REGULAR ARTICLE

Pulmonary Hypertension: Exercise Intolerance and the Benefits of Respiratory Muscle and Exercise Training

Seshika Ratwatte, B.Med
Department of Cardiology, Royal Prince Alfred Hospital
University of Sydney, Faculty of Medicine and Health, Sydney, New South Wales, Australia

Derek Tran, PhD
Department of Cardiology, Royal Prince Alfred Hospital
University of Sydney, Faculty of Medicine and Health
Heart Research Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

David S. Celermajer, MBBS, PhD
Department of Cardiology, Royal Prince Alfred Hospital
University of Sydney, Faculty of Medicine and Health
Heart Research Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

Rachael Cordina, MBBS, PhD
Department of Cardiology, Royal Prince Alfred Hospital
University of Sydney, Faculty of Medicine and Health
Heart Research Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

Pulmonary hypertension is characterized by significant remodeling of the pulmonary vasculature, leading to raised pulmonary vascular resistance. Despite advances in medical therapy, decreased exercise tolerance remains a predominant symptom experienced by patients. Reduced exercise capacity has been shown to have implications on quality of life and prognosis. There is growing acknowledgment that the etiology of exercise tolerance is multifactorial with cardiac, respiratory, and skeletal muscle contributors. There has been a shift in management approach with exercise training now included as a Class 1 recommendation indication in recent guidelines. In this review, we summarize the literature on the pathophysiology of exercise intolerance in pulmonary hypertension and then describe the literature assessing the safety and efficacy of inspiratory muscle and exercise training in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension.

Pulmonary hypertension (PH) is characterized by significant remodeling of the pulmonary vasculature, leading to raised pulmonary vascular resistance and eventually right heart failure.[1] It is defined hemodynamically as a mean pulmonary arterial pressure of ≥20 mmHg when measured invasively on right heart catheterization.[1] Despite numerous advances in medical therapy in treating group 1 pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH; group 4), decreased exercise tolerance remains a predominant symptom experienced by patients.[2-4] Reduced exercise capacity has been shown to have implications on quality of life (QoL), prognosis, and mortality[2].

Although traditionally the main drivers of reduced exercise tolerance in this population were thought to be cardiopulmonary factors such as increased afterload and ventriculoarterial uncoupling, there is growing acknowledgment that this is actually multifactorial with cardiac, respiratory, and skeletal muscle contributors.[2,5,6] Respiratory muscle dysfunction and weakness are 2 such factors that have been shown to correlate with exercise intolerance.[2,6,7]

Exercise training was previously discouraged in patients with PH due to

Key Words—pulmonary hypertension, exercise intolerance, exercise training, inspiratory muscle training
Correspondence: rachael.cordina@sydney.edu.au
Disclosure: The authors declare that there are no conflicts of interest.

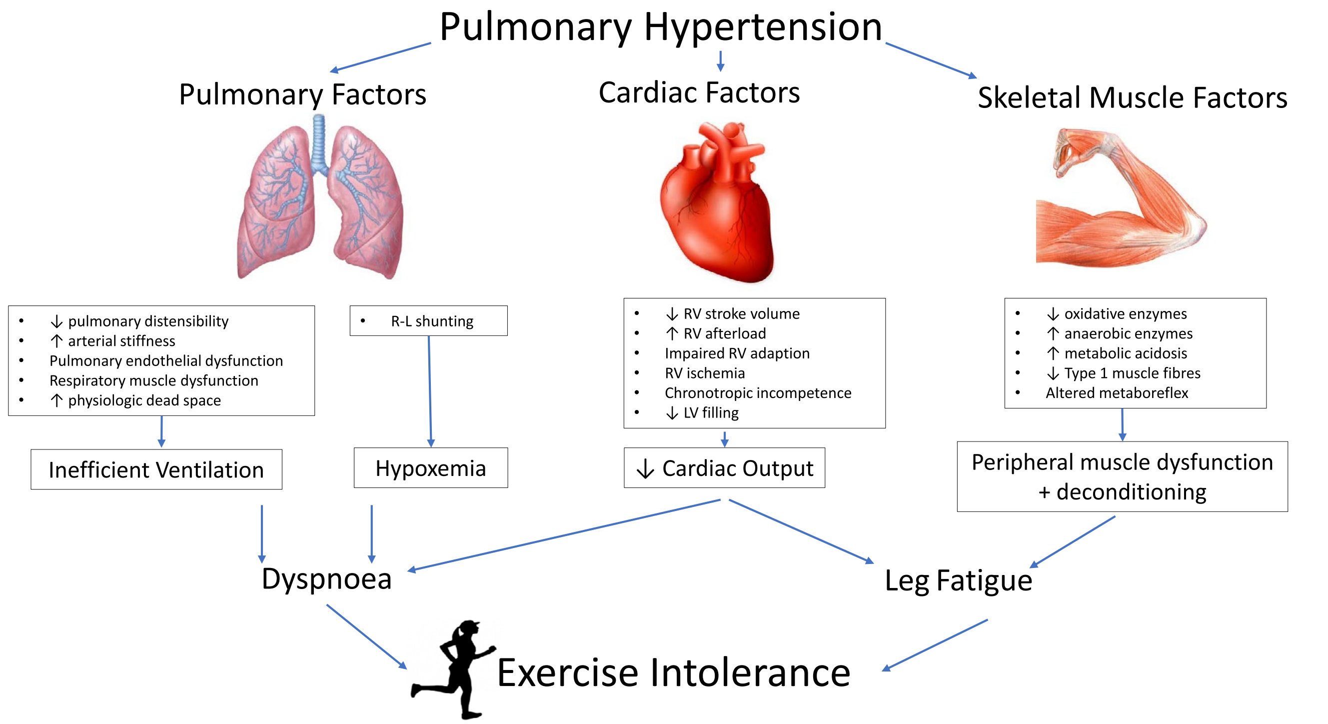

Figure 1: Multifactorial etiology of exercise intolerance in pulmonary hypertension. Abbreviations: L, left; LV, left ventricular; R, right; RV, right ventricular.

concerns about safety and potential worsening of cardiac function.[8] However, with increased understanding of the multifactorial nature of exercise intolerance, there has been a shift in management approach reflected by a Class 1 indication in international guidelines that emphasize the importance of supervised exercise training in PH cohorts in addition to optimal medical therapy.[1,9] It has been proposed that inspiratory muscle training (IMT) may ameliorate respiratory muscle weakness, while exercise training may improve skeletal muscle structure and function in PAH patients, thereby improving exercise capacity and QoL similar to heart failure and chronic obstructive pulmonary disease cohorts.[10-12]

In this review, we summarize the literature on exercise intolerance in PAH, with a particular focus on respiratory muscle weakness and inspiratory muscle and exercise training in these patients.

