Exercise-Based Rehabilitation to Improve Exercise Capacity and Quality of Life in Pulmonary Arterial Hypertension

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Abstract:

<LEAP> highlights the findings and application of Cochrane reviews and other evidence pertinent to the practice of physical therapy. The Cochrane Library is a respected source of reliable evidence related to health care. Cochrane systematic reviews explore the evidence for and against the effectiveness and appropriateness of interventions—medications, surgery, education, nutrition, exercise—and the evidence for and against the use of diagnostic tests for specific conditions. Cochrane reviews are designed to facilitate the decisions of clinicians, patients, and others in health care by providing a careful review and interpretation of research studies published in the scientific literature. Each article in this PTJ series summarizes a Cochrane review or other scientific evidence on a single topic and presents clinical scenarios based on real patients or programs to illustrate how the results of the review can be used to directly inform clinical decisions. This article focuses on people diagnosed with pulmonary arterial hypertension. Can exercise-based rehabilitation programs improve exercise capacity and quality of life in people with pulmonary arterial hypertension?

Pulmonary hypertension (PH) is a chronic disease that results in severe loss of function and poor quality of life. The aetiology of disease is heterogeneous**[AQ: OK to change "heterogenous" to "heterogeneous"?],** and the recent guidelines by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) divided pulmonary hypertension (PH) into 5 distinct groups: group 1 (pulmonary artery hypertension [PAH]), group 2 (PH secondary to left heart disease), group 3 (PH secondary to lung disease), group 4 (chronic thromboembolic PH), and group 5 (multifactorial mechanisms).[1] Group 1 PAH has a prevalence between 6.6% and 26% per million.[2]

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Individuals with PH have markedly reduced exercise capacity and reduced quality of life. Given the success of exercise training and rehabilitation programs in improving both exercise capacity and quality of life in other chronic heart and lung disease populations,[3, 4] recently there has been a growth in the interest of exercise as an adjunctive therapy in PH.[5] Up until a few years ago, there were only a handful of studies and on-going studies on exercise training in PH.[5] However, as the understanding of various contributing factors to poor exercise performance improved, so did the rationale for exercise training. We conducted a recent review summarising the physiological limitations of oxygen transport and utilisation in PH.[6] The review identified interactions between central (ie, cardiac and pulmonary systems) and peripheral (ie, musculoskeletal system) mechanisms contributing to the exercise intolerance. Additionally, the factors which limit exercise performance in PH may also be aetiology specific with some groups having potentially different factors limiting exercise performance.[7] Recent reviews on the topic have identified nearly 20 published studies (of varying quality) to date.[8-11] The impact of this literature has resulted in an evidence based recommendation (class IIa, level B) in favor of exercise training in the recent guidelines on the management of PH.[1] The Australian and New Zealand guidelines on pulmonary rehabilitation have recently

recommended exercise-based pulmonary rehabilitation for pulmonary hypertension (weak recommendation, based on low-quality evidence).[12]

Considering the growing burden of PH across the world,[2] this is a group of patients that will soon find a place in rehabilitation programs (either cardiac or pulmonary) and therefore will require expertise on the part of the physiotherapist for appropriate exercise evaluation and prescription. This scenario makes the recent 2017 Cochrane review and meta-analysis on "Exercise-based rehabilitation programmes for pulmonary hypertension" by Morris et al[11] an important paper for physiotherapists working in cardiopulmonary rehabilitation. This paper, which systematically reviewed randomized controlled trials (RCTs) on exercise-based rehabilitation interventions for PAH, was published until August 2016 with the aim of determining the efficacy and safety of exercise training in this group. The primary outcomes assessed through the review were exercise capacity, adverse events and quality of life. Secondary outcomes assessed from the review included cardiopulmonary hemodynamics, functional class, clinical worsening during follow up and changes to brain natriuretic peptide (BNP).

