ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension

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Specialised exercise training in patients with pulmonary hypertension appears to be effective, cost-efficient and safe. More support is necessary from healthcare institutions and politicians to establish such programmes throughout Europe. http://ow.ly/kLvS30mUbja

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ABSTRACT Objectives of this European Respiratory Society task force were to summarise current studies, to develop strategies for future research and to increase availability and awareness of exercise training for pulmonary hypertension (PH) patients.

An evidence-based approach with clinical expertise of the task force members, based on both literature search and face-to-face meetings was conducted. The statement summarises current knowledge and open questions regarding clinical effects of exercise training in PH, training modalities, implementation strategies and pathophysiological mechanisms.

In studies (784 PH patients in total, including six randomised controlled trials, three controlled trials, 10 prospective cohort studies and four meta-analyses), exercise training has been shown to improve exercise capacity, muscular function, quality of life and possibly right ventricular function and pulmonary haemodynamics. Nevertheless, further studies are needed to confirm these data, to investigate the impact on risk profiles and to identify the most advantageous training methodology and underlying pathophysiological mechanisms.

As exercise training appears to be effective, cost-efficient and safe, but is scarcely reimbursed, support from healthcare institutions, commissioners of healthcare and research funding institutions is greatly needed. There is a strong need to establish specialised rehabilitation programmes for PH patients to enhance patient access to this treatment intervention.

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Introduction

Pulmonary hypertension (PH), defined as invasively measured mean pulmonary artery pressure ⩾25 mmHg, occurs in many different diseases [1]. The focus of this task force was mainly on patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Here, these are summarised as PH unless otherwise stated. In the past decade great advances in medical therapy have been made [1]. Despite optimised medical treatment, most PH patients still suffer from symptoms, reduced exercise capacity and quality of life (QoL) and disease progression [2]. In most cases medication cannot entirely halt or reverse right ventricular dysfunction nor normalise pulmonary vascular resistance. Consequently, the need of non-pharmacological, high-quality treatments is rapidly growing.

Exercise training is one of the most important, safest and cost-effective treatment options, and has been shown to be beneficial in a wide range of diseases. In addition, it is strongly advocated in the healthy population to improve QoL, wellbeing and muscular strength [3]. The entire body including the heart is impacted upon by being physically active. Hence, haemodynamic differences can be noted in athletes in comparison to controls with a less active lifestyle [4]. In particular, long-term endurance exercise increased the size of the right ventricle and improved early diastolic right ventricular function [5] and left ventricular stiffness [6]. In contrast, a sedentary lifestyle in healthy subjects has been established as an independent risk factor for insulin resistance acting in concert with other cardiovascular risk factors such as smoking, obesity and high blood pressure [7]. Thus, moderate physical activity has been recommended for the prevention of several cardiovascular diseases [8].

Training for patients with left heart failure received a 1A recommendation in the recent guidelines [9], as it was shown to improve QoL [10, 11] and exercise capacity [12], reduce the risk of heart failure associated hospitalisation [9, 11] and even morbidity events [10]. The training should be supervised carefully as heavy physical activity, particularly in untrained individuals, can increase the risk of myocardial infarction [13]. Patients suffering from coronary artery disease are thus advised to participate in cardiac rehabilitation programmes to reduce cardiovascular mortality and hospitalisation events [14].

In contrast, for PH patients, these exercise recommendations have been lacking for a long time and in fact, physical activity has been discouraged due to the risk of worsening of the disease, right ventricular decompensation and sudden cardiac death. In most PH patients at time of diagnosis the right ventricle is increased in size and impaired in function [2]. There is concern that wall shear stress on the pulmonary vessels, evoked by higher blood flow due to exercise training, may trigger pulmonary vascular remodelling and worsen the disease; thus, in any exercise regimen extreme caution has to be warranted not to overexert these patients. A specialised, low-intensity, individually adjusted, closely supervised exercise training regimen has been developed and a first randomised controlled trial demonstrated its safety and feasibility [15]. Due to a growing body of evidence [15–23], in the recent guidelines a supervised and closely monitored exercise and respiratory training programme in specialised clinics as an add-on to medical therapy has been recommended for stable PH patients (class II, level of evidence B) [1]. Currently, exercise training for PH patients is only routinely reimbursed by insurance programmes or state funding in very few countries. Therefore, exercise training prescription as supportive therapy is limited. Furthermore, the

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best training modalities, individual adaptation and the optimal setting for this rehabilitation remain to be determined. Pathophysiological mechanisms are not completely clear.

The objectives of this European Respiratory Society (ERS) task force were to summarise the current state of knowledge and open questions regarding the clinical effects of exercise training, training modalities and mechanisms of action in patients with PH. Furthermore, it aimed to develop strategies for future research and implementation of a standardised PH rehabilitation programme in European countries to increase awareness and availability of this potentially important add-on therapy.

Methodology

In this ERS task force statement, PH experts were involved from 18 centres in 11 European countries. The task force members were selected by the chairs (E. Grünig and A. Peacock) according to their expertise in PH and exercise training in PH. The statement was reviewed by the PH patient organisation PHA Europe. All task force members completed conflict of interest forms.

The present ERS statement combines an evidence-based approach with the clinical expertise of the task force members, based on both literature search and face-to-face meetings. Subgroups of authors were formed for each section at a first face-to-face meeting (September 5, 2016). These groups prepared individual subsections, which were then presented and discussed within the entire group in a second meeting (September 11, 2017) and subsequently revised until consent among all co-authors was reached. All co-authors critically revised and approved the final statement.

Literature search was conducted using MEDLINE including phrases such as "exercise training", "rehabilitation", "pulmonary hypertension" and the relevant key words for each respective section (supplementary table S1). Identified original articles on exercise training in PH were used for the sections on clinical effects, training modalities and setting, implementation and mechanisms of action. The search was restricted to articles available in English. No time limitation was introduced to identified articles. Data from case reports of single patients, children and adolescents, clinical trial protocols and abstracts only were excluded. The literature search was performed in May 2015 and repeated after the task force meetings and at the end of the task force period in December 2017 to include latest publications. Additionally, hand searches of articles listed in the references lists were performed.

This document aims to provide an overview of the literature and current evidence and does not provide a systematic review or recommendations for clinical practice.

Part I: clinical effects of exercise training in pulmonary hypertension

Effect of exercise training on exercise capacity and QoL

The clinical impact of exercise training in PH has been investigated in several studies with 784 patients in total, including six randomised controlled trials [15, 22–26], three controlled trials [27–29], 10 prospective cohort studies [16–21, 30–35], three case series [34–36], two retrospective cohort studies [37, 38] and four meta-analyses [39–42] (table 1). In the first prospective randomised controlled trial in patients with severe chronic PH, exercise training improved the primary end-point, 6-min walk distance (6MWD), by 96±61 m after 15 weeks compared to the control group ($p<0.0001$) [15]. This positive result was supported by a further randomised controlled trial [22] and a prospective uncontrolled trial including 183 patients with different PH aetiologies [19]. Patients in World Health Organization (WHO) functional class IV presented with the strongest improvements, compared to functional classes II and III [19]. One recent randomised controlled study has demonstrated a significant increase of the primary end-point, mean peak oxygen uptake (V'_{O_2}), which improved up to almost 25% in the training group *versus* the control group (+3.1±2.7 $mL \cdot min^{-1} \cdot kg^{-1}$ *versus* −0.2±2.3 $mL \cdot min^{-1} \cdot kg^{-1}$; $p<0.0001$) [24].

The effects of exercise training on exercise capacity have been verified by four meta-analyses showing an improvement in 6MWD (53–72 m), peak V'_{O_2} (1.5–2.2 $mL \cdot min^{-1} \cdot kg^{-1}$) and workload (14.9 W) [39–42].

Exercise training performed in patients classified into different groups of PH has not only improved exercise capacity, but also different aspects of QoL, as shown in several studies [15, 17, 22] (table 2). Most studies used the 36-item short-form health survey (SF-36) questionnaire, a generic instrument. Mereles *et al.* [15] showed a significant improvement in the primary end-point, QoL, in the two summation scores and in five SF-36 subscales after 15 weeks of exercise training in severe chronic PH [20]. Further prospective studies confirmed improvements of SF-36 subscales in stable PAH and CTEPH at 3 months of follow-up [17, 19, 24]. Details of improvement in QoL are given in table 2. The improvements measured by SF-36 scales with different training modalities in various PH groups suggest a significant impact of exercise training on patients' QoL, which has been confirmed by a meta-analysis [41] and a Cochrane review [42] showing significant improvements in the SF-36 subscales: physical function, role physical, general health, social function, role emotional and vitality.This is remarkable, as the generic SF-36

TABLE 1 Studies on exercise training in patients with pulmonary hypertension including design and main results

First author, year [ref]	Study design	Sample	Diagnoses and severity of disease	Results parameters with significant improvement[#]	Parameters without significant improvement or deterioration[¶]
Randomised controlled trials n=6; patients n=224					
Mereles, 2006 [15]	Randomised controlled trial	30	IPAH (80%) CTEPH (20%) WHO-FC II–IV	Primary: 6MWD, QoL (SF-36) Secondary: WHO-FC, peak V'_{O_2}, V'_{O_2} at anaerobic threshold, workload, systolic pulmonary arterial pressure at rest (echocardiography)	No change: Borg scale, heart rate at rest, right heart size and function (echocardiography)
Weinstein, 2013 [23]	Randomised controlled trial	24	APAH/IPAH (75%/25%) WHO-FC I–IV	Fatigue, physical activity 6MWD, treadmill exercise test duration, peak power output	
Chan, 2013 [22]	Randomised controlled trial	23	APAH/IPAH (74%/22%) WHO-FC I–IV	Primary: 6MWD Secondary: time to exercise intolerance, peak workload, peak P_{ETCO_2}, time to anaerobic threshold, QoL (SF-36, CAMPHOR)	No change: peak V'_{O_2}, haemodynamics (bioimpedance cardiography: cardiac index, cardiac output, stroke volume)
Ley, 2013 [25]	Randomised controlled trial	20	APAH/IPAH (20%/55%) CTEPH (20%) WHO-FC II–III	Primary: mean blood flow peak velocity within cardiac MRI Secondary: perfusion (mean pulmonary blood volume), 6MWD	
Ehlken, 2016 [24]	Randomised controlled trial	87	PAH (70%) CTEPH (30%) WHO-FC II–IV	Primary: peak V'_{O_2} Secondary: haemodynamics (cardiac index at rest and during exercise), 6MWD, QoL (SF-36)	No change: NT-proBNP, heart rate at rest, peak mPAP, peak PVR
González-Saiz, 2017 [26]	Randomised controlled trial	40	APAH/IPAH (35%/25%) CTEPH (10%) NYHA-FC I–III	Primary: peak muscle power during bench/leg press Secondary: peak V'_{O_2}, 6MWD, five-repetition sit-to-stand, moderate–vigorous physical activity	No change: QoL (SF-12), 6MWD, peak V'_{O_2}, NT-proBNP
Non-randomised controlled trials n=3; patients n=71					
Martínez-Quintana, 2010 [28]	Non-randomised controlled trial	8	CHD-APAH (100%) WHO-FC II–III	NYHA-FC	No change: QoL (SF-36), 6MWD, peripheral muscle function, NT-proBNP
Fox, 2011 [27]	Non-randomised controlled trial	22	APAH/IPAH (46%/45%) CTEPH (9%) WHO-FC II–III	Primary: 6MWD, peak V'_{O_2} Secondary: no significant changes	No change: NT-proBNP, pulse pressure, Borg scale, peak oxygen saturation, peak workload, oxygen uptake efficiency, V'_E/V'_{CO_2}
Fukui, 2016 [29]	Non-randomised controlled trial	41	CTEPH (100%) WHO-FC I–III	Peak V'_{O_2}, workload, WHO-FC, quadriceps strength, oxygen pulse	No change: QoL (SF-36), 6MWD, NT-proBNP, V'_{O_2} at anaerobic threshold, heart rate at rest, oxygen saturation, V'_E/V'_{CO_2}, 6MWD, forearm muscle strength
Prospective uncontrolled cohort studies n=10; patients n=426					
de Man, 2009 [21]	Prospective cohort	19	IPAH (100%) WHO-FC II–III	Workload, exercise endurance time, quadriceps strength and endurance, increase of capillarisation	No change: 6MWD, endurance, NT-proBNP

