

Exercise training in pulmonary hypertension: improving performance but waiting for outcome

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This editorial refers to ‘Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial’[†], by N. Ehlken et al., on page 35.

Introduction

Pulmonary hypertension is a pathophysiological condition characterized by an increase of mean pulmonary arterial pressure ≥ 25 mmHg at rest.¹ Pulmonary hypertension may complicate multiple clinical disorders and invariably it reduces exercise and functional capacity and represents a risk factor for morbidity and mortality.² Although important progress in the pharmacotherapy of pulmonary arterial hypertension has been achieved in the past 15 years,^{3,4} limited functional capacity and reduced survival still characterize patient outcome. Further advances are needed in this area to improve the clinical results of a comprehensive treatment strategy.

Effects of exercise training

Ehlken and colleagues now present the data of a randomized controlled trial on the impact of exercise training on peak oxygen consumption and haemodynamics in 87 patients with pulmonary arterial hypertension or inoperable chronic thrombo-embolic pulmonary hypertension.⁵ The majority of subjects (91%) were on background approved pulmonary arterial hypertension therapies. The exercise training started with an in-hospital 3-week programme and was continued at home with at least 15 min/day for 5 days a week for the following 12 weeks.

After 15 weeks, the peak oxygen uptake (primary endpoint) significantly improved in the training group by +24.3% and the 6-min walk distance improved by 41 m. Haemodynamics at rest and during exercise significantly improved in the training group compared with

the control group. However, the haemodynamic data were collected only in 74 patients (85%). No significant changes in the N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels were observed, and data on WHO functional class changes were missing. Only one out of the eight quality of life domains explored by the SF-36 questionnaire was improved in the training group.

A recent meta-analysis including five randomized controlled studies on exercise training with 106 pulmonary arterial hypertension patients has confirmed an improvement on peak oxygen uptake by 2.16 mL/kg/min and of 6-min walk distance by 72.5 m.⁶ Interestingly, in this meta-analysis too the WHO functional class evaluation did not show significant improvements.

The data in the literature are concordant on the favourable effects of exercise training programmes in the improvement of peak oxygen uptake and exercise capacity in patients with pulmonary arterial hypertension. Interestingly, these improvements are achieved on top of the best standard of care with approved medications.

Mechanisms of exercise training effects

The underlying mechanisms causing the improvements on exercise performance with exercise training are not yet well established.

In patients with pulmonary arterial hypertension, the limitation of exercise capacity may be due to several factors including inactivity, skeletal muscle dysfunction, and right ventricular dysfunction with impaired cardiac output, limiting oxygen supply to the skeletal muscles (Figure 1).

In fact, both respiratory muscle dysfunction^{7,8} and quadriceps muscle dysfunction⁹ were shown in patients with pulmonary arterial hypertension. A study has analysed the physiological effects of exercise training on exercise capacity and quadriceps muscle function in patients with clinically stable idiopathic pulmonary arterial hypertension.¹⁰ In addition, the roles of muscle hypotrophy, fibre type