[H1]Take home message:

Morris et al,[11] reviewed the literature from 6 RCTs which studied the effects of exercise based interventions on various outcomes in PH. These 6 studies were identified after a comprehensive search in the various databases (ie, CINAHL, AMED, Embase, PubMed, MEDLINE, PsycINFO, CENTRAL, PEDro and registries of clinical trials) performed for studies published until August 2016. Even though the initial search resulted in 29 articles, the authors excluded 15 as they were not RCTs (n = 8), did not include exercise training (n = 3), used a wrong intervention (n = 2), included the wrong population (n = 1) and was a review (n = 1). Out of

the 6, data could be extracted only from 5 of them, as 1 was published only as a conference abstract and the authors did not respond to requests for further information. Thus, 6 RCTs[13-18] provided information from 206 participants with PH undergoing exercise training; however, only 5 studies contributed data to the analyses, including 165 patients. Of these, 3 studies used inpatient programs of 3 weeks' duration, followed by a 12-week home-based program, and the remaining studies used outpatient training programs. Sample sizes of these studies ranged between 10 and 87 participants aged between 47 and 56 years and having mean right atrial pressures (RAP) ranging between 40 and 52 mmHg.

All studies were assessed for risk of bias using the Cochrane risk of bias score. The assessment revealed that apart from a low risk of detection bias, all studies had a high risk of bias for selection (ie, random sequence generation and random allocation), attrition, and reporting. Further, there w a high risk for selection bias, as the way in which participants were chosen was unclear for several studies, which suggests there could limited generalisability.

All studies in the review compared exercise-based rehabilitation against no intervention or education alone or usual care. On average, exercise-based rehabilitation improved 6-minute walk distance (6MWD) by 60.1 m (minimal important difference (MID) for 6MWD in PAH is 31 m[19]) and peak oxygen consumption (peak $\dot{V}O_2$) by 2.4 mL/kg/min**[AQ: "ml.kg^{-1}.min^{-1}" was changed in several places to "mL/kg/min" for consistency with formatting used elsewhere in the article.]** (clinical improvement for peak $\dot{V}O_2$ from heart failure studies suggest an increase of 6% or approximately 0.6 mL/kg/min to be clinically relevant).[20] In addition, peak power and time to anaerobic threshold were also improved with exercise-based rehabilitation. Overall quality of life improved with both components of the SF-36 (ie, physical and mental components) improving by averages of 4.63 and 4.17 units, respectively (clinically significant gains in the physical and mental component scores of SF-36 have been reported as 5.8 points).[21] For the various subdomains, significant changes were observed for only role

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physical, vitality and social function. Other domains of the SF-36 did not show any significant changes.

Exercise-based rehabilitation also caused improvements in various secondary outcomes like mean pulmonary artery pressure (PAP) (9 mmHg), functional class (−0.6), and BNP (−236). There were limited data available for subgroup analysis by type or severity of PH. For PAH, there was an improvement in exercise capacity that was smaller in magnitude when compared to the group as a whole. However, these studies were also conducted in the outpatient setting, whereas many of the others were conducted in the inpatient setting, so it was difficult to establish whether the smaller effect was related to the diagnosis or the setting.

[H1]Applying evidence to a patient with PAH

[H2]Can an exercise program help this patient?

Mrs James is a 48-year-old female who presented with complaints of dyspnea on exertion, fatigue and difficulty in carrying out her activities of daily living for the last 5 months. The onset was gradual, and she noticed a progressive increase in difficulty climbing slopes and stairs. Her family physician examined her and ordered an electrocardiogram (ECG), transthoracic echocardiogram and an exercise stress test. On examination, she had a stable heart rate of 79 beats per minute, blood pressure of 105/64 mmHg, respiratory rate of 14 breaths per minute, and resting oxygen saturation of 92% on room air. Her functional class was put at WHO functional class III (ie, marked limitation of physical activity. Less than normal activity causes undue dyspnea, fatigue, chest pain or near syncope),[22] which is similar to the New York Heart Association classification III for heart failure. The electrocardiogram (ECG) showed she was in sinus rhythm, however there was evidence of right axis deviation with severe right

