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

Pandey et al: Exercise Training in Pulmonary Hypertension

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Abstract

**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 COPD. 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 six-minute walk distance (6MWD). We also assessed the effect of exercise on peak oxygen uptake (VO\textsubscript{2peak}), resting pulmonary arterial systolic pressure (PASP), peak exercise heart rate (HR\textsubscript{peak}), and quality of life. A total of 16 studies with 434 exercise-training participants were included. In the pooled analysis, exercise training was associated with significant improvement in 6MWD [Weighted mean difference (WMD): 57.7 meters (95% CI: 42.5 to 72.8)], VO\textsubscript{2peak} [WMD = 1.7 ml/kg/min (95% CI: 1.3 to 2.0)], PASP [WMD = -3.6 mmHg (95% CI = -5.8 to -1.4)], HR\textsubscript{peak} [WMD = 10.4 beats per min (95% CI: 5.5 to 15.3)], 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 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.

**Key Words:** exercise training, pulmonary hypertension, exercise intolerance, cardiorespiratory fitness
Pulmonary hypertension is a chronic cardiopulmonary disorder characterized by progressive increasing pulmonary vascular resistance, leading to right ventricular heart failure.\textsuperscript{1} Prevalence of pulmonary hypertension is estimated to be 10 to 15 cases per million with a mortality rate of 15% per year.\textsuperscript{2} Over the past two decades, targeted pharmacological therapies have been effective in reducing disease progression and improving the survival rate among patients with pulmonary hypertension.\textsuperscript{3,4} However, most patients remain symptomatic with significant exercise intolerance and reduced quality of life despite being on optimal medical therapy.\textsuperscript{5,6} Thus, there is an unmet need for adjunctive therapeutic strategies to improve exercise tolerance and quality of life among these patients.

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.\textsuperscript{7} 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.\textsuperscript{7-9} 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 pulmonary hypertension patients.\textsuperscript{10,11}

Exercise training has been shown to improve cardiorespiratory fitness, functional status, and clinical outcomes in patients with cardiopulmonary conditions such as heart failure and COPD.\textsuperscript{12,13} Considering the overlap in the pathophysiological derangements in pulmonary hypertension and these conditions, it can be hypothesized that similar benefits of exercise training may be derived in pulmonary hypertension patients. Several small studies have evaluated exercise training as an
adjunctive therapeutic strategy in patients with chronic pulmonary hypertension. While most of these studies were small and not designed to address clinical endpoints 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 regarding the benefit of structured exercise training programs in pulmonary hypertension patients, 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.

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, PAH, exercise, exercise training, pulmonary rehabilitation, cardiac rehabilitation, and cardiopulmonary rehabilitation for articles published between January 1st 1960 to April 15th 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 non-randomized 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 etiology (Figure 1). The primary outcome of
our study was change in exercise capacity measured as six-minute walk distance from baseline to
follow-up. Secondary outcomes included change in cardiorespiratory fitness (measured as change in
peak oxygen uptake in ml/kg/min), 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 one of the above pre-defined 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 two authors (AP and MK) using a
standardized questionnaire. All discrepancies concerning study inclusion or outcomes were resolved
by the senior author (JB). In cases of multiple publications arising from a single trial, only the
updated trial publication with the maximum number of patients was included. 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, SF-36 score),
dropout rates and adverse events. Both fatal and non-fatal 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)32 and Comprehensive Meta-analysis Software (Biostat, Englewood, NJ, USA).
In each trial, the effect size of exercise training was calculated as the difference between pre and
post-intervention measure of the continuous outcome variables (six-minute walk distance and peak
oxygen uptake) in the aerobic exercise trained participants. Each mean difference was weighted according to the inverse variance method and pooled across each trial using a random effects model. 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 aerobic exercise trained 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 (six minute walk distance). 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. Since the majority of our included studies were not randomized trials, we calculated the pooled incidence of adverse events (fatal and non-fatal) 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. Quality assessment of pre-post interventional studies was performed using the NIH quality assessment tool. Publication bias was assessed using the funnel plots and quantified by Begg’s Mazumdar test. All p-values were two-tailed with statistical significance specified at 0.05 and confidence intervals (CI) reported at the 95% level.

