Noninvasive follow-up strategy after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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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 post-operative haemodynamics, or N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiopulmonary exercise testing (CPET) and transthoracic echocardiography (TTE) 6 months after PEA.

Methods In an observational analysis, residual PH after PEA measured by RHC was related to haemodynamic data from the post-operative intensive care unit time and data from a 6-month follow-up assessment including NT-proBNP, cardiopulmonary exercise testing (CPET) and transthoracic echocardiography (TTE) 6 months after PEA.

Results Thirty-six out of 92 included patients had residual PH 6 months after PEA (39%). Correlation between early post-operative and 6-month follow-up mean pulmonary artery pressure was moderate (Spearman rho 0.465, p<0.001). Early haemodynamics did not predict late success. NT-proBNP >300 ng·L\(^{-1}\) 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 (\(V'_{\text{O}_2}\)) <80% predicted had the highest sensitivity (0.85) and NPV (0.84) for residual PH.

Conclusions CPET 6 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 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.

Cite this article as: Ruigrok D, Handoko ML, Meijboom LJ, et al. Noninvasive follow-up strategy after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. ERJ Open Res 2022; 8: 00564-2021 [DOI: 10.1183/23120541.00564-2021].
A definite diagnosis of residual PH requires a right heart catheterisation (RHC). A selection of patients with the lowest risk for residual PH would be helpful to avoid unnecessary invasive procedures. This selection can be based on the most recent haemodynamic data in the early post-operative period or by performing noninvasive procedures during follow-up such as transthoracic echocardiography (TTE) and cardiopulmonary exercise testing (CPET).

We performed an observational analysis with the aim of evaluating the efficiency and safety of a strategy using early post-operative haemodynamics and noninvasive data at follow-up 6 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 post-operative haemodynamics are not.

**Methods**

**Study subjects**

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

The study did not fall within the scope of the Medical Research Involving Human Subjects Act, because 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 Center (2017.313).

**Procedures**

RHC was performed as described previously [4]. In the intensive care unit (ICU), haemodynamic measurements were carried out using 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 to the RHC results.

CPET consisted of a symptom-limited maximal incremental exercise test using a cycle ergometer [6]. Electrocardiogram (ECG), oxygen consumption ($V'_O2$), CO2 production ($V'_CO2$), heart rate, tidal volume, breathing frequency, respiratory oxygen and CO2 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) $\geq 25$ mmHg according to the current guideline at the time of this study. In this study we analysed noninvasive markers for the presence of this residual PH.

Data are presented as mean±SD, median (interquartile range (IQR)) or number of patients (%) where appropriate. Missing data were not imputed. Normal distribution was tested using the 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-squared 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 dichotomised and tested with univariate logistic regression to evaluate their association with residual PH. Because 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, www.graphpad.com) and IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

**Results**

### Patient population

Between July 2012 and September 2019, 118 patients underwent PEA at our centre. All patients with data available from at least the RHC 6 months after PEA were selected. Five patients died within 6 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

**FIGURE 1** Flow chart of patient selection. CPET: cardiopulmonary exercise testing; ICU: intensive care unit; LTX: lung transplantation; NT-proBNP: N-terminal pro-brain natriuretic peptide; PEA: pulmonary endarterectomy; RHC: right heart catheterisation; TTE: transthoracic echocardiography.

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**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\(^{-1}\))             | 507 (132–1646) | 326 (115–1250) | 932 (224–2748) |

**Comorbidities**

| Ischaemic 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%) |

Data are presented as mean±sd, median (interquartile range) or n (%) unless otherwise stated. 6MWD: 6-min walk distance; BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.
overweight. Twenty-nine per cent of patients used PH-specific medication before PEA. Residual PH 6 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 pre-operative NT-proBNP.

None of the analysed patients were started on or continued PH-specific medication after PEA based on early haemodynamics in the ICU. In eight patients (out of 13 patients with mPAP $\geq 30$ mmHg), PH-specific medication was started after the 6-month re-evaluation. Five patients with mPAP $\geq 30$ mmHg at 6 months were not started on PH-specific medication. The decision to start additional treatment was at the treating physician’s discretion, based on haemodynamics and symptoms.

**Role of early haemodynamics**

The median time between PEA and the last haemodynamic profile in the ICU (data available in 88 patients) was 2 days (range 0–10). The complete haemodynamic profiles at baseline, in the ICU and 6 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 post-operative period and 6 months after PEA (Dunn’s multiple comparisons test $p>0.999$). The correlation between mPAP in the ICU and after 6 months was moderate (Spearman rho 0.465, 95% CI 0.278 to 0.619, $p<0.001$). The slope of the regression line (0.534) and x- and y-intercept did not indicate a close linear relationship (figure 2). There was no correlation between the cardiac index in the ICU and after 6 months (Spearman rho 0.226, 95% CI −0.029 to 0.453, $p=0.073$).

