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Individually tailored 12-week home-based exercise program improves both physical capacity and sleep quality in patients with pulmonary arterial hypertension

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SOUHRN

Kontext: Většina pacientů s optimální farmakologickou léčbou plicní arteriální hypertenze vykazuje klinické příznaky a trpí sníženou tolerancí zátěže i špatnou kvalitou života. V roce 2019 byl publikován dokument pracovní skupiny Evropské respirační společnosti (European Respiratory Society) pro cvičení a rehabilitaci pacientů s těžkou chronickou plicní hypertenzí, v němž se uvádí, že individuálně navržené a monitorované cvičební programy jsou pro z klinického hlediska stabilizované pacienty s farmakoterapií plicní hypertenze nejspíše bezpečné. V současné době je práce na rehabilitačních intervencích specifických pro jedince s plicní arteriální hypertenzí teprve ve stadiu výzkumu. Předkládáme předběžné výsledky rozsáhlejší studie s cílem ukázat účinnost individuálně navrženého 12týdenního domácího cvičebního programu v tom, že zlepšuje toleranci zátěže i kvalitu spánku a omezuje emoční vypětí pacientů s plicní arteriální hypertenzí.
Metody: Popisované výsledky byly získány v prospektivní randomizované kontrolované intervenční studii. Do analýzy byly zařazeny údaje 16 pacientů s plicní arteriální hypertenzí. Celá skupina absolvovala komplexní tréninkový program sestávající z 12týdenního individuálně navrženého cvičení, edukace, informací o zásadách sebeovládání a telerehabilitace. Součástí programu byly i posilování svalstva, dechové aerobní cvičení i relaxační techniky.
Výsledky: V trénované skupině bylo zaznamenáno statisticky významné průměrné prodloužení vzdálenosti překonané v 6minutovém testu chůze (6MWT) (Δ = 51,7 ± 45,1 m). U šesti účastníků studie (66,7 %) z trénované skupiny a dvou pacientů (28,6 %) z kontrolní skupiny byl pozorován minimální klinicky významný rozdíl ve vzdálenosti překonané v 6MWT (25–33 m). V trénované skupině se výsledky IP_{submax} testu změnily statisticky významně (Δ = 9,8 ± 4,7 cm H_20). V sebeposuzovacím dotazníku kvality spánku se hodnoty PSQI zlepšily ze špatné na dobrou u čtyř (44,5 %) pacientů z trénované skupiny. Skóre podškál nemocniční deprese a úzkosti (HADS) potvrdila klinicky významný úbytek symptomů úzkosti v obou skupinách. U symptomů deprese nebyly klinicky významné změny nalezeny. Nebyly zaznamenány žádné nežádoucí účinky.
Závěr: U pacientů se stabilizovanou plicní arteriální hypertenzí námi hodnocený 12týdenní individuálně navržený domácí cvičební program účinně zlepšuje jejich funkční kapacitu (toleranci zátěže) i kvalitu spánku. Další zdokonalení metodologie cvičebních programů v oblasti plicní arteriální hypertenze si vyžádá další studie. Tento text přináší předběžné výsledky dosud probíhající studie.

ABSTRACT

Background: Most patients with optimal PAH-targeted medical therapy suffer from clinical symptoms, reduced exercise tolerance and have a poor quality of life. The 2019 European Respiratory Society task force statement on physical exercise and rehabilitation in patients with severe, chronic PH suggests that individually adjusted and monitored exercise programs are likely to be safe for PH patients, who are clinically stable on medical therapy. Currently, the development of PAH-specific rehabilitation interventions is still in the research stage. We present the preliminary results of a more extensive study with the aim to show the effectiveness of a 12-week individualized, home-based exercise program in promoting physical capacity, quality of sleep and reducing signs of emotional distress in patients with PAH.

