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Title: Exercise Training in Pulmonary Hypertension: An Updated Systematic Review with Meta-analysis

Short running title: Exercise training in pulmonary hypertension

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Structured Abstract: (250 words)

Purpose: Given that previous reviews on exercise training in pulmonary hypertension (PH) were largely based on a small number of randomized trials (RCTs), their conclusions are subject to bias. This review sought to identify the impact of exercise training on functional capacity and health-related quality of life (HRQoL) in PH using advanced statistical approaches such as meta-analysis by stratification according to study design.

Review methods: Five databases were searched from January 2015 to April 2020 to update a previous review. Included articles had data extracted, risk of bias (ROB) assessed, and quality rating performed. Data were analysed using meta-analysis with a random effects model for six-minute walk test (6MWT) distance, and health-related quality of life (HRQoL). Heterogeneity was explored using stratified meta-analysis, within patient correlation and meta-regression.

Results: A total of 28 studies (11 RCTs, 12 pre-post studies, 2 two-group non-RCTs and 3 case series) consisting of 1264 patients, were included. Meta-analysis of six RCTs, demonstrated an improved 6MWT distance by 49.52 meters [95% CI (27.2, 71.8 , I^2 = 73 %; 254 participants; low-moderate ROB] with a low correlation co-efficient of 0.34, while the 12 pre-post non-RCTs showed an improvement of 68.36 meters [95% CI (-86.78, -49.94), I^2 = 37%; 746 participants; high ROB] along with improvements in VO2peak [WMD = 3.03ml/kg/min, 95% CI = (2.17, 3.90), I2 = 0%, p=0.82], and HRQoL [WMD = 2.74 (95% CI: -0.82, 6.30)]. Meta-regression showed that the benefit of exercise on 6MWT distance, did not significantly vary across the trial study characteristics.

Conclusion: This updated review identified an additional body of evidence supporting the efficacy of exercise training on 6MWT distance and HRQoL in stable PH patients. These benefits appeared to be consistent across models of delivery.

Condensed abstract: (<50 words)

This updated systematic review with meta-analysis found an improvement in functional capacity and quality of life among those with pulmonary hypertension receiving exercise training. These benefits are consistent across the various models of delivery and irrespective of the type of exercise intervention used.

Key perspective:

What is novel?

- This is the first time a stratified analysis and meta-regression has been performed on studies assessing the effects of exercise training in pulmonary hypertension
- Benefit of exercise on 6MWT distance, did not significantly vary across the trial study characteristics.

What are the clinical and/or research implications?

- Irrespective of the mode of delivery, exercise training is beneficial in pulmonary hypertension
- Need for greater understanding of dose response relationships

INTRODUCTION

Pulmonary hypertension (PH) has a global prevalence of ~1%, which increases with advancing age and affects 5-10% of the elderly (age> 65 years).[1] Pulmonary hypertension (PH) is associated with an increased mortality and worsening symptoms, irrespective of its underlying cause.[1] Although current therapy improves survival,[2] exercise capacity and health-related quality of life (HRQoL) continue to remain impaired.[3] Exercise intolerance in PH is the consequence of failure to increase stroke volume and decreased peripheral vascular resistance, resulting in a compensatory rise in heart rate and worsening hypoxemia due to ventilation-perfusion mismatch.[3] Furthermore, peripheral muscle dysfunction, causing inefficient peripheral oxygen uptake due altered mitochondrial function further contributes to exercise intolerance.[3,4]

Given the limitations to exercise that are amenable to exercise training, recent evidence-based guidelines have emphasized the importance of exercise training for PH.[5] However, despite its potential clinical and functional benefits, the findings of previous reviews of exercise training for PH have been inconclusive due to the quality of the studies and a wide variation in exercise interventions and settings (i.e. centre- versus home-based).[6,7]

With the growing body of evidence, there is a need to undertake a contemporary systematic review and meta-analysis on exercise training for PH. This updated review considers the impact of exercise training in terms of efficacy outcomes like functional capacity and HRQoL, and safety through advanced statistical approaches.

METHODOLOGY:

Search strategy and study selection criteria:

This review has been reported in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[8] and was registered in PROSPERO (CRD42020191787). The search was performed in the following databases: PubMed, CENTRAL (Cochrane database for randomized controlled trials), CINAHL (Cumulative Index to Nursing and Allied Health), Web of Science and PEDro in April 2020. Articles between January 2015 and April 2020 were screened for inclusion, using the same search strategy (**Supplemental Table S1**) as previously described by Babu AS et al.[6] In addition to the database search, back referencing of the reviews published between 2016 and 2019[9] was undertaken to identify any relevant articles. Studies from the previous review[6] were, as well, added to the included articles from the recent search. Studies were included if they provided an exercise intervention in patients with PH (irrespective of aetiology and functional class) through any study design and setting. Animal studies, studies published in foreign languages, and conference abstracts were excluded.

