Turk J Phys Med Rehab 2019;65(3):278-286
DOI: 10.5606/tftrd.2019.2758

Original Article

Effects of cardiopulmonary rehabilitation on pulmonary arterial hypertension: A prospective, randomized study

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Received: February 12, 2018 **Accepted:** June 12, 2018 **Published online:** May 08, 2019

ABSTRACT

Objectives: This study aims to investigate the effects of cardiopulmonary rehabilitation (CPR) on cardiopulmonary function, quality of life, depression, and hemodynamic parameters in patients with pulmonary arterial hypertension (PAH) and to compare the efficacy of hospital- and home-based exercise programs.

Patients and methods: Between December 2014 to May 2016, a total of 30 patients with PAH were included in the study. The patients were randomly assigned to either a hospital-based (n=15) or home-based exercise program (n=15). The hospital group was assigned to a cardiac rehabilitation (three days/week, 1 hour/week 50 to 70% maximal oxygen uptake [PvO_2]) program for eight weeks. The home-based exercise group received home exercises alone. Before and after eight weeks of rehabilitation, all patients were evaluated for their functional status (PvO_2), pulmonary function including forced expiratory volume in one sec (FEV_1), mL, forced vital capacity (FVC), mL and FEV_1/FVC%, quality of life using Short Form-36 (SF-36), depression severity using Beck Depression Inventory, and hemodynamic parameters including left ventricular ejection fraction, right ventricular ejection fraction, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and systolic pulmonary arterial pressure.

Results: Of the patients, 12 completed the study in each group. There was no statistically significant difference in the functional status, quality of life, depression severity, and hemodynamic parameters after the rehabilitation compared baseline between the groups.

Conclusion: Based on our study results, short-term CPR seems not to be beneficial in patients with PAH. We recommend long-term rehabilitation programs to achieve more benefits from aerobic exercise training in this patient population.

Keywords: Aerobic exercise, cardiopulmonary rehabilitation, echocardiography, hemodynamics, pulmonary arterial hypertension, pulmonary functional tests, quality of life.

Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by increased vascular resistance resulting in right heart failure and, eventually, death.[1] The diagnosis is made, when pulmonary arterial pressure is measured 25 mmHg at rest and 30 mmHg during exercise, which is obtained through right heart catheterization.[2,3] Additionally, obtaining values lower than 15 mmHg in pulmonary capillary wedge pressure confirms the diagnosis.[2,3]

Although the benefits of exercise has gained almost an universal acceptance in the treatment of PAH, there is no consensus in the intensity, duration or the methods of the exercise.[4] The offered programs usually contain aerobic, resistance, and breathing exercises. The intensity of the aerobic exercise should be decided by an exercise test based on existing symptoms.

The underlying mechanisms of the beneficial effects of exercise in PAH patients are mainly due to increased aerobic capacity through increased capillary density in the skeletal muscle, changes in the skeletal muscle function (increased oxidative capacity) and

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Cite this article as:
Karapolat H, Ece Çınar M, Tanıgör G, Nalbantgil S, Kayıkçıoğlu M, Moğulkoç N, et al. Effects of cardiopulmonary rehabilitation on pulmonary arterial hypertension: A prospective, randomized study. Turk J Phys Med Rehab 2019;65(3):278-286.

morphology (increased type 1 fibers and decreased type 2 fibers), improvement in cardiac functions (decreased right ventricular end-diastolic pressure results in remodeling in pulmonary artery), and improvement in hemodynamics.[4,5]

Although there are many treatment options in PAH, there is no curative therapy, and current pharmacological and non-pharmacological treatment options aim to slow the progression of the disease and to alleviate symptoms. With all the beneficial effects described above, cardiac rehabilitation and exercise can be considered among therapeutic modalities.

In the present study, we aimed to investigate the effects of cardiopulmonary rehabilitation (CPR) on cardiopulmonary function, quality of life (QoL), depression, and hemodynamic parameters in patients with PAH and to compare the efficacy of hospital- and home-based exercise programs.

