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"Recent Advances in Pulmonary
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Review

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Pulmonary Rehabilitation in Patients With Pulmonary Hypertension

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ABSTRACT

Traditionally, patients with pulmonary hypertension (PH) were advised to limit their physical activity because of the risk of fatal cardiovascular compromise. However, relatively little is known about the risks and benefits of exercise for patients with PH. The present article discussed the effects and safety of pulmonary rehabilitation in PH in light of the current literature. To sum up, exercise training has been reported to significantly improve exercise capacity and quality of life (QoL), whereas the method of intervention, exercise training duration, and patient status (including medically stable patients, immediately after intervention) varied slightly among studies. Furthermore, most of the adverse events were nonfatal and not a direct consequence of exercise training. Accordingly, exercise training in patients with PH seems safe and beneficial. However, the long-term effect of exercise in PH has not been shown. Thus, the precise mechanisms through which pulmonary rehabilitation may influence cardiopulmonary function remains unclear. Future multicenter randomized control trials with longer follow-up duration are needed to further demonstrate the safety, efficacy, and feasibility of exercise training in patients with various types of PH. Although some questions remain, exercise training in patients with PH seems safe and beneficial. Therefore, supervised rehabilitation programs for patients with PH including close monitoring should be encouraged.

KEY WORDS: Pulmonary rehabilitation; Pulmonary hypertension (PH).

ABBREVIATIONS: PH: Pulmonary Hypertension; PAP: Pulmonary Artery Pressure; PAWP: Pulmonary Artery Wedge Pressure; PEA: Pulmonary endarterectomy.

INTRODUCTION

In the past, physical activity was believed to carry a high risk of sudden cardiac death, increased pulmonary remodeling resulting from high shear stress, or worsening of right heart failure in patients with pulmonary hypertension (PH). Therefore, patients with PH were advised to avoid physical activity because of the risk of fatal cardiovascular compromise.^{1,2}

PH is a hemodynamic and pathophysiologic condition defined as an increase in the mean pulmonary artery pressure (PAP) to ≥ 25 mmHg at rest, as assessed with right heart catheterization. According to the values of pulmonary artery wedge pressure (PAWP), PH is defined as either precapillary (PAWP ≤ 15 mmHg) or postcapillary (PAWP > 15 mmHg).^{3,4} PH is categorized into five groups according to the clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy for the multiple clinical conditions.^{4,5} Table 1 shows the clinical classifications of PH. The disease results in a markedly reduced exercise capacity, which is mainly attributable to impaired cardiac output adaptation to the peripheral oxygen requirements.⁶⁻¹⁰ As a consequence, patients with PH can show reductions in peak oxygen uptake, anaerobic threshold, ventilatory efficiency, and 6 min walking distance (6MWD).⁸

Modern PH-specific medications lead to a significant improvement in the symptomatic

Table 1: Clinical Classifications of Pulmonary Hypertension.

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1". Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

BMPR=Bone morphogenic protein receptor type II; CAV1=caveolin-1; ENG=endoglin; HIV=Human immunodeficiency virus; PAH=Pulmonary arterial hypertension.
*5th WSPH Nice 2013.

status of patients and a slower rate of clinical deterioration. Especially, in patients with chronic thromboembolic PH (CTEPH), pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA) are highly effective in improving pulmonary hemodynamics and exercise capacity.¹¹⁻¹³

Traditionally, patients with PH were advised to limit their physical activity because of the risk of fatal cardiovascular compromise. This risk arises because during exercise, the PAP and right ventricular (RV) after load increase, resulting in a transient elevation of RV wall stress.² However, relatively little is

known about the risks and benefits of exercise for patients with PH. The present article discusses the effects and safety of pulmonary rehabilitation in PH in light of the current literature.

Pulmonary Rehabilitation in Patients with PH

Mereles et al¹⁴ first reported a prospective, controlled, randomized study showing that low-dose exercise (including interval bicycle ergometer training with a low workload, walking exercise, and dumbbell training) and respiratory training (including stretching, breathing techniques such as pursed lip breathing, body

perception exercises, yoga, and respiratory muscles strengthening) significantly improved exercise capacity, 6 MWD, quality of life (QoL), World Health Organization functional class, and peak oxygen consumption. Importantly, improvements in exercise capacity and QoL after pulmonary rehabilitation were observed although the medication remained unchanged during the study period. The results of the study indicated that respiratory and exercise training might add to the effectiveness of optimized medical therapy. Recently, Ehlken et al¹⁵ reported that exercise training (including interval cycle ergometer training with low workload, walking exercise, dumbbell training of single muscle groups by using low weights [500-1000 g]) and respiratory training improved peak oxygen consumption and hemodynamics in patients with severe pulmonary arterial hypertension and inoperable CTEPH. This study reported that exercise training significantly improved cardiopulmonary parameters such as pulmonary vascular resistance and cardiac index at rest and during exercise, leading to an increase in exercise capacity. The effect of exercise training on cardiopulmonary function is of high interest; however, the precise mechanism through which exercise-based interventions benefit patients with PH remains unclear.

