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Supervised Exercise Training in Patients with Chronic Thromboembolic Pulmonary Hypertension as Early Follow-Up Treatment after Pulmonary Endarterectomy: A Prospective Cohort Study

Christian Nagel[a–c] Mohammed Nasereddin[a, c] Nicola Benjamin[a, c] Benjamin Egenlauf[a, c] Satenik Harutyunova[a, c] Christina A. Eichstaedt[a, c, d] Panagiota Xanthouli[a, c] Eckhard Mayer[e] Ekkehard Grünig[a, c] Stefan Guth[e]

[a]Centre for Pulmonary Hypertension, Thoraxklinik Heidelberg gGmbH, Heidelberg University Hospital, Heidelberg, Germany; [b]Department for Respiratory Care Medicine and Thoracic Surgery, Klinikum Mittelbaden, Baden-Baden Balg, Baden-Baden, Germany; [c]Translational Lung Research Centre Heidelberg (TLRC), Member of the German Centre for Lung Research (DZL), Heidelberg, Germany; [d]Laboratory for Molecular Genetic Diagnostics, Institute of Human Genetics, Heidelberg University, Heidelberg, Germany; [e]Department of Thoracic Surgery, Kerckhoff Clinic, Bad Nauheim, Germany

Keywords
Chronic thromboembolic pulmonary hypertension · Exercise training · Pulmonary hypertension · Rehabilitation · Haemodynamics · Pulmonary endarterectomy

Abstract
Background: Data on exercise training in chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary endarterectomy (PEA) as well as data on clinical and haemodynamic changes shortly after PEA are lacking. ***Objective:*** The objective of this prospective study was to analyse the safety, feasibility, and the effectiveness of combined supervised inpatient rehabilitation in patients with CTEPH directly after PEA. ***Methods:*** CTEPH patients started a 19-week rehabilitation program (3 weeks as inpatients and continued at home for another 16 weeks) with supervised exercise training as follow-up treatment shortly after PEA. Haemodynamics were assessed by right heart catheterisation before PEA and 22 weeks after PEA. Non-invasive assessments as transthoracic echocardiography and 6-min walking distance (6MWD) were performed before PEA and after 3 (that is, beginning of rehabilitation), 6, and 22 weeks following PEA. Adverse events were recorded throughout the study. ***Results:*** Forty-five CTEPH patients were included (49% female, 57.6 ± 12.4 years old, 60% WHO functional class III). Rehabilitation was started 3.3 ± 0.9 weeks after PEA. Exercise training was well tolerated in all patients without severe side effects. Haemodynamics measured by right heart catheterisation significantly improved from pre-PEA to 22 weeks post-PEA in cardiac output (+1.2 ± 1.5 L/min, 33.4%, $p = 0.001$) and mean pulmonary arterial pressure (–19 ± 13 mm Hg, –39.6%, $p < 0.0001$). Right heart size measured by echocardiography, 6MWD, quality of life, and oxygen saturation significantly improved not only within the first 3 weeks after PEA but also during the following 19 weeks of exercise training. ***Conclusions:*** Supervised exercise training was feasible as early follow-up treatment after PEA. Further controlled studies are needed to discriminate the effects of PEA and early follow-up rehabilitation. ***Trial Registration:*** The study was regis-

karger@karger.com
www.karger.com/res

Christian Nagel
Centre for Pulmonary Hypertension
Thoraxklinik Heidelberg University Hospital
Röntgenstrasse 1, DE–69126 Heidelberg (Germany)
nagelchr@gmx.net

tered at clinicaltrials.gov (NCT01393327) on July 13, 2011. The study start date was January 2010, and completion date was December 2013.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of acute pulmonary embolism. According to current knowledge, it is caused by non-resolving fibrothrombotic obstructions of large pulmonary arteries. Some patients show an additional small vessel vasculopathy. Both kinds of obstruction lead to an increase in pulmonary vascular resistance (PVR), increase in mean pulmonary arterial pressure (mPAP), progressive right heart failure, and premature death if left untreated [1]. Current guidelines recommend pulmonary endarterectomy (PEA) as the potentially curative treatment of first choice [2], which aims to remove fibrotic obstructions from the pulmonary vasculature.

The survival of patients undergoing PEA surgery ranges between 76 and 91% after 3 years [3–7], which is superior to medical treatment in inoperable CTEPH patients [1]. The majority of operated patients experience almost complete normalisation of haemodynamics and improvements in symptoms [5–7]. However, 17–51% of operated patients will develop persistent or recurrent pulmonary hypertension (PH) [8]. Some patients remain limited in their exercise capacity and prognosis [9]. As patients are monitored on an intensive care unit immediately after PEA, immobilisation after the operation may lead to further peripheral deconditioning.

A recent study of 251 CTEPH patients with follow-up until 12 months after PEA showed a persistent exercise limitation in almost 40% of patients despite normalisation of PVR and haemodynamics [10]. This limitation was characterised by a multifactorial aetiology also involving respiratory function abnormalities.

Previous studies in patients with inoperable or persistent CTEPH have suggested beneficial effects of exercise training as an add-on to targeted medical therapy, increasing exercise capacity, and quality of life (QoL) [11, 12]. However, it is not known, whether early rehabilitation with exercise treatment is safe, feasible, and may further improve exercise capacity after PEA. Prospective studies on exercise training for CTEPH patients shortly after PEA surgery are lacking. Furthermore, to the best of our knowledge, there have been no studies yet describing the early effect within the first weeks after PEA.

The aim of this study was therefore to assess the feasibility of supervised exercise training in CTEPH patients shortly after PEA. Furthermore, changes of haemodynamic and clinical parameters including oxygen uptake, QoL, exercise capacity, and right heart function assessed by echocardiography and right heart catheterisation were obtained before and shortly after PEA.

Methods

Study Population and Design

Patients with CTEPH who had undergone PEA in the department of thoracic surgery in the Kerckhoff Clinic Bad Nauheim, Germany [13], from January 2010 until January 2012 were transferred and prospectively and consecutively assigned to an in-hospital start of an early rehabilitation program in the rehabilitation clinic Koenigstuhl Heidelberg, Germany. Patients were clinically examined before PEA, including right heart catheterisation at the Kerckhoff Clinic. The further clinical assessments at the beginning of rehabilitation (3 weeks after PEA) and after 3 (6 weeks after PEA) and 19 weeks (22 weeks after PEA) were performed at the Centre for Pulmonary Hypertension at the Thoraxklinik Heidelberg, Germany.

Our study was initially planned as a randomised controlled trial of early follow-up exercise training after PEA with peak oxygen consumption as the primary endpoint. Due to organisational reasons, a separation of patients in the intervention and control group was not possible, which led to patients of both groups being in the rehabilitation clinic at the same time. As patients in the control group started exercising on their own and were in close contact with patients of the intervention group, a proper implementation of the control group was not possible. Therefore, we performed a prospective trial with all patients eligible and willing to participate as an interventional cohort study without a control group to describe the invasively and non-invasively measured changes shortly after PEA, and to demonstrate the feasibility of an early follow-up training program initiated shortly after PEA and clinical presentation of patients shortly after PEA.

PEA and Assessments in Kerckhoff Clinic, Bad Nauheim

Before PEA, right atrial (RA) and right ventricular (RV) areas and tricuspid annular plane systolic excursion (TAPSE) were assessed by 2-dimensional echocardiography. Six-minute walking distance (6MWD), N-terminal pro-brain-type natriuretic peptide (NT-proBNP), and right heart catheterisation were performed according to current guidelines [14] and as previously described [11, 12]. Due to a severely impaired exercise capacity, patients did not routinely perform cardiopulmonary exercise testing before PEA.