PATIENTS AND METHODS

This single-blind, prospective, randomized study was conducted at Ege University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation between December 2014 to May 2016. A total of 30 patients with PAH were included in the study. *Inclusion criteria were as follows:* ≥18 years, PAH diagnosed by a physician and a resting pulmonary arterial pressure of ≥25 mmHg in right ventricle catheterization,[6] Group 1 PAH according to the modified Evian Classification,[6,7] being in a stable condition for medical treatment for the last three months, receiving no pulmonary rehabilitation within the last six months, and being in the World Health Organization Class II-III PAH.[8] *Exclusion criteria were as follows:* having a systemic, neurological, cognitive or musculoskeletal disease preventing the patient from exercise, psychiatric conditions hindering compliance to the study, receiving oxygen therapy, having Grade IV PAH, and having a history of syncope within the last six months. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Ege University, Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data including sociodemographic (age, sex, marital status, education, and working status), and clinical characteristics (etiology for PAH, other diagnoses, medications, body mass index [BMI] and pulmonary function tests) of the patients were recorded. All patients were, then, examined for all systems, focusing on musculoskeletal and neurological status. Physical activity status (sedentary lifestyle) was evaluated with questions based on the International Physical Activity Questionnaire (IPAQ).[9]

Forty of the patients were deemed eligible for the study. Ten of them withdrew their consent during

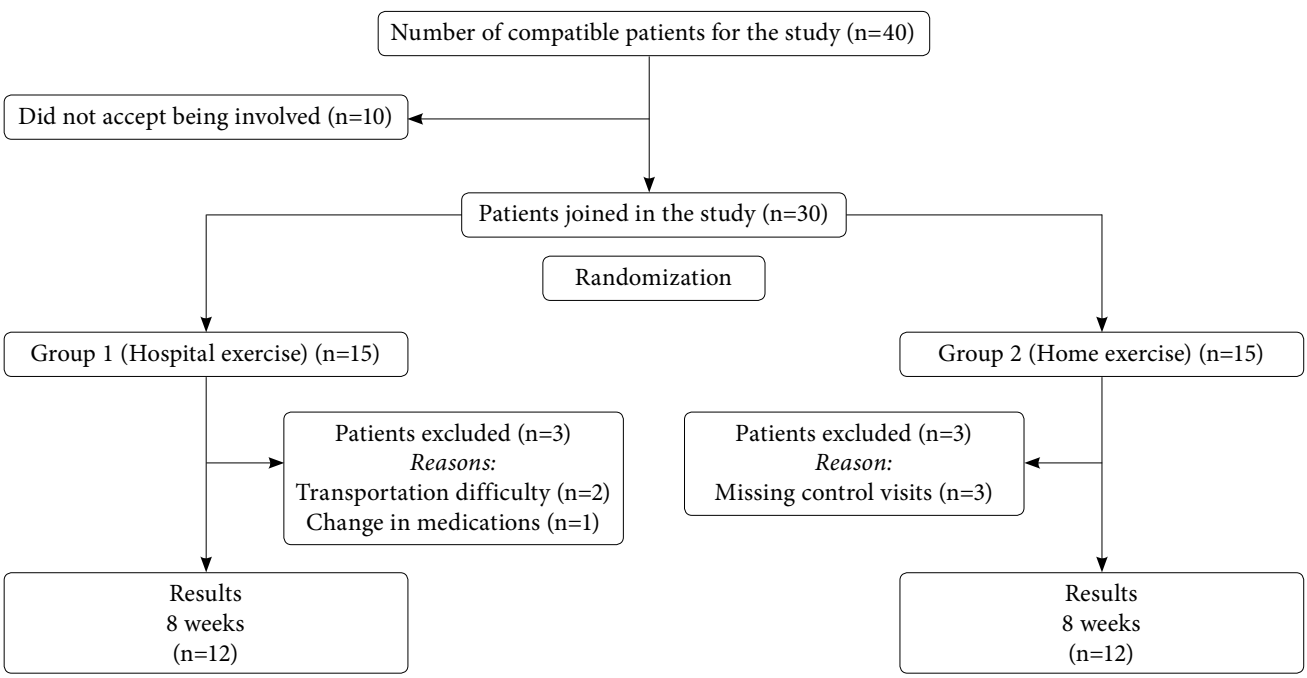

Figure 1. Study flow chart.