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Methods: This was a prospective randomized controlled interventional study. 16 PAH patients were included in the analysis. Training group underwent a complex training program, consisting of 12-week individually tailored home-based exercise training, education, self-control measures and tele-rehabilitation components. The program included muscle strength training, respiratory, aerobic exercise and relaxation techniques.
Results: A statistically significant mean increase in 6MWT distance was observed for the training group (Δ = 51.7 ± 45.1 m). In six participants (66.7%) from the training group and two patients (28.6%) from the control group, the minimal clinically significant difference for 6MWT distance was observed (25–33 m). IP_{submax} test results changed significantly in training group (Δ = 9.8 ± 4.7 cm H_20). PSQI values sleep quality improved from poor to good in four (44.5%) patients from training group. HADS sub-scales scores values confirmed clinically important reduction of anxiety symptoms in both groups. Depression symptoms did not show clinically important changes. No adverse events were observed.
Conclusion: The studied 12-week individually tailored home-based exercise program is effective in stable PAH patients by improving physical functional capacity, as well as sleep quality. Further studies are required to solidify the methodology of exercise programmes in the field of PAH. These are the preliminary results of ongoing study.

Keywords:
Exercise training
Home-based exercise
Physical capacity
Pulmonary arterial hypertension
Sleep quality

Introduction

Pulmonary arterial hypertension (PAH) is a rare and severe disease characterized by an increase in pulmonary artery pressure and pulmonary vascular resistance, which ultimately lead to right ventricular failure and death.[1] Most patients with optimal PAH-targeted medical therapy suffer from clinical symptoms, reduced exercise tolerance and have a poor quality of life.[2]

The significance of physical exercise as an important component of therapy has already been proven in the scope of various cardiopulmonary diseases. Over the last 15 years, benefits of exercise have also been extensively studied in the field of PAH.[3] The 2019 European Respiratory Society task force statement on physical exercise and rehabilitation in patients with severe, chronic PH suggests that individually adjusted and monitored exercise programs are likely to be safe for PH patients, who are clinically stable on medical therapy.

Currently, the development of PAH-specific rehabilitation interventions is still in the research stage. Nevertheless, the available studies provide recommendations based on strong evidence. The training program has to consist of different types of activity: aerobic exercise, resistance training, respiratory muscle training, breathing and relaxation techniques.[3] These programs should be created long-term, and all PAH patients should be encouraged to take part in regular exercise training.[4] Availability of such programs needs to be increased. For this reason, more recently outpatient and home-based rehabilitation programmes have been studied the most. Home-based rehabilitation programs appear to be safe, effective, as well as cost effective, although adequate self-control and monitoring requirements have to be met, including various practices of telerehabilitation.[3,5]

Physical exercise can improve exercise tolerance, muscle function, quality of life and potentially right ventricular function and pulmonary hemodynamics. Further studies are required to solidify the methodology of exercise programs in the field of PAH.[6]

The effect of physical exercise programs on the mental health of PAH patients is yet to be studied, even though benefits of exercise have been proven in patients with anxiety and depression.[7]

More recently, the role of sleep quality has been emphasized for patients with chronic diseases, as it can be a key factor in symptom management and more effective coping strategies, as well as in promotion of general health (e.g. reducing cardiovascular disease risk). Adequate quality of sleep is important for a healthy society, but it is also closely related to quality of life in patients with chronic diseases.[8–10] For patients with cardiovascular disease (including PAH), structural changes in sleep are observed – decreased length and the overall quality of sleep. As sleeping disorders become more prominent in PAH patients, deterioration of clinical symptoms and HRQoL results is noted. Strong association between depression, anxiety and quality of sleep has been found in patients with chronic diseases.[11,12] Patient education on sleep hygiene and/or cognitive behavioral therapy is highly recommended, and the positive effect of moderate physical exercise on improving the quality of sleep should not be forgotten.[13]

We present the preliminary results of a more extensive study with the aim to show the effectiveness of a 12-week individualized, home-based exercise program in promoting physical capacity, quality of sleep and reducing signs of emotional distress in patients with PAH.

