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Early View

Task force report

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

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

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Take home message

Specialised exercise training in patients with pulmonary hypertension appears effective, cost-efficient and safe. More support is necessary from health care institutions and politicians to establish such programmes throughout Europe.

Abstract

Objectives of this ERS 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 pathophysiologic mechanisms.

In studies with 784 PH patients in total, including 6 randomised controlled trials, 3 controlled trials, 10 prospective cohort studies, and 4 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 health care institutions, commissioners of health care and research funding institutions are of high need. There is a strong need to establish specialised rehabilitation programmes for PH patients to enhance patient access to this treatment intervention.

Introduction

Pulmonary hypertension (PH) defined as invasively measured mean pulmonary artery pressure (mPAP) ≥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). These are here summarised as PH unless otherwise stated. In the last 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, 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. It is also strongly advocated in the healthy population to improve quality of life, 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 life style [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 prevention of several cardiovascular diseases [8].

Training for patients with left heart failure has received a 1A recommendation in the recent guidelines [9] as it was shown to improve quality of life [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 carefully supervised, 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 may not 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 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 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. Exercise training prescription as supportive therapy is therefore limited. Furthermore, the best training modalities, individual adaptation and the optimal setting for this rehabilitation remain to be determined. Pathophysiologic mechanisms are not completely clear.

The objectives of this 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 out of 18 centres from 11 European countries. The Task Force members were selected by the chairs (E. Grünig; 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 have provided their 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 5th 2016). These groups prepared individual subsections which were then presented and discussed within the entire group in a second meeting (September 11th 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 (see supplementary table 1). 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. 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 enlisted 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 quality of life

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], ten prospective cohort studies [16-21, 30-35], three case series [34-36], two retrospective cohort studies [37, 38] 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 endpoint 6-minute walking 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 WHO functional class IV presented with the strongest improvements, compared to functional class II and III [19]. One recent randomised controlled study has demonstrated a significant increase of the primary endpoint, mean peak VO_2, which improved up to almost 25% in the training vs. control group (+3.1±2.7 ml/min/kg vs. -0.2±2.3 ml/min/kg; $p<0.0001$)[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 VO_2/kg (1.5-2.2 ml/min/kg), and of workload (14.9 Watts) [39-42].

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

	Author (year)	Study design	Sample	Diagnoses and severity of disease	Results Parameters with significant improvement*		Parameters without significant improvement or deterioration**
A	**Randomised controlled trials n=6; patients: n=224**						
1	Mereles et al. (2006) [15]	Randomised controlled trial	30	IPAH (80%) CTEPH (20%) WHO-FC II-IV	**Primary** 6MWD QoL (SF-36)	**Secondary:** WHO-FC, peak oxygen consumption, oxygen consumption 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)
2	Weinstein et al. (2013) [23]	Randomised controlled trial	24	A/IPAH (75%/25%) WHO-FC I-IV	Fatigue; physical activity 6MWD, treadmill exercise test duration, peak power output		-
3	Chan et al. (2013) [22]	Randomised controlled trial	23	A/IPAH (74%/22%) WHO-FC I-IV	**Primary:** 6MWD	**Secondary:** Time to exercise intolerance, peak workload, peak $PETCO_2$, time to anaerobic threshold, QoL (SF-36, CAMPHOR)	No change: peak VO_2, haemodynamics (bioimpedance cardiography: cardiac index, cardiac output, stroke volume)
4	Ley et al. (2013) [25]	Randomised controlled trial	20	A/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	-
5	Ehlken et al. (2016) [24]	Randomised controlled trial	87	PAH (70%) CTEPH (30%) WHO-FC II–IV	**Primary** peak VO_2	**Secondary**: Haemodynamics (CI at rest and during exercise) 6MWD, QoL (FS 36)	No change: NT-proBNP, heart rate at rest, peak mPAP, peak PVR
6	González-Saiz et al. (2017) [26]	Randomised controlled trial	40	A/IPAH (35%/25%) CTEPH (10%) NYHA class I-III	**Primary** peak muscle power during bench/leg press	**Secondary** peak VO_2, 6MWD, 5 repetition sit-to-stand, moderate-vigorous physical activity	No change: QoL (SF-12), 6MWD, peak VO_2, NT-proBNP
B	**Non-randomised controlled trials n=3; patients: n=71**						
7	Martinez-Quintana et al. (2010) [28]	Non-randomised controlled trial	8	CHD-APAH (100%)	NYHA functional class		No change: QoL (SF-36), 6MWD, peripheral muscle function, NT-proBNP

				WHO-FC II-III			
8	Fox et al. (2011) [27]	Non-randomised controlled trial	22	A/IPAH (46%/ 45%) CTEPH (9%) WHO-FC II-III	**Primary** 6MWD Peak VO_2	**Secondary** No significant changes	No change: NT-proBNP, pulse pressure, Borg scale, peak oxygen saturation, peak workload, oxygen uptake efficiency, VE/VCO_2
9	Fukui et al. (2016) [29]	Non-randomised controlled trial	41	CTEPH (100%) WHO-FC I-III	Peak VO_2, workload, WHO functional class, quadriceps strength, oxygen pulse		No change: QoL (SF-36), 6MWD, NT-proBNP, VO_2 at anaerobic threshold, heart rate at rest, oxygen saturation, VE/VCO_2, 6MWD, forearm muscle strength
C	**Prospective uncontrolled cohort studies n=10; patients: n= 426**						
10	de Man et al. (2009) [21]	Prospective cohort	19	IPAH (100%) WHO II-II	Workload, exercise endurance time Quadriceps strength and endurance, increase of capillarisation		No change: 6MWD, endurance, NT-proBNP
11	Grünig et al. (2011) [20]	Prospective cohort	58	A/IPAH (12%/64%) CTEPH (10%) WHO-FC II-IV	6MWD, peak VO_2, QoL (SF-36), WHO functional class Workload, heart rate at rest (decrease) and peak (increase) VO_2 at anaerobic threshold, workload at anaerobic threshold		No change: Borg Scale, respiratory equivalent for carbon dioxide
12	Grünig et al. (2012) [19]	Prospective cohort	183	A/IPAH (25%/45%) CTEPH (17%) WHO-FC I-IV	6MWD, peak VO_2, QoL (SF-36), VO_2 at anaerobic threshold, oxygen pulse, systolic pulmonary arterial pressure at rest, Workload		No change: Borg Scale, respiratory equivalent for carbon dioxide
13	Nagel et al. (2012) [17]	Prospective cohort	35	CTEPH (100%) WHO-FC II-III	6MWD, peak VO_2, QoL (S-36), workload Survival (1-year 97%, 2-year 94%, 3-year survival 86%)		No change: WHO functional class; NT-proBNP, oxygen saturation, oxygen pulse, respiratory equivalent for carbon dioxide; Significantly higher Borg scale after intervention
14	Grünig et al. (2012) [18]	Prospective cohort	21	CTD-APAH (100%) WHO-FC II-IV	6MWD, peak VO_2, QoL (SF-36), heart rate at rest, oxygen saturation, workload, VO_2 at anaerobic threshold Survival (1- and 2-years 100%, 3-year survival 73%)		No change: WHO functional class, Borg scale, oxygen pulse, oxygen saturation at rest, haemodynamics (echocardiography), C-reactive protein, Leukocytes
15	Becker-Grünig et al. (2013) [16]	Prospective cohort	20	CHD-APAH (100%) WHO-FC II-III	6MWD, peak VO_2, workload Survival (1-year 100%, 2-year survival 93%) QoL (bodily pain)		No change: QoL (SF-36 except bodily pain), WHO functional class, haemodynamics (echocardiography),

							oxygen pulse, VO2 at anaerobic threshold, oxygen saturation, Borg scale; Deterioration: NT-proBNP
16	Kabitz et al. (2014) [31]	Prospective cohort	7	A/IPAH (28%/72%) WHO-FC III-IV	Respiratory muscle strength 6MWD		-
17	Ehlken et al. (2014) [30]	Prospective cohort vs. retrospective control group	58#	A/IPAH (12%/63%) CTEPH (10%) WHO-FC II-IV	QoL,-Lower estimated health care costs due to less worsening events		-
18	Inagaki et al. 2014 [32]	Prospective cohort	8	CTEPH (100%) WHO-FC II-III	6MWD, QoL, quadriceps force, QoL (Saint George's Respiratory Questionnaire: activity), intensity of physical activity		No change: dyspnea, WHO functional class, heart rate at rest, pulmonary function, activities of daily living, QoL (Saint George's Respiratory Questionnaire: symptom and impact), heamodynamics (echocardiography), dyspnea and functional status, BNP, steps per day
19	Ihle et al. (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
D	**Case reports and retrospective studies n=5; patients: n=63**						
1	Shoemaker et al. (2009) [35]	Case reports	2	A/IPAH (50%/50%) WHO-FC I	6MWD, peak VO_2 at anaerobic threshold Workload at anaerobic threshold in both subjects		QoL (1 of 2 subjects improved)
2	Mainguy et al. (2010) [34]	Case series	5	IPAH (100%) WHO-FC II-III	6MWD, minute ventilation Decreased type IIx muscle fibre proportion		No change: endurance, muscle strength
3	Raskin et al. (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 Saint George's Respiratory Questionnaire)	No change: QoL (clinically significant: Saint George's Respiratory Questionnaire 2 main parts) Deterioration: QoL (clinically significant: Saint George's Respiratory Questionnaire: activity)
4	Talwar et al. (2017) [38]	Retrospective cohort	18	PAH (100%) WHO-FC I-IV	Treadmill speed		No change: exercise time
5	Bussotti et al. (2017) [36]	Case series	15	A/IPAH	**Primary:**	**Secondary:** 6MWD, O_2	No change: NT-proBNP

				(53%/47%) WHO-FC II-III	Peak VO_2	pulse, maximal heart rate, peak workload, QoL	
E	**Meta-analysis n=4**						
20	Yuan et al. (2015) [41]	Meta-analysis	12 Studies Total n = 449	Different aetiologies of pulmonary hypertension	6MWD (62.2 m, 95% confidence interval (CI) 45.6-78.8 m) peak VO_2/kg, workload VO_2 at anaerobic threshold Heart rate at rest (after three 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)
21	Buys et al. (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 VO_2/kg		-
22	Pandey et al. (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 VO_2/kg QoL Peak systolic pulmonary arterial pressure		-
23	Morris et al. 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 VO_2/kg 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)

6MWD: 6-minute walking distance, APAH: Associated Pulmonary Arterial Hypertension, CHD: Congenital Heart Disease, CTD: Connective Tissue Disease, CTEPH: Chronic Thromboembolic Pulmonary Hypertension, IPAH: Idiopathic Pulmonary Arterial Hypertension, LD-PH: Pulmonary Hypertension associated with lung disease, NYHA: New York Heart Association, VO_2: oxygen consumption, PAH: Pulmonary Arterial Hypertension, $PETCO_2$: partial pressure of end-tidal carbon dioxide, QoL: Quality of life, VO_2: oxygen consumption, WHO-FC: WHO functional class.

* If no division of primary/secondary endpoints is given, study endpoints were presented exploratory. Primary study endpoints 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. (2011) [20]

Exercise training performed in patients classified into different groups of PH has not only improved exercise capacity, but also different aspects of quality of life as shown in several studies [15, 17, 22] (Table 2). Most studies used the Short Form Health Survey 36 (SF-36) questionnaire, a generic instrument. Mereles and colleagues [15] showed a significant improvement of the primary endpoint quality of life in the two summation scores and in five SF-36 sub-scales 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 follow-up [17, 19, 24]. Details on improvement of QoL are given in Table 2. The improvements measured by SF-36 scales with different training modalities in various PH groups suggest significant impact of exercise training on patients' QoL, which have also been confirmed by a meta-analysis [41] and a Chochrane 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 instrument is designed to compare quality of life 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 with a significant improvement of exercise capacity and/or some quality of life subscales.

Table 2: Quality of life outcomes in exercise training studies of PH patients

Program	Patients	Study	Quality of life measure	
			Short Form 36	**Others**
In-patient	IPAH, CTEPH	Mereles et al. (2006) [15]*	PCS, MCS, PF, RP, SF, MH, VT	-
			BP, GH, RE	
	IPAH, CHD-APAH, CTD-APAH, CTEPH	Grünig et al. (2011) [20]	GH, MH, PF, RE, RP, SF, VT	-
			BP	
	CTD-APAH	Grünig et al. 2012 [18]	GH, MH, PF, SF, VT	-
			BP, RE, RP	
	Stable PAH, CTEPH	Grünig et al. 2012 [19]	MH, PF, RE, RP, SF, VT	-
			BP, GH	
	CTEPH	Nagel et al. (2012) [17]	PF, VT	-
			BP, GH, MH, RE, RP, SF	
	CHD-APAH	Becker-Grünig et al. 2013 [16]	BP	-
			GH, MH, PF, RE, RP, SF, VT	

	PAH, inoperable CTEPH	Ehlken et al. (2016) [24]	VT	-
			BP, GH, MH, PF, RE, RP, SF	
	CTEPH after BPA	Fukui et al. (2016) [29]	MH	Patient Health Questionnaire-9: Depression severity
			BP, GH, PF, RE, RP, SF, VT	
Out-patient	stable PAH, inoperable CTEPH	González-Saiz et al. (2017) [26]	RP, VT	-
			BP, GH, MH, PF, RE, SF	
	PAH, CHD-APAH	Martínez-Quintana et al. (2010) [28]	SF-12: MCS, PCS	
	IPAH, CTD-APAH, drug induced PAH	Chan et al. (2013) [22]	GH, MH PF, RP, SF, VT	CAMPHOR: quality of life, symptoms, energy, breathlessness, mood
			BP, RE	CAMPHOR: functioning
	IPAH, CTD-APAH	Weinstein et al. (2013) [23]	-	Fatigue severity scale; Human activity profile
	Aetiology not reported	Raskin et al. (2014) [37]	-	St. George's Respiratory Questionnaire (clinically significant changes >4 points): impact score
				St. George's Respiratory Questionnaire: symptom
				St. George's Respiratory Questionnaire: activity score
	PAH (children & adolescents)	Zöller et al. (2017) [43]	Tendency: MCS, PCS	-
	IPAH, portal hypertension-APAH, CTD-APAH, HIV-APAH	Bussotti et al. (2017) [36]	-	Hospital Anxiety and Depression Scale Questionnaire: anxiety, depression; EuroQoL-5 Dimensions; EuroQoL-visual analogue scale
	IPAH, HPAH, CTD-APAH,	Gerhardt et al. 2017 [44]	MCS, PCS	Living with PH: physical and emotional dimension score
Home	stable inoperable or residual CTEPH	Inagaki et al. (2014) [32]	-	St. George's Respiratory Questionnaire: activity score
				St. George's Respiratory Questionnaire: impact, symptom
	PAH, CTEPH	Ihle et al. (2014) [33]	BP, GH, MH, PF, RE, RP, SF, VT	CAMPHOR: activity
				CAMPHOR: quality of life, symptoms

Green colour: significant improvement ($p<0.05$). Yellow colour: no statistical difference. Red colour: deterioration

General abbreviations: APAH: associated pulmonary arterial hypertension, CHD: Congenital heart disease; BPA: Balloon angioplasty, CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review, CTD: Connective tissue disease, CTEPH: chronic thromboembolic pulmonary hypertension, HIV: human immunodeficiency virus, HPAH: hereditary pulmonary arterial hypertension, IPAH: idiopathic pulmonary arterial hypertension

Short form 36 scores: BP: Bodily pain, GH: General health, MCS: Mental component score, MH: Mental health, PCS: physical component score, PF: Physical functioning, RE: Role emotional, RP: Role physical, SF: Social functioning, VT: Vitality

* Co-primary endpoint

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 endpoints [24]. Altogether, 79 patients, either suffering from PAH or from non-operable 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% vs. -6.5%; $p<0.001$), a significant decrease in mean pulmonary arterial pressure (-7.3% vs. +16.1%; $p=0.007$) and pulmonary vascular resistance (-19.3% vs. +34.5%; $p<0.001$) at rest and a significant increase in cardiac index (+19.5% vs. -4.3%; $p=0.002$) 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 non-invasive 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 quality of life of patients (see also section on Quality of life). As invasive data are only available from a single prospective randomised study [24], further investigations are needed to confirm these data.

Muscle function in pulmonary hypertension patients

Leg fatigue and dyspnoea during exercise are the main indications of skeletal muscle dysfunction in patients with PAH [46]. Maximal volitional and non-volitional 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 also been reported after exercise training in PAH [34].

Inspiratory muscle training has been reported beneficial for inspiratory muscle function. PAH patients also report a better quality of life and decreased sensation of dyspnoea after inspiratory muscle training [31]. Finally, literature of 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].

Table 3: Summary of studies analysing muscle function in pulmonary hypertension

Study	Type of muscle	Sample size	Patients	Animal model	Muscle function	Cellular changes
Vescovo et al. (1998) [56]	Peripheral (M. soleus + EDL)	30 16/14^{+}	-	MCT30	-	↓: Fibre type I/II ratio ≈: CSA
Meyer et al. (2005) [49]	Respiratory	46 26/20^{+}	IPAH	-	↓: Pimax, PEmax	-
Kabitz et al. (2008) [47]	Respiratory	62 31/31^{+}	PH (25 PAH, 6 CTEPH)	-	↓: Pimax, PEmax; Sn*P*na, Sn*P*di; Tw*P*mo, Tw*P*di	-
Mainguy et al. (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 et al. (2011) [50]	Respiratory (diaphragm) Peripheral (EDL or M. quadriceps)	12 6/6^{+} 15 8/7^{+}	PH	MCT60	*Patients' Diaphragm* ↓: Maximal isometric force *Animal model diaphragm* Single muscle fibres: ↓: Twitch force, tetanic force, force-frequency *Peripheral muscle:* ≈: Twitch force, tetanic force, force-frequency	*Patients' Diaphragm* ↓: CSA diaphragm ≈: CSA quadriceps *Animal model diaphragm:* ↓: CSA ≈: Capillary density, SDH, Akt phosphorylation, MHC expression, 20s proteasome, Proteasome activity ↑: MAFbx, MuRF-1 *Peripheral muscle:* ≈: CSA
Manders et al. (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 et al. (2012) [54]	Peripheral (M. plantaris)	23 11/12^{+}	-	MCT60	-	↓: CSA, complex I activity, SDH ≈: Fibre type I/II ratio, capillary density
Batt et al. (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

Study	Type of muscle	Sample size	Patients	Animal model	Muscle function	Cellular changes
						↑: Atrogin-1, MuRF1 *Mitochondrial fusion* ↓: Mitofusin 1 and 2; ≈: DRP *Mitochondrial biogenesis* ≈: PGC1α, $MtCO_2$, NRF-1, TFA *Calcium cycling* ↑: pRyR ≈: SERCA2a, SERCA
Potus et al. (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 et al. (2015) [57]	Peripheral (M. quadriceps)	19 11/8[+]	IPAH	-	*Single muscle fibres:* ↓: Maximal tension, # attached cross-bridges during activation ≈: Fraction strongly bound cross-bridges, force per cross-bridge, calcium sensitivity ↑: Passive stiffness	-
Manders et al. (2016) [51]	Respiratory (diaphragm)	28 13/15[+]	CTEPH	-	Single muscle fibres: *Slow-twitch fibres:* ↓: Maximal tension, # attached cross-bridges during activation *Fast twitch fibres:* ↓: Calcium sensitivity, sub-maximal tension ≈: Force per cross-bridge	↓: MHC concentration (slow-twitch fibres) ≈: CSA

(I)/(H)PAH: (idiopathic)/(hereditary) pulmonary arterial hypertension, Akt: protein kinase B, ASD: atrial septum defect, CS: citrate synthase, CSA: cross sectional area, CTEPH: chronic thromboembolic pulmonary hypertension, DRP: dynamin-related protein, EDL: extensor digitorum longus (peripheral muscle), ERK: extracellular signal-regulated kinase, GSK3β: glycogen synthase kinase 3β, HADH: 3-hydroxyacyl-coA-dehydrogenase, MAFbx/MuRF-1: E3-ligases, MCT: monocrotaline, MHC: myosin heavy chain, miR-126: microRNA126, MtCO2: mitochondrial encoded cytochrome C oxidase subunit II, MuRF: muscle RING-finger protein, NRF-1: nuclear respiratory factor 1, PEmax (volitional): expiratory mouth pressure, PFK/CS: glycolysis to citric acid cycle, PFK/HADH: β-oxidation of fatty acids, PGC1α: peroxisome proliferator-activated receptor Ɣ coactivator, PImax (volitional): maximal inspiratory mouth pressure, PK: phosphofructokinase, RyR: ryanodine receptor, SDH: succinate dehydrogenase (oxidative enzyme activity), SERCA: sarco/endoplasmic reticulum Ca^{2+}-ATPase, Sn*P*di (volitional): sniff transdiaphragmatic pressure, Sn*P*na (volitional): sniff nasal pressure, SPRED1: Sprouty-related: EVH1 domain-containing protein 1, TFAM: mitochondrial transcription factor A, Tw*P*di (non-volitional): transdiaphragmatic pressure, Tw*P*mo (non-volitional): twitch mouth pressure, VEGF: vascular endothelial growth factor, VEGFR2: vascular endothelial growth factor receptor type 2

↓ = reduction; ↑ = increase; ≈ = no change; [+] for numbers displayed as 'x/y', x is number of disease, y is number of controls.

Limitations of training studies in PH

Though an emerging number 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, though allocated to the control arm. This bears the risk of an unsupervised training, in addition to biased trial results, which also hinders to gain long-term data of control patients. This may be one reason, why there is still no long-term data about 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 trial designs that address these issues, such as the offer to participate in the 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 endpoints for most outcomes (6MWD, peak VO_2, QoL, blood flow of the lung, peak muscle power), the presented randomised controlled trials are of different quality [42] and require further validation. Most of the data about training effects in PH is also relying on results of a single centre, which offered a rather intensive beginning of the exercise training programme. An intensive in-hospital programme demands a high amount of resources on personnel, time and money and may therefore not be widely available. Future research should be based on larger-scaled multicentre studies for external validity of the data.

Future directions - Challenges and research questions

Since the publication of the 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. The current data does however 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 chapters 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 health care systems to clarify if 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 endpoints in PH studies have evolved from the primary endpoint exercise capacity (6-minute walking distance) 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 is 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 the disease progression and patient survival. To determine the impact of any intervention in PH we need clinically relevant and robust endpoints. While traditionally the 6MWD has been used in drug development it has many limitations most particularly in the study of exercise effects. Similarly, while 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 VO_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 less than 15 hours/day (p=0.026) [66].

A composite morbidity and mortality endpoint 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 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 reasonable 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, which can offer this treatment to patients to participate 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. Several studies however 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. 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) have taken part in the "Heidelberg" training programme that started with an in-hospital stay for three 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 pre-defined saturation and heart rate safety parameters (for details see 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 ([21-23, 26-28, 34-36, 38], see Table 4). Outpatient programmes typically use 2 to 3 supervised sessions/week in hospital rooms for approximately twelve weeks. There have also 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/week with different total duration of training units in the programme/training day and with duration of the study lasting from six weeks up to one year.

The majority of studies have demonstrated clinical benefits (Table 1 and Table 2). Thirty per cent 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 quality of life 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].

Involvement of the medical team with PH expertise in the development and delivery of the exercise programme has also been a feature of all previous studies. The in-hospital programmes take place in

PH centres with a multidisciplinary team consisting of psychologists, PH nurse specialists and dieticians (Table 5; for more details see section on Requirements of different health care 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, psychologic counselling may often support the patients' wellbeing.

Table 4: Set-up of exercise training programmes

Type	Study	Patient Number*		Frequency	Length of programme	Monitoring
In-patient	Mereles et al. (2006) [15]	15/15+	511/560*	7 days/week	15 weeks Weeks 1-3 inpatient Weeks 4-15 at home	Subjective physical exertion HR <120 /min SaO_2 >85% (if lower supplemental O_2 supplied)
	Grünig et al. (2011) [20]	58				
	Becker-Grünig et al. (2013) [16]	20				
	Ehlken et al. (2014) [30]	58#				
	Ley et al. (2013) [25]	10/ 10+			3 weeks inpatient	
	Grünig et al. (2012) [18]	21			15 weeks Weeks 1-3 inpatient Weeks 4-15 at home	see Mereles et al. (2006) supplemental O_2 if SaO_2 <90%
	Grünig et al. (2012) [19]	183				
	Nagel et al. (2012) [17]	35				
	Ehlken et al. (2016) [24]	87				
	Kabitz et al. (2014) [31]	7				see Mereles et al. (2006) HR ≤130 /min Supplemental O_2 if SaO_2 <90%
	Fukui et al. (2016) [29]	17/24+		7 days/first week ~4 days/week 2-12	12 weeks Week 1 in hospital Weeks 2-12 at home	Borg 12-13 (scale 6/20) HR 40-60% of HR reserve SaO_2 ≥90%
Out-patient	Shoemaker et al. (2009) [35]	2	138/176*	3 days/week	6 weeks	Subjective exertion <4/10, HR ≤80% age predicted max, blood pressure ≤180 mmHg, SaO_2 >91%
	de Man et al. (2009) [21]	19		3 days/week	12 weeks	SaO_2>85% HR<120 /min
	Martinez-Quintana et al. (2010) [28]	4/4+		2 days/week	12 weeks	Borg scale, HR
	Mainguy et al. (2010) [34]	5		3 days/week	12 weeks	Borg scale <6/10 Resting allowed Intensity reduced if SaO_2 <85%
	Fox et al. (2011) [27]	11/ 11+		2 days/week	12 weeks	Subjective exertion, rest permitted, HR, SaO_2 "monitored" SaO_2 >90% (if lower supplemental O_2 supplied)
	Chan et al. (2013) [22]	10/13+		3 days/week	10 weeks	Subjective exertion, SaO_2, HR "monitored" (no values given)

Type	Study	Patient Number*		Frequency	Length of programme	Monitoring
	Weinstein et al. (2013) [23]	11/13+		3 days/week	10 weeks	Subjective exertion, SaO_2, HR "monitored" (no values given)
	Raskin et al. (2014) [37]	23		2-3 days/week	>8 weeks	Borg scale
	González-Saiz et al. (2017) [26]	20/20+		3 days/week	8 weeks	SaO_2>80% BP < -20mmHg BP systolic <220 mmHg, diastolic <110mmHg No ECG abnormalities
	Talwar et al. (2017) [38]	18		3 days/week	12 weeks	Only safety equipment specified (blood pressure monitor, ECG, pulse oximetry, supplemental oxygen)
	Bussotti et al. (2017) [36]	15		5 days/week	4 weeks	HR <70% of max at CPET Borg scale <5 SaO_2 >90%
Home	Inagaki et al. (2014) [32]	8	25	1 hospital session/week + 3 sessions at home/week	12 weeks	Subjective exertion
	Ihle et al. (2014) [33]	17		1 day/month	40 weeks	Subjective exertion: Borg scale <7/10 HR < +30/min SaO_2 >85%

BP: Blood pressure, ECG: electrocardiogram, HR: heart rate, SaO_2: oxygen saturation

+ for numbers displayed as 'x/y', x is number in exercise programme, y is number of controls.

* for totals, the second number takes into account all patient involved, including controls.

This study refers to the same patients as Grünig et al. (2011) [20]

Table 5: Components of multidisciplinary settings

Type	Study	exercise	Psychological support	Relaxation	Dietary support	Education on the disease	Team members
In-patient	Mereles et al. (2006) [15]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Grünig et al. (2011) [20]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Grünig et al. (2012) [18]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Grünig et al. (2012) [19]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Nagel et al. (2012) [17]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Becker-Grünig et al.	✓	✓	✓	✓	✓	PH expert,

Type	Study	exercise	Psychological support	Relaxation	Dietary support	Education on the disease	Team members
	(2013) [16]						physiatrist, physiotherapist, psychologist
	Kabitz et al. (2014) [31]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Ley et al. (2013) [25]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Ehlken et al. (2014) [30]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Ehlken et al. (2016) [24]	✓	✓	✓	✓	✓	PH expert, physiatrist, physiotherapist, psychologist
	Fukui et al. (2016) [29]	✓	✓	-	-	✓	PH expert, cardiologist, physiotherapist,
Out-patient	de Man et al. (2009) [21]	✓	-	-	-	-	Physiatrists, pulmonologists, physiotherapists
	Shoemaker et al. (2009) [35]	✓	-	-	-	-	physiotherapist
	Mainguy et al. (2010) [34]	✓	-	-	-	-	Rehabilitation center; no details given
	Martinez-Quintana et al. (2010) [28]	✓	Education on "emotional stress"	-	-	✓	Physician, physiotherapist
	Fox et al. (2011) [27]	✓	✓	-	-	-	Physician, physiotherapist
	Chan et al. (2013) [22]	✓	Educational lesson "panic control", "social wellbeing"	Educational lesson "relaxation techniques"	Educational lesson on "nutrition"	✓	Not stated
	Weinstein et al. (2013) [23]	✓	Educational lesson "panic control", "social wellbeing"	Educational lesson "relaxation techniques"	-	✓	Not stated
	Raskin et al. (2014) [37]	✓	Multidisciplinary approach is stated for this pulmonary rehabilitation, without giving any detail				PH centre and rehabilitation centre
	González-Saiz et al. (2017) [26]	✓	-	-	-	-	Fitness instructors
	Talwar et al. (2017) [38]	✓	-	✓	-	-	Not stated
	Bussotti et al. (2017) [36]	✓	✓	✓	-	-	Physician, physiotherapist
Home	Inagaki et al. (2014) [32]	✓	-	-	-	-	Pulmonologist, physiotherapist
	Ihle et al. (2014) [33]	✓	-	-	✓	✓	Physician,

Type	Study	exercise	Psychologi-cal support	Relaxation	Dietary support	Education on the disease	Team members
							physiotherapist, dietician, pharmacist, nurse

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 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 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, around 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 around 60% of peak heart rate, not exceeding 120 beats/min, with an oxygen saturation above 85 to 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/min) and subjective perception of exertion by Borg dyspnoea score were used. An oxygen desaturation of <85-90% or heart rate of >120/min 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 closely monitored the patients, 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.

Table 6: Training modalities and intensities in exercise training studies

Author (year)	Country	Exercise training modalities	Training intensity
Mereles et al. (2006) [15]	Germany (Heidelberg)	Bicycle ergometer, interval (1 min high / 30 sec low; 10-25 min), 10-60 Watts 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/ week	60-80% peak VO_2 ([15, 25]), progressive increase during programme
Ley et al. (2013) [25]			
Grünig et al. (2011) [20]			10-60 Watts ([16-20, 30, 31]) progressive increase during programme
Grünig et al. (2012) [19]			
Grünig et al. (2012) [18]			
Nagel et al. (2012)[17]			
Becker-Grünig et al. (2013) [16]			
Kabitz et al. (2014) [31]			
Ehlken et al. (2014) [30] #			
Ehlken et al. (2016) [24]			
Ihle et al. (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/ month	10-60 Watts
Mainguy et al. (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: three times/ week	60% max workload 85% mean speed during 6MWT 70% max voluntary contraction
Fox et al. (2011) [27]	Israel (Tel Aviv)	Week 1-6 Treadmill walking/ cycling/ step climbing, interval (60 min) Week 7-12 Resistance exercise (low weight dumbbell training or strength training) / aerobic training, continuous (60 min total) Frequency: twice/ week	60-80% HR at peak VO_2
Bussotti et al. (2017) [36]	Italy (Milan)	Bicycle ergometer, continuous (30 min) Resisted 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: five times/week	50% peak workload
Inagaki et al. (2014) [32]	Japan (Chiba)	Walking, continuous (>20 min) Resistance training, 1-3 sets with 10-15 repetitions Respiratory exercise (~20 min)	60% max HR Free from/minor subjective dyspnoea

		Frequency: in-hospital once/ week	
Fukui et al. (2016) [29]	Japan (Suita)	Walking (30-60 min) Bicycle ergometer Resistance training (low weights) Frequency: week 1 daily, week 2-12 Outpatient session twice/week	40-60% HR reserve
de Man et al. (2009) [21]	Netherlands (Amsterdam)	Cycling, interval (35-40 min) Week 1-3: 2 min 50% VO_2 max, 2 min rest Week 4-6:3 min 50% VO_2 max, 2 min rest Week 7-9:4 min 75% VO_2 max, 2 min rest Week 10-12:5 min 75% VO_2 max, 2 min rest Quadriceps strength (S); endurance € (~20 min) Week 1-3: (S) 50% ORM, (E) 30% ORM Week 4-6: (S) 50% ORM, (E) 30% ORM Week 7-9: (S) 75% ORM, (E) 40% ORM Week 10-12: (S) 75% ORM, (E) 40% ORM Frequency: three times/ week	75% VO_2 max % of maximum repetition (ORM) on 1st day
Martinez-Quintana et al. (2010) [28]	Spain (Las Palmas de Gran Canaria)	Warm up: stretching/ Resistance exercise with 1-2 kg (10 min) Bicycle ergometer, Interval: 30 sec high with 20-50 Watts / 30 sec low with 10-25 Watts (24 min) Educational lessons (Time not specified) Frequency: twice/ week	80% max HR during 6MWT Borg scale 3-6
González-Saiz et al. (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/ week Resistance 3 times/ week Inspiratory 6 times/ week	50% power output at anaerobic threshold Against 40% inspiratory pressure max
Shoemaker et al. (2009) [35]	United States of America (Michigan)	Bicycle ergometer, continuous (45 min) Frequency: three times/ week	50% peak workload
Talwar et al. (2017) [38]	United States of America (New York)	Treadmill walking, continuous (20-30 min) Educational lessons Frequency: three times/ week	Based on maximal speed and time on a treadmill measured at baseline
Raskin et al. (2014) [37]		Aerobic training (treadmill, bicycle, and crosstrainer exercises), continuous (30-60 min) Frequency: 2-3 times/ week	Borg scale, "moderate intensity"
Weinstein et al. (2013) [23]	United States of America (Virginia)	Treadmill walking, continuous (30-45 min) Educational lessons (60 min) Frequency: ≥ 2 times / week	70-80% max intensity
Chan et al. (2013)[22]			70-80% max HR

6MWT: 6 minute walking test, BP: blood pressure, HR: heart rate, SaO_2: oxygen saturation, VO_2: oxygen uptake;

[#] This study refers to the same patients as Grünig et al. (2011) [20]

In conclusion, different training modalities have been investigated in patients with PH. The common features of these programmes are a multidisciplinary approach, a 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 quality of life 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.

Outcome measures

Outcome measures used to assess the efficacy of exercise training in PH can be broadly split into six categories: symptoms, quality of life, 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 quality of life. There are many ways to assess exercise capacity. The most commonly applied tests are the 6-minute walk test (6MWT) and the shuttle walk test. However, the most comprehensive test is cardiopulmonary exercise testing (CPET). The European Society of Cardiology / European Respiratory Society (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 (VO_2) [70, 71] and the relationship of minute ventilation to carbon dioxide production as (VE/VCO_2)-slope. For example, a randomised controlled study from Germany showed peak VO_2 can be used to monitor training effects in PH [24].

In addition to peak VO_2, a second independent prognosticator, the capability of the patient to increase right ventricular systolic pressure even during low-level exercise by more than 30 mmHg has been identified [72]. Of note, this finding was valid only in patients with severe PH. A study from Sheffield analysing the shuttle walk test also 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. As compared to the 6MWT, 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 VO_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 VO_2 and the heart rate response to exercise, it can be speculated, that it may also improve survival, albeit such studies may not be conducted due to ethical reasons (see section on Future directions).

Table 7. Outcome measures for training programmes

Type	Study	Quality of life*			Functional ability					Peripheral muscle function	Biomarkers
		SF36	CAMPHOR	Other questionnaire	6MWD	Peak VO_2	Endurance	WHO Class	Treadmill speed	Muscle strength	(NT-pro)-BNP
Inpatient	Mereles et al. (2006) [15]	7/10									
	Grünig et al. (2011) [20]	7/8									
	Grünig et al. (2012) [18]	5/8									
	Grünig et al. (2012) [19]	2/8									
	Nagel et al. (2012) [17]	2/8									
	Becker-Grünig et al. (2013) [16]	1/8									
	Ley et al. (2013) [25]										
	Ehlken et al. (2014) [30]#	7/8									
	Kabitz et al. (2014) [31]										
	Ehlken et al. (2016) [24]	1/8									
	Fukui et al. (2016) [29]	1/8		PHQ-9							
Outpatient	de Man et al. (2009) [21]										
	Martinez-Quintana et al. (2010) [28]	SF-12: 0/2									
	Mainguy et al. (2010) [34]										
	Fox et al. (2011) [27]										
	Chan et al. (2013) [22]	6/8	5/6								
	Weinstein et al. (2013) [23]			FAS, HAP							
	Raskin et al. (2014) [37]			1/3 1/3							
	Zöller et al. (2017) [43]	0/2									
	Gerhardt et al. 2017 [44]	2/2									
	Talwar et al. (2017) [38]										
	Bussotti et al. (2017) [36]			HADS, EQ-5							
	González-Saiz et al. (2017) [26]	2/8									
Home	Inagaki et al. (2014) [32]			SGRQ 1/3							
	Ihle et al. (2014) [33]	0/8	1/3								

Legend

	Statistically significant improvement
	No significant improvement
	Statistically significant deterioration

SF-36: 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 brain 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; * 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. # This study refers to the same patients as Grünig et al. (2011) [20]

Safety

Extensive physical activity may increase pulmonary artery pressure, inducing circulatory collapse and leading to the right heart failure in PH patients. Some patients may be at risk for exercise-induced hypoxemia, 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 had to be on optimised and 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 (less than 5%) have been reported with regards to exercise training in PH (Table 8).

In the largest published prospective cohort study [19], in 13.6% out 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 5 out of 6 pre-syncopal episodes did not seem to have a direct relation to exercise training [19].

Adverse events were reported in 64 out of 674 (9.5%) exercise-trained PH patients. Exercise related complications, seemed to be more frequent in an outpatient compared to an inpatient setting (5.8% vs 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 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]. Non-sustained supraventricular arrhythmia [19, 28], syncope [17] and pre-syncope [19] during or briefly after exercise training were reported in less than 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 actually showed the largest improvement after very closely-supervised, low-intensity exercise and respiratory training [19]. The low patient numbers do however not allow valid conclusions about the safety of training in such patients.

In most studies, the PAH group was mainly represented by IPAH and PAH associated with connective tissue disease (also see 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 programs still needs further investigation, as only one study with a prospective intervention and retrospective control group has demonstrated less health-care 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 multi-disciplinary 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. Participation in unspecialised training programmes or unsupervised settings, e.g. home training, is therefore dissuaded. Strenuous exercise should still remain contraindicated in patients with PH [1].

Table 8. Exercise training associated adverse events in patients with chronic stable pulmonary hypertension

Adverse events		Number of cases (% of total study participants) n =674	Number of cases (% of exercise trained)			Studies
			In-patient setting (n=511)	Out-patient setting (n=138)	Home based (n=25)	
Exercise related:	Dizziness	8 (1.2%)	4 (0.8%)	4 (2.9%)	-	Mereles et al. (2006) [15], de Man et al. (2009) [21], Grünig et al. (2011) [20], González-Saiz et al.(2017) [26], Mainguy et al. (2010) [34]
	Desaturation	16 (2.4%)	14(2.7%)	2 (1.4%)	-	Mereles et al. (2006) [15], Martinez Quintana et al. (2010) [28], Becker-Grünig et al. (2013) [16]
	Arrhythmia	3 (0.4%)	2 (0.4%)	1 (0.7%)		Grünig et al. (2012) [19], González-Saiz et al. (2017) [26]
	Hypotension	1 (0.1%)	-	-	1 (4%)	Inagaki et al. (2014) [32]
	Syncope	1 (0.1%)	1 (0.2%)	-	-	Grünig et al. (2012) [19], Nagel et al. (2012) [17]
	Pre-syncope	1 (0.1%)	1 (0.2%)	-	-	Grünig et al. (2012) [19]
	Fatigue	1 (0.1%)	-	1 (0.7%)	-	Mainguy et al. (2010) [34]
	None reported					Bussotti et al. (2017) [36], Chan et al. (2013) [22], Ehlken et al. (2014) [30], Ehlken et al. (2016) [24], Fox et al. (2011) [27], Fukui et al. (2016) [29], Ihle et al. (2014) [33], Kabitz et al. (2014) [31], Ley et al. (2013) [25], Raskin et al. (2014) [37], Talwar et al. (2017) [38], Shoemaker et al. (2009) [35], Weinstein et al. (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 et al. (2012) [19]
	Pre-syncope	5 (0.7%)	5 (1.0%)	-	-	Grünig et al. (2012) [19]
	Mild haemoptysis	1 (0.1%)	1 (0.2%)	-	-	Grünig et al. (2012) [18]
	Respiratory infection	23 (3.4%)	23 (4.5%)	-	-	Grünig et al. (2012) [19], Grünig et al. (2011) [20], Nagel et al. (2012) [17], Becker-Grünig et al. (2013) [16]
	Herpes zoster infection	1 (0.1%)	1 (0.2%)	-	-	Nagel et al. (2012) [17]
	Gastrointestinal infection	1 (0.1%)	1 (0.2%)	-	-	Grünig et al. (2011) [20]
	Total	**33 (4.9%)**	**33 (6.5%)**			
Total		**64 (9.5%)**	**55 (10.8%)**	**8 (5.8%)**	**1 (4%)**	

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 4 key steps (see 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:

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

Medical therapy: Exercise therapy improves exercise capacity and quality of life 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 understudied 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 and colleagues [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 & anxiety
- Baseline 6MWD > 550m
- 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 program, 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 therefor 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
- **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 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 is usually taking place at the beginning of a programme; goals are contextualised and adjusted as needed; specific psychological techniques such as mental imagery can also 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 to enhance patient access to rehabilitation programmes by introduction of rehabilitation facilities offering these specialised training programmes, and to perform quality control, e.g. by assessment of outcomes and the conductance of scientific trials. Furthermore, cost-effectiveness analyses in future trials may help to convince healthcare providers and payers from 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 within this Task Force this issue has been discussed involving 18 centres of 11 European countries to get a better understanding of the 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 of the 11 countries (91%), 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 an increased attention and organisational effort, reimbursement often does not cover the full costs of such an intervention. Many European countries such as England, 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 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 health care institutions, commissioners of health care and research funding institutions are of high need. Supported by the PAH-self-help group members of this Task Force started the initiative to provide a standardised PH-rehabilitation-programme in their PH centres to make this therapy available for the patients within their country.

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, likely 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 VO_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 endpoints 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]
- 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 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]. A reduced oxidative stress and improved neurohumoral markers (lower N-terminal pro brain natriuretic peptide (NT-proBNP) and endothelin-1 myocardial expression) were also described in the right ventricle of trained PH animals. In contrast, only in one out of six studies a significant improvement of plasma NT-proBNP levels [17] was described in patients undergoing exercise training (see also 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]. Though the training was only short with three 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, mTOR) 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]. The underlying pathobiological mechanisms are however 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/ Conclusion

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, quality of life 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], ten 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 health care institutions, commissioners of health care 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 non-pharmacological intervention into standard care.

Acknowledgements: We would like to thank the Pulmonary Hypertension Association (PHA), the PH-self-help group phev.

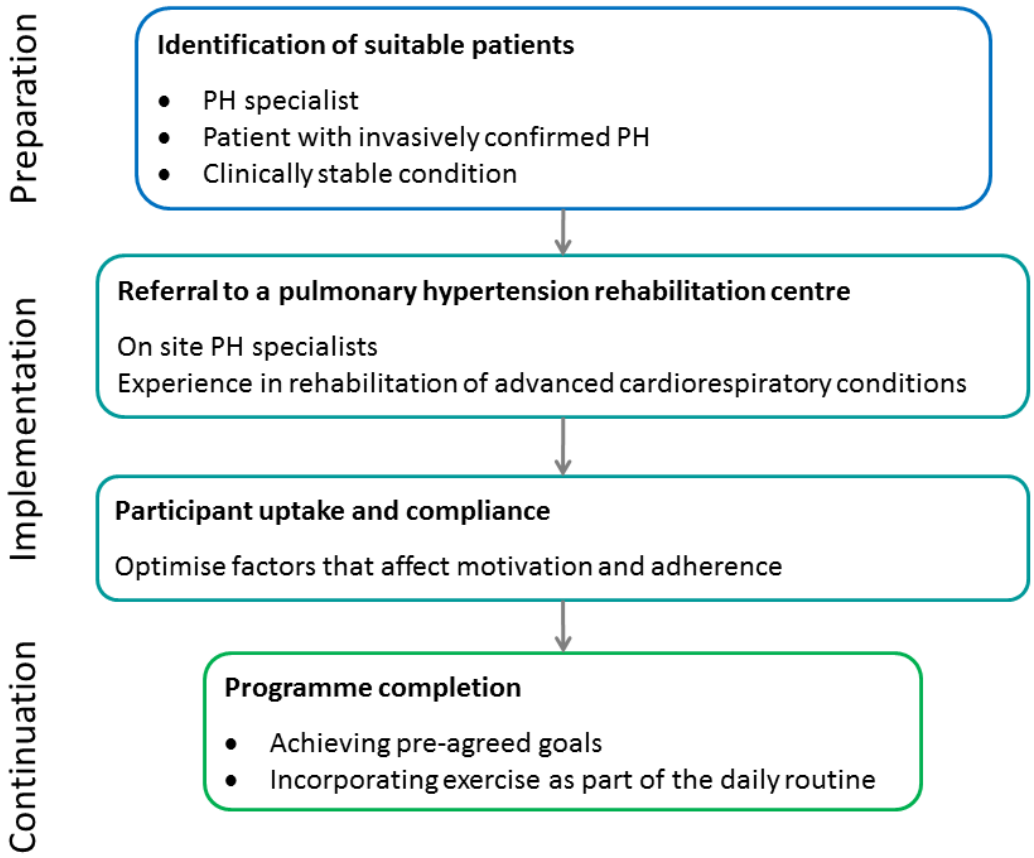
Figure Legends

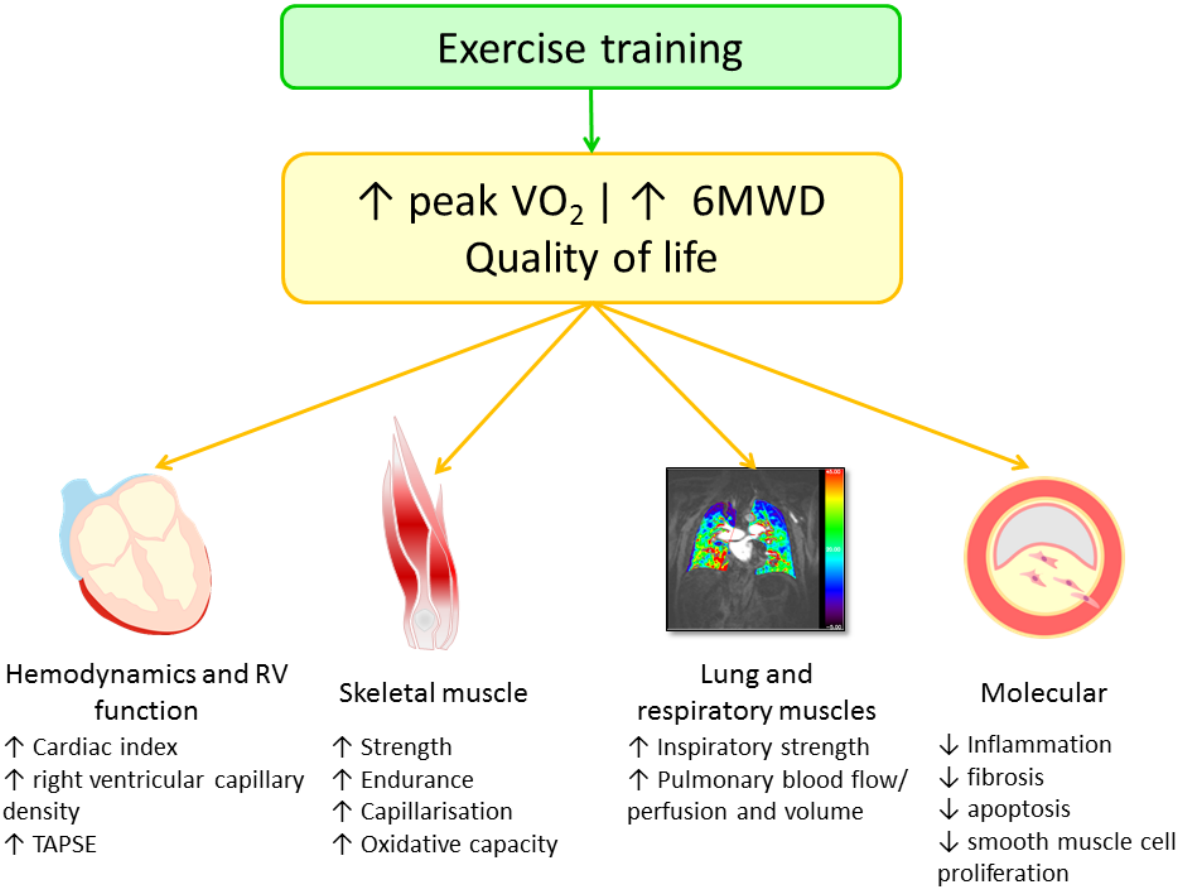
Figure 1: Four key steps for successful patient participation in an exercise training programme

These steps describe the way PH patient participation 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 programme completion, a continuation of exercises in the daily routine helps to maintain the training effect.

Figure 2: Main physiological effects of exercise training

Exercise training in pulmonary hypertension acts on heart function, skeletal and respiratory muscles on a macroscopic as well as molecular level. Inflammation and cell proliferation are reduced. 6MWD: 6-minute walking distance, peak VO_2: peak oxygen uptake, RV: right ventricular, TAPSE: Tricuspid annular plane systolic excursion


Preparation
Identification of suitable patients
PH specialist
Patient with invasively confirmed PH
Clinically stable condition
Implementation
Referral to a pulmonary hypertension rehabilitation centre
On site PH specialists
Experience in rehabilitation of advanced cardiorespiratory conditions
Participant uptake and compliance
Optimise factors that affect motivation and adherence
Continuation
Programme completion
Achieving pre-agreed goals
Incorporating exercise as part of the daily routine


Exercise training
↑ peak VO_2 | ↑ 6MWD
Quality of life
Hemodynamics and RV function
↑ Cardiac index
↑ right ventricular capillary density
↑ TAPSE
Skeletal muscle
↑ Strength
↑ Endurance
↑ Capillarisation
↑ Oxidative capacity
Lung and respiratory muscles
↑ Inspiratory strength
↑ Pulmonary blood flow/ perfusion and volume
Molecular
↓ Inflammation
↓ fibrosis
↓ apoptosis
↓ smooth muscle cell proliferation

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Supplementary Table 1: Keywords and literature searches performed for respective sections

Section	Key words
General	- pulmonary hypertension, exercise training - pulmonary hypertension, rehabilitation - pulmonary hypertension [MeSH] AND exercise therapy [MeSH]
Part I Clinical effects of exercise training in pulmonary hypertension	
Effect of rehabilitation on exercise capacity and quality of life	General key words for identification of original articles; studies on PH and exercise training were screened for quality of life assessments
Haemodynamics and echocardiography	Echocardiography, ultrasound, Doppler
Muscle function in pulmonary hypertension patients	Pulmonary hypertension, muscle function, molecular changes
Quadriceps and inspiratory muscle training	Studies on exercise training in PH were screened for muscle training
Future directions - disease progression and survival	Studies on exercise training in PH were screened for disease progression and survival
Part II Training modalities and setting	Studies on exercise training in PH were screened for the issues of the respective subsections
Part III Implementation of exercise training	
Participant selection, compliance and motivation	Studies on exercise training in PH were screened for patient selection process, compliance and motivation - further search for articles: rehabilitation OR rehabilitation [MeSH], implementation
Requirements of different healthcare systems	Exercise therapy [MeSH] AND pulmonary hypertension AND healthcare systems
Part IV Mechanisms of action of exercise training in PH	Studies on exercise training in PH were screened for mechanisms of action