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Early View

Original research article

Non-invasive follow-up strategy after pulmonary endarterectomy for CTEPH

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Non-invasive follow-up strategy after pulmonary endarterectomy for CTEPH

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Take home message

In approximately one-third to half of CTEPH patients, residual pulmonary hypertension after pulmonary endarterectomy can be excluded based on cardiopulmonary exercise testing or echocardiography, without the need for right heart catheterisation.

Abstract

Background

The success of pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) is usually evaluated by performing a right heart catheterisation (RHC). Here, we investigate whether residual pulmonary hypertension (PH) can be sufficiently excluded without the need for a RHC, by making use of early postoperative hemodynamics, or NT-proBNP, cardiopulmonary exercise testing (CPET) and transthoracic echocardiography (TTE) six months after PEA.

Methods

In an observational analysis, residual PH after PEA measured by RHC was related to hemodynamic data from the postoperative ICU time and data from a six-month follow-up assessment including NT-proBNP, TTE and CPET. After dichotomization and univariate analysis, sensitivity, specificity, positive predictive value, negative predictive value (NPV) and likelihood ratios were calculated.

Results

Thirty-six out of 92 included patients had residual PH six months after PEA (39%). Correlation between early postoperative and six-month follow-up mean pulmonary artery pressure was moderate (Spearman rho 0.465, $p < 0.001$). Early hemodynamics did not predict late success. NT-proBNP > 300 ng/L had insufficient NPV (0.71) to exclude residual PH. Probability for PH on TTE had a moderate NPV (0.74) for residual PH. Peak oxygen consumption (VO_2) < 80% predicted had the highest sensitivity (0.85) and NPV (0.84) for residual PH.

Conclusions

CPET six months after PEA, and to a lesser extent TTE can be used to exclude residual CTEPH, thereby safely reducing the number of patients needing to undergo re-RHC after PEA.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is unique among the different types of pulmonary hypertension (PH) because of the availability of a potentially curative treatment by pulmonary endarterectomy (PEA) in eligible patients. PEA leads to significant improvements in survival compared to medical treatment [1-2], although residual PH is a frequent finding [3]. Residual PH is often mild and then requires no additional treatment. However, for some patients with significant residual PH, additional treatment with PH-specific medication and/or balloon pulmonary angioplasty (BPA) may be considered.

A definite diagnosis of residual PH requires a right heart catheterisation (RHC). To avoid unnecessary invasive procedures, a selection of patients with the lowest risk for residual PH would be helpful. This selection can be based on the last hemodynamic data in the early postoperative period or by performing non-invasive procedures during follow-up such as transthoracic echocardiography (TTE) and cardiopulmonary exercise testing (CPET).

We performed an observational analysis with the aim to evaluate the efficiency and safety of a strategy using early postoperative hemodynamics and non-invasive data at follow-up six months after PEA (N-terminal pro-brain natriuretic peptide (NT-proBNP), CPET and TTE) to exclude residual PH. Our hypothesis was that NT-proBNP, CPET and TTE would be feasible in excluding residual PH 6 months after PEA, while early postoperative hemodynamics are not.

Methods

Study subjects

Patients undergoing PEA between July 2012 and September 2019 in the Amsterdam University Medical Centre were enrolled in this observational analysis if at least six-month follow-up RHC was available. As per clinical protocol, NT-proBNP, CPET, six-minute walking testing (6MWT), RHC and TTE were analysed six months after PEA.

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 was performed as described previously [4]. In the intensive care unit (ICU), hemodynamic measurements were done employing the intraoperatively placed Swan-Ganz catheter. The last complete assessment before removal of the catheter was used in the analysis. Due to the risk of pulmonary artery rupture immediately after PEA, pulmonary artery wedge pressure (PAWP) measurements were not performed in the ICU. In the absence of left atrial pressures as a substitute, pulmonary vascular resistance (PVR) in the ICU could not be determined in this analysis.

TTE were analysed and classified as low/intermediate/high probability for PH according to the 2015 ESC/ERS PH guideline [5] by an experienced cardiologist blinded for the RHC results.

CPET consisted of a symptom-limited maximal incremental exercise test using a cycle ergometer [6]. Electrocardiogram (ECG), oxygen consumption (VO_2), CO_2 production (VCO_2), heart rate, tidal volume, breathing frequency, expiratory oxygen and CO_2 pressures, and peripheral oxygen saturation were recorded continuously. The anaerobic threshold was determined using the V-slope method [7]. Reference values from the Study of Health in Pomerania (SHIP) were used [8]. 6MWT was performed according to the 2002 ATS statement [9].

Study design and statistical analysis

Primary outcome of this study was the presence of residual PH, defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg according to the current guideline at the time of this study. In this study we analysed non-invasive markers for the presence of this residual PH.

Data are presented as mean (standard deviation), median (interquartile range (IQR)) or number of patients (%) where appropriate. Missing data were not imputed. Normal distribution was tested by using D'Agostino-Pearson omnibus normality test. Differences regarding continuous data were tested using unpaired t-tests or paired t-tests where appropriate; Wilcoxon matched-pairs signed-rank tests or Mann-Whitney tests were used where appropriate when distribution was not normal. In the setting of comparing multiple time-points with paired data, ANOVA or Friedman testing was performed, and correction for multiple comparison testing applied. Differences regarding categorical data were tested using a Chi-square test or Fisher's exact test. Correlation analysis was performed using Spearman correlation.