ventricular hypertrophy. There were no signs of ischemic changes on ECG and an angiogram ruled out coronary artery disease. The transthoracic echocardiogram showed a dilated right ventricle (RV) with the D-sign. The tricuspid regurgitant (TR) velocity was found to be 5 mm/s. Using the Bernoulli formula, right ventricular systolic pressure (RVSP) was estimated as 122 mmHg. RV dysfunction as estimated from the tricuspid annular plane systolic excursion (TAPSE) was 13 mm. Mrs James had normal left ventricular function (ejection fraction of 58%) with no wall motion abnormalities. Her biochemistry evaluation was normal, although her NT-proBNP**[AQ: OK to change "NT pro BNP" to "BNP"? If not, what is "NT pro BNP"?]** was elevated (1685 pg/mL). Considering a possibility of PAH, she was referred to a PH specialist center for further evaluation and management.

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The PH specialist, after having evaluated Mrs James and screening for chronic thromboembolism and various other connective tissue disorders, arrived at a diagnosis of idiopathic PAH. Subsequently, she was referred for evaluation of exercise capacity using the 6-minute walk test (6MWT). She was able to walk only 255 m with a single rest and achieved a peak heart rate of 118 (+41 beats/min**[AQ: "beats.min^{-1}" was changed to "beats/min" for consistency with formatting used elsewhere in the article.]** from baseline); the nadir oxygen saturation was 82% (from 92% at rest), with a modified Borg Scale (0–10) rating of perceived exertion (RPE) of 6/10 at the end of the test. She was then started on PH specific therapy which included a phosphodiesterase inhibitor (eg, Sildenafil) and an endothelial receptor antagonist (eg, Macitentan) along with other supportive measures like anticoagulants (eg, warfarin) and diuretics (eg, furosemide). After the demonstration of clinical stability for 3 months, a repeat 6MWT showed an improvement of the distance to 380 m with no rest, a peak heart rate of 121 beats per minute**[AQ: "beat.min^{-1}" was changed to "beats per minute" in several places for consistency with formatting used elsewhere in the article.]** with a maximum desaturation to 85% from 97% at rest, and an end-exercise RPE of 4/10.**[AQ: Sense of sentence beginning**

Commented [AB4]: No objection to the change

Commented [AB5]: No objection to the change

"After the demonstration" OK as edited? If not, please clarify what is meant.] She was then referred to physiotherapy for rehabilitation. During this period, she reported no episodes of syncope and showed no other signs of right heart failure such as peripheral oedema or raised jugular venous pressure. To further evaluate exercise capacity, she was also referred for a cardiopulmonary exercise test (CPX) on a cycle ergometer. Using a ramped protocol, Mrs James achieved a maximal workload of 45 W, a maximal heart rate of 128 beats per minute, and a maximal breathlessness of 6/10 using the modified Borg Scale. Her peak oxygen consumption was 13.2 mL/kg/min, and her peak respiratory exchange ratio was 1.05. Her end-tidal carbon dioxide ($P_{ET}CO_2$) was found to be reduced at rest (31 mmHg) and reduced further with exercise (27 mmHg at the end of exercise). Likewise, her ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) was elevated at rest (42.1) and increased further at the end of exercise (48.2). Additionally, the physiotherapist (PT) assessed her quality of life using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)**[AQ: "SF36" was changed throughout to "SF-36" and the definition of this abbreviation was changed in accordance with information found at https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html. See also Table 2 footnote *a*.]**; she found low scores on both physical component and mental component scores (ie, PCS-32 and MCS-34, respectively). Not very sure if the patient should be treated as per cardiac rehabilitation or pulmonary rehabilitation guidelines, the PT initiated a search of literature to answer the following questions:

1) Can a patient with PH exercise? 2) Will exercise have any effect? 3) What kind of exercise is better—aerobic, resistance or a combination? and 4) Is it safe to have a patient with PH exercise?