In several previous studies, exercise training was implemented only in medically stable patients with no recent change in symptoms and medication/treatment. However, Fukui et al. reported the efficacy of cardiac rehabilitation after BPA for CTEPH.¹⁶ Importantly, the study rehabilitation protocol was initiated immediately after the final BPA. Moreover, no patient experienced adverse events or deterioration of right-sided heart failure or hemodynamics, as confirmed with catheterization. Concerning BPA, we previously reported the influence of this procedure on the respiratory function of patients with CTEPH.¹⁷ The study showed that the effect of BPA on respiratory func-

tion varies depending on the BPA fields. Taking these results together, the patient's condition and response to treatment, and differences in the exercise program, such as the type of exercise and the training intensity, should be taken into consideration in each case.

In several previous reports, exercise training has been reported to significantly improve exercise capacity and QoL, whereas the method of intervention, exercise training duration, and patient status (including medically stable patients, immediately after intervention) varied slightly among studies.^{14-16,18-27}

Risk Management for PH During Pulmonary Rehabilitation

According to previous reports on pulmonary rehabilitation, intensity was systematically reduced if SpO₂ decreased to <85-90% and heart rate was >120-130 beats/min, and exercise was stopped in cases of exercise-induced hypotension or excessive discomfort (Table 2).^{14,15,18-24,27} Despite these recent reports on the efficacy of pulmonary rehabilitation for PH, the safety of pulmonary rehabilitation is still controversial.

Patients with PH may be at a greater risk of developing complications during exercise, such as desaturation, syncope, chest pain, arrhythmia, or dizziness. However, there are no standard criteria for discontinuation of pulmonary rehabilitation in patients with PH. Moreover, it is not clear which parameters need to be continuously monitored during exercise.

Several studies have investigated exercise- and non-exercise related adverse events.^{28,29} Pandey et al²⁹ summarized the exercise and non-exercise-related adverse events reported in 17 studies. In their study, adverse effects were observed in 4.7%

Table 2: Indications for Termination of Exercise and Adverse Events.

Author	Year	n	WHO-FC	Indications for termination of exercise	Adverse events n (%)
Mereles et al ¹⁴	2006	30	II – IV	HR>120 bpm SpO ₂ <85%	3 (10%)
de Man et al ¹⁸	2009	19	II – III	SpO ₂ <85% HR>120 bpm	0%
Mainguy et al ¹⁹	2010	5	II – III	SpO ₂ <85%	2 (40%)
Fox et al ²⁰	2011	22	II – III	SpO ₂ <90%	4 (18)
Grunig et al ²¹	2011	58	II – IV	SpO ₂ <85%	12 (20.6%)
Grunig et al ²²	2012	183	II – IV	SpO ₂ <85%	24 (13%)
Grunig et al ²³	2012	21	II – IV	SpO ₂ <85%	3 (14.2%)
Nagel et al ²⁴	2012	35	II – IV	SpO ₂ <90%	5 (14.3%)
Kabitz et al ²⁷	2014	7	III – IV	HR>130 bpm SpO ₂ <85%	0%
Ehlken et al ¹⁵	2016	58	II -IV	SpO ₂ <90%	0%

