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Persistent exercise intolerance after pulmonary endarterectomy for CTEPH

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Take home message

Despite normalization of hemodynamics, exercise capacity remains abnormal in two-thirds of chronic thromboembolic pulmonary hypertension patients after pulmonary endarterectomy. Not all exercise intolerance is explained by the presence of residual PH.

Abstract

Aim Hemodynamic normalization is the ultimate goal of pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH). However, whether normalization of hemodynamics translates into normalization of exercise capacity is unknown. The incidence, determinants and clinical implications of exercise intolerance after PEA are unknown. We performed a prospective analysis to determine the incidence of exercise intolerance after PEA, assess the relationship between exercise capacity and (resting) hemodynamics, and search for preoperative predictors of exercise intolerance after PEA.

Methods According to clinical protocol all patients underwent cardiopulmonary exercise testing (CPET), right heart catheterization (RHC) and cardiac magnetic resonance (CMR) imaging before and 6 months after PEA. Exercise intolerance was defined as a peak VO_2 < 80% predicted. CPET parameters were judged to determine the cause of exercise limitation. Relationships were analysed between exercise intolerance and resting hemodynamics and CMR-derived right ventricular (RV) function. Potential preoperative predictors of exercise intolerance were analysed using logistic regression analysis.

Results 68 patients were included in the final analysis. 45 patients (66%) had exercise intolerance 6 months after PEA; in 20 patients this was primarily caused by a cardiovascular limitation. The incidence of residual PH was significantly higher in patients with persistent exercise intolerance (p 0.001). However, 27 out of 45 patients with persistent exercise intolerance had no residual PH. In the multivariate analysis, preoperative transfer factor for carbon monoxide (TLCO) was the only predictor of exercise intolerance after PEA.

Conclusions The majority of CTEPH patients has exercise intolerance after PEA, often despite normalization of resting hemodynamics. Not all exercise intolerance after PEA is explained

by the presence of residual PH, and lower preoperative TLCO was a strong predictor of exercise intolerance 6 months after PEA.

Introduction

Pulmonary endarterectomy (PEA) is a highly effective treatment for chronic thromboembolic pulmonary hypertension (CTEPH) resulting in excellent survival [1-2]. However, in approximately 40-50% of patients, pulmonary artery pressures remain elevated after PEA [2-3]. Residual pulmonary hypertension (PH) with a pulmonary vascular resistance (PVR) over 425 dynes·s·cm^{-5} is associated with increased long-term mortality [2-3], justifying treatment with PH-specific medication [1,4] or, in selected cases, balloon pulmonary angioplasty. While mortality and residual PH at rest are the most commonly reported outcome measures after PEA, few studies have focused on exercise capacity. Peak oxygen consumption (VO_2) determined during cardiopulmonary exercise testing (CPET) [5] predicts survival in pulmonary arterial hypertension (PAH) and CTEPH [6-8] and exercise capacity in general has an important impact on quality of life both in health [9] and disease [10-11]. It has been suggested that the recovery of exercise capacity lags behind hemodynamic recovery after PEA [12]. Overall, it is unknown how often exercise intolerance persists after PEA and it has not been determined whether persistent exercise intolerance always coincides with residual PH at rest. Because the correlation between PVR and peak VO_2 disappears after PEA [13], it is possible that other determinants than resting hemodynamics explain persistent exercise intolerance. In addition to residual PH, deconditioning or persistent RV dysfunction and ventilatory inefficiency could be responsible for persistent exercise intolerance after PEA. To determine the incidence of persistent exercise intolerance after PEA, to evaluate its determinants and relation with resting hemodynamics (*i.e.* residual PH) and to analyse potential preoperative predictors of exercise intolerance after PEA, we performed a prospective cohort study using hemodynamic assessments, CPET, lung function testing and cardiac magnetic resonance imaging (CMR) in 68 CTEPH patients after PEA.

Material and methods

Study subjects

All patients undergoing PEA in our centre were included in a prospective cohort study. According to our local clinical protocol, patients underwent CPET, six-minute walking testing (6MWT), right heart catheterization (RHC) and CMR imaging before and 6 months after PEA. All patients undergoing PEA between July 2012 and January 2018 who performed CPET 6 months (plus or minus 2 weeks) after PEA were enrolled in this analysis.

The study did not fall within the scope of the Medical Research Involving Human Subjects Act, since an analysis was performed based on available clinical data obtained for clinical purposes. This was confirmed by the Medical Ethics Review Committee of the VU University Medical Centre (2017.313).

Procedures

RHC (resting pulmonary hemodynamics) was performed as described previously [14]. The following variables were recorded: (mean) pulmonary artery pressure ((m)PAP), right atrial pressure (RAP), pulmonary artery wedge pressure (PAWP), heart rate (HR), and central venous oxygen saturation (SvO_2). Cardiac output (CO) was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index (CI)). PVR was calculated from (80 x [mPAP - PAWP]/CO). Pulmonary arterial compliance was calculated as stroke volume divided by pulse pressure. (Residual) PH was defined as mPAP $>$ 20 mmHg and PVR $\geq$ 240 dynes·s·cm^{-5}, in accordance with the new proposed definition of pre-capillary PH by the 6th World Symposium on Pulmonary Hypertension Task Force [15].

CMR was performed and analysed as previously described [14].

CPET consisted of a symptom-limited maximal incremental exercise test using a cycle ergometer [16]. Measurements consisted of continuous recording of ECG, VO_2, CO_2 production (VCO_2), HR, tidal volume, breathing frequency, expiratory oxygen and CO_2 pressures, peripheral oxygen saturation, and intermittent recording of blood pressure. The anaerobic threshold was determined using the V-slope method [17]. Predicted maximum ventilation (VE) was based on 40x FEV1 (with minute ventilation calculated as breathing frequency times tidal volume). Reference values from the Study of Health in Pomerania (SHIP) were used [18]. The majority of CPET was performed without arterial blood sampling, therefore Vd/Vt calculations were not included in the analysis. Exercise intolerance was defined as a peak VO_2 < 80% of predicted [19]. The cause of exercise limitation was determined using the flowcharts proposed by Wasserman *et al* [20]. Five different categories were used: normal peak VO_2, cardiovascular limitation (including left ventricular (LV) failure, myocardial ischemia, heart disease, pulmonary vascular disease (PVD)), ventilatory limitation (including obstructive lung disease, restrictive lung disease, lung disease with impaired peripheral oxygenation), other (including muscular-skeletal disorder, peripheral arterial disease and anaemia) and submaximal CPET.

6MWT was performed according to the 2002 ATS statement [21].

Single-breath carbon monoxide uptake, i.e. transfer factor of the lung for carbon monoxide (TLCO), was determined before surgery according to the 2005 joint ERS/ATS statement [22].

Baseline tests (RHC, CMR, CPET, 6MWT and TLCO) were defined as the most recent test performed before PEA; a minority of patients performed the test while using PH-specific medication.

Study design and statistical analysis

Primary outcome of this study was (decreased) peak VO_2 (*i.e.* persistent exercise intolerance). Secondary outcomes consisted of a variety of exercise parameters, hemodynamic parameters and CMR imaging based right ventricular (RV) function parameters.

Data are presented as mean (standard deviation (SD)), median (interquartile range (IQR)) or number of patients (%). Missing data were not imputed. Normal distribution was tested by using D'Agostino-Pearson omnibus normality test; log transformation was performed when distribution was not normal. Differences regarding continuous data were tested using unpaired t-test or paired t-test where appropriate; Wilcoxon matched-pairs signed rank test or Mann Whitney test were used where appropriate when distribution remained not normal despite log transformation. Differences regarding categorical data were tested using Chi-square test or Fisher's exact test. Correlation analysis was performed using Pearson correlation. Univariate and multivariate logistic regression analysis was performed to analyse preoperative parameters predicting persistent exercise intolerance.

Values of $P < 0.05$ were considered to reflect statistical significance. Statistical analysis was performed using GraphPad Prism version 8 (GraphPad Software Inc, La Jolla, California, USA) and IBM SPSS Statistics version 24.

Results

68 patients were enrolled in the cohort analysis, including 2 patients with chronic thromboembolic disease (CTED) without PH (figure 1). Median age at the time of PEA was 63 years (range 17-79 years), and there was a slight predominance of males (57%). Median time between CTEPH diagnosis and PEA was 153 days (IQR 92-251). Median BMI at time of

diagnosis was 26.5 kg/m^2 (IQR 24.3-29.3). At the time of CTEPH diagnosis 6% was in NYHA class I, 37% in NYHA class II, 51% in NYHA class III, and 6% in NYHA class IV. The proportions and changes in NYHA class after PEA are shown in figure A in the online supplement. In addition, 23 patients (34%) were pre-treated with PH-specific medication. The overall incidence of comorbidities was low (data not shown); eight patients (12%) had obstructive lung disease.

