Exercise Training and Rehabilitation in Pulmonary Hypertension

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KEYWORDS

• Pulmonary hypertension • Pulmonary arterial hypertension • Rehabilitation • Exercise training • Training effects

KEY POINTS

- Exercise training has shown to have a positive impact on exercise capacity, quality of life, hemodynamics, and possibly disease progression and survival.
- The ideal training modality including training frequency, intensity, duration and setting are still to be investigated.
- Owing to the high risks exercise training in pulmonary hypertension might bear, rehabilitation has to be performed in a supervised, closely monitored setting by a multidisciplinary team.
- Possible underlying mechanisms of training effects include a structural change in peripheral and respiratory muscles, improvement of right ventricular function, and reduction of inflammation.
- Further studies are needed to investigate the effects on hemodynamics, disease progression, and survival.

INTRODUCTION

Pulmonary hypertension (PH) is defined by an increase of mean pulmonary arterial pressure at rest of 25 mm Hg or greater and an increase in pulmonary vascular resistance, which is measured by right heart catheterization.[1] Within the last years, several treatments with disease-targeted medication have been developed.[2] However, patients still suffer from subsequent right heart insufficiency,[1] and impaired exercise capacity, quality of life, and prognosis.[3]

Impairment of exercise capacity is mainly influenced by a structural change of the peripheral muscles, as a decreased type I/type II muscle fiber ratio, with a smaller cross-sectional area in the type I fibers, depression of muscle hypertrophy forming a combination of muscle atrophy, and intrinsically impaired contractility,[4,5] which is furthered by weakened respiratory muscles.[6–8] The impairment in exercise capacity directly influences quality of life[9] and leads to anxiety and depression disorders, which are common in patients with PH.[10,11] Consequently, patients with PH are in need of treatment options that enhance their physical abilities, and improve their symptoms and quality of life.[12] Because exercise training might bear the risk of exhaustion causing right heart failure or even sudden cardiac death, patients were formerly advised to avoid overexertion.[13]

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Owing to the positive results of several trials investigating exercise training in PH,[14–22] the new European PH guidelines recommended a supervised and closely monitored exercise and respiratory training as add-on to medication therapy (class IIa, level of evidence B).[1,23] Excessive physical activity that may lead to distressing symptoms should still be avoided (European Society of Cardiology Guidelines, class III, level of evidence C).[1,23]

In this article, the effects, different training modalities and possible pathophysiologic mechanisms and future research questions of training in PH are discussed.

EFFECTS OF EXERCISE TRAINING

Exercise Capacity and Peak Oxygen Consumption

The clinical impact of exercise training in PH has been investigated in several studies, including 5 randomized controlled trials,[15,20–22,24] 2 controlled trials,[25,26] 10 prospective cohort studies,[14,16–19,27–30] 2 case series,[31,32] 1 retrospective cohort study,[33] and 3 metaanalyses.[34–36]

In the first prospective, randomized, controlled trial, exercise training improved the primary endpoint—the 6-minute walking distance (6MWD)—by 96 ± 61 m after 15 weeks compared with the control group (P<.0001).[15] This positive result was supported by a further randomized controlled trials,[21] showing a 14% improvement of 6MWD (P = .002 vs baseline; P = .008 vs controls) and a prospective uncontrolled trial including 183 patients with different PH etiologies reporting a mean 6MWD improvement of 78 ± 49.5 m after 15 weeks (P<.001).[14] Compared with World Health Organization functional classes II and III, class IV patients had the best improvement of exercise capacity.[14] In 14% of the patients, labeled as nonresponders, no improvement of 6MWD was detected.[14] Most of the nonresponders showed a near normal 6MWD (>550 m) at baseline, which most likely influenced the effect. This correlation between walking distance and benefit of exercise training was also confirmed by a retrospective study, showing a significant improvement by exercise training, with a greater benefit for those patients who had a lower 6MWD at baseline.[33] Thus, exercise training might be less effective in patients with higher/near-normal 6MWD.

Analogous to the improvement in walking distance, several studies reported a significant improvement of peak oxygen consumption (V_{O_2}) by exercise training.[14,15,17–19,24,25,27] In a randomized controlled trial, V_{O_2} improved by 3.1 ± 2.7 mL/min/kg (equals +24.3%) in the training group, whereas the control group showed a mild decrease of 0.2 ± 2.3 mL/min/kg (equals +0.9%; P<.001).[24]

The effects of exercise training on exercise capacity have been verified by a metaanalysis showing an improvement of 62.18 m (95% confidence interval [CI], 45.57–78.78 m; P<.0001) in 6MWD, on peak V_{O_2}/kg (pooled mean difference 1.49 L/min/kg; 95% CI, 109–1.90; P<.0001), and on workload (pooled mean difference 14.88 watt; 95% CI, 11.74–18.02; P<.0001).[34] The results of 2 further metaanalyses were similar.[35,36]

Further studies showed an improvement in overall activity level,[20] breathing economics, and gas exchange as oxygen pulse,[14] V_{O_2} at the anaerobic threshold,[15,17,31] minute ventilation,[32] and an improvement in dyspnea impact.[33]

MUSCLE FUNCTION

Several studies have shown that both peripheral as well as respiratory muscles are weakened in patients with PH.[5–7] Peripheral muscle strength may, however, be improved by exercise training, as was displayed by a 12-week standardized cycling and quadriceps training program, which significantly increased quadriceps strength by 13% (P = .005) and endurance by 34% (P = .001).[16] The pooled data of exercise studies in PH revealed a significant improvement of V_{O_2} at the anaerobic threshold (pooled mean difference, 63.55 mL/min; 95% CI, 26.07–101.03 mL/min; P = .0009), suggesting an improvement of muscle economy during exercise.[34]

The effect of exercise training on respiratory muscle strength has been investigated in 1 uncontrolled study.[29] An inpatient training program significantly improved nonvolitional respiratory muscle strength after 3 weeks compared with baseline.[29] Because the respiratory muscle strength was measured by nonvolitional supramaximal magnetic phrenic nerve stimulation, the measured effects were independent of patient compliance and learning effect. The results are however limited by the small sample size (n = 7) and are in need of confirmation in larger cohorts.

QUALITY OF LIFE

One randomized controlled trial displayed a significant improvement in both physical (P = .013) and mental (P = .027) component scale summation scores after 15 weeks of exercise training compared with the control group, in which these domains remained virtually unchanged.[15] The beneficial effect of exercise on quality of life has been confirmed for different forms of PH including chronic thromboembolic PH with a significant