To answer these questions, the therapist formulated the following PICO:

Commented [AB6]: Yes. The edited sentence is OK

Commented [AB7]: No objection to the change

P: Patients with PH; I: Exercise (aerobic, resistance or a combination); C: No exercise or routine care; O: Exercise capacity (6MWD, peak $\dot{V}O_2$), quality of life, and safety

The therapist performed a search in PubMed and retrieved the Cochrane review by Morris et al[11] and began to understand it to help her answer the 4 clinical questions.

[H2]How do we apply the results of the Cochrane Systematic Review to Mrs James?

The results of the review by Morris et al did answer the questions asked. We will discuss them under the PICO headings.

[H3] *Population – Pulmonary arterial hypertension:*

The studies included in the review did mostly include patients with PAH (ie, group 1 PAH or group 4 chronic thromboembolic PH). When a subgroup analysis was performed, it was seen that for those with group 1 PAH, the improvements in exercise capacity were less than for the entire group (mean = 33.84 m vs 60.12 m for 6MWD and 1.28 mL/kg/min vs 2.4 mL/kg/min for peak $\dot{V}O_2$). However, these could be affected by the settings and types of interventions. However, data from other systematic reviews have shown that exercise training in almost any form of PH does appear to be beneficial for these outcomes.[9,10]

[H3] Interventions – Exercise training:

Exercise interventions were provided to Mrs James through out-patient, supervised sessions and included a combination of lower limb endurance training and resistance training for both upper and lower limbs. Endurance training and resistance training prescriptions are summarised below:

- Endurance training

- Frequency; 2 or 3 d/wk for 12 weeks
- Intensity: 70% to 80% heart rate reserve or RPE of ≤3 (using the modified Borg Scale)
- Time: 20 minutes in the first week progressing to 40 minutes as tolerated
- Type: treadmill walking, cycling, walking

- Resistance training
  - Frequency: alternate days
  - Intensity: 60% to 70% of age-predicted maximum heart rate**[AQ: OK to change "HRmax" to "maximum heart rate"?]**
  - Time: 15 to 20 minutes
  - Type: functional strength training (step-up and sit-to-stand)

Commented [AB8]: Yes

During her exercise sessions, she was regularly monitored for episodes of syncope, chest pain, palpitations and signs of right heart failure.

[H3] Outcomes – exercise capacity, quality of life, functional class and cardiac function:

Studies included in the Cochrane review compared exercise-based interventions to either no intervention or education alone or usual care. Five of the included studies were used for the meta-analysis, which showed significant improvements in functional capacity, exercise capacity and quality of life with no significant changes in cardiac function (Tables 1 and 2).**[AQ: Please see the query preceding the tables.]**

In this case Mrs James was deconditioned and did not participate in any regular exercise or physical activity. The PT wanted to prescribe an exercise program that would help her improve functional capacity and quality of life. Mrs James's condition resembled that of the patients from the systematic review in that she had PAH which was moderate to severe and had poor functional capacity (<350 m), high functional class (class III), and poor quality of life.

[H2]How well do the outcomes of the intervention provided to our patient match those suggested by the systematic review?

Once Mrs James had been stabilised on her pharmacotherapy she was prescribed a rehabilitation program. After 3 months of dual pharmacotherapy and her supervised, out-patient rehabilitation program, which included a combination of aerobic training and resistance training 2 or 3 d/wk, her functional class improved by 1 grade to class II. Her 6MWT improved to 440 m, and her RPE was 6/10, with an increase in peak HR to 132 beats per minute from baseline and a reduction in oxygen saturation to 88% from a resting SpO_2 of 96% on room air. Her repeat echocardiograph showed that her estimated RVSP was now 88 mmHg, her TAPSE was 14 mm, and her BNP**[AQ: OK to change "NTPro-BNP" to "BNP"? If not, what is "NTPro-BNP"?]** was reduced to 823 pg/mL. Her quality of life in the physical and mental components improved by 5.6 and 6.2 units on the SF-36, respectively. During her rehabilitation sessions, she was regularly monitored for exercise related adverse events like syncope/presyncope, palpitations, chest pain, and dyspnea. She also was prescribed a home-based program to be completed unsupervised 2 d/wk. She was asked to monitor her symptoms during the unsupervised session and advised to cease exercise if she felt excessively breathless or lightheaded. The outcomes assessed in this patient align with the outcomes described in the systematic review by Morris et al,[11] along with other reviews on the same topic.[8-10]

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[H2]Can you apply the results of the systematic review to your own patients?