From baseline to 6 months after PEA all hemodynamic and CMR RV indices significantly improved (table 1). Baseline RHC, CMR and CPET were defined as the last test performed before PEA. Respectively 14, 9 and 7 patients were using PH-specific medication at the time of the last RHC, CMR and CPET. Median time between last CPET before PEA and PEA was 155 days (IQR 92-232 days). The majority of CPET parameters (including circulatory and gas exchange parameters) improved, while heart rate and breathing reserve remained unchanged 6 months after PEA (figure 2 and online supplement table A).

Persistent exercise intolerance (defined as peak VO_2 < 80% predicted) was present in 45 out of 68 patients (66%) at 6 months after PEA. According to the flowcharts by Wasserman *et al* [21], 20 patients (29% of total) had exercise limitation due to cardiovascular pathology (including the only patient receiving PH-specific medication at the time of this re-evaluation), five patients (7% of total) had a primarily ventilatory limitation (including two patients with a known diagnosis of obstructive lung disease), and in nine patients (13% of total) the primary cause of exercise limitation was musculoskeletal or peripheral arterial disease. 11 patients (16% of total) had decreased peak VO_2 in the context of a presumed submaximal test. Before PEA peak VO_2 was decreased in 89% of patients, and in 62% this was primarily due to cardiovascular pathology, while in 7% this was primarily ventilatory and in 8% due to

musculoskeletal or peripheral arterial disease; five patients (11%) had a decreased peak VO_2 in the context of a presumed submaximal test (figure 3).

In comparison to patients with a normalized peak VO_2, mPAP and PVR were slightly but significantly higher in those with persistent exercise intolerance post-PEA (figure 4). However, CMR-derived RV functional parameters were not different between groups (figure 4). While NT-proBNP was not different between those with or without persistent exercise intolerance (166 (96-390) ng/L versus 233 (115-365) ng/L, p 0.319), 6MWD was significantly higher in patients with normalized peak VO_2 post-PEA (539 (72) meters versus 454 (84) meters, $p < 0.001$)

Residual PH (mPAP $>$ 20 mmHg and PVR $\geq$ 240 dynes·s·cm^{-5}) was present in 16 out of 45 patients (36%) with persistent exercise intolerance post-PEA (RHC data were unavailable in two patients), and 75% of these patients had a primarily cardiovascular limitation during exercise. None of the patients with normalized peak VO_2 after PEA had residual PH (RHC data unavailable in three patients). Two patients had an increased PAWP at follow-up. PVR and diastolic pressure gradients (DPG) indicated isolated post-capillary PH in one patient and combined pre- and post-capillary PH in the other patient. The incidence of residual PH was significantly higher in patients with persistent exercise intolerance (Fisher's exact test p 0.001). To illustrate that exercise intolerance can persist after PEA despite normalization of resting hemodynamics, a Venn diagram is shown in the online supplement (figure B).
In a large UK cohort, the start of PH-specific medication was associated with a mPAP $\geq$ 30 mmHg after PEA [2]. Seven patients in our cohort fulfilled the criterium of mPAP $\geq$ 30 mmHg; none of these patients had a normalized peak VO_2 after PEA.

Weak correlations were observed between post-PEA peak VO_2 and mPAP (Pearson R^2 0.216, $p < 0.001$), PVR (R^2 0.090, p 0.017) and pulmonary arterial compliance (R^2 0.155, p 0.002) (figure 5). Post-PEA compliance was lower in patients with persistent exercise intolerance compared to those with normal peak VO_2 post-PEA (3.5 (3.3-6.1) vs 3.0 (2.0-3.9) mL/mmHg, p 0.003). A weak correlation was found between post-PEA peak VO_2 and RVEF (Pearson R^2 0.080, p 0.043), but not with any other CMR parameter.

Analysis of other circulatory and ventilatory/gas exchange parameters measurements during CPET showed that peak O_2 pulse was lower in those with exercise intolerance compared to those with normal exercise tolerance (77.4 (13.3) vs 99.7 (10.3) % predicted, $p < 0.001$). The correlation between peak VO_2 and O_2 pulse was strong (Pearson R^2 0.617, $p < 0.001$), while the correlations with VE/VCO_2 at the anaerobic threshold and $PETCO_2$ at maximal exercise were moderate to weak (Pearson R^2 0.217, $p < 0.001$ and Pearson R^2 0.076, p 0.023, respectively).

Patients with persistent exercise intolerance after PEA were characterized before surgery with more frequent treatment with PH-specific medication, a higher NYHA class, a lower 6MWD and a lower TLCO (table B in online supplement). Preoperative pulmonary hemodynamics, CMR-based RV functional parameters, and imaging characteristics (proximal vs distal disease) were not related to exercise intolerance after PEA (see comparison of groups and the univariate analysis). Preoperative CPET was more impaired in patients with persistent exercise intolerance after PEA (table C in online supplement). Pre-surgical TLCO was the only predictor of exercise intolerance after PEA in the multivariate analysis (table 2). The presence of obstructive lung disease in 8 patients was not predisposing to persistent

exercise intolerance after PEA nor was it predisposing to a lower TLCO at baseline compared to the patients without obstructive lung disease.

Discussion

In this prospective cohort of operated CTEPH patients, 66% of patients had exercise intolerance 6 months post-PEA, despite good hemodynamic results. Exercise capacity was limited mainly by cardiovascular constraints. Although exercise intolerance was associated with the presence of residual PH, the correlation between peak VO_2 and mPAP or PVR 6 months post-PEA was moderate at most, and not all exercise intolerance was explained by the presence of residual PH. Lower preoperative TLCO was a strong predictor of persistent exercise intolerance 6 months after PEA, while pre-surgical hemodynamics, CMR and imaging were not predictive.

This is the first study to describe the incidence and determinants of decreased peak VO_2 after PEA. Most studies on functional outcomes after PEA were based on a determination of the 6MWD [23-26]. It was shown that the presence of residual PH was associated with a lower 6MWD [23-25], but conflicting results were presented regarding correlations between (changes in) 6MWD and (changes in) mPAP and/or total pulmonary vascular resistance [24-26]. More consistent correlations were reported between exercise parameters and pulmonary arterial compliance [26-27]. In a recent study, 41% of patients were reported to have persistent exercise limitation twelve months after PEA, as defined by a distance walked < 400 meters in a modified Bruce protocol [28]. The cut-off of 400 m was somewhat arbitrary, however, and based on the median distance walked in their previous analysis [29].

Such a fixed cut-off is likely affected by factors such as age, gender, and height (i.e. stride length) and is therefore quite arbitrary as an indicator of exercise limitation. In addition, there is increasing discussion regarding the use of 6MWD as a biomarker and end-point in clinical trials [30], while peak VO_2 determined by CPET has been shown to be a strong predictor of survival in PAH and CTEPH patients [6-7].

The high frequency of exercise intolerance after PEA (66% in this study) contrasts with the considerably lower incidence of residual PH. The question is whether in this regard exercise intolerance (decreased peak VO_2) would constitute a more optimal outcome measure of PEA than presence or absence of residual PH. Moreover, it is important to consider the possible causes of exercise intolerance after PEA. We propose three possible explanations.

A likely explanation for persistent exercise intolerance is that even when resting hemodynamics normalize, exercise hemodynamics may remain abnormal post PEA. Although we did not do invasive hemodynamic measurements during exercise, our finding of a low exercise oxygen pulse (an index of stroke volume) is consistent with this hypothesis. Indeed, it was previously reported that the mPAP/CO slope during exercise remains elevated after PEA, indicating an abnormal pulmonary vascular response and increase in RV afterload during exercise [31-33]. The finding that preoperative TLCO predicts persistent exercise intolerance after PEA is interesting in this context. TLCO could be considered a marker of distal vasculopathy not accessible to PEA; distal vasculopathy and/or vascular remodelling could increase RV afterload especially during exercise and thereby explain persistent exercise intolerance. On the other hand, in patients with CTED significant improvements in exercise RHC and normalized mPAP/CO slope have been shown [34]. Exercise RHC was not performed in our analysis but would certainly have been useful in determining whether

abnormal exercise hemodynamics are a major factor. Correlations between peak VO_2 and resting PVR and mPAP were only weak to moderate in strength, but exercise mPAP and PVR are probably not predicted by resting values. In a previous cohort study of PAH and inoperable CTEPH patients, exercise cardiac index was the only good predictor of peak VO_2, whereas resting mPAP and PVR were not strongly related to peak VO_2 [7]. However, our observation of a low exercise O_2 pulse is not exclusively explained by an abnormal increase in afterload during exercise. An alternative explanation would be a low exercise stroke volume due to afterload independent RV dysfunction, for example related to changes of intrinsic RV contractility (e.g. due to irreversible RV damage or deconditioning) or diastolic dysfunction, for example caused by RV fibrosis. While CMR-based RV function significantly improved after PEA, RVEF was only weakly correlated with peak VO_2 (comparable to previous research in PAH [35]). RVEDVI or RVESVI did not correlate with peak VO_2, not even in the subgroup of patients with primarily cardiovascular limitation (data not shown). This discrepancy might again be explained by a poor correlation between resting and exercise measurements of RV dimensions.