Cut-offs for continuous and ordinal variables (NT-proBNP, TTE probability of PH and CPET parameters) were based on suggested criteria of normality used in clinical practice [5, 10-11]. Variables were dichotomized and tested with univariate logistic regression to evaluate their association with residual PH. Since CPET parameters are highly interrelated and the number of cases relatively small, multivariate logistic regression analysis was not performed. Instead, testing characteristics (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR)) were determined for all parameters with $p < 0.10$ in univariate logistic regression analysis. In addition, receiver-operating characteristic (ROC) curve analysis was performed.

Statistical analysis was performed using GraphPad Prism version 9 (GraphPad Software, San Diego, California, USA) and IBM SPSS Statistics version 24.

Results

Patient population

Between July 2012 and September 2019, 118 patients underwent PEA in our centre. All patients with data available from at least the RHC six months after PEA were selected. Five patients died within six months after PEA; one patient underwent lung transplantation after PEA. Twenty patients were excluded because of incomplete or missing data. Altogether, 92 patients were included in this analysis (figure 1).

Characteristics at baseline (before PEA) of the analysed cohort are described in table 1: the majority of patients were male and the median body mass index (BMI) indicated that the majority of patients were overweight. Twenty-nine percent of patients used PH-specific medication before PEA. Residual PH six months post-PEA was present in 36 patients (39%). Fifty-six patients without residual PH were comparable to 36 patients with residual PH regarding gender, age, BMI and preoperative NT-proBNP.

None of the analysed patients were started on or continued PH-specific medication after PEA based on early hemodynamics in the ICU. In eight patients (out of 13 patients with mPAP ≥ 30 mmHg) PH-specific medication was started after the six-months' re-evaluation. Five patients with mPAP ≥ 30 mmHg at six months were not started on PH-specific medication. The decision to start additional treatment was at the treating physician's discretion, based on hemodynamics and symptoms.

Role of early hemodynamics

The median time between PEA and the last hemodynamic profile in the ICU (data available in 88 patients) was two days (range 0-10). The complete hemodynamic profiles at baseline, in the ICU and six months after PEA are shown in supplementary table A. The individual changes in mPAP before and after PEA are illustrated in supplementary figure A. While mPAP decreased significantly after PEA (Friedman test $p < 0.001$), mPAP overall did not change between the early postoperative period and six months after PEA (Dunn's multiple comparisons test $p > 0.999$). The correlation between mPAP in the ICU and after six months was moderate (Spearman rho 0.465, 95% confidence interval (CI) 0.278-0.619, $p < 0.001$). The slope of the regression line (0.534) and X- and Y-intercept did not indicate a close linear relation (figure 2). There was no correlation between the cardiac index in the ICU and after six months (Spearman rho 0.226, 95% CI -0.029-0.453, p 0.073).

Seventeen out of 35 patients with residual PH six months after PEA had no residual PH in the ICU (ICU hemodynamics missing in one patient). Seventeen out of 35 patients with apparent residual PH in the ICU had normal pulmonary (resting) hemodynamics six months after surgery. Sensitivity and specificity of early hemodynamics for a diagnosis of residual PH at six months were 0.51 and 0.68, respectively, with a PPV and NPV of 0.51 and 0.68, respectively. Positive LR was 1.60, negative LR was 0.76. Using the absence of residual PH in the ICU as the criterium to determine whether patients should have RHC six months after PEA would reduce the "number-needed-to-catheterise" from 88 to 53/88 (60%); this would lead to missing 17/35 (49%) of residual PH cases, including two cases of residual PH started on PH-specific medication after the six-month re-evaluation (supplementary table B). The results of ROC curve analysis are shown in supplementary figure B.

Role of NT-proBNP six months post-PEA

NT-proBNP was determined in 84 patients six months after PEA (median 203 ng/L, IQR 105-365 ng/L). Based on the ESC/ERS risk assessment criteria for pulmonary arterial hypertension (PAH) a cut-off of 300 ng/L was used for further analysis. In the univariate logistic regression analysis, NT-proBNP > 300 ng/L was associated with residual PH (odds ratio (OR) 5.250, 95% CI 1.909-14.439,

p 0.001). Sensitivity and specificity were 0.50 and 0.84, respectively. PPV and NPV were 0.68 and 0.71, respectively. Positive LR was 3.13, negative LR was 0.60.
Using NT-proBNP > 300 ng/L as the criterium to proceed to RHC would lead to a reduction of the number of re-RHC to 25/84 (30%), at the expense of 17 missed cases of residual PH (50% of residual PH patients), including two cases of residual PH started on PH-specific medication after the six-month re-evaluation (supplementary table B). The results of ROC curve analysis are shown in supplementary figure B.

Role of echocardiography six months post-PEA

TTE six months after PEA with concurrent RHC were available in 52 patients. Increased probability of PH at TTE was associated with increased mPAP (figure 3). TTE with intermediate- or high probability for PH was associated with residual PH (OR 4.286, 95% CI 1.323-13.881, p 0.015). Twenty-five TTEs were classified as either intermediate- or high probability for PH; in 15 patients residual PH was confirmed with RHC, while in 10 patients no residual PH was present. Twenty-seven TTEs were classified as low probability for PH. In seven of those patients, however, residual PH was present. Following from these data, sensitivity of intermediate/high PH probability TTE for residual PH was 0.68, while specificity was 0.67; PPV and NPV were 0.60 and 0.74, respectively. Positive LR was 2.05, negative LR was 0.48. Thus, when using intermediate or high probability for PH on TTE as the criterium to proceed to RHC, the number-needed-to-catheterise would be reduced to 25/52 (48%), at the expense of seven missed cases of residual PH. These seven cases with false-negative TTE did not receive additional treatment (supplementary table B). The results of ROC curve analysis are shown in supplementary figure B.