PATHOPHYSIOLOGY OF EXERCISE INTOLERANCE IN PH

Cardiac Factors

Right ventricular (RV) dysfunction is a major factor that limits exercise in patients with PH. In the early stages of disease, a progressive rise in the pulmonary vasculature load leads to increased RV afterload.[2] The RV adapts by becoming hypertrophied to maintain stroke volume at rest. During exercise, the RV may not be able to meet increased metabolic demands, leading to a subsequent decrease in stroke volume[13] (Figure 1).

As the disease progresses, RV maladaptation occurs in response to the chronic, pressure-overloaded state.[14] This results in RV dilatation, eccentric hypertrophy, and decreased systolic function. Associated cellular changes include a decrease in α-myosin heavy chain filaments and an increase in β-myosin heavy chain filaments.[15,16] Ventriculoarterial uncoupling is the physiologic consequence of RV maladaptation and occurs when the increase in RV contractility is inadequate to meet the demands of high afterload.[17-19] In PAH patients, RV-PA coupling is often preserved at rest, but a deterioration is noted during exercise.

Myocardial ischemia may also contribute; perfusion is dependent on the gradient between aortic root pressure and intramural pressure.[20] In PAH, an increase in systolic RV pressure leads to biphasic right coronary flow. This leads to decreased systolic function, which is most pronounced in exercise.[20] Furthermore, external compression of the left main coronary artery by dilated main pulmonary arteries has been shown to be a cause of angina and decreased exercise tolerance in PAH patients.[21]

Pulmonary Factors

Pulmonary vasculopathy is central to the pathophysiology of PH and contributes to exercise limitation. Endothelial dysfunction leads to vascular remodeling via vasoconstriction, cellular hyperplasia, and sclerosis.[2,22-24] During exercise, there is an increase in blood flow to the lungs, and the pulmonary vasculature must distend to accommodate this. These mechanisms are impaired in PAH due to a decrease in pulmonary vasculature distensibility; this causes an increase in mean pulmonary arterial pressure and RV afterload on exertion (Figure 1).[25]

In the absence of concomitant lung disease or obesity, most PAH patients have preserved gas exchange at rest. During exercise, however, arterial desaturation can occur from reduced mixed venous oxygen content from a widening of the systemic arterial-venous oxygen difference from a low cardiac output state.[2] Hyperventilation and ventilatory insufficiency also contribute to dyspnea likely secondary to enhanced chemosensitivity and increased physiologic dead space from vascular obliteration.[26] Mechanical ventilatory limitations from dynamic hyperinflation and peripheral muscle dysfunction also contribute to dyspnea and exercise intolerance.[27]

Respiratory muscle dysfunction is now increasingly recognized as a key factor contributing to exercise limitation in PAH patients. Approximately 15% of cardiac output is directed to respiratory muscles during maximal exercise and thus may be affected by reduced blood flow in PAH and CTEPH.[28] PAH patients have been documented to have a >50% reduction in force-generating capacity and atrophy of the diaphragm.[29] This reduction in diaphragmatic strength likely contributes to exercise limitation and dyspnea. Furthermore, an association has been documented between peripheral muscle strength and maximal inspiratory pressure (MIP), suggesting that respiratory muscles may influence exercise intolerance.[30,31]

Weak respiratory muscle may impair the function of the respiratory muscle pump, which helps to increase RV stroke volume. In the setting of increased pulmonary vascular resistance, augmentation of the respiratory muscle pump may help enhance pulmonary blood flow.[2]

Skeletal Muscle Factors

Skeletal muscle abnormalities are now recognized as important factors contributing to reduced exercise capacity in PH.[5,31] Abnormalities include muscle atrophy, impaired oxygen extraction, reduced angiogenesis, and contractility.[5,31] These findings are similar to those observed in systemic myopathy seen in heart failure patients.[2,5] Unfortunately, while physical inactivity is known to lead to muscle atrophy and a myocyte fiber transition, PH patients often avoid physical activity to avoid precipitating symptoms, leading to an atrophy spiral (Figure 1).[2]

Skeletal muscle density correlates with exercise capacity and muscle strength. Diminished amounts of CD31+ cells, which promote revascularization, and miR-26, which is proangiogenic, are seen in the skeletal muscle of PAH patients.[32,33] Furthermore, low cardiac output leads to a hypoxic state during increased metabolic demand, which, combined with impaired skeletal oxygen extraction, leads to reduced exercise capacity. In addition, systemic inflammation, seen in chronic diseases, is known to have a catabolic effect on skeletal muscle and is seen in PAH.[34]

IMT

IMT is a feasible and well-tolerated physical therapy that aims to induce adaptive changes in respiratory muscle structures, thereby increasing inspiratory muscle strength and in turn reducing exercise intolerance.[35,36] Prior studies have objectively documented that MIP and maximal expiratory pressure are significantly lower in PAH patients, independent of ventilation efficiency or reduced pulmonary hemodynamics.[6,7] Respiratory muscle weakness has also been documented in the CTEPH population, with reduced diaphragmatic contractility noted within slow-contracting muscle fibers and reduced calcium sensitivity of fast-contracting fibers.[34] It is postulated that IMT may improve exercise capacity by increasing the strength, fatigue resistance, and endurance of diaphragm-based inspiratory muscles, thereby allowing patients to maintain higher ventilation volumes, increase gas exchange, and have a lesser sensation of dyspnoea.[15,35,37]