A third explanation for exercise intolerance and a low exercise O_2 pulse is impaired peripheral oxygen extraction due to peripheral muscle dysfunction or deconditioning. The importance of deconditioning to explain exercise intolerance after PEA cannot be deduced from our data. However, as peak VO_2 has been shown to improve after exercise training in severe PAH and inoperable CTEPH patients [36], this likely also holds true for operated patients and underlines the importance of a structured rehabilitation and exercise training program after PEA. Since a structured rehabilitation/exercise training program was not part of standard care after PEA, no conclusions regarding the role of deconditioning can be drawn.

Whether persistent dead space ventilation and ventilatory (in)efficiency are determining factors of exercise capacity after PEA is questionable. We made no direct measurements of dead space, but VE/VCO_2 at the anaerobic threshold (a marker of ventilatory efficiency) was only weakly correlated with peak VO_2. Surprisingly, $PETCO_2$ was similar between patients with a normal exercise tolerance and patients with exercise intolerance. Moreover, a ventilatory limitation as the primary cause of exercise intolerance was only present in 7% of patients; while eight patients had a known diagnosis of obstructive lung disease, in only two patients this led to a ventilatory limitation as the primary cause of exercise intolerance. Comorbidities did not seem to be a major explanation of exercise capacity in our cohort of patients. Median BMI was slightly increased but not different between patients with normal or low exercise capacity. Overall prevalence of comorbidities was low and similar in patients with or without exercise intolerance. The one exception is left ventricular function. Although median LVEF was normal and comparable between groups, a larger number of patients with exercise intolerance had a slightly decreased LVEF (figure 4). However, because PAWP was normal in both patient groups it seems unlikely that LV dysfunction (systolic or diastolic) was a relevant factor explaining exercise intolerance.

Preoperative prediction of postoperative exercise intolerance may help to select patients suitable for surgery and may also help to manage patients' expectations from the procedure. Lower preoperative TLCO was a strong predictor of persistent exercise intolerance 6 months after PEA, while pre-surgical hemodynamics, CMR and imaging were not predictive. This adds to the existing data on TLCO and outcomes after PEA in CTEPH. In a French cohort, pre-PEA TLCO predicted hemodynamic improvement (PVR decline) after PEA; an association with post-PEA mortality could not be found, perhaps because of the low mortality rates after PEA [37]. Another cohort analysis found a lower TLCO/VA to be a predictor for poor long-term

survival and a smaller decline in PVR after PEA [38]. While these previous publications provide evidence regarding pre-PEA TLCO and hemodynamic response, we add evidence of an association between pre-PEA TLCO and the functional response after PEA. TLCO probably reflects distal vasculopathy and (post) capillary remodelling, as previously shown to be present in CTEPH [39].

Since in our cohort 13 out of 86 patients did not undergo follow-up investigations due to logistical and/or medical reasons, there is a potential selection bias in our study. In our centre, approximately two third of CTEPH patients receive surgery. This is in agreement with rates of operability in a large international CTEPH registry [1]. In addition, outcomes after PEA (survival and hemodynamic outcomes) were comparable to other intermediate-size CTEPH centres [1].

16% of patients had a presumed submaximal test as the explanation for the decreased peak VO_2. This constitutes a minority and did not skew the results of our analysis. Since chronotropic incompetence is often present in pulmonary hypertension [7,35], applying the criteria for a maximal test may result in labelling a test as submaximal while in reality a cardiovascular limitation is present.

We did not analyse the consequences of exercise intolerance for quality of life. This would have provided more insight into the clinical importance of exercise intolerance post PEA and could have indicated whether exercise capacity would be a more useful outcome measure after PEA instead of resting hemodynamics. Previous studies showed clinically significant improvements in all domains after PEA, but in the physical domain scores remained behind in comparison with reported normal scores [40-41].

In conclusion, although PEA is the treatment of choice in eligible CTEPH patients and leads to excellent hemodynamic improvements and survival, exercise intolerance was present in two third of patients after PEA. While persistent exercise intolerance was mainly determined by a cardiovascular limitation, not all exercise intolerance could be explained by the presence of residual PH. While pre-PEA hemodynamics, RV function and imaging do not predict persistent exercise intolerance after PEA, a lower preoperative TLCO serves as a strong predictor of persistent exercise intolerance after PEA. TLCO thereby provides an easily accessible marker to predict the functional response to PEA in CTEPH.
Although additional research is needed regarding its impact on survival and need for additional treatment after PEA, CPET provides clinically meaningful outcome parameters in CTEPH after PEA.

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References

[1] Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk K, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E, Simonneau G. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 2016; 133: 859-871.

[2] Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, Treacy C, Ponnaberanam A, Condliffe R, Sheares K, Taboada D, Dunning J, Tsui S, Ng C, Gopalan D, Screaton N, Elliot C, Gibbs S, Howard L, Corris P, Lordan J, Johnson M, Peacock A, MacKenzie-Ross R, Schreiber B, Coghlan G, Dimopoulos K, Wort SJ, Gaine S, Moledina S, Jenkins DP, Pepke-Zaba J. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the United Kingdom National Cohort. Circulation 2016; 133: 1761-1771.

[3] Quadery SR, Swift AJ, Billings CG, Thompson AAR, Elliot CA, Hurdman J, Charalampopoulos A, Sabroe I, Armstrong IJ, Hamilton N, Sephton P, Garrad S, Pepke-Zaba J, Jenkins DP, Screaton N, Rothman AM, Lawrie A, Cleveland T, Thomas S, Rajaram S, Hill C, Davies C, Johns CS, Wild JM, Condliffe R, Kiely DG. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. Eur Respir J 2018; 52: 1800589.

[4] Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares J, Tsui SS, Armstrong IJ, Torpy C, Crackett R, Carlin CM, Das C, Coghlan JG, Pepke-Zaba J. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008; 177: 1122-1127.

[5] Balady GJ, Arena R, Sietsema K, Myers K, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Ketevian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; American Heart

Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010; 122: 191-225.

[6] Schwaiblmair M, Faul C, von Scheidt W, Berghaus TM. Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. BMC Pulm Med 2012; 12: 23.

[7] Blumberg FC, Arzt M, Lange T, Schroll S, Pfeifer M, Wensel R. Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension. Eur J Heart Fail 2013; 15: 771-775.

[8] Wensel R, Francis DP, Meyer FJ, Opitz CF, Bruch L, Halank M, Winkler J, Seyfarth HJ, Gläser S, Blumberg F, Obst A, Dandel M, Hetzer R, Ewert R. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol 2013; 167: 1193-1198.

[9] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MK, Lee I-M, Nieman D, Swain D. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011; 43: 1334-1359.

[10] Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth FFJ, Wilkens H, Katus HA, Olschewski H, Grünig E. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation 2006; 114: 1482-1489.

[11] Nagel C, Prange F, Guth S, Herb J, Ehlken N, Fischer C, Reichenberger F, Rosenkranz S, Seyfarth H-J, Mayer E, Halank M, Grünig E. Exercise training improves exercise capacity and quality of life in patients with inoperable or residual chronic thromboembolic pulmonary hypertension. PLoS ONE 2012; 7: e41603.

[12] Matsuda H, Ogino H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Kobayashi J, Yagihara T, Kitamura S. Long-term recovery of exercise ability after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg 2006; 82: 1338-1343.

[13] Iwase T, Nagaya N, Ando M, Satoh T, Sakamaki F, Kyotani S, Takaki H, Goto Y, Ohkita Y, Uematsu M, Nakanishi N, Miyatake K. Acute and chronic effect of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. Heart 2001; 86: 188-192.

[14] van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk Noordegraaf A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011; 58: 2511-2519.

[15] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913

[16] American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211-277.

[17] Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1985) 1986; 60: 2020-2027.

[18] Gläser S, Ittermann T, Schäper C, Obst A, Dörr M, Spielhagen T, Felix SB, Völzke H, Bollmann T, Opitz CF, Warnke C, Koch B, Ewert R. The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing. Pneumologie 2013; 67: 58-63.

[19] Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001; 104: 429-435.

[20] Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun X-G, Whipp BJ. Principles of exercise testing and interpretation, including pathophysiology and clinical applications. Fifth edition, 2011.

[21] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.

[22] Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26: 720-735.

[23] Freed DH, Thomson BM, Berman M, Tsui SS, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary endarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg 2011; 141: 383-387.

[24] van der Plas MN, Surie S, Reesink HJ, van Steenwijk RP, Kloek JJ, Bresser P. Longitudinal follow-up of six-minute walk distance after pulmonary endarterectomy. Ann Thorac Surg 2011; 91: 1094-1099.

[25] Reesink HJ, van der Plas MN, Verhey NE, van Steenwijk RP, Kloek JJ, Bresser P. Six-minute walk distance as parameter of functional outcome after pulmonary endarterectomy

for chronic thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 2007; 133: 510-516.