Role of cardiopulmonary exercise testing six months post-PEA

CPET six months after PEA with concurrent RHC was available in 88 patients. CPET outcomes for the different parameters were dichotomized based on criteria of normality from clinical practice. The results of univariate logistic regression analysis are summarised in table 2. All parameters with significance in this logistic regression analysis were further analysed for their testing characteristics regarding diagnosing residual PH (table 3). Based on NPV/false-negative rates, peak VO_2 < 80% predicted and VO_2/WR < 8.4 mL/min/Watt were the most appropriate parameters to identify

residual PH, where VO_2/WR < 8.4 mL/min/Watt would lead to the largest reduction in the number-needed-to-catheterise to 32/82 (39%), while missing 8/31 cases with residual PH. This includes two cases of residual PH started on PH-specific medication after the six-month re-evaluation. None of the five cases missed based on peak $VO_2 \geq 80\%$ required additional treatment (supplementary table B). Based on a combination of the highest sensitivity, highest NPV, lowest false-negative rate and lowest negative LR, peak $VO_2 \geq 80\%$ is the most appropriate parameter to exclude residual PH based on this analysis (table 3).

The results of ROC curve analysis are shown in supplementary figure B.

Discussion

In this observational analysis, CPET, and to a lesser extent TTE, appeared very useful for the exclusion of residual PH, thereby safely reducing the number of patients needing to undergo re-RHC after PEA with approximately one-third. Importantly, based on the number of false-positives, this finding cannot be reversed, and a diagnosis of residual PH should not be based on TTE or CPET. Data from the early postoperative ICU period should not be used to exclude residual PH or determine which patients do (not) need follow-up RHC. NT-proBNP as a single parameter had insufficient NPV to safely exclude residual PH.

Survival and residual PH are the most frequently used outcome parameters after PEA [2-3]. After an initial early mortality risk after PEA, which is in general below 5%, intermediate- and long-term survival after PEA is good [1,3] with minor differences compared to the general population [12]. However, in approximately one-third of patients residual PH remains present; hemodynamic abnormalities are usually mild and survival is comparable to those without residual PH [2,13]. Only a minority of patients receive additional treatment such as PH-specific medication and/or BPA. However, as previously shown, exercise intolerance is more frequent: in approximately two-thirds of patients exercise intolerance (defined by peak VO_2) is present, in patients with residual PH, but also in a significant proportion of patients with normal resting hemodynamics [14]. This reflects the persistence of an abnormal pulmonary vascular response to exercise [15-16]. Therefore, diagnosing residual PH is relevant: to provide additional treatment in selected patients, but also to acknowledge the persistent abnormal physiology associated with exercise intolerance especially in those with residual PH at rest. The higher burden on quality of life is also reflected by smaller

improvements in CAMPHOR scores after PEA in patients with residual PH compared to those without residual PH [17]. However, making a diagnosis of residual PH requires RHC. Current practice in most centres is to repeat RHC in all patients in the first year after PEA [5], although the majority will not have residual PH. Moreover, an RHC is invasive, can be accompanied by complications and frequently requires travel of patients to a reference centre. Therefore, we deemed it relevant to evaluate whether the immediate postoperative hemodynamic outcomes or later non-invasive diagnostic procedures are suitable to identify patients who do not require a repeat RHC because of a very low likelihood of residual PH.

Analysis of the early (*i.e.* in ICU) post-PEA hemodynamics indicated that these data should not be used to exclude or diagnose residual PH, since this would lead to an inappropriate number of missed cases of residual PH including two cases with therapeutic consequences, in addition to false diagnoses of residual PH in a number of patients while therapeutic consequences of early hemodynamics were absent. In our opinion, early hemodynamics should not be used to define (late) success. The moderate correlation between early and mid-term (3-6 months after PEA) hemodynamics have been addressed previously [3], just as the similar PVR immediately postoperatively versus 1-year post-PEA [18]. The findings in these previous studies are similar to ours, but caution is needed regarding the method used to compare hemodynamics. While the first study used correlation analysis, the second study compared median PVR. In our analysis, we used both methods, illustrating that descriptive statistics (mean or median) may imply similarity. We think correlation analysis provides better insight into the accuracy of early hemodynamics. Several factors influence these early hemodynamics: volume status (with a relatively volume-depleted state and low cardiac output to reduce the risk of reperfusion edema), use of vasopressor/inotropic agents, postoperative stunning, and ongoing reverse remodelling with reduced right ventricular (RV) contractility despite the significant decrease in PVR and immediate unloading of the RV. These factors explain the discrepancies between early and mid-term (*i.e.* six months after PEA) hemodynamics.

NT-proBNP six months after PEA was associated with residual PH. NT-proBNP cut-off > 300 ng/L provided a moderate NPV for residual PH, with a significant reduction of the number of patients needing to undergo follow-up RHC. However, using this cut-off comes at the expense of missing half of all cases of residual PH. It is likely that NT-proBNP performs better when combined with

other modalities. Unfortunately, the number of patients in our study did not allow multivariate analyses.

Intermediate or high probability of PH by TTE was a strong predictor for residual PH, and had a moderate NPV for excluding residual PH. The main advantage of TTE is its wide availability and non-invasive character. In the current analysis we used the echocardiographic criteria from the ESC/ERS guideline [5], of which peak tricuspid regurgitation velocity is the most important component. We did not evaluate tricuspid annular plane systolic excursion (TAPSE) and systolic tricuspid annular velocity; it remains to be determined whether these parameters, which correlate with pulmonary hemodynamics in CTEPH [19-20] can also be used within weeks to months after PEA. Others have shown that TTE in the first days after PEA did not reflect RV function or correlate with pulmonary hemodynamics [19,21].