Right heart catheterisation in Bad Nauheim and Heidelberg was performed according to current recommendations in a supine position using the transjugular access with an 8-F introducer set (MXI100, MEDEX, Smiths Group, UK) [14]. Catheterisation was performed with triple-lumen 7F-Swan-Ganz thermodilution catheters (ref. 131F7, Edwards Lifesciences LLC, Irvine, CA, USA). The

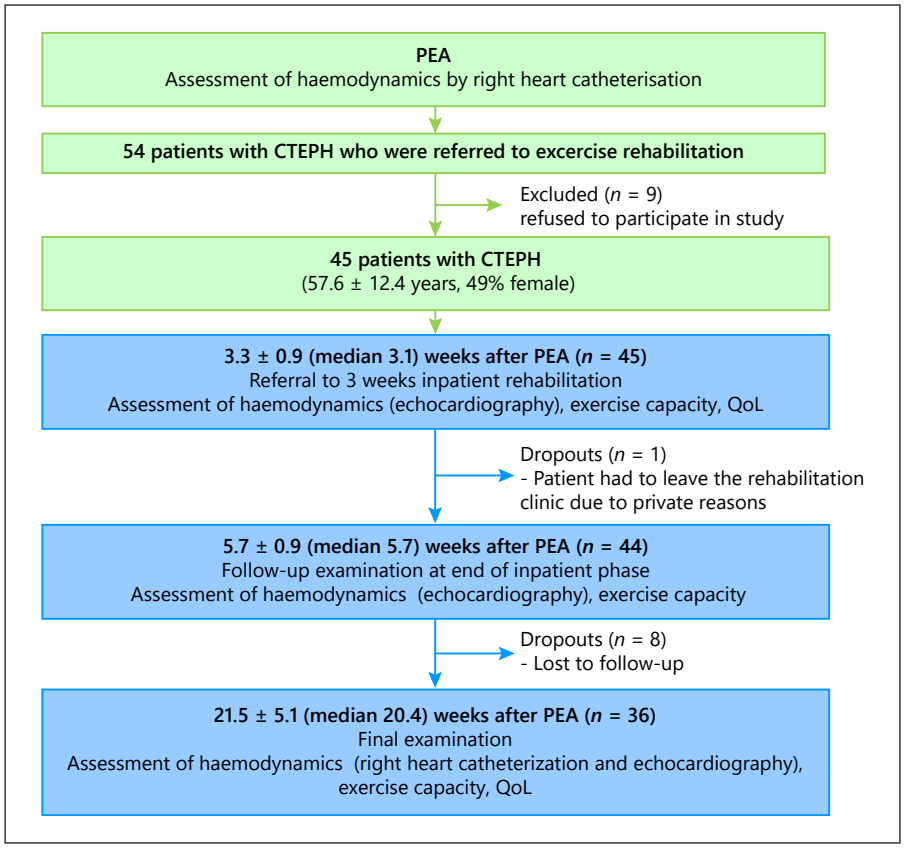

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Fig. 1. Study flow chart showing the study timeline with number of assigned patients, the number of patients valid for analysis, and the number and reasons for exclusion, respectively (original data).

zero reference point for pressure recordings was set at the level of the right atrium in the mid-axillary line (phlebostatic axis). Pulmonary vascular pressures were averaged throughout 3 respiratory cycles. Cardiac output (CO) was measured at least in triplicate by thermodilution with a variation of <10% between the measured values. All examinations and measurements were performed by the same experienced team.

PEA was performed as previously described [13]. Briefly, after sternotomy, cardiopulmonary bypass was established, and circulatory arrest in deep hypothermia ≤20 °C was induced to allow good visibility in the pulmonary arteries. True endarterectomy, including the intima layer and parts of the media, was conducted with the aim of removing all obstructive material from the pulmonary arteries. In selected patients, additional surgical procedures (e.g., coronary artery bypass graft surgery or valve replacement) were performed [13].

Rehabilitation Program with Exercise Training and Assessments in Heidelberg

The exercise and respiratory training was carried out as described before [15] and commenced in the hospital for 3 weeks in the Rehabilitation Clinic Koenigstuhl in Heidelberg. CTEPH patients performed a minimum of 1.5 h/day of exercise training (in intervals distributed over the day), consisting of daily interval cycle ergometer training, walking, dumbbell training of single muscle groups using low weights (0.5–1 kg), and respiratory training at 5 days/week. Besides physical training, patients received mental training to improve perception of their individual physical abilities and limitations. Psychological support was offered to all participants. The training program was closely supervised by physiotherapists and physicians specialised in rehabilitation medicine and by PH experts, as described before [15]. Oxygen saturation and heart rate were monitored continuously throughout the training and were used to adjust the training intensity. At discharge from the rehabilitation clinic after 3 weeks, patients received an individualised training manual and ordered a cycle ergometer for use at home. The training was continued at home with at least 15 min/day at 5 days a week for the following 19 weeks.

Outcome Measures

Clinical assessments included medical history, demographics, concomitant medication, physical examination, World Health Organization (WHO) functional class, vital signs, 12-lead electrocardiogram, 6MWD including Borg dyspnea score, 2-dimensional echocardiography at rest, clinical laboratory including pregnancy test, lung function test with blood gas analysis, and monitoring of adverse events. QoL was assessed by the SF-36 questionnaire at baseline and 19 weeks after the beginning of rehabilitation. Cardiopulmonary exercise testing was performed as described before [15] using upright cycling on a stationary, semi-recumbent cycle ergometer. A level protocol starting at 25 W with an increase of 25 W every other minute was performed up to the patients' maximum tolerance. The 2nd right heart catheterisation was performed in Heidelberg 22 weeks after PEA as described above. Adverse events

Table 1. Demographics and clinical characteristics of the patients (n = 45)