[26] de Perrot M, McRae K, Shargall Y, Thenganatt J, Moric J, Mak S, Granton JT. Early postoperative pulmonary vascular compliance predicts outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Chest 2011; 140: 34-41.

[27] Ghio S, Morsolini M, Corsico A, Klersy C, Mattiucci G, Raineri C, Scelsi L, Vistarini N, Oltrona Visconti L, D'Armini AM. Pulmonary arterial compliance and exercise capacity after pulmonary endarterectomy. Eur Respir J 2014; 43: 1403-1409.

[28] Corsico AG, D'Armini AM, Conio V, Sciortino A, Pin M, Grazioli V, Di Vincenzo G, Di Domenica R, Celentano A, Vanini B, Grosso A, Gini E, Albicini F, Merli VN, Ronzoni V, Ghio S, Klersy C, Cerveri I. Persistent exercise limitation after successful pulmonary endarterectomy: frequency and determinants. Respir Res 2019; 20: 34.

[29] Corsico AG, D'Armini AM, Cerveri I, Klersy C, Ansaldo E, Niniano R, Gatto E, Monterosso C, Morsolini M, Nicolardi S, Tramontin C, Pozzi E, Viganò M. Long-term outcome after pulmonary endarterectomy. Am J Respir Crit Care Med 2008; 178: 419-424.

[30] Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, Musella F, Gargiulo P, Marciano C, Perrone-Filardi P. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. J Am Coll Cardiol 2012; 60: 1192-1201.

[31] Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. J Am Heart Assoc 2015; 4: e001602.

[32] Richter MJ, Sommer N, Gall H, Voswinckel R, Seeger W, Mayer E, Wiedenroth CB, Rieth A, Grimminger F, Guth S, Ghofrani HA. Pulmonary hemodynamic response to exercise in chronic thromboembolic pulmonary hypertension before and after pulmonary endarterectomy. Respiration 2015; 90: 63-73.

[33] Bonderman D, Martischnig AM, Vonbank K, Nikfardjam M, Meyer B, Heinz G, Klepetko W, Naeije R, Lang IM. Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. Chest 2011; 139: 122-127.

[34] Guth S, Wiedenroth CB, Rieth A, Richter MK, Gruenig E, Ghofrain HA, Arlt M, Liebetrau C, Prüfer D, Rolf A, Hamm CW, Mayer E. Exercise right heart catheterisation before and after pulmonary endarterectomy in patients with chronic thromboembolic disease. Eur Respir J 2018; 52: 1800458.

[35] Groepenhoff H, Vonk Noordegraaf A, van de Veerdonk MC, Boonstra A, Westerhof N, Bogaard HJ. Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. PLoS ONE 2013; 8: e72013.

[36] Ehlken N, Lichtblau M, Klose H, Weidenhammer J, Fischer C, Nechwatal R, Uiker S, Halank M, Olsson K, Seeger W, Gall H, Rosenkranz S, Wilkens H, Mertens D, Seyfarth HJ, Opitz C, Ulrich S, Egenlauf B, Grünig E. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thromboembolic pulmonary hypertension: a prospective, randomized, controlled trial. Eur Heart J 2016; 37: 35-44.

[37] Tromeur C, Jaïs X, Mercier O, Couturaud F, Montani D, Savale L, Jevnikar M, Weatherald J, Sitbon O, Parent F, Fabre D, Mussot S, Dartevelle P, Humbert M, Simonneau G, Fadel E. Factors predicting outcome after pulmonary endarterectomy. PLoS One 2018; 13: e0198198.

[38] Suda R, Tanabe N, Ishida K, Kato F, Urushibara T, Sekine A, Nishimura R, Jujo T, Sugiura T, Shigeta A, Sakao S, Tatsumi K. Prognostic and pathophysiological marker for patients with chronic thromboembolic pulmonary hypertension: usefulness of diffusing capacity for carbon monoxide at diagnosis. Respirology 2017; 22: 179-186.

[39] Dorfmüller P, Günther S, Ghigna MR, Thomas de Montpréville V, Boulate D, Paul JF, Jaïs X, Decante B, Simonneau G, Dartevelle P, Humbert M, Fadel E, Mercier O. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. Eur Respir J 2014; 44: 1275-1288.

[40] Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, Kapelanski DP, Watt CN, Moser KM. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 1999; 160: 523-528.

[41] Mathai SC, Mayer E, Pepke-Zaba J, Nikkho S, Simonneau G. Quality of life in patients with chronic thromboembolic pulmonary hypertension. Eur Respir J 2016; 48: 526-537.

Table 1: comparison of hemodynamic and CMR parameters pre-PEA versus 6 months post-PEA

Parameter	Pre-PEA	Post-PEA	P value
RHC			
mPAP (mmHg)	43 (33-50)	23 (18-27)	< 0.001*‡
PVR (dynes.s.cm^{-5})	551 (330-726)	176 (131-243)	< 0.001*‡
PAWP (mmHg)	10.0 (2.7)	9.7 (3.3)	0.567
CI (L/min/m^2)	2.4 (2.1-2.8)	2.9 (2.6-3.4)	< 0.001*‡
RAP (mmHg)	7 (6-10)	5 (3-6)	< 0.001*‡
SvO_2 (%)	65 (61-70)	70 (68-74)	< 0.001*‡
CMR imaging			
RVEF (%)	46 (30-55)	58 (48-63)	< 0.001*‡
RVESVI (mL/m^2)	43 (29-67)	24 (17-34)	< 0.001*‡
RVEDVI (mL/m^2)	78 (68-96)	58 (46-69)	< 0.001*‡
LVEF (%)	64 (8)	64 (7)	0.663
Other			
6MWD (m)	418 (108)	482 (89)	< 0.001*
NT-proBNP (ng/L)	474 (144-1372)	204 (106-365)	< 0.001*‡

Data presented as mean (SD), median (IQR) or number of patients (%). Statistical tests used: paired t test. Statistical significance indicated with an *. ‡ parametric test performed after log-transforming data.

CMR: cardiac magnetic resonance; PEA: pulmonary endarterectomy; RHC: right heart catheterization; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; CI: cardiac index; RAP: right atrial pressure; SvO_2: central venous oxygen saturation; RVEF: right ventricular ejection fraction; RVESVI: right ventricular end-systolic volume index; RVEDVI: right ventricular end-

diastolic volume index; LVEF: left ventricular ejection fraction; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal pro brain natriuretic peptide.

Table 2: univariate and multivariate analysis of baseline predictors for persistent exercise intolerance after PEA

Parameters	**Univariate analysis**		**Multivariate analysis (backward, conditional)**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Time CTEPH diagnosis to PEA (days)	1.006 (1.000-1.013)	0.048	1.009 (1.000-1.019)	0.062
Baseline RAP (mmHg)	1.147 (0.982-1.338)	0.083		
Baseline 6MWD (m)	0.992 (0.985-0.999)	0.017		
Baseline TLCO (% predicted)	0.915 (0.866-0.967)	0.002	0.935 (0.883-0.991)	0.023

PEA: pulmonary endarterectomy; OR: odds ratio; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; RAP: right atrial pressure; 6MWD: 6-minute walking distance; TLCO: transfer factor of the lung for carbon monoxide.

Figure legends

Figure 1: timeline and flow chart of patient selection

PEA: pulmonary endarterectomy; CPET: cardiopulmonary exercise testing; CMR: cardiac magnetic resonance; RHC: right heart catheterization

Figure 2: CPET parameters pre-PEA compared to 6 months post-PEA

CPET: cardiopulmonary exercise test; PEA: pulmonary endarterectomy; VO_2: oxygen consumption; HRR: heart rate reserve; V_E/V_{CO2}: ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; S_pO_2: peripheral oxygen saturation.