Table 1. Cardiopulmonary exercise test protocol for patients

	Minutes	Velocity (km/hours)	Inclination (%)
Resting phase	2	2	0
Test phase	2	3	0
	2	4	2.3
	2	5	3.8
	2	6	4.7
	2	6	7.2
	2	6	9.6
	2	6	12.1
	2	6	14.5
	2	6	17
	2	6	19.4
	2	6	21.8
	2	6	24.3
Resting phase	2	2	0

enrollment. The remaining patients (n=30) were randomly assigned to two groups by a computer program: Group 1 (hospital-based exercise, n=15) and Group 2 (home-based exercise, n=15). Before completion, three patients from each group left the study due to changes in medical management (n=1) and difficulty in transportation (n=2) in Group 1 and due to failure to attend to control visits (n=3) in Group 2. Finally, 12 patients in each group completed the study (13 females, 11 males; mean age 41 years; range 20 to 74 years). The study flow chart is shown in Figure 1.

Assessment

Cardiopulmonary exercise test: Cardiopulmonary exercise (CPE) test was applied on treadmill (model 770 CE), while having electrocardiography patterns recorded throughout the whole process. Exercise test protocol is defined in Table 1. Oxygen consumption (VO_2) and carbon dioxide production (vCO_2) were measured every 30 sec by a metabolic card (Masterscreen CPX, Viasys Test, Healthcare, Jaeger, Würzburg, Germany) using the breath-by-breath technique. Exercise test stopped according to the CPE termination criteria. The peak VO_2 values were obtained.[10]

Six-minute walk test (6MWT): This test was applied a day before CPE test under the supervision of a physiotherapist. The patients were asked to walk on a 30-m aisle without obstacles within their normal movement speed. They were free to sit or rest, and test went on until they reached their maximum. Total walking distance was recorded in meters.[11]

Short Form-36: It is a multi-purpose QoL scale with a broad range of applications. It was first developed by Rand Corporation in 1992 and has been used since then.[12] The scale consists of 36 items belonging to eight subscales including physical functioning (10 items), social role functioning (2 items), physical role functioning (4 items), emotional role functioning (3 items), mental health (5 items), vitality (4 items), bodily pain (2 items), and general health perceptions (5 items). Subscales are rated from 0 to 100, 0 being

Table 2. Demographic and clinical properties of groups

	Hospital-exercise group (n=12)				Home-exercise group (n=12)				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Age (year)			34	26-62			40	20-74	0.86
Sex									0.052
Female	9	75			4	33.3			
Male	3	25			8	66.7			
Education									0.19
Elementary	4	33.3			8	66.7			
High school	6	50			2	16.7			
College/University	2	16.7			2	16.7			
Smoking									0.32
None	11	91.7			8	66.7			
Quit	1	8.3			4	33.3			
Sedentary lifestyle (positive)	10	83.3			11	91.7			0.1
Body mass index (kg/m^2)			22.75	11.70-28.90			25.20	16-25.20	0.31
Duration of disease			10	3-36			7	2-20	0.32

Min: Minimum; Max: Maximum.

the worst possible situation and 100 being the best.[12] Reliability and construct validity in the Turkish population were evaluated in 1999.[13]

Beck Depression Inventory (BDI): The BDI was developed by Beck in 1961 to assess the depressive mood in individuals with chronic diseases.[14] It is used to evaluate vegetative, emotional, cognitive, and motivational findings in patients with depression. It is a self-rated tool including 21 items which are scored from 0-3, which complies with behavioral concepts that are coherent with depression. The total score is between 0 and 63. The Turkish reliability and validity studies were performed by Sahin[15]

Hemodynamic parameters

Hemodynamic parameters were evaluated in all patients using echocardiography by a blind researcher using a 1.7/3.4 MHz transducer (Vivid 7; GE Vingmed Ultrasound, Horten, Norway). Echocardiographic scales were compatible with the recommendations of the American Society of Echocardiography. End-systolic (mm) and end-diastolic (mm) diameters,