	Mean ± SD or n (%)	95% CI of the mean	Median (IQR)	n	Mean ± SD or n (%)	95% CI of the mean	Median (IQR)	n
Time interval PEA to baseline (start of rehabilitation), weeks	3.26±0.89	2.98–3.53	3.14 (1.29)					
Time interval PEA to visit 2 (end of inpatient rehabilitation), weeks	5.74±0.89	5.48–6.01	5.71 (1.29)	44				
Time interval PEA to visit 3 (final examination), weeks	21.50±5.05	19.80–23.21	20.36 (3.14)	36				
Age, years	57.62±12.44	53.89–61.36	59 (21)					
Height, cm	171.82±9.83	168.87–174.78	172 (12.5)					
Weight, kg	78.36±16.66	73.35–83.36	76 (23)					
BMI	26.52±5.13	24.97–28.06	25.2 (5.25)					
Female, %	22 (48.90)							
	Pre-PEA				3 weeks after PEA at the beginning of rehabilitation			
	Mean ± SD or n (%)	95% CI of the mean	Median (IQR)	n	Mean ± SD or n (%)	95% CI of the mean	Median (IQR)	n
Right heart catheterisation								
RA pressure, mm Hg	10.48±6.20	7.92–13.04	9 (7.5)	25				
Systolic pulmonary arterial pressure, mm Hg	73.56±15.68	68.25–78.86	77 (23.5)	36				
Diastolic pulmonary arterial pressure, mm Hg	28.12±9.06	24.95–31.28	26 (11.75)	34				
Mean pulmonary arterial pressure, mm Hg	45.10±11.66	41.46–48.73	44 (15.5)	42				
CO, L/min	4.45±0.97	4.11–4.80	4.6 (1.59)	33				
Cardiac index, L/min/m²	2.28±0.51	2.10–2.46	2.3 (0.69)	33				
Pulmonary arterial wedge pressure, mm Hg	10.67±4.89	9.01–12.32	10.5 (5.75)	36				
Pulmonary vascular resistance, WU	8.54±3.63	7.36–9.72	8.11 (5.55)	39				
Pulmonary arterial compliance, mL/mm Hg	1.53±0.68	1.24–1.83	1.24 (0.78)	23				
Total pulmonary resistance, mm Hg/L/min	10.83±4.50	9.24–12.43	10 (5.45)	33				
Transthoracic echocardiography								
RA area, cm²	28.04±12.06	22.83–33.26	25 (17)	23	17.57±4.00	16.36–18.79	17.5 (5.75)	44
RV area, cm²	42.86±9.30	38.74–46.99	43 (8.5)	22	21.64±5.17	20.06–23.21	21.5 (8.75)	44
TAPSE, cm	1.49±0.30	1.34–1.63	1.5 (0.45)	20	1.48±0.27	1.40–1.57	1.5 (0.4)	
Left ventricular eccentricity index					1.12±0.13	1.08–1.16	1.1 (0.2)	
Pulmonary artery diameter, mm					24.13±5.52	22.39–25.87	25 (4)	41
Tissue Doppler imaging s RV free wall, cm/s					8.97±1.82	8.37–9.57	9 (2)	38
Systolic pulmonary arterial pressure at rest, mm Hg					34.36±15.10	29.82–38.89	30 (17.5)	
Laboratory								
NT-proBNP, ng/L	1,557.10±2,308.71	1,557.10±2,308.71	975 (1348.5)	21	1,190.09±1,415.06	764.96–1615.22	786 (863.5)	
WHO FC number, %								
II	10 (22.2)				18 (40.0)			
III	35 (77.8)				27 (60.0)			
6MWD, m	371.95±97.95	339.29–404.60	371 (137)		428.29±111.74	394.72–461.86	440 (145)	
Cardiopulmonary exercise test with stress echocardiography								
HR at rest, beats/min					88.62±12.02	85.01–92.23	88 (17)	
SaO_2 at rest, %					96.89±2.76	96.06–97.72	98 (2.5)	
VO_2 at anaerobic threshold, mL/min					724.93±227.04	640.15–809.71	710 (344.5)	30
Peak HR, beats/min					108.78±16.54	103.81–113.75	107 (13)	
Peak SaO_2, %					92.27±6.30	90.37–94.16	94 (6)	
Peak VO_2, mL/min					910.29±295.63	821.47–999.11	893 (354)	
Peak VO_2/kg, mL/min/kg					11.87±3.84	10.71–13.02	11.4 (4.55)	
Oxygen pulse, O_2/HR					8.35±2.33	7.65–9.05	7.7 (3.55)	
$EqCO_2$					44.39±9.87	40.89–47.89	42.5 (15.1)	33
Workload, W					66.11±27.78	57.77–74.46	75 (25)	
Borg perceived exertion (6–20)					15.61±1.35	15.20–16.02	15 (2)	44
Borg dyspnea ccale (6–20)					14.00±2.50	13.24–14.76	15 (3)	44
Peak sPAP, mm Hg					62.05±20.41	55.84–68.25	59 (20)	44
QoL (SF-36 questionnaire)								
Physical functioning					37.97±22.39	29.90–46.04	37.5 (28.75)	32
Physical role functioning					29.81±40.01	13.65–45.97	0 (75)	26
Bodily pain					50.96±17.15	44.31–57.62	52 (29.25)	28
General health perceptions					45.92±7.55	42.80–49.04	45 (7)	25
Vitality					39.33±12.37	34.71–43.95	40 (20)	30
Social role functioning					60.78±21.32	52.67–68.89	62.5 (31.25)	29
Emotional role functioning					51.89±48.35	32.76–71.01	67 (100)	27
Mental health					54.00±8.71	50.75–57.25	52 (12)	30
Physical summary score					42.78±18.37	36.16–49.40	39.5 (32)	32
Mental summary score					55.76±23.94	47.27–64.25	59 (45.5)	33

Baseline assessment was made 3 weeks post-PEA; right heart catheterisation assessment at baseline was made before PEA; in case of missing values, sample sizes are given in the column of n. SD, standard deviation; RA, right atrial; CO, cardiac output; WU, Wood units; RV, right ventricular; TAPSE, ricuspid annular plane systolic excursion; WHO FC, World Health Organisation functional class; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-min walking distance; QoL, quality of life; O_2, oxygen; HR, heart rate; SaO_2, arterial oxygen saturation; VO_2, oxygen consumption; sPAP, systolic pulmonary arterial pressure; $EqCO_2$, respiratory equivalent for CO_2.

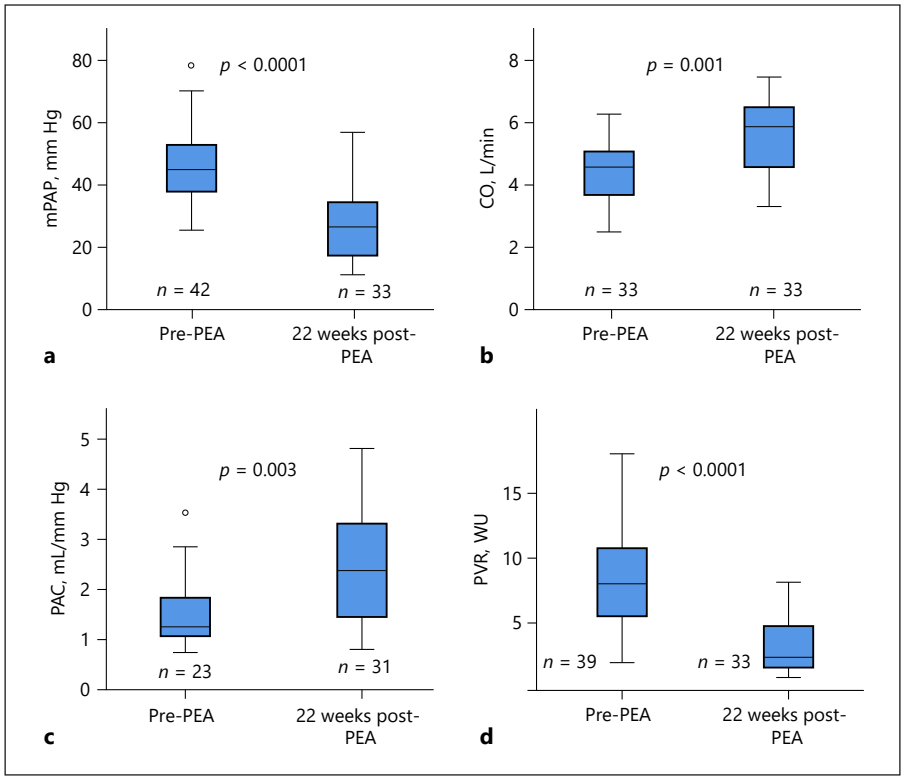

Fig. 2. Changes in haemodynamics after PEA. The boxplots show the distribution of values, including median, minimum, maximum, and lower and upper quartiles. Outliers are shown as circles. **a** mPAP significantly decreased from pre-PEA to 22 weeks post-PEA at the end of 15 weeks of exercise training ($p < 0.0001$). **b** CO significantly increased from pre-PEA to 22 weeks post-PEA ($p = 0.001$). **c** Pulmonary arterial compliance (PAC) significantly increased from pre-PEA to 22 weeks post-PEA at the end of 15 weeks of exercise training ($p = 0.003$). **d** PVR significantly decreased from pre-PEA to 22 weeks post-PEA at the end of 15 weeks of exercise training ($p < 0.0001$). All p values were derived from the Wilcoxon signed-rank test.

and their relation to the rehabilitation program were recorded throughout the study.

