Heart, Lung and Circulation (2022) **31**, 1341–1348
1443-9506/22/$36.00
https://doi.org/10.1016/j.hlc.2022.06.660

REVIEW

Exercise Rehabilitation Training in Patients With Pulmonary Hypertension: A Review

Chang Dong, MD, Yanxia Li, MD, PhD*

Pulmonary and Critical Care Medicine, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning Province, China

Received 19 March 2022; received in revised form 2 June 2022; accepted 6 June 2022; online published-ahead-of-print 13 July 2022

Background Pulmonary hypertension (PH) has a high morbidity and mortality. Despite the existing disease-targeted therapy, most patients with PH continue to suffer from difficulty in breathing, exercise intolerance, and reduced quality of life. Recently, a large body of research results has suggested that exercise rehabilitation training (ERT) seems to be a beneficial, safe, and cost-effective treatment for patients with PH. However, knowledge gaps still exist for a uniformly accepted ERT protocol, the modality, duration, intensity, and frequency of ERT in PH.

Aim The purpose of this review is to summarise the existing research evidence and knowledge, aiming to strengthen clinicians' awareness of the application of ERT in patients with PH.

Methods and Results PubMed databases were systematically searched for eligible studies. Twelve (12) randomised controlled trials and other important studies documenting effectiveness, safety, and adverse events of ERT are summarised. Additionally, the modality, duration, intensity, and frequency of various types of ERT and future research directions are discussed.

Conclusions In summary, ERT is generally effective and safe for PH patients as an adjuvant treatment to disease-specific therapy. It can improve the exercise capacity and tolerance, skeletal and respiratory muscle performance, cardiopulmonary function, and quality of life of PH patients.

Recommendations In view of the occurrence of a small number of adverse events, we currently recommend a combination of in-hospital and home-based ERT under close supervision. In the future, more multi-centre randomised controlled studies are needed to evaluate the effectiveness and feasibility of long-term, community, or home-based ERT, as well as to explore the molecular mechanism behind it.

Keywords Pulmonary hypertension • Exercise rehabilitation training • Exercise capability • Quality of life

Introduction

Pulmonary hypertension (PH) is defined as the mean pulmonary arterial pressure (mPAP) $\geq$25 mmHg measured by right heart catheterisation (RHC) at rest [1] with five major groups: group 1 is pulmonary arterial hypertension (PAH), group 2 is PH due to left heart disease (LHD), group 3 is PH due to lung diseases/hypoxia, group 4 is PH due to pulmonary artery obstruction, and group 5 is PH with unclear/multifactorial mechanisms [2]. Due to the progressive pathophysiological process of PH accompanied by the deterioration of right ventricular function, PH has a high morbidity and mortality. Despite the existing disease-targeted therapy, most patients continue to suffer from difficulty in breathing,

*Corresponding author at: Pulmonary and Critical Care Medicine, First Affiliated Hospital of Dalian Medical University, No. 222 Zhongshan Road, Dalian, Liaoning Province, 116011, China; Email: liyanxia001@163.com

© 2022 The Author(s). Published by Elsevier B.V. on behalf of Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) and the Cardiac Society of Australia and New Zealand (CSANZ). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

fatigue, fear, activity intolerance, and reduced quality of life [3,4]. In the past, it was not recommended for PH patients to exercise in case it would result in disease deterioration or sudden death. Recently, more and more research results suggest that exercise rehabilitation training (ERT) seems to be a beneficial, safe, and cost-effective treatment for patients with PH [5–8]. However, there are still discrepancies in the outcomes of various studies. Moreover, no uniform protocol exists for the modality, duration, intensity, and frequency of ERT. Therefore, we provide a review of the existing research evidence and knowledge, aiming to strengthen clinicians' awareness of the application of ERT in patients with PH.