Seventeen out of 35 patients with residual PH 6 months after PEA had no residual PH in the ICU (ICU haemodynamics missing in one patient). Seventeen out of 35 patients with apparent residual PH in the ICU had normal pulmonary (resting) haemodynamics 6 months after surgery. Sensitivity and specificity of early haemodynamics for a diagnosis of residual PH at 6 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 criterion to determine whether patients should have RHC 6 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 6-month re-evaluation (supplementary table B). The results of ROC curve analysis are shown in supplementary figure B.

**FIGURE 2** Correlation analysis of mean pulmonary artery pressure (mPAP) between ICU and 6-month re-evaluation after pulmonary endarterectomy (PEA). Spearman correlation performed. ICU: intensive care unit.
Role of NT-proBNP 6 months post-PEA

NT-proBNP was determined in 84 patients 6 months after PEA (median 203 ng·L\(^{-1}\), IQR 105–365 ng·L\(^{-1}\)). Based on the ESC/ERS risk assessment criteria for pulmonary arterial hypertension (PAH), a cut-off of 300 ng·L\(^{-1}\) was used for further analysis. In the univariate logistic regression analysis, NT-proBNP \(>300\) ng·L\(^{-1}\) was associated with residual PH (OR 5.250, 95% CI 1.909 to 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\(^{-1}\) as the criterion to proceed to RHC would lead to a reduction in 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 6-month re-evaluation (supplementary table B). The results of ROC curve analysis are shown in supplementary figure B.

Role of echocardiography 6 months post-PEA

TTE 6 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 to 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 these data, sensitivity of intermediate/high TTE PH probability 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 criterion 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 CPET 6 months post-PEA

CPET 6 months after PEA was available in 88 patients. CPET outcomes for the different parameters were dichotomised 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 V\(\dot{O}_2\) <80% predicted and V\(\dot{O}_2\)/work rate (WR) <8.4 mL·min\(^{-1}\)·W\(^{-1}\) were the most appropriate parameters to identify residual PH, where V\(\dot{O}_2\)/WR <8.4 mL·min\(^{-1}\)·W\(^{-1}\) 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 6-month re-evaluation of their PH status (supplementary table B). The results of ROC curve analysis are shown in supplementary figure B.

FIGURE 3 mPAP distribution according to TTE PH probability. Mann–Whitney test performed. mPAP: mean pulmonary artery pressure; PH: pulmonary hypertension; TTE: transthoracic echocardiography.
medication after the 6-month re-evaluation. None of the five cases missed based on peak \( V'_{O_2} \geq 80\% \) 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 \( V'_{O_2} \geq 80\% \) 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 by 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 post-operative 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; haemodynamic 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 \( V'_{O_2} \)) is present, both in patients with residual PH and also in a significant proportion of patients with normal resting haemodynamics [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 patients travelling to a reference centre. Therefore, we deemed it relevant to evaluate whether the immediate post-operative haemodynamic outcomes or later noninvasive 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 haemodynamics indicated that these data should not be used to exclude or diagnose residual PH, because 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 haemodynamics were absent. In our opinion, early haemodynamics should not be used to define (late) success. The moderate correlation between early and mid-term (3–6 months after PEA) haemodynamics has been addressed previously [3], just as the similar PVR immediately post-operatively 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 haemodynamics. While the first study used correlation analysis, the second study compared median PVR.
Several factors influence these early haemodynamics: volume status (with a relatively volume-depleted state and low cardiac output to reduce the risk of reperfusion oedema), use of vasopressor/inotropic agents, post-operative 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. 6 months after PEA) haemodynamics.

NT-proBNP 6 months after PEA was associated with residual PH. NT-proBNP cut-off >300 ng·L$^{-1}$ provided a moderate NPV for residual PH, with a significant reduction in 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 noninvasive 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 haemodynamics 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 haemodynamics [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 $V_{O2}$ with an inappropriate increase of $V_{O2}$ in relation to WR (low $V_{O2}$/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 $V_{E}/V_{CO2}$) and gas exchange abnormalities (high $V_{E}$/WR, low $P_{ETCO2}$, oxygen desaturation). All of these were associated with the presence of residual PH and peak $V_{O2}$ in particular 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.

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**TABLE 3 Test characteristics of CPET parameters for residual PH**

| Parameter                          | Sensitivity | Specificity | PPV    | False-positive rate | Positive LR | NPV    | False-negative rate | Negative LR | Number-needed-to-catheterise |
|-----------------------------------|-------------|-------------|--------|---------------------|-------------|--------|---------------------|-------------|-----------------------------|
| Peak load <80% predicted          | 28/34       | 0.82        | 25/57  | 0.46                | 28/57       | 0.51   | 29/57               | 1.53        | 25/31                       | 0.31        | 6/31                        | 0.38        | 57/88                       |
| Peak $V_{O2}$ <80% predicted      | 28/34       | 0.85        | 26/54  | 0.51                | 29/57       | 0.49   | 28/57               | 1.64        | 26/31                       | 0.84        | 5/31                        | 0.19        | 57/88                       |
| $V_{O2}$/WR <8.4 mL·min$^{-1}$·W$^{-1}$ | 23/31       | 0.74        | 42/51  | 0.51                | 23/32       | 0.72   | 9/32                | 4.20        | 42/50                       | 0.84        | 8/50                        | 0.31        | 32/82                       |
| $O_2$ pulse <80% predicted         | 17/34       | 0.50        | 41/54  | 0.76                | 17/30       | 0.57   | 13/30               | 2.08        | 41/58                       | 0.71        | 17/58                       | 0.66        | 30/88                       |
| $P_{ETCO2}$, peak exercise <4.0 kPa | 22/32       | 0.65        | 32/54  | 0.59                | 22/44       | 0.50   | 22/44               | 1.59        | 32/44                       | 0.73        | 12/44                       | 0.60        | 44/88                       |
| $V_{E}/V_{CO2}$ AT ≥34             | 22/32       | 0.69        | 37/54  | 0.69                | 22/39       | 0.56   | 17/39               | 2.18        | 37/47                       | 0.79        | 10/47                       | 0.46        | 39/86                       |