Statistical Methods

Analyses were performed by a statistician (N.B.). Data are given as mean values ± SD and 95% CI of the mean. Frequencies are given as the number and respective percent. As data were assumed to be not normally distributed, changes of clinical data were analysed by the Wilcoxon signed-rank test. The change of clinical parameters was also calculated as the percentage of change from the start of rehabilitation and percentage of change from pre-PEA.

Sample size calculation of the initially planned randomised controlled trial was based on the primary endpoint peak VO_2 with an assumed difference between groups (of change in peak VO_2) of 2 mL/min/kg and an equal SD of 3 mL/min/kg. Based on the Mann-Whitney U test and a sample size of 39 patients in each group (45 when including a dropout rate of 15%), a power of 80% would have been achieved with an effect size of at least 0.667 (based on the values above), using a 2-sided test with an alpha error of 0.05.

Results

Study Population

Out of 54 patients being referred to exercise rehabilitation after PEA, 45 consecutive patients after PEA were included in the study (Fig. 1). The mean age was 58 ± 12 years, 48.9% of the patients were female, and their body mass index was 26.5 ± 5.1 (Table 1). Out of 45 patients, 17 had a history of deep vein thrombosis. In total, 5 patients received additional surgery to PEA: 3 patients received a reconstruction of the pulmonary artery with a pericardial patch, 1 patient received a wedge resection of the right upper lobe, and a further patient had an aortic homograft due to resection of the pulmonary artery.

Assessment Schedule

The study schedule including assessments before and after PEA is shown in Figure 1. Eleven patients (24%) presented with persistent CTEPH at follow-up after 22 weeks with mPAP ≥25 mm Hg, PAWP ≤15 mm Hg, and PVR ≥3 Wood units (WU).

Safety and Tolerability of Early Follow-Up Rehabilitation

Exercise training and rehabilitation were well tolerated by all patients. During the inpatient phase of the rehabilitation, 2 patients had a urinary tract infection and 1 patient developed pneumonia of 1 middle lobe. These infections were successfully treated with antibiotics. Another patient had postoperative paralysis of the recurrent

Table 2. Changes from pre-PEA assessment to final examination (22 weeks)

	Baseline (pre-PEA; $n = 45$)				Change after final examination (22 weeks post-PEA; $n = 36$)				p value
	mean ± SD	95% CI of the mean	median (IQR)	n	mean ± SD	95% CI of the mean	median (IQR)	n	
Right heart catheterisation									
RA pressure, mm Hg	10.48±6.20	7.92 to 13.04	9 (7.5)	25	–4.05±7.54	–7.69 to –0.42	–4 (8)	19	0.017
Systolic pulmonary arterial pressure, mm Hg	73.56±15.68	68.25 to 78.86	77 (23.5)	36	–26.04±21.96	–34.91 to –17.17	–26 (33.5)	26	<0.0001
Diastolic pulmonary arterial pressure, mm Hg	28.12±9.06	24.95 to 31.28	26 (11.75)	34	–12.92±10.40	–17.12 to –8.72	–10.5 (15.75)	26	<0.0001
Mean pulmonary arterial pressure, mm Hg	45.10±11.66	41.46 to 48.73	44 (15.5)	42	–18.13±12.88	–22.77 to –13.48	–14 (19.75)	32	<0.0001
CO, L/min	4.45±0.97	4.11 to 4.80	4.6 (1.59)	33	1.19±1.48	0.59 to 1.78	1.35 (1.87)	26	0.001
Cardiac index, L/min/m^2	2.28±0.51	2.10 to 2.46	2.3 (0.69)	33	0.69±0.99	0.31 to 1.08	0.75 (1.11)	28	0.001
Pulmonary arterial wedge pressure, mm Hg	10.67±4.89	9.01 to 12.32	10.5 (5.75)	36	–1.50±6.95	–4.31 to 1.31	0 (7.5)	26	0.323
Pulmonary vascular resistance, WU	8.54±3.63	7.36 to 9.72	8.11 (5.55)	39	–5.41±4.12	–6.94 to -3.87	4.81 (4.77)	30	<0.0001
Pulmonary arterial compliance, mL/mm Hg	1.53±0.68	1.24 to 1.83	1.24 (0.78)	23	1.08±1.30	0.43 to 1.73	0.65 (1.74)	18	0.003
Total pulmonary resistance, mm Hg/L/min	10.83±4.50	9.24 to 12.43	10 (5.45)	33	–5.70±4.79	–7.63 to -3.76	–4.35 (5.41)	26	<0.0001
Laboratory									
NT-proBNP, ng/L	1,557.10±2,308.71	506.18 to 2,608.01	975 (1,348.5)	21	–1,029.73±2,556.16	–2,445.29 to 385.82	–507 (1339)	15	0.047
6MWD, m	371.95±97.95	339.29 to 404.60	371 (137)	37	150.54±84.49	117.77 to 183.30	135.5 (96.25)	28	<0.0001
Echocardiography									
RA area, cm^2	28.04±12.06	22.83 to 33.26	25 (17)	23	–12.93±14.22	–20.81 to -5.06	–9 (20)	15	0.005
RV, cm^2	42.86±9.30	38.74 to 46.99	43 (8.5)	22	–23.64±11.45	–30.25 to -17.03	–24.5 (23)	14	0.001
TAPSE, cm	1.49±0.30	1.34 to 1.63	1.5 (0.45)	20	0.10±0.44	0.11 to 0.40	0.1 (0.68)	14	0.400

Baseline assessment was made pre-PEA; right heart catheterisation assessment at baseline was made before PEA; in case of missing values, sample sizes are given in the column of *n*. SD, standard deviation; RA, right atrial; CO, cardiac output; WU, Wood units; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

nerve, 1 patient had gastroenteritis, 1 patient had pericardial effusion, which was treated with diuretics, 1 patient showed increased thyroxine-stimulating hormone values, and 1 patient had a haemodynamically relevant atrial flutter, which was treated with beta-blockers and digitalis and turned back to sinus rhythm. All adverse events were judged to be independent from the rehabilitation intervention by the treating physicians. No adverse events occurred during the following outpatient study period with continuation of training at home.

Clinical and Haemodynamic Characteristics

Before PEA the mean NT-proBNP serum level was 1,557 ± 2,308 ng/L, mean 6MWD was 372 ± 98 m, RA area was 28 ± 12 cm^2, RV area was 43 ± 9 cm^2, and mean TAPSE was 1.49 ± 0.30 cm. The mean haemodynamic values pre-PEA showed a severe CTEPH in the study cohort (Table 1) with mPAP of 45 ± 12 mm Hg, mean CO of 4.5 ± 1.0 L/min, mean cardiac index of 2.3 ± 0.5 L/min/m^2, and mean PVR of 8.5 ± 3.6 WU (Table 1).

At the beginning of the rehabilitation program, 3.26 ± 0.89 weeks after PEA, 40% of the patients were in WHO-FC II, 60% in WHO-FC III, 88.9% of patients had no targeted medical PH therapy ($n = 40$), and 11.1% ($n = 5$) were on medication with phosphodiesterase-5-inhibitors, which remained unchanged over the study period. The mean peak oxygen uptake per kg body weight (peak VO_2/kg) 3 weeks after PEA was 11.9 ± 3.8 mL/min/kg, the oxygen pulse at peak workload was 8.4 ± 2.3 mL/beat, and mean 6MWD was 428 ± 112 m.