Effectiveness of ERT

Exercise has always been considered to have a host of physiologic advantages for not only healthy individuals [9,10] but also in patients with a variety of serious cardiopulmonary diseases [11–13]. Due to impaired pulmonary and cardiac haemodynamics in PH patients, symptoms of dyspnoea, fatigue, and syncope often occur after physical activity, which seriously affects the patient's quality of life (QoL). A PH patients' exercise capacity, World Health Organization (WHO) functional class (FC), oxygen therapy, right heart failure symptoms, right atrial pressure, and mental disorders are closely related to the QoL of patients [14]. In 2006, the first randomised controlled trial (RCT) on ERT for patients with severe chronic PH was published. This study pointed out that through 15 weeks (3 weeks in the hospital, 12 weeks at home) exercise training at low workloads, including bicycle ergometer, dumbbell, walking, and respiratory training, the 6-minute walking distance (6MWD) of the training group significantly increased by 111 minutes (95% CI 65–139, $p<0.001$) compared with the control group. In addition, other parameters in cardiopulmonary exercise testing (eg, the peak oxygen consumption [VO_2], VO_2 at the anaerobic threshold [AT], achieved workload, mean WHO-FC, physical and mental questionnaire scores, and the QoL in the exercise group) were also significantly improved [15]. This study provided high-quality evidence-based evidence for the application of ERT to PH patients as an adjunct to optimal medical therapy. On this basis, the 2009 PH guidelines recommended supervised exercise to be considered for PAH patients within symptom limits [16]. After that, more and more other high-quality RCTs have been published. The 5th PAH World Symposium consensus statement [17] upgraded ERT as an add-on treatment for patients affected by PAH (class I, level of evidence: A). Current guidelines recommended that supervised exercise training should be applied to PAH patients who are physically deconditioned and clinically stable as an add-on to medical therapy (Class IIa recommendation, Level of Evidence B) [1,18,19].

The Effect of ERT on Different Groups of PH

We used "hypertension, pulmonary" Medical Subject Headings (MESH) terms as the keyword in the electronic PubMed database, combined with "exercise" (MESH) OR "rehabilitation" (MESH) OR "exercise training," respectively. Twelve (12) RCTs [15,20–30] were found, and the main contents were summarised in Table 1. All patients enrolled in the current studies have received optimised medical therapy and are in the clinically stable phase of PH. Studies suggest that ERT seems to be somewhat independent of the aetiology of PH and has an effect on various types of PH [31,32].

The connective tissue disease-associated PAH (CTD-APAH) in group 1 is the second most common cause of PAH after idiopathic PAH (IPAH) [33]. These patients may also be combined with CTD-related interstitial lung diseases and require immunosuppressive therapy, which further complicates the condition. Since patients with CTD-APAH were also included in most of the RCTs, the treatment strategy of CTD-APAH is the same as IPAH. However, it was reported that PAH-targeted drugs were less effective for CTD-APAH compared with IPAH [34], so other adjuvant treatments for this subgroup of PAH are particularly important. One self-control study [35] enrolled 21 patients with invasively confirmed CTD-APAH, 95% of which were women, with an average age of 52±18 years and mPAP being 49±13 mmHg. After 15 weeks of ERT, the patients' 6MWD increased by 71±35 minutes from the baseline, accompanied by improvements in the cardiopulmonary exercise test (CPET) and QoL. The survival rate in the first 2 years was 100%, and 73% in the third year, much better than previously reported [36].

Congenital heart disease associated PAH (CHD-APAH) in group 2 has a heterogeneous patient population, for whom the first choice of treatment should include consideration of the feasibility to perform shunt closure surgery. Those patients who developed Eisenmenger Syndrome are usually severely restricted in physical activities. There are relatively few studies on ERT as an add-on to medical therapy in patients with CHD-APAH. One self-controlled study [37] prospectively studied 20 CHD-APAH patients, 80% of which were women, with an average age of 48±11-years-old. Most of the patients had combined cardiac anomaly with mPAP of 60±23 mmHg, 50% of the patients had Eisenmenger syndrome, and nine patients had undergone surgery. The study found that 15-week ERT improved the patients' 6MWD, QoL, peak VO_2, and maximum workload without transplantation needed in the long-term follow-up. The 1-year and 2-year survival rates were excellent, 100% and 92%, respectively. Another small sample sized non-RCT [38] also found that the 6MWD and WHO-FC of the training group were significantly improved compared with the control group after 3-month ERT. These findings suggest that ERT can be used as an effective adjuvant therapy in addition to specific PAH drug therapy for patients with CHD-APAH.

As to the management of chronic thromboembolic PH (CTEPH) in group 4, pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA) can be considered in addition to the currently recommended oral drug, riociguat. A large number of clinical studies have suggested that ERT is beneficial for inoperable CTEPH patients with respect to the 6MWD, performance in CPET, QoL, WHO-FC, pulmonary

Table 1 A summary of published RCT studies on exercise training in PH.