Data extraction:

Two reviewers (AS and ASB) independently screened the obtained articles for duplicates, eligibility and inclusion for meta-analysis. In case of conflict, the third reviewer (RP) made the final decision. The data were extracted manually by the two independent reviewers on a standardized excel sheet. The information extracted by the reviewers were: Citation details: Author names and year of publication; Study characteristics: Study design, sample size, sample analysed in each group; Study population characteristics: Age, gender, type of PH, functional class; Intervention characteristics: intervention for each group according to frequency, intensity, type and time, exercise settings, difference in pre and post intervention values for functional capacity, HRQoL, adverse events, adherence and method used to calculate adherence. Functional capacity was assessed by six-minute walk test (6MWT) distance and peak oxygen uptake (VO2peak) and HRQoL would be assessed using any relevant questionnaire (generic or disease specific). Safety of the exercise program was assessed by determining the adverse events reported in each trial. Information was recorded and categorized as exercise and non-exercise related adverse events. This was as reported in the previous studies. For clarification, we have defined exercise related adverse events are defined as those events occurring during an exercise session, while non-exercise related adverse events are those events occurring beyond the exercise session. Where additional information was required for the analysis, authors were contacted via email. Where no response was received, data were not included in the final meta-analysis.

Quality assessment:

The risk of bias (ROB) was assessed by two independent reviewers (AS and GP) using the Cochrane risk of bias tool (ROB 1) with figures being generated by RevMan 3.5 (Reference Manager Software 3.5). Quality for all studies was assessed using the Down's and Black Quality Index (QI) rating scale.[13] In case of any conflict in the ROB or QI, it was resolved by the third reviewer (ASB). Based on the previous cut-off,[6] we classified the studies as excellent, good, moderate and poor. Publication bias was assessed using visual inspection of funnel plots, generated by RevMan 3.5 and by performing an Egger's test in STATA data sciences software.

Data analysis: The primary outcome was weighted mean difference (WMD) for 6MWT while the secondary outcomes were WMD for VO2peak, HRQoL, and odds ratio (OR) for number of adverse events. Continuous outcomes were pooled as weighted mean differences (WMD) and binary outcomes as odds ratios (OR) and reported with 95% confidence intervals. Studies reporting outcome measures as median and quartiles were converted to mean and standard deviation, using the formula given by Wan et al.[14] Data analysis: Data from the included RCTs (for all outcome measures, irrespective of the setting and exercise intervention) and non-RCTs (for primary outcome) were analysed separately using RevMan 3.5. Since the inclusion criteria was broad and the RCTs were of small study size, exclusively for the primary outcome measure, RCTs and non-RCTs that looked at effect of aerobic and/or resisted exercise (irrespective of the setting) were separately analysed. Keeping in mind the high heterogeneity and bias that the non-RCTs can offer to the meta-analysis, the 14 non-RCTs were separately analysed based on their study design. Given the clinical heterogeneity of included studies in terms of their patient population and types of intervention, a random effects meta-analysis model was used. [14]Statistical heterogeneity across the studies was assessed using the I^2 statistic and $I^2>50\%$ was considered to represent substantial heterogeneity. High heterogeneity in 6MWT in both RCTs and non-RCTs were explored by AS and GD, by performing a (1) sub-group analysis (2) within patient correlation, and (3) meta-regression. Furthermore, to account for multiple testing in the meta-regression, Bonferroni correction for the level of significance $p = 0.05/5 = 0.01$, was performed. Despite the low heterogeneity, we undertook a meta-regression as we anticipated a potential researcher group bias arising from the 6/12 pre-post studies.

Pre-specified stratified meta-analysis was undertaken based on the following exercise intervention characteristics i.e., 1) intervention setting i.e., centre-based (intervention given under complete supervision), home-based (intervention performed at home) and hybrid (a combination of both)], and 2) intervention type i.e., aerobic plus resistance, inspiratory muscle training (IMT) or other including whole-body vibration (WBV) and neuromuscular electrical stimulation (NMES) Statistical significance was taken a p-value <0.05.