Broadly speaking, IMT is performed using a handheld device that applies resistance to inspiration.[38] Patients can participate in training at home or in a supervised setting. Training protocols include cycles of resistive breathing (either a certain number of repetitions or a certain amount of time) multiple times a week over a 6- to 10-week period. The feasibility and effectiveness of this training has been well established in chronic obstructive pulmonary disorder and heart failure populations, but the utility in PAH and CTEPH populations remains less clear.[10-12]

The literature on IMT in the PAH and CTEPH populations is limited to 6 small, randomized control trials (n = 10-31).[15,35,37,39-41] Table 1 summarizes these 6 studies; the interventional groups undertook IMT of varying resistance 3 to 7 times per week over a 6- to 10-week period. At baseline, respiratory muscle strength was reduced, with pooled data from a recent meta-analysis showing a mean MIP of 61 cmH_2O in included studies (normal MIP is ≥80 cmH_2O).[15,36,37] The MIP increased significantly in the intervention group of all studies, with pooled results showing a mean increase of 19 cmH_2O ($P < .001$) compared with control groups.[15,36,37,39] After intervention, the mean MIP reached normal thresholds, highlighting that IMT can potentially help PAH patients reach normal levels of resting respiratory muscle function.[36] Several studies reported a concomitant improvement in maximal expiratory pressure, suggesting that expiratory muscles also become retrained through forced ventilation.[15] However, this was not a consistent finding across studies.[35,37]

Prior studies have sought to determine whether these improvements in respiratory muscle strength translate into improved functional capacity and outcomes. Six-minute walking distance (6MWD) is generally accepted as a surrogate endpoint for long-term clinical outcomes in PAH patients.[42] Another recent meta-analysis reported the pooled data from 4 studies and reported a mean increase in 6MWD of 39 m compared with control groups.[43] This improvement, while likely clinically significant,[44,45] does not quite meet the reported threshold of 42 m, which has been associated with reduced incidence of clinical events.[46] Furthermore, meta-analytic studies show that the lower limit of the 95% confidence interval is less than 33 m, which is generally considered to be the lower limit of clinical significance for 6MWD.[43] These modest improvements in 6MWD suggest that IMT is an adjunct form of exercise training rather than a replacement for exercise training.

The attenuation of the inspiratory muscle metaboreflex through IMT is likely to explain functional improvement.[35] During exercise, sympathoexcitation leads to vasoconstriction and decreased vascular conductance. Blood is redirected from exercising muscles toward respiratory muscles to sustain ventilation and is further accentuated when the diaphragm fatigues.[28,47-49] Increased work of

Table 1. Summary of Studies Looking at Inspiratory Muscle Training in Pulmonary Hypertension Cohorts

Reference	Design	Participants: Intervention	Participants: Control	Intervention	Outcomes[a]
Saglam et al (2015)[15]	RCT	n = 14 Female: 78.6% Age: 46.8 ± 15.6 PH group: group 1 = 14 (100%) WHO FC I/II/III/IV = 0/7/7/0	n = 17 Female: 82.4% Age: 52.2 ± 8.8 PH group: group 1 = 17 (100%) WHO FC I/II/III/IV = 0/9/8/0	Intervention: IMT Resistance: 30% MIP Regimen: 30 min × 7 times/wk for 6 wks Location: home Monitoring: wkly MIP assessment Control: IMT, 10% of MIP	Dyspnea: mMRC dyspnea score ▲ Resp muscle strength: MIP ▲, MEP ▲ Pulm function: FEV1 ▲, FVC ◊, FEV1/FVC ◊ Functional capacity: 6MWD ▲ QoL: emotional reaction ▲, nil else
Laoutaris et al (2016)[39]	RCT (pilot study)	n = 5 Female: 80% Age: 48.6 ± 12.7 PH group: group 1 = 5 (100%) WHO FC I/II/III/IV = NR	n = 5 Female: 40% Age: 60.6 ± 12.4 PH group: group 1 = 2 (40%), group 4 = 3 (60%) WHO FC I/II/III/IV = NR	Intervention: IMT Resistance: 60% SMIP Regimen: 30 min × 3 times/wk for 10 wks Location: hospital Monitoring: NR Control: none	Resp muscle strength: MIP ▲ Functional capacity: 6MWD ▲ QoL: IMT group ▲, CG ◊
Tran et al (2020)[35]	RCT (pilot study)	n = 6 Female: 83.3% Age: 55 ± 17 PH group: group 1 = 5 (83.3%), group 4 = 1 (16.7%) WHO FC I/II/III/IV = 0/6/0/0	n = 6 Female: 83.3% Age: 66 ± 10 PH group: group 1 = 5 (83.3%), group 4 = 1 (16.7%) WHO FC I/II/III/IV = 0/5/1/0	Intervention: IMT Resistance: 30 to 40% of SMIP Regimen: 30 rep × 5 times/wk for 8 wks Location: home Monitoring: wkly MIP assessment Control: none	Resp muscle strength: PImax ▲, PEmax Pulm function: ◊ Functional capacity: 6MWD ▲ CPET: peak VO_2 ◊ NT-ProBNP: ◊
Aslan et al (2020)[37]	RCT	n = 15 Female: 86.7% Age: 47.2 ± 13.3 PH group: group 1 = 10 (66.7%), group 4 = 5 (33.3%) WHO FC I/II/III/IV = 7/5/3/0	n = 12 Female: 83.3% Age: 50.6 ± 16.9 PH group: group 1 = 10 (83.3%), group 4 = 2 (16.7%) WHO FC I/II/III/IV = 1/7/4/0	Intervention: IMT Resistance: 30% of MIP Regimen: 30 min BD × 5 times/wk for 8 wks Location: home Monitoring: wkly MIP assessment Control: IMT at 9 cmH_2O without change in threshold pressure	Resp muscle strength: MIP ▲, MEP ◊ Pulm function: ◊ Functional capacity: 6MWD ◊ QoL: ◊
Fontoura et al (2021)[40]	RCT (full paper not yet published)	n = 17 Female: 100% Age: 38.8 ± 6.8 PH group: group 1 = 16 (94.1%), group 4 = 1 (5.9%) WHO FC I/II/III/IV = 0/14/3/0	n = 14 Female: 100% Age: 41.5 ± 10.6 PH group: group 1 = 13 (92.9%), group 4 = 1 (7.1%) WHO FC I/II/III/IV = 0/8/6/0	Intervention: IMT Resistance: 50 to 60% of MIP Regimen: 30 rep × 2 BD × 7 times/wk for 8 wks Location: home Monitoring: wkly MIP assessment Control: IMT at 3 cmH_2O without change in threshold pressure	Resp muscle strength: MIP ▲, MEP ▲ Pulm function: ◊ Functional capacity: 6MWD ▲ QoL: IMT group ◊
Kahraman et al (2023)[41]	RCT	n = 12 Female: 91.7% Age: 49.2 ± 17.1 PH group: group 1 = 10 (83.3%), group 4 = 2 (16.7%) WHO FC I/II/III/IV = 0/9/3/0	n = 12 Female: 91.7% Age: 55.5 ± 19.2 PH group: group 1 = 11 (91.7%), group 4 = 1 (8.3%) WHO FC I/II/III/IV = 0/7/5/0	Intervention: IMT Resistance: 40 to 60% of MIP Regimen: 30 min × 7 times/wk for 8 wks Location: home/ supervised 1 time/wk Monitoring: wkly MIP assessment Control: none	Resp muscle strength: MIP ▲, MEP ◊ Pulm function: ◊ Functional capacity: 6MWD ▲ Blood pressure: brachial SBP ▲, central SBP ▲ Peripheral muscle strength: IMT grip $p = 0.16$, quadriceps $p = 0.01$; no significant difference in CG QoL: ▲