Table 3. Baseline clinical characteristics of the groups

	Hospital-exercise group (n=12)				Home-exercise group (n=12)				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Etiology									0.78
Idiopathic PAH	1	33.3			2	66.7			
Congenital PAH	6	54.5			5	45.5			
PAH attributed to rheumatologic diseases	2	66.7			2	50			
WHO Functional Classification									0.1
Class II	10	83.3			8	66.7			
Class III	2	16.7			4	33.3			
Peak VO_2 (mL/kg/min)			15.05	7.7-17.4			13.4	7.6-21.3	0.77
6MWT (meter)			390	150-495			420	240-580	0.31
FeV_1 (mL)			1840	610-2420			2470	870-3070	0.11
FVC (mL)			2330	900-3500			3025	1450-4120	0.11
FeV_1/FVC (%)			78.40	62.6-88			78.15	29.7-85.7	0.64
VC (mL)			2300	725-3400			2780	1760-3670	0.17
Short Form-36									
Physical functioning			57.50	35-90			57.50	20-75	0.95
Physical role functioning			25	0-100			50	0-100	0.18
Bodily pain			80	41-100			67.50	10-100	0.49
General health perceptions			38.50	0-67			49.50	27-100	0.15
Vitality			57.50	40-70			57.50	0-75	0.64
Social role functioning			62	37-87			62	37-100	0.96
Emotional role functioning			33	0-100			49.50	0-66	0.33
Mental health			50	20-84			66	0-100	0.50
Beck Depression Index			11	0-19			4.14	7-0	0.03
Echocardiography parameters									
LVEF (%)			60	50-60			60	30-60	0.19
RVEF (%)			60	35-60			60	28-60	0.34
LVEDD (mm)			4.2	3-5.9			4.2	3.5-4.5	0.69
LVESD (mm)			2.8	1.6-3.6			2.7	1.8-3.1	0.49
Systolic pulmonary arterial pressure			90	40-125			86	45-125	0.29

Min: Minimum; Max: Maximum; PAH: Pulmonary arterial hypertension; WHO: World Health Organization Classification of the disease; 6MWT: 6 minute walk test; FeV_1: Volume exhaled in first second of forced expiration; FVC: Forced vital capacity; VC: Vital capacity; LVEF: Left ventricular ejection fraction; RVEF: Right ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter.

Table 4. Baseline and 8th week evaluation of the study groups

	Hospital-exercise group (n=12)					Home-exercise group (n=12)					
	Week 0		Week 8			Week 0		Week 8			
	Median	Min-Max	Median	Min-Max	p^*	Median	Min-Max	Median	Min-Max	p^*	p^{**}
Peak VO_2 (mL/kg/min)	15.05	7.7-17.4	15.35	7.8-21.3	0.06	13.4	7.6-21.3	14.2	8.1-21	0.67	0.56
6MWT (meter)	390	150-495	427	120-460	0.32	420	240-580	435	180-585	0.18	0.82
FeV_1 (mL)	1840	610-2420	1935	550-2400	0.50	2470	870-3070	2265	1030-2910	0.58	0.48
FVC (mL)	2330	900-3500	2575	920-3350	0.46	3025	1450-4120	3184	1650-3750	0.39	0.67
FeV_1/FVC (%)	78.40	62.6-88	72.2	55-81	0.06	78.15	29.7-85.7	76.51	44-93.9	0.81	0.25
VC (mL)	2300	725-3400	1945	800-3620	0.79	2780	1760-3670	2780	1760-3670	0.18	0.32
Short Form-36											
Physical functioning	57.50	35-90	57.5	10-90	0.67	57.50	20-75	57.5	25-85	0.89	0.88
Physical role functioning	25	0-100	25	0-100	1	50	0-100	50	0-75	0.37	0.46
Bodily pain	80	41-100	80	0-100	0.51	67.50	10-100	56.5	20-100	0.17	0.36
General health perceptions	38.50	0-67	33.5	5-67	0.59	49.50	27-100	50	15-56	0.84	0.77
Vitality	57.50	40-70	52.5	35-70	0.58	57.50	0-75	55	45-80	0.40	0.06
Social role functioning	62	37-87	62	12-87	0.67	62	37-100	50	37-75	0.06	0.15
Emotional role functioning	33	0-100	33	0-100	0.32	49.50	0-66	49.5	0-66	0.18	0.08
Mental health	50	20-84	50	20-76	0.07	66	0-100	64	20-75	0.26	0.22
Beck Depression Index	11	0-19	8.5	0-31	0.24	7	0-15	6.5	0-12	0.89	0.21
Echocardiography parameters											
LVEF (%)	60	50-60	60	40-60	0.65	60	30-60	60	30-60	0.71	0.39
RVEF (%)	60	35-60	60	35-60	0.58	60	28-60	60	40-60	0.59	0.34
LVEDD (mm)	4.2	3-5.9	4.3	2.9-5.5	0.37	4.2	3.5-4.5	4.6	3.4-8	0.67	0.48
LVESD (mm)	2.8	1.6-3.6	2.6	1.8-4	0.64	2.7	1.8-3.1	3.1	1.8-6.2	0.14	0.27
SPAP	90	40-125	86	45-125	0.86	86	45-125	75	29-132	0.92	0.79

