standard deviation.

To explore the difference between the groups, we used t-test with Welch's extensions for independent samples assuming unequal variances, but for detecting the change in mean values within each group between baseline and after 12 weeks or baseline and follow-up assessments, we performed paired two-sample t-test.

+Results are statistically significant and achieved appropriate power as both $p < 0.05$ and $1 - \beta \geq 0.8$ were observed.

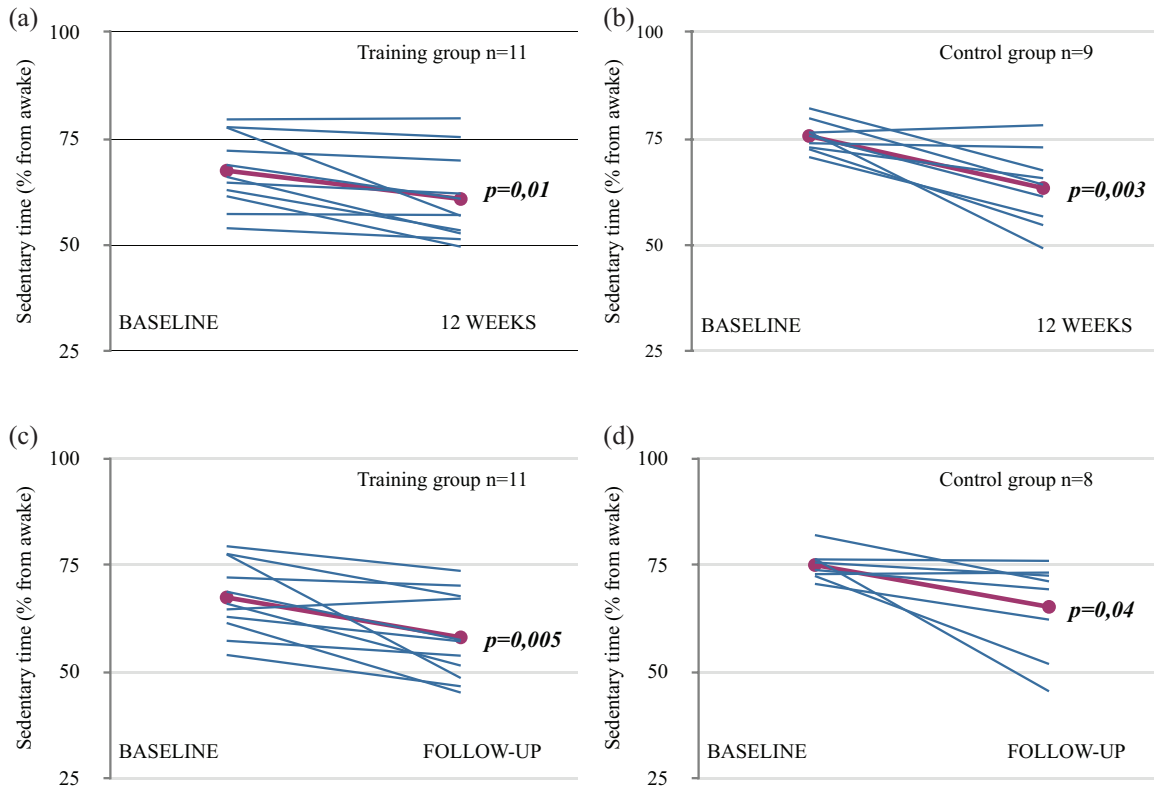


Figure 4. Paired profile of sedentary time (% of total awake time) at baseline and after 12 weeks or follow-up assessments in both groups. Accelerometry data results about daily sedentary time (as % from total awake time) at baseline and after 12 weeks for each participant (blue lines) and for group mean value (purple line) with levels of statistical significance (p values) are shown in (a) for training groups and (b) for control group, respectively. Similarly, for training group and control group, results about daily sedentary time at baseline and follow-up are shown in (c) and (d), respectively.

