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The benefit of exercise-based rehabilitation programs in patients with pulmonary hypertension: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Several studies have suggested that exercise capacity and quality of life are reduced in patients with pulmonary hypertension, and exercise-based rehabilitation can improve exercise capacity and quality of life in patients with pulmonary hypertension. The aim of this study is to assess the efficacy and safety of exercise-based rehabilitation in patients with pulmonary hypertension through a meta-analysis of randomized controlled trials. We searched PubMed, Embase, Medline, and the Cochrane Central Register of Controlled Trials up to November 2018. All randomized controlled trials comparing exercise capacity and quality of life between patients undergoing exercise-based rehabilitation and those undergoing non-exercise training were included. Data were extracted separately and independently by two investigators, and discrepancies were arbitrated by the third investigator. We used the random-effects model to analyze the results, the GRADE to assess the risk of bias in the included studies, and I^2 statistic to estimate the degree of heterogeneity. Nine randomized controlled trials are included; however, only seven randomized controlled trials were able to extract data. Including inpatients and outpatients, the total number of participants was 234, most of whom were diagnosed as pulmonary artery hypertension. The study duration ranged from 3 to 15 weeks. The mean six-minute walking distance after exercise training was 51.94 m higher than control (27.65–76.23 m, $n = 234$, 7 randomized controlled trials, low quality evidence), the mean peak oxygen uptake was 2.96 ml/kg/min higher (2.49–3.43 ml/kg/min, $n = 179$, 4 randomized controlled trials, low-quality evidence) than in the control group. In conclusion, our finding suggests that an exercise-based training program positively influences exercise capacity in patients with pulmonary hypertension.

Keywords

pulmonary hypertension, exercise training, rehabilitation

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Background

Pulmonary arterial hypertension (PAH) is a severe clinical condition characterized by a mean pulmonary artery pressure >25 mm Hg at rest, an expiratory pulmonary artery wedge pressure ≤15 mm Hg, and a pulmonary vascular resistance >3 Wood units.[1] PAH can usually be divided into idiopathic pulmonary arterial hypertension (IPAH) and PAH associated with congenital heart disease, systemic-to-pulmonary shunt, rheumatic diseases, portal hypertension, and human immunodeficiency virus infection.[1] Patients with PAH have reduced exercise capacity, quality of life (QoL), and survival.[2,3] Studies have suggested that exercise training (ET) can lead to benefits in patients with clinically stable chronic diseases,[4–6] in which

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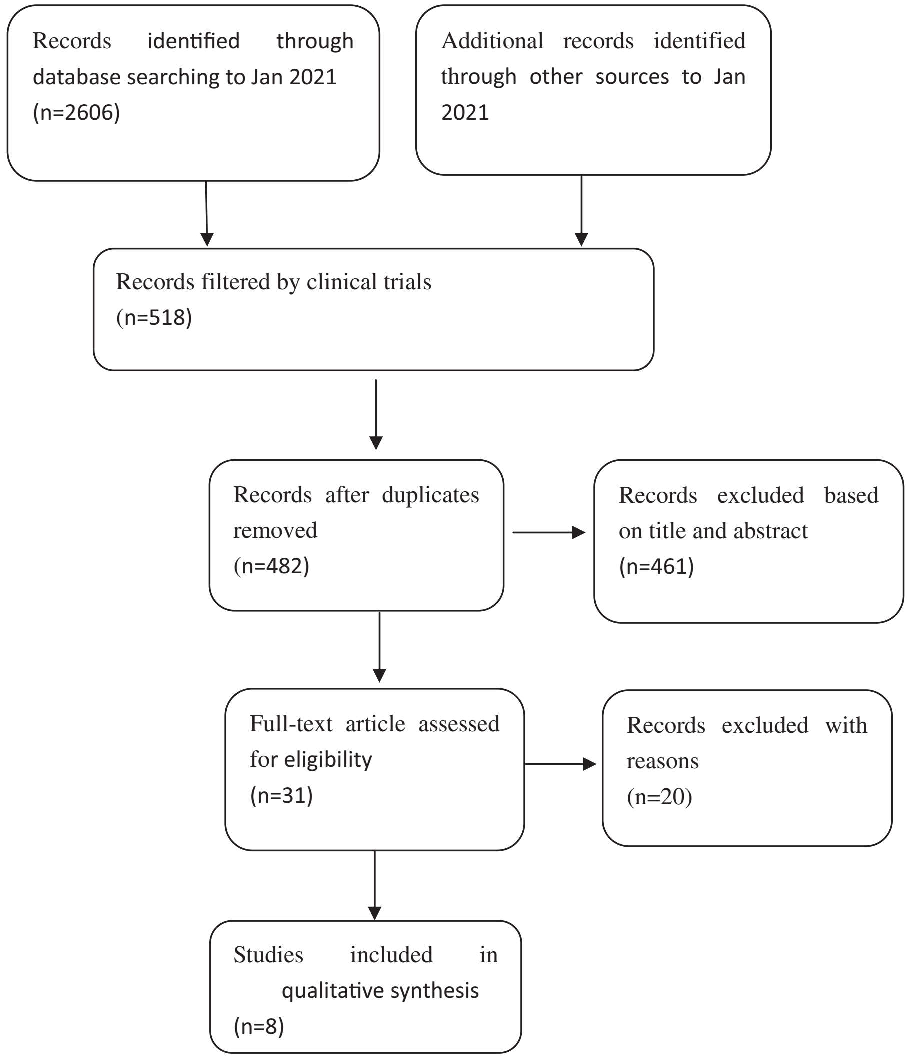