**Results**

**Study Characteristics:** We included 434 (71% women) exercise-training participants from 16 studies. This included 6 parallel group trials with an intervention and a control arm (4 randomized and 2 non-randomized trials) and 10 pre-post studies. 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 (Ilhe, et al.\textsuperscript{28}) did not provide information on underlying etiology of pulmonary hypertension among study participants. Among others studies, the majority of training participants had Class I pulmonary hypertension (73.8\%) or class IV (20.4\%) pulmonary hypertension (Supplemental Table 1). A very small proportion of training participants had Class II pulmonary hypertension related to left heart disease (1.9\%) or Class III pulmonary hypertension secondary to chronic lung disease (3.4\%).\textsuperscript{36} 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 presence of NYHA Class I or Class IV symptoms or co-existing conditions that impaired their participation in training (Supplemental Table 2 and 3).

Supervised exercise training protocols were used in all studies with a combination of aerobic (treadmill or cycle ergometer) and resistance training. Five studies trained pulmonary hypertension patients at outpatient rehabilitation centers; nine studies performed in-hospital exercise training for the first few weeks followed by home based exercise training; and one 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 60-80\% of peak exercise capacity in most studies. The study participants had exercise capacity and cardiorespiratory fitness assessment at baseline and follow up (Table 2 and 3)

\textit{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 was observed in 2 of the 4 included control trials. Incomplete outcome data or selective reporting of results was not observed in any of the selected studies. Quality assessment of pre-post interventional studies has been detailed in Supplemental Table 4. All
included studies had a clearly stated study question, prespecified 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 = 0.76; p-value = 0.63, Supplemental Figure 1)

**Effect of Exercise training on six-minute walk distance:** All included studies reported six-minute walk distance at baseline and after exercise training. Mean six-minute walk distance at baseline in the included studies was 414.3 m (SD: 35.7). We observed a significant heterogeneity on pooled analysis of studies reporting six-minute walk distance (I^2= 85%) at baseline and follow-up. Pooling across all studies using random effects analysis showed that exercise training was associated with a significant improvement in six-minute walk distance from baseline to follow-up. [Weighted mean difference (WMD): 57.7 m (95% CI: 42.5 to 72.8 m); Figure 2 panel A]. Meta-regression analysis showed a significant association of baseline age with the pooled WMD for six-minute walk distance (meta-regression coefficient = 0.02; P-value: 0.003, Supplemental Figure 2). We also performed sensitivity analyses including only data from trials with parallel intervention and control arms. The mean six-minute walk distance at baseline in the parallel group trials studies was 404.7 m (SD: 38.8). Furthermore, change in six-minute walk distance was significantly greater among exercise training participants as compared with control participants [WMD: 67.8 m (95% CI: 39.3 to 96.3); Figure 2 panel B].

**Effect of exercise training on peak oxygen uptake:** Eight studies reported peak relative oxygen uptake (ml/kg/min) at baseline and after exercise training while four studies reported data on
change in peak absolute oxygen uptake (ml/min). The mean peak relative oxygen uptake at baseline in the included studies was 12.4 ml/kg/min (SD: 2.6). We did not observe a significant heterogeneity on pooled analysis of studies reporting peak relative (ml/kg/min; I² = 0%) and absolute oxygen uptake (ml/min; I² = 0%) 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: 1.7 ml/kg/min (95% CI: 1.3 to 2.0); Figure 3 panel A] and peak absolute oxygen uptake [WMD: 107.1 ml/min (95% CI: 74.6 to 139.5); Figure 3 panel B] from baseline to follow up.

**Effect of exercise training on resting pulmonary arterial systolic pressure:** Seven studies estimated resting pulmonary arterial systolic pressure among study participants from tricuspid regurgitation velocity using Doppler echocardiography 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 = -3.6 mmHg (95% CI = -5.8 to -1.4), Figure 4 panel A]. Furthermore, we did not observe any significant heterogeneity among the studies included in the pooled analysis (I² = 0.0%).

**Effect of exercise training on peak exercise heart rate:** Eight 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 = 10.4 beats per min (95% CI: 5.5 to 15.3)]; Figure 4 panel B).

**Effect of exercise training on quality of life:** Impact of exercise training on quality of life was assessed in four pre-post intervention trials. Pooled analysis across these four 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, the overall dropout rate from exercise training was 5%. Episodes of dizziness, pre-syncope, syncope or palpitations were observed in 5.5% of training participants, half of which were related to exercise training (2.2%). Episodes of respiratory and non-respiratory infections that lead to an interruption in exercise training occurred in 6.7% 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 90.2% (13 deaths) and proportion of participants with transplant free survival was 88%.

**Discussion**

The principal finding of this systematic review and meta-analysis of 434 patients with established chronic pulmonary hypertension from 16 studies is that exercise training is associated with a significant improvement in exercise capacity and cardiorespiratory fitness from baseline to follow-up (Δ six-minute walk distance: 58 m; Δ peak VO2: 1.7 ml/kg/min). 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: 3.6 mmHg; Δ peak exercise heart rate: 10 bpm). 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 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 use of exercise training and cardiopulmonary rehabilitation for management of chronic pulmonary hypertension due to 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 six-minute walk distance, with exercise training. Previous studies have established an association between six-minute walk distance and long-term clinical outcomes in pulmonary hypertension patients. 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 six-minute walk distance has been used as a surrogate end-point in pulmonary hypertension clinical trials. 43 In the present study, we observed up to 57 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.\textsuperscript{44} Future studies are needed to determine if 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 pulmonary hypertension patients 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.\textsuperscript{45, 46} Furthermore, recent human studies have shown that exercise training is associated with significant improvements in “central” pulmonary perfusion as well as “peripheral” skeletal muscle function which could also contribute to the training related improvement in exercise capacity.\textsuperscript{17, 25} In the present 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 towards improvement in cardiorespiratory fitness among pulmonary hypertension patients. This is consistent with the findings among heart failure patients where partial reversal of the chronotropic incompetence has been shown to contribute to improvements in exercise capacity with exercise training.\textsuperscript{47}

Findings from the present 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 very low dropout rates and exercise associated adverse events, comparable to that
observed with exercise training in heart failure patients.\textsuperscript{48} Furthermore, the rate of major adverse events such as right heart failure, mortality, worsening pulmonary hypertension observed on pooled analysis was much lower than that reported in pulmonary hypertension specific pharmacotherapy trials. In a meta-analysis of randomized control trials performed in pulmonary hypertension patients, Galie et al\textsuperscript{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 pulmonary hypertension participants recruited for pharmacotherapy trials vs. exercise training studies. The rate of non-exercise related adverse events such as infections was also not different from what has been reported in pulmonary hypertension registries.\textsuperscript{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 as compared with current exercise recommendations for heart failure patients.\textsuperscript{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 pulmonary hypertension patients.
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 six parallel group trials included in the pooled analysis were non-randomized and the sample size of included studies is small. This highlights the significance of pooled analysis that has been conducted in the present 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 pulmonary hypertension patients in the present 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 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 if exercise training can be used to improve long-term clinical outcomes among these patients in the real world.

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The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. All authors have read and agree to the manuscript as written.

Disclosures

None.

References


## Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Mean age (Years)</th>
<th>Mean Weight (W, kg) / Height (H, cm) / BMI, kg/m²</th>
<th>WHO Function Class</th>
<th>PAH meds used</th>
<th>Baseline Peak Vo2 ml/kg/min</th>
<th>Baseline Six minute walk distance (m)</th>
<th>Etiology of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mereles 2006¹⁵</td>
<td>50 (13)</td>
<td>Ex: T: 15 Control: 15 Female: 66.7%</td>
<td>W: 76.5 (15.5) H: 168.5 (8)</td>
<td>20% Class II 73% Class III</td>
<td>ERA: 63% PD5-I: 33%</td>
<td>Ex T: 13.2 (3.1) Control: 11.9 (3.1)</td>
<td>80% IPAH 20% CTEPH</td>
</tr>
<tr>
<td>Martinez-Quintana 2010²⁸</td>
<td>28 (6)</td>
<td>Ex: T: 4 Control: 4 Female: 62.5%</td>
<td>W: 59 (9.1) H: 165.2 (14.8)</td>
<td>NA</td>
<td>ERA: 87.5%</td>
<td>NA</td>
<td>100% CHD</td>
</tr>
<tr>
<td>Fox 2011¹⁸</td>
<td>52 (19)</td>
<td>Ex: T: 11 Control: 11 Female: 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>45% IPAH 09% CTEPH 05% CHD 41% CTD</td>
</tr>
<tr>
<td>Chan 2013²⁴</td>
<td>54 (10)</td>
<td>Ex: T: 10 Control: 13 Female: 100%</td>
<td>BMI: 31(7.2)</td>
<td>91% Class II/III</td>
<td>Mono: 30% Dual: 26% Triple: 39%</td>
<td>Ex T: 17.5 (5.7) Control: 14.7 (5.1)</td>
<td>22% IPAH 74% CTD 4% Drug induced</td>
</tr>
<tr>
<td>Ley 2013²⁵</td>
<td>50 (11)</td>
<td>Ex: T: 10 Control: 10 Female: 70%</td>
<td>W: 72.5 (14.0) H: 166.5 (8.5)</td>
<td>20% Class II 80% Class III</td>
<td>Mono: 25% Dual: 60% Triple: 15%</td>
<td>NA</td>
<td>55% IPAH 20% CTEPH 10% CTD</td>
</tr>
<tr>
<td>Grunig 2013²⁶</td>
<td>54 (10)</td>
<td>Ex: T: 11 Control: 13 Female: 100%</td>
<td>BMI: 30.8 (7.2)</td>
<td>50% Class II 42% Class III</td>
<td>Mono: 29% Dual: 25% Triple: 38%</td>
<td>NA</td>
<td>25% IPAH 75% CTD</td>
</tr>
<tr>
<td>Becker Grunig 2013²³</td>
<td>48 (11)</td>
<td>Ex: T: 20 Control: 20 Female: 80%</td>
<td>W: 74 (18) H: 166 (8)</td>
<td>30% Class II 70% Class III</td>
<td>ERA: 70% PD5-I: 60%</td>
<td>Ex T: 11.4 (2.2) Control: 423 (90)</td>
<td>100% CHD</td>
</tr>
<tr>
<td>Grunig 2011²⁷</td>
<td>52 (18)</td>
<td>Ex: T: 21 Control: 21 Female: 95%</td>
<td>W: 68 (11) H: 165 (6)</td>
<td>43% Class II 33% Class III</td>
<td>Mono: 38% Dual: 48% Triple: 14%</td>
<td>Ex T: 11.8 (3.4) Control: 386 (121)</td>
<td>100% CTD</td>
</tr>
<tr>
<td>Grunig 2011²⁷</td>
<td>51 (12)</td>
<td>Ex: T: 58 Control: 58 Female: 72%</td>
<td>W: 72 (12) H: 168 (9)</td>
<td>17% Class II 76% Class III</td>
<td>Mono: 66% Dual: 31% Triple: 3%</td>
<td>Ex T: 12.5 (3.0) Control: 440 (90)</td>
<td>64% IPAH 02% CTEPH 04% CHD 04% CTD</td>
</tr>
<tr>
<td>Grunig 2012²⁰</td>
<td>53 (15)</td>
<td>Ex: T: 183 Control: 183 Female: 69%</td>
<td>W: 75 (17) H: 168 (9)</td>
<td>14% Class II 75% Class III</td>
<td>ERA: 59% PD5-I: 58% Mono: 44% Combi: 51%</td>
<td>Ex T: 12.2 (3.5) Control: 425 (106)</td>
<td>45% IPAH 17% CTEPH 08% CHD 10% CTD</td>
</tr>
<tr>
<td>Mainguy 2010¹⁰</td>
<td>40 (15)</td>
<td>Ex: T: 5 Control: 5 Female: 80%</td>
<td>W: 75 (20) H: 161(8)</td>
<td>60% Class II 40% Class III</td>
<td>ERA: 80% PD5-I: 20%</td>
<td>NA</td>
<td>100% IPAH</td>
</tr>
<tr>
<td>Nagel 2012²²</td>
<td>61 (15)</td>
<td>Ex: T: 35 Control: 35 Female: 46%</td>
<td>W: 78 (13) H: 170.5 (10)</td>
<td>20% Class II 74% Class III</td>
<td>ERA: 60% PD5-I: 60% Mono: 49% Combi: 46%</td>
<td>Ex T: 12.1 (1.7) Control: 408 (108)</td>
<td>100% CTEPH</td>
</tr>
<tr>
<td>De Man 2009¹⁶</td>
<td>42 (13)</td>
<td>Ex: T: 19 Control: 19 Female: 79%</td>
<td>W: 72 (14) H: 170 (9)</td>
<td>NA</td>
<td>Mono: 42% Combi: 58%</td>
<td>NA</td>
<td>100% IPAH</td>
</tr>
<tr>
<td>Kabitz 2014²⁷</td>
<td>60 (11)</td>
<td>Ex: T: 7 Control: 7 Female: 57%</td>
<td>BMI: 24.9 (4.8)</td>
<td>86% Class III 14% Class IV</td>
<td>ERA: 28% PD5-I: 86%</td>
<td>NA</td>
<td>72% IPAH 28% CTD</td>
</tr>
<tr>
<td>Inagaki 2014²⁰</td>
<td>64 (12)</td>
<td>Ex: T: 8 Control: 8 Female: 100%</td>
<td>BMI: 23(3.5)</td>
<td>75% Class II 25% Class III</td>
<td>ERA: 38% PD5-I: 62% Mono: 62%</td>
<td>NA</td>
<td>100% CTEPH</td>
</tr>
<tr>
<td>Ihle 2014²⁵</td>
<td>62 (13)</td>
<td>Ex: T: 17 Control: 17 Female: 65%</td>
<td>BMI: 26.7(5.9)</td>
<td>35% Class II 65% Class III</td>
<td>ERA: 47% PD5-I: 29% Mono: 71% Combi: 29%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Ex T: Exercise Training; W: Weight; H: Height; BMI: Body mass index; ERA: Endothelial receptor antagonist, PD5-I: Phosphodiaesterase-5 inhibitor
CTEPH: chronic Thromboembolic pulmonary hypertension; CTD: connective tissue disorder, CHD: congenital heart disease; Mono: Monotherapy; Dual: Dual therapy; Combi: combination therapy
IPAH: idiopathic pulmonary arterial hypertension
W, H, BMI measures among parallel group trials represent the weighted means of the intervention and control groups
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>Mereles et al 2006 15</td>
<td>• Interval bicycle ergometer training 7 days/week at low workloads</td>
<td>Common rehabilitation program based on healthy nutrition, physical therapy such as massages, inhalation, counseling, and muscular relaxation without exercise &amp; respiratory training</td>
<td>15 weeks</td>
</tr>
<tr>
<td></td>
<td>• Exercise intensity at 60-80% of peak VO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 60 minutes of walking 5 days/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 5 days/week of 30 minutes of resistance training</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 30 minutes of respiratory training 5 days/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 3 week in hospital supervised training followed by 12 week training at home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al 2013 24</td>
<td>• Aerobic training + Education intervention</td>
<td>Education intervention only with 1 hour lecture on different aspects of the disease</td>
<td>10 weeks</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 18</td>
<td>• Supervised 24 biweekly 1-hour sessions of exercise training in two six-week blocks.</td>
<td>Usual care with maintenance of routine daily activities and no specific exercise intervention</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>• Exercise intensity at 60-80% of Peak VO2</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>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In the second block, subjects performed longer periods of continuous aerobic exercise, with resistance training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ley et al 2013 25</td>
<td>• Supervised exercise training</td>
<td>Usual care with maintenance of routine daily activities and no specific exercise intervention</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>• Protocol same as Mereles et al 2006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Martinez-Quintana et al 2010 29 | • Supervised training 2 days/week  
• Training sessions with 10 mins of warming up + a brief period of resistance exercises + an interval of bicycle ergometer training during 24 minutes with bases at 10–25W and 30-second peaks of 20–50W | Usual care with maintenance of routine daily activities and no specific exercise intervention | 12 months|
| Weinstein et al 2013 26 | • Supervised training 24-30 sessions over 10 weeks  
• Treadmill walking for 30-45 mins/session at a target exercise intensity range of 70-80% | 1 Hour education session about the disease twice a week                                      | 10 weeks |
Table 3. Exercise Training Interventions Used in the Included Pre-Post Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Exercise Training group Intervention</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunig et al 2011 19</td>
<td>3 weeks supervised training followed by 12 week training at home</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Grunig et al 2012 20</td>
<td>1.5 h exercise training per day (in intervals distributed over the day) consisting of interval bicycle ergometer training at low workloads (10–60 W) 7 days a week</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Grunig et al 2012 21</td>
<td>Dumbbell-training of single muscle groups using low weights (500–1000 g)</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Nagel et al 2012 22</td>
<td>Respiratory training 5 days a week</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Becker Grunig et al 2013 23</td>
<td>Endurance training at 60% of target heart rate</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Kabitz et al 2014 27</td>
<td>Combination of strength, endurance and respiratory exercises involving single muscle groups (arms and quadriceps)</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Mainguy et al 2010 10</td>
<td>3 times/week exercise program comprising of</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>• 10 to 15 minutes of cycling exercise with workload initially set to 60% of the maximal workload achieved during incremental exercise test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2 sets of 10 to 12 repetitions for 6 to 8 different exercises involving single muscle groups (arms and quadriceps)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 15 minutes of brisk walking on a treadmill initially at 85% of the mean speed reached during the 6MWT</td>
<td></td>
</tr>
<tr>
<td>De Man et al 2009 16</td>
<td>Standardized exercise protocol was adopted from the AHA guidelines for rehabilitation of CHF patients</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Supervised exercise training with cycle training (based on VO2max assessed at baseline measurements) and quadriceps training (based on one repetition maximum assessed on the first day of training).</td>
<td></td>
</tr>
<tr>
<td>Inagaki et al 2014 30</td>
<td>12 week outpatient rehabilitation program with one in-hospital class each week and home based rehabilitation 24-30 sessions over 10 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Combination of strength, endurance and respiratory exercises</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endurance training at 60% of target heart rate</td>
<td></td>
</tr>
<tr>
<td>Ihle et al 2014 28</td>
<td>Once a month exercise for 90 minutes at low workloads (10 to 60 W).</td>
<td>40 weeks</td>
</tr>
<tr>
<td></td>
<td>This included 30 minutes breathing exercise and 30 minutes moderate strengthening exercises and very moderate endurance training of orthostatic leg muscles with general coordination movements</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Pooled Estimates for Changes in Quality of Life Subscale Scores With Exercise Training Among Participants With Pulmonary Hypertension

<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 to 0.7)</td>
<td>9.7% (0.34)</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>4</td>
<td>0.32 (0.05 to 0.57)</td>
<td>22.0% (0.27)</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>4</td>
<td>0.26 (0.02 to 0.50)</td>
<td>0% (0.99)</td>
</tr>
<tr>
<td>Vitality</td>
<td>4</td>
<td>0.44 (0.20 to 0.68)</td>
<td>0% (0.61)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>4</td>
<td>0.32 (0.08 to 0.56)</td>
<td>0% (0.82)</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>4</td>
<td>0.32 (0.08 to 0.56)</td>
<td>05 (0.48)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>4</td>
<td>0.26 (0.02 to 0.51)</td>
<td>15.7% (0.31)</td>
</tr>
</tbody>
</table>
### 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</td>
<td>15</td>
<td>Dizziness with training in 2 patients.</td>
</tr>
<tr>
<td>Martinez-Quintana et al 2010</td>
<td>4</td>
<td>Exercise intolerance with cyanosis in 2 patients</td>
</tr>
<tr>
<td>Fox et al 2011</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>Chan et al 2013</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>Ley et al 2013</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>Weinstein et al 2013</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>Becker Grunig et al 2013</td>
<td>20</td>
<td>None</td>
</tr>
<tr>
<td>Grunig et al 2012</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>Grunig et al 2011</td>
<td>58</td>
<td>Dizziness with training in 2 patients</td>
</tr>
<tr>
<td>Grunig et al 2012</td>
<td>183</td>
<td>Syncope in 2 patients few hours after training. Presyncope in 1 patient after training Self limiting SVT in 1 patient during exercise</td>
</tr>
<tr>
<td>Mainguy et al 2010</td>
<td>5</td>
<td>Recurrent light dizziness in 1 patient</td>
</tr>
<tr>
<td>Nagel et al 2012</td>
<td>35</td>
<td>Syncope during exercise in 1 patient Herpes zoster in 1 patient</td>
</tr>
<tr>
<td>De Man et al 2009</td>
<td>19</td>
<td>Minor dizziness in 2 patients</td>
</tr>
<tr>
<td>Kabitz et al 2014</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>Inagaki et al 2014</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>Ihle et al 2014</td>
<td>17</td>
<td>None</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Flow diagram for inclusion of studies in the systematic review.