It was previously shown that exercise stress testing with cycle ergometry provides a very efficient evaluation of the RV and pulmonary circulation [22]. The typical CPET pattern in pulmonary vascular disease, depending on the severity, is a cardiovascular limitation with early anaerobic threshold, reduced peak VO_2 with an inappropriate increase of VO_2 in relation to work rate (low VO_2/WR slope), and reduced O_2 pulse reflecting the impaired stroke volume response. Other typical features of pulmonary vascular disease during exercise are ventilatory inefficiency (high V_E/VCO_2) and gas exchange abnormalities (high Vd/Vt, low $P_{ET}CO_2$, oxygen desaturation). All of these were associated with the presence of residual PH and especially peak VO_2 provided good discriminatory value in selecting patients with a very low probability of residual PH.
Our analysis indicated that despite the marked improvements after PEA, CPET remains sensitive in revealing a persistently abnormal physiology in residual CTEPH. Another advantage of CPET is that it provides important information regarding exercise intolerance and an abnormal pulmonary vascular response to exercise even if residual PH at rest is absent, which is relevant information for both the patient and treating physician.

Some limitations of this study need to be recognised. First, since real-time PAWP or left atrial pressure measurements from the postoperative period were not present, we were not able to determine the diagnostic value of postoperative PVR, despite its known importance in predicting mortality. Second, due to the limited number of patients with residual PH we did not perform

multivariate analysis and were unable to develop a follow-up algorithm to exclude residual PH with combinations of different non-invasive modalities, and the findings have to be interpreted with caution. Also, only 55% of patients had data present from all methods used, mainly because of missing TTE. However, we think despite this limitation, the data provide a strong signal indicating the value of CPET in the follow-up after PEA.

It would be of value to further evaluate this in larger cohorts to enable the formulation of algorithms such as the DETECT algorithm for detection of PAH in systemic sclerosis [23].

Importantly, we aimed to predict or exclude residual PH in patients after PEA based on fixed hemodynamic criteria. This does not necessarily indicate clinically relevant residual PH with need for additional treatment. We did not cover the relative hemodynamic improvement achieved after PEA, which is essential to judge surgical success.

Conclusion

CPET (peak $VO_2 \geq 80\%$ predicted) six months after PEA can be used to select patients with a low probability of residual PH after PEA, thereby reducing the number of re-RHC in the follow-up after PEA in CTEPH without missing cases with clinically relevant residual PH. Validation of this strategy in a larger cohort is needed. Our study illustrates that CPET retains its diagnostic properties after PEA. Depending on local availability and preference, TTE can be an acceptable alternative to rule out residual PH, although with a lower negative predictive value and higher false-negative rate. Together, in the context of their wide availability TTE and/or CPET provide a practical follow-up strategy for PEA patients, where CPET also provides valuable information regarding exercise intolerance even if residual PH (at rest) is absent.

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Tables

Table 1: pre-operative characteristics

Parameters before PEA	**Total (n = 92)**	**Patients without residual PH after PEA (n = 56)**	**Patients with residual PH after PEA (n = 36)**
Age at PEA (years)	63 (range 17-79)	58 (range 18-79)	63 (range 17-79)
Women (%)	41 (45%)	24 (43%)	17 (47%)
BMI (kg/m^2)	26.7 (24.3-30.1)	26.7 (23.8-30.1)	26.5 (25.0-30.0)
Use of PH-specific medication before PEA	27 (29%)	13 (23%)	14 (39%)
NYHA class I/II/III/IV (%)	2/38/52/8%	4/37/48/11%	0/38/59/3%
6MWD (m)	412 (108) *n=67*	413 (112) *n=39*	411 (105) *n=28*
NT-proBNP (ng/L)	507 (132-1646)	326 (115-1250)	932 (224-2748)
Comorbidities			
Ischemic heart disease	3 (3%)	0 (0%)	3 (8%)
Obstructive lung disease	12 (13%)	6 (11%)	6 (17%)
Diabetes mellitus	8 (9%)	5 (9%)	3 (8%)
Systemic hypertension	35 (38%)	18 (32%)	17 (47%)
Malignancy	6 (7%)	4 (7%)	2 (6%)
Thyroid disease	7 (8%)	3 (5%)	4 (11%)

Mean (standard deviation) or median (interquartile range) or n (%) are shown unless otherwise stated.

PEA: pulmonary endarterectomy; BMI: body mass index; PH: pulmonary hypertension; NYHA: New York Heart Association; 6MWD: six-minute walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 2: Univariate logistic regression analysis of CPET parameters for residual PH

Parameter	**OR**	**95% CI**	**P value**
Peak load < 80% predicted	4.023	1.434-11.283	0.008
Peak VO_2 < 80% predicted	5.386	1.813-16.001	0.002
VO_2/WR < 8.4 mL/min/Watt	13.417	4.558-39.491	< 0.001
O_2 pulse < 80% predicted	3.154	1.260-7.891	0.014
$P_{ET}CO_2$ peak exercise < 4.0 kPa	2.667	1.097-6.484	0.030
V_E/VCO_2 AT ≥ 34.0	4.788	1.866-12.290	0.001
SpO_2 peak exercise ≤ 94%	1.920	0.771-4.781	0.161

CPET: cardiopulmonary exercise testing; PH: pulmonary hypertension; OR: odds ratio, CI: confidence interval; VO_2: oxygen consumption; WR: work rate; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; V_E/VCO_2: ventilatory equivalent for carbon dioxide; AT: anaerobic threshold; SpO_2: peripheral oxygen saturation.