6MWD, 6-minute walking distance; BD, bi-daily; CG, control group; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume; FVC, forced vital capacity; IMT, inspiratory muscle training; MEP, mean expiratory pressure; MIP, mean inspiratory pressure; mMRC, modified medical research council; NR, not recorded; NT-proBNP, N-terminal pro B-type natriuretic peptide; PEmax, maximum expiratory pressure; PH, pulmonary hypertension; PImax, maximum inspiratory pressure; Pulm, pulmonary; QoL, quality of life; RCT, randomized control trial; Rep, repetition; Resp, respiratory; SBP, systolic blood pressure; SMIP, sm; WHO FC, World Health Organization Functional Class.

[a]The symbol ▲ indicates a significant result, and the symbol ◊ indicates a nonsignificant result.

Table 2. Summary of Studies Looking at Exercise Training in Pulmonary Hypertension Cohorts

Reference	Design	Participants		Intervention	Outcomes
		Intervention	Control		
Atef and Abdeen (2021)[56]	RCT	n = 14 Female: NR Age: 48 ± 7 PH group: group 1 = 14 (100%) WHO FC I/II/III/IV = NR	n = 15 Female: NR Age: 47 ± 8 PH group: group 1 = 15 (100%) WHO FC I/II/III/IV = NR	Intervention: exercise, aerobic bike Target: 60-80% target HR Regimen: 15-30 min × 3 times/wk for 12 wks Location: outpatient supervised Control: no exercise intervention, usual care	Exercise capacity: VO_2 max ▲ PASP ▲
Butāne (2021)[57]	RCT	n = 9 Female: 88.9% Age: 61.6 ± 18.5 PH group: NR WHO FC I/II/III/IV = 0/4/5/0	n = 7 Female: 100% Age: 68.3 ± 16.6 PH group: NR WHO FC I/II/III/IV = 1/2/5/0	Intervention: exercise, aerobic (walk/bike), resistance, respiratory, education Regimen: 2-40 min, aerobic 3 times/wk, resistance 2 times/wk, respiratory 5 times/wk for 12 wks Location: home-based with supervision Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲
Chan et al (2013)[58]	RCT	n = 10 Female: 100% Age: 53 ± 13 PH group: group 1 = 100% WHO FC I/II/III/IV = 1/4/4/1	n = 13 Female: 100% Age: 55.5 ± 8.5 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/8/5/0	Intervention: exercise, aerobic (walk), education Target: 70-80% Regimen: 30-45 min × 2-3 times/wk for 10 wks Location: outpatient Control: education, usual care	Exercise capacity: 6MWD exercise group ▲ VO_2 max ▲ QoL ▲
Ehlken et al (2016)[53]	RCT	n = 46 Female: 56.5% Age: 55 ± 15 PH group: group 1 = 35 (76.1%), group 4 = 11 (23.9%) WHO FC I/II/III/IV = 0/8/36/0	n = 41 Female: 51.2% Age: 57 ± 15 PH group: group 1 = 26 (63.4%), group 4 = 15 (36.4%) WHO FC I/II/III/IV = 0/6/30/4	Intervention: exercise, aerobic, resistance, respiratory Target: 60-80% target HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min resistance, 30 min respiratory × 3-5 times/wk for 15 wks Location: inpatient 3 wks, unsupervised outpatient 12 wks Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Ertan et al (2022)[59]	RCT	n = 12 Female: 83.3% Age: 49.6 ± 9.9 PH group: group 1/ group 4 WHO FC I/II/III/IV = 0/10/2/0	n = 12 Female: 75% Age: 44.3 ± 9.4 PH group: group 1/ group 4 WHO FC I/II/III/IV = 0/9/3/0	Intervention: exercise-aerobic (walk) Regimen: 30-45 min × ≥3 times/wk for 8 wks Location: outpatient and home Control: no exercise intervention, usual care	Exercise capacity: 6MWD ◊ QoL ◊

(Continued)

Table 2. Summary of Studies Looking at Exercise Training in Pulmonary Hypertension Cohorts *(Continued)*