P*: In group comparison; P*: Intergroup comparison; 6MWT: 6 minute walk test; FeV1: Volume exhaled in first second of forced expiration; FVC: Forced vital capacity; VC: Vital capacity; LVEF: Left ventricular ejection fraction; RVEF: Right ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; SPAP: Systolic pulmonary arterial pressure.

Table 5. Correlation co-efficient between pVO_2, 6MWT before and after rehabilitation

	SPAP r1	SPAP r2	*p*
pVO_2 r1	0.09		0.68
pVO_2 r2		0.17	0.55
6MWT r1	0.35		0.14
6MWT r2		0.15	0.65

pVO_2: Maximal O_2 consumption; 6MWT: 6 minute walk test; SPAP: Systolic pulmonary arterial pressure; r1: Correlation coefficient before rehabilitation, r2: Correlation coefficient after rehabilitation; p>0.05.

ejection fraction of the left and right ventricles, and systolic pulmonary arterial pressure (SPAP) were recorded.

Treatment protocols

Exercise protocols were designed by a medical specialist who was experienced in CPR and the resulted protocol was three days a week for a total of eight weeks, and 45 to 60 min in each session. The patients in Group 1 received their treatment in the outpatient CPR setting and Group 2 received their treatment at home and each program was specifically designed to the individual's requirements. Exercise program consisted of flexibility exercises, aerobic exercises, and breathing exercises. Flexibility exercises contained stretching and range of motion exercises for the neck, low back, and upper and lower extremities. Aerobic exercises were adjusted to be 30 min, 50 to 70% of the PvO_2 and Borg scale of 13 to 15 on treadmill.[16] All aerobic exercise sessions consisted of five min of warming in the beginning and five min of cooling in the end. Breathing exercises included pursed lip breathing, thoracic expansion exercises, and abdominal breathing exercises.

In the home-based exercise group, the patients were instructed for their flexibility and breathing exercises by an experienced physiotherapist. They were also given guides for the exercises. Walking program was adjusted to be 50 to 70 of the PvO_2 and Borg scale of 13 to 15. They were asked to comply with the program as they did in the hospital as one hour each day for three days a week. They were provided with exercise table showing the dates, and placemarks for their compliance on it.

Statistical analysis

Power analysis revealed that 12 patients were needed for each group for 80% statistical power and alpha (α)=5%. Fifteen patients were planned to be recruited for each group considering a 20% dropout rate.

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), or number and frequency. The Shapiro-Wilk test was used to assess whether data were normally distributed. Parametric tests were used for data with normal distribution, while non-parametric tests were used for non-normally distributed data. To analyze the relationship between categorical variables, the chi-square test was used. The Mann-Whitney U test was used to compare variables between the two groups. The intra-group analysis was performed using the Wilcoxon signed-ranks test. Spearman correlation analysis was carried out to analyze correlation of variables between two groups. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 12 completed the study in each group. There were no significant differences between two groups in terms of the demographic and clinical characteristics. Baseline demographic and clinical data are shown in Table 2.

Data obtained from the questionnaires and clinical data at baseline are summarized in Table 3. There were no significant differences between the groups except for the BDI which was found to be significantly higher in the hospital-based exercise group, compared to the home-based exercise group (p=0.03).

The intra- and inter-group analysis results are shown in Table 4. There was no significant difference in the variables between the groups.