Methods

Study population and design

This is a prospective, randomized and controlled interventional study and we present the preliminary results, as the second follow-up assessment is still ongoing. The participants were enrolled from Latvian PH registry in two steps. After the screening of the registry data, all relevant PAH patients (n = 189) were selected and afterwards the study selection criteria were applied by a cardiologist specialized in PH. The inclusion criteria for this study were: NYHA functional class II–III, age between 18 and 80 years, clinically stable and on optimized medical therapy for at least 3 months before entering the study.

At the second stage, 27 of 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 on-site assessments were applied. Ultimately, 19 participants were enrolled in this study.

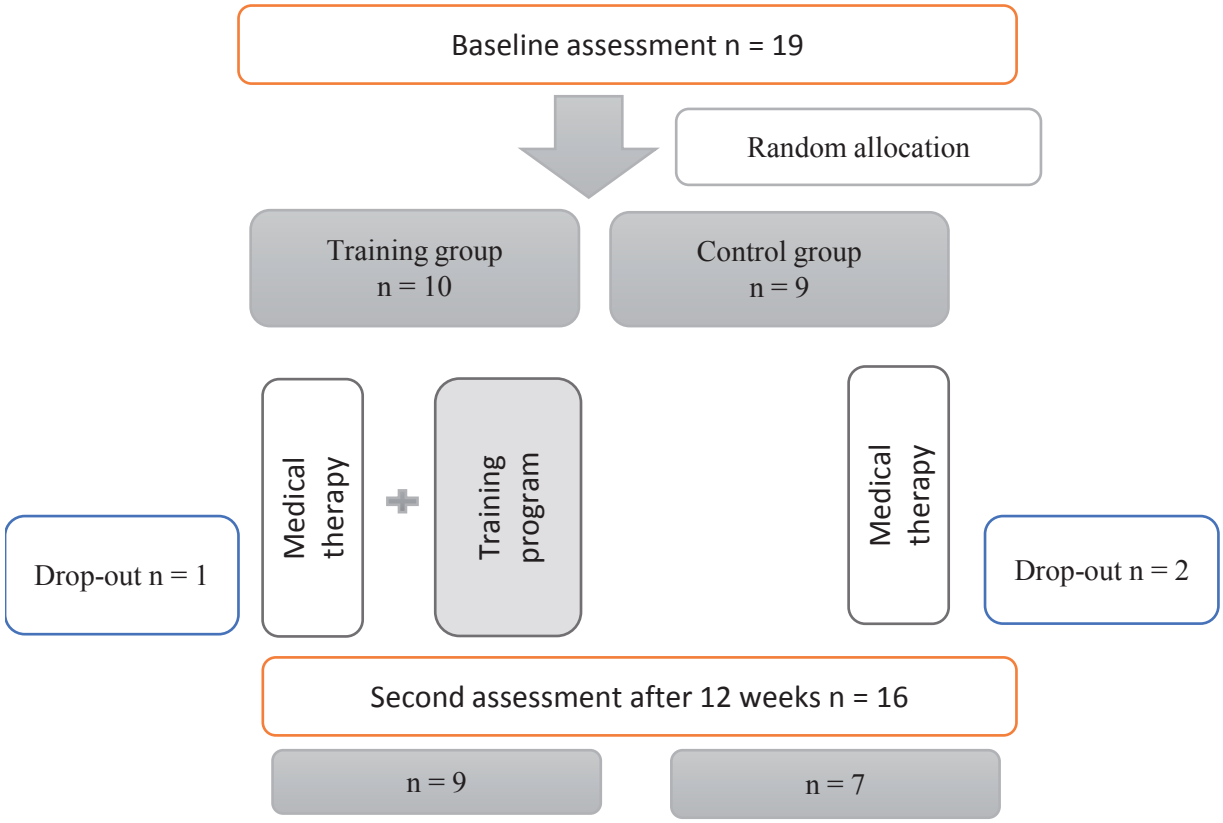

Fig. 1 – The study flow chart.