RESULTS:

A total of 28 articles were included in this updated review of which nine were obtained from the above-mentioned search strategy, 17 were from the previous review[6]6 and two[15,16] were obtained by back referencing previous reviews[9,10–12] (**Supplemental Figure S1**). The 28 studies consisted of 11 RCTs[14–24] and 17 non-RCTs.[12,13,25–39] The list of excluded full-text articles and the reasons for exclusion are summarised in **Supplemental Table S2.**

The study characteristics of the included articles are summarised in **Supplemental Table S3** and details of the exercise training protocols used in **Supplemental Table S4**.

Characteristics of the studies:

Most studies included patients with idiopathic pulmonary arterial hypertension[14,17-19,31,39,21,25,26,28–30] (12/28; 42%) and chronic thromboembolic pulmonary hypertension (CTEPH) (13/28; 46.6%).[16,17,19,20,22,26–28,34,40–43] Studies also explored operated CTEPH, corrected congenital heart diseases and rheumatic disorders related to PH (**Supplemental TableS3)**.[21,23,34] Patients were medically stable with WHO functional class II-III. Ten studies also included patients with functional class IV (10/28, 35.7%); the least explored area.[19,22,24,25,27,29,30,33,41,43]

17/28 studies used a combination of aerobic, resistance and flexibility exercises with or without inspiratory muscle training (IMT).[15,16,19,20,22,26–30,32–35,38–41,43] Two recently studied interventions included neuromuscular electrical stimulation (NMES) and whole-body vibration (WBV).[18,21] The intensity for aerobic exercise training ranged between 50-80% of maximum effort and duration of exercise lasted between 4 and 15weeks. Exercise was delivered through a hybrid (11/28),[15,22,27,29,30,32–34,40,41,43] supervised (14/28) [15,19,18,28,32,39,21–27] and home-based models (3/28)[16,17,19]. The in-patient phase of exercise training varied from 1 to 3 weeks, while home-based programs were of 12 weeks. Exercise training was seen to be safe with fewer exercise-related adverse events in comparison with non-exercise related events, as seen in **Supplemental Table S5.** Eight studies[16,17,19,20,23,27,33,37] reported adherence to exercise measured either via log books (2/8, 25%),[16,19] attendance to exercise site[17,20,33,35,37] (5/8, 62.5%) or phone calls and questionnaire[27] (1/8, 12.5%), **Supplemental, Table S6**. Overall, the adherence to exercise was reported to be good or excellent, with adherence being reported qualitatively as poor, good, excellent (3/8, 37.5%)[17,33,35] and quantitatively as mean and standard deviation (SD) (4/8, 50%)[16,19,20,37] or in frequency (1/8, 12.5%)**.**[27]

Quality rating & risk of bias of studies

The overall quality of the included studies was moderate, with differences being observed between RCTs and non-RCTs (**Supplemental Table S7**). The overall risk of bias was the highest for performance bias. The ROB for the included studies was low for RCTs (**Figure 1a**) and high for non-RCTs (**Figure 1b**). There was no reporting and attrition bias seen in this review. For all the studies, the reviewers identified treatment duration, difference in baseline characteristics, crossing-over and financial support as potential source of "other bias" and was thus marked 'unclear' (**Figure 1c**).

Effects of exercise training:

Meta-analysis of six RCTs (254 participants) demonstrated a mean improvement of 49.52 [95% CI (27.2, 71.8)], in functional capacity, with exercise training compared to control.[17,18,20,22,23,25–27,44] with evidence of substantial statistical heterogeneity (I^2 = 73%, p<0.01; **Figure 2a).** Twelve pre-post studies[15,16,29–33,35,36,39,41,42] (784 participants) showed that exercise training improved the man functional capacity by a WMD of -68.36 meters [95% CI (-86.78, -49.94) I^2 = 37%, p = 0.10], **Figure 2b**. Two group non-RCTs[34,38] (42 participants) showed no significant effect on 6MWT with high within patient correlation of 1 [WMD = 25.98 meters (-36.95, 88.90), I^2 = 0%, p = 0.39], **Figure 2c**.