Fig 1. Study flow diagram.

patients diagnosed as heart failure (HF) are the chronic disease population that best identifies the benefits of ET.[6,7] However, another chronic disease population, patients with PAH have worse exercise capacity and prognosis than patients with HF.[8,9] The prognosis of PH has greatly improved in the last 20 years due to advances in targeted drug therapy for the treatment of PH. However, overall the long-term prognosis of PAH patients remains unsatisfactory,[10] most patients with PH still have impaired exercise capacity and reduced survival.[11] In recent years, several studies have analyzed the effects of adding exercise-based rehabilitation programs to medical treatment in patients with PH (see Table1).[12–15] Recently, European guidelines recommend that ET should be considered under supervision in patients with PAH who are on optimal medical therapy and are clinically stable (level of evidence IIa, level B).[16] However, for PH patients, the appropriate duration, intensity, frequency, and type of exercise, as well as the mechanism of improvement, remain unclear.[17] There is insufficient evidence that ET should be performed in patients with PH, and we conducted the meta-analysis of randomized controlled trials (RCTs) to assess the efficacy and safety of supervised ET programs in patients with PH.

Methods

Type of study

We included RCTs comparing exercise-based rehabilitation with usual care or rehabilitation without exercise. We included all studies reported in full or abstract as well as any relevant, unpublished data.

Type of participants

Patients diagnosed with PH, all of whom were stable during treatment.