Figure 3: pie charts indicating main determinants of exercise limitation

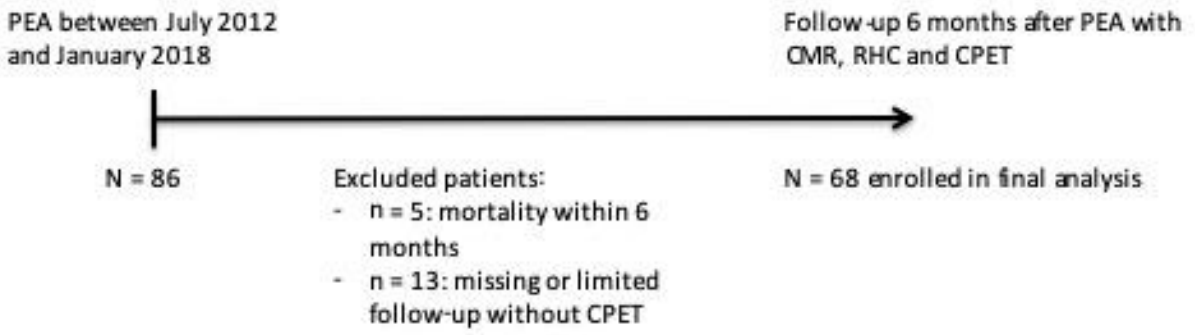
PEA: pulmonary endarterectomy; VO_2: oxygen consumption

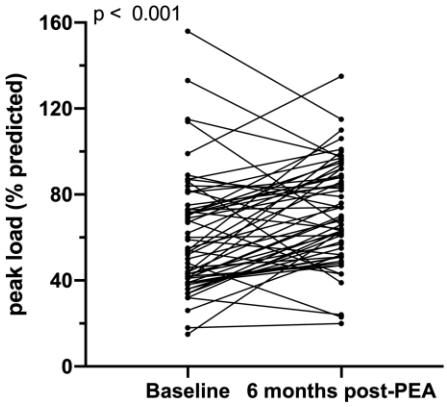
Figure 4: comparison of RHC and CMR parameters 6 months post-PEA between those with or without persistent exercise intolerance 6 months post-PEA

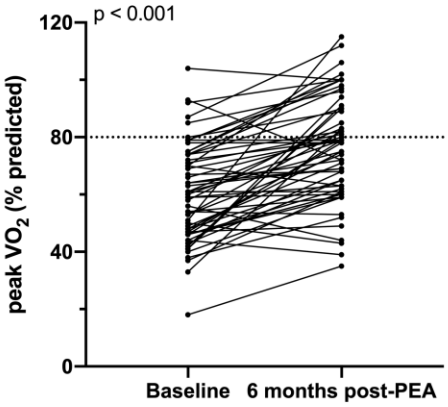
Horizontal bars indicate median and interquartile range (mPAP, PVR, RAP) or mean and standard deviation (CI, RVESVI, RVEDVI, RVEF and LVEF). Statistical test used: unpaired t test (after log transformation of non-normal distributed data). RHC: right heart catheterization; CMR: cardiac magnetic resonance; PEA: pulmonary endarterectomy; VO_2: oxygen consumption; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; CI: cardiac index; RVESVI: right ventricular end-systolic volume index; RVEDVI: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction.

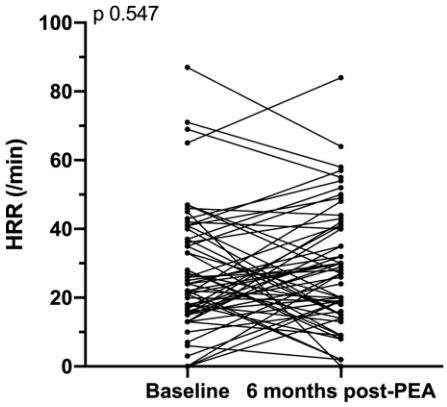
Figure 5: correlation between mPAP/PVR/pulmonary arterial compliance post-PEA and peak VO_2 post-PEA

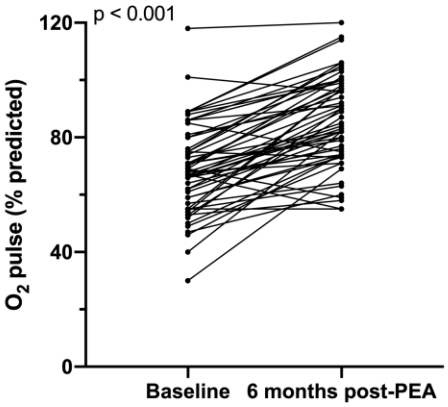
A: correlation between log-transformed mPAP and peak VO_2. The vertical dotted line indicates mPAP 20 mmHg; the horizontal dotted line indicates peak VO_2 80% of predicted. B: correlation between log-transformed PVR and peak VO_2. C: correlation between log-transformed pulmonary arterial compliance and peak VO_2. Pearson correlation coefficients shown, after log transformation of mPAP, PVR and compliance.
VO_2: oxygen consumption; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PEA: pulmonary endarterectomy.

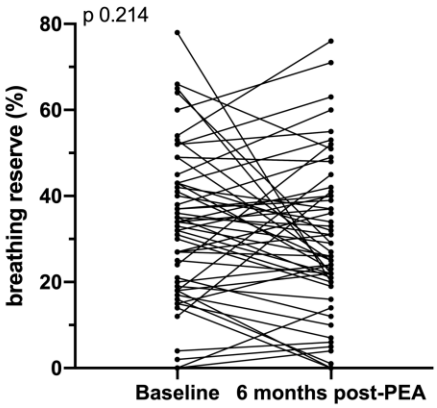

PEA between July 2012 and January 2018
Follow-up 6 months after PEA with CMR, RHC and CPET
N = 86
Excluded patients:
- n = 5: mortality within 6 months
- n = 13: missing or limited follow-up without CPET
N = 68 enrolled in final analysis

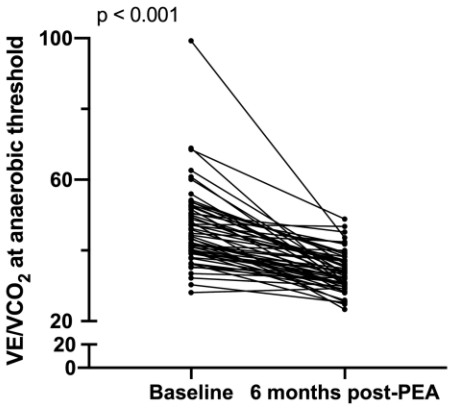

p < 0.001
peak load (% predicted)
160
120
80
40
0
Baseline
6 months post-PEA

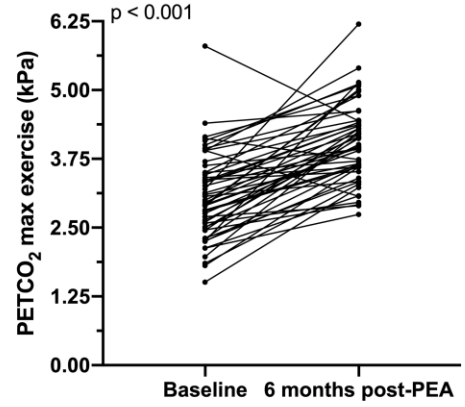

p < 0.001
peak VO2 (% predicted)
120
80
40
0
Baseline
6 months post-PEA

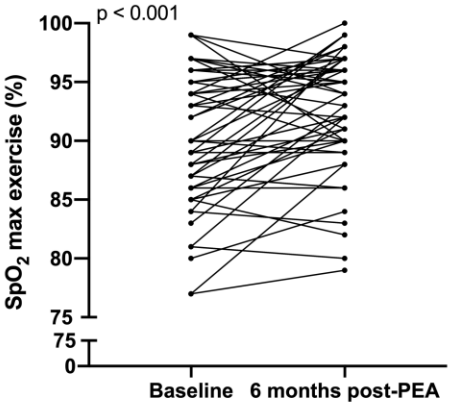

p 0.547
HRR (/min)
100
80
60
40
20
0
Baseline
6 months post-PEA

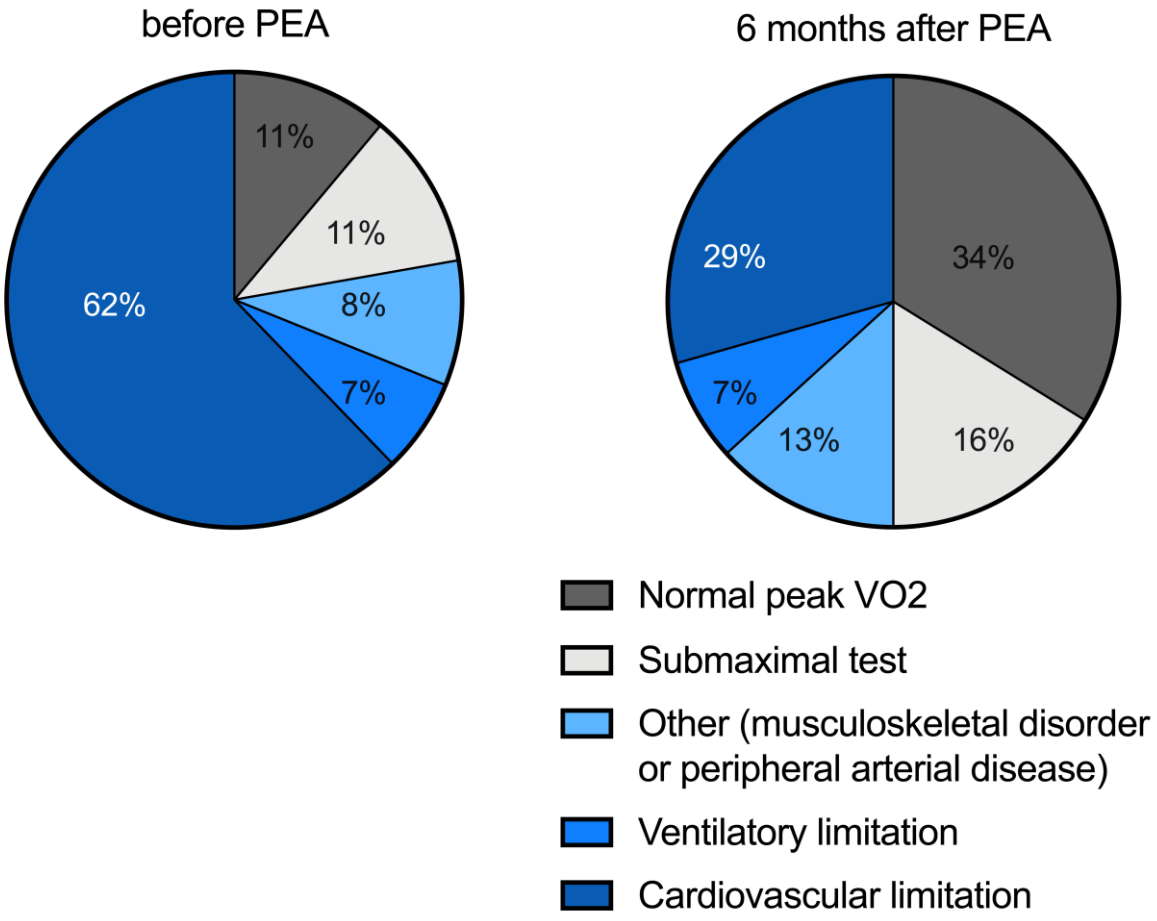

p < 0.001
O2 pulse (% predicted)
120
80
40
0
Baseline
6 months post-PEA

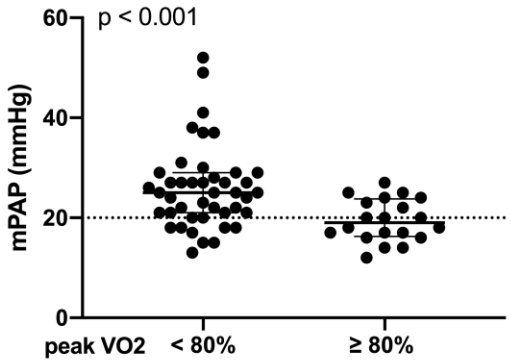

p 0.214
breathing reserve (%)
80
60
40
20
0
Baseline
6 months post-PEA

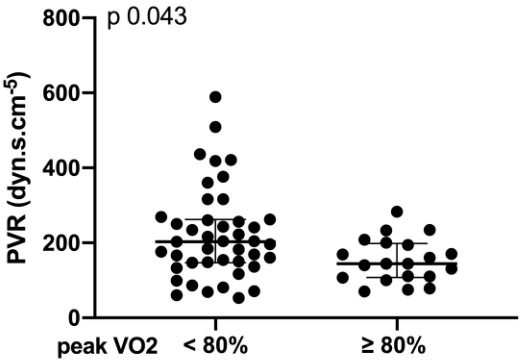

p < 0.001
VE/VCO2 at anaerobic threshold
100
60
20
20
0
Baseline
6 months post-PEA

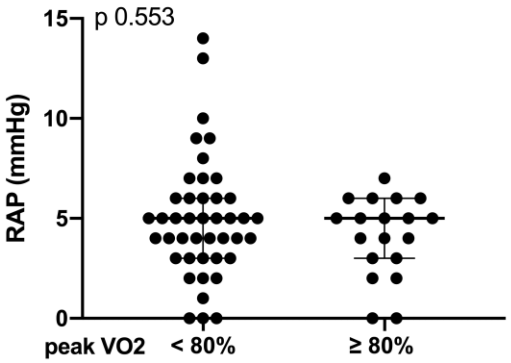

p < 0.001
PETCO2 max exercise (kPa)
6.25
5.00
3.75
2.50
1.25
0.00
Baseline
6 months post-PEA

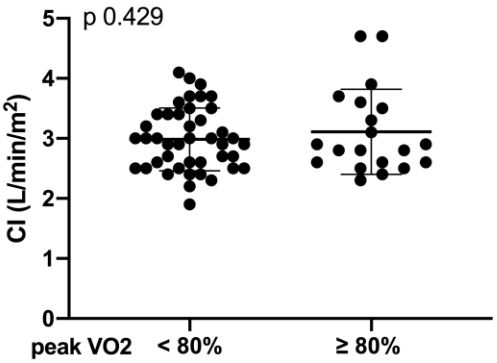

p < 0.001
SpO2 max exercise (%)
100
95
90
85
80
75
75
0
Baseline
6 months post-PEA

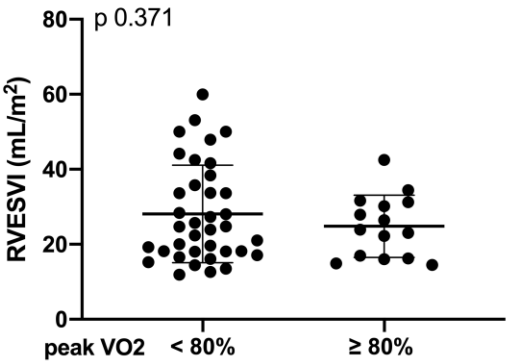

before PEA
11%
11%
8%
7%
62%
6 months after PEA
34%
16%
13%
7%
29%
Normal peak VO2
Submaximal test
Other (musculoskeletal disorder or peripheral arterial disease)
Ventilatory limitation
Cardiovascular limitation