Continued

TABLE 1 Continued

First author, year [ref]	Study design	Sample	Diagnoses and severity of disease	Results parameters with significant improvement[#]	Parameters without significant improvement or deterioration[¶]
Grünig, 2011 [20]	Prospective cohort	58	APAH/IPAH (12%/64%) CTEPH (10%) WHO-FC II–IV	6MWD, peak V'_{O_2}, QoL (SF-36), WHO-FC, workload, heart rate at rest (decrease) and peak (increase), V'_{O_2} at anaerobic threshold, workload at anaerobic threshold	No change: Borg Scale, respiratory equivalent for carbon dioxide
Grünig, 2012 [19]	Prospective cohort	183	APAH/IPAH (25%/45%) CTEPH (17%) WHO-FC I–IV	6MWD, peak V'_{O_2}, QoL (SF-36), V'_{O_2} at anaerobic threshold, oxygen pulse, systolic pulmonary arterial pressure at rest, workload	No change: Borg Scale, respiratory equivalent for carbon dioxide
Nagel, 2012 [17]	Prospective cohort	35	CTEPH (100%) WHO-FC II–III	6MWD, peak V'_{O_2}, QoL (SF-36), workload Survival (1 year 97%, 2 years 94%, 3 years 86%)	No change: WHO-FC, NT-proBNP, oxygen saturation, oxygen pulse, respiratory equivalent for carbon dioxide Significantly higher Borg scale after intervention
Grünig, 2012 [18]	Prospective cohort	21	CTD-APAH (100%) WHO-FC II–IV	6MWD, peak V'_{O_2}, QoL (SF-36), heart rate at rest, oxygen saturation, workload, V'_{O_2} at anaerobic threshold Survival (1 and 2 years 100%, 3 years 73%)	No change: WHO-FC, Borg scale, oxygen pulse, oxygen saturation at rest, haemodynamics (echocardiography), C-reactive protein, leukocytes
Becker-Grünig, 2013 [16]	Prospective cohort	20	CHD-APAH (100%) WHO-FC II–III	6MWD, peak V'_{O_2}, workload Survival (1 year 100%, 2 years 93%) QoL (bodily pain)	No change: QoL (SF-36 except bodily pain), WHO-FC, haemodynamics (echocardiography), oxygen pulse, V'_{O_2} at anaerobic threshold, oxygen saturation, Borg scale Deterioration: NT-proBNP
Kabitz, 2014 [31]	Prospective cohort	7	APAH /IPAH (28%/72%) WHO-FC III–IV	Respiratory muscle strength, 6MWD	
Ehlken, 2014 [30]	Prospective cohort *versus* retrospective control group	58+	APAH/IPAH (12%/63%) CTEPH (10%) WHO-FC II–IV	QoL, lower estimated healthcare costs due to fewer worsening events	
Inagaki, 2014 [32]	Prospective cohort	8	CTEPH (100%) WHO-FC II–III	6MWD, QoL, quadriceps force, QoL (St George's Respiratory Questionnaire: activity), intensity of physical activity	No change: dyspnoea, WHO-FC, heart rate at rest, pulmonary function, activities of daily living, QoL (St George's Respiratory Questionnaire: symptom and impact), haemodynamics (echocardiography), dyspnoea and functional status, BNP, steps per day
Ihle, 2014 [33]	Prospective cohort	17	PAH (82%) CTEPH (18%) WHO-FC II–III	QoL (CAMPHOR: activity)	No change: QoL (SF-36, CAMPHOR: symptoms, QoL), 6MWD
Case reports and retrospective studies n=5; patients n=63					
Shoemaker, 2009 [35]	Case reports	2	APAH/IPAH (50%/50%) WHO-FC I	6MWD, peak V'_{O_2} at anaerobic threshold, workload at anaerobic threshold in both subjects	QoL (1 out of 2 subjects improved)
Mainguy, 2010 [34]	Case series	5	IPAH (100%) WHO-FC II–III	6MWD, V'_E Decreased type IIx muscle fibre proportion	No change: endurance, muscle strength

Continued

TABLE 1 Continued

First author, year [ref]	Study design	Sample	Diagnoses and severity of disease	Results parameters with significant improvement[#]	Parameters without significant improvement or deterioration[¶]
Raskin, 2014 [37]	Retrospective cohort	23	Aetiology not reported WHO-FC II–IV	Primary: 6MWD (especially when baseline 6MWD was lower) Secondary: dyspnoea impact (clinically significant: subscale St George's Respiratory Questionnaire)	No change: QoL (clinically significant: St George's Respiratory Questionnaire: two main parts) Deterioration: QoL (clinically significant: St George's Respiratory Questionnaire: activity)
Talwar, 2017 [38]	Retrospective cohort	18	PAH (100%) WHO-FC I–IV	Treadmill speed	No change: exercise time
Bussotti, 2017 [36]	Case series	15	APAH/IPAH (53%/47%) WHO-FC II–III	Primary: peak V'_{O_2} Secondary: 6MWD, oxygen pulse, maximal heart rate, peak workload, QoL	No change: NT-proBNP
Meta-analysis n=4					
Yuan, 2015 [41]	Meta-analysis	12 studies total n=449	Different aetiologies of pulmonary hypertension	6MWD (62.2 m, 95% CI 45.6–78.8 m) Peak $V'_{O_2}{\cdot}kg^{-1}$, workload V'_{O_2} at anaerobic threshold Heart rate at rest (after 3 weeks) QoL (physical function 10.4, 95% CI 5.0–15.9; role physical 12.1, 95% CI 1.3–23.0; general health 4.0, 95% CI 0.04–7.9; social function 11.6, 95% CI 5.2–17.9; role emotional 14.3, 95% CI 6.2–11.4)	No change: heart rate at rest (after 12–15 weeks)
Buys, 2015 [39]	Meta-analysis	5 studies total n=106	Different aetiologies of pulmonary hypertension	6MWD (72.5 m, 95% CI 46.0–99.1) Peak $V'_{O_2}{\cdot}kg^{-1}$	
Pandey, 2015 [40]	Meta-analysis	16 studies total n=469	Different aetiologies of pulmonary hypertension	6MWD (53.3 m, 95% CI 39.5–67.2 m) Peak $V'_{O_2}{\cdot}kg^{-1}$ QoL Peak systolic pulmonary arterial pressure	-
Morris, 2017 [42]	Cochrane meta-analysis	6 studies total n=206	Different aetiologies of pulmonary hypertension	6MWD (60.1 m, 95% CI 30.2–90.1) Peak $V'_{O_2}{\cdot}kg^{-1}$ QoL (SF-36 summation scores, role physical 21.8, 95% CI 14.4–29.2; vitality 13.5, 95% CI 7.6–19.4; social function 14.0, 95% CI 9.8–18.2; CAMPHOR: QoL) Peak power	No change: adverse events, functional class, NT-proBNP, QoL (SF-36: physical function, bodily pain, general health, mental health, role emotional; CAMPHOR: activities, symptoms)

IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; QoL: quality of life; SF-36: 36-item short-form questionnaire; V'_{O_2}: oxygen consumption; APAH: associated pulmonary arterial hypertension; P_{ETCO_2}: end-tidal carbon dioxide tension; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; NYHA-FC: New York Heart Association functional class; SF-12: 12-item short-form questionnaire; CHD: congenital heart disease; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; CTD: connective tissue disease; PAH: pulmonary arterial hypertension. [#]: if no division of primary/secondary end-points is given, study end-points were presented as exploratory; primary study end-points were positive in all studies; [¶]: parameters with no change/deterioration were exploratory parameters only; [+]: this study refers to the same patients as Grünig *et al.* [20].

TABLE 2 Quality-of-life (QoL) outcomes in exercise training studies of pulmonary hypertension patients

First author, year [ref]	Patients	QoL measure	
		SF-36	Others
In-patient			
Mereles, 2006 [15]#	IPAH, CTEPH	PCS, MCS, physical functioning, role physical, social functioning, mental health, vitality	
		Bodily pain, general health, role emotional	
Grünig, 2011 [20]	IPAH, CHD-APAH, CTD-APAH, CTEPH	General health, mental health, physical functioning, role emotional, role physical, social functioning, vitality	
		Bodily pain	
Grünig, 2012 [18]	CTD-APAH	General health, mental health, physical functioning, social functioning, vitality	
		Bodily pain, role emotional, role physical	
Grünig, 2012 [19]	Stable PAH, CTEPH	Mental health, physical functioning, role emotional, role physical, social functioning, vitality	
		Bodily pain, general health	
Nagel, 2012 [17]	CTEPH	Physical functioning, vitality	
		Bodily pain, general health, mental health, role emotional, role physical, social functioning	
Becker-Grünig, 2013 [16]	CHD-APAH	Bodily pain	
		General health, mental health, physical functioning, role emotional, role physical, social functioning, vitality	
Ehlken, 2016 [24]	PAH, inoperable CTEPH	Vitality	
		Bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning	
Fukui, 2016 [29]	CTEPH after BPA	Mental health	Patient Health Questionnaire-9: depression severity
		Bodily pain, general health, physical functioning, role emotional, role physical, social functioning, vitality	

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instrument is designed to compare QoL in health and various diseases, but is usually less sensitive to detect changes under therapy compared with disease-specific instruments. In summary, most of the studies presented a significant improvement in exercise capacity and/or some QoL subscales.

