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Exercise training in patients with pulmonary and systemic hypertension: A unique therapy for two different diseases

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ABSTRACT

Pulmonary hypertension is a potentially life-threatening condition. Given its evolving definition, the incidence and prevalence of the disease is difficult to define, but registries suggest an increased global awareness. The management of patients with pulmonary arterial hypertension is highly specialised and requires multi-disciplinary input from a range of healthcare professionals, including cardiologists, respiratory physicians, rheumatologists, rehabilitation physicians and cardio-pulmonary physiotherapists. Historically, exercise training in pulmonary hypertension has not been recommended because of safety concerns. However, an increasing number of studies have demonstrated the benefit of exercise training on exercise capacity, peak oxygen consumption and quality of life.

Systemic hypertension is one of the most important risk factors for cardiovascular disease, and has been ranked as the leading cause for death and disability worldwide: therefore, adequate control of blood pressure is important for public health. Lowering of blood pressure and prevention of hypertension is in first instance preferable by lifestyle changes. These include weight loss, moderation of alcohol intake, a diet with increased fresh fruit and vegetables, reduced saturated fat, reduced salt intake, reduced stress, and, finally, increased physical activity. With regard to the latter, former guidelines predominantly recommended aerobic exercises such as walking, jogging, and cycling for lowering blood pressure.

The main focus of this narrative overview paper is to briefly examine and summarize the benefit of exercise training in patients with pulmonary and systemic hypertension, suggest mechanisms by which exercise may improve symptoms and function and provide evidence-based recommendations regarding the frequency and intensity of exercise in these patients.

1. Introduction

Pulmonary hypertension is a potentially life-threatening condition, defined by a mean resting pulmonary artery pressure ≥ 25 mmHg measured by right heart catheterisation [1,2], and is classified into five categories based on pathophysiology [3]. The estimated prevalence of pulmonary hypertension in the Australian population is 326 cases per 100,000, with pulmonary hypertension from left heart disease accounting for 250 cases per 100,000 [4]. While pulmonary arterial hypertension, a specific subgroup of pulmonary hypertension, only has an estimated prevalence of 26 cases per million [5], treatment for this condition has been recently revolutionised by the availability of targeted pharmacotherapies. Given the evolving definition of pulmonary hypertension, the incidence and prevalence of the disease is difficult to define, but registries of prevalent and incident cases from around the world are now available, suggesting an increased global awareness of the disease.

Regardless of etiology, all types of pulmonary hypertension may result in right ventricular remodeling, eventual right ventricular failure and death [6]. Early stages of pulmonary hypertension are often asymptomatic as the right ventricle compensates by maintaining cardiac output. However, with disease progression, patients develop worsening dyspnoea, fatigue, syncope and angina [7,8]. Recent advances in the pharmacological management of pulmonary arterial hypertension have included an increasing range of prostanoids, endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and soluble guanylate cyclase stimulators [9]. Diagnosis of pulmonary arterial hypertension also requires exclusion of significant lung disease and thromboembolic disease or other rare causes of pre-capillary pulmonary hypertension [1]. The management of patients with pulmonary arterial hypertension is highly specialised and requires multi-disciplinary input from a range

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of healthcare professionals, including cardiologists, respiratory physicians, rheumatologists, rehabilitation physicians and cardiopulmonary physiotherapists [7].

Historically, exercise training in pulmonary hypertension has not been recommended because of safety concerns [10]. However, an increasing number of studies have demonstrated the benefit of exercise training on exercise capacity, peak oxygen consumption and quality of life [11–14]. Recent European guidelines recommend that supervised exercise training should be considered in physically de-conditioned patients with pulmonary arterial hypertension that are clinically stable and on optimal pharmacological treatment (evidence Grade IIa, Level B) [2]. However, the optimal duration, intensity, frequency and type of exercise for patients with pulmonary arterial hypertension and the mechanisms of improvement remain a tough question with poor and unclear answers.

A sedentary lifestyle has been characterized as an independent risk factor for cardiovascular disease [15]. Many studies have shown the inverse association between physical activity level and the incidence of cardiovascular diseases [16–18]. Low aerobic fitness is a strong predictor for future cardiovascular disease and all-cause mortality in both healthy and cardiovascular disease patients, including those with hypertension [19–21]. Various mechanisms could be involved in the cardiovascular protective effects of physical activity, including improvement in endothelial function, a decrease in sympathetic neural activity and a reduction in arterial stiffness [22,23].

Systemic hypertension is one of the most important risk factors for cardiovascular disease, and has been ranked as the leading cause for death and disability worldwide: therefore, adequate control of blood pressure is important for public health [24]. Lowering of blood pressure and prevention of hypertension is in first instance preferable by lifestyle changes. These include weight loss, moderation of alcohol intake, a diet with increased fresh fruit and vegetables, reduced saturated fat, reduced salt intake, reduced stress, and, finally, increased physical activity [25,26]. With regard to the latter, former guidelines predominantly recommended aerobic exercises such as walking, jogging, and cycling for lowering blood pressure.

