Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension
Systematic Review and Meta-Analysis

Ambarish Pandey, MD; Sushil Garg, MD; Monica Khunger, MD; Sonia Garg, MD; Dharam J. Kumbhani, MD, SM; Kelly M. Chin, MD; Jarett D. Berry, MD, MS

**Background**—Exercise training has been shown to improve cardiorespiratory fitness, physical capacity, and quality of life in patients with cardiopulmonary conditions, such as heart failure and chronic obstructive pulmonary disease. However, its role in management of pulmonary hypertension is not well defined. In this study, we aim to evaluate the efficacy and safety of exercise training in patients with pulmonary hypertension.

**Methods and Results**—We included all prospective intervention studies that evaluated the efficacy and safety of exercise training in patients with pulmonary hypertension. Primary outcome of this meta-analysis was a change in 6-minute walk distance. We also assessed the effect of exercise on peak oxygen uptake, resting pulmonary arterial systolic pressure, peak exercise heart rate, and quality of life. A total of 469 exercise-training participants enrolled in 16 separate training studies were included. In the pooled analysis, exercise training was associated with significant improvement in 6-minute walk distance (weighted mean difference, 53.3 m; 95% confidence interval, 39.5–67.2), peak oxygen uptake (weighted mean difference, 1.8 mL/kg per minute; 95% confidence interval, 1.4–2.3), pulmonary arterial systolic pressure (weighted mean difference, −3.7 mmHg; 95% confidence interval, −5.4 to −1.9), peak exercise heart rate (weighted mean difference, 10 beats per min; 95% confidence interval, 6–15), and quality of life as measured on SF-36 questionnaire subscale scores. Furthermore, exercise training was well tolerated with a low dropout rate, and no major adverse events were related to exercise training.

**Conclusions**—Exercise training in patients with pulmonary hypertension appears safe and is associated with a significant improvement in exercise capacity, pulmonary arterial pressure, and quality of life. (Circ Heart Fail. 2015;8:1032-1043. DOI: 10.1161/CIRCHEARTFAILURE.115.002130.)

**Key Words:** exercise ■ heart failure ■ heart rate ■ hypertension, pulmonary ■ quality of life

Pulmonary hypertension is a chronic cardiopulmonary disorder characterized by progressive increasing pulmonary vascular resistance, leading to right ventricular heart failure. Prevalence of pulmonary hypertension is estimated to be 10 to 15 cases per million with a mortality rate of 15% per year. Over the past 2 decades, targeted pharmacological therapies have been effective in reducing disease progression and improving the survival rate among patients with pulmonary hypertension. However, most patients remain symptomatic with significant exercise intolerance and reduced quality of life despite being on optimal medical therapy. Thus, there is an unmet need for adjunctive therapeutic strategies to improve exercise tolerance and quality of life among these patients.

**Clinical Perspective on p 1043**

Exercise intolerance in patients with pulmonary hypertension is associated with a reduced maximal oxygen uptake and early onset of anaerobic threshold, similar to patients with severe heart failure. The decrease in pulmonary vasculature distensibility associated with pulmonary hypertension leads to marked increases in pulmonary arterial mean pressure during exercise. This results in reduced pulmonary blood flow and low cardiac output insufficient to meet the metabolic demands of exercise. Furthermore, pulmonary hypertension patients have significant skeletal muscle abnormalities leading to impaired peripheral oxygen utilization. These central and peripheral abnormalities contribute significantly to the exercise intolerance and functional limitation in patients with pulmonary hypertension.

Exercise training has been shown to improve cardiorespiratory fitness, functional status, and clinical outcomes in patients with cardiopulmonary conditions, such as heart failure and chronic obstructive pulmonary disease (COPD). Considering the overlap in the pathophysiological derangements

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From the Division of Cardiology, Department of Internal Medicine (A.P., Sonia Garg, D.J.K., J.D.B.), Division of Pulmonary Medicine, Department of Internal Medicine (K.M.C.), and Department of Clinical Sciences (J.D.B.), University of Texas Southwestern Medical Center, Dallas; Department of Internal Medicine, University of Minnesota School of Medicine, Minneapolis (Sushil Garg); and Department of Internal Medicine, Cleveland Clinic, OH (M.K.).

The Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.115.002130/-/DC1. Correspondence to Jarett D. Berry, MD, MS, Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390. E-mail jarett.berry@utsouthwestern.edu

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in pulmonary hypertension and these conditions, it can be hypothesized that similar benefits of exercise training may be derived in patients with pulmonary hypertension. Several small studies have evaluated exercise training as an adjunctive therapeutic strategy in patients with chronic pulmonary hypertension. Although most of these studies were small and not designed to address clinical end points, such as mortality or hospitalizations, related to pulmonary hypertension, they have demonstrated a variable degree of improvement in exercise tolerance and quality of life in response to training.

Therefore, because of the uncertainty about the benefit of structured exercise training programs in patients with pulmonary hypertension, we performed this systematic review and meta-analysis to assess the efficacy and safety of structured exercise training regimens in patients with pulmonary hypertension.

Methods

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.33

Data Sources and Searches

A comprehensive computerized literature search of Medline and EMBASE databases was conducted using MeSH terms and keywords, including pulmonary hypertension, pulmonary arterial hypertension, pulmonary arterial hypertension, exercise, exercise training, pulmonary rehabilitation, cardiac rehabilitation, and cardiopulmonary rehabilitation, for articles published between January 1, 1960, and April 15, 2015. We only included human studies involving adult participants in our literature search. In addition, the institutional records were manually searched for available theses using the expertise of a medical librarian.

Study Selection and Outcomes of Interest

We evaluated all prospective intervention studies, including parallel group trials (both randomized as well as nonrandomized trials) with an intervention and a control group, and pre–post intervention studies that enrolled adult patients (age ≥18 years) with pulmonary arterial hypertension of any cause (Figure 1). The primary outcome of our study was change in exercise capacity measured as 6-minute walk distance (6MWD) from baseline to follow-up. Secondary outcomes included change in cardiorespiratory fitness (measured as change in peak oxygen uptake in mL/kg per minute), resting pulmonary arterial systolic pressure, peak exercise heart rate, and quality of life parameters, as indicated by the SF-36 questionnaire subscale scores (physical functioning, role physical, general health perception, vitality, social functioning, and mental health). Studies failing to report at least 1 of the above predefined study outcomes were excluded from our analysis. We also evaluated the safety profile of exercise training by determining the pooled incidence of adverse events in the included studies as detailed below.