Haemodynamics and echocardiography

Most exercise training trials published so far in the field of PH focused on changes in exercise capacity. There is only one prospective, randomised, controlled trial available, which aimed to assess changes systematically with invasively measured haemodynamics at rest and during exercise as secondary end-points [24]. Altogether, 79 patients, either suffering from PAH or from nonoperable CTEPH, finished this study and 73 of them underwent right heart catheterisations at baseline and after 15 weeks. The study revealed a significant increase in cardiac index (+9.3% *versus* −6.5%; p<0.001), significant decreases in mean pulmonary arterial pressure (−7.3% *versus* +16.1%; p=0.007) and pulmonary vascular resistance (−19.3% *versus* +34.5%; p<0.001) at rest and a significant increase in cardiac index (+19.5% *versus* −4.3%;

TABLE 2 Continued

First author, year [ref]	Patients	QoL measure	
		SF-36	Others
Outpatient			
González-Saiz, 2017 [26]	Stable PAH, inoperable CTEPH	Role physical, vitality	
		Bodily pain, general health, mental health, physical functioning, role emotional, social functioning	
Martínez-Quintana, 2010 [28]	PAH, CHD-APAH	SF-12: MCS, PCS	
Chan, 2013 [22]	IPAH, CTD-APAH, drug-induced PAH	General health, mental health, physical functioning, role physical, social functioning, vitality	CAMPHOR: QoL, symptoms, energy, breathlessness, mood
		Bodily pain, role emotional	CAMPHOR: functioning
Weinstein, 2013 [23]	IPAH, CTD-APAH		Fatigue severity scale; human activity profile
Raskin, 2014 [37]	Aetiology not reported		SGRQ (clinically significant changes >4 points): impact score
			SGRQ: symptom
			SGRQ: activity score
Zöller, 2017 [43]	PAH (children and adolescents)	Tendency: MCS, PCS	
Bussotti, 2017 [36]	IPAH, portal hypertension-APAH, CTD-APAH, HIV-APAH		HADS questionnaire: anxiety, depression; EuroQoL-5 dimensions; EuroQoL-visual analogue scale
Gerhardt, 2017 [44]	IPAH, HPAH, CTD-APAH	MCS, PCS	Living with PH survey; physical and emotional dimension score
Home			
Inagaki, 2014 [32]	Stable inoperable or residual CTEPH		SGRQ: activity score
			SGRQ: impact, symptom
Ihle, 2014 [33]	PAH, CTEPH	Bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning, vitality	CAMPHOR: activity
			CAMPHOR: QoL, symptoms

Significant improvement (p<0.05) | No statistical difference | Deterioration

SF-36: 36-item short form questionnaire; IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; PCS: physical component score; MCS: mental component score; CHD: congenital heart disease; APAH: associated pulmonary arterial hypertension; CTD: connective tissue disease; PAH: pulmonary arterial hypertension; BPA: balloon angioplasty; SF-12: 12-item short form questionnaire; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; SGRQ: St George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; HPAH: hereditary pulmonary arterial hypertension. #: co-primary end-point.

p=0.002) during maximal exercise in the training group, compared with the control group. The observed haemodynamic changes during exercise may be of special importance, as recent data suggest that cardiac index during exercise may represent an independent predictor of survival in PAH [45]. Interestingly, echocardiography showed no statistically significant change in right heart areas and systolic pulmonary arterial pressure between the groups in this study.

Echocardiography has been performed in most exercise training studies in order to estimate systolic pulmonary arterial pressure and right ventricular functional variables. The results of these studies have been evaluated in a meta-analysis [40]. Although not all individual studies revealed a significant improvement of

echocardiographic parameters [15, 24], the pooled analysis of the available seven noninvasive studies and one invasive trial [24] showed that exercise training was associated with a significant decrease in resting systolic pulmonary artery pressure from baseline to follow-up (−3.7 mmHg; 95% CI −5.4 to −1.9).

In summary, supervised exercise training may improve right ventricular function and pulmonary haemodynamics in patients with stable PH. Improved haemodynamics may contribute to an increase of exercise capacity and QoL of patients. As invasive data are only available from a single prospective randomised study [24], further investigations are needed to confirm these data.

Muscle function in PH patients

Leg fatigue and dyspnoea during exercise are the main indications of skeletal muscle dysfunction in patients with PAH [46]. Maximal volitional and nonvolitional strength of both the quadriceps as well as the inspiratory muscles are reduced in PAH patients and are closely correlated to exercise capacity [47–49]. Moreover, on the cellular level, alterations are observed in both the respiratory as well as the peripheral muscles (table 3).

Inspiratory muscle strength largely depends on diaphragm muscle function. Data from PH rats and PAH patients suggest that part of the respiratory muscle dysfunction can be explained by a reduction in force generating capacity of the diaphragm muscle fibres [50–52].

Because of inconsistent data in the literature, it is more difficult to define the structural and contractile alterations that would explain the observed peripheral muscle weakness. Muscle fibre size has been reported to be decreased (atrophy) [53, 54] or unaltered [48, 50, 55, 56] in PAH patients and PH rats. In addition, a switch to the more fast-twitch fibre type has been reported [48, 53, 56], but not in all studies [53, 55]. Similarly, a loss in capillary density in quadriceps muscle of PAH patients and PH rats has been reported [55], but could not be confirmed in other studies [34, 54]. Finally, reduced force-generating capacity of quadriceps muscle fibres could only be observed in PAH patients [57], but not in PH animal models [50–52]; thus, the underlying cause of peripheral muscle weakness is not completely clear, but may involve atrophy, sarcomeric dysfunction, fibre type switch or capillary rarefaction [58].

The lack of standardisation and small sample size of the individual studies are possible explanations for the conflicting findings. In future, larger multicentre studies should be performed to determine the contribution of quadriceps muscle atrophy on reduced skeletal muscle function. In addition, the underlying pathophysiological mechanisms (*e.g.* physical activity, inflammation, hypoxia, insulin resistance, sympathetic activity, cardiac output) [59] should be investigated in order to generate specific treatment strategies (see section on mechanisms of action). Finally, a direct comparison of quadriceps abnormalities observed in PAH, chronic obstructive pulmonary disease and chronic heart failure would be helpful to assess the specificity of the skeletal muscle dysfunction in PAH patients.

Quadriceps and inspiratory muscle training

With the inclusion of specific quadriceps and inspiratory muscle training in the exercise training programme, peripheral and inspiratory muscle weakness can be targeted. Quadriceps muscle training and endurance training (cycling) has been shown to be effective in improving quadriceps muscle strength and endurance capacity in PAH patients [21]. In addition, aerobic capacity of the quadriceps muscle fibres improved, characterised by an increased capillary density and oxidative enzyme activity (table 3). A fibre type switch to more oxidative (type 1) muscle fibres has been reported after exercise training in PAH [34].

Inspiratory muscle training has been reported to be beneficial for inspiratory muscle function. In addition, PAH patients report a better QoL and decreased sensation of dyspnoea after inspiratory muscle training [31]. Finally, literature on left heart failure suggests that inspiratory muscle training and exercise training are able to reduce sympathetic drive, potentially leading to improved cardiac function and reduced respiratory drive [60].

Limitations of training studies in PH

Although an emerging body of data presents beneficial effects of rehabilitation programmes in PH, the findings are limited by several factors. It is a common problem of exercise training studies that they cannot be performed in a blinded design. This may lead to biased results, as patients may decline to participate after randomisation, or may start exercise training by themselves, despite being allocated to the control arm. This bears the risk of unsupervised training, in addition to biased trial results, which hinders the collection of long-term data on control patients. This may be one reason why there are still no long-term data on exercise training and rehabilitation effects in PH. A referral bias cannot be excluded in most studies, since more active and compliant patients may have participated. Consequently, there is a need for

TABLE 3 Summary of studies analysing muscle function in pulmonary hypertension

First author, year, [ref.]	Type of muscle	Sample size n	Patients	Animal model	Muscle function	Cellular changes
Vescovo, 1998 [56]	Peripheral (M. soleus + EDL)	30 16/14#		MCT30		↓ fibre type I/II ratio ≈ CSA
Meyer, 2005 [49]	Respiratory	46 26/20#	IPAH		↓ P_{Imax}, P_{Emax}	
Kabitz, 2008 [47]	Respiratory	62 31/31#	PH (25 PAH, 6 CTEPH)		↓ P_{Imax}, P_{Emax}, SnP_{na}, SnP_{di}, TwP_{mo}, TwP_{di}	
Mainguy, 2010 [48]	Peripheral (M. quadriceps)	20 10/10#	IPAH		↓ maximal voluntary contraction (volitional), quadriceps twitch (non-volitional)	↓ fibre type I/II ratio, PFK/HADH ratio ≈ capillary density, CS, CSA, HADH, PFK/CS ratio
de Man, 2011 [50]	Respiratory (diaphragm) Peripheral (EDL or M. quadriceps)	12 6/6# 15 8/7#	PH	MCT60	Patient diaphragm: ↓ maximal isometric force Animal model diaphragm: single muscle fibres: ↓ twitch force, tetanic force, force–frequency	Patients' diaphragm: ↓ CSA diaphragm ≈ CSA quadriceps Animal model diaphragm: ↓ CSA ≈ capillary density, SDH, Akt phosphorylation, MHC expression, 20 s proteasome, proteasome activity ↑ MAFbx, MuRF-1
					Peripheral muscle: ≈ twitch force, tetanic force, force–frequency	Peripheral muscle: ≈ CSA
Manders, 2012 [52]	Respiratory (diaphragm) Peripheral (EDL)	14 7/7#		MCT60	Diaphragm: single muscle fibres Fast twitch fibres ↓: maximal tension, calcium sensitivity, force per cross-bridge ≈: fraction strongly bound cross-bridges, tension cost Peripheral muscle: ≈: maximal tension, calcium sensitivity	Diaphragm ↓: fibre type I/II ratio, nitrosative stress ≈: oxidative stress
Wüst, 2012 [54]	Peripheral (M. plantaris)	23 11/12#		MCT60		↓: CSA, complex I activity, SDH ≈: fibre type I/II ratio, capillary density