The main focus of this narrative overview paper is to briefly examine and summarize the benefit of exercise training in patients with pulmonary and systemic hypertension, suggest mechanisms by which exercise may improve symptoms and function and provide evidence-based recommendations regarding the frequency and intensity of exercise in these patients. Our compelling hypothesis is that the exercise training could represent a reliable and effective unique therapy for both these two hypertensive diseases significantly different in terms of etiology, physiopathology, consequences and treatment strategy.

2. Benefits of exercise training in patients with pulmonary hypertension and potential mechanisms of improvement

Main results and conclusions of cited studies exploring the reliability and the effects of exercise training in patients with pulmonary hypertension are descripted and summarized in Table 1. The published studies examining the effect of exercise training on pulmonary hypertension explored a wide range of exercise interventions, ranging from an inpatient rehabilitation programme to pure inspiratory muscle training. Many studies reported an improvement in 6-min walking distance post-exercise, which ranged from 32 ± 11 m ($P = 0.0033$) [27] to 98 ± 61 m ($P = 0.0001$) [28]. Recent meta-analyses have concluded that exercise training improves 6-min walking distance by 53.3–72.5 m in patients with pulmonary hypertension (95% confidence interval 39.5–99.1 m) [11–13]. The difference in 6-min walking distance in the training compared to the control group in patients with pulmonary arterial hypertension was 72.5 m (95% confidence interval 46–99.1 m) [13]. This distance was greater than the minimum clinically significant difference of 25–33 m [29]. Interestingly, a meta-analysis of studies of pulmonary arterial hypertension-specific medication reported a mean increase in 6-min walking distance of 35.6 m (95% confidence interval 27–44 m) [30]. These findings suggest that exercise training may result in an improvement in 6-min walking distance at least as great as that achieved with pharmacotherapy. This is important given the low cost of exercise training and the low risk of side-effects. What is not known is whether the benefit of exercise training is limited to tests of exercise capacity or if exercise training improves right ventricular function. Three studies found no improvement in exercise capacity as measured by 6-min walking distance [31–33]. However, these studies were small (combined total of 44 participants) and not powered to detect a change in 6-min walking distance. Two of these studies [31,32] focused on cycling and lower limb strength training and did not include other types of endurance training, such as walking or respiratory muscle exercise. However, improvements in endurance, muscle capillarisation and oxidative enzymes [31] and World Health Organization functional class [32] were noted, suggesting that cycling and lower limb strength training may be beneficial. The remaining study only reported monthly supervision of participants during the exercise programme [33]. Such infrequent supervision may not have encouraged sufficient participant motivation or adherence to the exercise regimen. In addition, exercise training has been associated with improved quality of life with particular benefit on physical and social function [11,28].

Multiple small studies of exercise training have shown a benefit on peak oxygen consumption, possibly because of increased skeletal muscle capillary density [27,28,34].

Table 1
Main studies exploring the reliability and the effects of exercise training in patients with pulmonary hypertension.

Authors and year	Main conclusions
Pandey A et al., 2015 [12]	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.
Buys R et al., 2015 [13]	Exercise training programme positively influences exercise tolerance and functional capacity in patients with pulmonary arterial hypertension.
Babu AS et al., 2016 [14]	There is evidence to recommend the use of exercise training as an adjunct to medical treatment in pulmonary arterial hypertension.
Fox BD et al., 2011 [27]	Ambulatory rehabilitation is a safe and efficacious treatment for patients with pulmonary hypertension already on medical therapy.
Mereles D et al., 2006 [28]	Respiratory and physical training could be a promising adjunct to medical treatment in severe pulmonary hypertension. The effects add to the beneficial results of modern medical treatment.
de Man FS et al., 2009 [31]	Exercise training in idiopathic pulmonary arterial hypertension improves exercise endurance.
Martínez-Quintana E et al., 2010 [32]	Cardiopulmonary rehabilitation appears to be a safe intervention in patients with congenital heart disease and pulmonary hypertension.
Ehlken N et al., 2016 [34]	Exercise training significantly improved peak oxygen consumption, haemodynamics, and further clinically relevant parameters. The improvements of cardiac index indicate that exercise training may improve the right ventricular function.
Ley S et al., 2013 [37]	Respiratory and physical exercise may improve pulmonary perfusion in patients with pulmonary hyperternsion.
Grünig E et al., 2011 [73]	Exercise and respiratory training as add-on to medical treatment may improve exercise capacity and quality of life, and have also a good long-term safety in patients with pulmonary hypertension.
Grünig E et al., 2012 [74]	Exercise training in patients with different pulmonary hypertension forms and functional classes is an effective but not a completely harmless add-on therapy, even in severely diseased patients, and should be closely monitored.

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