Towards improved pathophysiological understanding in chronic thromboembolic pulmonary hypertension

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Towards improved pathophysiological understanding in chronic thromboembolic pulmonary hypertension

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CHAPTER 1

General introduction and thesis outline

Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH), characterised by thromboembolic obstruction of pulmonary arteries and pulmonary hypertension (PH), is defined by the following criteria after at least 3 months of effective anticoagulation [1]:

- mean pulmonary artery pressure (mPAP) ≥ 25 mmHg
- pulmonary artery wedge pressure (PAWP) (surrogate for the left ventricular end-diastolic pressure, LVEDP) ≤ 15 mmHg
- at least 1 (segmental) perfusion defect on perfusion scintigraphy, multidetector computed tomography pulmonary angiography (CTPA) or pulmonary angiography

Currently, new thresholds for pre-capillary PH have been proposed at the 6th World Symposium on PH: mPAP > 20 mmHg, PAWP ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 3 Woods units (240 dynes·s·cm^{-5}) [2], which at the time of writing were not yet formalised in new guidelines.

Pathologically, CTEPH is characterised by incomplete resolution and organisation of thromboembolic material together with vascular remodelling [3]. The exact pathogenesis is unknown, but likely determined by an interplay between three factors: defective angiogenesis, impaired fibrinolysis and endothelial dysfunction [3]. Altogether, redistribution of pulmonary arterial flow to non-obstructed areas leads to increased intravascular pressures and shear stress, and ultimately distal vasculopathy. Vascular changes in CTEPH are not restricted to the non-occluded areas, however, but also occur distal from vascular obstructions, pointing towards a role for anastomoses between the pulmonary arteries and veins and the bronchial circulation [4]. Together, the combination of proximal obstructions and distal vasculopathy leads to an increase in PVR, increased right ventricular (RV) afterload, RV dysfunction and ultimately RV failure.

While CTEPH is regarded a long-term complication after an acute venous thromboembolic event (VTE) (deep vein thrombosis and/or acute pulmonary embolism (PE)), approximately 25% of CTEPH patients have no known history of VTE [5]. Moreover, at the time of the index acute PE event, signs of CTEPH are often already present [6-7]. These clinical observations may be explained by occult VTE, and also by the occurrence of *in situ* thrombosis unrelated to VTE.

CTEPH has an incidence of approximately 3% in survivors after an acute PE [8]. With an estimated incidence of acute PE of 65-78 per 100.000 persons per year, this would lead to approximately 85-100 new cases of CTEPH each year in the Netherlands. This is a conservative estimate and probably an underestimation. However, the current

annual number of new CTEPH diagnoses is lower than the estimated number. Moreover, many patients are diagnosed after a long delay [9], which underlines the importance of awareness for CTEPH.

Incomplete resolution after acute PE is frequent. Evidence of residual perfusion defects is present in 15-50% of patients after 6 months of effective anticoagulation for PE [10-11]. Why only a minority of them develops CTEPH is unknown.

If CTEPH is left untreated, progressive RV dysfunction and RV failure will ultimately lead to death [3]. However, CTEPH differs from other types of PH by the presence of a potentially curative treatment. Pulmonary endarterectomy (PEA) is a viable option in approximately two-thirds of patients, and an international registry showed that 3-year survival was 89% in operated patients, compared to 70% in non-surgical patients [12].

Clinical manifestations

The most important clinical signs of CTEPH are progressive exercise intolerance and dyspnea. These symptoms are explained by ventilatory inefficiency due to dead space ventilation over areas of persistent perfusion defects, and by failure of the cardiac output to keep up with increased physiologic demands during exercise. Other clinical manifestations of CTEPH are signs of PH and RV failure in general such as peripheral edema, fatigue, chest tightness, syncope, haemoptysis and heart rhythm disorders.

Diagnostic evaluation

Diagnosing CTEPH is based on confirming the presence of pre-capillary PH in the context of thromboembolic lesions [1]. Cornerstone of the diagnostic evaluation is (transthoracic) echocardiography (TTE): the systolic pulmonary artery pressure can be estimated based on the peak tricuspid regurgitation velocity (TRV). TRV $\geq$ 2.9 m/s is an important clue pointing towards PH and needs further evaluation [1]. The next diagnostic step, in patients with signs of PH and no obvious left heart disease or lung disease as a plausible explanation, is a ventilation-perfusion scintigraphy: a normal perfusion scintigraphy excludes CTEPH with a negative predictive value of 97% [13]. The role of CTPA is increasing with specific improvement in its diagnostic properties for (sub)segmental lesions, and has the advantage of providing additional information regarding the pulmonary parenchyma and anatomic lesions, and providing essential information in the assessment of operability. Confirmation of a CTEPH diagnosis requires right heart catheterisation (RHC), ideally combined with a pulmonary angiography which has the advantage of visualising peripheral/distal perfusion defects. According to the recommendations of international guidelines, this invasive part of the diagnostic

evaluation should be performed in a CTEPH expertise centre offering the full range of potential treatment options, for optimal evaluation of operability in a multidisciplinary team [1].