Continued

TABLE 3 Continued

First author, year, [ref.]	Type of muscle	Sample size n	Patients	Animal model	Muscle function	Cellular changes
Batt, 2014 [53]	Peripheral (M. quadriceps)	20 10/10[#]	PAH (IPAH + PAH 1 year after ASD repair)			Overall ↓: CSA, fibre type I/II ratio Regulators muscle mass ↓: pAkt, p-p70S6kinase, pFOXO 3 ≈: pGSK3β ↑: Atrogin-1, MuRF1 Mitochondrial fusion ↓: Mitofusin 1 and 2; ≈: DRP Mitochondrial biogenesis ≈: PGC1α, $MtCO_2$, NRF-1, TFA Calcium cycling ↑: pRyR ≈: SERCA2a, SERCA
Potus, 2014 [55]	Peripheral (M. quadriceps)	40 20/20[#]	PAH (16 IPAH, 4 HPAH)		↓: quadriceps endurance	↓: ERK activity, capillary density, miR-126, RAF activity ≈: CSA, fibre type I/II ratio, VEGF, VEGFR2 ↑: SPRED-1
Manders, 2015 [57]	Peripheral (M. quadriceps)	19 11/8[#]	IPAH		Single muscle fibres: ↓: maximal tension, number of attached cross-bridges during activation ≈: fraction strongly bound cross-bridges, force per cross-bridge, calcium sensitivity ↑: passive stiffness	
Manders, 2016 [51]	Respiratory (diaphragm)	28 13/15[#]	CTEPH		Single muscle fibres: Slow-twitch fibres: ↓: maximal tension, number of attached cross-bridges during activation Fast-twitch fibres: ↓: calcium sensitivity, submaximal tension ≈: force per cross-bridge	↓: MHC concentration (slow-twitch fibres) ≈: CSA

↓: reduction; ↑: increase; ≈: no change; EDL: extensor digitorum longus (peripheral muscle); MCT: monocrotaline; CSA: cross-sectional area; IPAH: idiopathic pulmonary arterial hypertension; P_{Imax} (volitional): maximal inspiratory mouth pressure; P_{Emax} (volitional): expiratory mouth pressure; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; SnP_{na} (volitional): sniff nasal pressure; SnP_{di} (volitional): sniff transdiaphragmatic pressure; TwP_{mo} (non-volitional): twitch mouth pressure; TwP_{di} (non-volitional): transdiaphragmatic pressure; PFK/HADH: β-oxidation of fatty acids; CS: citrate synthase; HADH: 3-hydroxyacyl-coA-dehydrogenase; PFK/CS: glycolysis to citric acid cycle; SDH: succinate dehydrogenase (oxidative enzyme activity); Akt: protein kinase B; MHC: myosin heavy chain; MAFbx/MuRF-1: E3-ligases; MuRF: muscle RING-finger protein; ASD: atrial septum defect; DRP: dynamin-related protein; PGC1α: peroxisome proliferator-activated receptor-γ coactivator; GSK3β: glycogen synthase kinase 3β; MtCO2: mitochondrial encoded cytochrome C oxidase subunit II; NRF-1: nuclear respiratory factor 1; RyR: ryanodine receptor; SERCA: sarco/endoplasmic reticulum Ca^{2+}-ATPase; HPAH: hereditary PAH; ERK: extracellular signal-regulated kinase; miR-126: microRNA126; VEGF: vascular endothelial growth factor; VEGFR2: VEGF receptor type 2; SPRED1: Sprouty-related EVH1 domain-containing protein 1. [#]: for numbers displayed as "x/y", x is number of patients, y is number of controls.

trial designs that address these issues, such as the offer to participate in training after the control phase or the use of Zelen's design.

As PH is a rare disease, many studies included different subgroups of PH such as PAH and CTEPH. Training effects are generally described in the preceding paragraphs, but need to be investigated and distinguished between different types of PH in the future.

While the effects of exercise rehabilitation in PH have been investigated and shown to be beneficial as primary end-points for most outcomes (6MWD, peak V'_{O_2}, QoL, blood flow of the lung, peak muscle power), the presented randomised controlled trials are of varying quality [42] and require further validation. Most of the data about training effects in PH rely on results from a single centre, which offered a rather intensive beginning to the exercise training programme. An intensive in-hospital programme demands substantial personnel, time and money resources and may therefore not be widely available. Future research should be based on larger-scale multicentre studies for external validity of the data.

Future directions: challenges and research questions

Since the publication of the European Society of Cardiology (ESC)/ERS guidelines, two further randomised controlled trials [24, 26] and several meta-analyses have been published [39–42] that confirm the positive effect of training in PH. However, the current data do not provide any conclusion about the effects of exercise training on different types of PH, which should be stratified and analysed in future studies.

The large body of evidence presented in the preceding sections may influence the grading of exercise training in the next guideline recommendations. Nevertheless, multicentre studies involving PH expert centres are needed to assess the effect of exercise training in different countries with different healthcare systems to clarify whether this therapy can be widely used in PH patients.

Methodological aspects such as patient selection, optimal training methods as well as external validation of trial results should also be addressed in future trials. A current multicentre randomised controlled trial aims to gain further insights into the efficacy, safety and external validity of exercise training in PH. Current findings on these issues will be displayed in more detail later on.

Within the last decades, clinical trial end-points in PH studies have evolved from the primary end-point exercise capacity (6MWD) to event-driven time to clinical worsening outcomes. In this regard, a need of studies investigating the effect of exercise training on disease progression and survival has been pointed out [61, 62]. While the safety and beneficial outcome effects of exercise-based rehabilitation have been demonstrated in other disease areas such as left heart failure and cancer [10, 63, 64], few data are available addressing the potential impact of exercise training on disease progression or survival in PH [42].

Determining the effect of a dedicated exercise programme in PH is complicated by many factors. For example, the type of PH itself can have a significant impact on disease progression and patient survival. To determine the impact of any intervention in PH we need clinically relevant and robust end-points. While traditionally the 6MWD has been used in drug development it has many limitations, most particularly in the study of exercise effects. Similarly, while cardiopulmonary exercise testing (CPET) parameters do predict survival in PH patients, they only add marginally to the prognostic value of the 6MWD [65]. So, while improvements in 6MWD, peak V'_{O_2}, muscle strength and endurance, as well as physical and mental QoL (SF-36 questionnaire) have been demonstrated in response to exercise rehabilitation in PH, their impact on disease progression or as disease modifiers have not yet been shown in randomised, controlled studies. Moreover, a more PH-specific QoL questionnaire as a patient-reported outcome measure such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), the emPHasis-10 or the PAH-Symptoms and Impact Questionnaire (PAH-SYMPACT) might provide even better insights into the impact of exercise training than the generic SF-36, which has already shown significant improvements in various subscales.

Randomised controlled trials investigating the effect of exercise training on disease progression and survival are still lacking. One single prospective study with a retrospective control group detected a significantly better survival and less worsening events of the training group, compared to patients who were treated with targeted medication only ($p=0.005$) [30]. An association between activity level and outcome was demonstrated in a cohort study of 23 patients with PAH or CTEPH who showed a significantly lower survival, when being active for <15 h·day^{-1} ($p=0.026$) [66]. A composite morbidity and mortality end-point has been used recently in drug development and has highlighted that disease progression is frequently marked by hospitalisation. However, morbidity and mortality studies need large numbers of patients and prolonged monitoring to determine if disease progression has been affected. This is warranted, but difficult to reach, especially in studies analysing effects of exercise training as an add-on to optimised medical

treatment. There is no funding for such large trials and currently there are not enough rehabilitation/PAH centres experienced with this treatment to reach high patient numbers. Furthermore, patients who participate in such studies mostly want to receive the exercise training within a reasonably short time period. The next step to reach such studies could be to standardise the PH-specialised rehabilitation programme in different European countries and to establish more centres that could offer this treatment to patients in such long-scaled studies in the future. Changes in ERS/ESC risk classification could act as a possible surrogate to assess the effect of exercise rehabilitation on disease progression and survival. Whether the impact of new therapies, including dedicated exercise programmes, can modify the risk profile in PAH and impact on disease progression and survival remains to be determined.

In summary, there is no direct evidence for an impact of exercise training on survival and outcome in PH. However, several studies suggest a beneficial effect on prognostically important parameters. Studies with survival and time to clinical worsening as the primary outcome are hindered by ethical and methodological aspects. A future approach to this question could be to investigate the impact of exercise training on risk profiles in PH.

Part II: training modalities and setting

There have been different approaches in training modalities across countries and rehabilitation programmes. Exercise training was either started in hospital and subsequently performed at home, or was implemented as an entire outpatient programme. A thorough monitoring and supervision by PH centres of the exercise training was performed in all training studies. A summary of the different training set-ups is given in table 4.

Setting and outcome measures

In-hospital start of exercise training

Most of the subjects studied (n=519) participated in the "Heidelberg" training programme that started with an in-hospital stay for 3 weeks followed by a second ambulatory part continuing exercise training [15–20, 24, 30, 31]. The initial in-hospital training allowed close supervision of exercise by physiotherapists, with heart rate and oxygen saturation monitoring [67]. Up-titration of exercises and prescription of oxygen was performed based on predefined saturation and heart rate safety parameters (table 4).

Outpatient programmes

As inpatient settings are not available in all healthcare systems, several outpatient programmes have been investigated and results have been published so far from 176 PH patients (table 4) [21–23, 26–28, 34–36, 38]. Outpatient programmes typically use two to three supervised sessions per week in hospital rooms for ~12 weeks. In addition, there have been two small studies (n=25) looking at solely home-based exercise programmes [32, 33]. A wide range of training frequencies has been used, between two to five times per week, with different total duration of training units in the programme/training day and with duration of the study lasting from 6 weeks to 1 year.

The majority of studies have demonstrated clinical benefits (tables 1 and 2). 30% of the studies did not show an improvement in 6MWD, but reported improvement in other parameters such as muscle strength and endurance exercise capacity [21] or QoL scores [33].

Members of the multidisciplinary team

The involvement of a physiotherapist has been a constant feature in all studies involving exercise programmes. They are thought to be crucial to the delivery of the programme and can also provide support in other aspects, such as mobility, practical advice regarding activities of daily living, psychological support and relaxation therapies [15].

Additionally, involvement of the medical team with PH expertise in the development and delivery of the exercise programme has been a feature of all previous studies. In-hospital programmes take place in PH centres with multidisciplinary teams consisting of psychologists, PH nurse specialists and dieticians (table 5; for more details, refer to the section on Requirements of different healthcare systems). A multidisciplinary (physiatrist, cardiologist, pulmonologist) and multiprofessional (exercise physiologist, physical therapist, nurse, psychologist, dietician) approach offers to address different aspects of the disease during the intervention. As anxiety and depression show an increasing prevalence with higher WHO functional class, psychological counselling may often support the patients' wellbeing.