Change in Haemodynamics Pre-PEA to 22 Weeks Post-PEA

The mean mPAP decreased by 18.1 ± 12.9 mm Hg (39.6%, $p < 0.0001$), CO increased by 1.2 ± 1.5 L/min (33.4%, $p = 0.001$), and PVR decreased by 5.41 ± 4.12 WU (–55.5%, $p < 0.0001$) from pre-PEA to 22 weeks after PEA. Furthermore, pulmonary arterial compliance and total pulmonary resistance significantly improved from pre-PEA to 22 weeks after PEA ($p = 0.003$ and $p < 0.0001$, respectively; Table 2; Fig. 2).

Echocardiographic Changes

Patients showed a significant reduction in right heart dimensions for both RA and RV area from pre-PEA to 3 weeks after PEA (–10.9 ± 11.0 cm^2, –31.1 ± 24.5%, and –22.0 ± 8.6 cm^2, –50.5 ± 12.9%, both $p < 0.0001$). Three weeks after PEA, RV and RA were still dilated; the mean RV area was 21.6 ± 5.2 cm^2 (for reference, the 2 SD range in normal subjects is 8.9–23.8 cm^2, [16]) and the mean RA

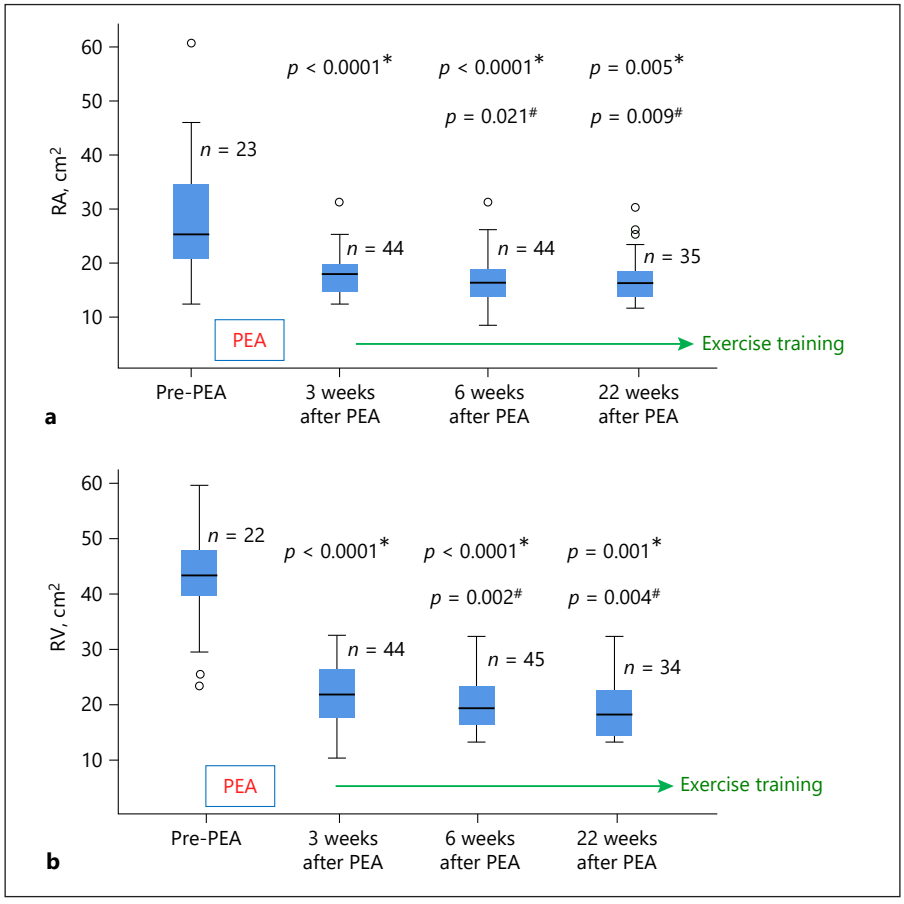

Fig. 3. Echocardiographic changes after PEA. The boxplots show the distribution of values, including median, minimum, maximum, and lower and upper quartiles. Outliers are shown as circles. **a** RA area significantly decreased from pre-PEA to 3 weeks after PEA at the beginning of rehabilitation ($p < 0.0001$), and 6 ($p < 0.0001$) and 22 weeks ($p = 0.005$) post-PEA. **b** RV area significantly decreased from pre-PEA to 3 weeks after PEA at the beginning of rehabilitation ($p < 0.0001$), and 6 ($p < 0.0001$) and 22 weeks ($p = 0.001$) post-PEA. * Compared to pre-PEA, # compared to 3 weeks after PEA (both Wilcoxon signed-rank test).

area was 17.6 ± 4.0 cm^2 (for reference, the upper limit of normal for women is 15 cm^2 and for men is 16 cm^2 [17]). During the in-hospital exercise training and the training phase at home until 22 weeks after PEA, right heart size showed a further significant decrease: the mean RV area to 18.8 ± 5.3 cm^2 (–3.1 ± 5.4 cm^2, –10.9%, $p = 0.004$) and the mean RA area to 16.5 ± 4.5 cm^2 (–1.6 ± 3.6 cm^2, –7.6%, $p = 0.009$; Table 3; Fig. 3). TAPSE increased from 1.48 ± 0.27 to 1.77 ± 0.41 cm (0.25 ± 0.41 cm, 18.9%, $p = 0.002$; Table 3). Tissue Doppler imaging systolic excursion of the free RV wall increased continuously from 9.0 ± 1.9 cm/s at 3 weeks to 10.9 ± 2.5 cm/s 22 weeks after PEA (1.8 ± 2.3, 21.1%, $p = 0.001$; Table 3).

Change in Biomarkers

NT-proBNP plasma levels decreased from pre-PEA to 3 weeks after PEA by 752 ± 2,397 ng/L. At 3 weeks after PEA, values were still increased in comparison with the normal range with 1,190 ± 1,415 ng/L, and continuously decreased to 594 ± 850 ng/L at 22 weeks after PEA (–611 ± 1,019 ng/L, –4.37%, $p < 0.0001$; Table 2).

Change in Exercise Capacity and Gas Exchange

Patients showed a significant improvement of 6MWD from pre-PEA to 3 weeks after PEA by 74 ± 81 m (25 ± 29%, $p < 0.0001$). 6MWD increased by 55 ± 54 m from 3 to 6 weeks after PEA and by 65 ± 64 m from 3 to 22 weeks after PEA (15.6 and 18.2%, respectively, both $p < 0.0001$; Fig. 4). The peak VO_2/kg increased by 4.4 ± 2.7 mL/min/kg (48.7%, $p < 0.0001$; Fig. 4) from 3 weeks to 22 weeks after PEA. Workload increased by 36 ± 25 W (58.2%, $p < 0.0001$) and peak ventilatory equivalent for carbon dioxide decreased by 7.2 ± 6.0 (–14.3%, $p = 0.0001$) from 3 weeks to 22 weeks after PEA. Heart rate at rest dropped by 5.5 ± 12.9 beats/min (–5.5%, $p = 0.0017$) and peak heart rate increased by 16.3 ± 20.1 beats/min (16.6%, $p = 0.0001$) from 3 to 22 weeks after PEA (Table 3).