Author (yr)	Aetiology	No. of participants	Mean age (yr)	WHO-FC	mPAP (mmHg)	Exercise Rehabilitation Training Intervention				Control	Improved factors (compared with Control)
						Duration	Type	Intensity	Frequency		
Mereles et al. [15], 2006	PAH CTEPH	Intervention: 15 Control: 15	50	II–IV	Intervention: 49.5 Control: 49.6	3 wk inhospital+12 wk home	bicycle ergometer dumbbell respiratory training walking	10–30 min/d 30 min/d 15–30 min/d 60 min/d	5–7 d/wk 5–7 d/wk 5–7 d/wk 2–5 d/wk	Usual care	6MWD, QoL WHO-FC peak VO_2 VO_2 at AT workload
Chan et al. [24], 2013	PAH	Intervention: 13 Control: 13	54.3	I–IV	Intervention: 40.3 Control: 43.8	10 wk	supervised treadmill walking	30–45 min per session	3 sessions/wk	Education only	6MWD, QoL time to exercise intolerance peak work rate
Ley et al. [26], 2013	PAH CTEPH	Intervention: 10 Control: 10	50.5	II–III	Intervention: 48 Control: 50	3 wk in-hospital	bicycle ergometer dumbbell respiratory training walking	10–25 min/d 30 min/d 15–30 min/d 60 min/d	7 d/wk 5 d/wk 5 d/wk 5 d/wk	Usual care	6MWD MR pulmonary flow MR pulmonary perfusion
Weinstein et al. [23], 2013	PAH	Intervention: 11 Control: 13	54.4	I–IV	NA	10 wk	supervised treadmill walking	30–45 min per session	24–30 sessions	Education only	6MWD treadmill duration peak power output Adjusted Activity Score, MAS, FSS
Saglam et al. [28], 2015	PAH	Intervention:14 Control: 15	49.7	II–III	Intervention: 77.1 Control: 59.5	6 wk	IMT	30 min/d	7 d/wk	Shame IMT	6MWD, QoL MIP, MEP FEV_1, % predicted FSS, MMRC

Table 1. **(continued).**

Author (yr)	Aetiology	No. of participants	Mean age (yr)	WHO-FC	mPAP (mmHg)	Exercise Rehabilitation Training Intervention				Control	Improved factors (compared with Control)
						Duration	Type	Intensity	Frequency		
Ehlken et al. [21], 20156	PAH CTEPH	Intervention:46 Control: 41	56	II–IV	Intervention: 41 Control: 37.6	3 wk in-hospital +12 wk home	bicycle ergometer dumbbell respiratory training walking	1.5 h/d (inpatient) 15 min/d (home)	7 d/wk 5 d/wk 5 d/wk 5 d/wk	Usual care	6MWD, QoL peak VO_2 CI mPAP PVR
Gerhardt et al. [22], 2017	PAH	Intervention: 11 Control: 11	55.6	II–IV	Intervention: 35.5 Control: 41.9	4 wk	oscillatory whole-body vibration	1 h per session	16 sessions	Usual care	6MWD, QoL peak VO_2 oxygen uptake at the AT muscle power, force, and contraction velocity
González-Sai et al. [27], 2017	PAH CTEPH	Intervention:19 Control: 16	45.5	I–III	Intervention: 47 Control: 47	8 wk	aerobic resistance IMT	20–40 min/d ~5 min/d	5 d/wk 3 d/wk 6 d/wk	Usual care	Body muscle power peak VO_2 5-STS and MIP
Aslan et al. [29], 2020	PAH CTEPH	Intervention:15 Control: 12	48.9	I–III	Intervention: 54.1 Control: 46.1	8 wk	Home-based IMT	30 min/d	5 d/wk	Shame IMT	MIP 6MWD
Tran et al. [30], 20201	PAH CTEPH	Intervention:6 Control: 6	60	II–III	Intervention: 37.9 Control: 38.3	8 wk	IMT	2 cycles of 30 breaths/d	5 d/wk	Usual care	6MWD MIP
Wojciuk et al. [20], 2021	PAH	Intervention:16 Control: 23	48.9	II–III	Intervention: 47.2 Control: 45.8	6 mo	home-based interval march training IMT	45–60 min/d 5 cycles	5-7 d/wk	Usual care	6MWD respiratory muscle strength SF-36
Kagioglou et al. [25], 2021	PAH CTEPH	Intervention:12 Control: 10	53.9	II–III	Intervention: 42.3 Control: 45.1	6 mo	aerobic strength	45–60 min/d	3 d/wk	Usual care	6MWD physical aspects psychological aspects