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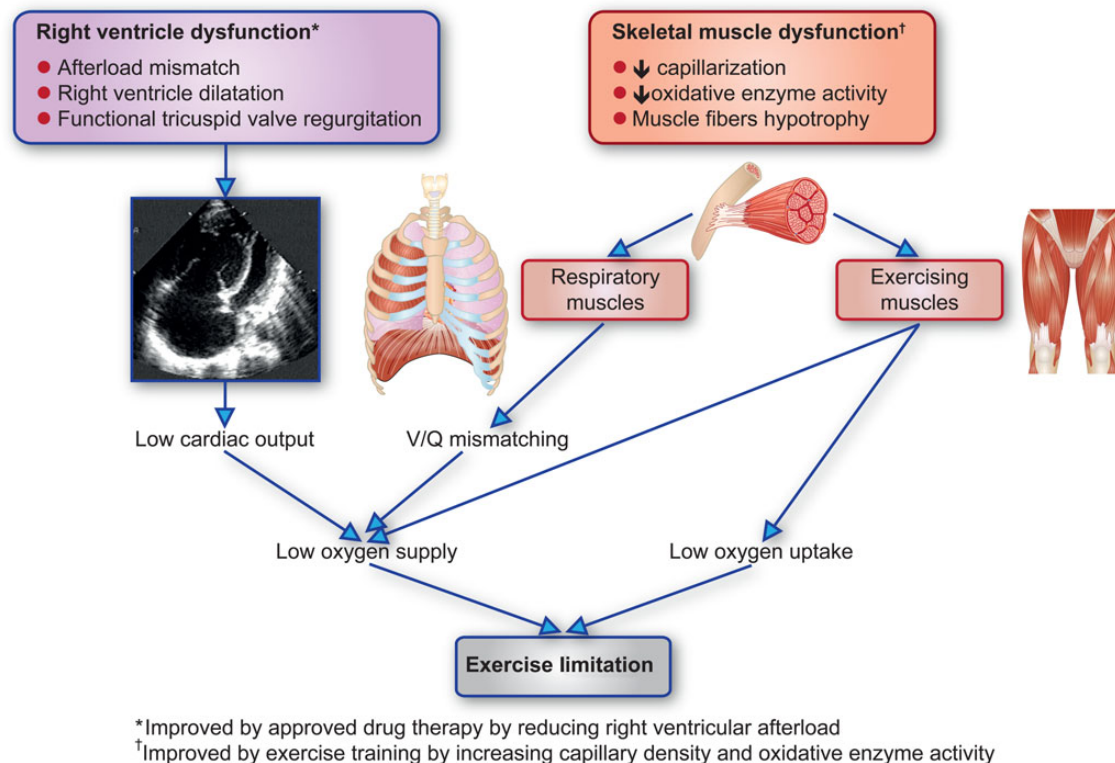


Figure 1 Mechanisms of exercise limitation in pulmonary arterial hypertension and potential effects of drugs therapy and exercise training. Right ventricle dysfunction and skeletal muscle dysfunction are both observed in patients with pulmonary arterial hypertension and those with non-operable chronic thrombo-embolic pulmonary hypertension. Right ventricle dysfunction is characterized by afterload mismatch, right ventricle dilatation, and functional tricuspid valve regurgitation, and it is responsible for a reduced cardiac output. Skeletal muscle dysfunction is characterized by a reduced capillarization and oxidative enzyme activity, and hypotrophy of muscle fibres. These changes affect both respiratory and skeletal muscles involved in exercise. Respiratory muscle dysfunction may impair ventilation and ventilation/perfusion (V/Q) matching, in particular on exercise, thus limiting oxygen supply. Dysfunctional exercising muscles have both a reduced oxygen supply due to a reduced capillary network and a decreased oxygen uptake due to a low oxidative enzyme activity. All the above changes contribute to exercise limitation. Approved drug therapies reduce the afterload, improving the right ventricular function and cardiac output, while exercise training decreases respiratory and exercising skeletal muscle dysfunction, improving both oxygen supply and uptake and also the exercise limitation.

switching, decreased oxidative enzyme activity, or reduced capillary density, were assessed as potential underlying mechanisms of skeletal muscle dysfunction. The 12-week outpatient training protocol increased endurance capacity, without an improvement of maximal capacity. The same phenomenon was seen on quadriceps function: a large improvement in quadriceps endurance was found, and a small (but significant) increase in quadriceps strength. Histological analyses revealed improved aerobic capacity by increased quadriceps capillarization and oxidative enzyme activity, without hypertrophy or fibre type switch. Finally, these morphological changes were strongly correlated with an improvement in quadriceps endurance.

Similar effects of exercise training on skeletal muscle efficiency, capillarization, and oxidative enzyme activity were also observed in chronic obstructive pulmonary disease¹¹ and congestive heart failure patients,¹² suggesting a common pathway for explaining the improvement of exercise capacity in these different clinical conditions.

According to the above data, at least a proportion of the improvement in exercise capacity in patients with pulmonary arterial

hypertension may be due to the favourable effect of exercise training on skeletal muscle dysfunction. The enhancement of the efficiency of respiratory and exercising skeletal muscles by enhanced capillarization and oxidative enzyme activity may improve both the oxygen supply and the oxygen uptake of the exercising muscles (Figure 1).