Treatment

All patients will continue lifelong anticoagulation to prevent *in situ* thrombosis and recurrent VTE [1,3].

PEA is the treatment of first-choice in eligible patients and the only potentially curative treatment. During a PEA obstructing thromboembolic material is removed from the pulmonary arteries, leading to a reduction of PVR and relief of RV pressure overload, and also improving ventilation-perfusion matching [1,14-15]. Operability is based on four criteria: 1) surgical accessibility of the lesions in the pulmonary arteries with a proportional increase in PVR in relation to the extent of accessible lesions; 2) the presence of a hemodynamic or ventilatory abnormality which correlates with the extent of thromboembolic disease on imaging; 3) the absence of relevant or significant comorbidity; and 4) motivation of the patient to undergo such extensive surgery. The role of an experienced PEA surgeon is crucial in this process. The more distal/subsegmental the lesions are located, the more (technically) difficult complete removal will be; incomplete removal will result in insufficient relief of PVR and unsuccessful PEA [14]. Figure 1 and 2 illustrate the findings on CTPA in proximal and distal (segmental) CTEPH, respectively.

Age is not a contraindication *per se* but does play a role in the estimated/perceived peri- and postoperative risk. Evidence of extensive parenchymatous lung disease is an absolute contraindication since restoration of perfusion to abnormal lung parenchyma will not lead to symptomatic relief [14].

Figure 1: proximal CTEPH. Axial thin slice CTPA illustrating extensive mural thrombus in the main left and right pulmonary artery.

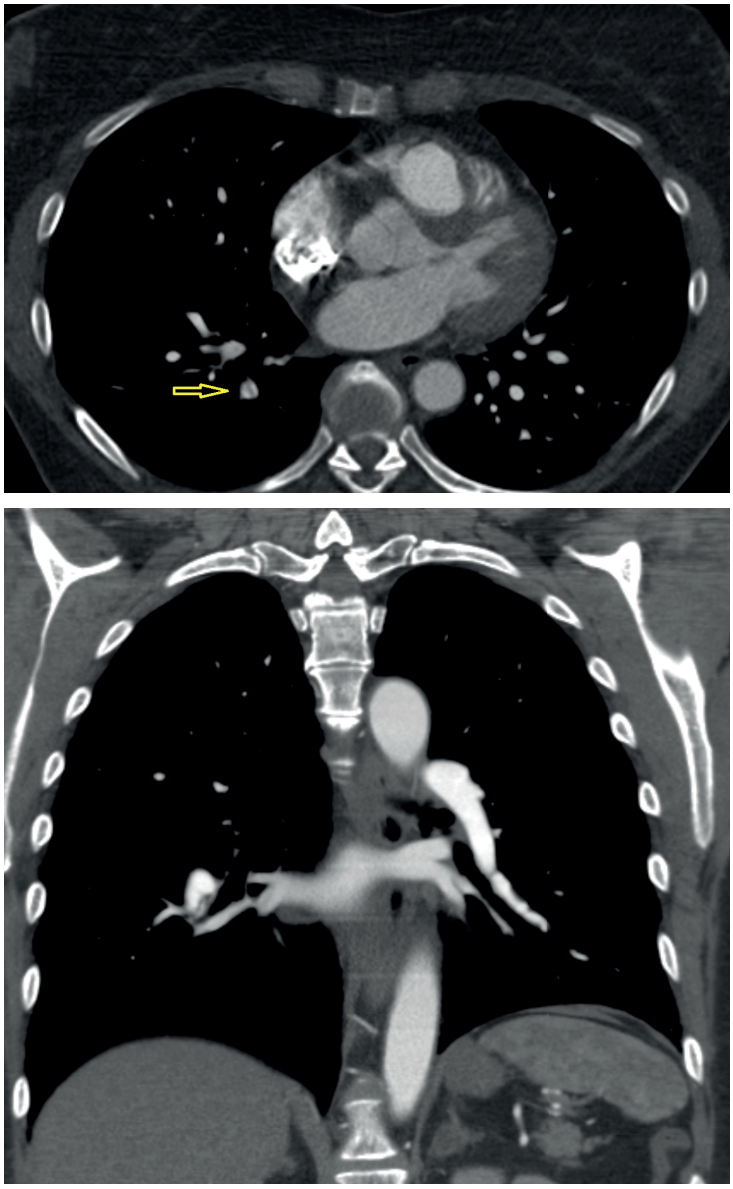

Figure 2: distal CTEPH. Axial (upper) and coronal (lower) thin slice CTPA indicating a web in the right lower lobe and band in the left lower lobe, respectively.

