Rehabilitation in patients with pulmonary arterial hypertension

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Abstract: Exertional dyspnoea is a leading symptom in patients with pulmonary arterial hypertension (PAH). Patients suffering from PAH report poor quality of life, have skeletal muscle dysfunction and in the absence of advanced medical therapy deteriorate progressively due to right heart failure which can lead to death. For decades, patients with PAH were advised to avoid exercise in fear of exacerbated right heart failure. Recently, it has been shown that a highly supervised rehabilitation programme in expert centres leads to significant improvements in symptoms, quality of life, exercise capacity and may even enhance haemodynamics in selected stable patients treated with advanced regimens of PAH-targeted drugs. As a consequence of these promising results, pulmonary rehabilitation performed in an expert centre has been included in recent guidelines. The underlying mechanisms are not completely understood, but positive effects can be measured in different organ systems such as skeletal muscles, the cardiopulmonary system and immune system (inflammation), and also on the psychological level. Thus, improvements in 6-minute walking distance (6MWD), peak oxygen uptake (VO2 peak), muscle strength and muscle endurance, as well as physical and mental quality of life scores (SF-36 questionnaire) have been shown. Different training protocols have been used. Essential are qualified patient selection in expert centres, a low workload endurance and dumbbell (weight lifting) training avoiding strenuous exercise and exhaustion, thorough patient education and close supervision by experts especially during the first weeks. Adverse events may occur (e.g., pre-/syncope, arrhythmia, respiratory infections). PAH patients tend to overestimate their physical capacity, not perceiving their own limits properly, which makes education and expert advice even more important as exercise training can also worsen the right heart failure. Therefore, a core issue of the multidisciplinary rehabilitation is the close cooperation between the experienced rehabilitation clinic offering a specialised programme for PAH patients and the PAH expert centre, which takes care of the patient and is thoroughly involved in the training programme. Further multicentre international randomised trials are needed to evaluate whether this specialised programme is feasible within different healthcare systems and to assess long term effects and survival.

DOI: https://doi.org/10.4414/smw.2017.14462

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Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Medical guidelines | Published 07 July 2017 | doi:10.4414/smw.2017.14462
Cite this as: Swiss Med Wkly. 2017;147:w14462

Rehabilitation in patients with pulmonary arterial hypertension

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Summary

Exertional dyspnoea is a leading symptom in patients with pulmonary arterial hypertension (PAH). Patients suffering from PAH report poor quality of life, have skeletal muscle dysfunction and in the absence of advanced medical therapy deteriorate progressively due to right heart failure which can lead to death. For decades, patients with PAH were advised to avoid exercise in fear of exacerbated right heart failure. Recently, it has been shown that a highly supervised rehabilitation programme in expert centres leads to significant improvements in symptoms, quality of life, exercise capacity and may even enhance haemodynamics in selected stable patients treated with advanced regimens of PAH-targeted drugs. As a consequence of these promising results, pulmonary rehabilitation performed in an expert centre has been included in recent guidelines. The underlying mechanisms are not completely understood, but positive effects can be measured in different organ systems such as skeletal muscles, the cardiopulmonary system and immune system (inflammation), and also on the psychological level. Thus, improvements in 6-minute walking distance (6MWD), peak oxygen uptake (VO_2 peak), muscle strength and muscle endurance, as well as physical and mental quality of life scores (SF-36 questionnaire) have been shown. Different training protocols have been used. Essential are qualified patient selection in expert centres, a low workload endurance and dumbbell (weight lifting) training avoiding strenuous exercise and exhaustion, thorough patient education and close supervision by experts especially during the first weeks. Adverse events may occur (e.g., pre-/syncope, arrhythmia, respiratory infections). PAH patients tend to overestimate their physical capacity, not perceiving their own limits properly, which makes education and expert advice even more important as exercise training can also worsen the right heart failure. Therefore, a core issue of the multidisciplinary rehabilitation is the close cooperation between the experienced rehabilitation clinic offering a specialised programme for PAH patients and the PAH expert centre, which takes care of the patient and is thoroughly involved in the training programme. Further multicentre international randomised trials are needed to evaluate whether this specialised programme is feasible within different healthcare systems and to assess long term effects and survival.