Training components and intensity

The rehabilitation programmes for severe chronic PH patients consist of a diverse array of training components (table 6). The resistance training mainly consisted of dumbbell training of distinct muscle

TABLE 4 Set-up of exercise training programmes

First author, year [ref.]	Patients[#] n	Frequency of training	Length of programme	Monitoring
Inpatient	511/560[#]			
Mereles, 2006 [15]	15/15[¶]	7 days per week	15 weeks	Subjective physical exertion HR <120 beats·min^{-1}
Grünig, 2011 [20]	58		Weeks 1–3 inpatient	SaO_2 >85% (if lower, supplemental oxygen supplied)
Becker-Grünig, 2013 [16]	20		Weeks 4–15 at home	
Ehlken, 2014 [30]	58[+]			
Ley, 2013 [25]	10/10[¶]		3 weeks inpatient	
Grünig, 2012 [18]	21		15 weeks	See Mereles *et al.* [15]
Grünig, 2012 [19]	183		Weeks 1–3 inpatient	Supplemental oxygen if SaO_2 <90%
Nagel, 2012 [17]	35		Weeks 4–15 at home	
Ehlken, 2016 [24]	87			
Kabitz, 2014 [31]	7			See Mereles *et al.* [15]
				HR ⩽130 beats·min^{-1}
				Supplemental oxygen if SaO_2 <90%
Fukui, 2016 [29]	17/24[¶]	7 days in first week	12 weeks	Borg scale 12–13 (scale 6/20)
		~4 days per week 2–12	Week 1 in hospital Weeks	HR 40–60% of HR reserve
			2–12 at home	SaO_2 ⩾90%
Outpatient	138/176[#]			
Shoemaker, 2009 [35]	2	3 days per week	6 weeks	Subjective exertion <4/10, HR ⩽80% age-predicted maximum, blood pressure ⩽180 mmHg, SaO_2 >91%
de Man, 2009 [21]	19	3 days per week	12 weeks	SaO_2>85%
				HR <120 beats·min^{-1}
Martínez-Quintana, 2010 [28]	4/4[¶]	2 days per week	12 weeks	Borg scale, HR
Mainguy, 2010 [34]	5	3 days per week	12 weeks	Borg scale <6/10
				Resting allowed
				Intensity reduced if SaO_2 <85%
Fox, 2011 [27]	11/11[¶]	2 days per week	12 weeks	Subjective exertion, rest permitted, HR, SaO_2 "monitored"
				SaO_2 >90% (if lower, supplemental oxygen supplied)
Chan, 2013 [22]	10/13[¶]	3 days per week	10 weeks	Subjective exertion, SaO_2, HR "monitored" (no values given)
Weinstein, 2013 [23]	11/13[¶]	3 days per week	10 weeks	Subjective exertion, SaO_2, HR "monitored" (no values given)
Raskin, 2014 [37]	23	2–3 days per week	>8 weeks	Borg scale
González-Saiz, 2017 [26]	20/20[¶]	3 days per week	8 weeks	SaO_2 >80%
				BP reduction <20 mmHg
				BP systolic <220 mmHg, diastolic <110 mmHg
				No ECG abnormalities
Talwar, 2017 [38]	18	3 days per week	12 weeks	Only safety equipment specified (blood pressure monitor, ECG, pulse oximetry, supplemental oxygen)
Bussotti, 2017 [36]	15	5 days per week	4 weeks	HR <70% of max at CPET
				Borg scale <5
				SaO_2 >90%
Home	25			
Inagaki, 2014 [32]	8	1 hospital session per week	12 weeks	Subjective exertion
		and 3 sessions at home per week		
Ihle, 2014 [33]	17	1 day per month	40 weeks	Subjective exertion: Borg scale <7/10
				HR increase <30 beats·min^{-1} SaO_2 >85%

BP: blood pressure; ECG: electrocardiogram; HR: heart rate; SaO_2: oxygen saturation; CPET: cardiopulmonary exercise testing. [#]: for totals, the second number takes into account all patients involved, including controls; [¶]: for numbers displayed as "x/y", x is number of patients, y is number of controls; [+]: this study refers to the same patients as Grünig *et al.* [20].

TABLE 5 Components of multidisciplinary settings

First author, year [ref.]	Exercise	Psychological support	Relaxation	Dietary support	Education on the disease	Team members
Inpatient						
Mereles, 2006 [15]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Grünig, 2011 [20]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Grünig, 2012 [18]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Grünig, 2012 [19]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Nagel, 2012 [17]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Becker-Grünig, 2013 [16]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Kabitz, 2014 [31]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Ley, 2013 [25]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Ehlken, 2014 [30]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Ehlken, 2016 [24]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
Fukui, 2016 [29]	✓	✓			✓	PH expert, cardiologist, physiotherapist,
Outpatient						
de Man, 2009 [21]	✓					Physiatrists, pulmonologists, physiotherapists
Shoemaker, 2009 [35]	✓					Physiotherapist
Mainguy, 2010 [34]	✓					Rehabilitation centre; no details given
Martínez-Quintana, 2010 [28]	✓	Education on "emotional stress"			✓	Physician, physiotherapist
Fox, 2011 [27]	✓	✓				Physician, physiotherapist
Chan, 2013 [22]	✓	Educational lesson "panic control", "social wellbeing"	Educational lesson "relaxation techniques"	Educational lesson on "nutrition"	✓	Not stated
Weinstein, 2013 [23]	✓	Educational lesson "panic control", "social wellbeing"	Educational lesson "relaxation techniques"		✓	Not stated
Raskin, 2014 [37]	✓	Multidisciplinary approach is stated for this pulmonary rehabilitation, without giving any detail				PH centre and rehabilitation centre
González-Saiz, 2017 [26]	✓					Fitness instructors
Talwar, 2017 [38]	✓		✓			Not stated
Bussotti, 2017 [36]	✓	✓	✓			Physician, physiotherapist
Home						
Inagaki, 2014 [32]	✓					Pulmonologist, physiotherapist
Ihle, 2014 [33]	✓			✓	✓	Physician, physiotherapist, dietician, pharmacist, nurse

PH: pulmonary hypertension.

groups. Aerobic training is conducted in form of ergometer training, treadmill walking or cross-trainer exercises [68].

For the studies based on an initial inpatient phase performed in Germany, exercise training was complemented by mental gait training and guided walks. The mental gait training was introduced to the

TABLE 6 Training modalities and intensities in exercise training studies

First author, year [ref.]	Country (city or state)	Exercise training modalities	Training intensity
Mereles, 2006 [15] **Ley, 2013 [25]** **Grünig, 2011 [20]** **Grünig, 2012 [19]** **Grünig, 2012 [18]** **Nagel, 2012 [17]** **Becker-Grünig, 2013 [16]** **Kabitz, 2014 [31]** **Ehlken, 2014 [30]#** **Ehlken, 2016 [24]**	Germany (Heidelberg)	Bicycle ergometer, interval (1 min high/30 s low; 10–25 min), 10–60 W Walking/mental gait training (60 min) Resistance exercise; low-weight dumbbell training or strength training (30 min) Respiratory muscle training (30 min) Frequency: each training item ⩾5 times per week	60–80% peak $V'O_2$ [15, 25]; progressive increase during programme 10–60 W [16–20, 30, 31]; progressive increase during programme
Ihle, 2014 [33]	Germany (Munich)	Breathing exercise (30 min) Resistance exercise/moderate endurance training of leg muscle (30 min) 3 sets of 5 repetitions, stretching, motion exercises Educational training (30 min) Frequency: in-hospital once per month	10–60 W
Mainguy, 2010 [34]	Canada (Québec)	Bicycle ergometer, continuous (10–15 min) Brisk treadmill walking (15 min) Resistance exercise, 2 sets 10–12 repetitions of 6–8 single muscle group exercises Frequency: 3 times per week	60% max workload 85% mean speed during 6MWT 70% max voluntary contraction
Fox, 2011 [27]	Israel (Tel Aviv)	Weeks 1–6: treadmill walking/cycling/step climbing, interval (60 min) Weeks 7–12: resistance exercise (low-weight dumbbell training or strength training)/aerobic training, continuous (60 min total) Frequency: twice per week	60–80% HR at peak $V'O_2$
Bussotti, 2017 [36]	Italy (Milan)	Bicycle ergometer, continuous (30 min) Resistance exercise, 10–15 repetitions of weight lifting (0.5–1 kg) Respiratory muscle training (10 min up to 30 min) Slow breathing sessions (25–30 min) Educational lessons Frequency: 5 times per week	50% peak workload
Inagaki, 2014 [32]	Japan (Chiba)	Walking, continuous (>20 min) Resistance training, 1–3 sets with 10–15 repetitions Respiratory exercise (~20 min) Frequency: in-hospital once per week	60% max HR Free from/minor subjective dyspnoea
Fukui, 2016 [29]	Japan (Suita)	Walking (30–60 min) Bicycle ergometer Resistance training (low weights) Frequency: week 1 daily, weeks 2–12 outpatient session twice per week	40–60% HR reserve
de Man, 2009 [21]	Netherlands (Amsterdam)	Cycling, interval (35–40 min) Weeks 1–3: 2 min 50% $V'O_2$ max, 2 min rest Weeks 4–6: 3 min 50% $V'O_2$ max, 2 min rest Weeks 7–9: 4 min 75% $V'O_2$ max, 2 min rest Weeks 10–12: 5 min 75% $V'O_2$ max, 2 min rest Quadriceps strength; endurance (~20 min) Weeks 1–3: strength 50% ORM, endurance 30% ORM Weeks 4–6: strength 50% ORM, endurance 30% ORM Weeks 7–9: strength 75% ORM, endurance 40% ORM Weeks 10–12: strength 75% ORM, endurance 40% ORM Frequency: three times per week	75% $V'O_2$ max % of maximum repetition on 1st day
Martínez-Quintana, 2010 [28]	Spain (Las Palmas de Gran Canaria)	Warm up: stretching/resistance exercise with 1–2 kg (10 min) Bicycle ergometer, interval: 30 s high at 20–50 W/30 s low at 10–25 W (24 min) Educational lessons (time not specified) Frequency: twice per week	80% max HR during 6MWT Borg scale 3–6

Continued

TABLE 6 Continued

First author, year [ref.]	Country (city or state)	Exercise training modalities	Training intensity
González-Saiz, 2017 [26]	Spain (Madrid)	Bicycle ergometer, interval (40 min) Resistance training (large muscle groups), 3 sets of 5 exercises each Inspiratory muscle training (30 breaths) Frequency: Aerobic: 5 times per week Resistance: 3 times per week Inspiratory: 6 times per week	50% power output at anaerobic threshold Against 40% inspiratory pressure max
Shoemaker, 2009 [35]	USA (Michigan)	Bicycle ergometer, continuous (45 min) Frequency: 3 times per week	50% peak workload
Talwar, 2017 [38]	USA (New York)	Treadmill walking, continuous (20–30 min) Educational lessons Frequency: 3 times per week	Based on maximal speed and time on a treadmill measured at baseline
Raskin, 2014 [37]		Aerobic training (treadmill, bicycle, and cross-trainer exercises), continuous (30–60 min) Frequency: 2–3 times per week	Borg scale, "moderate intensity"
Weinstein, 2013 [23] **Chan, 2013 [22]**	USA (Virginia)	Treadmill walking, continuous (30–45 min) Educational lessons (60 min) Frequency: ⩾2 times per week	70–80% max intensity 70–80% max HR

$V'O_2$: oxygen uptake; 6MWT: 6-min walk test; HR: heart rate; ORM: one-repetition maximum. #: this study refers to the same patients as Grünig [20].

patients in order to improve the estimation of their physical abilities and limitations. Training intensity was adjusted daily to the individual strengths and limitations. Oxygen supply was given according to patient's indication and needs. In general, training intensity was low, ∼50% of peak workload or ∼60% of maximal workload, and carefully monitored as patients were already severely compromised. Aerobic training was mainly conducted at 60–80% of peak heart rate (table 6). Data for 519 patients are available for exercise training at ∼60% of peak heart rate, not exceeding 120 beats·min^{-1}, with an oxygen saturation greater than 85–90% [68]. Additional respiratory training was performed in the inpatient studies in Germany, one outpatient based study in Italy [36] and one home-based study in Japan [32]. This training component was aimed at strengthening the respiratory muscles and to increase the awareness of different breathing patterns and techniques [69]. Outpatient programmes often included patient education and lectures to learn more about topics such as disease pathophysiology, behaviour in demanding situations and nutrition [23].

