Exercise training for patients with pulmonary arterial hypertension

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Summary

In spite of evidence-based consensus recommendations on exercise training for patients with pulmonary arterial hypertension (PAH) its use outside specialized rehabilitation Centers has been accounted a handful of reports. Dyspnoea and fatigue are common symptoms reducing the exercise tolerance of subjects with PAH even when specific drug are correctly administered. Moreover, the mechanisms of exercise limitation in subjects with PAH are known and thandful of reports. There is evidence of impaired signaling between the periphery and central hemodynamic performance. Exercise training has recently been proven to be effective and safe to enhance physical performance in patients with PAH already treated with specific drug therapy. The rationale of training in PAH has been specifically proven also in experimental animal models of PAH. Moreover, repeated positive results in randomized controlled trials and observational studies in humans gave convincing evidence on the beneficial effects of exercise training as a routine treatment for patients with PAH. To date only 3 small randomized controlled trials and several non-randomized experiences were published in the last decade. Nevertheless, there is a full concordance among all studies, unrespective of the design, training protocol and any possible bias. Exercise training showed to improve physical performance and daily activity, reducing dyspnoea and fatigue, and enhancing the quality of life and muscle strength. So, the final message from the available literature reports is a strong recommendation to adopt exercise training and cardiopulmonary rehabilitation programs for any patient suffering from exertional dyspnoea and fatigue. Many questions remain unanswered regarding the optimization of the exercise training and rehabilitation programs. Ongoing rehabilitative trials in patients with PAH will help answer some of the remaining questions.

KEY WORDS: pulmonary arterial hypertension; dyspnoea; exercise limitation; exercise training; pulmonary rehabilitation.

Introduction

Pulmonary arterial hypertension (PAH) is a hemodynamic condition defined by a pre-capillary resting pulmonary artery pressure at or above 25 mm Hg mean value that can be the result of a variety of diseases of different causes, but similar clinical picture and virtually identical pathological changes of the distal pulmonary arteries (1, 2). During the Fifth World Symposium on pulmonary hypertension (PH) held in 2013 in Nice, the clinical classification of pulmonary hypertension (2) identified five groups of disorders according to pathological, pathophysiological and therapeutic characteristics, but the term PAH may only be applied to a subgroup of the group 1 including eight rare clinical conditions characterized by pre-capillary PH in absence of other causes of pre-capillary PH such as lung diseases, chronic pulmonary thromboembolism (CTEPH), or rare diseases related-PH with unclear multi-factorial mechanisms. Despite a number of specific drugs are available by now for PAH treatment, exertional dyspnoea is a common progressively disabling symptom, shared either by idiopathic and secondary PAH, still affecting well treated patients. Exercise training (ET), a major component of pulmonary rehabilitation programs, is an established treatment to enhance exercise limitation for patients with chronic obstructive pulmonary disease (COPD), systolic left heart failure, and a variety of chronic respiratory diseases (3). Past recommendations supported limitation of any exertion or physical

A recent growing body of evidence supported monitored exercise training programs for patients with PAH as a safe tool to improve exercise tolerance and quality of life.

activity by PAH patients to avoid the risk of severe dyspnoea persisting post-exercise, dizziness, syncope or chest pain, and it was also commonly believed that physical training may have a negative impact on patients by contributing to the evolution and progression of PH (4, 5). Nevertheless, a recent growing body of evidence supported monitored ET programs for patients with PAH as a safe tool to improve exercise tolerance and quality of life (6, 7). For this reason a recent international consensus updated treatment algorithm for PAH suggested the upgrading of the recommendation for rehabilitation and exercise training to Class I with a level of evidence A (8). This review is aimed to provide an insight on the physiological and clinical basis of exercise training in PAH, giving evidence-based practical advice for its safe application.

Exercise limitation in PAH

Physiopathology of Exercise limitation in PAH

The physiological response of the pulmonary vasculature to exercise is characterized by distension of pulmonary vessels and recruitment of previously closed vascular branches. So, to increase blood flow, pulmonary artery pressure minimally rises and pulmonary vascular resistances reduced. This mechanism is impaired in the altered remodeled pulmonary circulation present in PAH.