12-week-long programs ($n=5$), out of which only one (Brown *et al.*)¹⁰ was home-based and revealed 40 m improvement in 6MWT distance. Compared to Babu *et al.*¹¹ randomized-controlled trial of a 12-week-long home-based exercise program, which showed a statistically and clinically significant increase in mean 6MWT distance in the study group (48.55 ± 44.98 m), our results are quite similar. Until recently, home-based exercise programs for PAH patients have been a relatively innovative approach, with only a few studies and scarce data of long-term results of such programs. A pilot study published by Wojciuk *et al.*²⁴ on 6-month home-based exercise program effectiveness showed a mean improvement in 6MWT by 71.38 ± 83.4 m, seen also on follow-up a year later. Our results on long-term improvement of 6MWT 6 months from commencement of the 12-week intervention with a mean increase from baseline of 75.5 m highlight the acquirement of the individually tailored program that fitted

persons' needs and possibilities to implement the therapeutic modalities in their daily life.

Besides the covered distance, observed desaturation during 6MWT was used to describe exercise tolerance and its dynamics. This choice was justified by the cardiopulmonary response during 6MWT of the PAH patients studied, which was characterized by a reduced chronotropic HR response and a significant drop in SpO_2 . At baseline, 76.2% of participants in both groups experienced significant desaturation during 6MWT, which is consistent with data from the literature for PH patients.¹⁸ Yoshimura *et al.*²⁵ analyzed patients with heart failure during 6MWT and approved that patients with heart failure who had a lower exercise tolerance (distance covered less than 300 m) observed a more inefficient breathing stereotype, which was characterized by higher respiratory frequency in combination with lower respiratory volume, and slower kinetics of oxygen