The study was approved by Riga Stradins University Ethics Committee and all of the patients signed written informed consent form prior to inclusion in the study. An independent researcher ensured a blinded assessment. Randomization process was done by block randomization method. The study flow chart is shown in Fig.1.

Intervention – the training program

All of the patients continued medical therapy under the care of a cardiologist and their primary care doctor. Patients in the training group underwent a complex training program developed specifically for PAH patients, consisting of 12-week individually adjusted home-based exercise training, education, self-control measures and tele-rehabilitation components (Fig. 2).

A specialized physiotherapist led the training program and included muscle strength training, respiratory, aerobic exercise and relaxation techniques as described in Figure 2. The exercises were adapted individually and clearly explained for each patient. The included training modalities had the following characteristics:

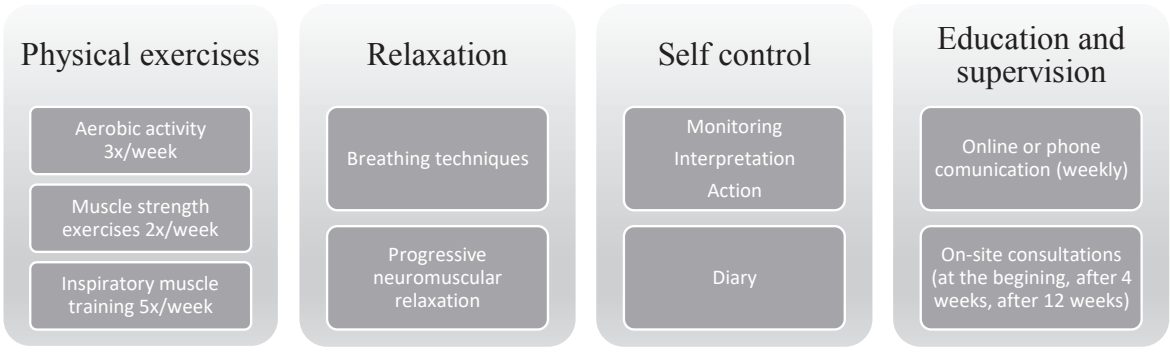

Fig. 2 – The training program content.

(I) Aerobic activity: 20–40 min cyclic activity, three times a week. Type of activity was selected individually (e.g., walking, bicycle ergometer). Intensity: perceived exertion as 5–6 on 10 points Borg scale and sustained SpO_2 or decrease of no more than 5% from the baseline. Progression was based on individual tolerability and provided by an increase in training duration and limited by "alarm signs": peak heart rate of more than 120 bpm, decrease in SpO_2 to 85%; perceived exertion as very hard (>6 on Borg scale) and subjective symptoms of exercise intolerance (severe dyspnea or fatigue, dizziness, pain etc.).

(II) 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).

(III) Inspiratory muscle training: with Philips breathing trainer Threshold IMT, five times a week. Progression: repetitions from 3×3 to 3×7 in each set; resistance from 30% to 65–70% from max.

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

Self-control included monitoring of heart rate, SpO_2, perceived exertion on Borg scale, subjective clinical symptoms, recognition of alarm and warning signs with appropriate action that was initially discussed. To enhance compliance, patients were required to fill a daily study diary. Each participant of the training group was provided with a paper or online format diary and pulse oximeter (Beurer PO 60) to ensure self-control measures.

The educational and motivational elements provided by a physiotherapist (both in verbal and visual handout material) was a part of the program. Education included both 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. Weekly phone communication and three on-site consultations (at the beginning, after 4 weeks, after 12 weeks) were carried out by a physiotherapist to ensure both individualized adjustments and proper execution, and to maximize clinical safety as well as provide education (training) and encouragement.

Outcome measures

Six-minute walk test (6MWT) was performed according to guidelines,[14] with SpO_2, heart rate, and blood pressure monitoring. Distance (m) covered during the test was recorded and minimal clinically significant difference (25–33 m) was determined based on previous studies.[15]

IP_{submax} (inspiratory pressure) test with Philips Threshold IMT was performed. The patients were asked to perform an uninterrupted, maximal deep inhalation through mouth with a special nose clip on, and the pressure reached (cm H_20) was recorded.