Ganderton et al (2013)[60]	RCT	n = 5 Female: 100% Age: 51, range 40-53 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/3/2/0	n = 5 Female: 80% Age: 53, range 42-57 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/3/2/0	Intervention: exercise (walk, cycle) Target: 60-70% of target HR Regimen: 60 min × 3 times/wk for 12 wks Location: outpatient supervised Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
González-Saiz et al (2017)[61]	RCT	n = 19 Female: 60% Age: 46 ± 11 PH group: group 1 = 17 (89.5%), group 4 = 2 (10.5%) WHO FC I/I-II/II-III/IV = 3/2/11/4/0	n = 16 Female: 60% Age: 45 ± 12 PH group: group 1 = 14 (87.5%), group 4 = 2 (12.5%) WHO FC I/I-II/II-III/IV = 6/2/10/0/2/0	Intervention: exercise, aerobic bike, resistance, respiratory Regimen: 20-40 min aerobic × 5 times/wk, resistance × 3 times/wk, respiratory BD × 6 times/wk for 8 wks Location: outpatient supervised Control: no exercise intervention, regular scheduled visits with clinicians	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Grünig et al (2020)[54]	RCT	n = 58 Female: 58.8% Age: 52 ± 12 PH group: group 1 = 51 (87.9%), group IV = 7 (12.1%) WHO FC I/II/III/IV = 12/24/21/1	n = 58 Female: 77.6% Age: 55 ± 13 PH group: group 1 = 47 (81%), group 4 = 11 (19%) WHO FC I/II/III/IV = 0/34/24/0	Intervention: exercise (walk/cycle), respiratory Target: 40-60% HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min resistance, 30 min resp 3-7 times/wk for 12 wks Location: inpatient 10-30 days, 12 wks home Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Kagioglou et al (2021)[62]	RCT	n = 12 Female: 50% Age: 54.7 ± 15.6 PH group: group 1/group 4 WHO FC I/II/III/IV = 0/10/2/0	n = 10 Female: 70% Age: 53.1 ± 12.1 PH group: group 1/group 4 WHO FC I/II/III/IV = 0/10/0/0	Intervention: exercise, aerobic (walk, cycle) Target: 60-80% target HR Regimen: 45-60 min × 3 times/wk for 6 months Location: outpatient and home Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Ley et al (2013)[63]	RCT	n = 10 Female: 80% Age: 47 ± 8 PH group: group 1 = 9 (90%), group 4 = 1 (10%) WHO FC I/II/III/IV = 0/3/7/0	n = 10 Female: 60% Age: 54 ± 14 PH group: group 1 = 7 (70%), group 4 = 3 (30%) WHO FC I/II/III/IV = 0/1/9/4	Intervention: exercise, aerobic, resistance, respiratory Target: 60-80% target HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min respiratory × 5 times/wk for 3 wks Location: inpatient Control: no exercise intervention, usual care	Exercise capacity: 6MWD▲

(Continued)

Table 2. Summary of Studies Looking at Exercise Training in Pulmonary Hypertension Cohorts *(Continued)*

Mereles et al (2006)[64]	RCT	n = 15 Female: 66.7% Age: 47 ± 12 PH group: group 1 = 13 (86.7%)/group 4 = 2 (13.3%) WHO FC I/II/III/IV = 0/2/12/1	n = 15 Female: 66.7% Age: 53 ± 14 PH group: group 1 = 11 (73.3%)/group IV = 4 (26.7%) WHO FC I/II/III/IV = 0/4/10/1	Intervention: exercise, aerobic (walk/cycle), resistance, respiratory Target: 60-80% target HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min resistance, 30 min respiratory × 5 times/wk for 15 wks Location: inpatient (3 wks) and outpatient (12 wks) Control: common rehabilitation	Exercise capacity: 6MWD ▲ QoL ▲
Rakhmawati et al (2020)[65]	RCT	n = 20 Female: 95% Age: 37.5 ± 8.8 PH group: group 1, ASD-PH = 100% WHO FC I/II/III/IV = 4/16/0/0	n = 18 Female: 88.9% Age: 35.5 ± 10.4 PH group: group 1, ASD-PH = 100% WHO FC I/II/III/IV = 4/14/0/0	Intervention: exercise (walk) Target: 60-70% of target HR Regimen: 30 min × 3 times/wk for 12 wks Location: outpatient Control: no information	Exercise capacity: 6MWD▲ QoL▲
Wilkinson et al (2007)[66]	RCT	n = 18 Female: NR Age: NR PH group: NR WHO FC I/II/III/IV = NR	n = 18 Female: NR Age NR PH group: NR WHO FC I/II/III/IV = NR	Intervention: exercise Regimen: 3 months Location: outpatient, 1 supervised, then unsupervised Control: no exercise intervention, usual care	Incremental shuttle walk Endurance shuttle walk
Wojciuk et al (2021)[67]	RCT	n = 16 Female: 43.7% Age: 48.9 ± 18.3 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/8/8/0	n = 23 Female: 56.5% Age: 53.7 ± 12.8 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/2/5/0	Intervention: exercise (interval) Target: 60-70% of target HR Regimen: 45-60 min × 5 times/wk for 24 wks Location: home based with supervision Control: no exercise intervention, usual care	Exercise capacity: 6MWD▲ QoL▲

[a]The symbol ▲ indicates a significant result, and the symbol ◊ indicates a nonsignificant result.