Exercise training should only be considered in patients who are stable on optimised medical therapy, as these are the patients who were enrolled in the trials examined in the systematic review. A supervised exercise training program (inpatient or outpatient) should be used, similar

to the studies in the review, although unsupervised home training may be useful to maintain or increase the gains after the initial training period is complete. The results of this systematic review are applicable to adults with PH of any aetiology, although there are most data for group 1 and 4**[AQ: Correct to change "I and IV" to "1 and 4" for consistency with the group designations used earlier in the article?]** PH. The nature of exercise limitations and response to exercise training seem to be common across the various groups of PH. This suggests the potential for exercise training in improving function and quality of life among patients with PH. The ideal exercise prescription is unknown, although the results of the review suggest that the standard exercise prescription used in many cardiac and pulmonary rehabilitation programs is likely to be effective in most patients with PH.

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[H2]What can be advised based on the results of this systematic review?

Exercise training for PH remains underutilised despite the strong physiological basis for exercise intolerance in various types of PH. The evidence from the included trials in the systematic review suggests that exercise testing, with either CPX or 6MWT, is useful prior to enrolment into exercise training programs to enable accurate exercise prescription and assessment of exercise outcomes. It should be acknowledged that there are currently insufficient studies to evaluate whether the effects of exercise training vary by etiology, functional class, disease severity, or setting (outpatient vs inpatient). Large, robust RCTs will be needed to answer these questions. Nevertheless, the evidence is in favor of prescribing a combination of aerobic and resistance training, performed at a moderate intensity, for patients in PAH etiological groups 1 and 4 (PAH and chronic thromboembolic PH) and in functional classes II and III under supervision, until there is stronger and more generalizable evidence to support unsupervised programs. To conclude, stable PAH patients should be enrolled into

existing cardiac or pulmonary rehabilitation programs with the goal of improving function and quality of life.

Author Contributions
Concept/idea/research design: A.S. Babu, A.E. Holland, N.R. Morris
Writing: A.S. Babu, A.E. Holland, N.R. Morris
Data collection: N.R. Morris
Data analysis: A.E. Holland
Consultation (including review of manuscript before submitting): A.E. Holland

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Commented [AB11]:

[AQ: The Table was reorganized and edited in accordance with PTJ style because the original table did not meet PTJ table formatting requirements. Two tables were used because it could not be determined which improvements belonged with each of the 6 studies. Please check carefully. Some material in the first table was moved to a footnote because it did meet PTJ table formatting requirements; please check the wording of footnote *a* carefully. Have "F," "I," "T," and "T" been spelled out correctly in the column headings of Table 1?]

Table 1.

Exercise Program for Patients With Pulmonary Arterial Hypertension: Summary of Cochrane Review[a]

Study	Intervention			
	Frequency	**Intensity**	**Type**	**Duration**
Mereles et al[13] (2006)	7 times/wk for aerobic training and 5 times/wk for resistance training (inpatient for 3 wk); 5 times/wk for cycling, 2 d/wk for walking, and alternate days for respiratory and resistance training (outpatient for 12 wk)**[AQ: Entry OK as edited?]**	60%–80% of heart rate reserve**[AQ: OK to change "heart rate" to "heart rate reserve"? Or is "peak heart rate" meant?]** on CPX; heart rate maintained at <120 bpm; oxygen saturation of >85%	Treadmill walking	30–45 min
Wilkinson et al[14] (2007)[b]**[AQ: Correct to change reference 23 to 14? Reference 23 is Vos et al,**	Not clear	Not clear	Not clear	Not clear