Change in QoL

The subscales for physical functioning (+29.8 ± 35.5, $p = 0.001$), physical role functioning (+29.8 ± 37.6, $p = 0.004$), bodily pain (+11.1 ± 21.1, $p = 0.019$), and social role functioning (+13.1 ± 24.8, $p = 0.031$) significantly

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Table 3. Changes from 3 weeks post-PEA at the beginning of rehabilitation to 6 and 22 weeks post-PEA

	3 weeks post-PEA, start of rehabilitation (n = 45)				Mean difference from 3 to 6 weeks post-PEA (n = 44)				p value	Mean difference from 3 to 22 weeks post-PEA (n = 36)				p value
	mean ± SD	95% CI of the mean	median (IQR)	n	mean ± SD	95% CI of the mean	median (IQR)	n		mean ± SD	95% CI of the mean	median (IQR)	n	
Laboratory														
NT-proBNP, ng/L	1,190.09±1,415.06	764.96 to 1,615.22	786 (863.5)		484.30±726.29	263.48 to 705.11	−262 (547.75)		<0.0001	611.21±1019.05	271.47 to 951.01	−378 (844.5)		0.0001
6MWD, m	428.29±111.74	394.72 to 461.86	440 (145)		55.31±53.67	39.19 to 71.43	47 (72.5)		<0.0001	65.11±63.96	43.14 to 87.09	76 (85)	35	<0.0001
Echocardiography														
RA area, cm^2	17.57±4.00	16.36 to 18.79	17.5 (5.75)	44	−0.93±2.70	−1.74 to −0.11	0 (4)		0.021	−1.59±3.56	−2.83 to −0.35	−1.75 (4.25)	34	0.009
RV area, cm^2	21.64±5.17	20.06 to 23.21	21.5 (8.75)	44	−1.98±3.53	−3.05 to −0.90	−2 (5)		0.002	−3.12±5.44	− 5.05 to −1.19	−3 (8.5)	33	0.004
TAPSE, cm	1.48±0.27	1.40 to 1.57	1.5 (0.4)		0.10±0.23	0.03 to 0.16	0 (0.3)		0.009	0.25±0.41	0.11 to 0.40	0.2 (0.5)	35	0.002
Left ventricular eccentricity index	1.12±0.13	1.08 to 1.16	1.1 (0.2)		−0.04±0.08	−0.06 to −0.02	0 (0.1)		0.003	−0.06±0.16	−0.11 to −0.01	−0.1 (0.1)	35	0.039
Pulmonary artery diameter, mm	24.13±5.52	22.39 to 25.87	25 (4)	41	−0.55±1.76	−1.10 to 0.01	0 (1)	41	0.064	−0.93±5.33	−2.85 to 0.99	−2 (4)	32	0.024
Tissue Doppler imaging s RV free wall, cm/s	8.97±1.82	8.37 to 9.57	9 (2)	38	0.61±1.37	0.16 to 1.05	0 (1)	38	0.011	1.76±2.34	0.87 to 2.65	2 (3.5)	29	0.001
Systolic pulmonary arterial pressure at rest, mm Hg	34.36±15.10	29.82 to 38.89	30 (17.5)		−1.29±7.47	−3.61 to 1.04	0 (5)	42	0.213	6.37±12.49	2.08 to 10.66	5 (15)	35	0.007
Cardiopulmonary exercise test with stress echocardiography														
HR at rest, beats/min	88.62±12.02	85.01 to 92.23	88 (17)		−0.36±9.46	−3.20 to 2.49	−1 (9)		0.561	−5.54±12.93	−9.85 to −1.23	−7 (17.5)		0.017
SaO_2 at rest, %	96.89±2.76	96.06 to 97.72	98 (2.5)		0.39±2.13	−0.26 to 1.03	0 (1.75)		0.239	0.94±2.95	−0.09 to 1.97	0 (1.25)	34	0.047
VO_2 at anaerobic threshold, mL/min	724.93±227.04	640.15 to 809.71	710 (344.5)	30	37.07±197.25	−37.96 to 112.1	18 (240)	29	0.531	244.50±252.79	126.19 to 362.81	154 (182.25)	20	0.0001
Peak HR, beats/min	108.78±16.54	103.81 to 113.75	107 (13)		4.95±17.44	−0.35 to 10.26	6.5 (18.25)		0.018	16.25±20.07	9.46 to 23.04	18.5 (22.25)		0.0001
Peak SaO_2, %	92.27±6.30	90.37 to 94.16	94 (6)		0.57±6.37	−1.37 to 2.50	0 (3)		0.756	1.85±5.75	−0.19 to 3.89	1 (5)	33	0.072
Peak VO_2, mL/min	910.29±295.63	821.47 to 999.11	893 (354)		158.50±121.83	121.46 to 195.54	159 (143.75)		<0.0001	432.09±248.52	346.72 to 517.46	472 (330)	35	<0.0001
Peak VO_2/kg, mL/min/kg	11.87±3.84	10.71 to 13.02	11.4 (4.55)		1.99±1.73	1.47 to 2.52	1.95 (2.18)		<0.0001	4.37±2.72	3.45 to 5.29	4.55 (3.97)		<0.0001
Oxygen pulse, O_2/HR	8.35±2.33	7.65 to 9.05	7.7 (3.55)		0.98±1.68	0.47 to 1.49	0.95 (1.58)		0.0002	2.15±1.98	1.48 to 2.82	1.9 (2.27)		<0.0001
$EqCO_2$	44.399±9.87	40.89 to 47.89	42.5 (15.1)	33	−3.96±4.39	−5.58 to −2.35	−3.7 (5.6)	31	<0.0001	−7.23±6.02	−9.72 to −4.75	−7.2 (6.85)	25	0.0001
Workload, W	66.11±27.78	57.77 to 74.46	75 (25)		18.18±17,36	12.9 to 23.46	25 (25)		<0.0001	35.83±25.42	27.23 to 44.44	25 (25)		<0.0001
Borg perceived exertion (6–20)	15.61±1.35	15.20 to 16.02	15 (2)	44	−1.00±3.92	−2.19 to 0.19	0 (2)		0.089	−0.76±2.46	−1.62 to 0.09	0 (3)	34	0.096
Borg dyspnea scale (6–20)	14.00±2.50	13.24 to 14.76	15 (3)	44	0.02±2.77	−0.84 to 0.89	0 (4)	42	0.841	0.18±2.43	−0.67 to 1.02	0 (4)	34	0.739
Peak sPAP, mm Hg	62.05±20.41	55.84 to 68.25	59 (20)	44	−0.95±12.38	−4.86 to 2.96	0 (5)	41	0.436	10.35±20.57	3.18 to 17.53	5 (15)	34	0.006
QoL														
Physical functioning	37.97±22.39	29.90 to 46.04	37.5 (28.75)	32						29.78±35.53	14.42 to 45.15	30 (45)	23	0.001
Physical role functioning	29.81±40.01	13.65 to 45.97	0 (75)	26						29.76±37.60	12.65 to 46.88	25 (75)	21	0.004
Bodily pain	50.96±17.15	44.31 to 57.62	52 (29.25)	28						11.05±21.12	1.43 to 20.66	10 (21)	21	0.019
General health perceptions	45.92±7.55	42.8 to 49.04	45 (7)	25						4.47±10.51	−0.59 to 9.54	5 (17)	19	0.079
Vitality	39.33±12.37	34.71 to 43.95	40 (20)	30						−4.76±14.62	−11.42 to 1.89	−5 (15)	21	0.212
Social role functioning	60.78±21.32	52.67 to 68.89	62.5 (31.25)	29						13.13±24.83	1.51 to 24.74	6.25 (37.5)	20	0.031
Emotional role functioning	51.89±48.35	32.76 to 71.01	67 (100)	27						6.70±52.53	−17.89 to 31.29	0 (33)	20	0.570
Mental health	54.00±8.71	50.75 to 57.25	52 (12)	30						1.33±8.52	−2.54 to 5.21	0 (8)	21	0.623
Physical summary score	42.78±18.37	36.16 to 49.40	39.5 (32)	32						19.55±19.42	10.94 to 28.16	23 (31.5)	21	0.001
Mental summary score	55.76±23.94	47.27 to 64.25	59 (45.5)	33						6.36±20.44	−2.70 to 15.43	5 (25.25)	21	0.137

Baseline assessment was made 3 weeks post-PEA; right heart catheterisation assessment at baseline was made before PEA; in case of missing values, sample sizes are given in the column of n. SD, standard deviation; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-min walking distance; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; O_2, oxygen; HR, heart rate; SaO_2, oxygen saturation; VO_2, oxygen consumption; sPAP, systolic pulmonary arterial pressure; $EqCO_2$, respiratory equivalent for CO_2.

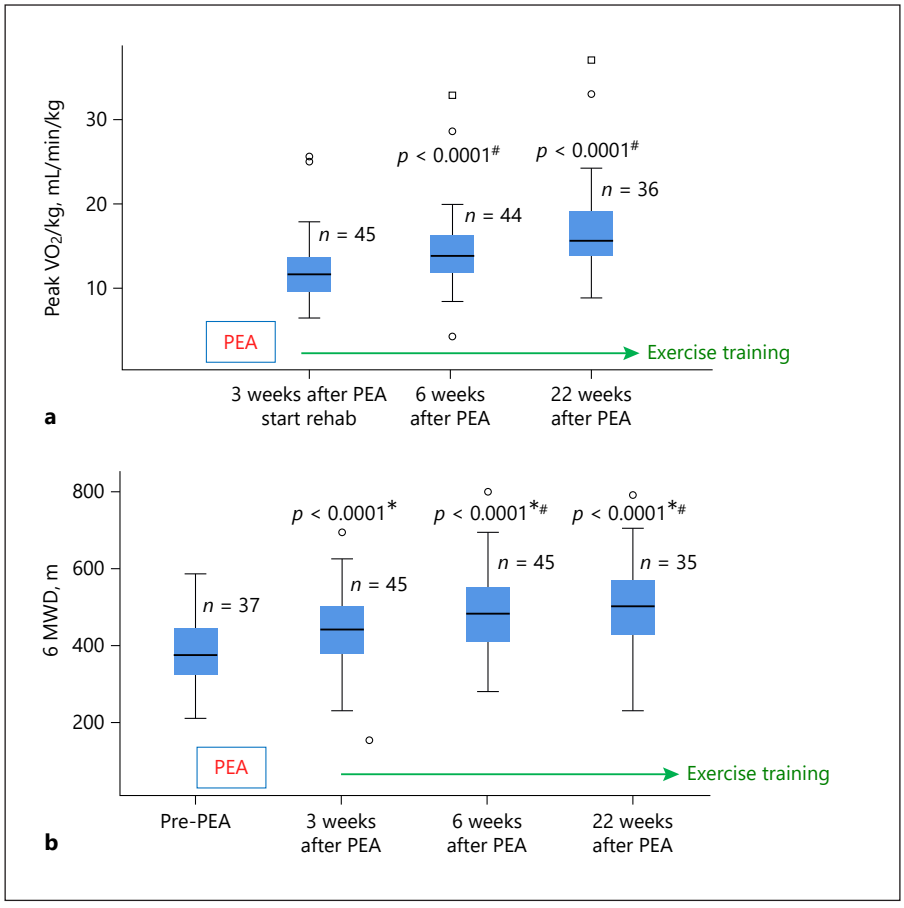

Fig. 4. Exercise capacity. The boxplots show the distribution of values, including median, minimum, maximum, and lower and upper quartiles. Outliers are shown as circles and extreme outliers as squares. **a** Peak oxygen uptake per kilogram bodyweight (peak VO_2/kg) in the cardiopulmonary exercise testing significantly improved after 6 ($p < 0.0001$) and 22 ($p < 0.0001$) weeks post-PEA, compared to 3 weeks post-PEA at the beginning of rehabilitation. **b** Significant increase of 6MWD from pre-PEA to 3 weeks post-PEA at the beginning of exercise training ($p < 0.0001$), and 6 ($p < 0.0001$) and 22 weeks ($p < 0.0001$) post-PEA. * Compared to pre-PEA, # compared to 3 weeks after PEA (both Wilcoxon signed-rank test).

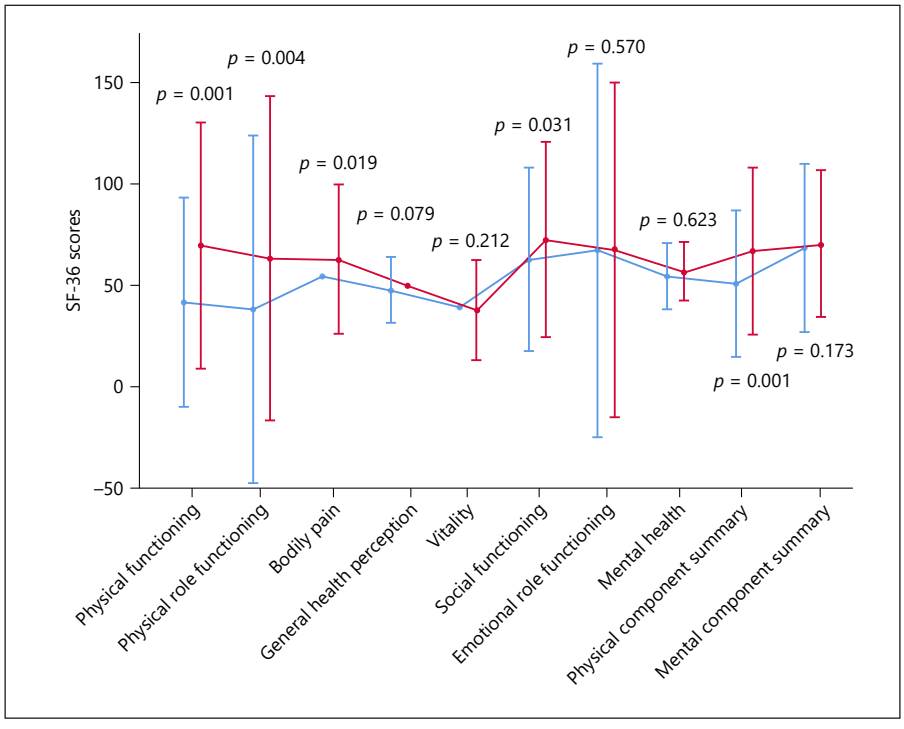

Fig. 5. QoL, measured by the SF-36 questionnaire, significantly improved in 4 of 8 subscales from the beginning of rehabilitation 3 weeks post-PEA (shown in blue) to 22 weeks post-PEA (shown in red). Significant improvements are shown for the subscales for physical functioning ($p = 0.001$), role limitations due to physical restrictions ($p = 0.004$), bodily pain ($p = 0.019$), and social functioning ($p = 0.031$). Mean changes of QoL ±2 SE of the mean and sample sizes are shown below each bar. p values denote differences compared to 3 weeks after PEA (Wilcoxon signed-rank test).

improved from 3 weeks after PEA at the beginning of rehabilitation to the final examination 22 weeks after PEA (Table 3; Fig. 5). The patients reported that supervised exercise training helped them to get to know their improved physical abilities and limitations after PEA.

Discussion

To the best of our knowledge, this is the first prospective study to describe haemodynamic and further clinical changes by a combined treatment of PEA and supervised early follow-up rehabilitation program. The results of the study showed that the early start (approx. 3 weeks after PEA) of a specialised exercise training program was feasible and may further improve clinical parameters such as right heart function and exercise capacity.

Further Improvement of Right Heart Function and Exercise Capacity

This study confirms the rapid improvement and recovery of RV function and pulmonary haemodynamics at rest after successful PEA, which has been described previously [18–21]. In several studies major improvements in echocardiographic parameters within a few days after PEA versus pre-PEA have been reported [18–21]. A recent retrospective analysis of 110 patients with CTEPH after PEA showed a decline of 6MWD after PEA, which was followed by a significant increase after exercise training, and further improvement in exercise capacity after 3 months did not significantly differ between patients with persistent CTEPH and a good haemodynamic response after PEA [22]. Another recent study by Guth et al. [23] showed similar improvements mainly using exercise right heart catheterisation to examine patients 1 year after surgery. The study also illustrated a decrease in mPAP by about 3 mm Hg and further reductions of systolic pulmonary arterial pressure and PVR [23]. Li et al. [19] reported a decrease of about 50 mm Hg in RV systolic pressure at 3 months post-PEA. Furthermore, they showed that the RV end-diastolic area and end-systolic area can each drop by about 9 cm^2, 3 months after surgery [19]. It is also known that patients who have undergone PEA can have an increase in peak VO_2 up to 3.7 mL/kg/min at 2 years post-surgery [18]. Our study is the first to characterise the haemodynamics within the first 3 weeks after PEA. The maximum drop in mean right heart size (about 50%) and improvement of mean 6MWD (by 20%) occurred within 3 weeks after PEA. Therefore, it seems reasonable to start the rehabilitation program at an early point in time to enhance clinical improvements and prevent them from worsening or reaching a plateau. The reduced right heart size was associated with a significant increase in CO by 33% at rest and an increase of 28% of oxygen pulse (VO_2/heart rate) in the cardiopulmonary exercise test over 22 weeks. Our cohort showed a significant decrease in pulmonary pressures in combination with a significant increase in cardiac index from pre-PEA to 22 weeks. Subsequently, mPAP decreased by approximately 40%, PVR dropped by 55%, and the ventilatory equivalent of carbon dioxide as a marker of ventilatory efficiency and gas exchange improved by 14% after 22 weeks.

Morphologic changes in right heart size took place immediately after PEA due to the disobliteration of the pulmonary vascular bed. In contrast, functional improvement of the initially insufficient RV (TAPSE), most likely also peripheral muscle weakness, deconditioning, and impaired gas exchange is delayed and improves continuously over the weeks after PEA. Therefore, another important finding of this study is that all patients who participated in the training program after PEA reported an improvement of their exercise capacity, even those 11 patients with persistent CTEPH. Apart from the PEA, specialised rehabilitation with exercise training has previously been shown to improve mPAP, PVR, and right heart size [11]. Furthermore, autonomic balance [24, 25] and endothelial [26] and skeletal muscle function [27] can be improved by increasing oxygen delivery and by reversing both systemic and local inflammatory processes. Therefore, exercise training may be a useful add-on therapy to PEA to also further improve those exercise-limiting factors which persist even after the normalisation of haemodynamics, as described by Corsico et al. [10] in up to 40% of patients. Specialised rehabilitation programs have also shown to significantly improved exercise capacity in other conditions post-surgery, such as after heart transplantation [28].

Safety, Feasibility, and Effects of Exercise Training

Rehabilitation 3 weeks after PEA demonstrated a good safety profile and was feasible in all patients. The supervised training therapy encouraged patients after PEA to perform continuous physical exercise and re-established self-assurance at home after months or even years of relative inactivity and deconditioning due to the disease. This effect was emphasised by all participating patients.

Limitations

Although a control group would have been desirable to distinguish the effects of PEA and early exercise rehabilitation, data on early rehabilitation are scarce and our study may provide some insight into the safety, tolerabil-

ity, and clinical course of patients undertaking an early exercise training program after PEA. As patients usually present with an improved exercise capacity and haemodynamics after PEA, the intensity of the exercise training applied in this study may have been too low. The intensity of our training program was derived from training programs that were evaluated by our group before in the same rehabilitation clinic with the same dedicated personnel for manifest PH [11, 12, 15]. Our approach was oriented towards safety and tolerability, especially due to the fast initiation after successful PEA with cost application in-hospital right after surgery (median start of rehabilitation 3.1 weeks after PEA) as an early follow-up rehabilitation.

Future Research

An early rehabilitation program was shown to be feasible and may further improve clinical parameters, such as right heart function and exercise capacity. Multicentre studies are desirable to further investigate early rehabilitation after PEA. Although patients with manifest CTEPH have been included in several exercise training studies, further studies are needed with a special focus on patients with inoperable CTEPH.

The optimal training intensity and methodology might be an important point to address in future studies. Before PEA, CTEPH patients experienced long periods of relative inactivity and deteriorating RV pump function. They were limited not only by their pulmonary circulation, but also by their deconditioned peripheral muscles. These data and observations of our study might therefore encourage and help to develop further studies to investigate the effects, optimal training methodology, and intensity of early follow-up rehabilitation after PEA. As a parallel-group design led to methodological issues concerning separation of the training and the control group while both groups stayed in the rehabilitation clinic at the same time, a waiting group design (with delayed start of rehabilitation in the control group) could offer both data on the course of reverse remodelling and the effects of early and later exercise rehabilitation after PEA.

Conclusion

Supervised exercise training was feasible shortly after PEA. Patients significantly improved in exercise capacity, peak oxygen uptake, and haemodynamics by the combination of PEA and rehabilitation. Further data are needed on the effect of exercise training shortly after PEA and its impact on reverse remodelling of the right heart and pulmonary vasculature.

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Statement of Ethics

This study was conducted in accordance with Good Clinical Practice and the current version of the revised Declaration of Helsinki (WMA Declaration of Helsinki). The Ethics Committee of the Medical Faculty, University of Heidelberg had no objections against the conduct of the study (internal number S488/2009). The study was registered at clinicaltrials.gov (NCT01393327). Written informed consent was obtained from each patient prior to enrolment and all data were anonymised.

Conflict of Interest Statement

C.N. reports honoraria for lectures and participation in clinical trials by Actelion, Bayer/MSD, Novartis, speaker honoraria from Boehringer, Astra Zeneca, Berlin Chemie, and participation in clinical trials by GSK, United Therapeutics outside the submitted work. N.B. received speaker honoraria and travel support from Actelion and Bayer outside the submitted work. S.H. received travel support from Actelion and OMT outside the submitted work. E.M. reports non-financial support from the German Centre for Lung Research during the conduct of the study, and personal fees from Actelion Pharmaceuticals, Bayer, Pfizer, GSK, and MSD outside the submitted work. E.G. received advisory board member and speaker honoraria from Actelion, Bayer/MSD, GSK, United Therapeutics, Novartis, Pfizer, OrphaSwiss GmbH outside the submitted work. S.G. reports non-financial support from the German Centre for Lung Research during the conduct of the study, and personal fees from Actelion Pharmaceuticals, Bayer, Pfizer, and GSK outside the submitted work. M.N., B.E., C.A.E., and P.X. have nothing to disclose.

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Author Contributions

This work was the doctoral thesis of M.N. E.G., C.N., M.N., S.G., E.M., and N.B. contributed substantially to the study conception and design. E.G., C.N., M.N., B.E., S.H., S.G., E.M., and P.X. performed the assessments and patient examinations. C.N. and M.N. performed the data collection. N.B. performed the data anal-

ysis. All authors contributed to data interpretation and to the writing of the manuscript. All authors have read and approved the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors had full access to the data and took full responsibility for its integrity.

Availability of Data

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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