Monitoring

For monitoring, supervision and adjustment of the training intensity, oxygen saturation (>85–90%), heart rate (<120–130 beats·min^{-1}) and subjective perception of exertion by Borg dyspnoea score were used. An oxygen desaturation of <85–90% or heart rate of >120 beats·min^{-1} were mainly used as limiting criteria to adjust training intensity, leading to a short interruption or intensity reduction of the training (compare table 4). The intensity, in particular of the aerobic training, was either individually adjusted on a day-to-day basis or followed a set increase during the course of the training [21, 68]. While all studies monitored the patients closely, the in-hospital programmes had the advantage of giving the patients time to learn the exercises under close supervision with an emphasis on avoiding overexertion.

In conclusion, different training modalities have been investigated in patients with PH. The common features of these programmes are a multidisciplinary approach, close supervision and monitoring, combinations of low-to-moderate intensity endurance, strength and breathing exercises and an assessment of functional aspects and muscular strength, as well as QoL and laboratory parameters. Future studies should be aimed at direct comparisons of training modalities to find out the most advantageous training properties. Furthermore, the components of the multidisciplinary setting should be defined and investigated upon their impact.

TABLE 7 Outcome measures for training programmes

First author, year [ref]	QoL#			Functional ability					Peripheral muscle function	Biomarkers
	SF-36	CAMPHOR	Other questionnaire	6MWD	Peak V'_{O_2}	Endurance	WHO functional class	Treadmill speed	Muscle strength	(NT-pro)-BNP
In-patient										
Mereles, 2006 [15]	7/10									
Grünig, 2011 [20]	7/8									
Grünig, 2012 [18]	5/8									
Grünig, 2012 [19]	2/8									
Nagel, 2012 [17]	2/8									
Becker-Grünig, 2013 [16]	1/8									
Ley, 2013 [25]										
Ehlken, 2014 [30]¶	7/8									
Kabitz, 2014 [31]										
Ehlken, 2016 [24]	1/8									
Fukui, 2016 [29]	1/8		PHQ-9							
Outpatient										
de Man 2009 [21]										
Martinez-Quintana, 2010 [28]	SF-12: 0/2									
Mainguy, 2010 [34]										
Fox, 2011 [27]										
Chan, 2013 [22]	6/8	5/6								
Weinstein, 2013 [23]			FAS, HAP 1/3							
Raskin, 2014 [37]			1/3							
Zöller, 2017 [43]	0/2									
Gerhardt, 2017 [44]	2/2									
Talwar, 2017 [38]										
Bussotti, 2017 [36]			HADS, EQ-5D							
González-Saiz, 2017 [26]	2/8									
Home										
Inagaki, 2014 [32]			SGRQ 1/3							
Ihle, 2014 [33]	0/8	1/3								

Statistically significant improvement | No significant improvement | Statistically significant deterioration

QoL: quality of life; SF-36: 36-item short-form health survey; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; 6MWD: 6-min walk distance; V'_{O_2}: oxygen uptake; WHO: World Health Organization; NT-proBNP: N-terminal pro-brain natriuretic peptide; PHQ-9: Patient Health Questionnaire-9; SF-12: 12-item short-form health survey; FAS: Fatigue Assessment Scale; HAP: Human Activity Profile; HADS: Hospital Anxiety and Depression Scale; EQ-5D: EuroQoL-5 dimensions; SGRQ: St George's Respiratory Questionnaire. #: the number of subscales with significant improvement/number of tested subscales is given; the numbers given for the SF-36 are in reference to the analysed scales, as follows 10: all subscales and two summation scales, 8: all subscales, 2: two summation scales; detailed results of specific subscales of QoL assessments are presented in table 2. ¶: this study refers to the same patients as Grünig *et al.* [20].

Outcome measures

Outcome measures used to assess the efficacy of exercise training in PH can be broadly split into six categories: symptoms, QoL, pulmonary artery haemodynamics, exercise capacity, peripheral muscle strength and biomarkers (table 7).

In PH, exercise capacity plays a major role, both as a prognostic factor and as a factor strongly associated with QoL. There are many ways to assess exercise capacity. The most commonly applied tests are the 6-min walk test (6MWT) and the shuttle walk test. However, the most comprehensive test is CPET. The ESC/ERS guidelines recommend CPET for patients with PH not only for decision making concerning therapy, but also because it shows a typical pattern in patients with PH and thus may serve for early

diagnosis and differential diagnosis [1]. The highlighted prognostic factors are peak oxygen uptake ($V'O_2$) [70, 71] and the relationship of minute ventilation to carbon dioxide production. For example, a randomised controlled study from Germany showed htat peak $V'O_2$ can be used to monitor training effects in PH [24].

In addition to peak $V'O_2$, a second independent prognosticator, the capability of the patient to increase right ventricular systolic pressure by >30 mmHg even during low-level exercise has been identified [72]. Of note, this finding was valid only in patients with severe PH. In addition, a study from Sheffield (UK) analysing the shuttle walk test found that an inadequate heart rate response was associated with mortality [73]. They concluded that the shuttle walk test was easy to perform and sensitive to the effects of therapy. In comparison to the 6-min walk test, there is no ceiling effect.

In conclusion, exercise tests are important prognosticators in PH patients and are thus valuable tools to assess effects of training. A low peak $V'O_2$, a high pulmonary vascular resistance, a decreased heart rate response during exercise and a lowered blood pressure response to exercise appear as independent prognostic factors. Additional stress echocardiography may reveal an additional independent prognosticator, the right ventricular systolic pressure response to exercise. As training improves both peak $V'O_2$ and the heart rate response to exercise, it can be speculated that it may also improve survival, although such studies may not be conducted due to ethical reasons (see the Future directions section).

Safety

Extensive physical activity may increase pulmonary artery pressure, inducing circulatory collapse and leading to right heart failure in PH patients. Some patients may be at risk of exercise-induced hypoxaemia, malignant arrhythmia, pulmonary artery dissection, left main coronary artery compression and even sudden death if overexertion takes place. Safety precautions were nicely illustrated in an animal model, investigating exercise training in stable *versus* progressive PH [74]. Exercise training may significantly decrease survival and lead to a decrease in workload in unstable and progressive compared to stable PH. In progressive PH, training triggered pulmonary vascular remodelling and led to an increase of right ventricular fibrosis, whereas these effects could not be observed in stable PH [74]. Thus, it seems essential to perform a comprehensive evaluation of PH patients before exercise training and safety measures should be applied during performance because serious adverse events could occur [75]. The precondition that patients be on optimised, stable, disease-targeted treatment to participate in the low-intensity, carefully monitored training programme might be the reason, why up to now, only a few adverse events (<5%) have been reported with regards to exercise training in PH (table 8).

In the largest published prospective cohort study [19], in 13.6% of 183 patients adverse events occurred, and most of them were mild and not directly attributable to the exercise training itself (table 8). Mild haemoptysis was observed in a patient with acute respiratory infection, and syncope occurred hours after the training at night (n=1) or when rising up from a chair (n=1). These events, as well as five out of six pre-syncopal episodes did not seem to have a direct relationship to exercise training [19].

Adverse events were reported in 64 (9.5%) out of 674 exercise-trained PH patients. Exercise-related complications seemed to be more frequent in outpatient compared to inpatient settings (5.8% *versus* 4.3%) [21, 26, 28, 34]. Interestingly, all side-effects not directly related to exercise were reported only in prospective inpatient rehabilitation cohorts from the Heidelberg (Germany) centre [16–20]. The most frequent adverse event (3.4%) was respiratory infection [16–20], which led to antibiotic treatment and short discontinuation of the training. In only a few cases was exercise training permanently discontinued. In some studies, training protocols required minor adjustment due to dizziness [15, 20, 21, 28, 34], fatigue [34] or hypotension [32]. Nonsustained supraventricular arrhythmia [19, 28], syncope [17] and pre-syncope [19] during or briefly after exercise training were reported in <1% of all patients. Similar adverse event rates of 10% [69] and 3% [40] were calculated in recently published meta-analyses. Clinical worsening of symptoms and heart failure was not observed in any study during exercise training.

Emergency equipment and qualified, well-trained personnel is a prerequisite during exercise training to treat potential complications. Commonly employed safety measures for rehabilitation and patient monitoring during exercise are discussed in the sections Training modalities and setting and Requirements of different healthcare systems.

Rehabilitation seems to be most effective and safe in physically deconditioned moderate-risk patients with PAH and inoperable CTEPH [19, 24]. The lowest therapeutic range of this new PH treatment modality may be expected in patients with WHO functional class IV. While only few of them were included in the studies, they showed the largest improvement after very closely supervised, low-intensity exercise and respiratory training [19]. However, the low patient numbers do not allow valid conclusions about the safety of training in such patients.

TABLE 8 Exercise training-associated adverse events in patients with chronic stable pulmonary hypertension

	Cases n (% of total study participants)	Cases n (% of exercise-trained subjects)			First author, year [ref.]
		Inpatient setting	Outpatient setting	Home based	
Subjects	674	511	138	25	
Exercise related					
Dizziness	8 (1.2)	4 (0.8)	4 (2.9)		Mereles, 2006 [15], de Man, 2009 [21], Grünig, 2011 [20], González-Saiz, 2017 [26], Mainguy, 2010 [34]
Desaturation	16 (2.4)	14 (2.7)	2 (1.4)		Mereles, 2006 [15], Martínez-Quintana, 2010 [28], Becker-Grünig, 2013 [16]
Arrhythmia	3 (0.4)	2 (0.4)	1 (0.7)		Grünig, 2012 [19], González-Saiz, 2017 [26]
Hypotension	1 (0.1)			1 (4)	Inagaki, 2014 [32]
Syncope	1 (0.1)	1 (0.2)			Grünig, 2012 [19], Nagel, 2012 [17]
Pre-syncope	1 (0.1)	1 (0.2)			Grünig, 2012 [19]
Fatigue	1 (0.1)		1 (0.7)		Mainguy, 2010 [34]
None reported					Bussotti, 2017 [36], Chan, 2013 [22], Ehlken, 2014 [30], Ehlken, 2016 [24], Fox, 2011 [27], Fukui, 2016 [29], Ihle, 2014 [33], Kabitz, 2014 [31], Ley, 2013 [25], Raskin, 2014 [37], Talwar, 2017 [38], Shoemaker, 2009 [35], Weinstein, 2013 [23]
Total	31 (4.6)	23 (4.3)	8 (5.8)	1 (4)	
Not related to exercise					
Syncope	2 (0.3)	2 (0.4)			Grünig, 2012 [19]
Pre-syncope	5 (0.7)	5 (1.0)			Grünig, 2012 [19]
Mild haemoptysis	1 (0.1)	1 (0.2)			Grünig, 2012 [18]
Respiratory infection	23 (3.4)	23 (4.5)			Grünig, 2012 [19], Grünig, 2011 [20], Nagel, 2012 [17], Becker-Grünig, 2013 [16]
Herpes zoster infection	1 (0.1)	1 (0.2)			Nagel, 2012 [17]
Gastrointestinal infection	1 (0.1)	1 (0.2)			Grünig, 2011 [20]
Total	33 (4.9)	33 (6.5)			
Total	64 (9.5)	55 (10.8)	8 (5.8)	1 (4)	

In most studies, the PAH group was mainly represented by IPAH and PAH associated with connective tissue disease (table 1). Physical training could be challenging in patients with PAH due to congenital heart disease and in syndromal diseases [16, 28]. Low oxygen saturation even at rest is common in patients with Eisenmenger syndrome and it may drop further during exercise despite oxygen supply. Further investigations are needed to explore the advantages and risks of training in this group. Studies should systematically compare training modalities and intensities within subgroups of PAH and CTEPH.

In order to obtain a good safety profile, thorough patient selection and monitoring as well as highly specialised personnel are obligatory. An in-hospital beginning may further help to obtain a safe training environment and careful supervision. The cost-effectiveness of specialised training programmes still needs further investigation, as only one study with a prospective intervention and retrospective control group has demonstrated lower healthcare costs following exercise rehabilitation (with in-hospital start), compared to sole medication treatment [30].

In summary, the evidence shows that careful patient selection, appropriate setting, well-prepared multidisciplinary teams from PH and rehabilitation specialists, individualised and flexible exercise training protocols and close monitoring are very important in order to provide a good safety profile in patients with PH. Using the right setting, exercise training has shown to be a safe and effective treatment, especially when applied in patients on adequate medical therapy. Therefore, participation in unspecialised training programmes or unsupervised settings, *e.g.* home training is dissuaded. Strenuous exercise should still remain contraindicated in patients with PH [1].

Part III: implementation of exercise training

Participant selection, compliance and motivation

The process of successful patient participation in a PH-specific exercise therapy programme involves four key steps (figure 1).

Patient selection

Patients must have confirmed PH in a clinically stable condition, with no PH-specific treatment changes for 2 months [19].

Additional considerations should be made on an individual patient basis, as follows.

- Age: 18–80 years is the range in which the therapy has been most widely studied.

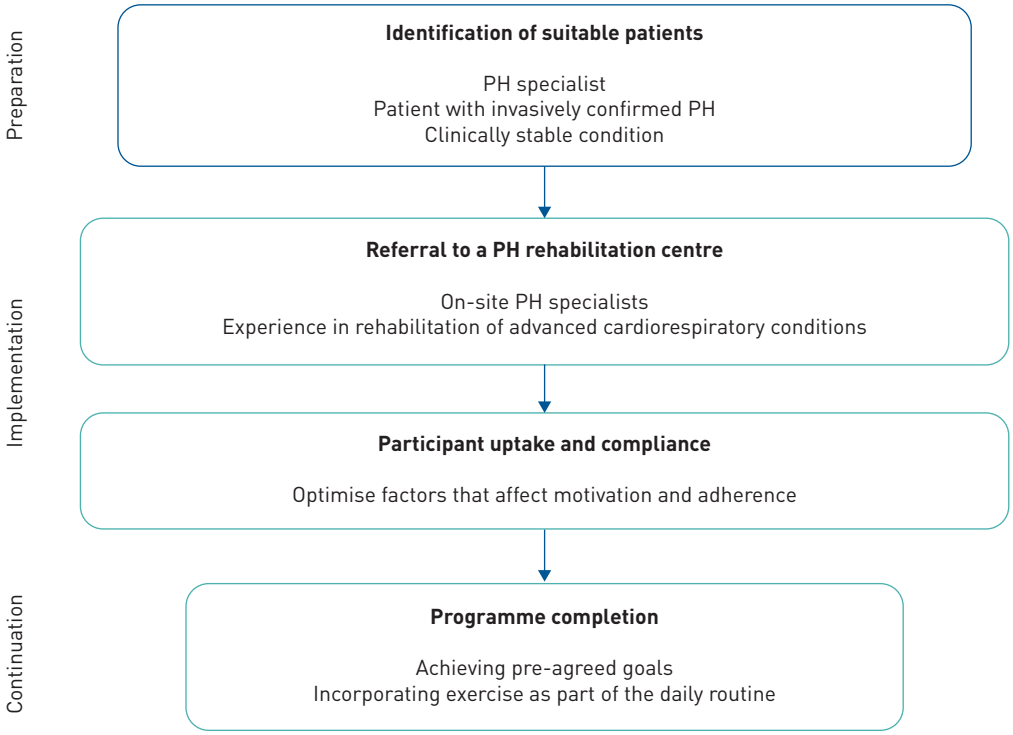

FIGURE 1 Four key steps for successful patient participation in an exercise training programme. These steps describe the way the participation of patients with pulmonary hypertension (PH) is enhanced in specialised programmes. It is not intended as a recommendation. As preparation for the programme, suitable patients must be identified. The programme is implemented together with a rehabilitation centre enhancing patients' motivation. After completion of the programme, a continuation of exercises in the daily routine helps to maintain the training effect.

- Medical therapy: exercise therapy improves exercise capacity and QoL in patients on mono-, dual and triple therapy. The optimal timing of exercise therapy in relation to treatment changes is unclear and requires further research.
- Determining the likelihood of improvement: this is an under-studied area in all forms of cardiorespiratory rehabilitation. In cardiac rehabilitation, patients with impaired chronotropic response have poorer outcomes following cardiac rehabilitation [76]. In chronic obstructive pulmonary disease, those who responded favourably to rehabilitation had a higher symptom burden, lower frequency of hospital admissions and poorer baseline exercise performance [77]. GRÜNIG *et al.* [19] found that PAH patients with <15% improvement in 6MWD following rehabilitation were more likely to have associated PAH; recurrent respiratory tract infection; orthopaedic problems; significant/untreated depression and anxiety; baseline 6MWD >550 m; recently completed a training programme

As PH is a rare disease and patients have to be in stable condition to participate in an exercise training programme, a strong involvement of the PH expert centre in patient selection, supervision and conductance of exercise training seems desirable. Increasing awareness in PH expert centres may therefore enhance referral and patient access to this treatment.

Compliance

In PH-specific rehabilitation, compliance ranges from 58% to 100% and benefits are dose-dependent [26]. Dedicated studies have not assessed factors that influence or improve compliance in PAH. These areas have been more closely studied in cardiac and pulmonary rehabilitation [78, 79]. Common factors associated with reduced compliance are environmental (work commitments, travel, disruption to the patients' usual routine, cost burden); medical (current smokers, lower baseline functional status, higher body mass index); and patient and physician beliefs (too ill or not ill enough, beliefs around the role or safety of exercise, cultural reasons).

Developing an individualised therapy programme, psychological support, regular telephone or email support and involving a family or friend in the exercise routine have all been shown to enhance compliance. Furthermore, education on the disease, exercise pathophysiology and the influence of activity on the body may help to increase patient motivation and good conduct of the programme.

Motivation

Patient motivation and education directly influence compliance. Validated strategies exist to enhance motivation [19]. According to the American Thoracic Society (ATS)/ERS statement on pulmonary rehabilitation, patient self-management may be enhanced by thorough education and support of self-efficacy by goal-setting and motivation [80]. Long-term, realistic goal setting usually takes place at the beginning of a programme; goals are contextualised and adjusted as needed; in addition, specific psychological techniques such as mental imagery can be employed with specialist training of staff [15].

In conclusion, a thorough patient selection process seems to be crucial for the outcome of exercise rehabilitation. While general recommendations to enhance compliance may be implemented, studies are needed to find the optimal strategy for long-term continuation of exercise training in patients with PH.

Requirements of different healthcare systems

While the 2015 ESC/ERS guidelines recommend supervised exercise training for stable PH patients in a supervised and monitored setting [1], in many European countries specialised PH-training programmes are not yet available. The ATS/ERS policy statement recommends that patient access to rehabilitation programmes be enhanced by the introduction of rehabilitation facilities offering these specialised training programmes, the performance of quality control assessment, *e.g.* by assessing outcomes and conducting scientific trials. Furthermore, cost-effectiveness analyses in future trials may help to convince healthcare providers and payers of the beneficial effects of exercise training in this patient cohort [81].

Official information on the requirement of healthcare systems for the implementation of such programmes for PH in different countries is scarce, therefore this issue has been discussed within this task force involving 18 centres in 11 European countries to get a better understanding of local conditions. Furthermore, it was the aim of this task force to summarise crucial aspects, such as training modalities and settings, physical conditions of the facilities, safety measures and which professionals should be involved. Implementation of these programmes is greatly dependent on the organisation of healthcare systems and financing models in each country. Most of the countries have a national healthcare system exclusively public (n=4) or complemented by private insurance (n=7). In 10 (91%) out of the 11 countries, costs of exercise and rehabilitation programmes for chronic diseases are fully covered by the public or mixed healthcare system. As exercise training and rehabilitation in PH requires increased attention and

organisational effort, reimbursement often does not cover the full costs of such an intervention. Many European countries such as the United Kingdom, Ireland and Spain do not have rehabilitation clinics/facilities which could be used for an in-hospital start of the exercise training programme. Nevertheless, specialised PAH/PH-referral centres of 10 European countries started in cooperation with rehabilitation facilities with exercise and rehabilitation programmes for chronic PH within this task force project. Most of the involved rehabilitation units have facilities and equipment that allows common training modalities for chronic PH (aerobic, muscle, mental gait and respiratory) and multidisciplinary (physiatrist and/or cardiologist and/or pulmonologist) and multiprofessional (exercise physiologist and/or physical therapist and/or nurse) teams. All units are equipped with emergency equipment in the gym or nearby, and have emergency trained personnel on-site.