Table 3: Test characteristics of CPET parameters for residual PH

Parameter	Sensitivity	Specificity	PPV	False-positive rate	Positive LR	NPV	False-negative	Negative LR	Number-needed-to-catheterise
Peak load < 80% predicted	28/34 (0.82)	25/54 (0.46)	28/57 (0.49)	29/57 (0.51)	1.53	25/31 (0.81)	6/31 (0.19)	0.38	57/88 (0.65)
Peak VO_2 < 80% predicted	29/34 (0.85)	26/54 (0.48)	29/57 (0.51)	28/57 (0.49)	1.64	26/31 (0.84)	5/31 (0.16)	0.31	57/88 (0.65)
VO_2/WR < 8.4 mL/min/Watt	23/31 (0.74)	42/51 (0.82)	23/32 (0.72)	9/32 (0.28)	4.20	42/50 (0.84)	8/50 (0.16)	0.31	32/82 (0.39)
O_2 pulse < 80% predicted	17/34 (0.50)	41/54 (0.76)	17/30 (0.57)	13/30 (0.43)	2.08	41/58 (0.71)	17/58 (0.29)	0.66	30/88 (0.34)
$P_{ET}CO_2$ peak exercise < 4.0 kPa	22/34 (0.65)	32/54 (0.59)	22/44 (0.50)	22/44 (0.50)	1.59	32/44 (0.73)	12/44 (0.27)	0.60	44/88 (0.50)
V_E/VCO_2 AT ≥ 34	22/32 (0.69)	37/54 (0.69)	22/39 (0.56)	17/39 (0.44)	2.18	37/47 (0.79)	10/47 (0.21)	0.46	39/86 (0.45)

CPET: cardiopulmonary exercise testing; PH: pulmonary hypertension; PPV: positive predictive value; LR: likelihood ratio; NPV: negative predictive value; VO_2: oxygen consumption; WR: work rate; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; V_E/VCO_2: ventilatory equivalent for carbon dioxide; AT: anaerobic threshold.

Figure legends

Figure 1: flowchart of patient selection

PEA: pulmonary endarterectomy; LTX: lung transplantation; RHC: right heart catheterisation; CPET: cardiopulmonary exercise testing; TTE: transthoracic echocardiography; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Figure 2: correlation analysis of mPAP between ICU and 6-months re-evaluation after PEA

Spearman correlation performed.

mPAP: mean pulmonary artery pressure; ICU: intensive care unit; PEA: pulmonary endarterectomy.

Figure 3: mPAP distribution according to TTE PH probability

Mann-Whitney test performed.

mPAP: mean pulmonary artery pressure; TTE: transthoracic echocardiography; PH: pulmonary hypertension.

