

## Review Article

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# A review of ongoing trials in exercise based rehabilitation for pulmonary arterial hypertension

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**Exercise based rehabilitation for patients with pulmonary arterial hypertension (PAH) is a new treatment option for these patients to improve their functional capacity and quality of life. Despite the benefits seen in cardiopulmonary rehabilitation in various other conditions, it has been underutilized for the patients with PAH. A review of currently registered ongoing trials on exercise training for patients with PAH from the World Health Organization International Clinical Trial Registry Platform was done using the key words “rehabilitation”, “exercise training”, “pulmonary artery hypertension” and “pulmonary hypertension” for a period of 10 years (2002-2012). The search revealed 57 registered trials in various trial registries from which seven met the inclusion criteria. The current studies are being carried out in Germany (n=4), Brazil (n=1), Australia (n=1) and India (n=1). This indicates a shift in focus from the only medical management to the rehabilitation and long term care for patients with PAH.**

**Key words** Clinical trials - exercise training - International Clinical Trial Registry Platform - pulmonary artery hypertension - trial registry

## Introduction

Pulmonary arterial hypertension (PAH) is a condition in which there is an increase in pulmonary vascular resistance due to multiple, complex problems requiring a multidisciplinary approach<sup>1</sup>. Limitations of patients with PAH to perform cardiopulmonary exercise testing have been thought to be due to problems in the cardiovascular, pulmonary and peripheral skeletal systems thereby causing a decrease in aerobic capacity<sup>2</sup>. These factors lead to severe functional limitations causing a poor quality of life (QoL), emphasizing the need for rehabilitation among these patients with PAH.

Patients with PAH have severe exercise limitations which have been thought to be due to relative hypoperfusion of the well ventilated areas, low lactate threshold and hypoxemia leading to dyspnoea and fatigue<sup>3</sup>. Severe ventilation-perfusion mismatch has been shown to cause intolerable dyspnoea even at low workloads. Another abnormality seen is an impaired rise in stroke volume in response to exercise. This is accompanied by an abnormal rise in heart rate to compensate for the decreased stroke volume. Along with this, the pulmonary vascular system shifts from a high flow/low resistance system to a low flow/high resistance system and there is also a poor recruitment

of the vascular bed due to the absence of free vascular vessels<sup>4</sup>. Other reasons for the symptoms and clinical course are due to an increase in physiological dead space leading to an increase in the ventilatory requirement and exercise induced hypoxia<sup>5</sup>. Another proposed mechanism for exercise limitation is the existence of inspiratory muscle weakness<sup>6</sup> and peripheral muscle weakness causing a “generalised myopathy” among patients with idiopathic pulmonary hypertension<sup>7</sup>.

The trend of advancement in rehabilitation and exercise training for patients with PAH appears to be following a similar trend as in exercise training in congestive heart failure (CHF) which began in 1980<sup>8</sup>. At that time, patients with CHF were excluded from any form of exercise training as it was believed to be detrimental to their condition. However, with a better understanding of pathophysiology and the peripheral muscle involvement, the role of exercise was soon justified. Now, we have substantial evidence to support the need for exercise training in CHF. Even then, patients with class IV symptoms were not considered ideal candidates for rehabilitation and were excluded till the results of the recent HF-ACTION study showed that exercise training was safe in patients even with class IV symptoms<sup>9</sup>. These findings were also supported in a recently published study on home based exercises involving patients with CHF having class IV symptoms<sup>10</sup>.

Exercise training is now gaining popularity and is still in the early stages of research. The first randomized trial was published in 2006 by Mereles *et al*<sup>11</sup>. Following this study, there have been various case series and non-randomized controlled trials published assessing the effects of various rehabilitation interventions on functional capacity and quality of life in patients with PAH. However, most of the studies were conducted on small sample sizes with short durations of follow up. Guidelines by the British Thoracic Society have recommended that patients with PAH ‘remain as active as their symptoms allow’ and that mild breathlessness is acceptable<sup>12</sup>. This is further re-emphasized by the European Society of Cardiology guidelines<sup>13</sup>.

Since 2006 until July 2012, there are currently nine published trials/studies on exercise training in patients with PAH from various parts of the world<sup>11,14-21</sup>. Of these studies, there is only one randomized controlled trial and the remaining are either pre-post designs or case series/reports. One study from UK was presented at the British Thoracic Society conference in which the effects of a rehabilitation programme were studied.