Abbreviations: 6MWD, 6-minute walk test distance; 5-STS, five-repetition sit-to-stand test; AT, anaerobic threshold; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; FEV_1, forced expiratory volume in 1 second; FSS, fatigue severity scale; IMT, inspiratory muscle training; mPAP, mean pulmonary arterial pressure; MR, magnetic resonance imaging; MAS, the maximum activity score; MMRC, modified Medical Research Council; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; PH, pulmonary hypertension; PAH, pulmonary artery hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; RCT, random control trails; SF-36, 36-Item short form health survey; VO_2, oxygen consumption; WHO-FC, World Health Organization-functional class.

flow and perfusion, mPAP, pulmonary vascular resistance (PVR), muscle strength, respiratory muscle function, and five-repetition sit-stand test [15,21,25–27,29,30]. Recently published studies have shown that ERT is also beneficial to patients who have just received PEA and BPA, and is an effective means of follow-up treatment after surgery. In 2020, Nagel et al. [30] reported the first results of supervised ERT as an early follow-up treatment for CTEPH patients after PEA. The study enrolled 45 CTEPH patients who had undergone PEA surgery at an average of 3.3 weeks before. After 19 weeks of ERT (3 weeks in hospital, 16 weeks at home), the results showed that the cardiac output (CO), mPAP, PVR, and other haemodynamic indicators measured by RHC were all significantly improved, accompanied by an increased 6MWD, QoL, oxygen saturation, and decreased size of the right ventricle as assessed by echocardiography. A recently published systematic review and meta-analysis [39] analysed four studies [40–43] with a total of 208 CTEPH patients after PEA. The results suggested that short-term ERT can significantly improve the patients' 6MWD, peak VO_2, maximal workload, and O_2 pulse. Three (3) months of ERT further improved right ventricular ejection fraction, QoL scores and reduced N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma level. For patients with inoperable CTEPH, BPA can also be considered. A non-RCT [44] divided 41 CTEPH patients after BPA into an early (6.8 days) ERT group or no training group. The results found that compared with the control group, most of the exercise capacity indices in the CPET, such as peak workload and peak VO_2, were significantly improved in the ERT group. The quadriceps isometric strength and WHO-FC were also significantly improved. The above studies suggest that ERT as a follow-up therapy after PEA and BPA may be effective as an add-on to routine medical therapy.

The Effect of ERT on the Functional and Physiological Factors

The 6MWD is one of the most commonly used indicators to evaluate the exercise capacity of patients with PH. All the 11 RCTs listed in Table 1, except for one whose primary endpoint was peak muscle power [27], evaluated 6WMD and all came to the same conclusion that ERT can effectively improve the patients' 6WMD. There are also a few non-RCTs that did not find a statistically significant change in the 6MWD [44,45].

Cardiopulmonary exercise test (CPET) is another important examination to evaluate the exercise capacity of patients with PH. CPET can simultaneously monitor the variables changes in exercise capacity, cardiac function, ventilation efficacy, and gas exchange during exercise. Together with the 6MWD, it provides important information for the diagnosis and prognosis of PH [46]. The important variables of CPET include work rate, workload, heart rate, ventilation (VE), oxygen consumption, carbon dioxide output (VCO_2), VE/VCO_2 ratio and AT. Peak VO_2 is the most commonly used and effective method to evaluate aerobic capacity and exercise tolerance. High-levels of peak VO_2 indicates good aerobic exercise capacity, which corresponds positively with an increasing workload. Besides, high VO_2 at the AT also indicates an improved aerobic metabolism during exercise. Patients with PH typically experience high VE/VCO_2, low end-tidal partial pressure of carbon dioxide and low peak VO_2 compared with normal adults, which may be a result of ventilatory inefficiency and increased ventilatory drives in patients with PH [47,48]. In return, continuous ventilatory inefficiency and limited lung neutralisation capacity will also hinder the patient's exercise tolerance and exercise adaptability [49]. Ehlken et al. [21] reported their RCT with peak VO_2 as the primary endpoint that after 15 weeks of ERT, the 6MWD and peak VO_2 of the training group were significantly improved compared with the control group. The results of this study are consistent with most other studies [15,22,25,27,32,35,37,50]. In addition, Ehlken et al. also invasively measured the haemodynamic changes of studied patients by RHC. The results showed that both cardiac index and CO at rest and during exercise were significantly improved, with resting mPAP and PVR decreased significantly compared with the control group. The results of this study suggested that ERT may reduce PVR and improve right heart function, which is an important factor related to the prognosis of PH patients [51–53]. A study that assessed estimated PAPs by non-invasive methods of stress Doppler echocardiography has not found any difference [15].

The Effect of ERT on the Skeletal Muscle System

The abnormalities of pulmonary, cardiac, and skeletal muscle systems in PH patients together lead to exercise intolerance. Impaired oxygen supply, reduced CO, chronic hypoxaemia, and mitochondrial dysfunction are associated with peripheral muscle dysfunction and respiratory muscle weakness in PH patients [54]. On this basis, an RCT included an 8-week resistance training of large muscle groups combined with the inspiratory muscle training (IMT). The results of the study showed a significant interaction (group × time) effect for leg/bench press in the training group but not in the control group. At the same time, five-repetition sit-to-stand test, maximal inspiratory pressure, and peak VO_2 are also significantly increased in the training group [27]. Muscle biopsy had shown that exercise can induce the decrease in proportion of type IIx fibres [55], while capillary density of type I fibre and oxidative enzyme activity of skeletal muscle fibres increased [45], thereby increasing aerobic capacity. Other RCTs have also found that IMT can significantly increase the respiratory muscle strength of PH patients as indicated by the significantly increased maximum inspiratory pressure [28–30,56], maximum expiratory pressure [20,28], forced expiratory volume in 1 second (% predicted), and dyspnoea and fatigue score [28]. The above research results suggested that resistance training and IMT could enhance muscle performance, improve exercise capability, and respiratory function, thereby improving the QoL of patients with PH.

The Effect of ERT on the Molecular Factors

NT-proBNP is another important indicator for the risk assessment of PH patients. In most studies, it has not been found that ERT as add-on to medicine can result in significant differences in NT-proBNP levels [21,27,30,57,58], but there are studies that have reported statistically significant improvement [20] or deterioration [37]. The discrepancy may be owing to different comorbidities of PH patients before the study, and the significant difference of NT-proBNP levels in baseline [21].

The Effect of ERT on PH in the Long Term

Most of the studies were short-term ERT (3 wks to 15 wks). Recently, two ERT studies lasting 6 months were designed aiming to evaluate the long-term effects of ERT on PH. Studies have shown that after 6 months of combined aerobic and strength training, the physical function of the patients as reflected by the 6MWD, lower limb strength, CPET variables, and mental health scores have been significantly improved compared with the control group [20], and these beneficial results were still maintained 3 months after the termination of the ERT [25]. In follow-up, the survival rate in the first 2 years for these patients with PH was 100% and 95%, respectively [50]. The research suggests that long-term ERT may be beneficial for patients with PH in terms of favourable prognosis.

Safety and Adverse Events of ERT

Most clinical research results has suggested that ERT is an effective and safe adjuvant treatment to disease-targeted medical therapy without serious adverse reactions, such as clinical deterioration and death, reported [22,24,44]. However, ERT is not without risk. One study reported that the incidence of adverse reactions was 13.6% [32], which included decreased blood oxygen during exercise [15], excessive fatigue [20], muscle aches and back pain [22], tachycardia [20,27], transient dizziness [15,27,50], presyncope [42], and syncope [32]. Some other adverse events judged to be unrelated to training by physicians were also commonly reported, for example, respiratory, urinary tract and gastrointestinal infections, and pericardial effusion [25,35,40]. Moreover, the most adverse events occurred during the initial 3 weeks of training in the hospital and the incidence decreased during the study period at home after the patients became aware of their limitations. Therefore, supervised ERT under close guidance and monitoring is very important.

Various Types of ERT

The protocol of ERT has not yet been unified. Different types of ERT includes aerobic exercise, strength training, respiratory function training, or a combination thereof. The duration varies from 3 weeks [26] to 6 months [20,25]. First, aerobic exercise typically includes bicycle ergometer, treadmill, or walking. The intensity of aerobic exercise in most studies is low (10 watts–60 watts) and progressively increased during the program. Second, strength training can be composed of dumbbell, leg and bench press, leg extension, lateral pulldown, and abdominal crunches. The strength training is also generally using low weights (500 g–1,000 g). The length of aerobic exercise and strength training is generally 30 to 60 minutes per day, 3 to 7 days per week. Close monitoring of the patients' peak heart rate (for example, not >120 bpm or 60% to 80% max heart rate) and blood oxygen saturation (for example, >85%) during exercise are necessary. Third, respiratory training includes threshold inspiratory muscle training and breathing technique, such as pursed lip breathing. Besides, Gerhardt et al. [22] reported that oscillatory whole-body vibration is a new type of exercise mode. Rapid vibration can make the whole-body muscles contract reflexively, combining static and dynamic exercises. The study found that patients who received 4 weeks of whole-body vibration significantly improved their 6MWD, CPET variables, muscle power, and QoL.

The appropriate place for ERT is also being studied, from only in-hospital, and combination of hospital and home, to completely home-based or community-based [57,59]. Home-based ERT is undoubtedly a better direction to develop, not only because it can potentially improve the patient's compliance but also is convenient and cost-effective. However, in view of a certain probability of adverse events, the patients should firstly be trained on how to exercise safely at home, and a sound supervision mechanism should be developed.

Future Directions

One recently published RCT study focussed on outpatient ERT programs and their feasibility and acceptability to PAH patients [60]. Similarly, several open label RCTs are running. One is about the safety, economic applicability, feasibility, and patient compliance of home-based ERT for PH patients, which is supervised by telehealth or distance-based programs [61]. Another one has included clinical deterioration time as the endpoint to evaluate the effectiveness of long-term ERT for PH patients as a routine treatment outside the hospital [62]. A survey composed of 280 physicians, including cardiologists, pulmonologists, rheumatologists, and general practitioners from 22 countries published in 2020, showed that 86% of physicians recommend ERT for patients with PH. It is consistent with the current guidelines, but the main systemic obstacle is the lack of financial support and limited rehabilitation places [63]. Moreover, the report format of ERT needs to be standardised [64] for professional supervision and future research. Last but not least, the underlying molecular mechanism of ERT in PH still need further studies.

Conclusion

Exercise rehabilitation training is generally effective and safe for PH patients as an adjuvant treatment to disease-specific therapy. It can improve the exercise capacity and tolerance, skeletal and respiratory muscle performance, cardiopulmonary function and the QoL of PH patients. In view of the incidence of a small number of adverse events, we currently recommend a combination of in-hospital and home-based ERT under close supervision. More multi-centre RCTs are needed to evaluate the effectiveness and feasibility of long-term, community, or home based ERT, as well as to explore the underlying molecular mechanism.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

[1] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. ESC Scientific Document Group. 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.

[2] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913.

[3] Chia KSW, Brown K, Kotlyar E, Wong PKK, Faux SG, Shiner CT. 'Tired, afraid, breathless … .' An international survey of the exercise experience for people living with pulmonary hypertension. Pulm Circ. 2020;10: 2045894020968023.

[4] Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol. 2013;168:871–80.

[5] Yuan P, Yuan XT, Sun XY, Pudasaini B, Liu JM, Hu QH. Exercise training for pulmonary hypertension: a systematic review and meta-analysis. Int J Cardiol. 2015;178:142–6.

[6] An QY, Wang L, Yuan P, Zhao QH, Gong SG, Zhang R, et al. Effectiveness and safety of exercise training and rehabilitation in chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. Ann Palliat Med. 2021;10:8134–46.

[7] 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.

[8] Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. Cochrane Database Syst Rev. 2017;1:CD011285.

[9] Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med. 1994;330:1769–75.

[10] Liu-Ambrose T, Davis JC, Best JR, Dian L, Madden K, Cook W, et al. Effect of a home-based exercise program on subsequent falls among community-dwelling high-risk older adults after a fall: a randomized clinical trial. JAMA. 2019;321:2092–100.

[11] Spruit MA, Pitta F, McAuley E, ZuWallack RL, Nici L. Pulmonary rehabilitation and physical activity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;192:924–33.

[12] Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E, et al. Aerobic or resistance exercise, or both, in dieting obese older adults. N Engl J Med. 2017;376:1943–55.

[13] Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail. 2011;13:347–57.

[14] Halank M, Einsle F, Lehman S, Bremer H, Ewert R, Wilkens H, et al. Exercise capacity affects quality of life in patients with pulmonary hypertension. Lung. 2013;191:337–43.

[15] 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.

[16] Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the 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 the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493–537.

[17] Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62:D60–72.

[18] Grünig E, Eichstaedt C, Barberà JA, Benjamin N, Blanco I, Bossone E, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J. 2019;53: 1800332.

[19] Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST Guideline and Expert Panel Report. Chest. 2019;155:565–86.

[20] Wojciuk M, Ciolkiewicz M, Kuryliszyn-Moskal A, Chwiesko-Minarowska S, Sawicka E, Ptaszynska-Kopczynska K, 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;13:79.

[21] 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.

[22] Gerhardt F, Dumitrescu D, Gärtner C, Beccard R, Viethen T, Kramer T, et al. Oscillatory whole-body vibration improves exercise capacity and physical performance in pulmonary arterial hypertension: a randomised clinical study. Heart. 2017;103:592–8.

[23] Weinstein AA, Chin LM, Keyser RE, Kennedy M, Nathan SD, Woolstenhulme JG, et al. Effect of aerobic exercise training on fatigue and physical activity in patients with pulmonary arterial hypertension. Respir Med. 2013;107:778–84.

[24] Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. Chest. 2013;143:333–43.

[25] Kagioglou O, Mouratoglou SA, Giannakoulas G, Kapoukranidou D, Anifanti M, Deligiannis A, et al. Long-term effect of an exercise training program on physical functioning and quality of life in pulmonary hypertension: a randomized controlled trial. Biomed Res Int. 2021;2021: 8870615.

[26] Ley S, Fink C, Risse F, Ehlken N, Fischer C, Ley-Zaporozhan J, et al. Magnetic resonance imaging to assess the effect of exercise training on pulmonary perfusion and blood flow in patients with pulmonary hypertension. Eur Radiol. 2013;23:324–31.