Sleep quality was assessed by self-reported questionnaire PSQI (Pittsburgh Sleep Quality Index), general score was recorded (higher total scores indicating poor sleep quality). The cutoff score of 5 and more was defined as poor sleep quality.[16]

HADS (Hospital Anxiety and Depression Scale) questionnaire was used to detect symptoms of anxiety and depression, and score of subscales HADS – anxiety, HADS – depression was recorded. Cutoff score of 7 and more was defined as clinically significant symptoms.[17]

Statistical analysis

Data are presented as mean ± standard deviation (SD) and as absolute values for individuals. Intragroup comparison between baseline and 12 weeks was done using Wilcoxon signed-rank test for all outcome variables. Group comparison was done using Mann Whitney U test for all outcome variables. A value of p <0.05 was considered statistically significant. All analyses were carried out with the SPSS v. 23.0 software program.

Table 1 – Baseline characteristics of the participants

	Training group (n = 9)	Control group (n = 7)
Age (years)	61.6 ± 18.5	68.3 ± 16.6
Gender (n)		
Women/Men	8/1	7/0
BMI (kg/m^2)	26.0 ± 5.3	25.8 ± 5.1
IPAH/APAH (n)	7/2	5/2
NYHA (n)		
II/III	4/5	2/5
PAH therapy (n)		
PDE5 inhibitor	8	7
ERA	4	4
Ventavis	1	0
Spironolactonum	9	6
Oxygen therapy	0	2
Co-morbidities (n)		
Hypertension	5	4
Dyslipidemia	3	5
CHF	7	4
AF	5	4
Time since diagnosis (years)	3.1 ± 3.0	2.7 ± 1.1
Cardiac catheterization		
mPAP (mmHg)	44.1 ± 15.7	49.1 ± 14.4
PCWP (mmHg)	10.1 ± 2.2	11.0 ± 3.2
PVR (WU)	8.7 ± 5.4	9.1 ± 7.4

Data are presented as n, or mean ± SD. AF – atrial fibrillation; APAH – associated pulmonary arterial hypertension; BMI – body mass index; CHF – chronic heart failure; ERA – endothelin receptor antagonist; IPAH – idiopathic pulmonary arterial hypertension; mPAP – mean pulmonary arterial pressure; NYHA – New York Heart Association; PAH – pulmonary arterial hypertension; PAWP – pulmonary arterial wedge pressure; PDE – phosphodiesterase; PVR – pulmonary vascular resistance.

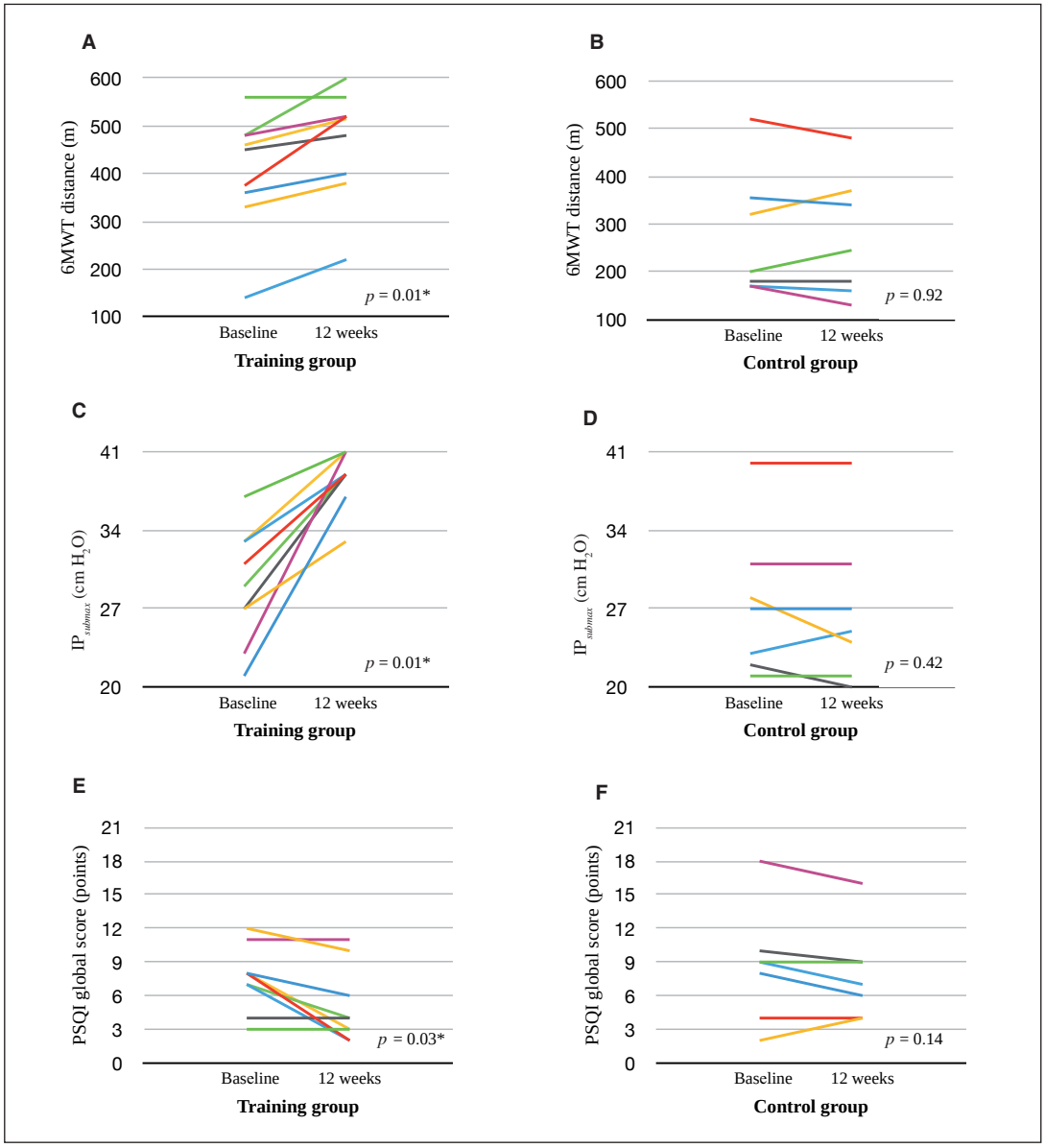

Fig. 3 – Individual changes in 6MWT, IP_{submax} and PSQI at baseline and after 12 weeks. (A) 6MWT distance (m) for each participant (n = 9) in the training group; (B) 6MWT distance (m) for each participant (n = 7) in the control group; (C) IP_{submax} test results (cm H_2O) for each participant (n = 9) in the training group; (D) IP_{submax} test results (cm H_2O) for each participant (n = 7) in the control group; (E) PSQI global score (points) for each participant (n = 9) in the training group; (F) PSQI global score (points) for each participant (n = 7) in the control group. 6MWT – 6-min walk test; IP_{submax} – sub-maximal inspiratory pressure test; PSQI – the Pittsburgh Sleep Quality Index. Wilcoxon signed-rank test was used to prove difference between baseline and 12 weeks for all outcome variables. * $p < 0,05$ indicating a statistically significant difference.

Results

Baseline characteristics of training and control groups are summarized in Table 1. When compared with the baseline values, the 6MWT distance increased for eight of nine patients in the training group and for three patients in the control group. A statistically significant (p <0,05) mean increase in distance was observed for the training group (Δ = 51.7 ± 45.1m) with almost no changes for control group (Δ = –1.4 ± 36.6 m) (Figs 3A, 3B, Table 2). For six participants (66.7%) from the training group and two patients (28.6%) from the control group, the minimal clinically significant difference for 6MWT distance was observed. For one participant from training group and one from control group 6MWT distance remained the same as at the baseline, but from control group four patients showed decreased 6MWT distance in assessment after 12 weeks, compared with baseline.