Data Extraction

Full text articles were retrieved for all title abstracts that met the inclusion criteria. Data extraction was then independently performed by 2 authors (A.P. and M.K.) using a standardized questionnaire. All discrepancies about study inclusion or outcomes were resolved by the senior author (J.B.). In cases of multiple publications arising from a single trial, only the updated trial publication with the maximum number of participants was included. The following information was recorded for each study: author, year of publication, nature of study, baseline demographic and clinical characteristics, baseline invasive measures of pulmonary artery pressure, pre and post exercise intervention measures of outcome variables (6MWD, peak oxygen uptake, and SF-36 score), dropout rates, and adverse events. Both fatal and nonfatal adverse events among the exercise-training participants were recorded.

Data Synthesis and Statistical Analysis

Pooled analysis was conducted using Metan and Metareg functions available for Stata version 12.1 statistical software (Stata Corporation, College Station, TX)34 and Comprehensive Meta-analysis Software (Biostat, Englewood, NJ). In each trial, the effect size of exercise training was calculated as the difference between preintervention and postintervention measure of the continuous outcome variables (6MWD and peak oxygen uptake) in the aerobic exercise–trained participants. Each mean difference was weighted according to the inverse variance method35 and pooled across each trial using a random effects model.34 We also analyzed the trials with parallel intervention and control arms separately and calculated the effect size of the exercise training intervention as the difference in the change in outcome variables after intervention between exercise–trained participants and control group participants. We assessed for heterogeneity using the I² statistic (I²≥50% was assumed to be a result of significant heterogeneity). To assess the effect of age on treatment outcomes, random effects meta-regression models were constructed for the primary outcome (6MWD). We also evaluated the overall safety profile of exercise training in the included studies by determining the pooled dropout rate and frequency of adverse events during exercise training. Because the majority of our included studies were not randomized trials, we calculated the pooled incidence of adverse events (fatal and nonfatal) among the exercise-training participants of the included studies. Risk of bias analysis for the randomized intervention trials was performed using Cochrane collaboration’s assessment tool in RevMan version 5.2 software.36 Quality assessment of pre–post interventional studies was performed using the National Institutes of Health quality assessment tool. Publication bias was assessed using the funnel plots and quantified by Begg’s Mazumdar test. All P values were 2-tailed with statistical significance specified at 0.05 and confidence intervals (CI) reported at the 95% level.

Results

Study Characteristics

We included 16 studies with 469 participants (69% women) in the final meta-analysis. Pooled analysis included exercise training participants enrolled in 6 parallel group trials with an intervention and a control arm (4 randomized and 2 nonrandomized trials) and 10 pre–post studies. One study with duplicate population was included in descriptive review but not in the pooled analysis.30 The median follow-up duration was 15 weeks (range, 3–40 weeks). Baseline demographic and clinical characteristics of the study participants are summarized in Table 1. One study (Ihle et al23) did not provide information on underlying cause of pulmonary hypertension among study participants. Among others studies, the majority of training participants had class I pulmonary hypertension or class IV pulmonary hypertension (Table I in the Data Supplement) and a small proportion had class II pulmonary hypertension related to left heart disease or class III pulmonary hypertension secondary to chronic lung disease.30 All studies included well-compensated patients with pulmonary hypertension stabilized on cardiac medications with no recent hospitalizations. Common exclusion criteria used in the studies were the presence of New York Heart Association class I or class IV symptoms or coexisting conditions that impaired their participation in training (Tables II and III in the Data Supplement). Supervised exercise-training protocols were used in all studies with a combination of aerobic (treadmill or cycle ergometer) and resistance training. Six studies trained patients with pulmonary hypertension at outpatient rehabilitation centers; 9 studies performed in-hospital exercise training for the first few weeks followed by home-based exercise training; and 1 study included only home-based training protocol. Training
participants in the majority of included studies underwent low workload aerobic exercise training (10–60 W) with some form of resistance and respiratory training. Exercise intensity was titrated at 60% to 80% of peak exercise capacity in most studies. The study participants had exercise capacity and cardiopulmonary fitness assessment at baseline and follow-up (Tables 2 and 3).

Quality Assessment
The Cochrane risk of bias assessment tool was used to perform quality assessment of controlled intervention trials. During quality assessment, random sequence generation and blinded assessment of outcomes were performed in 4 and 3 of the 6 included trials, respectively. Incomplete outcome data or selective reporting of results were not observed in any of the selected studies. Quality assessment of pre–post interventional studies has been detailed in Table IV in the Data Supplement. All included studies had a clearly stated study question, pre-specified inclusion criteria, participants representative of the pulmonary hypertension patient population in the real world, clearly defined intervention and outcome variables, and a low proportion of loss to follow-up. Potential risks of biases were lack of information on blinding of the assessment of the outcomes and lack of multiple measurements of outcomes of interest before and after exercise intervention. We did not observe a significant risk of publication bias for the primary outcome in the included studies (Egger’s regression intercept = −1.32; P value = 0.36; Figure I in the Data Supplement).