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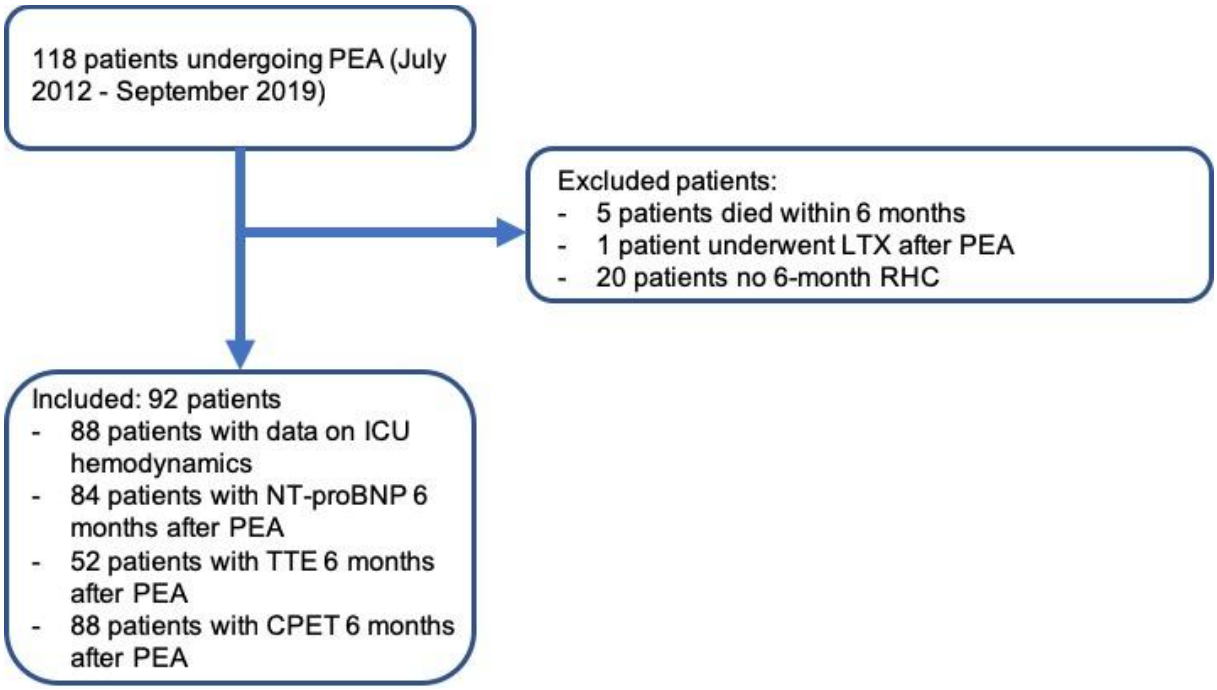
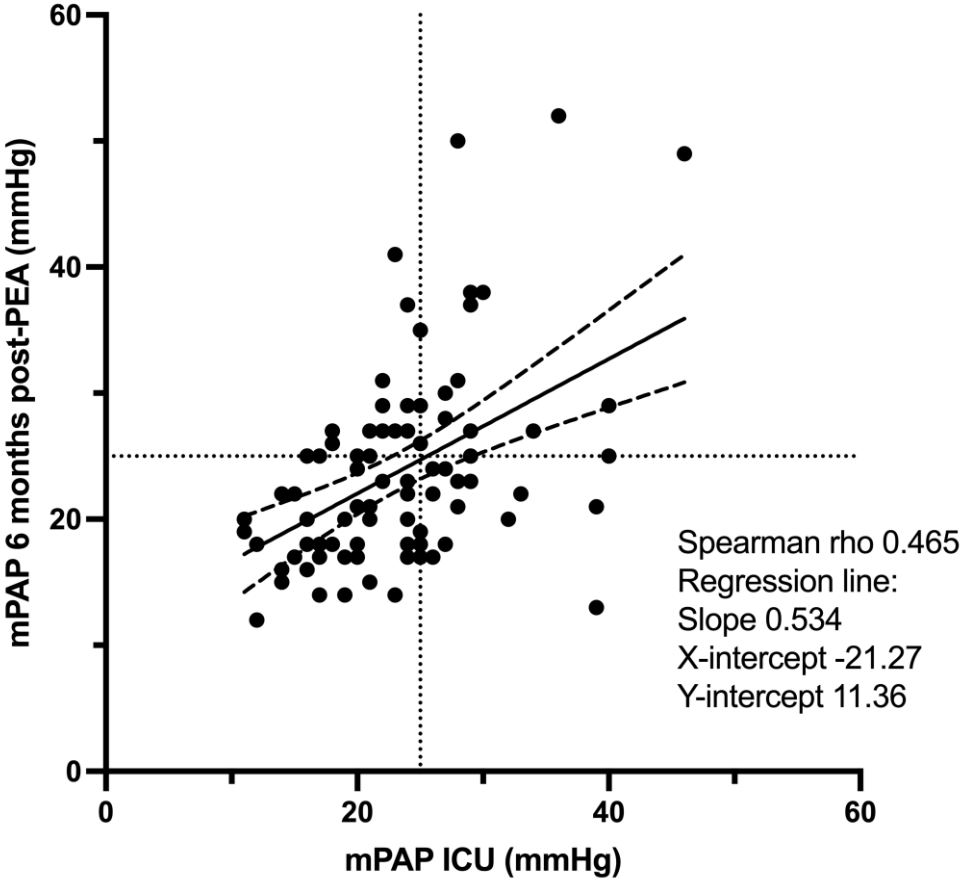
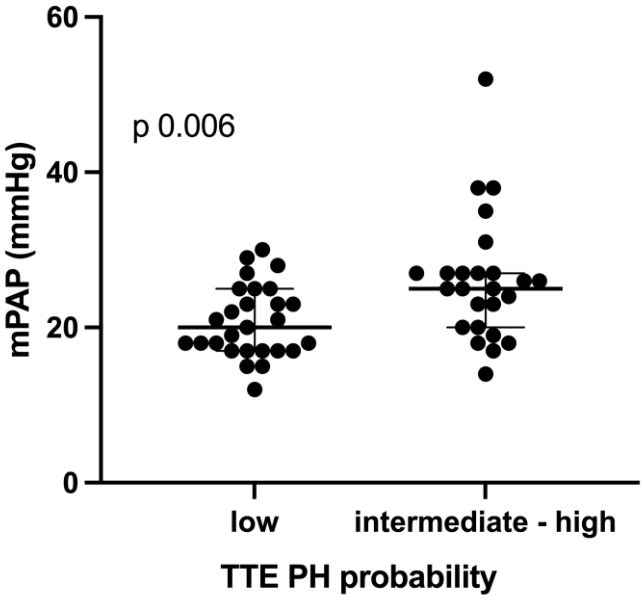

118 patients undergoing PEA (July 2012 - September 2019)
Excluded patients:
- 5 patients died within 6 months
- 1 patient underwent LTX after PEA
- 20 patients no 6-month RHC
Included: 92 patients
- 88 patients with data on ICU hemodynamics
- 84 patients with NT-proBNP 6 months after PEA
- 52 patients with TTE 6 months after PEA
- 88 patients with CPET 6 months after PEA


60
40
20
0
0
20
40
60
mPAP 6 months post-PEA (mmHg)
mPAP ICU (mmHg)
Spearman rho 0.465
Regression line:
Slope 0.534
X-intercept -21.27
Y-intercept 11.36


60
40
20
0
mPAP (mmHg)
p 0.006
low
intermediate - high
TTE PH probability

Supplement

Table A: hemodynamics before and after PEA

	Baseline	**ICU post-PEA**	**six months post-PEA**	**P-value**
mPAP (mmHg)	43 (33-50)	24 (18-27)	23 (18-27)	< 0.001[a]
PAWP (mmHg)	10.3 (3.1)		9.9 (3.2)	0.273[b]
CI (L/min/m^2)	2.4 (2.0-2.8)	2.7 (2.3-3.1)	2.9 (2.6-3.4)	0.002[a]
PVR (dynes·s·cm^{-5})	544 (330-740)		163 (116-235)	< 0.001[c]
RAP (CVP in ICU)	7.5 (6-10)	7 (5-10)	5 (3-6)	< 0.001[a]

Statistical tests used: [a] Friedman test, [b] paired t-test, [c] Wilcoxon matched-pairs signed rank test. Mean (standard deviation) or median (interquartile range) are shown.

PEA: pulmonary endarterectomy; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; CVP: central venous pressure; ICU: intensive care unit.

Table B: overview of false-negatives based on non-invasive modalities.