IP_{submax} test results after 12 weeks compared to the baseline values changed significantly only in training group (Δ = 9.8 ± 4.7 cm H_20, p = 0,01) (Table 2).

The baseline PSQI global score values revealed poor sleep quality for seven (77.8%) patients in training group and five in control group (71.4%). The significant

Table 2 – Change in 6MWT, IP_{submax}, PSQI and HADS results

Variable	Training group (n = 9)	Control group (n = 7)	*Between groups difference*
6MWT distance (m)			
Baseline	412.2 ± 120.8	278.6 ± 128.9	$p = 0.08$
12 weeks	463.9 ± 118.0	277.1 ± 125.2	$p = 0.01$*
Δ	51.7 ± 45.1	–1.43 ± 36.6	$p = 0.04$*
Intra-group difference:	$p = 0.01$*	$p = 0.50$	
IP_{submax} (cm H_2O)			
Baseline	29 ± 5.1	27.6 ± 6.9	$p = 0.46$
12 weeks	38.8 ± 2.5	27 ± 7.2	$p = 0,01$*
Δ	9.8 ± 4.7	–0.7 ± 2.1	p <0.001*
Intra-group difference:	$p = 0.01$*	$p = 0.42$	
PSQI global score (points)			
Baseline	7.2 ± 2.5	8.9 ± 5.2	$p = 0.40$
12 weeks	5.3 ± 3.1	7.7 ± 4.1	$p = 0.17$
>5 points (n, %)			
Baseline	7 (77.8)	5 (71.4)	
12 weeks	3 (33.4%)	5 (71.4)	
Intra-group difference:	$p = 0.03$*	$p = 0.18$	
HADS anxiety sub-scale (points)			
Baseline	6.3 ± 5.4	5.9 ± 5.1	$p = 0.71$
12 weeks	6.3 ± 2.3	7.7 ± 3.7	$p = 0.56$
≥ 7 points (n, %)			
Baseline	5 (55.6)	3 (42.6)	
12 weeks	3 (33.4%)	3 (42.6)	
Intra-group difference:	$p = 0.91$	$p = 0.17$	
HADS depression sub-scale (points)			
Baseline	3.7 ± 2.5	6.7 ± 4.2	$p = 0.08$
12 weeks	3.4 ± 2.6	7.1 ± 4.0	$p = 0.04$*
≥ 7 points (n, %)			
Baseline	1 (11.1)	3 (42.6)	
12 weeks	1 (11.1)	3 (42.6)	
Intra-group difference:	$p = 0.55$	$p = 0.58$	

Values are mean ± SD. Wilcoxon signed-rank was used to analyze changes between the baseline and at the end of 12 weeks in both outcome variables within each group. Mann-Whitney U test was used to compare both outcome values in training and control group at the baseline and at the end of 12 weeks. * $p < 0.05$ indicating a statistically significant difference. 6MWT – 6-min walk test; IP_{submax} – sub-maximal inspiratory pressure test; PSQI – the Pittsburgh Sleep Quality Index; HADS – the Hospital Anxiety and Depression Scale.

improvement in PSQI score only in training group was observed. (Figs 3C, 3D, Table 2) After 12 weeks according to PSQI values sleep quality improved from poor to good in four (44.5%) patients only from training group. Compared with the baseline values domains of PSQI had changed after 12 weeks in both groups for sleep latency (C2) and sleep disturbances (C5), but only participants from training group showed improvement in domains describing sleep quality (C3) and daytime dysfunction due to sleepiness (C7).

HADS results approved clinically important anxiety symptoms at the baseline assessment in five (55.6%) patients from the training group and three (42.6%) patients from the control group and depression symptoms in one patient from the training group and in three patients from the control group. Compared with the baseline after 12 weeks HADS sub-scales scores values confirmed clinically important reduction of anxiety symptoms in two of five patients from the training group and in one from three patients from the control group who had elevated anxiety level at the baseline assessment, but one patient from the control group showed clinically important increase of anxiety. Depression symptoms did not show clinically important changes for any of the participants (Table 2).