Key words: pulmonary arterial hypertension, pulmonary hypertension, rehabilitation, exercise

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Introduction

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculature leading to an increase in pulmonary vascular pressure (mean arterial pulmonary pressure ≥25 mm Hg) causing exertional dyspnoea and progressive right heart failure. Exertional dyspnoea is the hallmark symptom of the disease. In early stages the exertional dyspnoea is often not attributed to PAH, which leads to a delay in the diagnosis in many cases. When the vascular remodelling is more advanced and the pulmonary artery pressure rises, further symptoms of right heart failure develop such as presyncope or syncope and clinical signs of right-sided heart failure [1]. For many years, PAH patients were advised not to practice strenuous activities and sports. Exercise was feared because of a possible risk of sudden cardiac death, increased pulmonary remodelling resulting from higher shear stress during activity, and worsening of right heart failure [2]. Because of a lack of efficacy data, in the guidelines of 2009 rehabilitation was considered only in special circumstances, such as in deconditioned PAH patients, and only in a highly supervised setting with avoidance of strenuous and excessive physical activity [3]. Since then, more studies have been performed that provided clearer evidence of improvements of symptoms and exercise performance with reassuring data on safety [4, 5]. However, it must be emphasised that the patients in these studies were all in a stable condition, on advanced drug therapy, under close supervision in PAH expert centres and the training was specially designed for PAH patients. In the new updated guidelines of 2015, this highly specialised PAH rehabilitation is recommended for stable patients on optimised pharmacological treatment and with the notion that supervised rehabilitation should be implemented by centres experienced in both PAH patient care and rehabilitation of compromised patients (class IIa

recommendation, evidence level B). Optimised pharmacological treatment is defined as single or combination therapy with PAH-targeted drug therapy such as calcium-channel blockers, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators and prostacyclin analogues. The guidelines also clearly suggest that such an expert centre should consist of a multidisciplinary team including cardiology and respiratory medicine physicians, specialised nurses and radiologists. Furthermore, a direct link to adult congenital heart disease units, pulmonary endarterectomy surgeons and a lung transplantation programme is proposed. Regarding size and daily routine of the expert centre, it is required that at least 50 patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) should be followed up, and the expert centre should have two new referrals per months [1].

Rehabilitation, reactivation and physical activity

In ancient times, walking and physical activity were already recognised as one of the most effective medicines. Hippocrates, the famous Greek physician and outstanding figure in the history of medicine, was reputed to have said "walking is man's best medicine". Chronic cardiorespiratory disorders with disabling symptoms lead to physical inactivity, skeletal muscle dysfunction and compromised quality of life. In addition to optimal medical therapy, it is thus important to improve exercise capacity and physical activity in these patients [6, 7]. Rehabilitation is a very potent, important and evidence-based intervention to achieve these essential goals. It is a comprehensive intervention that not only consists of exercise training, but also includes a multidisciplinary team, which provides information, counselling and therapeutic interventions leading to an improved physical and emotional status, and supports behavioural changes to a more health promoting lifestyle in daily life [6, 7]. Especially for PAH patients, it is essential to recognise their physical limits and avoid overexercise in order to prevent dangerous side effects of exercise.
It is known that healthy persons and chronically ill patients with higher physical activity in their daily life have a better long-term survival than less active controls [8–11]. Epidemiological studies also showed a reduced incidence of cardiovascular disease, cancer and diabetes with a more active lifestyle [12, 13]. In patients with chronic obstructive pulmonary disease (COPD), higher physical activity is linked to lower hospital admissions and reduced mortality [9]. Therefore, it is a great issue in rehabilitation to get disabled chronic respiratory patients back on track by improving their exercise capacity and promoting an active lifestyle that leads to a sustained behavioural change, improved self-management and increased self-efficacy. This knowledge and practice in general cardiopulmonary rehabilitation cannot be extrapolated to PAH patients without modification, because this patient group is different in many ways. Patients are often unaware of their own physical limits and tend to overexercise, which could worsen right heart failure.