[27] González-Saiz L, Fiuza-Luces C, Sanchis-Gomar F, Santos-Lozano A, Quezada-Loaiza CA, Flox-Camacho A, et al. Benefits of skeletal-muscle exercise training in pulmonary arterial hypertension: the WHOLEi+12 trial. Int J Cardiol. 2017;231:277–83.
[28] Saglam M, Arikan H, Vardar-Yagli N, Calik-Kutukcu E, Inal-Ince D, Savci S, et al. Inspiratory muscle training in pulmonary arterial hypertension. J Cardiopulm Rehabil Prev. 2015;35:198–206.
[29] Aslan GK, Akıncı B, Yeldan I, Okumus G. A randomized controlled trial on inspiratory muscle training in pulmonary hypertension: effects on respiratory functions, functional exercise capacity, physical activity, and quality of life. Heart Lung. 2020;49:381–7.
[30] Tran D, Munoz P, Lau EMT, Alison JA, Brown M, Zheng Y, et al. Inspiratory muscle training improves inspiratory muscle strength and functional exercise capacity in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a pilot randomised controlled study. Heart Lung Circ. 2021;30:388–95.
[31] Arena R, Lavie CJ, Borghi-Silva A, Daugherty J, Bond S, Phillips SA, et al. Exercise training in group 2 pulmonary hypertension: which intensity and what modality. Prog Cardiovasc Dis. 2016;59:87–94.
[32] Grünig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. Eur Respir J. 2012;40:84–92.
[33] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023–30.
[34] Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J. 2002;346:896–903.
[35] Grünig E, Maier F, Ehlken N, Fischer C, Lichtblau M, Blank N, et al. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. Arthritis Res Ther. 2012;14:R148.
[36] Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med. 2009;179:151–7.
[37] Becker-Grünig T, Klose H, Ehlken N, Lichtblau M, Nagel C, Fischer C, et al. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol. 2013;168:375–81.
[38] 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.
[39] Zhao YL, Yuan P, Zhao QH, Gong SG, Zhang R, He J, et al. Comparative effectiveness of exercise training for patients with chronic thromboembolic pulmonary hypertension after pulmonary endarterectomy: a systematic review and meta-analysis. Front Cardiovasc Med. 2021;8:664984.
[40] Nagel C, Nasereddin M, Benjamin N, Egenlauf B, Harutyunova S, Eichstaedt CA, et al. Supervised exercise training in patients with chronic thromboembolic pulmonary hypertension as early follow-up treatment after pulmonary endarterectomy: a prospective cohort study. Respiration. 2020;99:577–88.
[41] Nagel C, Prange F, Guth S, Herb J, Ehlken N, Fischer C, et al. Exercise training improves exercise capacity and quality of life in patients with inoperable or residual chronic thromboembolic pulmonary hypertension. PLoS One. 2012;7:e41603.
[42] Inagaki T, Terada J, Tanabe N, Kawata N, Kasai H, Sugiura T, et al. Home-based pulmonary rehabilitation in patients with inoperable or residual chronic thromboembolic pulmonary hypertension: a preliminary study. Respir Investig. 2014;52:357–64.
[43] La Rovere MT, Pinna GD, Pin M, Bruschi C, Callegari G, Zanotti E, et al. Exercise training after pulmonary endarterectomy for patients with chronic thromboembolic pulmonary hypertension. Respiration. 2019;97:234–41.
[44] Fukui S, Ogo T, Takaki H, Ueda J, Tsuji A, Morita Y, et al. Efficacy of cardiac rehabilitation after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Heart. 2016;102:1403–9.
[45] 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.
[46] Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. J Heart Lung Transplant. 2010;29:159–73.
[47] Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104:429–35.
[48] Sabbahi A, Severin R, Ozemek C, Phillips SA, Arena R. The role of cardiopulmonary exercise testing and training in patients with pulmonary hypertension: making the case for this assessment and intervention to be considered a standard of care. Expert Rev Respir Med. 2020;14:317–27.
[49] Morris ZV, Chin LMK, Chan L, Guccione AA, Ahmad A, Keyser RE. Cardiopulmonary exercise test indices of respiratory buffering before and after aerobic exercise training in women with pulmonary hypertension: differentiation by magnitudes of change in six-minute walk test performance. Respir Med. 2020;164:105900.
[50] Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, et al. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. Respiration. 2011;81:394–401.
[51] McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, et al. American College of Chest Physicians. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:78S–92S.
[52] Chaouat A, Sitbon O, Mercy M, Ponçot-Mongars R, Provencher S, Guillaumot A, et al. Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. Eur Respir J. 2014;44:704–13.
[53] Blumberg FC, Arzt M, Lange T, Schroll S, Pfeifer M, Wensel R. Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension. Eur J Heart Fail. 2013;15:771–5.
[54] Riou M, Pizzimenti M, Enache I, Charloux A, Canuet M, Andres E, et al. Skeletal and respiratory muscle dysfunctions in pulmonary arterial hypertension. J Clin Med. 2020;9:410.
[55] Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, et al. Effects of a rehabilitation program on skeletal muscle function in idiopathic pulmonary arterial hypertension. J Cardiopulm Rehabil Prev. 2010;30:319–23.
[56] Kabitz HJ, Bremer HC, Schwoerer A, Sonntag F, Walterspacher S, Walker DJ, et al. The combination of exercise and respiratory training improves respiratory muscle function in pulmonary hypertension. Lung. 2014;192:321–8.
[57] Koudstaal T, Wapenaar M, van Ranst D, Beesems R, van den Toorn L, van den Bosch A, et al. The effects of a 10-wk outpatient pulmonary rehabilitation program on exercise performance, muscle strength, soluble biomarkers, and quality of life in patients with pulmonary hypertension. J Cardiopulm Rehabil Prev. 2019;39:397–402.
[58] Fox BD, Kassirer M, Weiss I, Raviv Y, Peled N, Shitrit D, et al. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. J Card Fail. 2011;17:196–200.
[59] Babu AS, Padmakumar R, Nayak K, Shetty R, Mohapatra AK, Maiya AG. 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;71:161–5.
[60] Chia KSW, Shiner CT, Brown K, Holloway CJ, Moreyra C, Bart N, et al. The exercise in pulmonary arterial hypertension (ExPAH) study: a randomized controlled pilot of exercise training and multidisciplinary rehabilitation in pulmonary arterial hypertension. Pulm Circ. 2022;12:e12069.
[61] McCormack C, Kehoe B, Hardcastle SJ, McCaffrey N, McCarren A, Gaine S, et al. Pulmonary hypertension and home-based (PHAHB) exercise intervention: protocol for a feasibility study. BMJ Open. 2021;11:e045460.
[62] McGregor G, Bruce J, Ennis S, Mason J, Lall R, Ji C, et al. Supervised pulmonary hypertension exercise rehabilitation (SPHERe): study protocol for a multi-centre randomised controlled trial. BMC Pulm Med. 2020;20:143.
[63] Chia KSW, Wong PKK, Gonzalez S, Kotlyar E, Faux SG, Shiner CT. Attitudes towards exercise among medical specialists who manage patients with pulmonary hypertension. Pulm Circ. 2020;10:2045894020922806.
[64] McGregor G, Powell R, Finnegan S, Nichols S, Underwood M. Exercise rehabilitation programmes for pulmonary hypertension: a systematic review of intervention components and reporting quality. BMJ Open Sport Exerc Med. 2018;4:e000400.