No adverse events (defined as clinical worsening or exacerbation, hospitalization, significant raise in BNP level) were observed during the course of the training program, confirming a safety of the program. A reason for dropout (n = 1) in the training group was excessively increased psychosocial distress due to the emergency situation in COVID-19 pandemic during the study.

Discussion

Our findings show that 12-week, individually tailored home-based exercise program is effective in stable PAH by improving physical functional capacity, as well as improving sleep quality. 6MWT and IP_{submax} test results showed significantly higher improvement in the training group, when compared to control group. Mean improvement in 6MWT distance (51.7 m) was higher than in our preliminary study (39 m).[5] Comparing results with the data from other studies – the reported improvement ranged from 40–69 meters in 12-week-long programs.[4] But only one of the studies analyzed home-based program, in which the improvement in mean distance was 40 meters, therefore our results demonstrate similar improvement.[18]

Visible heterogeneity of participants in both patient groups according to 6MWT results was present, but similarly to our previous research,[5] a possibility to individually adapt the program for each patient ensured achievement of improvement both in patients with relatively low (baseline distance 140 m, improvement 80 m) and high (baseline distance 480 m, improvement 120 m) exercise capacity.

The study results confirmed a significant improvement of inspiratory muscle function described by IP_{submax} test results after the 12-week-long home-based exercise program and significant difference between groups was noted. It is difficult to compare with results from other studies because we did not test maximal inspiratory pressure. Otherwise, the IP_{submax} test used in the study was appropriate to detect inspiratory muscle dysfunction and improvements after training in study population. Results of recently published studies on inspiratory muscle training in PAH patients have showed improvements in IP_{max} (Δ 17.8–Δ 30.8 cm H_20) after 8-week inspiratory muscle training compared to our results (Δ 9.8 cm H_20). This could be explained with training intensity (lower in our study) and baseline values (mean 29 cm H_20 in our study, 55.7–78.2 cm H_20 in other).[19,20]

More than 70% of the participants presented with poor sleep quality at baseline assessment pointing out important health concern in PAH patients.[16,21] Contrary to expected, we did not find clinically significant symptoms of depression in the studied population and approximately half of patients had clinically significant symptoms of anxiety that can also explain poor quality of sleep. Prevalence of mental disorders in PAH patients lies between 7.8–53%.[17] We want to highlight the improvement in sleep quality that reached level of statistical significance, as well as clinically significant change of proportion of patients with poor sleep quality (from 77.8% at baseline to 33.4% after training). This could be attributed to improvement of sleep habits and daytime planning, as well as positive impact on autonomic balance by exercise training.[11,22] Most likely inspiratory muscle training and relaxation techniques made higher impact on sleep quality in the training group, and the results are similar to recently published pilot study findings about slow breathing in PAH.[11] Positive influence on relaxation could explained clinical important reduction of anxiety symptoms in two of five patients from the training group.

Study limitations

As mentioned above these are the preliminary results of a bigger ongoing study. One of the main limitations is the small sample size which could potentially limit statistical power for some of the outcome measures. Since we did not use maximal inspiratory pressure measurements, it was difficult to compare our results with other studies.

Our findings about the effectiveness of home-based exercise program acquire a special meaning in the context of unexpected external conditions created by COVID-19 pandemic. The 12-week intervention study period coincided with state emergency lockdown time in Latvia. Therefore, process and results of the training program reflect the opportunity to carry out a safe and effective exercise training at home environment using remote control by a specialist to provide optimal rehabilitation in such high-risk group patients as PAH during virus pandemic.

Conclusion

The studied 12-week individually tailored home-based exercise program is effective in stable PAH patients by improving physical functional capacity, as well as sleep quality. Further studies are required to solidify the methodology of exercise programmes in the field of PAH. These are the preliminary results of ongoing study.

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