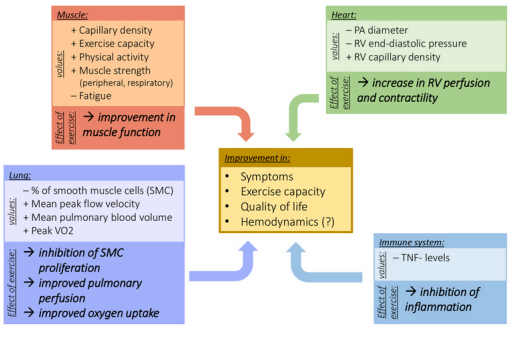
Pathogenetic mechanisms

The exact pathophysiological mechanisms by which exercise leads to beneficial or harmful effects are not yet fully understood. In mice, exercise training prevented hypoxia-induced pulmonary vascular remodelling, and improved exercise capacity and pulmonary haemodynamics [14]. The effect on physical capacity was greatest in mice who received drug treatment (sildenafil) in combination with exercise training. Prevention of right ventricular hypertrophy was not achieved, though. In other rat and mice experiments, reduction in pulmonary artery diameter and right ventricular end-diastolic pressure, improved capillary density and attenuation of acute vasoconstriction in response to hypoxia were demonstrated [15, 16]. Inflammation is involved in the development of PAH, and exercise training has been shown to reduce inflammation in patients with chronic heart failure and PAH [17–19].
Skeletal muscle is a key component of exercise performance. Nowadays, skeletal muscle has been identified not only as an organ translating energy into force but also as a secretory organ. It is the largest organ in the body and exerts paracrine, autocrine and endocrine effects by releasing different mediators [20]. These various mediators, some of them not known in detail yet, lead to multiple effects such as better adipose tissue oxidation, improvement in insulin sensitivity, better osteogenesis, anti-inflammatory effects, higher antitumoural defence, improved pancreas function and probably even favourable neurocognitive effects [21, 22]. The skeletal muscle in PAH patients is altered and shows lower capillarisation, fewer type IIa fibres, less oxidative enzyme activity, reduced contractility and muscle atrophy [23–25]. Exercise training can significantly improve these alterations in muscle tissue. The mechanisms and effects of exercise training on PAH are summarised in figure 1.

Rehabilitation programme in pulmonary arterial hypertension

Most of the evidence, understanding and experience in pulmonary rehabilitation results from patients with COPD, as this is the largest group of patients referred to pulmonary rehabilitation programmes. The rehabilitation programme for patients with PAH should be clearly distinguished from these common programmes, and specifically tailored for this rare patient group with its special needs. Besides a distinct patient educational programme, there are important issues to consider in the exercise training protocols in or-

Figure 1: Effects of exercise training in PAH patients. Adapted from [26].



der to guarantee the highest level of safety possible in this sensitive disease group. Other interventions such as psychological, social and nutritional support are widely shared over chronic diseases, but have to be individualised based on a careful initial assessment.