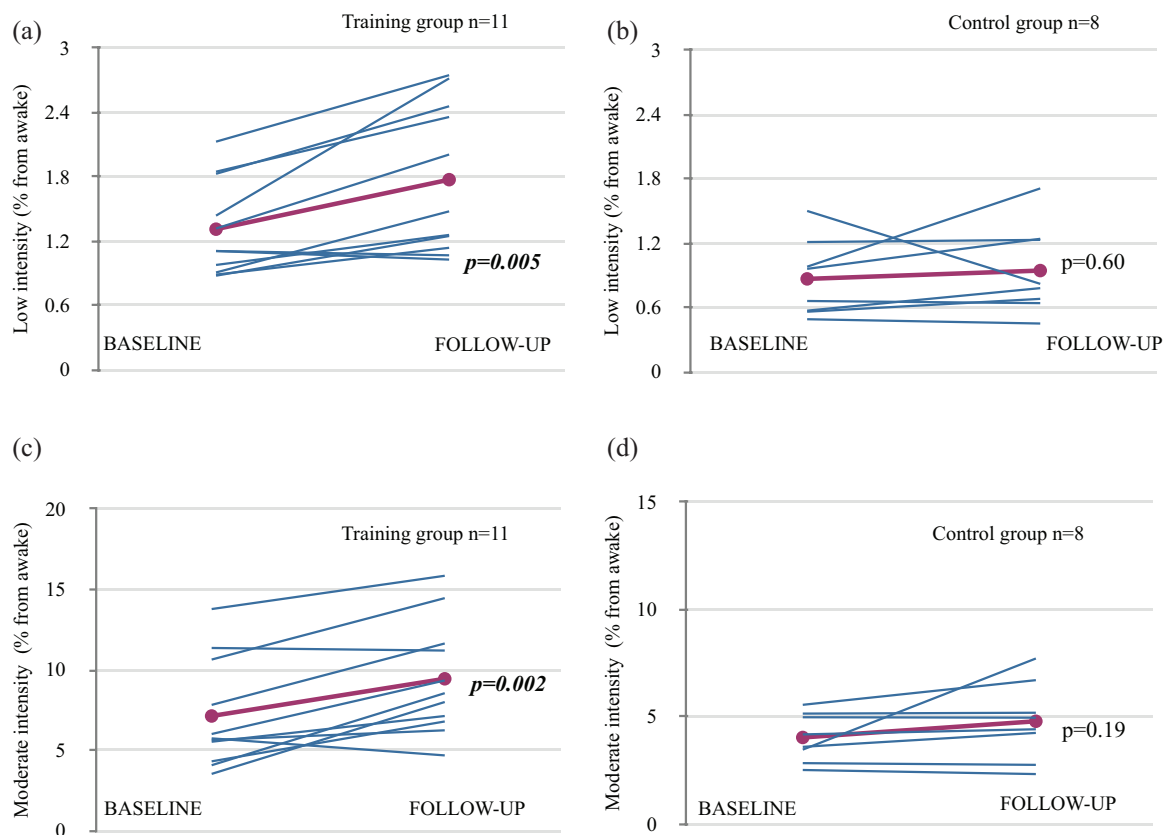


Figure 5. Paired profile of time in low- or moderate-intensity activities (% of total awake time) at baseline and follow-up assessments in both groups. Accelerometry data result about daily time spent in low-intensity physical activities (as % from total awake time) at baseline and follow-up for each participant (blue lines) and group mean value (purple line) with levels of statistical significance (p values) is shown in (a) for training group and (b) for control group, respectively. Similarly, for training group and control group, results about time spent in moderate-intensity physical activities are shown in (c) and (d), respectively.

consumption under exercise, which in patients with heart failure is explained by both inadequate peripheral mechanisms and reduced cardiac output.²⁵ Considering all of the above, there is a reason to believe that the decrease in observed desaturation during 6MWT in TG could be mainly related to the benefit of inspiratory muscle training and relaxation, including conscious control of breathing and conscious modification of the breathing stereotype.

This successful implementation in a person's particular everyday life is also seen through accelerometry results of an increase in daily time in low- and moderate-intensity physical activities for the TG 6 months after the commencement of the intervention. Numerous studies have already concluded that the level of daily physical activities is an independent indicator of prognosis and mortality for

patients with lung disease and cardiovascular disease.^{26,27} At the same time, results show that more than half of the time spent awake was spent sedentary. The results of a systematic review of studies analyzing daily activities in PAH patients confirm that time spent sedentary is associated with higher hospitalization and mortality rates.²⁶ Importantly, the time spent sedentary in both groups decreased by 6.7–13% at 12 weeks and follow-up. This indicates that approximately 1–2h of daily sedentary time was altered. It should be noted that this trend was similar in both groups and could be explained by seasonality because the baseline assessment was done at the end of winter, the 12-week assessment was in spring, and the follow-up assessment was during early summer. This hypothesis is supported by results of a scoping review, showing a decrease in time spent sedentary during spring and summer months when compared to winter and autumn, in

various age groups irrespective of location.²⁸ Likewise, patients with chronic obstructive lung disease (COPD) demonstrate higher physical activity levels during warmer months of the year.²⁹ Pulmonary hypertension patients are specifically warned about the negative effects of hot and humid weather,³⁰ which is not attributable to our study, because the weather in Latvia during spring and early summer is moderately warm and dry. Due to the potential influence of seasonality, similar future interventions, which are implemented in the daily lives of patients, should purposefully include a longer time of observation, to include different seasons, especially for studies conducted in Latvia, as a large proportion of the study population live in rural areas and their hobbies involve gardening activities, forest berry, and mushroom picking.

Despite a decrease in the time spent sedentary in both groups, a statistically significant increase in dynamic activities was noted only in the study group. For CG, time spent sedentary was replaced by doing various daily activities while standing (i.e. housekeeping, being in the garden, meeting with friends/family). An increase in the daily time of low- and moderate-intensity activities at follow-up indicates the effectiveness of the intervention in changing daily habits and implementing healthy activities. There is no data on studies analyzing the role of interventions on the daily physical activity level in PAH patients; however, a systematic review of the effectiveness of various interventions in enhancing the amount of physical activities for patients with COPD concluded that current evidence does not show benefits from any intervention, and there is insufficient data on long-term effectiveness.³¹ In similar, authors of a systemic review of various interventions for patients with congenital heart disease came to the conclusion that studies are mostly low quality and show little potential improvement in the daily physical activity level.³² The study by Awick *et al.*³³ analyzed the physical activity level in the elderly before and after participation in a 6-month-long intervention (dancing, hiking, and exercise programs), revealing a small ($d=0.23$) increase in moderate- and high-intensity level activities. The randomized controlled trial by De Roos *et al.*³⁴ on 10-week outpatient group physiotherapy and unsupervised home walking programs for patients with COPD showed a moderate ($d=0.51$) increase in low-intensity physical activity levels, but no data were collected on long-term results. When compared to the aforementioned