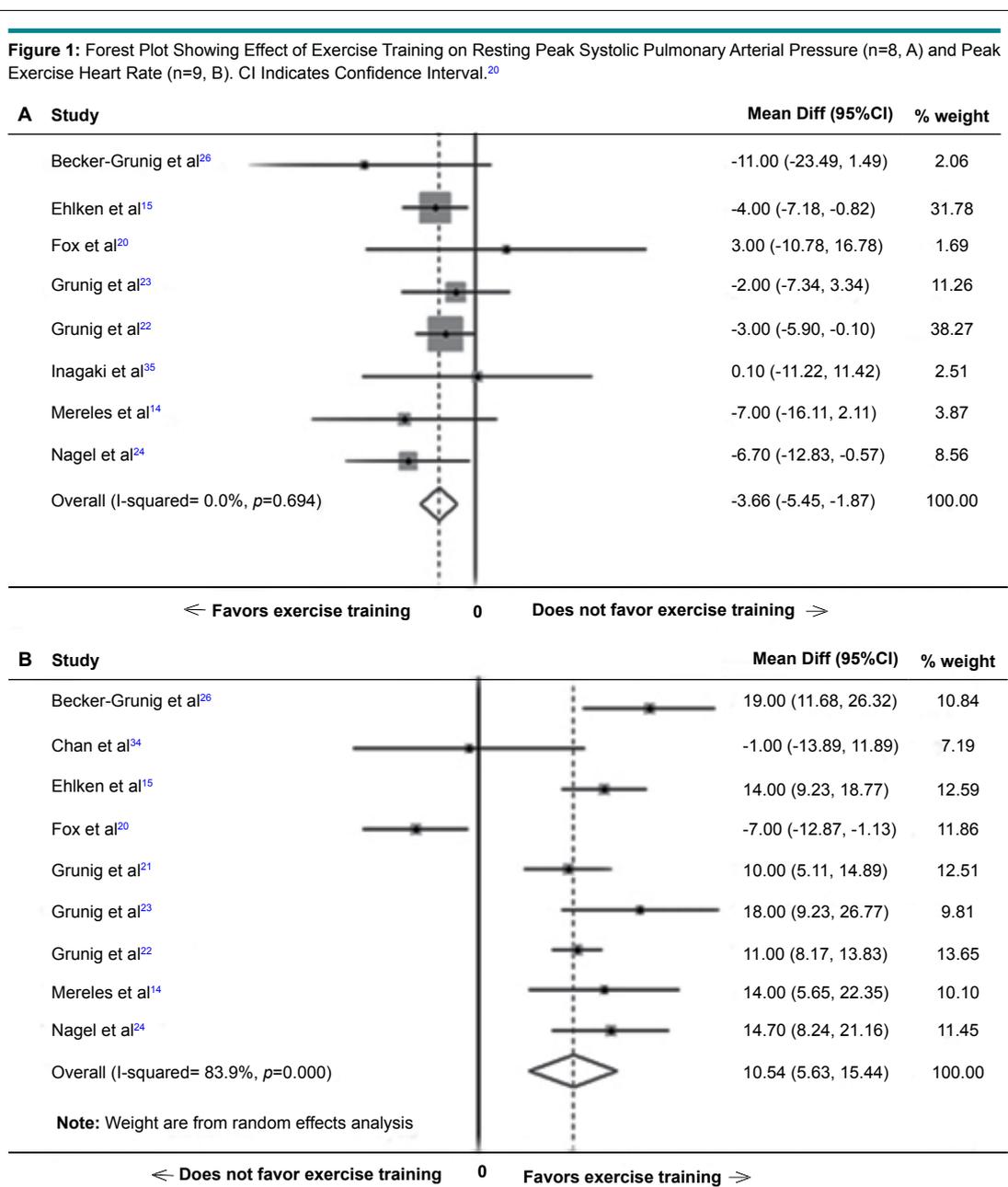
WHO-FC = World Health Organization functional class.

of all patients (N=480), two-third of which were related to exercise training (in 3.1% patients). Most of the adverse events were nonfatal and not a direct consequence of exercise training.

The meta-analysis showed that exercise was associated with significant improvements in 6 MWD, peak VO₂, and QoL, whereas the method of intervention and the exercise training duration varied slightly among studies.²⁹ Moreover, the study showed that exercise training was associated with a significant improvement in resting PAP and peak exercise heart rate from baseline to follow-up (Figure 1). Importantly, exercise training was well tolerated and had a low dropout rate, and no major adverse events related to exercise training were reported. Never-

theless, more adverse events may have possibly occurred during the exercise stress test.

Cardiopulmonary exercise training (CPX) is widely recommended for evaluating disease severity in patients with PH.^{30,31} In most of the reported studies, a symptom-limited maximal test had been performed (rating of perceived exertion $\geq 17/20$ in the Borg scale), unless patients met another indication for test termination, including the development of significant angina, hypotensive blood pressure response (defined as a drop in systolic blood pressure >10 mmHg below the resting blood pressure), horizontal or down-sloping ST depression of >2.0 mm, or ventricular tachycardia of >5 beats in duration. Skalski



et al³² reported the safety of CPX in their study that included 194 patients with PH. More than half of the patients with PH had an echocardiographic estimate of RV systolic pressure of >40 mmHg. None of the adverse events occurred in patients with PH during CPX; thus, it can be performed safely.

Changes in the 6 MWD are used to evaluate the efficacy of therapeutic interventions including drugs, PEA, BPA, and rehabilitation. The risk of adverse events during the 6 min walking test (6MWT) was recently demonstrated by Morris et al³³ in their report of three cases. Therefore, although exercise training did not result in many adverse events, there is some evidence to suggest that performing simple tests such as the 6 MWT requires careful monitoring to ensure safety in these patients.

Future Recommendations

This study shows that exercise training may be highly effective in patients with PH. However, the long-term effect of exercise in PH has not been shown. Thus, the precise mechanisms through which pulmonary rehabilitation may influence cardiopulmonary function remains unclear. Future multicenter randomized control trials with longer follow-up duration are needed to further demonstrate the safety, efficacy, and feasibility of exercise training in patients with various types of PH.

CONCLUSION

Although some questions remain, exercise training in patients with PH seems safe and beneficial. Therefore, supervised rehabilitation programs for patients with PH including close monitoring should be encouraged.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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