Most of the participating centres include aerobic, muscle and respiratory training in an exercise and rehabilitation programme for chronic PH as well as mental gait training. Physical therapists and nurses were considered essential for the programme (100% and 90%, respectively), as well as a cardiologist (90%) and/or pulmonologist (90%) and/or a physiatrist (50%). Emergency equipment and trained personnel were available in all participating centres.

Most respondents considered exercise and rehabilitation programmes for chronic PH to be validated (92%), essential (75%) and useful (100%). Such programmes are available in a case-by-case analysis in the majority of participating centres.

In summary, the establishment of specialised rehabilitation programmes for PH patients would further patient access to this treatment intervention. A multiprofessional and multidisciplinary setting, as well as quality control measures seem desirable for this patient cohort. As exercise training appears to be effective, cost-efficient and safe, but is scarcely sufficiently and sustainably reimbursed and supported by healthcare systems, an increased awareness among and support by healthcare institutions, commissioners of healthcare and research funding institutions are of high need. Supported by the PAH self-help group, members of this task force started an initiative to provide a standardised PH rehabilitation programme in their PH centres to make this therapy available for the patients within each of their countries.

Part IV: mechanisms of action of exercise training in PH

The exercise limitation in PAH is multifactorial. It is caused by right ventricular dysfunction, chronotropic incompetence, ventilatory abnormalities and skeletal muscle dysfunction. Mechanisms of exercise intolerance are more complex than initially expected, probably including respiratory muscle weakness, dynamic hyperinflation and mechanical constraints [82], poor skeletal muscle and cerebral oxygenation [83–85], hyperventilation and enhanced sympathetic drive. Likewise, exercise training improves the function of different body organs such as heart, lung and skeletal muscle (figure 2). Exercise can modulate several mechanisms acknowledged in PAH pathophysiology such as oxidative stress, inflammation, vasoconstriction, vascular remodelling and thrombosis.

Compared to controls, PAH patients randomised to exercise training showed an increased 6MWD, peak $V'O_2$ and maximal workload. These can be partially attributed to improved haemodynamics at rest and during exercise with lower mean pulmonary arterial pressure and pulmonary vascular resistance, and increased stroke volume, cardiac index and cardiac output [24, 40, 41].

The mechanisms of improved haemodynamics and exercise capacity by exercise training in PAH and CTEPH remain incompletely understood. Decreased pulmonary artery pressure in the presence of an increased cardiac output strongly suggests a decrease in pulmonary vascular tone, but whether there might also be structural changes ("reverse remodelling") in the pulmonary vessels is not known. Increased cardiac output at rest and at maximum exercise may be explained either by a decreased afterload of the right ventricle, or a direct myocardial training effect. Finally, improved exercise capacity is at least in part to be explained by improved skeletal muscle function, but there are no reported direct measurements of an improved diffusional muscle oxygen uptake by exercise training. To clarify these issues, further research on the effects of exercise training in severe PH should consider the following end-points of dedicated studies: pulmonary vascular function defined by multipoint pulmonary vascular pressure/flow plots [86]; right ventriculo-arterial coupling defined by pressure–volume relationships [87]; and the coupling of convectional and diffusional mechanisms of oxygen delivery [88].

Besides the effects on the muscular system (see section on Muscle function), there is some evidence, that exercise training may also affect the pulmonary vasculature. In animal PH models, inconsistent results on the impact of exercise training on pulmonary vascular remodelling had been reported with unchanged, increased and reduced pulmonary arterial hypertrophy across different studies [89]. However, several animal models detected a beneficial effect of training on the right ventricle as an increase of right ventricular capillary density (+86%, $p<0.05$) up to near-normal values, a reduction of right ventricular

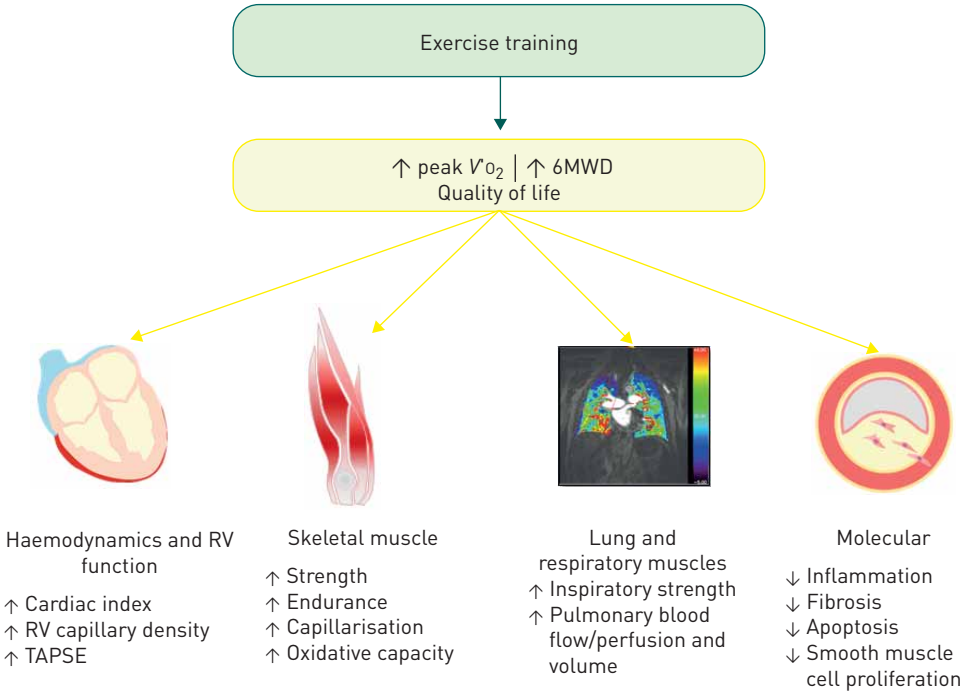

FIGURE 2 Main physiological effects of exercise training. Exercise training in pulmonary hypertension acts upon heart function and skeletal and respiratory muscles, on a macroscopic as well as molecular level. Inflammation and cell proliferation are reduced. 6MWD: 6-min walk distance; peak V'_{O_2}: peak oxygen uptake; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion.

end-diastolic pressure [74, 90] and reduction of interstitial volume (−60%, p<0.05) [74]. There are no histological data available on human PAH vessels. The precise molecular impact of exercise training on right ventricular function remains unclear. In PH rats, exercise training improved right ventricular function assessed by echocardiography (tricuspid annular plane maximal systolic velocity, tricuspid annular plane systolic excursion) and invasive haemodynamics (end-diastolic and end-systolic pressure–volume relationship) [91]. These functional changes were associated with an anti-inflammatory, antifibrotic and antiapoptotic effect [91]. In addition, a reduced oxidative stress and improved neurohumoral markers (lower N-terminal pro-brain natriuretic peptide (NT-proBNP) and endothelin-1 myocardial expression) were described in the right ventricle of trained PH animals. In contrast, in only one out of six studies a significant improvement of plasma NT-proBNP levels [17] was described in patients undergoing exercise training (table 7). One study in patients with congenital heart disease-associated pulmonary arterial hypertension even showed a significant increase of NT-proBNP after the training intervention [16].

In a contrast-enhanced magnetic resonance imaging based study, a significant increase of lung perfusion in 20 patients with PAH and CTEPH could be detected after exercise training [25]. Although the training was only short (3 weeks duration), patients showed a significant improvement of mean flow velocity and perfusion (mean pulmonary blood volume) of the lung (figure 2). This result might be evoked by a modulating effect on pulmonary vascular remodelling. Consistently, exercise training prevented skeletal muscle wasting and modulated muscle proteolysis pathways (Akt, mammalian target of rapamycin) in PH animal models.

Exercise training was able to improve hypoxia-induced pulmonary vascular remodelling in mice to the same extent as sildenafil treatment [92]. However, the underlying pathobiological mechanisms are indistinct, as exercise training did not change the targeted pathways for medication treatment including nitric oxide/phosphodiesterase-5/soluble guanylate cyclase pathways.

Despite the remarkable advances recently made in understanding the pathobiology of PAH, the mechanistic understanding of the functional improvement of PAH patients undergoing exercise training is still limited. A combined effect on different molecular pathways and organs is likely to be the pathophysiological underpinning of the improvement associated with exercise training in PH. Further

research is needed to elucidate the relevance of each of these mechanisms, in particular the direct influence on right ventricular function and pulmonary vascular disease progression. It is also of great interest, if exercise training leads to epigenetic changes which may modulate several PH pathways.

Summary

The evidence summarised in this statement suggests that individually adjusted exercise training rehabilitation programmes supervised by PH expert centres and rehabilitation professionals are likely to be safe for patients with PH who are stable on medical therapy. Exercise training can lead to meaningful improvements in exercise capacity, muscular function, QoL and possibly right ventricular function and pulmonary haemodynamics [3]. Beneficial effects of exercise training have been shown in six randomised controlled trials [15, 22–26], three controlled trials [27–29], 10 prospective cohort studies [16–21, 30–35], three case series [34–36], two retrospective cohort studies [37, 38] and four meta-analyses [39–41] including one Cochrane review [42]. Beside the clinical effects, it has also been shown that exercise training may reduce inflammation and cell proliferation on a molecular level and may have a beneficial effect on the pulmonary vessels.

Further randomised controlled trials are needed to confirm the data on the effect of exercise training on clinical parameters as right ventricular function and haemodynamics. Although there is no direct evidence for an impact of exercise training on survival in PH, several studies suggest a beneficial effect on prognostically important parameters. Studies with survival and time to clinical worsening as primary outcome are hindered by ethical and methodological aspects. Therefore, a future approach to this question could be to investigate the impact of exercise training on risk profiles in PH. Furthermore, the most advantageous training methodology including setting, monitoring, modality, frequency, intensity and length of the training programme still needs to be determined. Further pathophysiological research is needed for a better understanding of the mechanisms by which exercise training is beneficial to patients with severe PH.

In summary, the establishment of specialised rehabilitation programmes for PH patients would further patient access to this treatment intervention. As exercise training appears to be effective, cost-efficient and safe, but is scarcely reimbursed and supported by healthcare systems, an increased awareness among and support from healthcare institutions, commissioners of healthcare and research funding institutions are of high need. Supported by the PAH self-help group, the members of this ERS task force including 10 European countries started the initiative to provide a standardised PH rehabilitation programme in their centres to make this therapy available for the patients within their country and to implement this nonpharmacological intervention into standard care.

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