Case number	**Diagnostic modality**	**mPAP six months post-PEA**	**PVR six months post-PEA**	**NT-proBNP six months post-PEA**	**Additional PH-specific treatment**
1	ICU hemodynamics	27 mmHg	269 dynes·s·cm^{-5}	365 ng/L	no
2	ICU hemodynamics	29 mmHg	316 dynes·s·cm^{-5}	352 ng/L	no
3	ICU hemodynamics	31 mmHg	241 dynes·s·cm^{-5}	649 ng/L	yes
4	ICU hemodynamics	27 mmHg	203 dynes·s·cm^{-5}	754 ng/L	no
5	ICU hemodynamics	25 mmHg	316 dynes·s·cm^{-5}	572 ng/L	no
6	ICU hemodynamics	29 mmHg	227 dynes·s·cm^{-5}	2361 ng/L	no
7	ICU hemodynamics, NT-proBNP	26 mmHg	204 dynes·s·cm^{-5}	282 ng/L	no
8	ICU hemodynamics, NT-proBNP	37 mmHg	418 dynes·s·cm^{-5}	115 ng/L	no
9	ICU hemodynamics, NT-proBNP, peak VO_2	25 mmHg	208 dynes·s·cm^{-5}	81 ng/L	No
10	ICU hemodynamics, NT-proBNP, VO_2/WR	41 mmHg	436 dynes·s·cm^{-5}	202 ng/L	yes
11	ICU hemodynamics, VO_2/WR	27 mmHg	256 dynes·s·cm^{-5}	363 ng/L	no
12	ICU hemodynamics, TTE	25 mmHg	166 dynes·s·cm^{-5}	402 ng/L	no
13	ICU hemodynamics, peak VO_2, VO_2/WR, TTE	25 mmHg	140 dynes·s·cm^{-5}		no
14	ICU hemodynamics, NT-proBNP, TTE	27 mmHg	243 dynes·s·cm^{-5}	73 ng/L	no
15	ICU hemodynamics, NT-proBNP, peak VO_2	27 mmHg	200 dynes·s·cm^{-5}	238 ng/L	no
16	ICU hemodynamics, NT-proBNP, peak VO_2	27 mmHg	133 dynes·s·cm^{-5}	258 ng/L	no
17	ICU hemodynamics, VO_2/WR, TTE	25 mmHg	192 dynes·s·cm^{-5}	797 ng/L	no
18	NT-proBNP	27 mmHg	117 dynes·s·cm^{-5}	52 ng/L	no
19	NT-proBNP	38 mmHg	360 dynes·s·cm^{-5}	234 ng/L	no
20	NT-proBNP	26 mmHg	138 dynes·s·cm^{-5}	273 ng/L	no
21	NT-proBNP	31 mmHg		253 ng/L	no
22	NT-proBNP	26 mmHg	116 dynes·s·cm^{-5}	261 ng/L	no
23	NT-proBNP	25 mmHg	250 dynes·s·cm^{-5}	278 ng/L	no
24	NT-proBNP, peak VO_2, VO_2/WR, TTE	30 mmHg	249 dynes·s·cm^{-5}	161 ng/L	no
25	NT-proBNP, VO_2/WR, TTE	28 mmHg	184 dynes·s·cm^{-5}	158 ng/L	no

26	NT-proBNP, VO_2/WR	37 mmHg	234 dynes·s·cm^{-5}	191 ng/L	no
27	NT-proBNP, VO_2/WR	49 mmHg	589 dynes·s·cm^{-5}	235 ng/L	yes
28	TTE	29 mmHg	222 dynes·s·cm^{-5}	396 ng/L	no

Overview of residual PH cases missed (false-negatives) based on ICU hemodynamics (mPAP in ICU < 25 mmHg), NT-proBNP (≤ 300 ng/L), TTE (low PH probability) or CPET (peak VO_2 ≥ 80% predicted and/or VO_2/WR ≥ 8.4 mL/min/Watt), with their respective mPAP, PVR and NT-proBNP six months after PEA and additional treatment consequences.

PH: pulmonary hypertension; mPAP: mean pulmonary artery pressure; ICU: intensive care unit; PVR: pulmonary vascular resistance; NT-proBNP: N-terminal pro-brain natriuretic peptide; TTE: transthoracic echocardiography; CPET: cardiopulmonary exercise testing; VO_2: oxygen consumption; PEA: pulmonary endarterectomy.