In addition, there was no significant correlation between the PVO_2 and SPAP in either group before and after rehabilitation (before: r=0.09, p=0.68; after r=0.17, p=0.55), (Table 5).

No adverse events attributed to CPR including syncope, arrhythmia, severe hypotension, and hemoptysis were reported throughout the study. No treatment modification was performed in any of the patients.

DISCUSSION

Pulmonary arterial hypertension is a mortal and debilitating disease, and any intervention which may alleviate symptoms or increase the QoL is valuable. Contributions of exercise to physical fitness in patients with PAH have been shown in previous studies.

Exercise in PAH patients should be started in low intensities (<50% of maximum aerobic capacity) and short durations (<30 min per session) and should be stepped up according to the tolerance of the patient. In an ideal maintenance of the program, exercise intensity should be moderate (50 to 75% of maximum aerobic capacity) with duration of 30 to 60 min and three to seven days per week. Exercise frequency should be at maximum the patient can tolerate almost all days of the week.

Although bicycle ergometry causes less symptoms, the ideal modality is treadmill, which is more similar to the daily activities. As an alternative, bicycle ergometry can be used as a step to an easier transition to the treadmill. Exercise with resistance can be given in one session of low-to-medium intensity (about 50% of one repetitive maximum) with a high number of repeats (10 to 15) and two to three days per week. Respiratory muscle exercises should be considered, when weakness is observed in the respiratory muscles. Exercises should be given in one or two sessions of 15 to 30 min in three to seven days a week with ≥30% of the maximal inspiratory pressure.[17] Working with intervals may cause sudden changes in hemodynamics and carry the risk of syncope and is contraindicated. Valsalva maneuver and exercises in water should be also avoided.[18] As high intensity exercise in PAH patients may result in shortness of breath, chest pain and syncope, it is not advisable.[19] In our study, no significant difference in the functional capacity, pulmonary function tests, QoL, depression severity, and parameters of echocardiography was observed between the groups.

One of the most significant findings in PAH is hindrance in exercise.[20] Although the pharmacological therapies developed in recent years has remarkable beneficial effects on disease progression and survival, many patients still exhibit exertional dyspnea and fatigue symptoms. The European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension in 2015 recommends exercising while under medical treatment in physically deconditioned patients.[21] Several studies included in meta-analyses to show the effects of exercising on PAH patients revealed that aerobic, resistive, inspiratory muscle or combination of each exercise types increase the exercise capacity.[20,22,23] However, these results should not be generalized to all PAH patients, since the ones selected for the studies were between the WHO Class I-IV.[23] There are also studies with no significant beneficial results of exercise on functional capacity similar to our study.[24-26] One of the reasons may be due to the fact that the exercise protocol was inappropriate for these patients. Another reason is probable incompatibility with PAH patients on therapeutic exercise's frequency, duration, and intensity. Also, patients included in the study were WHO Class II-III, unlike other studies, and this may be an explanation for the discrepancy in the results. Still, progressive nature of PAH and both groups may have resulted in deviations in the exercise capacity. As reported in previous meta-analyses, we agree with the need of more clinical studies to evaluate the effects of exercising on exercise capacity.[20,22,23]

Due to physical and psychological challenges and being in need of constant medication, PAH patients may also have problems in social relationships with impaired QoL.[27] In several meta-analyses, exercise was found to have beneficial effects on the QoL, particularly on physical functioning.[20,23] However, our study was unable to show an improvement on the QoL with exercising. Although this can be explained by progressive, unpredictable, and complex nature of the disease, lack of a scale specifically designed for PAH patients may be also the reason for these controversial results.

Furthermore, PAH patients have problems in managing daily activities of life due to exertional intolerance, dyspnea, and fatigue.[28] This results in a higher incidence of depressive mood disorders in these patients.[28] Several studies have shown that problems in physical functioning may induce depression.[29,30] Moreover, depression itself may cause worse scores on mental and physical health scales.[31] Progressive nature of the disease and not being completely curable by treatments result in social isolation, leading to depression.[28] In our study, depression scores were higher in the hospital-based exercise group, compared to the home-based exercise group at baseline only. While exercise was helpful to maintain lower scores of depression, changes were non-significant in both groups. Although pulmonary rehabilitation is considered an effective method of treating depression in PAH,[31,32] no studies have shown effects of exercise on depression. Not having an actual treatment besides exercise and a lack of a multidisciplinary approach for depression may be the reason for failed achievement of significant results of exercise on depression, particularly in the hospital-based exercise group.