studies, we observed a larger effect ($d=1.2$ and $d=1.3$) of increase in time in low- and moderate-intensity activities 6 months after the commencement of the intervention approving a significant difference between TG and CG. At the same time, these results reached appropriate statistical power ($>80\%$) even in our relatively small sample size. The mean increase in the moderate-intensity physical activity level was 2.3%, which indicates that on follow-up, the patients from the study group had modified their daily habits and replaced 30–40 min sedentary time with moderate-intensity physical activities. Contrary to the confirming results of observational studies in PAH patients^{27,35–38} on the correlation between 6MWT results and daily time in low- or moderate-intensity activities, we did not observe such a relationship (these results are not included in a particular article). This leads to the assumption that daily time in low- or moderate-intensity activities relates not only to exercise capacity but also such intrinsic factors as self-control skills, self-efficacy, and emotional state. Studies on patients' perspectives illustrate insecurity, fear, and incomprehension as fundamental factors limiting full-fledged daily participation and confirm patients' preference for individually adjusted interventions – one of the basic elements of our physiotherapy program.^{39,40}

Strength and limitations

One of the main limitations of this study is the small sample size, but to decrease the possibility of statistical error, adequate statistical methods were used, as well as post hoc result analysis of statistical power was done. As the main results showed a large effect size, the appropriate statistical power ($>80\%$) of both intragroup and intergroup was reached; thus, meaningful conclusions may be drawn. The other limiting factor was the COVID-19 pandemic and the state of emergency in Latvia during the study, which was unusual both for participants and researchers. This could have potentially influenced the results because the study subjects were under additional tension and their daily habits changed to an extent. At the same time, this can be viewed as an opportunity for the study team to test the accessibility of the program at a setting with limited in-person services.

The use of accelerometry data in this study was proven to be a valuable addition to 6MWT. Already Pugh *et al.*³⁶ emphasized the need for

clinical trials to implement an objective tool for the evaluation of daily activities in patients with PAH, which has recently been supported by practical recommendations for use of accelerometry in the patient population with cardiovascular disease.²⁷ One of the strengths of our study was the follow-up assessment 6 months after the commencement of the intervention, which allows making conclusions on the sustainable impact of the program, especially regarding results on the improvement of daily physical activities, indicating changes in individual habits.

Conclusion

The individually tailored 12-week home-based physiotherapy program with supervision through telehealth elements comprising comprehensive physical exercise training, relaxation, self-control skills training, and education, added to stable medical target therapy, is effective in improving exercise capacity and increasing daily time in low or moderate physical activities 6 months after the commencement of the intervention in patients with PAH. It discloses a possible cost-effective physiotherapy approach for a part of PAH patients, as supervised hospital-based programs limit patients' accessibility to these important services. Underlying determinants that are responsible for a sustainable increase in both exercise capacity and daily time in low or moderate physical activities warrant further investigation.

Declarations

Ethics approval and consent to participate

This study was conducted according to the 2000 revised version of the Helsinki Declaration and approved by Riga Stradins University Science Ethics Committee (Nr 3/08.09.2018). All of the patients signed written informed consent form prior to inclusion in the study. The trial was conducted as PhD research project and registered in Riga Stradins University Department of Doctoral Studies.

Consent for publication

Not applicable.

Author contributions

Lina Butāne: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft.

Liene Spilva-Ekerte: Formal analysis; Software; Visualization; Writing – review & editing.

Matīss Šablinskis: Formal analysis; Investigation; Writing – review & editing.

Andris Skride: Conceptualization; Supervision; Validation; Writing – review & editing.