The possible effects of exercise training on right ventricular function have not yet been established. The improvement of haemodynamics observed at rest and on exercise after training in the study of Ehlken and colleagues seems to support favourable results on the right ventricular function. At rest, a treatment effect in favour of the training group was observed on mean pulmonary arterial pressure (-5 mmHg), cardiac index ($+0.4$ L/min/m²), and pulmonary vascular resistance (-1.3 Wood Units); a similar effect size was observed on cardiac index at peak exercise. However, the authors recognize that an asymmetric rate of missing values may have influenced the haemodynamic results. In fact, 12 (26%) patients in the training group had missing haemodynamic data as compared with only 1 (2%) in the control group. Sensitivity analyses or substitution

rules cannot reconcile this relevant difference. We should await additional more solid and reproducible data before accepting these favourable haemodynamic results.

In addition, the authors do not provide any rationale to justify the haemodynamic improvement, if any, induced by exercise training. Possible hypotheses should include a sort of adaptation of the pulmonary circulation to repeated submaximal increases of cardiac output that may induce a persistent reduction of pulmonary vascular resistance and right ventricular afterload at rest and on exercise. In any case, the average reduction of pulmonary vascular resistance reported in this study was quite small.

Exercise training in patients with congestive heart failure has induced an improvement of the left ventricular ejection fraction in a couple of studies.^{13,14} The authors suggested as potential mechanisms a training-induced improvement of endothelial dysfunction associated with decline in left ventricle afterload. Alternative hypotheses included beneficial effects on cardiomyocytes. However, neither endothelial function nor cardiomyocyte function was assessed in these studies. In addition, data extrapolation to a different model of right ventricular failure with predominant afterload mismatch of patients with severe pre-capillary pulmonary hypertension is not possible.¹⁵

A relevant limitation of all studies on the effects of exercise training is that they cannot be performed in a blinded fashion. The motivation of the patients randomized to the training group could influence the final performance of the primary endpoint test. On the other hand, this unavoidable bias could be considered paradoxically as one of the favourable components of the training programme.

Effects of exercise training on patient outcome

The cardiovascular benefits of regular exercise are established in both world-class athletes and normal individuals;^{16,17} subjects exercising regularly have a longer average life expectancy and a lower incidence of coronary artery disease than their sedentary counterparts.

Ehlken and colleagues also entertain some expectations on outcome improvements by exercise training in patients with pulmonary arterial hypertension or non-operable chronic thrombo-embolic pulmonary hypertension. The improvement of exercise capacity and haemodynamics at rest and on exercise, which are 'strong prognostic predictors in these patients', is their supporting evidence. This quite common misunderstanding includes the concept that both exercise capacity and haemodynamics are surrogate endpoints for outcome in cardiopulmonary diseases.¹⁸ Surrogacy with outcome has never been demonstrated in pulmonary arterial hypertension, and exercise and haemodynamic data are considered only biomarkers.¹⁸ Interestingly, in a recent trial, imatinib, a tyrosine kinase inhibitor, improved consistently both exercise capacity and haemodynamics in patients with pulmonary arterial hypertension but impaired the outcome.¹⁹ A dedicated randomized controlled trial adequately sized and including outcome as the primary endpoint could establish the prognostic effect of exercise training in pulmonary arterial hypertension patients treated with optimized medical therapy.

Exercise training in clinical practice

Exercise training is a well-established adjunct therapy in several chronic diseases such as chronic obstructive pulmonary disease and congestive heart failure. Recent guidelines on pulmonary hypertension also support the use of exercise training in physically deconditioned patients.² Different components of training programmes need to be further clarified before an appropriate application in clinical practice, including the specific indications, the optimal method of exercise rehabilitation, and the intensity and duration of the training. In addition, the characteristics of the supervision are relevant to optimize results, safety, and costs. The 3-week in-hospital initial training period included in the study of Ehlken and colleagues may not be feasible in different healthcare systems. Finally, the recommendation that patients with pulmonary arterial hypertension should avoid excessive physical activity that leads to distressing symptoms needs to be maintained.

Conclusions and take-home messages

There is a large concordance in the medical literature on the favourable effects of exercise training on the physical performance of pulmonary arterial hypertension patients on top of optimized medical therapy. The additional or synergistic effects of training and pharmacotherapy may be related to their different influences on the complex mechanisms leading to exercise impairment (Figure 1): approved drugs reduce the afterload, improving the right ventricular function and cardiac output,²⁰ while exercise training decreases respiratory and exercising skeletal muscle dysfunction, improving both oxygen supply and uptake. There are no conclusive data on the potential favourable haemodynamic and prognostic effects of training. The practical application of exercise programmes in the real world requires further developments and adaptations to different healthcare systems.

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