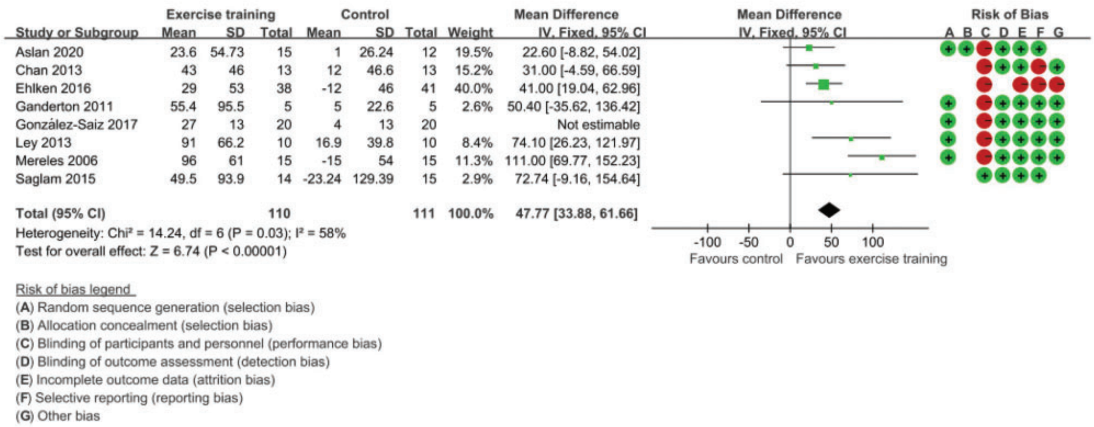

Fig. 2. Forest plot of the average net changes and corresponding 95% confidence intervals for six-minute walking distance.

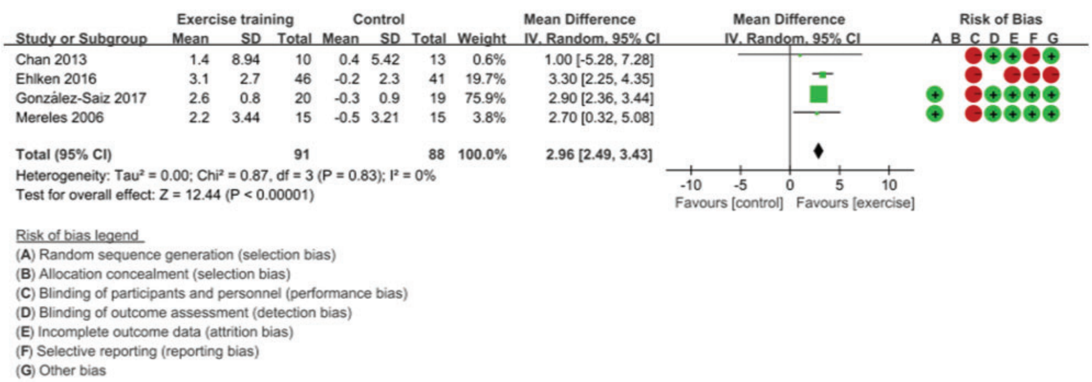

Fig. 3. Forest plot of the average net changes and corresponding 95% confidence intervals for peak oxygen uptake.

Type of interventions

There were no restrictions on the type, frequency, and duration of exercise. We included ET programs that included any length of duration, settings including inpatient, outpatient, and home, including aerobic or strength training programs, or both.

Type of outcome measures

The primary outcome was the changing of six-minute walking distance (6MWD). Secondary outcomes included changes in peak oxygen uptake (peak VO_2)

Search methods for identification of studies

A systematic literature search was conducted in the electronic PubMed database from its inception to November 2018 using following terms: ((("Exercise"[Mesh]) OR "Rehabilitation"[Mesh]) OR exercise training) AND "Hypertension, Pulmonary"[Mesh]; results were filtered by "clinical trials" and limitations were English language. Embase, Ovid (MEDLINE), and The Cochrane Central Register of Controlled Trials were furthermore consulted with the same search terms. In addition, the reference lists from published original and review articles were searched manually to identify other possible eligible studies.

Studies were included in the meta-analysis if they completed the following conditions: (1) RCTs including a control group and an intervention group; (2) with an intervention program of at least three weeks duration; (3) reported the mean and standard deviation (SD) of the 6MWD before and after the intervention (or standard error) or the mean change and SD of the 6MWD between the intervention and control groups; and (4) time was up to November 2018 (see Figure 1).

Data extraction

We produced a specific data extraction form that included items such as study source, study design, study quality, sample size, participant characteristics, exercise intervention, and data on different outcomes. Data were extracted independently by two authors (L.Y. and W.S.). Two authors screened titles and abstracts separately and classified them as "eligible" or "possibly eligible/unclear" or "ineligible". Two authors independently screened the full text, identified included studies, and documented reasons for exclusion of ineligible studies. The initial overall

Table 1. Description of the patient populations and characteristics of the exercise training programs.

Author	Year	Origin	Design	Patient population	NYHA	Age (year)	Number at baseline	Exercise intervention	Control	Assessment of physical fitness	Outcome (exercise training vs control)
Mereles et al.	2006	Germany	RCT	PAH (80%) CTEPH (20%)	II–IV	50	Intervention: 15 (10 female/5 male); Control: 15 (10 female/5 male)	3 weeks in-hospital + 12 weeks home-based aerobic interval training along with resistance and respiratory exercise, 5 sessions/week, 30–60 min/session, 60–80% of peak HR	Usual care	6MWD, CPET	6MWD 96 ± 61 vs -15 ± 54; CPET 2.2 ± 3.44 vs -0.5 ± 3.21
Chan et al.	2013	USA	RCT	PAH	I–IV	54.4	Intervention: 13 (10 female/3 male); Control: 13 (13 female/0 male)	10 weeks supervised treadmill walking, 3 sessions/week, 30–45 min/session, 70–80% of heart rate reserve + patient education	Patient education only	6MWD, CPET	6MWD 43 ± 46 vs 12 ± 46.6; CPET 1.4 ± 8.94 vs 0.4 ± 5.42
Ley et al.	2013	Germany	RCT	PAH (80%) inoperable CTEPH (20%)	II–III	50.5	Intervention: 10 (8 female/2 male); Control: 10 (6 female/4 male)	Three weeks supervised aerobic interval training along with resistance and respiratory exercise, five sessions/week, 30–60 min/session, 60–80% of peak HR	Usual care	6MWD	6MWD 91 ± 66.2 vs -16.9 ± 39.8
Weinstein et al.	2013	USA	RCT	PAH	I–IV	54.4	Intervention: 11 (11 female/0 male); Control: 13 (13 female/0 male)	3 days per week over the 10 weeks, the aerobic exercise training consisted of 24–30 sessions of treadmill walking for 30–45 min per session at an intensity of 70–80% of heart rate reserve	Patient education only	6MWD, CPET	Not estimable
Ganderton et al.	2011	Sydney	RCT	PAH	I–IV	52	Intervention: 5 (5 female/0 male); Control: 5 (4 female/1 male)	60 min/times, 3 times/week, 12 weeks, intensity for the lower limb endurance exercises will be prescribed with the aim of achieving 60–70% HR max	Usual care	6MWD	6MWD 55.4 ± 95.5 vs 5 ± 22.6

(continued)

Table 1. Continued.

Author	Year	Origin	Design	Patient population	NYHA	Age (year)	Number at baseline	Exercise intervention	Control	Assessment of physical fitness	Outcome (exercise training vs control)
Saglam et al.	2015	Turkey	RCT	PAH	II–III	49.7	Intervention: 14 (11 female/3 male); Control: 15 (14 female/1 male)	30 min per day, 7 days per week, for 12 weeks home inspiratory muscle training (IMT) program	Shame inspiratory muscle training (IMT)	6MWD	6MWD 49.5 ± 93.9 vs -23.24 ± 129.39
Ehlken et al.	2016	Germany	RCT	PAH (80%) inoperable CTEPH (20%)	II–IV	56	Intervention: 46 (26 female/20 male); Control: 41 (21 female/20 male)	3 weeks inpatient 12-week home program, low-dose training 4–7 days/week	Usual care	6MWD, CPET	6MWD 29 ± 53 vs -12 ± 46; CPET 3.1 ± 2.7 vs -0.2 ± 2.3
González-Saiz et al.	2017	Spain	RCT	PAH (80%) inoperable CTEPH (20%)	I–III	45.5	Intervention: 19 (12 female/7 male); Control: 16 (12 female/4 male)	Eight-week inpatient, including aerobic, resistance, and specific inspiratory muscle training	Usual care	6MWD, CPET	6MWD 27 ± 13 vs 4 ± 13; CPET 2.6 ± 0.8 vs -0.3 ± 0.9
Aslan et al.	2020	Turkey	RCT	PAH (74%) inoperable CTEPH (26%)	I–III	47.2	Intervention: 15 (13 female/2 male); Control: 12 (10 female/2 male)	Home-based TIMT (threshold inspiratory muscle training) program for eight weeks	Shame inspiratory muscle training (IMT)	6MWD	6MWD 23.6 ± 54.73 vs 1 ± 26.24

RCT: randomized controlled trials; PAH: pulmonary artery hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; 6MWD: six-minute walking distance; CPET: cardiac pulmonary exercise testing; PH: pulmonary hypertension; NYHA: New York heart association; HR: heart rate.

agreement rate was 0.84, and disagreements were resolved by negotiation, resulting in a final agreement rate of 1.

