Treating Pulmonary Arterial Hypertension With Exercise: The Role of Rehabilitative Medicine

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Exercise training as treatment has become well established in many cardiorespiratory conditions. This is also increasingly the case in pulmonary arterial hypertension, where several studies have demonstrated improvements in symptoms, exercise capacity and quality of life. There remains, however, much potential for development. Current research is focused on clarifying the mechanism of benefit in pulmonary hypertension and exploring strategies for both optimizing the treatment effect and widening access to this intervention.

HISTORICAL BACKGROUND

Compared with practice in other cardiorespiratory conditions such as chronic obstructive pulmonary disease (COPD) or left heart failure,[1,2] pulmonary hypertension (PH) specialists have arrived relatively recently to the realization of the benefits of rehabilitation for their patients. For many years advice given was to the contrary—that patients with pulmonary arterial hypertension (PAH) should avoid exercise.[3] There are plausible physiological reasons for this cautious position. Increased flow and pressure within the pulmonary arteries might accelerate the disease. The right ventricle is already overworked, dilated and often failing. Patients with PAH can experience exertional presyncope or syncope and even sudden death. Increased exertion would surely only aggravate these problems. However, these views were unsubstantiated and have now largely been superseded by evidence to the contrary.

The benefits of regular exercise training are seen in several domains of human wellbeing and have been demonstrated in many chronic conditions. Not only is there improvement in cardiorespiratory and peripheral muscle function but there are beneficial effects on metabolism, weight management, bone density, mental health, and cognitive function.[4] Greater peak oxygen consumption, the "gold standard" measurement of aerobic exercise capacity, has been repeatedly linked to improved survival in both health and disease.[5]

The first randomized controlled trial to show the benefits of exercise training in PAH was performed in Heidelberg and published in 2006.[6] With only 30 patients divided between the control and treatment arms, this study showed an improvement in functional class, exercise capacity, and quality of life. Over 19 studies investigating rehabilitation in PH have now been published, usually but not always with similar results.[7] This body of work has provided much data on the efficacy and safety of exercise training in PAH and led to a Class IIa recommendation for this as a useful intervention in the 2015 European Society of Cardiology–European Respiratory Society guidelines.[8]

RATIONALE FOR REHABILITATION IN PAH

There is a logical argument for the utility of exercise training in PAH. Using disease-targeted therapy, we can improve pulmonary artery hemodynamics and right heart function.[9] Exercise training is then needed to reverse the concomitant deconditioning and maximize the benefit to be derived from the pharmacotherapy.

Although it is debatable whether exercise training will improve the right ventricle, it can have a definite, beneficial effect on other muscle function. It increases the strength and efficiency of skeletal muscles in PAH.[10] It also improves left ventricular function in both health[11] and disease, even when the primary problem affects the left ventricle.[12] It can also increase respiratory muscle function[13] and may enhance breathing control.[14] From a wider perspective, there can be improvement in perception of symptoms during exercise. Exercise training delivered by a rehabilitation program therefore optimizes the efficiency of training, educates the patients on safe limits, and improves their confidence that exercise is safe, all of which can be significant barriers to exercise. Lastly there are benefits from outside the cardiovascular system such as weight control, improved mental health, and metabolic effects.[4]

OUTCOMES FOR REHABILITATION IN PAH

The benefit of rehabilitation in PH has been tested predominantly in mixed populations of PAH and chronic thromboembolic PH patients, in settings varying from residential to home-based and using a range of outcome measures summarized in Table 1.

Exercise Capacity

There is strong evidence from a Cochrane meta-analysis of randomized controlled trials and from many other

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Table 1. Outcome Measures Used in Pulmonary Hypertension Rehabilitation Studies