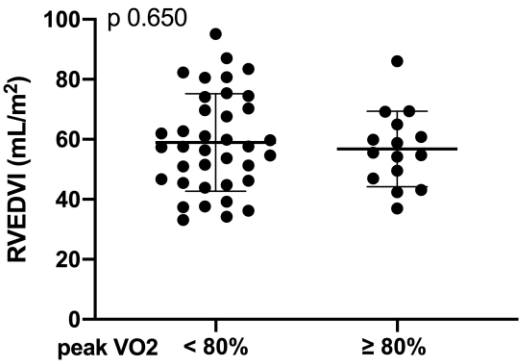

p < 0.001
mPAP (mmHg)
60
40
20
0
peak VO2 < 80%
≥ 80%

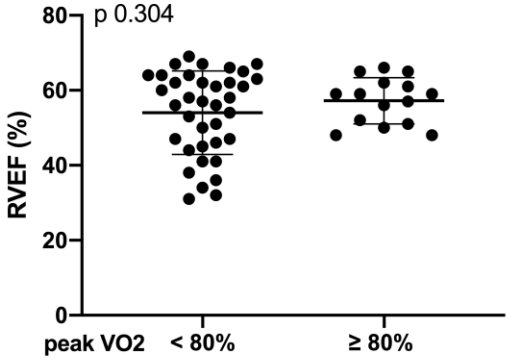

p 0.043
PVR (dyn.s.cm-5)
800
600
400
200
0
peak VO2 < 80%
≥ 80%

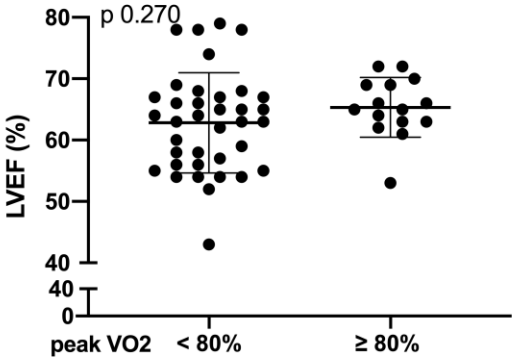

p 0.553
RAP (mmHg)
15
10
5
0
peak VO2 < 80%
≥ 80%


p 0.429
CI (L/min/m2)
5
4
3
2
1
0
peak VO2 < 80%
≥ 80%


p 0.371
RVESVI (mL/m2)
80
60
40
20
0
peak VO2 < 80%
≥ 80%


p 0.650
RVEDVI (mL/m2)
100
80
60
40
20
0
peak VO2 < 80%
≥ 80%


p 0.304
RVEF (%)
80
60
40
20
0
peak VO2 < 80%
≥ 80%


p 0.270
LVEF (%)
80
70
60
50
40
40
0
peak VO2 < 80%
≥ 80%

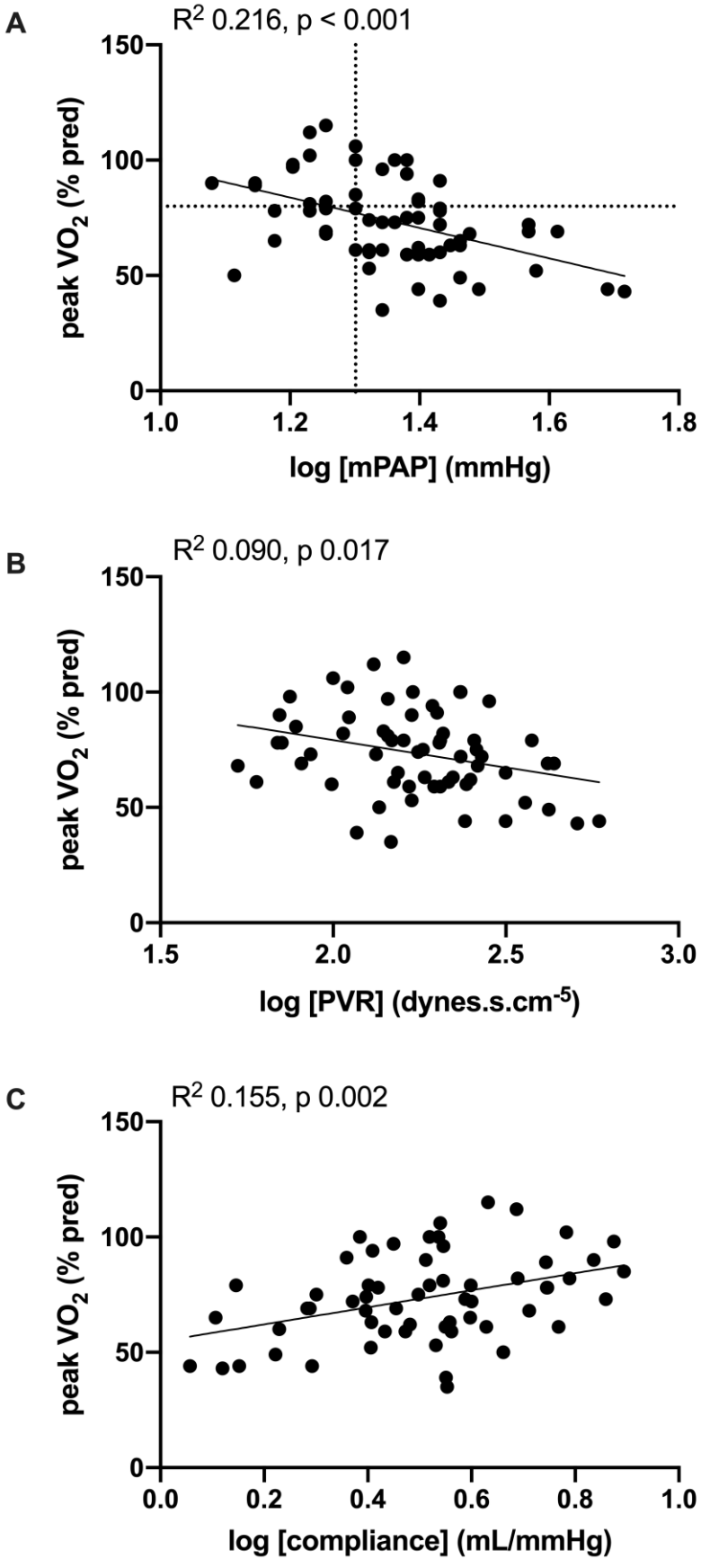

A
R2 0.216, p < 0.001
peak VO2 (% pred)
150
100
50
0
1.0
1.2
1.4
1.6
1.8
log [mPAP] (mmHg)
B
R2 0.090, p 0.017
peak VO2 (% pred)
150
100
50
0
1.5
2.0
2.5
3.0
log [PVR] (dynes.s.cm-5)
C
R2 0.155, p 0.002
peak VO2 (% pred)
150
100
50
0
0.0
0.2
0.4
0.6
0.8
1.0
log [compliance] (mL/mmHg)

Table A: comparison of CPET parameters pre-PEA versus 6 months post-PEA

Parameter	**Pre-PEA**	**Post-PEA**	**P value**
Peak load (% predicted)	54 (41-73)	69 (52-92)	< 0.001*
Peak VO_2 (% predicted)	60.0 (16.9)	75.8 (18.3)	< 0.001*
VO_2 at AT (% predicted peak VO_2)	42.0 (9.7)	48.6 (11.5)	< 0.001*
VO_2/work rate (mL/min/W)	7.2 (1.8)	8.8 (1.4)	< 0.001*
Max HR (/min)	135 (21)	133 (23)	0.423
HRR (/min)	24 (15-37)	27 (15-41)	0.547
O2 pulse (% predicted)	69.1 (15.7)	85.8 (15.8)	< 0.001*
BR (%)	33.3 (17.4)	30.6 (17.7)	0.214
$P_{ET}CO_2$ at max exercise (kPa)	2.96 (2.48-3.50)	3.98 (3.60-4.43)	< 0.001*‡
V_E/V_{CO2} at AT	44.0 (39.7-51.6)	33.5 (30.4-37.2)	< 0.001*‡
S_pO_2 at max exercise (%)	90 (86-95)	93 (90-96)	< 0.001*

Data presented as mean (SD), median (IQR) or number of patients (%). Statistical tests used: paired t test and Wilcoxon matched-pairs signed rank test. Statistical significance indicated with an *. ‡ parametric test performed after log-transforming data.

CPET: cardiopulmonary exercise test; PEA: pulmonary endarterectomy; VO_2: oxygen consumption; AT: anaerobic threshold; HR: heart rate; HRR: heart rate reserve; O_2 pulse: oxygen pulse; BR: breathing reserve; $P_{ET}CO_2$: end-tidal partial pressure of carbon dioxide; V_E/V_{CO2}: ventilatory equivalent for carbon dioxide; S_pO_2: peripheral oxygen saturation.

Table B: baseline characteristics in patients with exercise intolerance after PEA compared to patients with normalized exercise capacity after PEA

Parameter	**Peak VO_2 < 80% post-PEA** **N = 45**	**Peak $VO_2 \geq$ 80% post-PEA** **N = 23**	**P value**
Age at PEA (years)	63 (54-68)	59 (48-68)	0.573
Male gender (n, %)	27 (60%)	12 (52%)	0.537
Time CTEPH diagnosis to PEA (days)	161 (132-279)	119 (84-147)	0.106‡
BMI (kg/m^2)	26.0 (23.9-29.1)	27.1 (24.5-29.7)	0.649‡
NYHA class I-II-III-IV (%)	0/30/63/7%	18/50/27/5%	0.001*
PH-specific medication pre-PEA (n, %)	20 (44%)	3 (13%)	0.014*
NT-proBNP (ng/L)	569 (173-1491)	316 (88-1250)	0.195‡
Proximal vs distal disease	40-60%	47-52%	0.516
Pre-PEA RHC			
mPAP (mmHg)	42.4 (10.2)	39.5 (10.6)	0.279
PVR ($dynes.s.cm^{-5}$)	544 (330-729)	553 (332-732) *n = 22*	0.691‡
PAWP (mmHg)	10.3 (2.7) *n = 44*	9.2 (2.9)	0.104
CI ($L/min/m^2$)	2.5 (2.0-2.8) *n = 44*	2.4 (2.2-2.9) *n = 22*	0.545‡
RAP (mmHg)	8 (6-12) *n = 44*	7 (5-9) *n = 21*	0.118‡
S_vO_2 (%)	64 (59-70) *n = 40*	67 (63-70) *n = 22*	0.147
Pre-PEA CMR			
RVEF (%)	45 (30-55) *n = 30*	46 (29-61) *n = 15*	0.552‡
RVESVI (mL/m^2)	42.0 (30.5-68.4) *n = 30*	44.4 (26.5-67.0) *n = 15*	0.491‡

RVEDVI (mL/m^2)	79.1 (67.0-98.7) *n = 30*	75.8 (67.6-92.0) *n = 15*	0.583‡
LVEF (%)	64 (8.8) *n = 30*	64 (8.9) *n = 15*	0.934
Pre-PEA functional tests			
6MWD (meters)	393 (103) *n = 36*	473 (101) *n = 17*	0.010*
TLCO (% predicted)	61 (56-67) *n = 38*	76 (71-83) *n = 19*	< 0.001*‡

Data presented as mean (SD), median (IQR) or number of patients (%). Data apply to the total cohort (45 and 23 patients) unless otherwise stated. Statistical tests used: unpaired t test, Mann Whitney test, Chi-square test, Fisher's exact test.

‡ parametric test performed after log-transforming data. Statistical significance indicated with an *.

PEA: pulmonary endarterectomy; VO_2: oxygen consumption; CTEPH: chronic thromboembolic pulmonary hypertension; BMI: body mass index; NYHA: New York Heart Association; PH: pulmonary hypertension; NT-proBNP: N-terminal pro brain natriuretic peptide; RHC: right heart catheterization; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index; RAP: right atrial pressure; S_vO_2: central venous oxygen saturation; CMR: cardiac magnetic resonance; RVEF: right ventricular ejection fraction; RVESVI: right ventricular end-systolic volume index; RVEDVI: right ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; 6MWD: 6-minute walking distance; TLCO: transfer factor of the lung for carbon monoxide.