Assessment of risk of bias in included studies

We independently assessed risk of bias using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The following domains were included to assess risk of bias: random sequence generation; allocation concealment; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other biases. Each potential source of bias was graded as high, low, or unclear as assessed independently by two authors (L.Y. and W.S.), and all disagreements were resolved by discussion.

Statistical analysis

Excel 2017 and Review Manager software (RevMan 5.1) were used for statistical analysis. Descriptive data were described using mean and SD. We used I^2 Statistics to measure heterogeneity between trials in each analysis. Data were pooled using a random-effects model to incorporate between-study heterogeneity into the meta-analysis.

Summary of main results

The aim of this review is to assess the safety and efficacy of exercise rehabilitation in patients with PH. Assessment using both 6MWD (see Figure 2) and cardiac pulmonary exercise testing (see Figure 3) showed significant improvement in exercise capacity (see Table 3). However, there is marked heterogeneity in 6MWD. There were also improvements in QoL, although the magnitude of these changes may not be clinically meaningful. The above results are based on a relatively small number of participants (258 participants in the trial, but only 234 in the forest plot with the most data), from only seven RCTs. The majority of patients in the study had a diagnosis of PAH and only a small number of patients were diagnosed as CTEPH, so our results should be applied primarily to this group. The results for patients with CTEPH could not be extracted separately, so the effect of the rehabilitation exercise in CTEPH is still unclear. Fewer patients were included in level IV, so the impact of exercise rehabilitation training on patients with the most severe disease is unclear. Importantly, all studies included only medically stable patients (including those without recent syncope), so that exercise rehabilitation training could be applied in this group (see Table 2).

Table 2. Baseline characteristics of the study participants.

Patients (*n*)	261
Mean age (years)	50.5
Sex (female)	213
WHO-FC	
I	78
I–II	23
II	129
II–III	0
III	31
Pulmonary hypertension diagnosis (*n*)	
PAH	220
Idiopathic	63 (28.6%)
Hereditary	20 (9%)
Toxic oil syndrome	20 (9%)
HIV	20 (9%)
Connective tissue disorders	57 (25.9%)
Congenital cardiopathy	40 (19.5%)
CTEPH	41

n: number; PAH: pulmonary arterial hypertension; WHO-FC: World Health Organization Functional Class; HIV: human immunodeficiency virus; CTEPH: chronic thromboembolic pulmonary hypertension.

Discussion

This systematic review focused on the analysis of exercise-based rehabilitation training on exercise capacity and QoL in patients with PAH and CTEPH. Including total of seven studies (Chan et al.[15]; Ehlken et al.[18]; Ganderton et al.[19]; Ley et al.[20]; Mereles et al.[21]; Saglam et al.[22]; González-Saiz et al.[23]), the findings suggest that exercise-based rehabilitation training can improve clinically relevant exercise capacity.

The idea that ET programs may be beneficial for PH patients has been increasingly accepted in recent years.[24] At present, it is believed that exercise rehabilitation training provides a new additional treatment option for PAH patients, aiming to improve their exercise capacity and QoL. Most of the existing studies have shown a significant improvement in exercise capacity and QoL with exercise rehabilitation training, but not all findings are consistent.[15,25]

There are currently five systematic reviews on ET in patients with PH[26–30] that have been published. However, the trials, analysis methods, and study quality assessment methods included in these reviews varied within these reviews. The systematic review of Buys et al. included controlled trials up to December 2013, not all of which were randomized. The authors extracted five studies, three of which were also included in our analysis (Mereles et al.; Chan et al.; Ley et al.). Overall, the results of this review are similar to ours, with large increases in 6MWD and VO_2 peak. Babu et al. included 15 studies, which contained four RCTs. Yuan et al. included 12 studies, including 2

Table 3. Effect sizes of primary outcomes of the meta-analysis.