Patients with PAH may have severe exercise limitation due to relative hypoperfusion of the well ventilated areas, low lactate threshold and hypoxemia leading to dyspnoea and fatigue (9, 10). Severe ventilation-perfusion mismatch has been shown to cause intolerable dyspnoea even at low workloads. The mismatch ventilation/perfusion and the reduction in diffusion capacity during exercise induces hemoglobin desaturation because of the rapid passage of red blood cells in the pulmonary capillary bed (11). Hypoxemia by itself stimulates hyperventilation via peripheral chemoceptors and, when hypoxemia is severe, by central chemoceptors. Along with this, the pulmonary vascular system shifts from a high flow/low resistance system to a low flow/high resistance system and there is also a poor recruitment of the vascular bed due to the absence of free vascular vessels (11, 12). Another abnormality seen is an impaired rise in stroke volume (SV) in response to exercise (13) accompanied by an abnormal rise in heart rate (HR) to compensate for the decreased stroke volume. PAH is characterized by progressive alterations in the pulmonary circulation leading to a reduction of the branches and of the distensibility of pulmonary blood vessels (14). During exercise cardiac output is increased and therefore if the pulmonary vascular bed can't increase the capacitance and the pressures in the system will be increased. So the after-load of the system will be increased and SV will scarcely increase inducing small increase of cardiac output (CO) (13). Right heart shows also chronotropic impairment proportional to disease severity because of down-regulation of β receptors and therefore insufficient increase of stroke volume and HR are related to inadequate increase of CO. Right atrial pressure increase has the strongest impact to exercise limitation and the presence of mechanoreceptors located of the right atrium and ventricle via afferent sympathetic pathway to central nervous system (14). At advanced levels of pulmonary hypertension the right hearth muscle is remodeled and pulmonary gas exchange is impaired, but also at earlier stages pulmonary hypertension may affect normal breathing sensation and exercise tolerance causing disability according to the degree of exercise limitation (15). So, breathlessness in these patients may be evidence of impaired signaling between the periphery and central hemodynamic performance (14). Other reasons for the symptoms and clinical course are due to an increase in physiological dead space leading to an increase in the ventilatory requirement and exercise induced hypoxia (16, 17). It has been demonstrated that respiratory mechanics abnormalities could contribute to and aggravate exertional dyspnoea in a subgroup of patients with PAH who progressively experience decrease inspiratory capacity throughout exercise and dynamic lung hyperinflation (18). This may happen in those PAH patients exhibiting reduced expiratory flows at low lung volumes at spirometry despite a preserved FEV1/VC ratio (19).

Patients with PAH may have severe exercise limitation due to relative hypoperfusion of the well ventilated areas, low lactate threshold and hypoxemia leading to dyspnoea and fatigue.

Another proposed mechanism for exercise limitation is the existence of inspiratory muscle weakness and peripheral muscle weakness causing a "generalized myopathy" among patients with idiopathic pulmonary hypertension (20, 21). Systemic inflammatory activation and local inflammation in the skeletal muscles may affect muscle metabolism and strength and may be important factors contributing to muscular dysfunction and exertional symptoms in PAH patients (10, 20). According to de Man et al. (22), pulmonary hypertension predominantly impairs respiratory muscle function, because of an increased proteolytic activity in the diaphragm and muscle specific protein degradation (22). It has also been shown a switch of type I muscolar fibres towards type II muscolar fibres (prone to anaerobic metabolism) (23). In patients who have PAH, fatigue may be associated not only with primary factors, which are related to the disease process itself, but also to secondary factors such as sleep disturbance and depression (24). The interactions among these contributors to fatigue severity are confluent and difficult to isolate. There has been some evidence that patients with PAH do not routinely engage in physical activity (25) and it seems reasonable to suspect that fatigue may deter them from participating. This may induce a vicious circle, as functional limitation may lead to anxiety and depression which increase as the severity of PAH progresses, but even a depressive state may affect quality of life and activities of daily living (26).

Table 1 - Published prospective clinical trials on exercise training in PAH with at least 15 patients enrolled.

Author	Year	Study design	# Pts	End points or Outcomes	Exercise protocol	Exercise Training results	Adverse events
Mereles (53)	2006	Randomized controlled trial	30	Changes from baseline to week 15 of 6MW distance and change in quality of life as measured by the Short Form Health Survey (SF-36) questionnaire	Bicycle training low workload, 7 d/wk, Walking 60 min, 5 d/wk Dumbbell 30 min, 5 d/wk Respiratory training 30 min, 5 d/wk Mental training At-home: bicycle15-30 min, 5 d/wk; respiratory and dumbbell 15-30 min, 3 d/wk; walk 2 d/wk	↑6MWD; ↑QOL scores ↑WHO FC ↑ V˙ O 2 (peak + AT) ↑Workload = PAPs	None
De Man (44)	2009	Prospective observational study	19	Maximal exercise capacity (CPET), 6MW distance quadriceps muscle function	Rehabilitation session 3d/week per 12 weeks in a Rehabilitation Centre consisting in bicycle training 50%-75% V˙ O 2 max + Quadriceps strength and endurance exercise	= 6MWD, = Peak exercise capacity,↑Anaerobic threshold,↑exercise endurance time, ↑Quadriceps strength and endurance. ↑Capillaries per muscle fiber(muscle biopsies) ↑Oxidative enzyme activity, = BNP levels	Dizziness in 2 patients
Fox (61)	2011	Clinical Trial	22	Δ 6MW and Δ VO2 through CPET after 12 wks	Aerobic interval training 1h/d: bicycle, treadmill, walking, step climbing Resistance training last 6 wk Daily home-based exercise	↑6MWD,↑Peak V˙ O 2 ↑Peak work rate = BNP levels, = SPAP; = CO	None
Grünig (70)	2011	Prospective observational trial	58	6MW distance, Quality of life assessed by the Short-Form Health Survey (SF-36), survival	3 weeks in hospital with exercise and respiratory training followed by 12 weeks at home	↑ 6MW distance (84 ±49 m), improved QoL scores and WHO functional class, peak oxygen consumption, heart rate at rest and maximal CEPT workload Survival at 1 -2 yrs100-95%	15 events not directly dependent from exercise training
Grünig (71)	2012	Prospective observational study	183	Assess safety and efficacy of exercise training in a large cohort of patients with different forms of PH	Total ≥ 1.5 h/d Daily interval bicycle training (low workload) Walking training Respiratory training 5 d/wk Dumbbell training 5 d/wk Mental training Home training ≥ 30min/d; 5 d/wk	↑6MWD (in all PH forms and FC, including IV). ↑QOL scores; ↑WHO FC ↑Peak V˙ O 2 ↓Rest heart rate ↓SPAP rest and exercise	22 events during the study period: 14 Respiratory tract infections, 2 Syncope, 6 Presyncope
Becker – Grünig (64)	2012	Prospective observational study	20	Assess the efficacy of exercise training as add-on to medical therapy in patients with congenital heart disease associated pulmonary arterial hypertension (CHD-APAH)	Total ≥ 1.5 h/d Daily interval bicycle training (low workload) Walking training 5 d/wk Respiratory training 5 d/wk Dumbbell training 5 d/wk Mental training . Home training: ≥ 30 min/d; 5 d/wk	↑6MWD; ↑QOL scores ↑Peak V˙ O 2 ↑Maximal workload Survival: 2y, 100%	4 Respiratory tract infections through the study period
Grünig (65)	2012	Prospective observational study	21	Assess short- and long-term efficacy of exercise training (ET) as add-on to medical therapy in patients with (CTD-APAH)	Total ≥ 1.5 h/d, Daily interval bicycle training Walking training (5 d/wk) Respiratory training(5 d/wk) Dumbbell training(5 d/wk) Mental training Home training:≥30min/d; 5 d/wk	↑6MWD; ↑QoLscore ↑Peak V˙ O 2 ↓Rest heart rate ↑O 2 saturation ↑Maximal workload ↑SPAP (3 wk) Survival at 2-3 yrs,100-73%	None
Weinstein (55)	2013	Randomized controlled trial	24	Fatigue severity scale (FSS) score Human activity profile (HAP) 6MW distance	10-week exercise training + education. 24-30 sessions treadmill walking, 30-45min per session at 70-80% of heart rate reserve, 3 days/wk over 10 wks	↑6MW distance (53±44mt) ↑FSS score ↑Human Activity Profile	None
Chan (54)	2013	Randomized controlled trial	23	Primary outcome: Δ 6MW distance. Secondary outcomes: improvement of CPET parameters and QoL	24-30 sessions of medically supervised treadmill walking for 30-45 min per session over the same 10-week period. A target exercise intensity of 70% to 80% of each patient's heart rate reserve obtained from the baseline CPET was used to guide each exercise session	↑6MWT distance, ↑ time to exercise intolerance, ↑peak WR, improved QoL	None

Assessment of exercise limitation in PAH

At present, the 6-minute walking test distance (6MWTD) is the most used method to assess exercise tolerance in PAH (27); it is also useful to monitor the response to therapy and provides prognostic information (28). In a clinical trial of 178 patients with pulmonary arterial hypertension, treatment improved 6MWD but not the peak VO_2 (29). It was then performed a correlation study to verify this result, but an unexpected discrepancy between the 6MW distance and peak VO_2 during cardio-pulmonary exercise test (CPET) was found (30). Differences in the subjects' body weight may be more important determinants of the 6MWD than aerobic capacity (31). In fact, when the 6MWD is adjusted for patient's weight (6MWD x weight), the 6MWD correlates better with peak VO_2 (32). However, the assessment of functional capacity by CPET seems to be more complete, because CPET allows for discrimination between the metabolic, cardiovascular and pulmonary components of exercise limitation (32). Patients with PAH can safely undergo CPET to their maximal tolerance (12). Moreover, CPET estimates the severity of disease and assesses patients' prognosis and response to therapy (30). In PAH, a typical CPET-response is observed, characterized by a reduced exercise tolerance with severe reduction in peak VO_2, work rate, O_2 pulse (VO_2/HR) and anaerobic threshold and by a marked increase in VE/VCO_2 slope and in the dead space to tidal volume ratio (12). High increase of VE/VCO_2 ratio shows hyperventilation. Elevated VE/VCO_2 and low PaO_2 are related to the severity of PAH and VE/VCO_2 is closely related to NYHA functional class (17). End tidal CO_2 tension ($PetCO_2$) shows difference in different severity of PAH: in particular only in severe stages it's decreased at rest and during exercise and it increases during recovery time showing delayed recovery after exercise. VE/VCO_2 is strongly related to pulmonary arterial pressure and also related to PVR (pulmonary vascular resistance) and it progressively increases in patients with PAH (15).

The remodeling and reduction of pulmonary arterial bed are detectable as a reduction of carbon monoxide diffusion by a reduction in the membrane conductance.

The remodeling and reduction of pulmonary arterial bed reduces both lung's units perfusion and diffusion of gases through alveolar-capillary barrier, this measurable as reduction of carbon monoxide diffusion (DL-CO) by a reduction in the membrane conductance (31). The mismatch ventilation/perfusion and the reduction in diffusion capacity during exercise induce hemoglobin desaturation because of the rapid passage of red blood cells in the pulmonary capillary bed. Hypoxemia by itself stimulates hyperventilation via peripheral chemoceptors and, when hypoxemia is severe, by central chemoceptors. DL-CO may be considered as an independent predictor for death in PAH, and it is also the only resting lung function parameter that correlates by stepwise regression analysis with CPET in patients with PAH, showing to be an independent factor that is a determinant for peak O_2 uptake (33, 34).

The pathophysiological rationale of exercise training in PAH

Inactivity has been liked with reduced survival, poorer quality of life, increased hospitalization and healthcare utilization (35). On the other hand, daily physical activity has been recently recommended even to ageing people and subjects with chronic cardio-respiratory diseases by the World Health Organization (36) for its benefit for health. Exercise training is the regular participation in aerobic exercise programs that mostly was reported to improve cardiopulmonary status, to reduce the severity of fatigue, to enhance exercise tolerance and activity levels in severely ill patients with chronic disabling diseases (37-40). Till recently, the most severe patients were excluded from any form of ET, but a better insight of the pathophysiology lead to justification of exercise even for patients with functional class IV NYHA. In fact, the results of the recent HF-ACTION study showed that ET was safe in patients even with class IV symptoms, previously not considered ideal candidates for rehabilitation (41). Generally, a frequent mobilitation and physical exercise adopted as a lifestyle approach involving the promotion of common daily activities, seems to better than inactivity both for healthy and diseased subjects (36), but structured exercise training programs obtained most attention in the literature and evidence-based results. Exercise training has chronic anti-inflammatory effects on the skeletal musculature, and reduces local cytokine expression and skeletal muscle inflammation (42). Physiological benefits of training in cardiovascular patients are: improvement of muscle oxidative capacity jointly with a reduction of cytokines inflammation, improvement of endothelial function, enhancement of vagal tone with lower sympathetic tone (43). Dutch researchers showed that training enhance aerobic capacity of the quadriceps muscles in PAH, by increasing capillarisation and oxidative enzyme activity, especially of the type-1 (slow) muscle fibers (44). These results were confirmed by Mainguy et al. (45) who demonstrated a decreased proportion of type II muscle fibers and improvement in peripheral muscle characteristics as a consequence of ET in idiopathic PAH patients. A magnetic resonance imaging (MRI) study assessed the effects of 3-weeks in-hospital exercise training on pulmonary perfusion and blood flow in patients with PAH and CTEPH showing a significant improvement of MRI parameters of pulmonary perfusion and peak flow velocity in comparison with sedentary controls (46). In the physiologic study by Kabitz et al. (47), seven PAH patients received supervised (physiotherapists and

The beneficial effect of exercise training in vascular and cardiac remodeling was accomplished by signaling proteins leading to a reduction of right ventricular and diastolic pressures.

physicians) training every for a 15-week period showing a significant improvement of respiratory muscle strength assessed by twitch mouth pressure and exercise capacity (6MWD).
Recent experimental studies provided further pathophysiological basis for ET in patients with PAH. In a rat model of PAH complicated with cor-pulmonale, Colombo et al. (48) showed that ET promoted positive changes in the right ventricle and pulmonary artery remodeling accomplished by signaling proteins leading to a reduction of right ventricular and diastolic pressures. Previously, experimental studies showed that ET limits the development of pulmonary hypertension in hypoxia exposure models (49, 50).
Other researchers demonstrated that ET restores endothelium-dependent relaxation in the pulmonary circulation of pulmonary hypertensive rats, provided that endogenous l-arginine in endothelial cells was not limited (51). Opposite effects of training in rats with stable and progressive PH were found by another group using the same standard program of ET either in rats with stable mild PAH and in rats with advanced PAH and right heart failure (52), raising the question wheter a non-invidualized standardized ET may have opposing effects and consequences in different stages of the disease.

Randomised controlled trials (RCTs) on exercise training in PAH

To date only three very small randomized controlled trials (RCTs) on exercise training in PAH were published in the international literature (53-55). Moreover, the last two RCTs (54, 55) were performed by a single Centre specialized in pulmonary rehabilitation and pulmonary hypentension almost in the same patient population. Nonetheless, the last World symposium on pulmonary hypertension (8) considered the data of these trials enough convincing to suggest the upgrading of the recommendation for rehabilitation and exercise training to Class I with a level of Evidence: A.

Mereles et al. performed the first landmark RCT that demonstrated an improvement in exercise and functional capacity and in quality of life in patients with PAH.

Mereles et al. (53) performed the first landmark RCT that demonstrated an improvement in exercise and functional capacity and in quality of life in 23 patients with PAH and 7 patients with CTEPH who took part in a training program as compared with a control untrained group. The enrolled patients had functional class from II to IV and were stable and compensated under optimized medical therapy that remained unchanged during the study period. The study was a 15-week randomized controlled trial, with the control group also entering the training arm after completing the initial protocol after 15 weeks. Primary end points were the changes from baseline to week 15 in the 6MWD and in scores of the Short Form Health Survey quality-of-life questionnaire (53). Systolic pulmonary artery pressure values at rest did not change significantly after 15 weeks (from 61±18 to 54±18 mm Hg) within the training group. The protocol considered that for the first 3 weeks all patients stayed in the hospital and thereafter exercise training was continued at home. Patients in the control group received a common rehabilitation program based on healthy nutrition, physical therapy such as massages, inhalation, counseling, and muscular relaxation without ET but were allowed to perform daily activity as usual. Patients in the training group participated in an additional exercise program 7 days/week at low workloads (10 to 60 W) that was supervised by physical therapists and physicians (50). The program consisted of an interval bicycle ergometer training with a lower workload for 0.5 min and a higher workload for 1 min (e.g., 20 to 35 W) for 10 to 25 min/d, corresponding to 60% to 80% HR reached during peak oxygen uptake at baseline CPET. The training intensity was increased according to the individual tolerability and limited by peak HR (not more than 120 bpm), oxygen saturation 85%, and subjective physical exertion. Furthermore, 60 min of walking was performed 5 days/week and consisted of flat-ground and uphill walking. During this training, patients received additional "mental training" to improve perception of their individual physical abilities and limits to keep physical exercise safe even in demanding situations.
The researchers coordinated by Chan et al. concluded two other trials (54, 55). In the first one (54) they evaluated supervised outpatient ET in PAH patients in a scenario similar to that available in most current rehabilitation programs. Twenty-six patients, mostly CTD at WHO class II-III, were randomized to a 10-week education only or a combined education/exercise program (54). The aerobic exercise was of relatively high intensity (70%-80% of heart rate reserve), differently from the afore mentioned Mereles' trial (53), and included only treadmill walking. The education/exercise group showed improvement in 6MWD, quality of life scores, increased time to exercise intolerance, and peak work rate. In contrast, no significant improvement was observed for any of the outcome measures following education alone. No adverse events were noted. Although this is a small study, it supports a more vigorous, supervised, outpatient treadmill walking program than used in most rehabilitation programs. However, it may be sufficient for improving functional capacity, cardiorespiratory function, and quality of life in PAH patients, without increasing adverse events (54).
In a second similar publication by Weinstein et al. (55) the objective was to investigate the effectiveness of an exercise intervention for decreasing fatigue severity and increasing physical activity in individuals with PAH. Patients were randomized into a 10-week program that consisted of patient education only (EDU: 13 pts) or patient education plus an aerobic exercise-training regimen (EXE: 11pts) (55). The Authors (55) used two scores: the Maximum Activity Score (MAS) and the Adjusted Activity Score (AAS) (56, 57). After

10-weeks of intervention no change in fatigue severity was observed in the EDU group, while the EXE group significantly increased both AAS ($p = 0.036$) and MAS ($p = 0.022$) following aerobic ET (55). Ongoing randomized trials from India, Germany and Australia registered in two major registry platforms (www.clinicaltrials.gov, and http://apps.who.int/trialsearch/) will provide answers to open remaining questions (58).

Other non-RCTs studies in humans

Additional controlled nonrandomized studies, and uncontrolled experiences utilizing different training and rehabilitation programs have supported the data from the RCTs on benefits of ET in patients with PAH. The first uncontrolled report on cardiopulmonary rehabilitation in patients with PAH included 24 young patients aged 5 to 37 yrs who underwent breathing exercise, training of upper extremity muscles, gait training, bicycle ergometer training, and treadmill walking for 30 to 60 min per day, 5 days a week (59). At the end of 6.7 weeks average period of rehabilitation the patients showed improved functional class, ambulatory capacity and 6MWD, decreased HR at rest, enhanced daily activity assessed by the Barthel index (60), and lower extremity strength (59).

A non-randomized controlled trial of outpatient rehabilitation program was administered to 22 patients with pulmonary hypertension (20 with PAH and 2 affected by CTEPH) (61). A conventional program of 24 sessions of conventional 1-hr exercise training performed bi-weekly by class II-III patients already receiving optimal treatment for pulmonary hypertension. 6MWD and peak VO_2 improved, whilst CO unchanged, but no adverse events occurred in the study population (61). The Authors' conclusions (61) stated that "exercise rehabilitation might be a safe and efficacious treatment in an ambulatory setting in stable PAH patients on disease-targeted medical therapy".

A retrospective chart review and data analyses of a previously published RCT were undertaken evaluating pulmonary arterial hypertension pharmacotherapy versus the same therapy with the addition of pulmonary rehabilitation in a retrospective analysis of 23 patients (62). There was no improvement in 6MWD post-pharmacotherapy alone. Patients with low 6MWD <250 meters had substantial gains in 6MWD post-rehabilitation (average of 86 meters). As well, also those with initial 6MWD >250 meters had a significant improvement of >52 meters. So, it was shown that also patients with 6MWD as low as <250 meters and worse prognosis may be candidates for pulmonary rehabilitation (62).

Two small trials evaluated the efficacy of ET in PAH associated with congenital heart disease (CHD-APAH) (63, 64). A Spanish group studied and followed up during a 1-year period 8 patients with CHD-APAH who were non-randomly assigned to a 3-month rehabilitation and education program or only education (63). Patients in the training group participated in an exercise program 2 days/week during 3 months, supervised by physical therapists and physicians (63). The daily training consisted of 10 min warming up, with stretching of long muscles, a brief period of resisted exercises lifting 1-2kg weight, and afterwards an interval of bicycle ergometer training during 24 min with bases at 10-25W and 30-sec peaks of 20-50 W, depending on individual tolerability. Borg scale symptoms and HR were used to limit the intensity of the exercise. The training intensity was increased with respect to the individual tolerability with a maximum HR which corresponded to 80% of the HR they had reached in the 6MWD and a 3-6 rating on the modified Borg scale. Patients in the rehabilitation group improved 6MWD minimum oxygen hemoglobin saturation, and functional class at the end of the training program without having adverse events (63). A German group performed an uncontrolled prospective clinical trial investigating short- and long-term effects of ET as add-on to PAH-targeted medication in patients with CHD-APAH (64). The supervised ET program began in a specialized rehabilitation Center and after 3 w followed at home for other 12 w (64). Each patients performed at least 1.5 h exercise per day (in intervals distributed over the day) consisting of interval bicycle ergometer training at low worloads (10-60 W) at 7 days/week, walking, dumbbell-training of single groups using low weights (300-1000 g) for at least 30 min per day at 5 days/week and a bicycle ergometer (64). Maximum HR during the training corrisponded to 60-80% of the HR reached during CPET and was monitored throughout to adjust the training intensity. The results of this German study suggested that ET may improve exercise capacity and oxygen consumption in CHD-APAH providing an overall survival of 100% and 95% respectively after 2 and 3 years (64).

Another prospective uncontrolled trial of ET in PAH was performed by the same group in 21 patients with CTD-associated PAH (65). Patients received ET in-hospital for 3 w and continued at home for 12 w showing improvement of the mean distance walked in 6 minutes compared to baseline by 67 ± 52 meters after 3 weeks ($p < 0.001$) and by 71 ± 35 mt after 15 w ($p = 0.003$), the scores of quality of life ($p < 0.05$), HR at rest, peak oxygen consumption, oxygen saturation and maximal workload (65). The 1- and 2-year overall-survival rates were 100%, and the 3-year survival 73%. This is more than expected according the Kaplan-Meier estimates of survival seen in drug RCT and National registries (65-68).

Shoemaker et al. (69) described the experience of ET in two patient with PAH. Albeit, this report has relative poor scientific relevance, it could be useful to be transferred in daily practice. The training consisted of monitored cycle ergometry 3 days per week for 6 weeks. Each session consisted of 5 minutes of warm-up, 35 min of loaded cycling, and 5 min of cool down. Intensity started approximately 50% of peak workload as mesured by CPET, and was progressed as tolerated based on dyspnoea, HR, blood pressure, and O_2 saturation checked every 5 min (69).

The largest cohort studies on ET in PAH were two ob-

servational prospective trials (70, 71), respectively recruiting 58 and 183 patients with several type of pulmonary hypertension, but mostly PAH. The Heildelberg's group (70) prospectively evaluated 47 PAH patients, functional class II-IV, and 11 patients with CTEPH. Exercise training was well tolerated by all patients that obtained after 15 weeks the following results: increased 6MWD at week 15 compared to basline (by 84 ± 49 m, $p < 0.001$), as well as Quality of Life scores, WHO functional class, peak oxygen consumption, HR at rest, and maximal workload. Survival at 1 and 2 years was 100 and 95%, respectively (70). The largest cohort was collected by an European multicenter network (71) recruiting 194 patients functional class II-IV,133 patients out of them with PAH. The patients received ET for 3 weeks in-hospital and other 12 weeks at home as add-on treatment to optimized drug therapy. After 3 and 15 weeks, patients significantly improved the 6MWD compared to baseline, scores of quality of life, WHO functional class, peak oxygen consumption, oxygen pulse, HR and systolic pulmonary artery pressure at rest and maximal workload (71). Due to less worsening events within 2 years, average healthcare costs lower of €675,00 in the group of patients who performed a specialized rehabilitation program (72).
Obviously, non-RCT design presented several potential bias, but no published study contrasted the safety and potential benefits of ET for PAH patients anyway.

Exercise training modes for PAH

The general principles of ET for patients are no different from those of healthy individuals or even athletes (3). For exercise training to be effective the total training load should reflect the subjective requirements, it must exceed loads encountered during daily life to improve aerobic capacity and muscle strength, and must progress as improvement occurs. Exercise training may be applied to improve cardiorespiratory endurance, muscles strength and flexibility, but various modes exist to provide endurance training, resistance training, neuromuscular electrical stimulation, and respiratory muscle training. Aerobic training may be interval-based or continuous one. Both interval and continuous training can be safely and effectively applied in patients with PAH. Therefore, the choice of interval or continuous training will be down to the patient or physiotherapist preference. From a clinical practice point of view, interval training may require a higher therapist to patient ratio to ensure adequate work rate and rest intervals are achieved in comparison with continuous training (73).

Although aerobic exercise should be considered the core training intervention, additional approaches should be considered: resistance training, inspiratory muscle training, neuromuscular electric stimulation.

For individuals with PAH who intend to undertake an ET program, a prior CPET should be encouraged, wherever possible (74). A CPET not only allows the opportunity to screen individuals for risks associated with exercise (e.g., an abnormal blood pressure or heart rate response), but also an accurate determination of exercise intensity (10). The exercise intensity employed during training should be prescribed according to the individuals' CPET results, including the maximum HR response and symptomatic responses at submaximal and maximal exercise. Clinicians are strongly encouraged to utilize symptoms to monitor and guide exercise workload and physical activity levels. Increasing or severe fatigue and/or severe dyspnea during exercise suggest a high level of RV work, which may have a detrimental impact on RV function. The published trials on ET in PAH were either in-hospital and outpatients based, but both approaches obtained beneficial effects. Some Centre proposed a mixed protocol began in-hospital for 3 weeks and then continued at home for other 12 weeks (65). Almost all protocols were supervised and monitored by physiotherapists and/or physician from rehabilitation Centers also being referral Unit for PAH.
Although aerobic exercise should be considered the core training intervention, additional approaches should be considered: resistance training (75), inspiratory muscle training (IMT) (76), neuromuscular electric stimulation (NMES) (77).
Resistance (or strength) training is an exercise modality in which local muscle groups (e.g. upper limb) are trained by repetitive lifting of relatively heavy load (78). Resistance training appears to be indicated in individuals with PAH who have reduced muscle mass and strength of their peripheral muscles, but in general is considered important for adults to promote healthy aging (78).
IMT uses specific resistive devices to load the inspiratory muscles without constraining the breathing pattern. IMT show to be effective in COPD (79), post-cardiosurgery (80), and chronic heart failure (81), but it was not yet studied in PAH patients.
NMES involves applying an intermittent electrical current to a superficial peripheral muscle using electrodes and a stimulator (77). The electrical current serves to trigger an action potential and depolarize the motor nerve to elicit an involuntary muscle contraction. Although any superficial peripheral muscle can be stimulated to contract in this way, most studies have focused on stimulating the quadriceps femoris (82). The stimulator can be programmed to elicit contractions that are more likely to favor gains in strength or endurance. Strength protocols involve relatively few contractions, using high- frequency stimulation, at the highest current that can be tolerated. A short duty cycle, characterized by a long contraction period followed by an even longer rest period, may be advantageous. In contrast, endurance protocols involve multiple contractions over prolonged periods (often hours), using low- frequency stimulation and a moderate current with relatively short contractions followed by short rest periods. Electrical stimulation is an attractive option to train

the peripheral muscles in people characterized by profound ventilatory limitation, because it evokes minimal ventilatory response and therefore minimal experience of dyspnea (83).

Exercise training in PAH: practical advice for users

The evidence from exercise training studies, to date, suggests that, at least in the short term, exercise training at moderate intensity is associated with improved exercise capacity, without adverse outcomes, in individuals who are stable on PAH-specific therapy. Furthermore, there is a consensus to date on the safety, effectiveness, and utility of monitored physical activity in patients with PAH unrespective of the severity of functional impairment. However, there is also a lack of clarity on which ET mode is preferable, because of the variety of training programs used in different studies. Most literature's experiences suggested an individualization of exercise to provide correct intensity. However, as recommended in COPD and other chronic cardiopulmonary diseases, there is no evidence that individually targeted exercise programme can offer any advantage over simple conventional generic exercise training (84).

A bicycle ergometer may be better tolerated with respect to symptoms, but a treadmill more closely approximates the muscle activity required of daily living.

Aerobic ET entails rhythmical and continuous movement of large muscle groups. This can be achieved through several modes of aerobic exercise including walking, biking, and elliptical training, dictated by patient preference and availability of equipment. General recommendations for aerobic training include 30 to 60 minutes of moderate-intensity exercise most, if not all, days of the week (85). Patients should already be under optimal medical therapy for PAH and clinically stable.

The initial prescription should be formulated on the basis of CPET and the symptoms associated with exertion. An advantage of using CPET is the potential to define ventilatory threshold. A proposed training range of 40 to 85% of a given patient's maximal aerobic capacity. Setting the training exercise intensity approximately at the point of ventilatory threshold may assist in optimizing the physiologic adaptations experienced through chronic aerobic exercise. However, any level of participation in an aerobic exercise training program is preferable to a sedentary lifestyle. Most of the current evidence supporting the implementation of aerobic exercise training support programs with a ET frequency of 3 to 5 times per week. A bicycle ergometer may be better tolerated with respect to symptoms, but treadmill more closely approximates the muscle activity required in activities of daily living. So, the initial phase of training should use a bicycle ergometer and the patient may be graduated to a treadmill later in the training program.

Patients with PAH commonly experience skeletal muscle weakness and thus diminished muscle force production, which negatively impacts the ability to perform functional activities. As such, there is a clear rationale for implementing a resistance training program in conjunction with aerobic exercise. General resistance training guidelines put forth by the American Heart Association may serve as a template for PAH subjects (86). These recommendations include:

a) from 8 to 10 exercises
b) one set per exercise
c) from 10 to 15 repetitions per set
d) incorporation of all major muscle groups of the upper and lower extremities.

These programs use a moderate level of resistance relative to a patient's, and a repetition maximum for any given exercise.

The key messages shared by several rehabilitation protocols are shown in Table 2.

Table 2 - Key messages shared by most PAH dedicated ET protocols.

1)	Patients must be on optimized drug therapy before ET
2)	A supervised individualized ET program is always recommended for patients with PAH
3)	Both in-hospital and at home ET are effective, but a structured home-based program needs remote supervision, provision of exercise equipment at home, and careful patient selection
4)	A moderate-intensity aerobic ET program should be initiated first and served as the core intervention
5)	Once an aerobic ET program is well tolerated, a resistance training program should be added
6)	ET should include low-intensity aerobic and strength training of the upper and lower extremities, as well as stretching, range of motion, and flexibility or respiratory muscle exercises
7)	The intensity of training can be advanced gradually to submaximal target levels, avoiding intensities leading to greater than 70% to 80% of HR reserve or peak HR higher than 120 bpm
8)	Supplemental O2 should be provided to avoid desaturations less than 88% to 90% during exercise
9)	ET should be administered only to clinically stable patients, and immediately stopped whenever severe symptoms occur (e.g. dizziness, presyncope, chest pain, hypertension, or hypotension)
10)	NMES program may be considered for patients with advanced PAH and/or severe deconditioning who have difficulty in participating in aerobic and/or resistance training.

Legend: ET= exercise training; PAH=pulmonary arterial hypertension, HR=heart rate; NMES= neuromuscular electric stimulation; bpm=beats per minute.

Conclusions

In spite of no single publication on the present topic has a high quality of evidence, there are concordant multiple results from a number of data sources supporting the rationale and the effectiveness of exercise training in patients with PAH. So, even though a well designed RCT should be useful, there are several reasons to advice patients with PAH and limitation to physical exercise to participate in exercise training program either at home or in-hospital under the supervision of an expert Centre. Reported programs had varying ratios of strength *versus* aerobic exercise. It is likely that a combination of both strength and endurance training is helpful, but the optimal combination is still unknown. Many other questions remain unanswered regarding the optimization of the exercise training and rehabilitation programs. Ongoing rehabilitative trials in patients with PAH will help answer some of the remaining questions.

It is likely that a combination of both strength and endurance training is helpful, the optimal combination is still unknown.

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