The meta-analysis of four RCTs (174 participants) showed exercise interventions to have significant effect on VO2peak, with a WMD of 3.03ml/kg/min, 95% CI = [(2.17, 3.90), I2 = 0%, p=0.82)], VO2peak**Figure 3.**[20,22,25,27]

The four RCTs[20,21,27,44] showed no significant effect of exercise training on SF36 physical component summary (PCS) [WMD = 2.26 (95% CI: -3.01, 7.53) I^2=68%, p=0.03, 176 participants], mental component summary (MCS) scores [WMD 3.46 (95% CI: -2.38 to 9.31), I^2=72%, p=0.01, 141 participants] or overall QoL [WMD = 2.74 (95% CI: -0.82, 6.30), I^2=65%, p=0.005, 317 participants], **Figure 4a.** Exercise significantly improved each of the PCS sub-components of physical function, physical role, bodily pain and general health [overall WMD: 9.49 (4.90, 14.09), I^2 = 79%, p<0.01, 804 participants], **Figure 4b.**[22,27,44] Three of the four MCS sub-components (social function, emotional role, vitality) showed no significant improvement in mental health [overall WMD = 6.62 (95% CI 3.97, 9.28), I^2 = 44%, p=0.05, 603 participants, **Figure 4c.**[22,27,44] Twenty-six out of the 28 studies reported an overall adverse event rate of 8.5% (98/1152) (**Supplemental Table S5)**.[18,20,21,23–26,28,35–39,42] There was an overall odd ratio of 0.14 (85% CI 0.08, 0.25, I^2 = 8%, p=0.12) for non-exercise related events compared to control **Supplemental, Figure S2.**

Stratified meta-analysis and meta-regression:

Between the models, The hybrid model showed the greatest improvement in 6MWT distance with a WMD of 132.75 meters (95% CI: 79.49 to 186.00, I^2 = 45%, p=0.18) (**Supplemental, Figure S3)**.[22,27] The home-based model was also beneficial (WMD = 41.87, 95% CI = 0.72 to 83.01, I^2 = 36%, p=0.21).[17,19] Interestingly, the supervised model showed non-significant improvement in 6MWT distance (WMD= 44.36, 95% CI: -32.31 to 121.03), however, with a high heterogeneity score of I^2 = 88%, p<0.01 (**Supplemental, Figure S3).**[18,20,23,25,26]

The hybrid model was associated with the lowest risk of adverse events [O.R = 0.12 (0.06, 0.24), I^2=0%] with only non-exercise related adverse events being reported (**Supplemental, Figure S2).** The home-based and supervised models demonstrated a comparable safety profile [OR = 0.16 (0.03, 0.72) and OR = 0.25 (0.08, 0.83) respectively], though the home-based model was associated with a higher heterogeneity than the supervised model (I^2 = 76%, p = 0.04 and I^2 = 40%, p= 0.17, respectively).Although the largest magnitude of 6MWT distance gain with exercise training appeared to be seen with hybrid setting, meta-regression showed no evidence of statistically significant interaction between the study characteristics (publication year, sample size) or intervention characteristics (duration, model, type) and 6MWT distance for RCTs (**Supplemental, Table S7**). For non-RCTs, there was evidence of interaction between 6MWT distance and publication year and intervention type, **(Supplemental, Table S8).**

Publication bias:

There was no evidence of small study bias for RCTs (**Supplemental Figure S4a**, Egger test, p=0.10) and non-RCTs (**Supplemental Figure S4b**, Egger test, p=0.25) for the primary outcome 6MWT distance.

DISCUSSION:

This updated systematic review and meta-analysis showed that exercise training was safe and effective in improving 6MWT distance and HRQoL in stable PH patients. These benefits appeared to be consistent across centre-, home-based and hybrid models of exercise training delivery.

Exercise training and 6MWT distance

Irrespective of the study design, 6MWT distance improvement was significant as well as clinically meaningful i.e., minimum clinically important difference (MCID) for PH patients being 33 meters (25.1 to 38.5 m).[45] The non-RCTs showed a similar improvement when compared to the other reviews,[46,47] whereas the RCTs in our review showed a lesser improvement than previously reported.[7,9,46–48 97,46,477,9,46–4818]

We encountered a significant heterogeneity for 6MWT distance across RCTs, which was higher when compared to the other studies.[7,9,46–48] This could be attributed to: 1) the difference in statistical approach wherein, unlike other reviews, we have separately analysed RCTs and non-RCTs, 2) difference in the inclusion and exclusion criteria and 3) the overall high ROB in our review due to greater number of non-RCTs.[7,9,46–48]

A further quality assessment and meta-regression across RCTs, ruled out both methodological and clinical cause of heterogeneity. 6MWT distance6MWT distance

Exercise training and HRQoL

PH impacts activities of daily life, working abilities, psychosocial health, and overall HRQoL.[10,11] This review found that exercise training had no significant effect on overall HRQoL, but improved the physical and mental sub-components. This finding is similar to the other reviews which have analysed the sub-components of SF-36 individually.[7,9,46,47] However, results for PCS should be interpreted with caution as the heterogeneity remained high and analysis is based on a limited number of studies. The non-significant change in overall HRQoL indicates that exercise training played only a partial role in improving HRQoL.