Daina Šmite: Conceptualization; Formal analysis; Methodology; Supervision; Validation; Writing – original draft.

Acknowledgements

None.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study did not receive funding but was financially supported by Pauls Stradins Clinical University Hospital Scientific Institute (provision of IMT devices) and the Latvian Rare Diseases Research Foundation along with Beurer Company (provision of pulse oximeters).


Competing interests

The authors declare that there is no conflict of interest.

Availability of data and material

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

References

1. Levine DJ. Pulmonary arterial hypertension: updates in epidemiology and evaluation of patients. *Am J Manag Care* 2021; 27: S35–S41.
2. Lan N, Massam B, Kulkarni S, *et al.* Pulmonary arterial hypertension: pathophysiology and treatment. *Diseases* 2018; 6: 38.
3. Khirfan G, Naal T, Abuhalmeh B, *et al.* Hypoxemia in patients with idiopathic or heritable pulmonary arterial hypertension. *PLoS ONE* 2018; 13: 1–11.

4. Tran DL, Lau EMT, Celermajer DS, *et al.* Pathophysiology of exercise intolerance in pulmonary arterial hypertension. *Respirology* 2018; 23: 148–159.
5. Waller L, Krüger K, Conrad K, *et al.* Effects of different types of exercise training on pulmonary arterial hypertension: a systematic review. *J Clin Med* 2020; 9: 1689.
6. Delcroix M and Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. *Eur Respir Rev* 2015; 24: 621–629.
7. Zeng X, Chen H, Ruan H, *et al.* Effectiveness and safety of exercise training and rehabilitation in pulmonary hypertension: a systematic review and meta-analysis. *J Thorac Dis* 2020; 12: 2691–2705.
8. Grunig E, Eichstaedt C, Barbera JA, *et al.* ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J* 2019; 53: 1800332.
9. Yuan P, Yuan XT, Sun XY, *et al.* Exercise training for pulmonary hypertension: a systematic review and meta-analysis. *Int J Cardiol* 2015; 178: 142–146.
10. Brown MB, Kempf A, Collins CM, *et al.* A prescribed walking regimen plus arginine supplementation improves function and quality of life for patients with pulmonary arterial hypertension: a pilot study. *Pulm Circ* 2018; 8: 1–12.
11. Babu AS, Padmakumar R, Nayak K, *et al.* Effects of home-based exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: a randomized clinical trial. *Indian Heart J* 2019; 71: 161–165.
12. Bashshur RL, Shannon GW, Smith BR, *et al.* The empirical foundations of telemedicine interventions for chronic disease management. *Telemed J e-Health* 2014; 20: 769–800.
13. Butane L, Šmite D, Šablinskis M, *et al.* Individualized home-based exercise program for idiopathic pulmonary arterial hypertension patients: a preliminary study. *Cor Vasa* 2019; 61: 403–410.
14. Zelniker TA, Huscher D, Vonk-Noordegraaf A, *et al.* The 6MWT as a prognostic tool in pulmonary arterial hypertension: results from the COMPERA registry. *Clin Res Cardiol* 2018; 107: 460–470.
15. Demir R and Küçüköğlü MS. Six-minute walk test in pulmonary arterial hypertension. *Anadolu Kardiyol Derg* 2015; 15: 249–254.
16. Issues S, Test MW, Equipment R, *et al.* ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
17. Mathai SC, Puhan MA, Lam D, *et al.* The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012; 186: 428–433.
18. Gupta R, Ruppel GL and Espiritu J. Exercise-induced oxygen desaturation during the 6-minute walk test. *Med Sci*, 2020; 8: 8.
19. van der Weegen S, Essers H, Spreeuwenberg M, *et al.* Concurrent validity of the MOX activity monitor compared to the actigraph GT3Xle. *Telemed E-health* 2015; 21: 259–266.
20. Migueles JH, Cadenas-Sanchez C, Ekelund U, *et al.* Accelerometer data collection and processing criteria to assess physical activity and other outcomes: a systematic review and practical considerations. *Sports Med* 2017; 47: 1821–1845.
21. Morgan CJ. Use of proper statistical techniques for research studies with small samples. *Am J Physiol – Lung Cell Mol Physiol* 2017; 313: L873–L877.
22. Van Belle G, Fisher LD, Heagerty PJ, *et al.* *Biostatistics: A methodology for the health sciences*. Hoboken, NJ: Wiley, 2004.
23. Serdar CC, Cihan M, Yücel D, *et al.* Sample size, power and effect size revisited: Simplified and practical approach in pre-clinical, clinical and laboratory studies. *Biochem Med* 2021; 31: 1–27.
24. Wojciuk M, Ciolkiewicz M, Kuryliszyn-Moskal A, *et al.* Effectiveness and safety of a simple home-based rehabilitation program in pulmonary arterial hypertension: an interventional pilot study. *BMC Sports Sci Med Rehabil* 2021; 13: 1–14.
25. Yoshimura K, Urabe Y, Maeda N, *et al.* Dynamics of cardiorespiratory response during and after the six-minute walk test in patients with heart failure. *Physiother Theory Pract* 2020; 36: 476–487.
26. Sehgal S, Small B and Highland KB. Activity monitors in pulmonary disease. *Respir Med* 2019; 151: 81–95.
27. Vetrovsky T, Clark CCT, Bisi MC, *et al.* Advances in accelerometry for cardiovascular patients: a systematic review with practical recommendations. *ESC Heart Fail* 2020; 7: 2021–2031.
28. Turrisi TB, Bittel KM, West AB, *et al.* Seasons, weather, and device-measured movement behaviors: a scoping review from 2006 to 2020. *Int J Behav Nutr Phys Act* 2021; 18: 1–26.

29. Hoas H, Zanaboni P, Hjalmsen A, *et al.* Seasonal variations in objectively assessed physical activity among people with COPD in two Nordic countries and Australia: a cross-sectional study. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 1219–1228.
30. Jehn M, Gebhardt A, Liebers U, *et al.* Heat stress is associated with reduced health status in pulmonary arterial hypertension: a prospective study cohort. *Lung* 2014; 192: 619–624.
31. Burge AT, Cox NS, Abramson MJ, *et al.* Interventions for promoting physical activity in people with chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2020; 4: CD012626.
32. Williams CA, Wadey CA, Pieles G, *et al.* Cochrane corner: physical activity interventions for people with congenital heart disease. *Heart* 2021; 107: 447–449.
33. Awick EA, Ehlers DK, Aguinaga S, *et al.* Effects of a randomized exercise trial on physical activity, psychological distress and quality of life in older adults. *Gen Hosp Psychiatry* 2017; 49: 44–50.
34. De Roos P, Lucas C, Strijbos JH, *et al.* Effectiveness of a combined exercise training and home-based walking programme on physical activity compared with standard medical care in moderate COPD: a randomised controlled trial. *Physiotherapy* 2018; 104: 116–121.
35. Okumus G, Aslan GK, Arseven O, *et al.* The role of an activity monitor in the objective evaluation of patients with pulmonary hypertension. *Clin Respir J* 2018; 12: 119–125.
36. Pugh ME, Buchowski MS, Robbins IM, *et al.* Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest* 2012; 142: 1391–1398.
37. Matura LA, Shou H, Fritz JS, *et al.* Physical activity and symptoms in pulmonary arterial hypertension. *Chest* 2016; 150: 46–56.
38. Nakazato L, Mendes F, Paschoal IA, *et al.* Association of daily physical activity with psychosocial aspects and functional capacity in patients with pulmonary arterial hypertension: a cross-sectional study. *Pulm Circ* 2021; 11: 1–9.
39. Ferrari P and Skara H. My life with pulmonary arterial hypertension: a patient perspective. *Eur Heart J Suppl* 2019; 21: K54–K59.
40. Chia KSW, Brown K, Kotlyar E, *et al.* ‘Tired, afraid, breathless . . .’. An international survey of the exercise experience for people living with pulmonary hypertension. *Pulm Circ* 2020; 10: 1–10.