6MWD, 6-minute walking distance; ASD-PH, atrial septal defect - pulmonary hypertension; CG, control group; HR, heart rate; NR, not recorded; PH, pulmonary hypertension; QoL, quality of life; RCT, randomized control trial; SBP, systolic blood pressure; WHO FC, World Health Organization Functional Class.

breathing therefore increases the cardiac output required to maintain ventilation. In PAH, this is particularly significant as cardiac output is often limited; thus, the redirection of blood flow comes at the expense of premature exercise muscle fatigue.[35] Increased ventilatory load and weak respiratory muscle capacity augment neural respiratory drive, while the recruitment of accessory respiratory muscles to facilitate ventilation during diaphragmatic fatigue provides further sensory feedback to the central nervous system.[48,50] These further compound the sensation of breathlessness. Increasing inspiratory muscle strength through IMT increases the ventilatory load needed for the onset of the metaboreflex and may thus improve exercise capacity.[35]

Interestingly, despite objective improvements in respiratory muscle strength and functional capacity, only Saglam et al[15] reported significant improvements in forced expiratory volume in the first second, with no other studies reporting significant improvements in lung function as measured by spirometry.[15,35,37,39-41] This was reflected in the pooled data reported in both recent meta-analyses.[36,43] The sensation of dyspnea during daily activities was only reported in 2 studies (modifiec medical research council scale). Pooled analysis showed a small but significant decrease of 0.5 points in the IMT group compared with the control group.[15,40] QoL scores were assessed in 4 studies; pooled analysis of 3 studies showed no significant difference in emotional or physical measures of QOL.[15,37,40] One of the remaining studies showed that the IMT group had significant improvements in physical QoL measures (P = .002) and some subcomponents of emotional QoL but had no significant differences between intervention and control groups.[39] Safety of IMT has been reported in 2 studies, with Aslan et al reporting no adverse outcomes and Saglam et al having 1 patient self-report wrist pain.[15,37] Compliance to IMT training programs was reported as ≥98% in the 3 studies that reported on completion rates.[15,35,37]

Exercise Training

Exercise training has been shown to be a feasible, safe, and efficacious treatment for PH patients.[51] It has been reported to improve skeletal muscle function by increasing capillarization and changing muscle fiber type.[29] Exercise training also influences the pulmonary vasculature through regulating pulmonary vascular remodeling and has recently been shown to improve pulmonary hemodynamics, with reductions in mean pulmonary arterial pressure noted on right heart catheterization following exercise-based rehabilitation.[52-54] It is important to note, however, that to achieve hemodynamic improvements, high volumes of exercise per patient (>220 hours) was needed, with a recent study unable to replicate this at lower levels.[55]

Exercise training in this setting refers to a combination of aerobic and low-load resistance exercise training. Aerobic exercise involves activation of large skeletal muscle groups through walking or cycling for 20 to 40 minutes. Resistance training may also be used with upper and/or lower body muscle groups targeted through repetitions of set exercises. However, evidence on the safety and efficacy of isolated resistance training in PH remains limited. Exercise training is often supervised and can occur in an inpatient, outpatient, or remote setting. Sessions are generally 2 to 3 times per week over a minimum of 4 weeks.[51]

A recent Cochrane review analyzed data from 14 parallel grouped randomized control trials (n = 10-129) that looked at the impact of exercise rehabilitation on outcomes in patients with PH.[51] Included studies enrolled 571 patients with PAH or CTEPH who were stable on medical therapy. All exercise training programs were similar to standardized recommended cardiac and pulmonary rehabilitation programs. Programs were primarily aerobic, although some included additional resistance training components. Table 2 summarizes the studies and their outcomes.[53,54,56-67]

Exercise capacity was the key outcome assessed across studies. A pooled analysis of 11 studies showed a mean difference in 6MWD of 49 m following exercise training when comparing the intervention and control groups,[53,54,57-65] which exceeds both the minimal threshold for clinical significance and the threshold for reduced clinical events. Cardiopulmonary exercise testing was also assessed in 7 studies and showed a significant increase in peak oxygen uptake (VO_2 max), the gold standard measure of cardiopulmonary fitness, following intervention when comparing the exercise groups with the control groups (mean difference of 2.1 mL/kg/min, 95% confidence interval of 1.57-2.57).[53,54,58,60-62,64] A significant increase in peak power between groups was also noted. There was a large amount of heterogeneity between studies, and it remains unclear if these variations were due to disease severity, location of program (inpatient versus outpatient), or study population.[51]

Aerobic exercise training in athletes has been shown to lead to an increase in skeletal muscle capillarization with elevated capillary density and capillary-to-fiber ratio.[68,69] This leads to enhanced transport and extraction of oxygen from skeletal muscles causing increased aerobic activity. In chronic heart failure patients, exercise training has been shown to reverse skeletal muscle atrophy, improve ventilatory efficacy, and attenuate endothelial dysfunction.[70-72] These mechanisms are also likely to play a role in increasing exercise capacity in PH patients.[51] Further research is needed to determine if there are PH-specific mechanisms.

No increased risk of serious adverse events were seen in a recent metanalysis when comparing exercise programs to usual care.[51] Only 5 serious adverse events were reported across 11 studies (439 patients).[51] Grünig et al reported 3 events in the exercise group (stroke, generalized edema, and decompensated diabetes), whereas Ganderton et al reported that 1 patient experienced presyncope during 1 training session.[54,60]

Exercise training programs have also been shown to significantly improve physical and emotional indicators of QoL in PH patients undergoing training compared with controls using both general and PH-specific QoL scores.[56-58,65-67] This emphasizes the holistic approach adopted in such rehabilitation programs, which enables patients to not only improve in objective measures of functional capacity but also extend their individual spectrum of daily activity.[51] Future studies should investigate the optimal type, intensity, and volume of exercise required to improve physiological measures and clinical outcomes. Major PH treatment centers are often located within major cities; thus, access to face-to-face exercise programs may be limited for patients who face geographic or socioeconomic barriers. More recently, entirely remote exercise programs have been evaluated and have been shown to be effective, suggesting that this may be suitable for stable patients as a more scalable intervention.[73]

CONCLUSIONS

Exercise intolerance is a predominant symptom in patients with both PAH and CTEPH, with complex pathophysiology. IMT and exercise training target different pathophysiologic pathways and can feasibly be used as an adjunct to standard medical therapy. Both exercise training programs and IMT have been shown to lead to significant objective improvements in functional capacity, although increases with the former are more marked. Exercise training also consistently improves QoL indicators and should be incorporated into standard care models for stable patients.