However, only the abstract from the conference proceedings is available<sup>22</sup>. Another presentation by Boutet and colleagues found improvements in endurance with a 12 week exercise programme<sup>23</sup>. Apart from these studies, recent reviews have been published on exercise testing<sup>2,24,25</sup> and training<sup>2,26,27</sup> for patients with PAH. These studies have assessed various forms of training like aerobic training and a combination of aerobic, resistance and respiratory muscle training in patients with idiopathic PAH<sup>11,14,17,18,19</sup>, PAH secondary to congenital heart disease<sup>16</sup>, secondary to connective tissue disorders<sup>15,21</sup> and among various forms of PAH<sup>20</sup>. These studies also found improvements in the six minute walk distance (6 MWD) ranging from 32-87 m following supervised exercise training for 12-18 wk. The studies and their key findings have been summarised in Table I. Grunig and colleagues recently published their study on 183 patient with PAH wherein they found that 13 per cent of those undergoing exercise training experienced adverse events like pre-syncope and supraventricular tachycardia occurring directly due to the exercise<sup>20</sup>. Other adverse events like syncope, respiratory infections and haemoptysis were not linked directly to exercise. Overall, they found patients tolerating exercises well with no worsening of the clinical condition. In another study they showed that exercise training was useful in patients with connective tissue disorders suffering from PAH<sup>21</sup>.

The need for more research in this area is apparent and currently there have been several trials registered in the various clinical trial registries in the world. Therefore, to create awareness and raise interest in exercise training for upcoming researchers and to facilitate more collaborative research in this area, this review was aimed at highlighting the ongoing trials on exercise training in patients with PAH.

### Search strategy

The World Health Organization-International Clinical Trial Registry Platform (WHO-ICTRP) was searched using the key words “pulmonary hypertension”, “pulmonary artery hypertension” “rehabilitation” and “exercise”. The ongoing trials on exercise training (any mode of training) or rehabilitation on patients with PAH were included. Completed and published trials were excluded from the review. Trials were searched between January 2002 and January 2012.

### Observations

The search revealed 56 trials of which seven met the inclusion criteria. The 49 trials were excluded because

**Table I.** Summary of published studies on exercise training in pulmonary artery hypertension

Author (yr)	Study design	Number	Intervention (Intensity)	Duration	Results
Mereles <i>et al</i> (2006) <sup>11</sup>	RCT	30	Exercise + respiratory muscle training	3 weeks – institution based and 15 weeks – home based	Improved 6MWD and QoL for physical function and vitality ( $P<0.005$ )
deMann <i>et al</i> (2009) <sup>14</sup>	Non-randomized, single group pre-post	19	Cycling and quadriceps training	12 weeks – institution based	Improved 6MWD
Shoemaker <i>et al</i> (2009) <sup>15</sup>	Case report	2	Exercise training (50 to 80% of peak workload)	6 weeks – institution based	Improved VO <sub>2</sub> peak and 6MWD
Martinez-Quintana <i>et al</i> (2010) <sup>16</sup>	Non-randomized controlled trial	8	Interval training on bicycle and resistance training	2 days a week for 12 weeks – institution based	No change in 6MWD and QoL
Mainguy <i>et al</i> (2010) <sup>17</sup>	Case series	5	Aerobic and resisted exercises (60% max workload and 70% MVC)	12 weeks – institution based	Improved 6MWD ( $P=0.01$ )
Fox <i>et al</i> (2011) <sup>18</sup>	Non-randomized controlled trial	22	Aerobic and resisted exercises + stair climbing (60-80% HRmax)	12 weeks – institution and home based	Improved VO <sub>2</sub> peak ( $P<0.05$ )
Gurnig <i>et al</i> (2011) <sup>19</sup>	Non-randomized, single group pre-post	58	Aerobic and resistance training + respiratory muscle training	3 weeks – institution based and 15 weeks – home based	Improved 6MWD ( $P<0.001$ ), VO <sub>2</sub> peak ( $P<0.001$ ) and QoL ( $P<0.05$ )
Grunig <i>et al</i> (2012) <sup>20</sup>	Non-randomized, single group pre-post	183	Aerobic and resistance training + respiratory muscle training	3 weeks – institution based and 15 weeks – home based	Improved 6MWD ( $P<0.001$ ), VO <sub>2</sub> peak ( $P<0.001$ ) and QoL ( $P<0.05$ )
Grunig <i>et al</i> (2012) <sup>21</sup>	Non-randomized, single group pre-post	21	Aerobic and resistance training + respiratory muscle training	3 weeks – institution based and 15 weeks – home based	Improved 6MWD ( $P=0.003$ ), VO <sub>2</sub> peak ( $P=0.008$ ) and QoL

6MWD, six minute walk distance; HRmax, heart rate maximum; MVC, maximal voluntary contraction; QoL, quality of life; RCT, randomized controlled trial

these did not include exercise training as part of the intervention (n=45) or were completed trials with their results published (n=4). The included trials registered in the WHO-ICTRP (which is an international platform that links the various trial registries like Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, ISRCTN and other national registries from Brazil, China, India, Korea, Cuba, Germany, Iran, Japan, Pan Africa, Sri Lanka and Netherlands) are summarised in Table II. Recently, Ganderton and colleagues published their study protocol on the short term effects of exercise training in patients with PAH<sup>28</sup>. The National Heart, Lung, and Blood Institute in their recent multidisciplinary

workshop has identified exercise training as a primary thrust area for future research<sup>29</sup>.

The studies currently in process began in 2008. Consequently, there have been studies which have been registered in 2009 and 2010 with three studies being registered in 2011. Of these trials, four are being conducted in Germany and one each in Brazil, Australia and India.