Effect of Exercise Training on 6MWD
All included studies reported 6MWD at baseline and after exercise training. Mean 6MWD at baseline among training participants in the included studies was 416.9 m (SD, 37.0). We observed a significant heterogeneity on pooled analysis of studies reporting 6MWD (I² = 87%) at baseline and follow-up. Pooling across all studies using random effects analysis showed that exercise training was associated with a significant improvement in 6MWD from baseline to follow-up. (weighted mean difference [WMD], 53.3 m; 95% CI, 39.5–67.2; Figure 2A). Meta-regression did not show a significant association of baseline age with the change in 6MWD after exercise training (P value = 0.13; Figure II in the Data Supplement). We also performed sensitivity analyses including only data from trials with parallel intervention and
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Mean Age, y</th>
<th>No. of Participants (% Women)</th>
<th>Mean Weight (W, kg)/Height (H, cm)/BMI, kg/m²</th>
<th>WHO Function Class</th>
<th>PAH Medications Used</th>
<th>Baseline Peak VO₂ mL/kg per minute</th>
<th>Baseline 6-Minute Walk Distance (m)</th>
<th>Cause of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mereles et al 2006¹⁴</td>
<td>50 (13)</td>
<td>Ex T: 15 Control: 15 (Women: 66.7%)</td>
<td>W: 76.5 (15.5) H: 168.5 (8)</td>
<td>20% Class II ERA: 63% PD5-I: 33%</td>
<td>Ex T: 13.2 (3.1) Control: 11.9 (3.1)</td>
<td>Ex T: 439 (82) Control: 411 (86)</td>
<td>80% IPAH</td>
<td>20% CTEPH</td>
</tr>
<tr>
<td>Martinez-Quintana et al 2010²⁰</td>
<td>28 (6)</td>
<td>Ex T: 4 Control: 4 (Women: 62.5%)</td>
<td>W: 59 (9.1) H: 165.2 (14.8)</td>
<td>NA</td>
<td>ERA: 87.5%</td>
<td>Ex T: 364 (50) Control: 442 (193)</td>
<td>100% CHD</td>
<td></td>
</tr>
<tr>
<td>Fox et al 2011¹⁷</td>
<td>52 (19)</td>
<td>Ex T: 11 Control: 11 (Women: 68%)</td>
<td>W: 69.5 (37.3) H: NA</td>
<td>NA</td>
<td>ERA: 63% PD5-I: 45% Mono: 54% Combi: 45%</td>
<td>Ex T: 8.2 (1.9) Control: 11.6 (5.5)</td>
<td>Ex T: 353 (60) Control: 425 (80)</td>
<td>45% IPAH</td>
</tr>
<tr>
<td>Chan et al 2013²²</td>
<td>54 (10)</td>
<td>Ex T: 10 Control: 13 (Women: 100%)</td>
<td>BMI: 31 (7.2)</td>
<td>91% class II/III Mono: 30% Dual: 26% Triple: 39%</td>
<td>Ex T: 17.6 (5.7) Control: 14.7 (5.1)</td>
<td>Ex T: 411 (73) Control: 377 (97)</td>
<td>74% CTD</td>
<td>4% drug induced</td>
</tr>
<tr>
<td>Ley et al 2013²³</td>
<td>50 (11)</td>
<td>Ex T: 10 Control: 10 (Women: 70%)</td>
<td>W: 72.5 (14.0) H: 166.5 (8.5)</td>
<td>20% class II 80% class III Mono: 25% Dual: 60%</td>
<td>Control: 449 (80) Control: 423 (101)</td>
<td>Ex T: 13.8 (4.0) Control: 12.7 (4.0)</td>
<td>71% PAH</td>
<td>55% IPAH</td>
</tr>
<tr>
<td>Weinstein et al 2013²⁷</td>
<td>54 (10)</td>
<td>Ex T: 11 Control: 13 (Women: 100%)</td>
<td>BMI: 30.8 (7.2)</td>
<td>50% class II 42% class III Mono: 29% Dual: 25%</td>
<td>Control: 412 (69) Control: 383 (96)</td>
<td>Ex T: 453+91 Control: 413+95</td>
<td>7% CTEPH</td>
<td>25% IPAH</td>
</tr>
<tr>
<td>Ehlken et al 2015²⁹</td>
<td>56 (15)</td>
<td>Ex T: 46* Control: 41 (Women: 54%)</td>
<td>H: 170.5 (8) W: 77 (18)</td>
<td>Class II: 16% Class III: 76% Mono: 31% Combi: 60%</td>
<td>Ex T: 13.3+ (3.6) Con: 12.7+ (4.0)</td>
<td>Ex T: 453+91 Con: 413+95</td>
<td>29% CTEPH</td>
<td></td>
</tr>
<tr>
<td>Becker-Grünig et al 2013³¹</td>
<td>48 (11)</td>
<td>Ex T: 20 Control: 20 (Women: 80%)</td>
<td>W: 74 (18) H: 166 (8)</td>
<td>30% class II 70% class III Mono: 25% PD5-I: 60%</td>
<td>Ex T: 11.4 (2.2) Ex T: 11.8 (3.4) Ex T: 386 (121)</td>
<td>Ex T: 423 (90) Ex T: 424 (101)</td>
<td>100% CHD</td>
<td>02% CHD</td>
</tr>
<tr>
<td>Grünig et al 2012²⁰</td>
<td>52 (18)</td>
<td>Ex T: 21 Control: 13 (Women: 95%)</td>
<td>W: 68 (11) H: 165 (6)</td>
<td>43% class II 33% class III Mono: 38% Dual: 48%</td>
<td>Ex T: 13.8 (4.1) Ex T: 386 (121)</td>
<td>Ex T: 425 (106) Ex T: 424 (101)</td>
<td>100% CTD</td>
<td>17% CTEPH</td>
</tr>
<tr>
<td>Grünig et al 2011³⁸</td>
<td>51 (12)</td>
<td>Ex T: 58 Control: 58 (Women: 72%)</td>
<td>W: 72 (12) H: 168 (9)</td>
<td>17% class II Mono: 66% Ex T: 12.5 (3.0) Ex T: 440 (90)</td>
<td>Ex T: 12.8 (3.0) Ex T: 440 (90)</td>
<td>Ex T: 441 (75) Ex T: 441 (75)</td>
<td>64% IPAH</td>
<td>10% CTEPH</td>
</tr>
<tr>
<td>Mainguy et al 2010³⁰</td>
<td>40 (15)</td>
<td>Ex T: 5 Control: 5 (Women: 80%)</td>
<td>W: 75 (20) H: 161 (8)</td>
<td>60% class II 40% class III PD5-I: 20%</td>
<td>Ex T: 12.1 (1.7) Ex T: 408 (108)</td>
<td>Ex T: 425 (106) Ex T: 424 (101)</td>
<td>100% CTEPH</td>
<td></td>
</tr>
<tr>
<td>Nagel et al 2012²⁷</td>
<td>61 (15)</td>
<td>Ex T: 35 Control: 35 (Women: 46%)</td>
<td>W: 78 (13) H: 170.5 (10)</td>
<td>20% class II 74% class III Mono: 49% Combi: 46%</td>
<td>Ex T: 12.1 (1.7) Ex T: 408 (108)</td>
<td>Ex T: 425 (106) Ex T: 424 (101)</td>
<td>100% CTEPH</td>
<td></td>
</tr>
<tr>
<td>De Man et al 2009³³</td>
<td>42 (13)</td>
<td>Ex T: 19 Control: 19 (Women: 79%)</td>
<td>W: 72 (14) H: 170 (9)</td>
<td>NA Mono: 42% Combi: 58%</td>
<td>Ex T: 12.1 (1.7) Ex T: 408 (108)</td>
<td>Ex T: 425 (106) Ex T: 424 (101)</td>
<td>100% IPAH</td>
<td>100% CTEPH</td>
</tr>
</tbody>
</table>
| Kabitz et al 2014³⁴  | 60 (11)     | Ex T: 7 Control: 7 (Women: 57%) | BMI: 24.9 (4.8) | 86% class III 14% class IV ERA: 28% PD5-I: 86% | Ex T: 147 (51) | Ex T: 417 (51) | 72% IPAH | 28% CTD | (Continued)
control arms. The mean 6MWD at baseline among training participants in the parallel group trials studies was 411.6 m (SD, 43.6). Furthermore, change in 6MWD from baseline to follow-up was significantly greater among exercise training participants than control participants (WMD, 60.2 m; 95% CI, 36.8–83.5; Figure 2B).

### Table 2. Exercise Training and Control Group Interventions in the Included Parallel Group Trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Exercise Training Group Intervention</th>
<th>Control Group Intervention</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Quintana et al 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>• Supervised endurance training 3 times per week (track walking+cycling)</td>
<td></td>
<td>16 wk</td>
</tr>
<tr>
<td></td>
<td>• Week 1 to 2: exercise at 40% to 50% of peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Week 3 to 16: exercise at 60% to 70% of peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
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</tr>
<tr>
<td>Mereles et al 2006&lt;sup&gt;14&lt;/sup&gt;</td>
<td>• Interval bicycle ergometer training 7 d/wk at low workloads</td>
<td>Common rehabilitation program based on healthy nutrition, physical therapy such as massages, inhalation, counseling, and muscular relaxation without exercise and respiratory training</td>
<td>15 wk</td>
</tr>
<tr>
<td></td>
<td>• Exercise intensity at 60% to 80% of peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• 60 min of walking 5 d/wk</td>
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<tr>
<td></td>
<td>• 5 d/wk of 30 min of resistance training</td>
<td></td>
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<tr>
<td></td>
<td>• 30 min of respiratory training 5 d/wk</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• 3 wk in hospital supervised training followed by 12 wk training at home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al 2013&lt;sup&gt;12&lt;/sup&gt;</td>
<td>• Aerobic training+education intervention</td>
<td>Education intervention only with 1 h lecture on different aspects of the disease</td>
<td>10 wk</td>
</tr>
<tr>
<td></td>
<td>• 24–30 sessions of medically supervised treadmill walking for 30–45 min per session. Target exercise intensity of 70% to 80% of each patient’s heart rate (HR) reserve obtained from the baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fox et al 2011&lt;sup&gt;17&lt;/sup&gt;</td>
<td>• Supervised 24 biweekly 1-h sessions of exercise training in two 6-wk blocks</td>
<td>Usual care with maintenance of routine daily activities and no specific exercise intervention</td>
<td>12 wk</td>
</tr>
<tr>
<td></td>
<td>• Exercise intensity at 60% to 80% of peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In the first block, subjects did interval training with treadmill walking, cycling, and step climbing</td>
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<tr>
<td></td>
<td>• In the second block, subjects performed longer periods of continuous aerobic exercise, with resistance training</td>
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<tr>
<td>Ley et al 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Same as Mereles et al 2006&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Usual care with maintenance of routine daily activities and no specific exercise intervention</td>
<td>3 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-h education session about the disease twice a week</td>
<td>10 wk</td>
</tr>
<tr>
<td>Weinstein et al 2013&lt;sup&gt;16&lt;/sup&gt;</td>
<td>• Supervised training 24–30 sessions over 10 wk</td>
<td>Usual care with maintenance of routine daily activities and no specific exercise intervention</td>
<td>12 mo</td>
</tr>
<tr>
<td></td>
<td>• Treadmill walking for 30–45 min/session at a target exercise intensity range of 70% to 80%</td>
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<td></td>
<td>• Supervised training 2 d/wk for 3 mo followed by home training</td>
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<td></td>
<td>• Training sessions with 10 min of warming up+a brief period of resistance exercises+an interval of bicycle ergometer training during 24 min with bases at 10–25 W and 30-s peaks of 20–50 W</td>
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</tr>
<tr>
<td>Ehlken et al 2015&lt;sup&gt;20&lt;/sup&gt;</td>
<td>• In-hospital training for 3 wk with at least 1.5 h/d exercise consisting of interval cycle ergometer training at low workloads 7d/wk</td>
<td>Usual care</td>
<td>15 wk</td>
</tr>
<tr>
<td></td>
<td>• Walking, dumbbell training of single muscle groups using low weights and respiratory training at 5 d/wk</td>
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<tr>
<td></td>
<td>• The training was continued at home with at least 15 min/d at 5 days a week for the following 12 wk</td>
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</tbody>
</table>
minute (SD, 2.4). We observed a significant heterogeneity on pooled analysis of studies reporting peak relative (mL/kg per minute; F=56.5%) and absolute oxygen uptake (mL/min; F=63.8%) at baseline and follow-up. Pooling across all studies that reported peak oxygen uptake at baseline and after exercise training showed that exercise training was associated with a significant improvement in peak relative oxygen uptake (WMD, 1.8 mL/kg per minute; 95% CI, 1.4–2.3; Figure 3A) and peak absolute oxygen uptake (WMD, 135.8 mL/min; 95% CI, 80.1–191.5; Figure 3B) from baseline to follow-up.

Effect of Exercise Training on Resting Pulmonary Arterial Systolic Pressure
Eight studies estimated resting pulmonary arterial systolic pressure among study participants using Doppler echocardiography (n=7 studies) or right heart cath (n=1 study) before and after exercise training. Pooling across these studies showed that exercise training was associated with a significant improvement in resting pulmonary artery systolic pressure from baseline to follow-up (WMD, −3.7 mmHg; 95% CI, −5.4 to −1.9; Figure 4A). Furthermore, we did not observe any significant heterogeneity among the studies included in the pooled analysis (F=0.0%).

Effect of Exercise Training on Peak Exercise Heart Rate
Nine studies reported the peak exercise heart rate among study participants before and after exercise training. Pooling across these studies showed that exercise training was associated with a significant improvement in peak exercise heart rate from baseline to follow-up (WMD, 10 beats per min; 95% CI, 6–15; Figure 4B).

Effect of Exercise Training on Quality of Life
Impact of exercise training on quality of life was assessed in detail in 4 pre–post intervention trials. Pooled analysis across these 4 studies showed a significant improvement in quality of life as measured by the SF-36 questionnaire subscale scores (Table 4).

Safety of Exercise Training
Exercise training was well tolerated among the participants of most included studies. On pooled analysis, overall dropout rate from exercise training was <1%. Episodes of dizziness, presyncope, syncope, palpitations, hypotension, or oxygen desaturation were observed in 4.7% of training participants, two-third of which were related to exercise training. Episodes of respiratory and nonrespiratory infections that lead to an interruption in exercise training occurred in 6.6% participants. Furthermore, no major adverse events, such as progression of symptoms, progression of PH, right heart failure, or death, were reported among the participants during the training period (Table 5). Four pre–post training studies reported long-term follow-up data (>2 years) among exercise-training participants (n=134). On median follow-up of 29.5 months (range, 21–36 months), the proportion of participants alive was 91% (12 deaths), and the proportion of participants with transplant-free survival was 89%.
Discussion

The principal finding of this systematic review and meta-analysis of patients with established chronic pulmonary hypertension is that exercise training is associated with a significant improvement in exercise capacity and cardiorespiratory fitness from baseline to follow-up (Δ 6MWD, 53.3 m; Δ peak VO₂, 1.8 mL/kg per minute). There was also a significant reduction in resting pulmonary arterial systolic pressure and an improvement in peak exercise heart rate after exercise training (Δ pulmonary arterial systolic pressure, 3.7 mm Hg; Δ peak exercise heart rate, 10 beats per minute). Furthermore, exercise training was well tolerated among these patients and was associated with significant improvements in quality of life. Taken together, these findings suggest that exercise

Figure 2. Forest plot showing effect of exercise training on 6-minute walk distance on pooled analysis of all included studies14–29 (A) and parallel group trials with an intervention and control arm only14,17,22,26,29 (n=6; B). CI indicates confidence interval.
training could be used as a safe and effective adjunctive treatment strategy among stable and well-compensated patients with chronic pulmonary hypertension.

Our study has important clinical implications. Exercise training and cardiac rehabilitation are strongly recommended for patients with chronic cardiopulmonary conditions, such as heart failure and COPD.12,13 Similarly, the recent treatment guidelines for pulmonary hypertension have upgraded the recommendations for exercise training among these patients to a class IA status.37 However, clinicians have traditionally been skeptical about the use of exercise training and cardiopulmonary rehabilitation for management of chronic pulmonary hypertension because of concerns of exertional syncope and progressive right ventricular dysfunction with strenuous physical activity.38–40 Contrary to these notions, our study findings provide comprehensive evidence in favor of efficacy and safety of exercise training in patients with pulmonary hypertension and highlight its potential role as an adjunct to medical therapy designed to alleviate symptoms in patients with pulmonary hypertension.

We observed significant improvements in exercise tolerance, measured as 6MWD, with exercise training. Previous studies have established an association between 6MWD and long-term clinical outcomes in patients with pulmonary hypertension.41 In a recent study, improvement in 6MWD of >41.8 m was found to correlate with lower odds of a clinical event at 12 weeks.42 As a result, improvement in 6MWD has been used as a surrogate endpoint in pulmonary hypertension trials.43 In this study, we observed up to 53 m improvement in 6MWD at 15 weeks with exercise training on pooled analysis, which is greater than that reported with pulmonary hypertension-specific pharmacotherapies.44 Furthermore, we observed significant improvement in resting systolic pulmonary arterial pressure with exercise training, suggesting that exercise training has a favorable disease-modifying effect, similar to that observed with well-established pharmacotherapies.44 Future studies are needed to determine whether these favorable effects of exercise training can translate into a reduction in long-term major adverse clinical outcomes.
The mechanisms underlying improvement in exercise tolerance with exercise training among patients with pulmonary hypertension are not well understood. Studies in animal models of pulmonary hypertension have shown that exercise training is associated with improvement in endothelium-dependent relaxation in the pulmonary circulation, favorable remodeling of pulmonary vasculature, and reduced right ventricle end-diastolic pressure. Studies in human pulmonary hypertension have shown that exercise training is associated with significant improvements in central pulmonary perfusion and peripheral skeletal muscle function, which could also contribute to the training-related improvement in exercise capacity. In this study, we observed a significant improvement in the pulmonary arterial systolic pressure with training, which could lead to significant reductions in pulmonary vascular resistance and a concomitant improvement in blood flow through the pulmonary vascular system. Improved pulmonary perfusion would be associated with improved oxygenation and cardiac output, thus leading to improvement in exercise tolerance and cardiorespiratory fitness. We also observed a significant increase in peak exercise heart rate with exercise training that could contribute toward improvement in cardiorespiratory fitness among patients with pulmonary hypertension. This is consistent with the findings among patients with heart failure, where partial reversal of the chronotropic incompetence has been shown to contribute to improvements in exercise capacity with exercise training.

The findings from this study also support the safety profile of exercise training among well-compensated patients with pulmonary hypertension. We observed a high degree of tolerance to training with low dropout rates and exercise-associated adverse events comparable with that observed with exercise training in patients with heart failure. Furthermore, the rate of major adverse events, such as right heart failure, mortality, and worsening pulmonary hypertension observed on pooled analysis, was much lower than that reported in pulmonary hypertension.
hypertension–specific pharmacotherapy trials. In a meta-analysis of randomized control trials performed in patients with pulmonary hypertension, Galie et al\(^44\) reported an overall mortality rate of 1.5% in the actively treated group in 14 weeks of mean observation period. In contrast, no deaths were reported among the exercise-training participants across all the included studies in the 15 weeks of median training period. This could be related to the difference in severity of the condition between participants with pulmonary hypertension recruited for pharmacotherapy trials versus exercise training studies. The rate of nonexercise-related adverse events, such as infections, was also not different from what has been reported in pulmonary hypertension registries.\(^49\) Taken together, our study findings suggest that exercise training regimens can be safely implemented for management of chronic pulmonary hypertension.

Several important aspects of exercise training protocols implemented in the included studies are noteworthy. All studies used supervised exercise training protocols, particularly for the first few weeks of training. Furthermore, the exercise-training protocols used in most studies were at a lower workload when compared with current exercise recommendations for heart failure patients.\(^50\) Moreover, the majority of exercise-training participants belonged to class I or class IV pulmonary hypertension, therefore, the benefits of exercise training observed in this may not be applicable to patients with other classes of pulmonary hypertension. Finally, exercise training was implemented only in medically stable patients with no recent change in the medication regimen. These characteristics should be considered when recommending exercise training to patients with pulmonary hypertension.

There are several limitations in this study. First, we only have a limited number of clinical trials that have assessed the safety and efficacy of exercise training among patients with pulmonary hypertension. Two of the 6 parallel group trials included in the pooled analysis were nonrandomized, and the sample size of included studies is small. This highlights the significance of pooled analysis that has been conducted in this study. Second, most of the included studies have not evaluated clinical end points, such as mortality and hospitalization events; therefore, we were unable to assess the impact of exercise training on these clinical end points. Third, it is difficult to evaluate the sustainability of effects of exercise-training intervention on exercise capacity among patients with pulmonary hypertension in this study. Fourth, most of the included studies were single-center based and had a relatively short duration of follow-up. Future multicenter randomized control trials with longer duration follow-up are needed to

<p>| Table 4. Pooled Estimates for Changes in Quality of Life Subscale Scores With Exercise Training Among Participants With Pulmonary Hypertension |</p>
<table>
<thead>
<tr>
<th>SF-36 Subscale</th>
<th>Studies (n)</th>
<th>Pooled SMD (95% CI)</th>
<th>I(^2) (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>4</td>
<td>0.45 (0.2–0.7)</td>
<td>9.7% (0.34)</td>
</tr>
<tr>
<td>Role: physical</td>
<td>4</td>
<td>0.32 (0.05–0.57)</td>
<td>22.0% (0.27)</td>
</tr>
<tr>
<td>General health perception</td>
<td>4</td>
<td>0.26 (0.02–0.50)</td>
<td>0% (0.99)</td>
</tr>
<tr>
<td>Vitality</td>
<td>4</td>
<td>0.44 (0.20–0.68)</td>
<td>0% (0.61)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>4</td>
<td>0.32 (0.08–0.56)</td>
<td>0% (0.82)</td>
</tr>
<tr>
<td>Role: emotional</td>
<td>4</td>
<td>0.32 (0.08–0.56)</td>
<td>0% (0.48)</td>
</tr>
<tr>
<td>Mental health</td>
<td>4</td>
<td>0.26 (0.02–0.51)</td>
<td>15.7% (0.31)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; SF-36, short form health survey; and SMD, standardized mean difference.

### Table 5. Training-Associated Adverse Effects Reported in Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No. of Exercise Training Participants</th>
<th>Exercise Training–Related Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mereles et al 2006(^{14})</td>
<td>15</td>
<td>Dizziness in 2 patients, low oxygen saturation in 1 patient</td>
</tr>
<tr>
<td>Martinez-Quintana et al 2010(^{20})</td>
<td>4</td>
<td>Exercise intolerance with cyanosis in 2 patients</td>
</tr>
<tr>
<td>Fox et al 2011(^{17})</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>Chan et al 2013(^{22})</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>Ley et al 2013(^{23})</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>Weinstein et al 2013(^{20})</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>Ehiken et al 2015(^{24})</td>
<td>46</td>
<td>None</td>
</tr>
<tr>
<td>Becker-Grünig et al 2013(^{21})</td>
<td>20</td>
<td>None</td>
</tr>
<tr>
<td>Grünig et al 2012(^{26})</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>Grünig et al 2011(^{16})</td>
<td>58</td>
<td>Dizziness with training in 2 patients</td>
</tr>
<tr>
<td>Grünig et al 2012(^{19})</td>
<td>183</td>
<td>Dizziness with training in 2 patients</td>
</tr>
<tr>
<td>Mainguy et al 2010(^{18})</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>Nagel et al 2012(^{27})</td>
<td>35</td>
<td>Syncope during exercise in 1 patient</td>
</tr>
<tr>
<td>De Man et al 2009(^{31})</td>
<td>19</td>
<td>Herpes zoster in 1 patient</td>
</tr>
<tr>
<td>Kabitz et al 2014(^{24})</td>
<td>7</td>
<td>Minor dizziness in 2 patients</td>
</tr>
<tr>
<td>Inagaki et al 2014(^{23})</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>Ihle et al 2014(^{33})</td>
<td>17</td>
<td>One patient with hypotension during training</td>
</tr>
</tbody>
</table>
better characterize the long-term benefits of exercise training in these patients. Finally, as with all meta-analyses, selection bias cannot be completely ruled out because articles were only retrieved from published trials.

In conclusion, exercise training is associated with significant improvement in exercise capacity, cardiorespiratory fitness, and quality of life among patients with pulmonary hypertension. Future studies with longer follow-up duration are needed to determine whether exercise training can be used to improve long-term clinical outcomes among these patients in the real world.

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Disclosures
None.

References

Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Exercise training and cardiopulmonary rehabilitation are strongly recommended for management of patients with cardiopulmonary conditions, such as heart failure and chronic obstructive pulmonary disease. Despite guideline recommendations supporting exercise training among patients with chronic pulmonary hypertension, clinicians have been skeptical about its use among these patients because of concerns of exertional syncope and right ventricular dysfunction with strenuous physical activity. The findings from this study provide comprehensive evidence in favor of safety and efficacy of exercise training among patients with pulmonary hypertension. The magnitude of improvement in exercise capacity with training among these patients was similar to that reported with pulmonary hypertension–specific pharmacotherapies. Furthermore, a high degree of tolerance to exercise training and low rates of exercise-related adverse events was also observed. Taken together, these findings suggest that exercise training can be safely used as an adjunct to medical therapy to alleviate exercise intolerance and improve quality of life among patients with chronic pulmonary hypertension. This study also provides some insight into the potential mechanisms through which exercise may exert its beneficial effects in these patients. This includes reduction in resting pulmonary artery peak systolic pressure and improvement in peak exercise heart rate among the training participants.
Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis
Ambarish Pandey, Sushil Garg, Monica Khunger, Sonia Garg, Dharam J. Kumbhani, Kelly M. Chin and Jarett D. Berry

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**Supplemental Table 1.** Etiology of Pulmonary hypertension among exercise training participants included in the pooled analysis

<table>
<thead>
<tr>
<th>Pulmonary hypertension Class#</th>
<th>Total Participants N (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I pulmonary hypertension</td>
<td>308 (73.8%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>176</td>
</tr>
<tr>
<td>CTD</td>
<td>67</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>41</td>
</tr>
<tr>
<td>Hereditary</td>
<td>8</td>
</tr>
<tr>
<td>Drug Induced</td>
<td>4</td>
</tr>
<tr>
<td>HIV associated</td>
<td>4</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>8</td>
</tr>
<tr>
<td>Class II pulmonary hypertension (Left Sided Heart Failure)</td>
<td>8 (1.9%)</td>
</tr>
<tr>
<td>Class III pulmonary hypertension (Related to lung disease)</td>
<td>14 (3.4%)</td>
</tr>
<tr>
<td>Class IV pulmonary hypertension (Chronic thromboembolic)</td>
<td>85 (20.4%)</td>
</tr>
<tr>
<td>Others (not otherwise classified)</td>
<td>2 (0.5%)</td>
</tr>
</tbody>
</table>

Pulmonary hypertension classes I, II, III & IV based on the updated classification published in 2013.

% Out of 417 exercise training participants since 1 study (Ilhe et al1, N= 17) did not report the etiology of pulmonary hypertension among its study participants

CTD: connective tissue disorder
**Supplemental Table 2.** Inclusion and exclusion criteria used in the included control studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
</table>
| Mereles et al 2006    | • Patients with severe chronic PAH who were stable and compensated under optimized medical therapy for at least 3 months  
• World Health Organization (WHO) functional class II to IV  
• No recent syncope or skeletal muscle disorder | Patients not meeting inclusion criteria                                                                                                                                                                         |
| Martinez-Quintana et al 2010 | • Patients with age ≥14 years who were clinically stable with no change in PAH medications over last 6 months  
• New York Heart Association (NYHA) functional class ≥II/IV | Patients not meeting inclusion criteria                                                                                                                                                                          |
| Fox et al 2011        | • Patients with RHC mPAP >25 mm Hg at rest, PCWP ≤15 mm Hg; PVR ≥3 Wood Units  
• Clinically stable on PAH-specific medication for 3 months  
• New York Heart Association (NYHA) functional class II-III. | • NYHA class I or IV (safety concerns); PAH due to CHD with a right-to-left shunt, left heart disease, chronic hypoxemia, or chronic lung diseases (defined as total lung capacity or forced exhaled volume in 1 second ≤60% of predicted);  
• Acute intercurrent illness requiring hospital admission in the month preceding screening  
• Any non-PAH medical condition likely to interfere with participation in or completion of the program.  
• Participation in another rehabilitation scheme within 6 months of enrollment. |
| Chan et al 2013       | • Patients with WHO group I PAH  
• PH diagnosed by a RHC resting mPAP ≥ 25 mm Hg  
• On stable PAH therapies for at least 3 months  
• Sedentary, and had no pulmonary rehabilitation for last 6 months | • WHO and NYHA class I or IV  
• FEV 1/FVC ratio ≤65%  
• Hx of ischemic heart disease;  
• EF ≤40%; documented PCWP ≥ 18 mm Hg  
• Significant hepatic, renal, or mitochondrial dysfunctions;  
• Severe psychiatric disease  
• Use of medications that may limit exercise  
• Antiretroviral therapies; drug abuse; tobacco use; pregnancy. |
| Ley et al 2013        | • Patients ≥ 18 years of age  
• Stable under optimized medical therapy) for at least 3 months  
• WHO functional class II to III  
• No recent syncope, and no skeletal or muscle disorders | • Patients ≤ 18 years of age  
• NYHA class I or IV  
• Others not meeting the inclusion criteria |
| Weinstein et al 2013⁷ | - Patients ≥ 21 years of age  
- Not pregnant, Tobacco free  
- Stable under optimized medical therapy) for at least 3 months  
- WHO functional class II to III  
- No recent syncope, and no skeletal or muscle disorders | - Recent Participation in an exercise program  
- WHO function class I or IV  
- >400 feet or < 50 feet six minute walk distance at baseline  
- EF < 40%, ischemic cardiomyopathy, beta blocker use  
- Severe obstructive pulmonary disease  
- Significant hepatic, renal or metabolic abnormalities |

PAH: Pulmonary arterial Hypertension; RHC: Right heart catheterization; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; CHD: Congenital heart disease; FEV1: Forced expiratory volume (1 second); FVC: Forced vital capacity; Hx: History; EF: Ejection Fraction; PCWP: Pulmonary capillary wedge pressure; WHO: World Health Organization
### Supplemental Table 3. Inclusion and exclusion criteria used in the included pre-post studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
</table>
| Becker Grunig et al 2013<sup>8</sup> | - Adult patients with invasively confirmed severe chronic congenital heart disease associated PAH, who received exercise training between 9/08 and 10/11  
- Patients on optimized stable advanced medical therapy for PAH for at least 2 months  
- Those with PAH who were newly diagnosed had an interval of at least 6 months between initiation of a new PAH-targeted medical treatment and the start of exercise training | Patients not meeting inclusion criteria |
| Grunig et al 2012<sup>9</sup> | - Patients with guideline based diagnosis connective tissue disease associated PAH who received exercise training as an add-on to disease-targeted medication between 10/07 & 7/11  
- Patients classified as WHO-FC II to IV  
- Patients on optimized medical therapy for PAH and for the underlying rheumatologic disease for at least 2 months before entering the study. | - Patients with severe interstitial lung disease excluded  
- 1 patient excluded on follow-up due to development of respiratory tract infection |
| Grunig et al 2011<sup>10</sup> | - Severe chronic PAH and right heart failure with diagnosis established according to current guidelines who received exercise and respiratory training as add-on to disease-targeted medication between 1/03 & 4/07  
- WHO FC II–IV  
- Patients had to be stable and compensated with optimized medical therapy for at least 3 months before entering the study. | - 1 Patient excluded due to presence of underlying mitral stenosis as a etiology for PAH  
- 1 patient excluded due to changes in PAH specific medications  
- 1 patient excluded due to familial reasons |
| Grunig et al 2012<sup>11</sup> | - Patients with severe chronic PH who received exercise and respiratory training as add-on to disease-targeted medication between 1/05 & 10/10.  
- WHO FC II–IV  
- Stable on optimized medical therapy for at least 2 months before entering the study.  
- Patients newly diagnosed with PH had an interval of 2–6 months between initiation of a new PH-targeted medical treatment and the start of exercise training. | - Clinically unstable course (6 Patients)  
- Lower extremity muscle palsy (1 Patient)  
- PAD impairing 6MWD (1 patient)  
- Familial problems (2 patients);  
- MRSA infection (1 patient) |
| Mainguy et al 2010<sup>12</sup> | - WHO FC II to III participants with IPAH  
- All patients had significant PAHTN defined as a mPAP > 25 mm Hg at rest with a PCWP< 15 mm Hg.  
- Stable on optimized medical therapy for at least 6 months before entering the study. | Patients with other causes of PH, as well as those with musculoskeletal abnormalities  
- Patients with recent syncope and functional class IV patients |
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Nagel et al 2012  | - Patients with CTEPH and WHO-FC II–IV who received exercise and respiratory therapy as add-on to PH-targeted medication between 06/06 & 10/11  
- Patients had to be stable under optimized medical therapy for at least 2 months prior to enrollment.                                                                 | - 2 excluded due to a change in their PA-targeted medication 2–4 weeks before training  
- 2 excluded due to misdiagnosis                                                                                                                          |                                                                    |
| De Man et al 2009 | - Diagnosed with iPAH according to WHO criteria established by RHC  
- Stable clinical condition, defined as a change in 6-min walk distance (6MWD) of <10% in three consecutive measurements prior to inclusion (over a period of minimally 1 yr.), and no change in medical therapy for > 3 months | Patients not meeting inclusion criteria                                                                                                                         |                                                                    |
| Kabitz et al 2014 | - PAH in WHO-FC II–IV, no recent syncope, who underwent combined exercise, and respiratory training as an adjunct to disease-targeted medication.  
- The diagnosis of “PAH” was established in accordance with the current clinical classification of PH.  
- Stable on optimal medical therapy for at least 2 months before study inclusion | Exclusion criteria covered patients with left heart disease, lung disease, rib cage abnormalities, neuromuscular disorders or cachexia, and systemic steroid therapy |                                                                    |
| Inagaki et al 2014| - Outpatients with inoperable or residual CTEPH who were stable on disease-targeted medication for at least 3 months  
- Age between 18 and 80 years and a WHO functional class of II–IV.                                                                                                                                   | Individuals with other unstable/severe pulmonary disease or cardiac, orthopedic, or neurological disorders limiting exercise performance |                                                                    |
| Ihle et al 2014   | - Clinically stable patients on optimized targeted PH therapy  
- For at least 3 months before enrollment  
- Confirmed PH diagnosis by our institution according to the standard haemodynamic criteria at right-heart catheterization  
- WHO FC II-III                                                                                                                                      | WHO FC I or IV  
- Ailments associated with a contraindication for physical workout  
- Pulmonary HTN due to left heart disease  
- Patients with nerves and motor dysfunction as well as with psychological problems |                                                                    |

PAH: Pulmonary arterial Hypertension; PH: Pulmonary hypertension; RHC: Right heart catheterization; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; CHD: Congenital heart disease; FEV1: Forced expiratory volume (1 second); FVC: Forced vital capacity; Hx: History; EF: Ejection Fraction; PCWP: Pulmonary capillary wedge pressure; WHO FC: World Health Organization functional class; CTEPH: Chronic thromboembolic pulmonary hypertension; 6MWD: Six minute walk distance
**Supplemental Table 4. Quality assessment of included pre-post studies**

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Question Clearly Stated</th>
<th>Eligibility/Selection Criteria</th>
<th>Participants Representative</th>
<th>Entry Criteria Enrolled</th>
<th>Sample Size Large</th>
<th>Test/Intervention Consistent</th>
<th>Outcome Measures Prespecified</th>
<th>Participants Blinded</th>
<th>Loss to Follow-up Accounted for</th>
<th>Statistical Changes Examined</th>
<th>Interrupted Time-Series Design</th>
<th>Statistical Tests for Changes</th>
<th>Statistical Analysis Individual-Level Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker 2013</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Grunig 2012</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Grunig 2012</td>
<td>Y</td>
<td>Y</td>
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<tr>
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<td>Y</td>
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<td>Y</td>
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<tr>
<td>De Man 2009</td>
<td>Y</td>
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<td>Y</td>
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<tr>
<td>Kabitz 2014</td>
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<td>Y</td>
<td>Y</td>
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Supplemental Figure 1. Publication bias assessment in the included studies
Supplemental Figure 2. Meta-regression of change in six-minute walk distance with age
References