ACKNOWLEDGMENTS

SR has received a PhD Scholarship from the National Heart Foundation (106796). DT was supported by the Medical Research Future Fund, Cardiovascular Health Mission, Congenital Heart Disease Grant (ARGCH-DG000016) and by an Additional Ventures Tools & Technology Expansion Award (1048066).

References

1. Humbert M, Kovacs M, Hoeper M, Badagliacca R, Berger R, et al; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43(38):3618-3731.
2. Tran DL, Lau E, Celermajer DS, Davis GM, Cordina R. Pathophysiology of exercise intolerance in pulmonary arterial hypertension. *Respirology.* 2018;23(2):148-159.
3. Filusch A, Ewert R, Altesellmeier M, et al. Respiratory muscle dysfunction in congestive heart failure—the role of pulmonary hypertension. *Int J Cardiol*. 2011;150(2):182-185.
4. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest* 2012;142(6):1391-1398.
5. Bauer R, Dehnert C, Schoene P, et al. Skeletal muscle dysfunction in patients with idiopathic pulmonary arterial hypertension. *Respir Med*. 2007;101(11):2366-2369.
6. Meyer FJ, Lossnitzer D, Kristen AV, et al. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2005;25(1):125-130.
7. Kabitz HJ, Schwoerer A, Bremer HC, et al. Impairment of respiratory muscle function in pulmonary hypertension. *Clin Sci.* 2008;114(2):165-171.
8. Galie N, Corris P, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2013;62(25 Suppl):D60-72.
9. Grünig E, Eichstaedt C, Barberà JA, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J.* 2019;53(2):1800332.
10. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis. *Clin Respir J*. 2018;12(7):2178-2188.
11. Cahalin LP, Arena R, Guazzi M, et al. Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes. *Expert Rev Cardiovasc Ther*. 2013;11(2):161-177.
12. Bosnak-Guclu M, Arikan H, Savci S, et al. Effects of inspiratory muscle training in patients with heart failure. *Respir Med*. 2011;105(11):1671-1681.
13. Sharma T, Lau E, Choudhary P, et al. Dobutamine stress for evaluation of right ventricular reserve in pulmonary arterial hypertension. *Eur Respir J.* 2015;45(3):700-708.
14. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II. Pathophysiology, clinical importance, and management of right ventricular failure. *Circulation.* 2008;117(13):1717-1713.
15. Saglam M, Arikan H, Vardar-Yagli N, et al. Inspiratory muscle training in pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev.* 2015;35(3):198-206.
16. Laveneziana P, Albuquerque A, Aliverti A, et al. ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J.* 2019;53(6):1801214.
17. Vonk-Noordegraaf A, Hadded F, Chin KM, et al. Right heart adaptation to pulmonary arterial hypertension physiology and pathobiology. *J Am Coll Cardiol.* 2013;62(25 Suppl):D22-D33.
18. Sanz J, Garcia-Alvarez A, Fernández-Friera L, et al. Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study. *Heart.* 2012;98(3):238-243.
19. Bellofiore A, Dinges E, Naeije R, et al. Reduced haemodynamic coupling and exercise are associated with vascular stiffening in pulmonary arterial hypertension. *Heart.* 2017;103(6):421-427.
20. van Wolferen SA, Marcus J, Westerhof N, et al. Right coronary artery flow impairment in patients with pulmonary hypertension. *Eur Heart J*. 2008;29(1):120-127.
21. Galiè N, Saia F, Palazzini M, et al. Left main coronary artery compression in patients with pulmonary arterial hypertension and angina. *J Am Coll Cardiol.* 2017;69(23):2808-2817.
22. Budhiraja R, Tudor R, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. *Circulation.* 2004;109(2):159-165.
23. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1995;333(4):214-221.
24. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993;328(24):1732-1739.
25. Waxman AB. Exercise physiology and pulmonary arterial hypertension. *Prog Cardiovasc Dis.* 2012;55(2):172-177.
26. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respir Physiol Neurobiol.* 2009;167(1):11-32.
27. Weatherald J, Farina S, Bruno N, Laveneziana P. Cardiopulmonary exercise testing in pulmonary hypertension. *Ann Am Thorac Soc.* 2017;14(Supplement_1):S84-S92.
28. Harms CA, Wetter T, McClaran SR, et al. Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J Appl Physiol.* 1998;85(2):608-618.
29. de Man FS, van Hees H, Handoko ML, et al. Diaphragm muscle fiber weakness in pulmonary hypertension. *Am J Respir Crit Care Med.* 2011;183(10):1411-1418.
30. Aslan GK, Akinci B, Yeldan I, Okumus G. Respiratory muscle strength in patients with pulmonary hypertension: the relationship with exercise capacity, physical activity level, and quality of life. *Clin Respir J.* 2016;12(2):699-705.
31. Breda AP, de Albuquerque A, Jardim C, et al. Skeletal muscle abnormalities in pulmonary arterial hypertension. *PLoS One.* 2014;9(12):e114101.
32. Potus F, Malenfant S, Graydon C, et al. Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2014;190(3):318-328.
33. Malenfant S, Potus F, Mainguy V, et al. Impaired skeletal muscle oxygenation and exercise tolerance in pulmonary hypertension. *Med Sci Sports Exerc.* 2015;47(11):2273-2282.
34. Manders E, Rain S, Bogaard HJ, et al. The striated muscles in pulmonary arterial hypertension: adaptations beyond the right ventricle. *Eur Respir J.* 2015;46(3):832-842.
35. Tran D, Munoz P, Lau EMT, 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(3):388-395.
36. Luo Z, Qian H, Zhang X, Wang Y, Wang J, Yu P. Effectiveness and safety of inspiratory muscle training in patients with pulmonary hypertension: a systematic review and meta-analysis. *Front Cardiovasc Med*2022;9:999422.
37. Aslan GK, Akinci 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(4):381-387.
38. Charususin N, Gosselink R, Decramer M, et al. Inspiratory muscle training protocol for patients with chronic obstructive pulmonary disease (IMTCO study): a multicentre randomised controlled trial. *BMJ Open*. 2013;3(8):e003101.
39. Laoutaris ID, Dritsas A, Kariofyllis P, Manginas A. Benefits of inspiratory muscle training in patients with pulmonary hypertension: a pilot study. *Hellenic J Cardiol*. 2016;2016:S1109-9666(16)30155-5.
40. de Fontoura FF, Roncato G, Watte G, et al. Effects of inspiratory muscle training on the sensation of dyspnea in patients with pulmonary hypertension group I and IV—randomized controlled clinical trial. *Eur Respir J.* 2018;52(suppl 62):PA1718.
41. Kahraman BO, Tanriverdi A, Savci S, et al. Effects of inspiratory muscle training in patients with pulmonary hypertension. *Am J Cardiol.* 2023;203:406-413.
42. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):487-492.
43. Gutierrez-Arias R, Hinojosa-Riadi J, Sandoval-Cañío A, Santana-Garrido H, Valdovinos-Guerrero N, Seron P. Effectiveness of respiratory muscle training in adults