Type	Study	Quality of life[a]			Functional ability					Peripheral muscle function	Biomarkers
		SF-36	CAMPHOR	Other questionnaire	6MWD	Peak VO_2	Endurance	WHO Class	Treadmill speed	Muscle strength	NT-proBNP
Inpatient	Mereles et al (2006)[6]	7/10 [green]			[green]	[green]		[green]			
	Grünig et al (2011)[15]	7/8 [green]			[green]	[green]		[green]			
	Grünig et al (2012)[16]	5/8 [green]			[green]	[green]		[yellow]			[yellow]
	Grünig et al (2012)[17]	2/8 [green]			[green]	[green]		[green]			
	Nagel et al (2012)[18]	2/8 [green]			[green]	[green]		[yellow]			[yellow]
	Becker-Grünig et al (2013)[19]	1/8 [green]			[green]	[green]		[yellow]			[red]
	Ley et al (2013)[20]				[green]						
	Ehlken et al (2014)[21b]	7/8 [green]									
	Kabitz et al (2014)[13]				[green]					[green]	
	Ehlken et al (2016)[22]	1/8 [green]			[green]	[green]					[yellow]
	Fukui et al (2016)[23]	1/8 [green]		PHQ-9 [yellow]	[yellow]	[green]				[green]	[yellow]
Outpatient	de Man et al (2009)[10]				[yellow]	[yellow]	[green]			[green]	[yellow]
	Martinez-Quintana et al (2010)[24]	SF-12: 0/2 [yellow]			[yellow]			[green]		[yellow]	[yellow]
	Mainguy et al (2010)[25]				[green]		[yellow]			[yellow]	
	Fox et al (2011)[26]				[green]	[green]					
	Chan et al (2013)[27]	6/8 [green]	5/6 [green]		[green]	[yellow]					
	Weinstein et al (2013)[28]			FAS, HAP [green]	[green]						
	Raskin et al (2014)[29]			1/3 [green] 1/3 [red]	[green]						
	Zöller et al (2017)[30]	0/2 [yellow]				[yellow]					
	Gerhardt et al 2017 [31]	2/2 [green]			[green]	[green]				[green]	[yellow]
	Talwar et al (2017)[32]								[green]		
	Bussotti et al (2017)[33]			HADS, EQ-5 [green]	[green]						[yellow]
	González-Saiz et al (2017)[34]	2/8 [green]			[yellow]	[yellow]				[green]	[yellow]
Home	Inagaki et al (2014)[35]			SGRQ 1/3 [green]	[green]					[green]	
	Ihle et al (2014)[36]	0/8 [yellow]	1/3 [green]		[yellow]						

Legend

[green]	Statistically significant improvement
[yellow]	No significant improvement
[red]	Statistically significant deterioration

Adapted from Table 7 from Grunig E, Eichstaedt C, Barberà J-A, et al ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J*. 2019;53(2):1800332. Reproduced with permission of the © ERS 2019.

SF-36 indicates short-form health survey 36; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; 6MWD, 6-minute walking distance; peak VO_2, peak oxygen consumption; WHO, World Health Organisation; NT-proBNP, N-terminal pro B-type natriuretic peptide; PHQ-9, patient health questionnaire 9; FAS, fatigue severity scale; HAP, human activity profile; HADS, hospital anxiety and depression scale; EQ-5, EuroQoL-5 dimensions; SGRQ, St George's respiratory questionnaire.

[a]The number of subscales with significant improvement/number of tested subscales is given. For detailed results of specific subscales of quality of life assessments please see Table 2.

[b]This study refers to the same patients as Grünig et al (2011).[15]

less rigorous studies[7,37–39] that rehabilitation leads to improved exercise capacity in PAH. The most consistent outcome measure used as the measure of exercise capacity is the 6-minute walk test (6MWT). The estimate of the size of the treatment effect was an improvement in 6MWT distance of 60 m.[37] This is a strikingly positive result compared both with the minimum clinically important difference of 33 m[40] and the typical size of treatment effect seen in pharmacological studies of 30 to 40 m.[41] On incremental cardiopulmonary exercise testing, an increase in peak oxygen consumption of 2.41 mL/kg/min was seen.[37] Such an improvement, which represents a 10% to 20% change in this patient group, is impressive as incremental cardiopulmonary exercise testing is generally considered to be an insensitive test for an intervention.[42] Even in a study where no increase of 6MWT distance or peak oxygen consumption were seen, such as de Man 2009,[10] a more sensitive instrument (endurance exercise testing) was still able to show a benefit for the intervention.

Quality of Life

Quality of life (QoL) has principally been measured in the rehabilitation studies using a generic tool (the Short Form 36).[7,37] The analysis reported in the Cochrane review showed an improvement in several domains, namely physical role, vitality, and social function. Physical and mental composite scores were also improved. It would be expected that disease-specific QoL questionnaires would be more sensitive to change. Despite data being available on very few subjects in the studies included in the Cochrane review (n = 18), a significantly improved score was seen in the QoL domain of the Cambridge Pulmonary Hypertension Outcome Review instrument.

Functional Class

Evidence of improvement in functional class is largely available from the earliest randomized controlled trial.[6] Here, of 15 subjects in the intervention group, 6 improved from functional class III to II and one from functional class IV to III.

Peripheral Muscle Function

Patients with PAH are known to have abnormalities of their peripheral muscles including reduced strength, muscle atrophy, impaired contractility, reduced oxidative capacity, and fewer muscle capillaries.[43–45] Rehabilitation has been shown to ameliorate these problems. De Man et al[10] demonstrated that exercise training could increase muscle capillarization, oxidative enzyme activity, quadriceps strength, and quadriceps endurance. Mainguy et al[44] added to this by showing that training caused a reduction in type IIx fiber proportion in the muscles and hence a switch to improved aerobic muscle function.

N-Terminal Pro B-Type Natriuretic Peptide

The N-terminal pro B-type natriuretic peptide (NT-proBNP) assay is a straightforward and widely available assay for detecting impaired cardiac function and hence has been extensively measured in rehabilitation studies in PAH.[7] Reassuringly, exercise training does not appear to lead to an increase in NT-proBNP. On the other hand, unlike other outcome measures such as 6MWT distance and QoL, there does not appear to be an improvement (ie, a reduction) in this biomarker with exercise training. This is at odds with what is seen in several recent pharmacotherapy studies where a reduction in NT-proBNP can be seen in the active intervention arm.[46,47]

Hemodynamics

In a randomized controlled trial (n = 79), Ehlken et al in 2016[48] performed right heart catheterization at rest and exercise pre- and postexercise training in a subset of patients in the trial. At rest (n = 59) they found in the treatment group a fall in mean pulmonary artery pressure of 4 mm Hg and increase in cardiac index of 0.2 L/min/m^2. There was greater change in these values in the adverse direction in the control arm (5 mm Hg and 0.3 L/min/m^2, respectively). The pressures on exercise were unchanged but this represented an improvement as it was in the context of a larger cardiac index in the treatment group (n = 49) where there was an increase of 1.0 L/min/m^2. In support of these findings, there is evidence of reduced pressures seen on transthoracic echocardiogram.[38]

This apparent improvement in function by lowering of cardiac work is in direct contrast with the failure to show a fall in NT-proBNP following exercise training and remains to be explained. It is also unclear why exercise training should improve resting hemodynamics. Such an unsuspected result requires confirmation. A further small, uncontrolled study published only in abstract form so far performed multiple cardiac output measurements during exercise right heart catheterization. They found no change in resting pulmonary artery hemodynamics but did see the same pattern of response as Ehlken et al during exercise.

Survival

There are no reliable data on the impact of exercise training on survival. It is unlikely that this will ever be a useful outcome measure for this intervention because of the size of the study required and the difficulty in controlling for the active intervention which is freely available throughout the patient's lifetime. Some of the other outcome measures that have been used are surrogate markers of survival including, for example, 6MWT distance, functional class, cardiac index, and NT-proBNP.[8] Whilst there is a clear improvement in 6MWT distance, this is counterbalanced by the lack of fall in NT-proBNP.[7] The data on functional class and cardiac index are currently limited. It may be possible in the future to use one of the emerging risk scores[9] linked to survival to provide further information here.

An early animal study did provide some potential concerns regarding survival.[49] A monocrotaline rat model was used to generate 2 subsets of PH, one stable, one progressive and in right ventricular failure. The latter group appeared to show accelerated deterioration when exposed to exercise training.

In summary, exercise training improves symptoms, quality of life, and functional capacity but cannot at this point be claimed to improve survival.

Adverse Effects

The issue of safety in PAH rehabilitation has recently been reviewed in detail by a European Respiratory Society task force.[7] The amalgamated study data suggest exercise-related safety issues in 4.6% of study participants. However, half of these (2.4%) were due to desaturation, which is a predictable consequence of the disease pathophysiology rather than an adverse effect of exercise training. Of more concern, dizziness, hypotension, or syncope were described in 1.9% of cases and required a change in exercise prescription. Unsustained supraventricular dysrhythmias were seen in 0.4% of participants.

Adverse events not related to exercise were seen in 4.9% of participants, the largest contributor coming from respiratory infection in the group trained in an inpatient setting and leading in some cases to a short interruption to the training program. This finding could simply reflect the background incidence of this common ailment in a more closely scrutinized patient group. However, it is also recognized that exercise can sometimes lead to a suppression of immune function.[50]

Cost Effectiveness

Given that exercise training and PAH therapy can produce similar outcomes in randomized controlled trials, it could be postulated that exercise training could replace PAH therapy in some cases and reduce the cost of treatment. However, this would probably be unacceptable on several fronts. Firstly, there is no direct comparison of exercise training and PAH treatment and unlikely ever to be one for cost and ethical reasons. Secondly, the safety of exercise training without concomitant PAH therapy has not been tested. As discussed earlier, there remains some doubt as to whether exercise training will improve survival in PAH, unlike the case for PAH therapy, where a survival benefit is largely accepted.[51] Consequently, any cost saving attributable to exercise training in PAH patients will be due to reduced escalation of PAH therapy rather than replacement.

One study[21] (n = 106) has performed an economic evaluation of exercise training in PH. As control, this study used an age- and gender-matched patient group not proceeding to rehabilitation. This suggested benefit in the active intervention arm, where there was longer time to clinical worsening, higher quality-adjusted life years, and lower medication costs. However, this was not a randomized controlled trial and the possibility of bias cannot be excluded. In addition, medication for PAH is increasingly available in more economical, generic formulations and any cost effectiveness benefit relying on medication cost may disappear.

Predictors of Response

In the large case series described by Grünig et al,[17] it was possible to identify patterns of poorer response. These were largely non-PAH characteristics including recurrent respiratory tract infections, musculoskeletal problems, and issues with mental health. The other major cause of poor treatment response was in those entering the study with a high 6MWT distance (> 550 m). Whilst this may reflect the reduced sensitivity of this outcome measure at higher walk distances (ceiling effect),[52] it may also indicate an absence of deconditioning in this patient subset, which is likely to be necessary for a positive treatment effect.

A surprising outcome from this case series was that functional class IV patients fared as well as those in functional class II or III. This may be explained by the subjective nature of the functional class descriptor. The baseline 6MWT distance in the functional class IV subgroup was 239 ± 95 m. In other settings these patients would probably have been assessed as in functional class III.

In short, it is likely that there are 3 prerequisites for a response to exercise training:

- stable condition,
- presence of deconditioning, and
- ability to perform exercise.

HOW TO DESIGN A REHABILITATION PROGRAM FOR PATIENTS WITH PAH

Whilst the concept that rehabilitation works in PAH is generally accepted, little of the research data so far have focused on the optimal model of delivery. Features of design of that must be considered in setting up a service are shown in Figure 1.

Most of the data available to guide on the establishment of a service come from the Heidelberg model.[7] The program that they have implemented consists of a 3-week inpatient stay in a rehabilitation hospital followed by 12 weeks of remotely supervised exercise at home. The remaining approaches have largely been outpatient based, both specialized for and restricted to PH patients or enrolled into a generic rehabilitation service. These would typically run over a few months with several short visits to the service each week. There is a small amount of data from patients rehabilitated in a home setting. There is a suggestion from the data in the Cochrane review[37] and elsewhere[10] that outpatient services may be less successful. When the Cochrane review analyzed trials by setting, the Heidelberg-based studies achieved a 6MWT distance of 73 m compared with 34 m in the outpatient studies. There is also an unproven concern that outpatient services, especially those run by generic services, may be less safe. Such statements are largely speculative as there is no head-to-head comparison. On the other hand, outpatient services are undoubtedly cheaper. One problem with outpatient rehabilitation services specific to PH patients that may prove insuperable is the fact that PAH is a rare condition. Hence, achieving a sufficiently large local cohort of patients to make PH-specific outpatient rehabilitation a viable practical option requires a high population density. This will not be true for most patients with PAH who are geographically dispersed. Table 2 contrasts the relative merits of different settings for a PH rehab service.

One striking pattern seen in the Heidelberg model is that all of the benefit is generally achieved by the end of the 3-week stay.[6,17] This raises the possibility of designing a short, intensive, 3-week model that uses a hybrid residential-home format to try to achieve the same results with shorter inpatient stays.

The modalities of exercise training have been generally consistent although different in detail. Aerobic training has been delivered by walking (outdoors or treadmill) or cycle ergometry.[7] Some features used may enhance the effectiveness of the training. In the Heidelberg

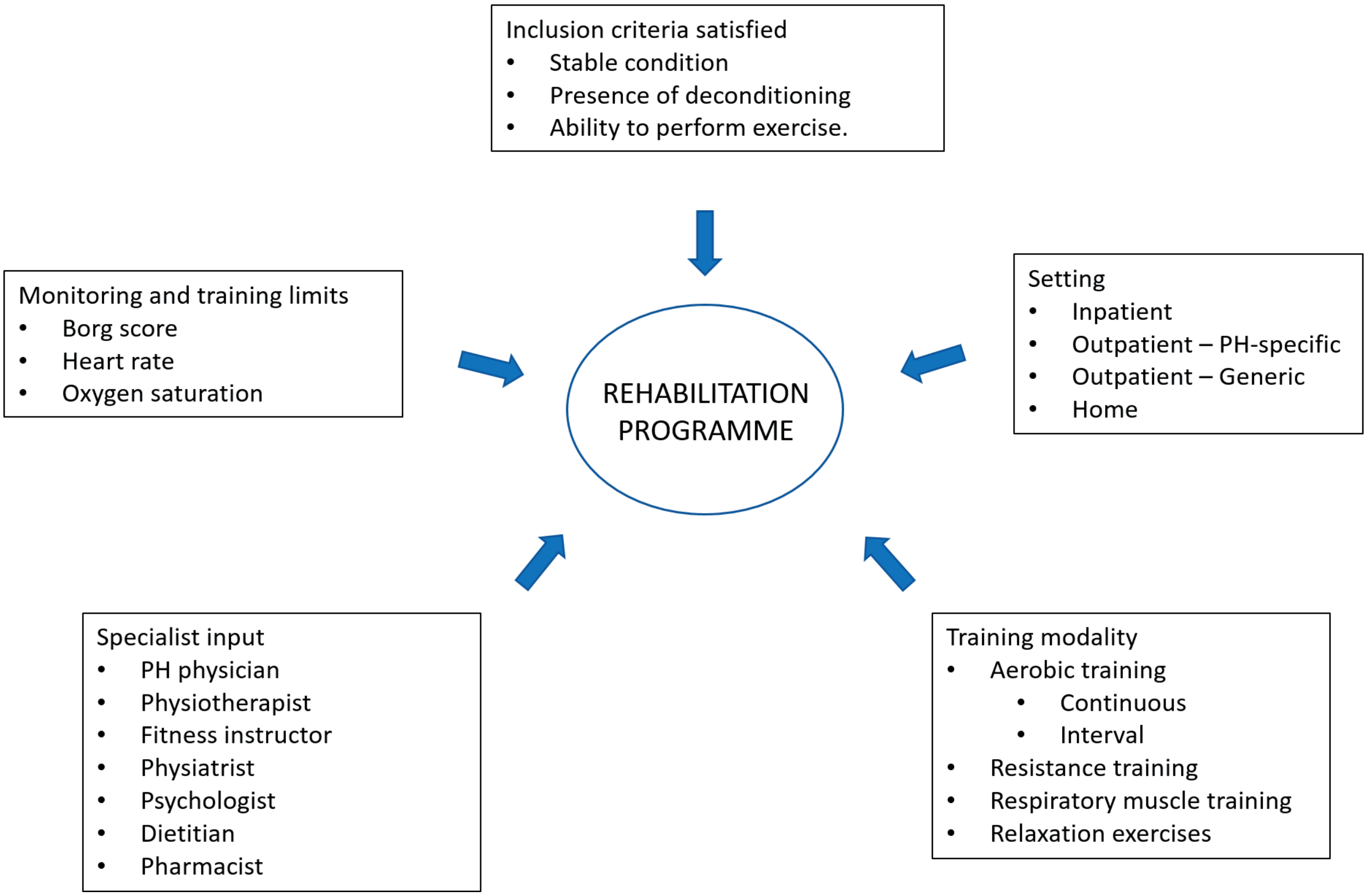

Figure 1: Design features to be considered in setting up a pulmonary hypertension rehabilitation service.

model, exercise training workloads start low and are continually reassessed and increased during the program. This gives patients an impression of progress and reinforces compliance. Several of the rehabilitation programs used interval training rather than continuous training models, an approach that tends to optimize the efficiency of the training process.[53] Attention was paid to the maintenance of minimum oxygen saturations and the use of oxygen supplementation where required.[7] This is an approach recognized to increase exercise capacity and thereby improve the intensity of training and hence the training effect.[54]

Table 2. Relative Merits of Different Settings for a Pulmonary Hypertension (PH) Rehabilitation Service

	Inpatient then home	Outpatient: PH specific	Outpatient: generic	Home
Efficacy	+++	++	+	+
Cost	High	Moderate	Moderate	Low
Safety and monitoring	++++	+++	++	+
Accessibility	+	–	++	+++

Low-level resistance training was also widely used[7]. However, the use of relaxation therapy and respiratory muscle training were less widespread.[7] Respiratory muscle weakness is an unexpected feature of PAH which has been convincingly demonstrated.[55] A small uncontrolled study of 7 patients[13] received inspiratory muscle training as a part of their exercise training program. Inspiratory muscle strength increased when tested in a nonvolitional manner. Inspiratory muscle training has also been used as the sole intervention in 2 studies.[56,57] Respiratory muscle strength assessed by mouth pressure was increased but improvements were also seen in exercise capacity and quality of life. A similar effect in a larger patient group has been demonstrated in patients with left heart disease.[58,59]

Monitoring of exercise training is described in most studies and typically employed a combination of Borg score, heart rate, and oxygen saturation. These are useful both for monitoring safety and assessing intensity of training. The precise limits used in the studies are summarised in the recent European Respiratory Society task force statement.[7] Lastly, rehabilitation services generally utilize the skills of a wide range of specialists. In the PH rehabilitation studies, there has been involvement of PH physicians, physiotherapists, physiatrists, psychologists, fitness instructors, dietitians, and pharmacists.[7]

THE FUTURE OF REHABILITATION IN PAH

Attitudes to activity and exercise for PAH patients have been completely reversed over the last 15 years. PH physicians are convinced that physical rehabilitation helps their patients. The focus now is on the optimal model for delivery of the intervention, which inevitably is a compromise between efficacy, cost, and accessibility.

The most effective approach may well vary country to country or even between PH clinics and there are a number of variables yet to be fully explored. Examples include the setting of the program. Would short-burst inpatient training with several stays of 1 to 2 days spread over 3 weeks be as effective as a 3-week continuous inpatient stay? Alternatively, would local, generic outpatient rehabilitation delivered alongside other cardiopulmonary patients be as effective as PH-specific programs? The advantage of both these approaches would be an improvement in cost and accessibility. Another variable is the form of exercise training and standardization of the exercise prescription together with use of adjuncts such as oxygen supplementation. Should respiratory muscle training be universally adopted bearing in mind that its role in rehabilitation in COPD has been much more intensively investigated and is currently out of favour?[60] Are there mechanisms of improving peripheral muscle training without overstressing the cardiopulmonary system such as the concept of single-leg exercise that has been used in COPD and heart failure?[61]

Some questions have yet to receive any attention, such as the timing of the rehabilitation in the disease process—at diagnosis or after pharmacotherapy has been optimized? Also what is the potential role for widely available motivational aids such as internet-based videos and "fitness watches," which represent an as yet untapped resource?

In consequence, there is a clear role for rehabilitation in PAH and this area of therapy is currently in an early phase of development for our patients. We should expect many changes in this area in the coming years.

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