AT: anaerobic threshold; CPET: cardiopulmonary exercise testing; LR: likelihood ratio; NPV: negative predictive value; $P_{ETCO2}$: end-tidal carbon dioxide partial pressure; PH: pulmonary hypertension; PPV: positive predictive value; $V_{O2}/V_{CO2}$: ventilatory equivalent for carbon dioxide; $V_{O2}$: oxygen consumption; WR: work rate.
Some limitations of this study need to be recognised. First, because real-time PAWP or left atrial pressure measurements from the post-operative period were not present, we were not able to determine the diagnostic value of post-operative 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 noninvasive 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 that 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 haemodynamic criteria. This does not necessarily indicate clinically relevant residual PH with need for additional treatment. We did not cover the relative haemodynamic improvement achieved after PEA, which is essential to judge surgical success.

Conclusion

CPET (peak $V'_\text{O}_2 \geq 80\%$ predicted) 6 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 NPV 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.

Provenance: Submitted article, peer reviewed.

Acknowledgements: We would like to thank Patrick Jak and Frank Oosterveer (Dept of Pulmonary Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands) for their work in performing the cardiopulmonary exercise testing and right heart catheterisation with the participating patients.

Conflict of interest: None declared.

References

1 Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 2016; 133: 859–871.
2 Condliffe R, Kiely DG, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008; 177: 1122–1127.
3 Cannon JE, Su L, Kiely DG, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the United Kingdom National Cohort. Circulation 2016; 133: 1761–1771.
4 van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011; 58: 2511–2519.
5 Galié N, Humbert M, Vachiery J-L, et al. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 2015: 903–975.
6 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.
7 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1965) 1986; 60: 2020–2027.
8 Gläser S, Ittermann T, Schäper C, et al. The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing. Pneumologie 2013; 67: 58–63.
9 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.
10 Sun XG, Hansen JE, Oudiz RJ, et al. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001; 104: 429–435.
11 Wasserman K, Hansen JE, Sue DY, et al., eds. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. 5th Edn. Philadelphia, Lippincott Williams & Wilkins, 2011.
12 Kallonen J, Glaser N, Bredin F, et al. Life expectancy after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a Swedish single-center study. Pulm Circ 2020; 10: 2045894020918520.
13 Freed DH, Thomson BM, Berman M, et al. Survival after pulmonary endarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg 2011; 141: 383–387.
14 Ruigrok D, Meijboom LJ, Nossent EJ, et al. Persistent exercise intolerance after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Eur Respir J 2020; 55: 2000109.
15 Waziri F, Mellemkjaer S, Clemmensen TS, et al. Long-term changes of exercise hemodynamics and physical capacity in chronic thromboembolic pulmonary hypertension after pulmonary thromboendarterectomy. Int J Cardiol 2020; 317: 181–187.
16 Claessen G, La Gerche A, Dymarkowski S, et al. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. J Am Heart Assoc 2015; 4: e001602.
17 Newnham M, Bunclark K, Abraham N, et al. CAMPHOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. Eur Respir J 2020; 56: 1902096.
18 Skoro-Sajer N, Marta G, Gerges C, et al. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. Thorax 2014; 69: 116–122.
19 Wong DJ, Sampat U, Gibson MA, et al. Tricuspid annular plane systolic excursion in chronic thromboembolic pulmonary hypertension before and after pulmonary thromboendarterectomy. Echocardiography 2016; 33: 1805–1809.
20 Gurudevan S, Malouf PJ, Kahn AM, et al. Noninvasive assessment of pulmonary vascular resistance using Doppler tissue imaging of the tricuspid annulus. J Am Soc Echocardiogr 2007; 20: 1167–1171.
21 Rézaiguia-Delclaux S, Haddad F, Pilorge C, et al. Limitations of right ventricular annular parameters in the early postoperative period following pulmonary endarterectomy: an observational study. Interact Cardiovasc Thorac Surg 2020; 31: 191–198.
22 Motoji Y, Forton K, Pezzuto B, et al. Resistive or dynamic exercise stress testing of the pulmonary circulation and the right heart. Eur Respir J 2017; 50: 1700151.
23 Coghlan JG, Denton CP, Grünig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014; 73: 1340–1349.