Over the last 10 years, several studies in PAH patients investigated different training protocols. A worldwide consensus on how to train PAH patients does not exist. The need for clarification through further studies is underscored by the foundation of a specific task force on rehabilitation endorsed by the European Respiratory Society, which will hopefully lead to high quality research in this field. PAH training programmes consist of aerobic and resistance training, which may vary among centres. Most published studies were conducted in the PAH centre in Heidelberg, Germany [2, 26]. They established a training programme, which started as a 3-week inpatient training followed by a home-based training after profound instruction and supervision of the respective expert centre. Before the rehabilitation and right after the 3-week in-hospital programme, patients are evaluated in the PAH centre to assess stable status under optimal PAH medical therapy, to assess the initial exercise training intensity, and to counsel patients and trainers. During these visits at the expert centre, every PAH patient is assessed by echocardiography at rest and during exercise and by ergospirometry to evaluate peak oxygen uptake (peak VO_2), heart rate response to exercise, contractile reserve and further safety parameters. During the following 3 weeks of in-hospital rehabilitation, the physicians for rehabilitation stay in daily contact with the PAH experts. The rehabilitation programme consists of low-intensity interval bicycle ergometer training (average workloads only 5 to 40 watts) for 10 to 25 minutes in a supervised and monitored setting, low-dose dumbbell training of single muscle groups with low weights, and respiratory therapy, in which patients are taught perception of breathing and methods to relieve dyspnoea (deep breathing exercises and positions facilitating respiration). Patients are also educated in perceiving their physical limits and optimal pacing in guided mental walking training under supervision of specially trained physiotherapists [4]. Other centres have also used treadmill walking for 30 to 45 minutes under similarly intensive supervision [27, 28]. In summary, the majority of published studies used aerobic exercise training with low workload (intensity titrated between 40 to 80% of peak exercise capacity). Participants in these studies were clinically stable and treated with optimised PAH drug therapy without signs of overt right heart failure. Training was performed under close supervision by PAH experts [26, 28]. The different components of the rehabilitation programme are listed in table 1.

Evidence and effects of rehabilitation in pulmonary vascular disease

The body of clinical data has grown over the last years, but randomised controlled studies are still scarce. Most studies are performed in an in-hospital setting for safety reasons and, as underscored above, all these studies have been performed in a highly specialised setting under close expert supervision. To increase knowledge in this field, larger multicentre international studies including patients in various healthcare systems are highly desired, and hopefully the task force on PAH rehabilitation of the European Respiratory Society will advance this field. In a review article and a systematic review, the pooled number of patients included in studies were approximately 470 [26, 28]. Beneficial effects of exercise training are improvement in exercise capacity measured by the 6-minute walking distance (6MWD), VO_2 peak and higher oxygen uptake at anaerobic threshold (VO_2 at anaerobic threshold), increased cardiac output [29], and improvement in muscle strength and muscle endurance. Also, patient-reported outcomes such as the physical and mental quality of life scores measured with the SF-36 questionnaire improved significantly, especially in the domains of physical functioning, role physical, general health perception, vitality, social functioning, role emotional and mental health [4].

The improvement in the 6MWD was replicated in several studies. In a systematic review of 16 studies with a total of 469 participants, the weighted mean improvement was 53.3 m, exceeding the minimum clinically important difference of 33 m by far [28, 30]. This significant improvement of exercise capacity in patients on advanced disease-targeted drug treatment highlights the value of this structured rehabilitation. The effects were robust in different forms of pulmonary vascular diseases, such as idiopathic PAH, associated PAH, CTEPH and pulmonary hypertension due to respiratory or left heart diseases [5]. Self-reported compliance rates with the regular physical exercise training after the inpatient rehabilitation were high (vary from 92 to 61%) and patients with higher compliance had a better increase in their physical capacity. The follow-up period ranged from 15 weeks up to 5 years. If effective self-management behaviour can be achieved, the effects are sustainable and a very favourable long-term survival has been observed [2, 31–33].

As for every intervention, there are nonresponders to exercise training, and future research may clarify which patients may not respond or even deteriorate. Some patients experience adverse effects during the rehabilitation programme (e.g., syncope, worsening of right heart failure or respiratory tract infection). Exercise training may also not be suitable for every patient with pulmonary vascular dis-

Table 1: Different components of the rehabilitation programme in patients with pulmonary arterial hypertension (PAH).

Intervention	Comment
Expert education and supervision	It is a prerequisite for training in PAH to perform this in collaboration with a PAH expert centre with programmes specifically tailored to groups of PAH patients.
Aerobic exercise training	Low workload, e.g., aerobic bicycle training (40–80% of peak exercise capacity). Monitoring oxygen saturation (>90%) and heart rate (<120/min). For 10 to 25 minutes. Frequency: daily.
Resistance training	Dumbbell with low weights for 30 minutes. Frequency: 5 times/week.
Mental walking training	Guidance in exploring individual physical limits and pacing. Frequency: several times/week.
Respiratory therapy	For 30 minutes. Frequency: 5 times/week.
Psychological support	If needed.
Nutritional support	If needed.
Social service	If needed.
Instruction in inhalation device	If needed.

ease, or may need to be specifically tailored to subgroups, such as patients with comorbidities (orthopaedic problems, mental disorders such as depression and anxiety) or for very young patients with an early diagnosis who are already relatively fit, as indicated by near-normal 6MWD (>550 m) [26].

Adverse events and practical aspects

In published studies, adverse events in highly specialist centres under expert supervision were relatively rare. In the largest study, a total of 13.6% of participants suffered adverse events. Nearly half of these patients developed acute respiratory infections that had to be treated with antibiotics and needed intermittent discontinuation of the training programme [5]. Other events were presyncope, syncope, arrhythmias and haemoptysis. In some studies dizziness, palpitation, hypotension and oxygen desaturation were also reported. These adverse events occurred in less than 5% of patients [28]. PAH participants are often not aware of their physical limitations, tend to exaggerate physical training and need to be slowed down. They also have to be guided and taught to recognise their own limits. In some centres, including ours, a mental gait training, in which patients learn to perceive their limit and learn to pace themselves adequately, is successfully established to address this need. To reach this goal, a good relationship between the patient and the therapist is needed, which can be built during individual sessions and therapy in small groups.

To minimise adverse events, some safety precautions have to be implemented when starting any PAH patient on a physical training programme. As repeatedly stated, it is a prerequisite that every PAH patient is in a clinically stable condition on optimised PAH targeted medication for at least 2 months under expert supervision [26]. Additionally, it is strongly recommended to start the rehabilitation programme in an inpatient setting, where both close supervision during training and observation after the training is possible, especially for patients in functional class III–IV, as adverse events can occur hours after training. It is crucial that training is initiated with very low workloads (between 40–-80% of peak exercise capacity). Oxygen saturation and heart frequency should be monitored closely (saturation >85%, peak heart rate <120 per minute). The dumbbell training has to be performed with low weights involving single muscle groups only. The main recommendations are summarised in table 2.

Conclusions

Pulmonary rehabilitation in PAH patients is a recommended therapy in addition to optimal medical therapy with PAH targeted drugs, if performed in a highly experienced team under expert supervision. Supervised rehabilitation should be implemented by centres experienced in both PAH patient care and rehabilitation of compromised patients, and be especially tailored to groups of PAH patients. It leads to significant improvements in symptoms, exercise capacity and quality of life. The pathomechanisms are not fully understood yet. Patients starting exercise training have to be in stable condition on optimised medical therapy. In close collaboration with and supervision by a PAH expert centre, specially tailored exercise training for PAH patients is relatively safe. It is essential to use a low workload exercise protocol with careful individual adjustments, to avoid overloading of patients. The core piece of the pulmonary rehabilitation programme is to teach PAH patients to accept the disease, not to overdo themselves and to continue with low-dose exercise training for at least 15 minutes per day at least 5 days per week. Further randomised controlled studies are needed to assess whether this specialised PAH training programme can be implemented in different healthcare systems and to evaluate the effect of exercise training on follow-up and survival.

Acknowledgements

We would like to thank Leonie Lagler Martin and Chris Martin for the critical review of the manuscript and their appreciated suggestions.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

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Table 2: Safety precautions and adverse effects of exercise training in pulmonary arterial hypertension (PAH).

Safety precautions
Inclusion of stable patients on optimised PAH targeted therapy and without signs of heart congestion after a thorough assessment in an expert centre
Intensively supervised start of the exercise programme, if possible in an in-hospital setting
Continuously supervised exercise training by experts
Avoidance of exhausting exercise (low workload ; training range between 40 and 80% of peak exercise capacity)
Adequate oxygen supplementation; avoidance of deep desaturation
Dumbbell training of single muscle groups with low weights
Potential adverse effects to be considered and immediately treated
Respiratory infections
Presyncope, syncope, dizziness, hypotension
Arrhythmias
Haemoptysis

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