In the literature, previous studies have not evaluated the effects of exercise on cardiac functions.

In a meta-analysis by Babu et al.,[20] it was found to be appropriate not to evaluate the effects of exercise on cardiac functions. It has not been clearly elucidated that improvements in symptoms should be attributed to exercise or functional improvements on the right ventricular function itself. A study conducted by Mereles et al.[33] showed no effects of exercise on the pulmonary arterial pressure. Still, Ehlken et al.[34] observed that 12 weeks of exercise had beneficial effects on the pulmonary arterial pressure and cardiac index. In our study, neither right or left ventricular functional parameters were affected by exercise. In their study, Brown et al.[35] reported that high intensity interval training had hemodynamic effects in PAH patients over non-interval training. Since we used non-interval exercise in our study, this might have contributed to the lack of significant effects on hemodynamics.

In our study, the number of patients with a congenital etiology, whose exercise capacities are better preserved, unless it is terminal stage, was relatively high. This might have led to minor changes in these parameters that could not be observed with mild exercise and statistical non-significance.[36]

Compared to previous studies, our patients had a remarkably higher SPAP.[33] This finding indicates that exertional dyspnea is compensated in context of chronicity. Still, we believe that further studies are needed to show the effects of exercise on PAH patients with higher SPAP levels. We were unable to find a correlation between exercise capacity and pulmonary hypertension. Butler et al.[37] also did not find any correlation in 50% of their patients, consistent with our findings. It is assumed that the reason behind this concept may be the importance of right ventricular functions on cardiac output. Therefore, we suggest that further studies should focus on the right ventricular functional tests.

A lack of control group without exertional intervention is one of the main limitations of our study. For a better assessment of exercise, a control group with an absolute lack of intervention may be useful. In addition, this study was completed at eight weeks and all assessments and recordings were obtained at baseline and at the end of treatment. A longer course of exercise may make its effects more significant, thus having meaningful results. One of the other limitations is the lack of assessment of the effects of exercise on endurance capacity. In their studies, de Man[26] and Boutet et al.[38] did not find beneficial effects of exercise on the functional capacity; however, they claimed that exercise improved endurance. Although all of our patients belonged to Group 1 PAH classification, still selection of all patients from the same etiology could have yielded more accurate results.

In conclusion, based on our study results, short-term CRP seems not to be beneficial without any significant effect on exercise capacity, QoL, depression, and hemodynamic responses in patients with PAH. We recommend long-term rehabilitation programs to achieve more benefits from aerobic exercise training in this patient population. Elucidating underlying mechanisms of PAH would greatly contribute to future studies to evaluate the effects of exercise on symptoms and functionality.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Kaymaz C, Mutlu B, Küçükoğlu MS, Kaya B, Akdeniz B, Kılıçkıran Avcı B, et al. Preliminary results from a nationwide adult cardiology perspective for pulmonary hypertension: RegiStry on clInical outcoMe and sUrvival in pulmonaRy hypertension Groups (SIMURG). Anatol J Cardiol 2017;18:242-50.
2. Teo YW, Greenhalgh DL. Update on anaesthetic approach to pulmonary hypertension. Eur J Anaesthesiol 2010;27:317-23.
3. Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet 1998;352:719-25.
4. Alan B, Nalbantgil S. Genetic, cellular and molecular mechanisms of pulmonary arterial hypertension. [Article in Turkish] Anadolu Kardiyol Derg 2010;10:9-13.
5. Galie N, Manes A, Palazzini M. Exercise training in pulmonary hypertension: improving performance but waiting for outcome. Eur Heart J 2016;37:45-8.
6. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5-12.
7. Fishman AP. Primary pulmonary arterial hypertension: a look back. J Am Coll Cardiol 2004;43:2-4.
8. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:40-7.
9. Hagströmer M, Oja P, Sjöström M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. Public Health Nutr 2006;9:755-62.
10. Shimizu M, Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, et al. The ventilatory threshold: method, protocol, and evaluator agreement. Am Heart J 1991;122:509-16.

11. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
12. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
13. Kocyigit H, Aydemir O, Olmez N, Memis A. Reliability and validity of the Turkish version of Short-Form-36 (SF-36). Turkish J Drugs Therap 1999;12:102-6.
14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
15. Şahin N. Beck depresyon envanterinin üniversite öğrencileri için geçerliği güvenirliği. Türk Psikoloji Dergisi 1989;23:3-13.
16. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-81.
17. Desai SA, Channick RN. Exercise in patients with pulmonary arterial hypertension. J Cardiopulm Rehabil Prev 2008;28:12-6.
18. Arena R, Cahalin LP, Borghi-Silva A, Myers J. The effect of exercise training on the pulmonary arterial system in patients with pulmonary hypertension. Prog Cardiovasc Dis 2015;57:480-8.
19. Tamura Y, Channick RN. New paradigm for pulmonary arterial hypertension treatment. Curr Opin Pulm Med 2016;22:429-33.
20. Babu AS, Padmakumar R, Maiya AG, Mohapatra AK, Kamath RL. Effects of exercise training on exercise capacity in pulmonary arterial hypertension: a systematic review of clinical trials. Heart Lung Circ 2016;25:333-41.
21. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
22. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. BMC Pulm Med 2015;15:40.
23. Pandey A, Garg S, Khunger M, Garg S, Kumbhani DJ, Chin KM, et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. Circ Heart Fail 2015;8:1032-43.
24. Martínez-Quintana E, Miranda-Calderín G, Ugarte-Lopetegui A, Rodríguez-González F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. Congenit Heart Dis 2010;5:44-50.
25. Ihle F, Weise S, Waelde A, Meis T, Kneidinger N, Schild C, et al. An integrated outpatient training program for patients with pulmonary hypertension-the Munich Pilot Project. Int J Phys Med Rehabil 2014;2:1-5.
26. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2009;34:669-75.
27. Gu S, Hu H, Dong H. Systematic review of health-related quality of life in patients with pulmonary arterial hypertension. Pharmacoeconomics 2016;34:751-70.
28. Verma S, Sahni S, Vijayan VK, Talwar A. Depression in pulmonary arterial hypertension: An undertreated comorbidity. Lung India 2016;33:58-63.
29. Looper KJ, Pierre A, Dunkley DM, Sigal JJ, Langleben D. Depressive symptoms in relation to physical functioning in pulmonary hypertension. J Psychosom Res 2009;66:221-5.
30. Löwe B, Gräfe K, Ufer C, Kroenke K, Grünig E, Herzog W, et al. Anxiety and depression in patients with pulmonary hypertension. Psychosom Med 2004;66:831-6.
31. Talwar A, Sahni S, Kim EJ, Verma S, Kohn N. Dyspnea, depression and health related quality of life in pulmonary arterial hypertension patients. J Exerc Rehabil 2015;11:259-65.
32. Verma S, Cardenas-Garcia J, Mohapatra PR, Talwar A. Depression in pulmonary arterial hypertension and interstitial lung diseases. N Am J Med Sci 2014;6:240-9.
33. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation 2006;114:1482-9.
34. Ehlken N, Lichtblau M, Klose H, Weidenhammer J, Fischer C, Nechwatal R, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. Eur Heart J 2016;37:35-44.
35. Brown MB, Neves E, Long G, Graber J, Gladish B, Wiseman A, et al. High-intensity interval training, but not continuous training, reverses right ventricular hypertrophy and dysfunction in a rat model of pulmonary hypertension. Am J Physiol Regul Integr Comp Physiol 2017;312:197-210.
36. Kayikçioğlu M, Kültürsay H. Current approach to the treatment of pulmonary arterial hypertension and our experience in the Cardiology Department of Medicine Faculty of Ege University. [Article in Turkish] Turk Kardiyol Dern Ars 2009;37:580-90.
37. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol 1999;34:1802-6.
38. Boutet K, Garcia G, Degano B. Results of a 12-week outpatientcardiovascular rehabilitation in patients with idiopathic pulmon-ary arterial hypertension. Eur Respir J 2008;32(Suppl 52):240.