Commented [AB13]: It should be peak heart rate

Commented [AB12]: Yes

and reference 14 is Wilkinson et al.]				
Chan et al[16] (2013)	2 or 3 times/wk (24–30 sessions), 10 wk	70%–80% of heart rate reserve	Treadmill walking	30–45 min
Ley et al[15] (2013)	5 times/wk, 3 wk	60%–80% of heart rate reserve**[AQ: OK to change "heart rate" to "heart rate reserve"? Or is "peak heart rate" meant?]** on CPX	Same as Mereles et al[13] (2006)	10–25 min/d for cycle ergometer; 60 min/d for walking; 30 min for respiratory training
Ganderton et al[17] (2013)	3 times/wk, 12 wk	60%–70% of heart rate maximum; SpO_2 of ≥92%; RPE of <4	Lower limb endurance training (walking, cycling); lower limb functional strength training (step-up and sit-to-stand) and upper limb endurance training	60 min
Ehlken et al[18] (2016)	Same as Mereles et al[13] (2006)	Same as Mereles et al[13] (2006)	Same as Mereles et al[13] (2006)	Same as Mereles et al[13] (2006)

[a]Six randomized controlled trials up to August 2016 involved 206 participants with pulmonary hypertension (mainly groups 1 and 4), the majority in functional classes II and III, with sample sizes ranging from 10 to 87. Inclusion criteria were as follows: randomized controlled trial, any

Commented [AB14]: Yes

Commented [AB15]: It should be peak heart rate

study reported in full/abstract form, or relevant unpublished data; adults with a diagnosis of pulmonary hypertension (irrespective of medical stability); and a comparison of exercise-based rehabilitation (which could include exercises of any duration, setting, supervision, and length and consisting of a combination of aerobic and resistance exercises) with no exercise–based rehabilitation. The exclusion criterion was an intervention that provided only advice on exercise. CPX = cardiopulmonary exercise test; RPE = rating of perceived exertion; SpO_2 = oxygen saturation.**[AQ: Has "SpO_2" been defined correctly?]**

Commented [AB16]: Yes

[b]No data from this study could be included in the analyses.

[AQ: Are the title and column headings provided for Table 2 acceptable? The dashes in the 95% CIs in the table were changed to "to" for consistency.]

Table 2.

Improvements in Groups Receiving Exercise Program[a]

Outcome	Change		
	~~Median~~Control group	~~Mean~~Intervention group	Other
Functional capacity (6-min walk distance)	5 m in control group	60.12 m (95% CI = 30.17 to 90.07) after intervention	
Exercise capacity (peak $\dot{V}O_2$ [mL/kg/min] and peak power [W])	−0.25 mL/kg/min and 1 W in control group	2.41 mL/kg/min (95% CI = 1.38 to 3.44) and 16.44 W (95% CI = 10.90 to 21.99) after intervention	
Quality of life from SF-36 (physical component)	−0.49 unit in control group	4.63 (95% CI = 0.80 to 8.47) after intervention	

Commented [AB17]: This column can be deleted

Quality of life from SF-36 (mental component)	−0.31 unit in control group	4.17 (95% CI = 0.01–8.34) after intervention	
Quality of life from CAMPHOR	-	−5.42 units (95% CI = −8.03 to −2.81) after intervention	
WHO functional class	-	Improvement in functional class of 0.60 (95% CI = −0.85 to −0.35) after intervention in 2 studies	~~Improvement in functional class of 0.60 (95% CI = −0.85 to −0.35) after intervention in 2 studies~~
Cardiac function	-	Reduction of 9.00 mmHg (95% CI = −13.60 to −4.40) after intervention in 1 study	~~Reduction of 9.00 mmHg (95% CI = −13.60 to −4.40) after intervention in 1 study~~

[a]CAMPHOR = **[AQ: Please provide a definition for "CAMPHOR."]**; SF-36 = 36-item Short-Form Health Survey; WHO = World Health Organization.

Commented [AB18]: Cambridge Pulmonary Hypertension Outcome Review