Figure 2. Forest plot showing effect of exercise training on six-minute walk distance on pooled analysis of all included studies\(^{15-30}\) (N = 16, Panel A) and parallel group trials with an intervention and control arm only\(^{15, 18, 24, 25, 29}\) (N = 5, Panel B). WMD: Weighted Mean Difference.

Figure 3. Forest plot showing effect of exercise training on peak relative oxygen uptake (ml/kg/min) (N = 8, Panel A)\(^{15, 18-24}\) and peak absolute oxygen uptake (ml/min) on pooled analysis of included studies (N = 5, Panel B)\(^{15, 20-23}\). WMD: Weighted Mean Difference.

Figure 4. Forest plot showing effect of exercise training on resting peak systolic pulmonary arterial pressure (N = 7, Panel A)\(^{15, 18, 20-23, 30}\) and peak exercise heart rate (N = 8, Panel B)\(^{15, 18-24}\). WMD: Weighted Mean Difference.
Titles & abstracts identified from literature search (n = 1,977)

Duplicate articles excluded (n = 43)

Titles & abstracts reviewed (n = 1,934)

Full text articles retrieved for independent review (n = 31)

Excluded Studies (n = 15)
- 7 review articles
- 2 retrospective studies
- 2 systematic reviews
- 2 studies with ILD, COPD patients
- 1 protocol publication
- 1 study with patients not on stable medical therapy

Studies included in final analysis and review (n = 16)
Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: A Systematic Review and Meta-Analysis
Ambarish Pandey, Sushil Garg, Monica Khunger, Sonia Garg, Dharam J. Kumbhani, Kelly M. Chin and Jarett D. Berry

Circ Heart Fail. published online July 16, 2015;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2015/07/16/CIRCHEARTFAILURE.115.002130

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2015/07/16/CIRCHEARTFAILURE.115.002130.DC1
Supplemental Material

**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 proceeding 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 1 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 2013

- 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 ot 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 (Year)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
</table>
| Nagel et al 2012<sup>13</sup> | - 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 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<sup>14</sup> | - 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<sup>15</sup> | - 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<sup>16</sup> | - 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<sup>1</sup> | - 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></th>
<th>Becker Grunig 2013&lt;sup&gt;8&lt;/sup&gt;</th>
<th>Grunig 2012&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Grunig 2011&lt;sup&gt;10&lt;/sup&gt;</th>
<th>Grunig 2012&lt;sup&gt;11&lt;/sup&gt;</th>
<th>Mainguy 2010&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Nagel 2012&lt;sup&gt;13&lt;/sup&gt;</th>
<th>De Man 2009&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Kabitz 2014&lt;sup&gt;15&lt;/sup&gt;</th>
<th>Inagaki et al 2014&lt;sup&gt;16&lt;/sup&gt;</th>
<th>Ilhe 2014&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study Question Clearly Stated</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were eligibility/selection criteria for the study population prespecified and clearly described?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were all eligible participants that met the prespecified entry criteria enrolled?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Was the sample size sufficiently large to provide confidence in the findings?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Was the test/ intervention clearly described and delivered consistently across the study population?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were the people assessing the outcomes blinded to the participants' exposures/interventions?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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</tr>
<tr>
<td>Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?</td>
<td>Y</td>
<td>Y</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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</tr>
<tr>
<td>Did the statistical methods examine changes in outcome measures from before to after the intervention?</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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</tr>
<tr>
<td>Were statistical tests done that provided p values for the pre-to-post changes?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?</td>
<td>N</td>
<td>N</td>
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<td>N</td>
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<td>N</td>
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</tr>
<tr>
<td>If the intervention was conducted at a group level did the statistical analysis take into account the use of individual-level data to determine effects at the group level?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
</tr>
</tbody>
</table>
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