Exercise training and its safety

This analysis, similar to previous studies, proved that exercise can be safely administered in stable PH patients.

The occurrence of overall rate of adverse events in our review, was higher in comparison with the other reviews.[7,9,47] However, the exercise-related adverse event rate in this review was lower than that reported in other studies.[9,47] The reasons could be: 1) the difference in the number of studies reporting adverse events,[7,9,47] and 2) the pragmatic approach to defining adverse events as described in individual studies.

The sub-analysis further projected that of all the models, the hybrid model was the safest, which is similar to other studies, **Table 2.**[7,30]

Quality of evidence

The overall ROB was high for this review due to the greater number of non-RCTs; which is an obligatory drawback in the methodology of a non-RCT. Thus, the ROB for RCTs and non-RCTs were separately assessed, to reveal a low ROB for RCTs with only "blinding of the participants" being a matter of concern. However, it is difficult to perform any exercise training programs-based studies in a blinded manner. Nevertheless, in our review, Down's and Black QI revealed the overall quality of the included studies as moderate, and the publication bias for the primary outcome low.

Limitations

This review is limited by the exclusion of studies published by other languages and overall high ROB due to a greater number of non-RCTs in the analysis. Variations in reporting of exercise related adverse events and adherence further confound the findings of this meta-analysis and need to be considered while interpreting the results. Additionally, meta-regression and Egger test were limited by the small number of studies (n=9).

Future research should look at generating high quality evidence to strengthen future meta-analysis. Reporting of adverse events and adherence need to improve in exercise training studies for PH. It may also be prudent to expand the sphere of exercise training to include technology driven methods to deliver exercise training.[49]

CONCLUSION:

This updated systematic review and meta-analysis with meta-regression showed that exercise training is effective in improving functional capacity and HRQoL safely in patients with stable PH. These benefits appeared to be consistent across different models of delivery.

Author's contribution: AS, GP, PK and ASB developed the objective and update for this study. ASB and PK developed the original search strategy, and it was further developed by AS. AS, GP and ASB were involved in the screening and selection of articles. AS and GP, pilot tested the data extraction sheet, extracted the data, completed the risk of bias and quality assessment of included article. AS, GD and RS conducted the meta-analysis and meta-regression, along with their interpretation. AS and GP drafted the first version of the manuscript. GD, PK, ASB and RS edited, provided scientific input, and revised the manuscript. All authors have read and approved the final version of the manuscript.

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Conflict of Interest: None

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Supplemental Digital files:

Supplemental Tables:

Supplemental Table S1: Search strategies for various databases searched for the systematic review

Supplemental Table S2: Excluded studies with reasons

Supplemental Table S3: Summary of articles included in the review (n=28)

Supplemental Table S4: Exercise training protocols utilised in the various studies included

Supplemental Table S5: Exercise and non-exercise related adverse events reported in various studies

Supplemental Table S6: Adherence to exercise training reported in studies (n=8)

Supplemental Table S7: Adherence to exercise training reported in studies (n=8)

Supplemental Table S6: Summary of quality of studies included in the review

Supplemental Table S7: Meta-regression for RCTs

Supplemental Table S8: Meta-regression for non-RCTs

Supplemental Figures:

Supplemental Figure S1: PRISMA flow chart

Supplemental Figure S2: Adverse events between models

Supplemental Figure S3: Effect of exercise on 6MWT distance between models

Supplemental Figure S4: Publication bias for 6MWT distance for a) RCTs and b) non-RCTs

Figure legends:

Figure 1: Risk of bias of the included studies for (1a) randomized controlled trials and (1b) non-randomized controlled trials (1c) Summary of findings across all the studies

Figure 2: Effects of exercise on 6MWT distance among (2a) randomized controlled trials, (2b) non-randomized controlled trials and (2c) two-group non-randomized controlled trials

Figure 3: Effects of exercise on peak oxygen uptake (VO_2 peak) among randomized controlled trials

Figure 4: Effects of exercise training on quality of life (SF36) for (4a) major domains along with (4b) physical component sub-domain scores and (4c) mental component sub-domain scores from randomized controlled trials

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Figure legends:

Figure 1: