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ABSTRACT

Background: The Post-Pulmonary Embolism Syndrome (PPES) comprises heterogeneous entities, including chronic thromboembolic disease with/without pulmonary hypertension (CTEPH/CTEPD), and deconditioning.
Objectives: To assess underlying physiological determinants of PPES, and efficacy and safety of rehabilitation training in these patients.
Methods: 56 consecutive PE patients with persistent dyspnea and/or functional limitations despite ≥3 months of anticoagulation underwent standardized diagnostic work-up including exercise testing as part of routine practice. All diagnostic (imaging and cardiopulmonary function) tests were interpreted by a core group of experienced clinicians. A subgroup of patients without CTEPH or other treatable conditions was referred for a 12-week personalized rehabilitation program, studying changes in physical condition and patient-reported outcome measures.
Results: Persistent vascular occlusions were observed in 21/56 patients (38%) and CTEPH was confirmed in ten (18%). Regarding those without CTEPH, impaired cardiopulmonary responses were evident in 18/39 patients with available CPET data (46%), unrelated to chronic thrombi. Rehabilitation was completed by 27 patients after excluding 29 (patients with CTEPH or treatable comorbidities, refusal, ineligibility, or training elsewhere). Training intensity, PE-specific quality of life (PEmb-QoL) and fatigue (CIS) improved with a median difference of 20 W ($p = 0.001$), 3.9 points ($p < 0.001$) and 16 points ($p = 0.003$), respectively. Functional status (Post-VTE Functional Status Scale) improved ≥1 grade in 18 (67%) patients, and declined in one (3.7%).

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Conclusions: Our findings suggest that abnormal cardiopulmonary responses to exercise are common in patients with PPES and are not limited to those with chronic thrombi. Offering pulmonary rehabilitation to patients not treated otherwise seems safe and promising.

1. Introduction

After acute pulmonary embolism (PE), up to half of patients report persistent dyspnea and/or functional limitations despite adequate anticoagulant treatment [1–6]. The so-called Post-PE Syndrome (PPES) is characterized by a combination of abnormalities in echocardiographic parameters of right ventricular function, pulmonary artery hemodynamics and impaired gas exchange with increased dead-space ventilation at rest or during exercise, all possibly caused by the persistent thrombotic obstruction of the pulmonary arteries [7–11]. The most severe presentation of PPES is chronic thromboembolic pulmonary hypertension (CTEPH), with a 2–4% incidence among PE survivors [12]. Even if pulmonary artery pressures at rest are normal in the presence of persistent perfusion defects, a relatively high pulmonary vascular resistance, reduced right ventricular contractile reserve and increased dead-space ventilation may account for debilitating exertional dyspnea, also referred to as chronic thromboembolic pulmonary disease (CTEPD) [13–16]. Etiologies explaining persistent complaints in patients without persistent perfusion defects include chronic right ventricular impairment, deconditioning and/or pre-existing comorbidities [5,17–20]. Depressive disorders, fear for potential complications or recurrences, and post-thrombotic panic syndrome further contribute to long-term functional impairment, which may lead to physical inactivity, subsequent deconditioning and a downward spiral as result [21,22]. Altogether, PPES is associated with decreased quality of life, unemployment and increased utilization of healthcare resources, although the underlying physiological determinants are largely unknown [19,23,24].

Curative treatment for CTEPH is available, preferably pulmonary endarterectomy (PEA), whereas the optimal management of other forms of the PPES is not well established [25]. Small studies have shown promising results of PEA or balloon pulmonary angiography (BPA) in patients with CTEPD, but this is currently not the standard of care [26–29]. Although only few experience is available for pulmonary rehabilitation in patients with PPES, small studies do suggest positive effects on exercise capacity and quality of life in both PE patients [30–35] and those with CTEPH [36–40]. In the setting of other acute and chronic cardiopulmonary conditions e.g. coronary heart disease, chronic obstructive pulmonary disease (COPD), and interstitial lung disease, cardiac and/or pulmonary rehabilitation programs are routinely offered because of established reduction of cardiovascular mortality and morbidity, as well as improvement in quality of life, symptoms and exercise capacity [41,42]. We hypothesized that a personalized rehabilitation program may also improve functional status in patients with PPES.

In this study, we studied the underlying determinants of persistent complaints in patients with PPES, and aimed to get insight into the efficacy and safety of an outpatient pulmonary rehabilitation program in patients with PPES in whom CTEPH and CTEPD suitable for PEA or BPA were ruled out.

2. Methods

2.1. Study design and patients

This observational cohort study is a description of routine care. We prospectively followed all consecutive patients with imaging-confirmed acute PE [43,44] referred to the 'post-PE syndrome clinic' of the Leiden University Medical Center (LUMC) between May 2017 and May 2019 [45]. Firstly, in this dedicated clinic, adult PE patients with persistent moderate-to-severe dyspnea (modified Borg scale $\geq$3 at rest) and/or patient-reported relevant functional limitations despite adequate anticoagulation for at least 3 months were subjected to a standardized diagnostic work-up. Secondly, a subgroup of these patients that were not subjected to specific CTEPH/CTEPD treatment and did not have underlying comorbidities explaining their persistent symptoms, were invited to follow a post-PE-specific pulmonary rehabilitation program in an expertise center for specialist medical rehabilitation care (Basalt, Leiden, the Netherlands).

The local Ethics Committees of both LUMC and Basalt waived the need for informed consent because of the observational design of this study. All patients were actively informed of the intention to use the results and outcome of the dedicated clinic for scientific purposes and we have explicitly offered all patients to opt out. None objected to the use of anonymized data.

2.2. Objectives

The primary objectives of this study were: 1) to evaluate the underlying physiological determinants of exertional dyspnea in all patients referred to our 'post-PE syndrome clinic'; and 2) to get insight in the safety and efficacy of a rehabilitation program on training intensity, and patient-reported outcome measures in a subgroup of patients in whom CTEPH and CTEPD suitable for PEA or BPA were ruled out after standardized diagnostic work-up.

2.3. Procedures

2.3.1. Diagnostic work-up

This includes routine blood testing, resting echocardiography, computed tomography pulmonary angiography (CTPA) with subtraction perfusion mapping, cardiopulmonary exercise test using a stationary cycle ergometer (CPET), and pulmonary function test, if relevant followed by invasive right heart catheterization (RHC), ventilation/perfusion imaging and/or pulmonary angiography [46]. The baseline test results were discussed in a multidisciplinary team of pulmonary hypertension experts, including cardiologists, pulmonologists, rheumatologists and vascular medicine specialists. Patients with (suspected) CTEPH or CTEPD potentially suitable for PEA or BPA were referred to the VU University Medical Center (CTEPH expertise center) for appropriate treatment. CTEPH was established if the following strict diagnostic criteria were met: 1) $\geq$1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion (V/Q) scanning after $\geq$3 months of adequate therapeutic anticoagulation; 2) mean pulmonary artery pressure (mPAP) $\geq$25 mm Hg at rest measured by RHC; *and* 3) pulmonary artery wedge pressure (PAWP) $\leq$15 mm Hg [46]. In case a treatable comorbidity was found, e.g. asthma, interstitial lung disease or left heart failure, treatment optimization was provided by the relevant medical specialist of the multidisciplinary team.

2.3.2. Rehabilitation program

The 12-week outpatient rehabilitation program in the previously mentioned subgroup was based on the Official ATS/ERS Statement: Key Concepts and Advances in Pulmonary Rehabilitation [42]. Patients participated in twice-weekly sessions of 90 min of supervised exercise training and, after two weeks, supplemented with one unsupervised training at home (Appendix A). During the supervised sessions, patients performed 30 to 40 min of endurance exercise, and 30 min of strength exercises. The endurance training was performed on a stationary cycle ergometer and/or a treadmill, and comprised endurance and/or interval exercise. According to current guidelines, each training was targeted at

70 to 80% of patients' individual maximum heart rate, which was routinely checked by the physiotherapist supervising the training [42,47]. When patients were over- or underperforming, if tolerable, this was corrected by adjusting the workload of the training in order to acquire the targeted heart rate. Strength training was aimed at either improving absolute muscle strength or improvement in muscle endurance using medical fitness equipment. For improvement of strength, patients trained at 75% of their one repetition maximum (1RM), performing 3 series of 8 repetitions. When training muscle endurance, 2 series of 15 repetitions at 65% of the 1RM were performed. Concerning the third training each week performed at home, patients were instructed to reach the same intensity as they did in the supervised training sessions. Additional counselling was tailored to the individual patient's needs and included support by a psychologist, dietician, occupational therapist or social worker including smoking cessation counselling if relevant (Appendix A).

2.4. Measurements

2.4.1. Diagnostic work-up

An incremental symptom-limited CPET was performed, if possible along with arterial blood sampling. Individual CPET results were used to evaluate cardiopulmonary responses to exercise in PPES according to the ATS/ACCP Statement and Wasserman's algorithms, particularly concerning presence of respiratory gas exchange, ventilatory efficiency and abnormal dead-space ventilation. Typical patterns of impaired (i.e. insufficient) cardiopulmonary responses to exercise are shown in Table 1 [48,49]. Evaluation of results was done by 2 independent researchers (GJAMB and MKN). Parameters collected throughout the test include: oxygen uptake (VO2), heart rate (HR), minute ventilation (VE), O2 pulse (VO2/HR), anaerobic threshold (AT, determined using the V-slope method), carbon dioxide production (VCO2), arterial oxygen saturation, ventilatory equivalents for carbon dioxide (VE/VCO2, point measure at AT), dead-space fraction (Vd/Vt), alveolar-arterial gradient (p(A-a)O2). Since maximum voluntary ventilation (MVV) was not directly measured, it was calculated using the following prediction equation (FEV1 × 40) [50]. All parameters were obtained during peak exercise except for AT and VE/VCO2 at AT, reference values from the ATS-ACCP Statement on CPET were used [49].

Table 1
Typical patterns of insufficient cardiopulmonary responses to exercise, useful for determining causes of exercise limitation.

	Cardiovascular impairment[a]	Respiratory impairment[b]	Pulmonary vascular impairment[c]
Peak VO2	Reduced	Reduced	Reduced
Peak HR	Normal/slightly reduced	Reduced	Normal
Peak O2 pulse	Reduced/plateau	Normal	Reduced/plateau
Peak SpO2	Normal/drop	Normal/drop	Drop
VE/MVV	Normal	Increased	Normal
VE/VCO2 at AT	Increased	Increased	Increased
Vd/Vt	Increased	Increased	Increased
P(A-a)O2	Normal/increased	Increased	Increased

Note: adapted from references [48,49,51,52]. Maximum or peak cardiopulmonary responses except for VE/VCO2 at AT.
Abbreviations: CPET, cardiopulmonary exercise testing; VO2, oxygen uptake, pred, predicted; HR, heart rate; O2 pulse, oxygen consumed per heart rate; SpO2, arterial oxygen saturation; VE/MVV, ventilatory reserve; VE/VCO2, ventilatory equivalent for carbon dioxide; AT, anaerobic threshold; Vd/VT, dead-space fraction; p(A-a)O2, alveolar-arterial gradient; V/Q, ventilation/perfusion; Y, yes; CTEPH, chronic thromboembolic pulmonary hypertension.
[a] Cardiovascular impairment refers to left ventricular failure, congestive heart disease and myocardial ischemia.
[b] Respiratory impairment refers to parenchymal disease including obstructive and restrictive lung diseases and lung disease with impaired peripheral oxygenation.
[c] Pulmonary vascular impairment refers to diseases with increased dead-space ventilation.

Pulmonary function testing comprised spirometry, body plethysmography, and single breath carbon monoxide diffusion [53]. Echocardiographic explanations of persistent dyspnea were classified as signs of pulmonary hypertension, signs of diastolic or systolic dysfunction, valvular heart disease, and/or cardiomyopathy. CTPA with iodine perfusion mapping was performed to assess the presence of residual thrombotic lesions and/or persistent perfusion defects on CT scanners with at least 64 slices and a reconstructed slice thickness of 1 to 3 mm.

2.4.2. Rehabilitation program

Training intensity (defined as peak power output in W) was used as a surrogate for measuring the effect of rehabilitation since maximal workload as determined by CPET was not available at discharge. Peak power output was assessed during the first and last training sessions of the rehabilitation program. Questionnaires on self-reported quality of life (PEmb-QoL, PE-specific Quality of Life), fatigue (CIS, Checklist Individual Strength-Fatigue), and anxiety and depression (HADS, Hospital Anxiety and Depression Scale) were completed before start and after completion of the rehabilitation program [54–57]. Two independent researchers (SMJJ and GJAMB) evaluated functional status before and after the rehabilitation program for each participant and assigned a grade on the Post-VTE Functional Status (PVFS) Scale (Appendix B) [58–60]. Subsequently, the degree of improvement or decline was evaluated, both at group and at individual level. Safety issues were closely monitored and reported 1) during a specific training session (i.e. syncope or arrhythmia); or 2) while completing the rehabilitation program (i.e. symptomatic recurrent venous thromboembolism, new cardiopulmonary diagnoses, death). Data on relevant patient demographics, the PE diagnosis, comorbidities, relevant outpatient follow-up details, results of the standardized diagnostic testing and details of the rehabilitation program were extracted from the medical charts by the treating physician.

2.5. Statistical analysis

Baseline characteristics are described as mean with standard deviation (SD), median with interquartile range (IQR), or numbers with proportions if appropriate. Comparison of variables before start and after completing the rehabilitation program was performed using the paired *t*-test or Wilcoxon matched-pairs signed rank test where appropriate. Measures of odds ratio (OR) are reported as point estimates with corresponding 95% confidence intervals (95% CI). All statistical tests were performed using SPSS Statistics software (version 25.0, IBM) and visualisation was conducted using SankeyMATIC (http://sankeymatic.com/build/). Validated minimal clinically important differences (MCIDs) of the individual tests and questionnaires have been used if available to determine relevant outcomes when comparing results before and after completing the rehabilitation program [61,62].

3. Results

3.1. Baseline

The baseline characteristics of 56 patients referred to the 'post-PE syndrome clinic' after adequate anticoagulant treatment are displayed in Table 2, all of whom underwent standardized diagnostic work-up (Fig. 1). Of the total study population, cardiopulmonary responses were evaluated in 45 patients after excluding those with alternative diagnoses (N = 3) and those whom refused to undergo a CPET (N = 8). A total of 27 patients participated in the PE-specific rehabilitation program after the exclusion of 29 patients (CTEPH, N = 10; alternative diagnoses, N = 3; ineligibility to participate, N = 3; or lack of motivation, N = 6). Rehabilitation was performed elsewhere because of patient

Table 2
Baseline characteristics of the patients with Post-PE Syndrome subjected to the standardized diagnostic work-up.

	All PE patients (N = 56)
Age at PE event (years, mean ± SD)	54 (14)
Male sex (N, %)	22 (39%)
BMI (kg/m^2, mean ± SD)	29 (6.3)
Located in main pulmonary artery	14 (25%)
Unprovoked PE (N, %)	29 (52%)
Previous VTE (N, %)	15 (27%)
Pre-existing comorbidity (N, %)	
COPD/asthma	10 (18%)
Diabetes mellitus	3 (5.4%)
Coronary artery disease	2 (3.6%)
Heart failure	2 (3.6%)
Active malignancy	1 (1.8%)
Smoking status (N, %)	
Never	30 (54%)
Quit smoking	19 (34%)
	Pack years (mean ± SD): 16 (11)
Currently smoking	7 (13%)
	Pack years (mean ± SD): 35 (18)
Type of anticoagulant treatment (N, %)	
DOAC	27 (48%)
VKA	26 (46%)
LMWH	2 (3.6%)
Indefinite anticoagulant treatment (N, %)	34 (61%)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant.

preferences in 7 patients.

3.2. Diagnostic work-up

Median time from PE diagnosis till referral was 6.4 months (IQR 4.3–31). A total of 16 of 56 (29%) patients had at least one pre-existing comorbidity, including 10 patients (18%) having COPD/asthma and 3 (5.4%) having diabetes mellitus. After completing standardized diagnostic work-up in the total population, CTEPH was confirmed by right heart catheterization (RHC) in ten patients (18%). Median time between PE and CTEPH diagnosis was 4.5 months (IQR 3.0–11). Echocardiography revealed signs of PH in three other patients, whom had no PH at invasive measurement by RHC, and diastolic dysfunction was observed in two. In addition to CTEPH patients, unresolved thrombi (according to CTPA assessment) and/or persistent perfusion defects (based on V/Q scan) were present in 21 patients (38%), none of whom were treated with PEA or BPA. Of the remaining 25 patients, previously unknown conditions were considered to be the primary etiology of the persistent dyspnea in three (5%) patients: iron deficiency anemia in one and interstitial lung disease in two patients.

3.3. Exercise-induced cardiopulmonary response evaluation

During peak exercise, CPET revealed a median power output of 120 W (IQR 80 to 180) with a mean heart rate of 146/min (SD 24) and a median breathing frequency of 35/min (IQR 31 to 43) (Table 3). Mean peak VO2 was 1683 (SD 785) ml/min and was reduced (<85% of predicted) in 19 of 45 patients (42%). Mean minute ventilation at peak exercise consisted of 71 L/min (SD 27), which is 61% of MVV (SD 0.16). Unresolved thrombi and/or persistent perfusion defects were present in 24 of 45 patients (53%) including 6 with CTEPH. Of 39 non-CTEPH cases, either pulmonary vascular or cardiovascular impairment was observed during incremental exercise in 21 (54%) patients, of whom 11 (52%) had residual vascular occlusions (odds ratio 1.7, 95%CI 0.48 to 6.2). Pulmonary vascular impairment was the exclusive underlying determinant in six (15%) patients and cardiovascular impairment in one (2.6%). All CTEPH patients had either signs of pulmonary vascular or cardiovascular impairment. Parenchymal lung disease was ruled out as

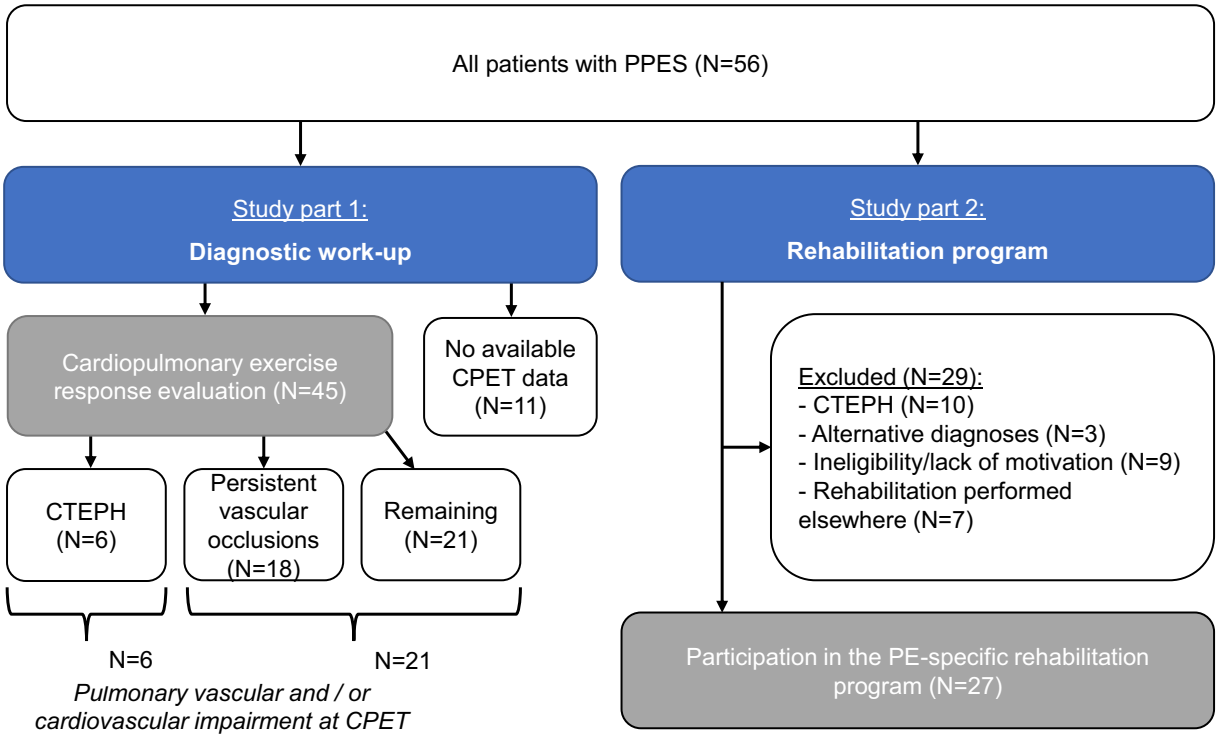


Fig. 1. Flowchart of study patients highlighting both stages of the study: 1) Diagnostic work-up with CTPA and echocardiography was performed in all patients, but CPET allowing cardiopulmonary response evaluation data was only available for 45 patients. The presence/absence of CTEPH and the presence/absence of persistent vascular occlusions are shown, with corresponding CPET findings. 2) The rehabilitation program was completed by 27 patients.
Abbreviations: PPES, Post-PE Syndrome; CPET, cardiopulmonary exercise test; CTEPH, chronic thromboembolic pulmonary hypertension.

Table 3
Cardiopulmonary responses to exercise in PPES patients.

	Peak VO2 (% of pred)	Peak HR (% of pred)	Peak O2 pulse (% of pred)	Peak SpO2[a]	VE / MVV × 100	VE/ VCO2 at AT	Peak Vd/VT	Peak p(A-a)O2 (kPa)	Unresolved thrombi and/or persistent perfusion defects[b]	Interpretation cardiopulmonary response
No. 1	35	68	52	93	47%				Y: CTEPH	Cardiovascular impairment
No. 2	51	88	58	92	45%	46,6			Y: CTEPH	Pulmonary vascular and cardiovascular impairment
No. 3	69	99	70	93	64%	53,2			Y: CTEPH	Pulmonary vascular and cardiovascular impairment
No. 4	65	73	89	94	55%	33,5			Y: CTEPH	Cardiovascular impairment
No. 5	90	98	92	89	54%	38,3	42	6,65	Y: CTEPH	Pulmonary vascular impairment
No. 6	47	91	52	81	63%	52,3			Y: CTEPH	Pulmonary vascular and cardiovascular impairment
No. 7	62	86	72	95	72%				Y	Cardiovascular impairment
No. 8	74	93	80	82	74%	38,1			Y	Pulmonary vascular and cardiovascular impairment
No. 9	115	89	128	99	65%	24,8	14	3,38	Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 10	99	103	96	95	68%	33,8		5,54	Y	Pulmonary vascular impairment
No. 11	129	93	136	95	67%	27			Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 12	93	100	101		94%	48,2	23		Y	Pulmonary vascular impairment (combined with a component interstitial lung disease)
No. 13	78	80	98	99	44%	25,4			Y	Cardiovascular impairment
No. 14	61	62	87	100	46%	38,3			Y	Pulmonary vascular and cardiovascular impairment
No. 15	93	101	92	97	80%	33,5	18	4,22	Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 16	101	103	98	98	73%	29,2			Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 17	101	98	104	99	54%		28	4,1	Y	Pulmonary vascular impairment
No. 18	74		89		48%	28,9	34		Y	Pulmonary vascular and cardiovascular impairment
No. 19	97	99	95	99	72%	26,6			Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 20	79	118	67	97	69%	40,6	34	6,09	Y	Pulmonary vascular and cardiovascular impairment
No. 21	97	109	87	91	85%	32,7			Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 22	101	77	131	99	61%	27,1			Y	No cardiovascular, respiratory or pulmonary vascular impairment
No. 23	96	84	114	96	64%	37	30	5,93	Y	Pulmonary vascular impairment
No. 24	62		82						Y	Cardiovascular impairment
No. 25	117	89	132	97	50%	25,4	15	2,12	–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 26	95	94	101	100	72%	24,8	25		–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 27	119	73	178	99		29,9			–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 28	83	94	74	100		27,8			–	Cardiovascular impairment[c]
No. 29	95	78	121	100	53%	31,7			–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 30	103	79	131	99	62%	29,5	23	3,1	–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 31	85	70	120	100	53%	34,4			–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 32	89	97	91	98	107%	35,4	31	2,79	–	Pulmonary vascular impairment[c] (combined with a component asthma)
No. 33	83	58	143	98	53%	39,4			–	Pulmonary vascular impairment and cardiovascular impairment[c]
No. 34	105	106	99	97	42%	28,7		3,82	–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 35	85	97	89	99	49%	31,1			–	No cardiovascular, respiratory or pulmonary vascular impairment

(*continued on next page*)

Table 3 (*continued*)

	Peak VO2 (% of pred)	Peak HR (% of pred)	Peak O2 pulse (% of pred)	Peak SpO2[a]	VE / MVV × 100	VE/ VCO2 at AT	Peak Vd/VT	Peak p(A-a)O2 (kPa)	Unresolved thrombi and/or persistent perfusion defects[b]	Interpretation cardiopulmonary response
No. 36	74	70	107	96	28%	27,5			–	Cardiovascular impairment[c]
No. 37	88	96	135						–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 38	77	86	90	100	58%	31,5			–	Cardiovascular impairment[c]
No. 39	77	77	100	100	46%	25	6	1,85	–	Cardiovascular impairment[c]
No. 40	81	74	110	100	33%	29,5			–	Cardiovascular impairment[c]
No. 41	104	98	106	98	69%	26,6	17	3,77	–	No cardiovascular, respiratory or pulmonary vascular impairment
No. 42	95	80	118	96	61%	35	19	3,04	–	Pulmonary vascular impairment[c]
No. 43	59	79	74	96	44%	48			–	Pulmonary vascular and cardiovascular impairment[c]
No. 44	93	93	80	92	88%	35,8		5,35	–	Pulmonary vascular and cardiovascular impairment[c]
No. 45	114	91	126	98	57%	23,3	12		–	No cardiovascular, respiratory or pulmonary vascular impairment

Abbreviations: VO2, oxygen uptake, pred, predicted; HR, heart rate; O2 pulse, oxygen consumed per heart rate; SpO2, arterial oxygen saturation; VE/MVV, ventilatory reserve; VE/VCO2, ventilatory equivalent for carbon dioxide; AT, anaerobic threshold; Vd/VT, dead-space fraction; p(A-a)O2, alveolar-arterial gradient; Y, yes; CTEPH, chronic thromboembolic pulmonary hypertension.

[a] Peripheral oxygen saturation is mentioned given lack of arterial blood gases in the majority of patients.

[b] Unresolved thrombi according to CTPA assessment and/or perfusion defects based on V/Q scan.

[c] Patients with insufficient cardiopulmonary responses as determined by CPET despite the absence of objectified persistent vascular occlusions on CTPA and/or V/Q scan.

primary etiology in any of these study patients. Mild respiratory impairment, however, contributed partially in two patients, i.e. asthma and interstitial lung disease (Table 3).

3.4. Rehabilitation program

Our personalized 12-week rehabilitation program was completed by 27 patients, of whom 17 were female (63%) and mean age was 51 years (SD 14). At baseline, PEmb-QoL score was median 15 points (IQR 12 to 17) whereas the median CIS score was above the cut-off value for problematic fatigue (≥76): 93 (IQR 76 to 104) [63]. HADS anxiety and depression scores exceeded the cut-off value of ≥8.0 points in three and four patients, respectively, indicating a possible anxiety or depressive disorder before start of the rehabilitation program. Median score for anxiety was 4.0 points (IQR 2.0 to 7.0), and for depression 6.0 points (IQR 3.0 to 8.0). Supervised training sessions were provided twice a week in 23 participants, and three times a week in 4 participants since full supervision in exercise training was required in these patients. Additional counselling was provided by a social worker in 24 (89%), a dietician in 19 (70%), occupational therapist in 17 (63%), and a psychologist in 15 (56%) patients. Two patients underwent smoking cessation counselling (7.4%), of whom one quitted smoking.

The duration of the rehabilitation program was median 13 weeks (IQR 11 to 16). Peak power output during the first versus the last training session was median 65 W (IQR 40 to 90) versus 75 W (IQR 40 to 135) with a median difference of 20 W (IQR 5.0 to 40; $p = 0.001$). Quality of life was improved after rehabilitation with a median difference of 3.9 points (IQR −6.2 to −1.2; $p < 0.001$) on the PEmb-Qol total score (Table 4). Changes in individual dimensions of the Pemb-QoL questionnaire are displayed in Fig. 2. The burden of fatigue decreased with a median difference of 16 points on the CIS score (−39 to −3.5; $p = 0.003$), reflecting statistically relevant improvement. Lower burden on both anxiety and depression domains of the HADS were reported (median difference 1.0 point, IQR −2.0 to 1.0 for each) with no improvement ($p = 0.19$ and $p = 0.096$), respectively (Table 4).

Moderate or severe functional limitations (PVFS scale grade ≥3) were present in 18 of 27 (67%) patients before rehabilitation, and in 7/27 (26%) at post-rehabilitation assessment, which is reflected by an overall improvement on the PVFS scale ($p < 0.001$; Fig. 3). Fourteen patients (52%) improved one grade on the PVFS scale and four patients (15%) improved two grades. Functional status remained unchanged in 8 patients (30%), whereas the remaining patient had a decline of one

Table 4
Patient-reported outcome measures.

Questionnaire[a]	Available records	Median value before start of the rehabilitation program (IQR)	Median value after completing the rehabilitation program (IQR)	Median of differences (IQR)	p value[b]	MCID
PEmb-QoL (range 0–27 points)	23	15 (12 to 17)	11 (8.7 to 13)	−3.9 (−6.2 to −1.2)	<0.001	15 (61)
CIS (range 20–140 points)	18	93 (76 to 104)	67 (53 to 85)	−16 (−39 to −3.5)	0.003	N.A.
HADS anxiety (range 0–21 points)	19	4.0 (2.0 to 7.0)	4.0 (1.0 to 6.0)	−1.0 (−2.0 to 1.0)	0.189	1.6 (validated in COPD patients) (62)
HADS depression (range 0–21 points)	19	6.0 (3.0 to 8.0)	4.0 (2.0 to 6.0)	−1.0 (−2.0 to 1.0)	0.096	1.6 (validated in COPD patients) (62)

Abbreviations: IQR, interquartile range; MCID, minimal clinically important difference; PEmb-QoL; PE-specific Quality of Life; CIS, Checklist Individual Strength-Fatigue; N.A., not available; HADS, Hospital Anxiety and Depression Scale.

[a] Lower scores indicate better self-reported quality of life (PEmb-QoL), less fatigue (CIS), or a lower burden of anxiety/depression (HADS).

[b] Wilcoxon signed rank test.

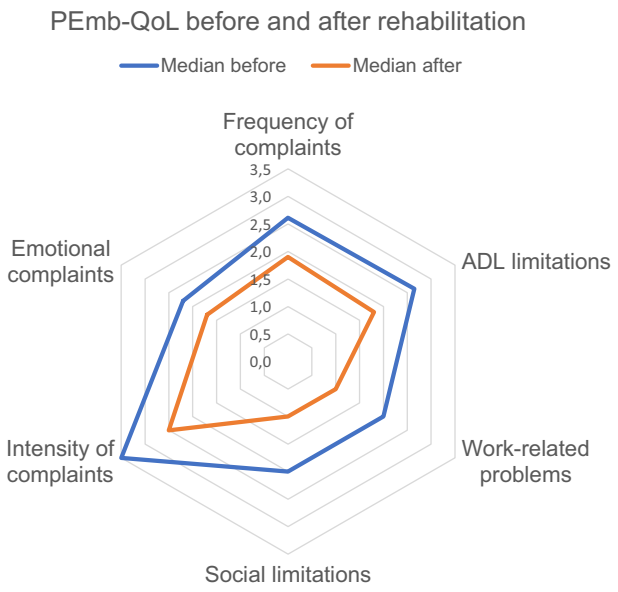


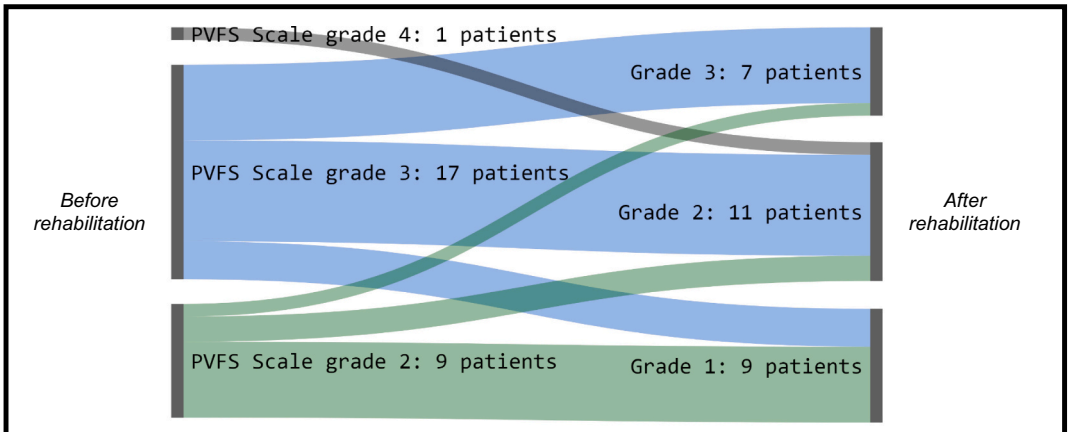
Fig. 2. Radar chart representing the change in all dimensions of the PEmb-Qol questionnaire before and after the rehabilitation program (N = 22); lower scores indicate better quality of life.
Abbreviations: ADL, activities of daily living.

grade (3.7%). Importantly, while closely monitoring safety during the rehabilitation program, no thromboembolic or cardiac complications were observed besides one patient with new-onset atrial fibrillation.

4. Discussion

This study demonstrates that insufficient cardiopulmonary responses to exercise are common among patients who suffer from the PPES, which is not limited to patients with persistent vascular occlusions. Exercise limitation was consistent with pulmonary vascular and/or cardiovascular impairment rather than respiratory impairment in all CTEPH patients, and also in more than half of non-CTEPH cases. A personalized 12-week rehabilitation program in patients with PPES in whom CTEPH and CTEPD suitable for PEA or BPA were ruled out, appeared to improve the training intensity, the PE-specific quality of life as well as the burden of fatigue. Functional status in patients' daily lives improved as well during the rehabilitation program. During the program, one patient was diagnosed with new-onset with atrial fibrillation, no other complications occurred.

Persistent thrombotic obstruction of pulmonary arteries was identified in about half of the non-CTEPH cases. However, increased dead-space ventilation or cardiovascular impairment was not observed in all of these patients. This illustrates the heterogeneous nature of physiological etiologies explaining exertional dyspnea in this patient group. The lack of correlation between reduced exercise capacity and imaging abnormalities in our and previous studies further suggests a multifactorial etiology rather than vascular disease in pulmonary arteries as only physiological determinant of post-PE dyspnea [64]. This study was not designed to identify deconditioning since clear diagnostic criteria are lacking. Therefore, the prevalence of deconditioning may be underestimated, also because alternative reasons for exercise limitation might be predominant. An incremental symptom-limited CPET is the recommended tool to comprehensively evaluate cardiovascular, ventilatory and peripheral metabolism responses in case of exertional dyspnea [51,52]. As such, non-invasive differentiation between mechanisms limiting exercise in PPES can be made [65]. In a Canadian prospective



PVFS scale grade		Description
0	No functional limitations	No symptoms, pain, or anxiety.
1	Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2	Slight functional limitations	Usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3	Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety.
4	Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D	Death	-

Fig. 3. Assignments of the Post-VTE Functional Status (PVFS) scale grades before and after completing the 12-week pulmonary rehabilitation program (N = 27).
Note: The width of lines in the figure are proportional to the flow rate.

cohort study, the majority (87.5%) of patients with an abnormal 12-month CPET after their first episode of PE had deconditioning, 12.5% were classified to have ventilatory impairment and none were considered to have cardiovascular impairment [19,20]. Of note, this was an unselected PE population with relatively low-risk PE patients. A recent observational study including 40 patients with PPES revealed increased dead-space ventilation and/or decreased stroke volume reserve in up to 65% after 90 days of anticoagulant therapy [66]. Importantly, given the absence of unambiguous clinical algorithms for interpreting cardiopulmonary responses to exercise, some phenotypes of exercise intolerance overlap. As such, CPET mainly functions as a first means of identifying patterns rather than making a clear distinction between different causes. Taking into account our results, we argue that rehabilitation is a safe and promising approach that is mainly valuable in a population of adequately selected PE patients suffering from persistent dyspnea. This is fueled by a recent randomized trial in which an 8-week home-based exercise program was initiated shortly after acute PE regardless of symptoms or pre-existing physical fitness [31]. Although this physiotherapist-guided program proved to be safe, the predefined criteria for efficacy have not been met. A currently ongoing randomized study evaluates whether a rehabilitation program improves exercise capacity in PPES patients (NCT03405480). Speculating, exercise training might also contribute to functional improvements in PPES patients treated with surgical, angioplasty or PH targeted therapy. Further randomized studies are needed to define criteria for adequate selection of particular PE patients who will likely benefit most from a rehabilitation program.

Strengths of our study include the standardized diagnostic work-up in all patients including pulmonary perfusion imaging, CPET and echocardiography in all patients, as well as the application of a state-of-the art supervised rehabilitation program [42]. Limitations include its relatively small sample size, the single-center design and the likely selection bias leading to an enriched CTEPH prevalence in the study population due to referral from elsewhere to our unique 'post-PE syndrome clinic'. Therefore, the proportion of CTEPH versus CTEPD is probably not representative. Moreover, since pulmonary angiography was performed in case of suspected CTEPH only, i.e. in those patients with intermediate or high probability of CTEPH based on echocardiography, we cannot state with complete certainty that none of the other patients with persistent perfusion defects actually had CTEPH. Also, the observational nature of our study without a control group hinders to reliably quantify the full effect of a rehabilitation program compared to standard recovery. Interestingly, most study patients also received other types of allied healthcare, which may have contributed to an improvement in the functional status, a better quality of life and reduction in fatigue. However, previous prospective studies have shown limited improvement in the natural course of acute PE, especially when no rehabilitation program is offered. For example, a recent German cohort study following 620 PE patients showed that quality of life using the PEmb-QoL score improved between 3- and 12-month follow-up, but the MCID of 15 points was only attained in 118 patients (19%) [67]. Of note, this MCID was obtained in a small selected cohort of 82 patients, which may have limited its generalizability [61]. Lastly, limitations of the pre-post study design are known and includes the lack of clear causality of the intervention on the observed changes, also due to unexpected temporal changes, regression to the mean, testing threat, and non-specific effects of the intervention.

In summary, insufficient cardiopulmonary responses to exercise seem to play an important role in the etiology of exertional dyspnea and functional limitations after acute PE, and were independent of persistent perfusion defects in the studied cohort. Our data suggest that offering a personalized pulmonary rehabilitation program to patients with PPES not otherwise treated is safe and promising given the observed improvement in patient-relevant outcomes. Randomized studies are nonetheless required to validate our findings and to further determine which PPES patients benefit most from rehabilitation.

Prior abstract publication/presentation

Boon GJAM, Janssen SMJ, Bogaard HJ, Kroft LJM, Meijboom LJ, Ninaber MK, Nossent EJ, Symersky P, Vliegen HW, Vonk Noordegraaf A, Huisman MV, Abbink JJ, Klok FA. Results of a Dedicated Diagnostic Work-up of Patients with Post-PE Syndrome [abstract]. *Res Pract Thromb Haemost.* 2020; 4 (Suppl 1). https://abstracts.isth.org/abstract/results-of-a-dedicated-diagnostic-work-up-of-patients-with-post-pe-syndrome/. Accessed November 11, 2020.

CRediT authorship contribution statement

GJAMB and FAK were responsible for design of the study, data collection, analysis and interpretation as well as drafting of the manuscript. Both guarantor of the paper.

SMJJ, JJA were responsible for design of the study, data collection, and critically revised the manuscript for important intellectual content.

HJB, MKN, MAS and AVN were responsible for design of the study, data analysis and interpretation and critically revised the manuscript for important intellectual content.

SB, WG, LJMK, LJM, EJN, PS, HWV, MVH and BS were responsible for data analysis and interpretation and critically revised the manuscript for important intellectual content.

Declaration of competing interest

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SMJJ, SB, HJB, WG, LJMK, LJM, MKN, EJN, PS, HWV, AVN, BS, JJA have nothing to disclose.

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Appendix A. Supplementary data

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References

[1] A.K. Sista, L.E. Miller, S.R. Kahn, J.A. Kline, Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis, Vasc. Med. 22 (1) (2017) 37–43.

[2] F.A. Klok, S. Barco, Follow-up after acute pulmonary embolism, Hamostaseologie 38 (1) (2018) 22–32.

[3] M. Delcroix, A. Torbicki, D. Gopalan, O. Sitbon, F.A. Klok, I. Lang, et al., ERS statement on chronic thromboembolic pulmonary hypertension, Eur. Respir. J. 57 (6) (2021).

[4] G.J.A.M. Boon, H.J. Bogaard, F.A. Klok, Essential aspects of the follow-up after acute pulmonary embolism: an illustrated review, Res. Pract. Thromb. Haemost. 4 (6) (2020) 958–968.
[5] F.A. Klok, K.W. van Kralingen, A.P. van Dijk, F.H. Heyning, H.W. Vliegen, M. V. Huisman, Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism, Respir. Med. 104 (11) (2010) 1744–1749.
[6] M.V. Huisman, S. Barco, S.C. Cannegieter, G. Le Gal, S.V. Konstantinides, P. H. Reitsma, et al., Pulmonary embolism, Nat. Rev. Dis. Primers. 4 (2018) 18028.
[7] F.A. Klok, T. van der Hulle, P.L. den Exter, M. Lankeit, M.V. Huisman, S. Konstantinides, The post-PE syndrome: a new concept for chronic complications of pulmonary embolism, Blood Rev. 28 (6) (2014) 221–226.
[8] A.K. Sista, F.A. Klok, Late outcomes of pulmonary embolism: the post-PE syndrome, Thromb. Res. 164 (2018) 157–162.
[9] M. Tavoly, H.S. Wik, P.A. Sirnes, L.P. Jelsness-Jorgensen, J.P. Ghanima, F.A. Klok, et al., The impact of post-pulmonary embolism syndrome and its possible determinants, Thromb. Res. 171 (2018) 84–91.
[10] T. Fernandes, B. Planquette, O. Sanchez, T. Morris, From acute to chronic thromboembolic disease, Ann. Am. Thorac. Soc. 13 (Suppl 3) (2016) S207–S214.
[11] G.J.A.M. Boon, M.V. Huisman, F.A. Klok, Determinants and management of the post-pulmonary embolism syndrome, Semin. Respir. Crit. Care Med. 42 (2) (2021) 299–307.
[12] Y.M. Ende-Verhaar, S.C. Cannegieter, A. Vonk Noordegraaf, M. Delcroix, P. Pruszczyk, A.T. Mairuhu, et al., Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature, Eur. Respir. J. 49 (2) (2017) 1601792.
[13] S.C. Pugliese, S.M. Kawut, The post-pulmonary embolism syndrome: real or Ruse? Annals of the American Thoracic Society. 16 (7) (2019) 811–814.
[14] F.A. Klok, M. Delcroix, H.J. Bogaard, Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism, J. Thromb. Haemost. 16 (6) (2018) 1040–1051.
[15] M. Held, P. Kolb, M. Grun, B. Jany, G. Hubner, A. Grgic, et al., Functional characterization of patients with chronic thromboembolic disease, Respiration 91 (6) (2016) 503–509.
[16] M. Claeys, G. Claessen, A. La Gerche, T. Petit, C. Belge, B. Meyns, et al., Impaired cardiac reserve and abnormal vascular load limit exercise capacity in chronic thromboembolic disease, J. Am. Coll. Cardiol. Img. 12 (8 Pt 1) (2019) 1444–1456.
[17] B.G. Stevinson, J. Hernandez-Nino, G. Rose, J.A. Kline, Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients, Eur. Heart J. 28 (20) (2007) 2517–2524.
[18] J.A. Kline, M.T. Steuerwald, M.R. Marchick, J. Hernandez-Nino, G.A. Rose, Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure, Chest 136 (5) (2009) 1202–1210.
[19] S.R. Kahn, A. Akaberi, J.T. Granton, D.R. Anderson, P.S. Wells, M.A. Rodger, et al., Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study, Am. J. Med. 130 (8) (2017) 990.
[20] S.R. Kahn, A.M. Hirsch, A. Akaberi, P. Hernandez, D.R. Anderson, P.S. Wells, et al., Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study, Chest 151 (5) (2017) 1058–1068.
[21] R. Hunter, S. Noble, S. Lewis, P. Bennett, Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community, BMJ Open 9 (2) (2019), e024805.
[22] I. Kirchberger, S. Ruile, J. Linseisen, S. Haberl, C. Meisinger, T.M. Berghaus, The lived experience with pulmonary embolism: a qualitative study using focus groups, Respir. Med. 167 (2020), 105978.
[23] F.A. Klok, F. Couturaud, M. Delcroix, M. Humbert, Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism, Eur. Respir. J. 55 (2020) 2000189.
[24] F.A. Klok, K.W. van Kralingen, A.P. van Dijk, F.H. Heyning, H.W. Vliegen, A. A. Kaptein, et al., Quality of life in long-term survivors of acute pulmonary embolism, Chest 138 (6) (2010) 1432–1440.
[25] N. Galie, M. Humbert, J.L. Vachiery, S. Gibbs, I. Lang, A. Torbicki, et al., 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the european Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur. Heart J. 37 (1) (2016) 67–119.
[26] T. Inami, M. Kataoka, H. Kikuchi, A. Goda, T. Satoh, Balloon pulmonary angioplasty for symptomatic chronic thromboembolic disease without pulmonary hypertension at rest, Int. J. Cardiol. 289 (2019) 116–118.
[27] C.B. Wiedenroth, K.M. Olsson, S. Guth, A. Breithecker, M. Haas, J.C. Kamp, et al., Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic disease, Pulm. Circ. 8 (1) (2018) 1–6.
[28] S. Olgun Yildizeli, A. Kepez, S. Tas, M. Yanartas, A.F. Durusoy, A. Erkilinc, et al., Pulmonary endarterectomy for patients with chronic thromboembolic disease, Anatol. J. Cardiol. 19 (4) (2018) 273–278.
[29] D. Taboada, J. Pepke-Zaba, D.P. Jenkins, M. Berman, C.M. Treacy, J.E. Cannon, et al., Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease, Eur. Respir. J. 44 (6) (2014) 1635–1645.
[30] R.S. Cires-Drouet, M. Mayorga-Carlin, S. Toursavadkohi, R. White, E. Redding, F. Durham, et al., Safety of exercise therapy after acute pulmonary embolism, Phlebology 35 (10) (2020) 832–842.
[31] N. Rolving, B.C. Brocki, J.R. Bloch-Nielsen, T.B. Larsen, F.L. Jensen, H. R. Mikkelsen, et al., Effect of a physiotherapist-guided home-based exercise intervention on physical capacity and patient-reported outcomes among patients with acute pulmonary embolism: a randomized clinical trial, JAMA Netw. Open 3 (2) (2020), e200064.
[32] S. Nopp, F.A. Klok, F. Moik, M. Petrovic, I. Derka, C. Ay, et al., Outpatient pulmonary rehabilitation in patients with persisting symptoms after pulmonary embolism, J. Clin. Med. 9 (6) (2020).
[33] M. Amoury, F. Noack, K. Kleeberg, D. Stoevesandt, B. Lehnigk, S. Bethge, et al., Prognosis of patients with pulmonary embolism after rehabilitation, Vasc. Health Risk Manag. 14 (2018) 183–187.
[34] F. Noack, B. Schmidt, M. Amoury, D. Stoevesandt, S. Gielen, B. Pflaumbaum, et al., Feasibility and safety of rehabilitation after venous thromboembolism, Vasc. Health Risk Manag. 11 (2015) 397–401.
[35] S.G. Lakoski, P.D. Savage, A.M. Berkman, L. Penalosa, A. Crocker, P.A. Ades, et al., The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial, . Thromb. Haemost. 13 (7) (2015) 1238–1244.
[36] C. Nagel, M. Nasereddin, N. Benjamin, B. Egenlauf, S. Harutyunova, C. A. Eichstaedt, et al., Supervised exercise training in patients with chronic thromboembolic pulmonary hypertension as early follow-up treatment after pulmonary endarterectomy: a prospective cohort study, Respiration 99 (7) (2020) 577–588.
[37] E. Grunig, C. Eichstaedt, J.A. Barbera, N. Benjamin, I. Blanco, E. Bossone, et al., ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension, Eur. Respir. J. 53 (2) (2019) 1800332.
[38] T. Koudstaal, M. Wapenaar, D. van Ranst, R. Beesems, L. van den Toorn, A. van den Bosch, et al., The effects of a 10-wk outpatient pulmonary rehabilitation program on exercise performance, muscle strength, soluble biomarkers, and quality of life in patients with pulmonary hypertension, J. Cardiopulm. Rehabil. Prev. 39 (6) (2019) 397–402.
[39] N.R. Morris, F.D. Kermeen, A.E. Holland, Exercise-based rehabilitation programmes for pulmonary hypertension, Cochrane Database Syst. Rev. (1) (2017), CD011285.
[40] N. Ehlken, M. Lichtblau, H. Klose, J. Weidenhammer, C. Fischer, R. Nechwatal, et al., Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial, Eur. Heart J. 37 (1) (2016) 35–44.
[41] Task Force Members, G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, et al., 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology, Eur. Heart J. 34 (38) (2013) 2949–3003.
[42] M.A. Spruit, S.J. Singh, C. Garvey, R. ZuWallack, L. Nici, C. Rochester, et al., An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation, Am. J. Respir. Crit. Care Med. 188 (8) (2013) e13–e64.
[43] M.V. Huisman, F.A. Klok, How I diagnose acute pulmonary embolism, Blood 121 (22) (2013) 4443–4448.
[44] M.V. Huisman, F.A. Klok, Diagnostic management of clinically suspected acute pulmonary embolism, J. Thromb. Haemost. 7 (Suppl 1) (2009) 312–317.
[45] M.V. Huisman, F.A. Klok, Diagnostic management of acute deep vein thrombosis and pulmonary embolism, J. Thromb. Haemost. 11 (3) (2013) 412–422.
[46] N. Galie, M. Humbert, J.L. Vachiery, S. Gibbs, I. Lang, A. Torbicki, et al., 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension, Eur. Heart J. 69 (2) (2016) 177.
[47] American College of Sports Medicine, D. Riebe, J.K. Ehrman, G. Liguori, M. Magal, ACSM's Guidelines for Exercise Testing and Prescription, LWW, 2018.
[48] K. Wasserman, Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, 5th ed., Wolters Kluwer Health/ Lippincott Williams & Wilkins, Philadelphia, 2012.
[49] American Thoracic Society, American College of Chest Physicians, ATS/ACCP Statement on cardiopulmonary exercise testing, Am. J. Respir. Crit. Care Med. 167 (2) (2003) 211–277.
[50] S.C. Campbell, A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation, J. Occup. Med. 24 (7) (1982) 531–533.
[51] T. Radtke, S. Crook, G. Kaltsakas, Z. Louvaris, D. Berton, D.S. Urquhart, et al., ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases, Eur. Respir. Rev. 28 (154) (2019) 180101.
[52] A.H. Herdy, L.E. Ritt, R. Stein, C.G. Araujo, M. Milani, R.S. Meneghelo, et al., Cardiopulmonary exercise test: background, applicability and interpretation, Arq. Bras. Cardiol. 107 (5) (2016) 467–481.
[53] B.L. Graham, V. Brusasco, F. Burgos, B.G. Cooper, R. Jensen, A. Kendrick, et al., 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung, Eur. Respir. J. 49 (1) (2017) 1600016.
[54] D.M. Cohn, E.A. Nelis, L.A. Busweiler, A.A. Kaptein, S. Middeldorp, Quality of life after pulmonary embolism: the development of the PEmb-QoL questionnaire, J. Thromb. Haemost. 7 (6) (2009) 1044–1046.
[55] F.A. Klok, D.M. Cohn, S. Middeldorp, M. Scharloo, H.R. Buller, K.W. van Kralingen, et al., Quality of life after pulmonary embolism: validation of the PEmb-QoL questionnaire, J. Thromb. Haemost. 8 (3) (2010) 523–532.
[56] J.H. Vercoulen, C.M. Swanink, J.F. Fennis, J.M. Galama, J.W. van der Meer, G. Bleijenberg, Dimensional assessment of chronic fatigue syndrome, J. Psychosom. Res. 38 (5) (1994) 383–392.

[57] R.P. Snaith, The hospital anxiety and depression scale, Health Qual. Life Outcomes 1 (2003) 29.
[58] F.A. Klok, S. Barco, B. Siegerink, Measuring functional limitations after venous thromboembolism: a call to action, Thromb. Res. 178 (2019) 59–62.
[59] G.J.A.M. Boon, S. Barco, L. Bertoletti, W. Ghanima, M.V. Huisman, S.R. Kahn, et al., Measuring functional limitations after venous thromboembolism: optimization of the post-VTE functional status (PVFS) scale, Thromb. Res. 190 (2020) 45–51.
[60] F.V.C. Machado, R. Meys, J.M. Delbressine, A.W. Vaes, Y.M.J. Goërtz, M. van Herck, et al., Construct validity of the post-COVID-19 functional status scale in adult subjects with COVID-19, Health Qual. Life Outcomes 19 (1) (2021) 40.
[61] A. Akaberi, F.A. Klok, D.M. Cohn, A. Hirsch, J. Granton, S.R. Kahn, Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life, J. Thromb. Haemost. 16 (12) (2018) 2454–2461.
[62] M.A. Puhan, M. Frey, S. Büchi, H.J. Schünemann, The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease, Health Qual. Life Outcomes 6 (1) (2008) 46.
[63] J. De Vries, H.J. Michielsen, G.L. Van Heck, Assessment of fatigue among working people: a comparison of six questionnaires, Occup. Environ. Med. 60 (Suppl 1) (2003), i10-5.
[64] M.S. Albaghdadi, D.M. Dudzinski, N. Giordano, C. Kabrhel, B. Ghoshhajra, M. R. Jaff, et al., Cardiopulmonary exercise testing in patients following massive and submassive pulmonary embolism, J. Am. Heart Assoc. 7 (5) (2018) e006841.
[65] M. Guazzi, V. Adams, V. Conraads, M. Halle, A. Mezzani, L. Vanhees, et al., EACPR/AHA scientific statement. clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations, Circulation 126 (18) (2012) 2261–2274.
[66] T.M. Fernandes, M. Alotaibi, D.M. Strozza, W.W. Stringer, J. Porszasz, G. G. Faulkner, et al., Dyspnea postpulmonary embolism from physiological dead space proportion and stroke volume defects during exercise, Chest 157 (4) (2020) 936–944.
[67] L. Valerio, S. Barco, M. Jankowski, S. Rosenkranz, M. Lankeit, M. Held, et al., Quality of life three and twelve months after acute pulmonary embolism: analysis from a prospective multicenter cohort study, Chest 159 (6) (2021) 2428–2438.