#### The future

Physiological responses of persons with various aetiologies of PAH will be worth exploring to establish if different forms of exercise training are more

**Table II.** Summary of ongoing trials registered in various databases

Database trial registered	Scientific title	Year of registration	Country	Design	Inclusion criteria	Sample size	Intervention	Duration (wk)	Outcome	Status
ClinicalTrials.gov	The NIH Exercise Therapy for Advanced Lung Disease Trials: Response and Adaptation to Aerobic Exercise in Patients With Pulmonary Hypertension: Initial Studies for Establishing Guidelines	2008	Germany	RCT with placebo, single blinded	PH secondary to ILD WHO class I-IV Stable	175	Supervised aerobic exercise	10	Primary outcome: Oxygen consumption, 6MWD, QoL Secondary outcome: Cardiac output Muscle oxygenation	Recruiting
ANZCTR	The effect of exercise training on safety, exercise capacity and quality of life in people with pulmonary arterial hypertension - a pilot study	2009	Australia	RCT	iPH and PH secondary to CTD, CHD and HIV, NYHA II-III	10	Supervised exercise training	8	Primary outcomes: Recruiting Adverse events Adherence Symptoms Secondary outcomes: 6MWD Quadriceps strength QoL	Recruiting
CTRI	Effects of exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: A randomized controlled trial	2010	India	RCT with placebo, single blinded	PPH and PH secondary to CTD, CTEPH	90	Home based exercise training	12	Primary outcome: Recruiting 6MWD, QoL Secondary outcome: Depression Function	Recruiting
ClinicalTrials.gov	Study of Influence of Respiratory and Exercise Therapy on Oxygen Uptake, Quality of Life and Right Ventricular Function in Severe Pulmonary Hypertension	2011	Germany	Randomized, single group, open label	PH	90	Respiratory and exercise therapy	15	Primary outcome: Peak O <sub>2</sub> uptake Secondary outcome: Haemodynamics	Recruiting

*Contd...*

Database trial registered	Scientific title	Year of registration	Country	Design	Inclusion criteria	Sample size	Intervention	Duration (wk)	Outcome	Status
ClinicalTrials.gov	Influence of Respiratory and Exercise Therapy on Oxygen Uptake, Quality of Life and Right Heart Function in Chronic Thromboembolic Pulmonary Hypertension After Thromboendarterectomy	2011	Germany	Randomized, single group, open label	CTEPH after thromboendarterectomy	90	Inspiratory muscle training	15	Primary outcome: Peak O <sub>2</sub> uptake Secondary outcome: Haemodynamics	Recruiting
ClinicalTrials.gov	Influence of Respiratory and Exercise Therapy on Oxygen Uptake, Quality of Life in Patients With Severe Associated Pulmonary Arterial Hypertension (APAH) as Part of a Congenital Heart Defect With/Without Eisenmenger's Syndrome	2011	Germany	Randomized, open label	PH due to congenital heart defects with / without Eisenmenger syndrome	50	Respiratory and exercise therapy	15	Primary outcome: QoL 6MWD Secondary outcomes: Haemodynamics	Recruiting
ClinicalTrials.gov	Inspiratory Muscle Training Effect on the Functional Capacity and the Quality of Life in Chronic Pulmonary Hypertension	2011	Brazil	Randomized, Parallel group, single blind	PAH	34	Inspiratory muscle training	8	Primary outcome: 6MWD Secondary outcome: QoL	Recruiting

6MWD, six minute walk distance; ANZCTR, Australia New Zealand Clinical Trial Registry; CHD, congenital heart disease; CTD, connective tissue disorders; CTEPH, chronic thromboembolic PH; CTRI, Clinical Trial Registry India; ILD, interstitial lung disease; iPH, idiopathic pulmonary hypertension; PAH, pulmonary artery hypertension; PH, pulmonary hypertension; QoL, quality of life

beneficial for PAH of different aetiologies. Dose-response relationships and benefits of various forms of training (either in isolation or combination) with long term follow up need to be assessed. Inspiratory muscle dysfunctions and the effects of training in PAH is an understudied area of research in this domain. The role of peripheral muscle dysfunction has been investigated over the last few years. However, more in-depth studies with cellular, biochemical and radiological outcomes will help in obtaining better insight into the natural course of peripheral muscle dysfunctions and benefits of exercise.

Understanding the cellular response to exercise, both in PAH and healthy subjects, will help understand the benefits seen with exercise training in this group of patients. The influence of exercise on various biomarkers seen in PAH (*e.g.*, NT-proBNP, BNP, Troponin-T, *etc.*) will also need to be explored in future studies. Lastly, epidemiological studies from various geographical regions of the world are essential in determining the burden of the disease. Development of National registries will help in obtaining this information and should be the primary focus of researchers in PAH.

More trials need to focus on rehabilitation of patients with PAH who suffer from severe morbidity. Collaborative studies with those ongoing trials will help expand the horizons of rehabilitation in PAH.

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