Table C: pre-PEA CPET in patients with exercise intolerance after PEA compared to patients with normalized exercise capacity after PEA

	Peak VO_2 < 80% post-PEA N = 45	**Peak $VO_2 \geq$ 80% post-PEA N = 23**	**P value**
Peak load (% predicted)	43 (37-70) *n = 36*	71 (54-82)	< 0.001*‡
Peak VO_2 (% predicted)	54.8 (14.1) *n = 36*	68.0 (18.0)	0.003*
VO_2 at AT (% predicted peak VO_2)	40.0 (8.8) *n = 24*	45.1 (10.4) *n = 16*	0.105
VO_2/WR (mL/min/Watt)	7.2 (1.8) *n = 23*	7.4 (1.8) *n = 16*	0.752
HRR (/min)	27 (17-41) *n = 36*	18 (13-33)	0.023*‡
Peak O_2 pulse (% predicted)	65.1 (13.8) *n = 35*	75.3 (16.7) *n = 22*	0.016*
BR (%)	35.4 (18.5) *n = 34*	29.9 (15.3) *n = 21*	0.251
V_E/V_{CO2} at AT	46.5 (40.0-52.4) *n = 34*	42.1 (38.0-49.0) *n = 22*	0.357
$P_{ET}CO_2$ (kPa) at max exercise	2.8 (2.5-3.9) *n = 32*	3.1 (2.8-3.4) *n = 21*	0.662
S_pO_2 rest (%)	94 (3) *n = 33*	96 (2) *n = 22*	0.006*
S_pO_2 max exercise (%)	90 (6) *n = 34*	92 (5)	0.066

Data presented as mean (SD) or median (IQR). Data apply to the total cohort (45 and 23 patients) unless otherwise stated.

Statistical tests used: unpaired t test, Mann Whitney test. ‡ parametric test performed after log-transforming data.

Statistical significance indicated with an *.

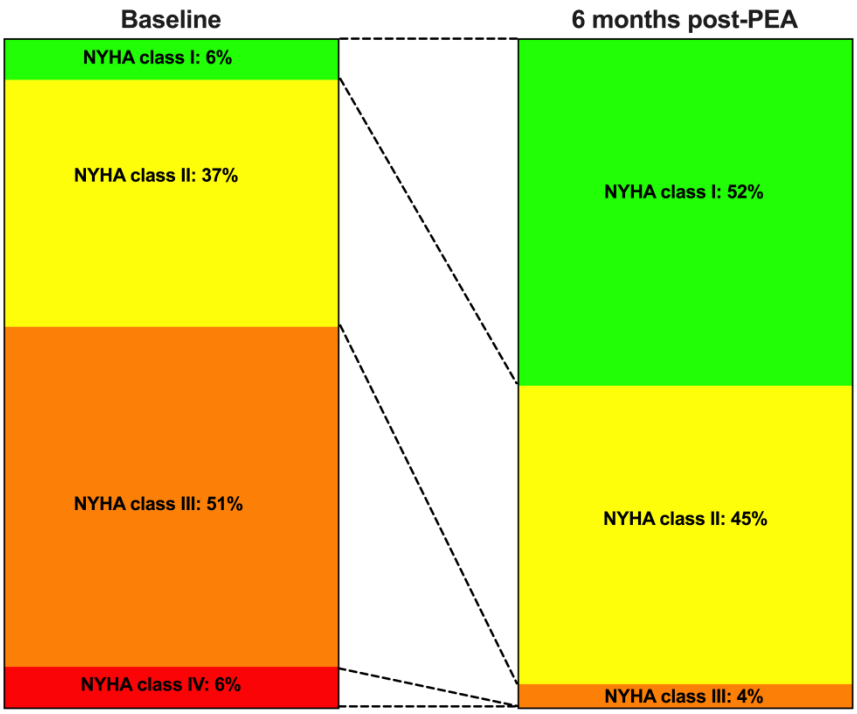
PEA: pulmonary endarterectomy; CPET: cardiopulmonary exercise test; VO_2: oxygen consumption; AT: anaerobic threshold; WR: work rate; HRR: heart rate reserve; O_2: oxygen; BR: breathing reserve; V_EV_{CO2}: ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; S_pO_2: peripheral oxygen saturation

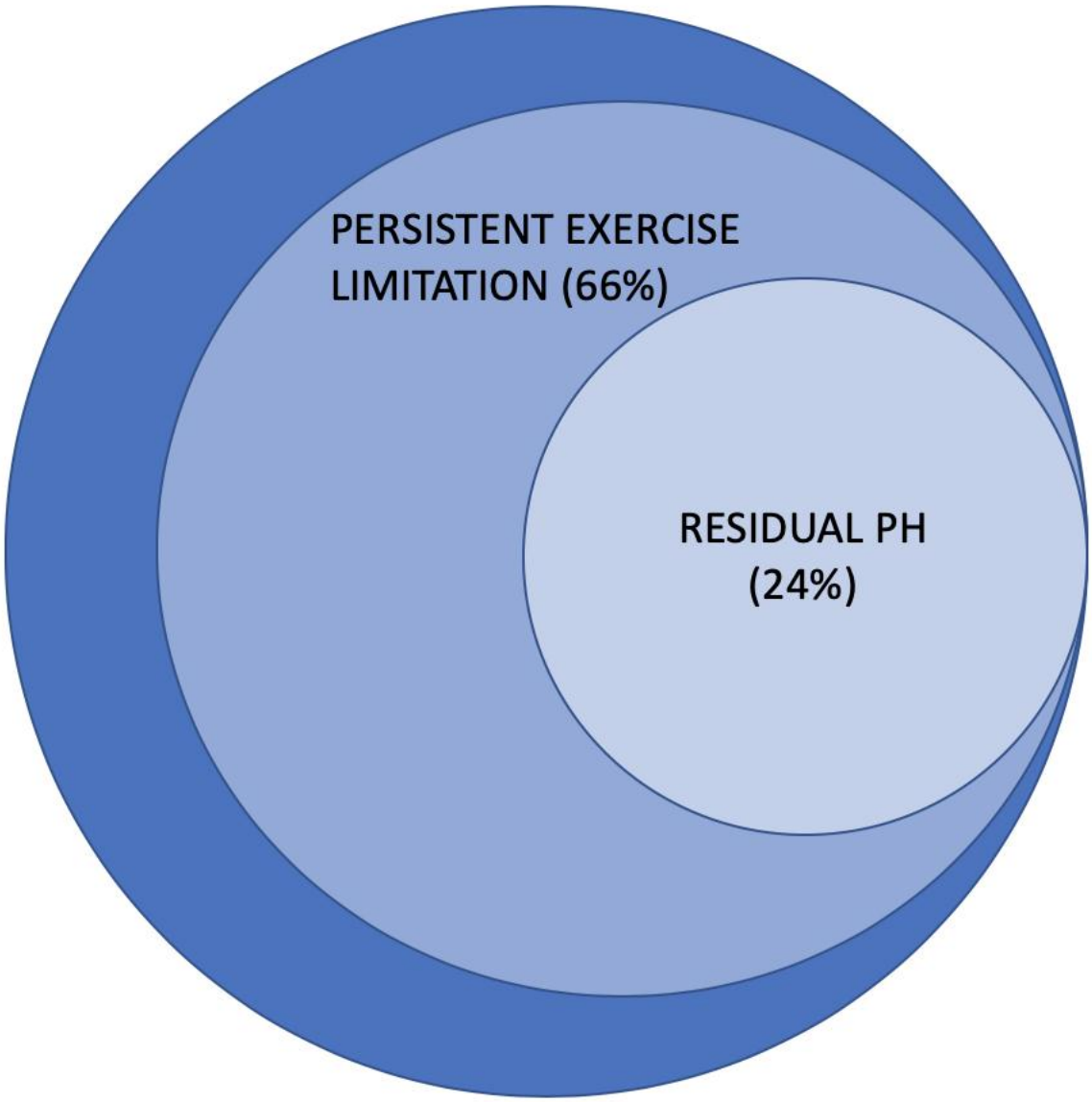
Figure A: NYHA class distribution at baseline (at time of CTEPH diagnosis) and 6 months after PEA

NYHA: New York Heart Association; CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy.

Figure B: Venn diagram indicating the relation between persistent exercise intolerance and residual pulmonary hypertension (PH).

The dark blue circle indicates the whole cohort; the smallest lightest blue circle indicates the patients with residual PH; the middle blue circle indicates the patients with persistent exercise intolerance after PEA. Residual PH defined by mPAP > 20 mmHg and PVR $\geq$ 240 dynes·s·cm^{-5}. The overlap between both residual PH and persistent exercise intolerance constitutes 23% of the whole cohort. None of the patients had residual PH without exercise intolerance; 40% had exercise intolerance without residual PH.


Baseline
6 months post-PEA
NYHA class I: 6%
NYHA class II: 37%
NYHA class III: 51%
NYHA class IV: 6%
NYHA class I: 52%
NYHA class II: 45%
NYHA class III: 4%


PERSISTENT EXERCISE LIMITATION (66%)
RESIDUAL PH (24%)