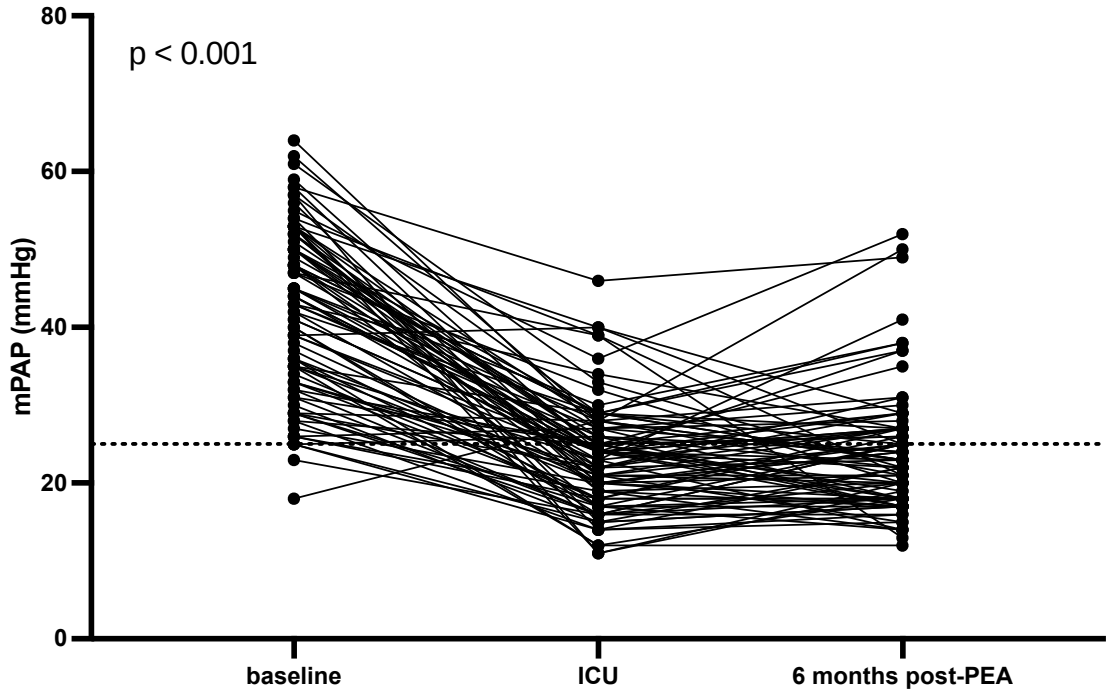


Figure A: individual evolution of mPAP before and after PEA. Statistical test used: Friedman test.

mPAP: mean pulmonary artery pressure; PEA: pulmonary endarterectomy; ICU: intensive care unit

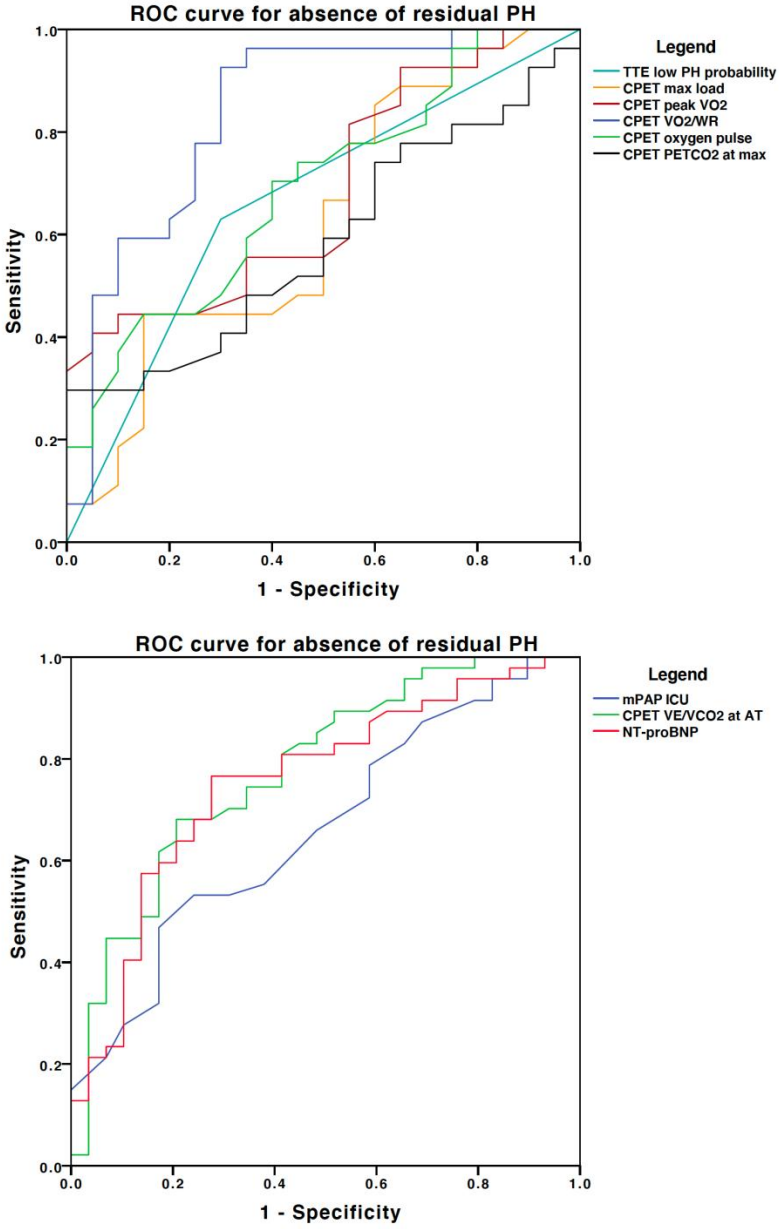


Figure B: receiver operating characteristic (ROC) curves for the absence of residual PH. Upper panel shows the results for TTE low PH probability 6 months post-PEA and the CPET parameters maximal load, peak VO_2, VO_2/WR, oxygen pulse and $PETCO_2$ at max exercise, all 6 months after PEA. Lower panel shows the results for early mPAP in the ICU, CPET VE/VCO2 at the anaerobic threshold, and NT-proBNP, the latter two six months after PEA (these parameters are depicted in a separate panel because of their inverse relation with the absence of residual PH, with a lower result being more associated with the absence of residual PH).

PH: pulmonary hypertension; TTE: transthoracic echocardiography; PEA: pulmonary endarterectomy; CPET: cardiopulmonary exercise testing, VO_2: oxygen consumption; WR: work rate; $PETCO_2$: end-tidal carbon dioxide tension; mPAP: mean pulmonary artery pressure; ICU: intensive care unit; VE/VCO_2: ventilatory equivalent for carbon dioxide; AT: anaerobic threshold; NT-proBNP: N-terminal pro-brain natriuretic peptide.