with pulmonary hypertension. A systematic review and meta-analysis. *Heart Lung Circ*. 2023;32(3):315-329.
44. Mathai SC, Puhan M, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2012;186(5):428-433.
45. Holland AE, Spruit M, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44(6):1428-1446.
46. Gabler NB, French B, Strom BL, et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. *Circulation.* 2012;126(3):349-356.
47. Sheel AW, Boushel R, Dempsey JA. Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. *J App Physiol.* 1985;125(3):820-831.
48. McConnell AK, Lomax M. The influence of inspiratory muscle work history and specific inspiratory muscle training upon human limb muscle fatigue. *J Physiol*. 2006;577(Pt 1):445-457.
49. Romer LM, Lovering A, Haverkamp HC, Pegelow DF, Dempsey JA. Effect of inspiratory muscle work on peripheral fatigue of locomotor muscles in healthy humans. *J Physiol*. 2006;571(Pt 2):425-439.
50. Chiappa GR, Roseguini B, Vieira PJ, et al. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. *J Am Coll Cardiol.* 2008;51(17):1663-1671.
51. Morris NR, Kermeen F, Jones AW, Lee JYT, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev.* 2023;3(3):CD011285.
52. Weissmann N, Peters DM, Klopping C, et al. Structural and functional prevention of hypoxia-induced pulmonary hypertension by individualized exercise training in mice. *Am J Physiol Lung Cell Mol Physiol.* 2014;306(11):986-995.
53. Ehlken N, Lichtblau M, Klose H, 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*. 2015;37(1):35-44.
54. Grünig E, MacKenzie A, Peacock AJ, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. *Eur Heart J.* 2020;14:2284-2295.
55. Chia KSW, Shiner C, Brown K, 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(2):e12069.
56. Atef H, Abdeen H. Effect of exercise on sleep and cardiopulmonary parameters in patients with pulmonary artery hypertension. *Sleep Breath*. 2021;25(4):1953-1960.
57. Butāne L, Šablinski M, Skride A, Šmite D. Individually tailored 12-week home-based exercise program improves both physical capacity and sleep quality inpatients with pulmonary arterial hypertension. *Medicina (Kaunas)*. 2021;58(5):662.
58. Chan L, Chin L, Kennedy M, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. *Chest.* 2013;143(2):333-343.
59. Ertan O, Aslan G, Akinci B, Bilge AK, Inanc M, Okumus G. Effect of ground-based walk training in pulmonary hypertension. *Am J Cardiol.* 2022;174:172-178.
60. Ganderton L, Gain K, Fowler R, et al. Effects of exercise training on exercise capacity and quality of life in pulmonary arterial hypertension. In: *Respirology*. Volume 18. Hoboken, NJ: Wiley-Blackwell; 2013:74.
61. González-Saiz L, Fiuza-Luces C, Sanchis-Gomar F, et al. Benefits of skeletal-muscle exercise training in pulmonary arterial hypertension: the WHOLEi+12 trial. *Int J Cardiol*. 2017;231:277-283.
62. Kagioglou O, Mourantoglou S, Giannakoulas G, 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.
63. Ley S, Fink C, Risse F, 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(2):324-331.
64. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation.* 2006;114(14):1482-1489.
65. Rakhmawati A, Achmad I, Hartopo AB, et al. Exercise program improves functional capacity and quality of life in uncorrected atrial septal defect-associated pulmonary arterial hypertension: a randomized-control pilot study. *Ann Rehabil Med.* 2020;44(6):468-480.
66. Wilkinson A, Elliot C, Mawson S, Armstrong I, Billings C, Kiely DG. A randomised controlled trial to investigate the effects of a physiotherapist-led rehabilitation programme on exercise capacity and quality of life measures in patients with pulmonary hypertension. *Thorax.* 2007;62.
67. Wojciuk M, Cioliewics M, Kuryliszyn-Moskal A, et al. Effectiveness and safety of a simple home-based rehabilitation program in pulmonary arterial hypertension: an interventional pilot study. *BMC Sports Sci Med Rehabil*. 2021;13(1):79.
68. Broad P, Ingjer F, Hermansen L. Capillary supply of skeletal muscle fibers in untrained and endurance-trained men. *Am J Physiol.* 1977;232(6):H705-H712.
69. Hudlicka O, Brown M, Egginton S. Angiogenesis in skeletal and cardiac muscle. *Physiol Rev*. 1992;72(2):369-417.
70. Coats AJ, Adamopoulos S, Radelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*. 1992;85(6):2119-2131.
71. Drexler H, Riede U, Muzel T, et al. Alterations of skeletal muscle in chronic heart failure. *Circulation*. 1992;85(5):1751-1759.
72. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998;98(24):2709-2715.
73. McCormack C, Kehoe B, Hardcastle SJ, et al. Pulmonary hypertension and home-based (PHAHB) exercise intervention: protocol for a feasibility study. *BMJ Open*. 2021;11(5):e045460.