Variables	Study groups	*N*	Mean effect size (95% CI)	*Z*(p)
Six-minute walking test distance (m)	8	261	29.24 (22.27–36.21)	8.22 (<0.00001)
Peak oxygen uptake (ml/kg/min)	4	179	2.96 (2.49–3.43)	12.44 (<0.00001)

N: number.

randomized studies, 4 observational controls, and 6 observational studies. In addition, the authors performed a subgroup analysis of the RCTs and the conclusions were similar to ours. Pandey et al. included studies from Martinez-Quintana 2010, which were not included in our analysis. Babu et al. rated the four included RCTs as high quality evidence using Downs and Black quality indicators and found no possible selection bias. Pandey used the Cochrane risk of bias assessment tool, similar to our findings. In Yuan et al.'s meta-analysis, the authors did not attempt to report the quality of evidence. Morris included five RCT studies and reached similar conclusions as before. Our analysis included two studies (Saglam et al.[22] and González-Saiz et al.[23]) more than Morris.

The underlying mechanisms that bring about these effects of ET may primarily lie in the lungs and cardiovascular as well as peripheral organs, but further studies are still needed to clarify them. A non-randomized study of five patients with IPAH showed that patients had improved skeletal muscle function, and muscle biopsies showed changes in muscle fiber morphology with an increase in type I fibers and a decrease in type II, which changed to a less fatigable type.[31] Animal studies suggest exercise can improve cardiac function by reducing right ventricular end-diastolic pressure and improving pulmonary artery remodeling, while it has not been demonstrated in humans.[32] Currently, several small studies have shown peak oxygen consumption increased post-ET, possibly through increased skeletal muscle capillary density. A small sample size study found that peak velocity reduced in pulmonary artery and pulmonary blood volume increases after ET,[33] which suggests that exercise-based rehabilitation may improve cardiac function and hemodynamics. Furthermore, it remains to be determined whether exercise-related improvements in exercise capacity reflect better short-term and long-term outcomes in patients with pulmonary hypertension.

Conclusions

This systematic review suggests that supervised exercise-based rehabilitation is likely to be safe and result in significant improvements in exercise capacity for patients with pulmonary hypertension who are medically stable. The clinical significance of improvements in health-related QoL is currently unknown. Although the inpatient setting may confer greater benefits, the applicability is not high and the outpatient program still has clinically meaningful benefits. These results are mainly applicable to New York Heart Association functional classification, class II and III population, and the role of exercise rehabilitation training for class IV population is unclear. Further RCTs are needed to confirm the effect of exercise rehabilitation in patients with CTEPH and in patients with more severe disease PH. In addition, further studies are needed to determine the optimal ET program for PH patients, including the type and intensity of exercise, exercise duration, degree of regulation, and the optimal environment for ET. In addition, longer-term studies are needed to assess the durability of benefit and to determine the effect of exercise rehabilitation training on primary outcomes such as time to clinical deterioration and survival.

Authors' Contributions

L.Y. designed the overall project, drafted and revised the manuscript; W.S. performed literature search, critically reviewed and revised the manuscript; Z.L., Z.Z., Q.L., and Q.Z. provided professional advice on data interpretation, critically reviewed and revised the manuscript; Q.J., Y.Z., X.L., and A.D. critically reviewed and revised the manuscript.

Ethical statement

The study was performed with the approval of Fuwai Hospital Ethics Committee (No. 2009215). Written Informed Conferences of all participants were obtained.

Consent to publish

All authors approved to publish this manuscript on the journal: Pulmonary Circulation in a Case report.

A statement of guarantor

The work described has not been submitted elsewhere for publication, in whole or in part, and all the authors listed have approved the manuscript that is enclosed.

Conflict of interests

The author(s) declare that there is no conflict of interest.

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