PEA is performed through a median sternotomy, under cardiopulmonary bypass and during periods of deep hypothermic circulatory arrest [14-15]. Hospital mortality is dependent on patient selection and expertise, and also on preoperative PVR (mortality increased in PVR > 1200 dynes·s·cm^{-5}) [16]. In experienced high-volume centres in-hospital mortality is < 5% [12,14]. The most important early complications after PEA are reperfusion pulmonary edema and residual PH [14-15]. Prevention and treatment consist of a combination of restrictive volume suppletion, diuretics and lung protective ventilation; extracorporeal membrane oxygenation (ECMO) and emergency lung transplantation have a role in selected severe cases [14-15]. Persistent or residual PH in the long-term is present in 31-51% [17-18], and it is hypothesized that residual PH is the result of residual lesions (*i.e.* technically insufficient PEA) and/or distal vasculopathy.

For inoperable patients, treatment with PH-specific medication is proposed, with the purpose of decreasing PVR and PAP, and improving symptoms, exercise tolerance and oxygenation. While sildenafil and bosentan were shown to lead to improved hemodynamic parameters, their studies were negative regarding the primary end-point (6-minute walking distance) [19-20]. While these studies precluded the registration of sildenafil and bosentan for treatment of CTEPH, their off-label use is considered in symptomatic but inoperable patients. More recently, riociguat was registered for treatment of inoperable CTEPH patients in NYHA class II-III and patients with persistent PH after PEA [21-22]. Survival benefit in inoperable patients with or without medical therapy was not shown; this is possibly the result of selection bias where more severe patients were treated with medical therapy [12].

Balloon pulmonary angioplasty (BPA) is an invasive procedure to open stenotic and obstructing lesions of the pulmonary arteries using a balloon catheter. The exact role of BPA in comparison to PEA and medical therapy is still to be determined. So far, PEA remains the treatment of first-choice in eligible patients; BPA is considered in eligible patients, but preferably only after medical therapy is optimised. In this setting, BPA is an effective treatment leading to improved hemodynamics and functional class [23].

When PEA is not an option or when significant residual PH is present after PEA and medical treatment is not effective, in selected patients with severe exercise intolerance (NYHA III-IV) and compromised hemodynamics or signs of RV failure, bilateral lung transplantation can be considered.

Clinical vignettes

Patient A is a 28-year old man analysed for exercise intolerance. Echocardiography revealed signs of RV overload after which acute PE was diagnosed on CTPA. Despite anticoagulation severe exercise intolerance persisted. Five months after start of anticoagulation, CTEPH was diagnosed: extensive webs, thrombus and complete occlusions on CTPA, and RHC mPAP 48 mmHg, PAWP 10 mmHg and PVR 779 dynes·s·cm^{-5}. He was deemed operable, and a PEA was performed with an uncomplicated postoperative course. At follow-up 18 months later, his exercise tolerance normalised, just as the findings at RHC.

Patient B is a 42-year old man, with a previous history of acute PE 5 years ago, diagnosed with recurrent PE. Dyspnea persisted and 4 months later CTEPH was diagnosed: extensive thrombus in the main and lobar pulmonary arteries, with mPAP 35 mmHg, PAWP 6 mmHg and PVR 569 dynes·s·cm^{-5} during RHC, and a severely compromised RV function on cardiac magnetic resonance (CMR) imaging. After PEA his pulmonary hemodynamics normalised (mPAP 20 mmHg and PVR 182 dynes·s·cm^{-5} during rest) but he kept experiencing exercise intolerance, keeping him from running 10 km as he used to do before the first acute PE was diagnosed.

Patient C is a 68-year old woman diagnosed with CTEPH after having progressive dyspnea for several years, previously regarded the result of her (mild) COPD. CTPA revealed webs, thrombus and occlusions at the segmental level of both lower lobes and the right upper lobe; RHC: mPAP 62 mmHg, PAWP 10 mmHg, PVR 924 dynes·s·cm^{-5}. PEA was performed, but 6 months later resting pulmonary hemodynamics remained abnormal (mPAP 36 mmHg, PAWP 12 mmHg, PVR 460 dynes·s·cm^{-5}), qualifying her as residual PH for which riociguat was started.

These cases describe three patients with CTEPH, all receiving surgical treatment but with different pre- and postoperative courses, illustrating some of the diverse manifestations and outcomes of CTEPH: patient A has both normalised hemodynamics and exercise capacity, while patient B has normalised hemodynamics but persistent exercise intolerance; patient C has substantial residual PH for which additional treatment after PEA is started. Several questions arise from these clinical vignettes:

1. Despite the more severe pulmonary hemodynamic abnormalities in patient A, RV function was more compromised in patient B. What determines pulmonary hemodynamics and RV function in CTEPH and how can the differences between these two patients be explained?

2. What determines residual PH?

3. Considering potential therapeutic consequences of residual PH, is RHC 6 months after PEA a mandatory part of follow-up in all patients?

4. Despite normalised resting hemodynamics, exercise tolerance remains impaired in patient B: what explains the persistent exercise intolerance and could we have foreseen this before PEA, in order to manage patient expectations of the surgery?

Outline of this thesis

These previous questions are the common thread through this thesis.

Despite the more severe pulmonary hemodynamic abnormalities in patient A, RV function was more compromised in patient B. What determines pulmonary hemodynamics and RV function in CTEPH and how can the differences between these two patients be explained?

Chapter 2 provides an overview of the pathophysiology in acute PE; acute PE and CTEPH are pulmonary vascular diseases within the same spectrum, sharing many pathophysiological mechanisms, although with a different time course. The final common pathway in both acute PE and CTEPH is an increased RV afterload leading to RV dysfunction and failure. Especially the transition from adaptation to maladaptation is crucial in the time course of pulmonary hypertension. Traditionally, RV afterload is mainly determined by pulmonary vascular resistance and compliance [24], which are known to be inversely related to each other (*i.e.* RC time constant) [25]. However, how the RV responds to abnormalities in the pulmonary vasculature and when compensatory mechanisms become maladaptive differs between patients. The question is whether intrinsic (cardiac) properties or just the load imposed on the RV determines the (mal) adaptive RV response. And is the traditional three-element windkessel model of the pulmonary vasculature covering all aspects or are other factors relevant such as wave reflections in the pulmonary arteries towards the RV? CTEPH has manifestations ranging from very proximal (*i.e.* thrombotic lesions in the main pulmonary arteries) to very distal disease (*i.e.* small vessel disease). This provided us with a unique opportunity to perform an analysis on the differential effects of location of CTEPH lesions (proximal versus distal) on RV load and RV function. By analysing pulmonary hemodynamics (integrating static and pulsatile components of afterload) and CMR-based RV function in 21 patients with proximal disease and 25 patients with distal disease, we aimed to determine the influence of proximal and distal vascular lesions on RV afterload and function, as described in **chapter 3**. We hypothesized that location of CTEPH lesions does influence RV function despite similar afterload as determined by the classical components PVR and compliance.

What determines residual PH?

Successful PEA in eligible patients will lead to a substantial reduction in PVR and increased compliance, resulting in RV afterload reduction, reverse remodelling of the RV and normalisation of pulmonary hemodynamics, associated with a significant improvement in survival compared to CTEPH patients not eligible for PEA [12]. However, residual PH after PEA is frequent: in a large UK cohort with structured follow-up 3-6 months after PEA, 51% had mPAP ≥ 25 mmHg [18]. With the emergence of additional treatment options (BPA and medical therapy), identifying residual PH becomes more relevant. mPAP ≥ 30 mmHg was proposed as a cut-off for clinically relevant PH at risk for functional deterioration; mPAP ≥ 38 mmHg and PVR ≥ 425 dynes·s·cm^{-5} was associated with a higher CTEPH-related mortality risk [18].

Residual PH is hypothesized to be the result of either (very) distal vasculopathy, or macrovascular lesions near the subsegmental level beyond the reach of the surgeon, or residual lesions in the setting of a technically insufficient PEA, or a combination of these. Multidisciplinary discussion in experienced CTEPH centres and appropriate patient selection will minimise the risk of technically insufficient PEA. Distal vasculopathy is difficult to quantify, especially before PEA when extensive central abnormalities may hinder appropriate evaluation of the distal compartment. Although pulmonary artery occlusion waveforms analysis can be used to estimate upstream and downstream resistance and thereby the degree of small vessel disease [26], this technique is not widely available/feasible and dependent on specific expertise.

The role of residual (sub)segmental macrovascular lesions and distal vasculopathy was further analysed in **chapter 4**. We hypothesized that remaining (sub)segmental macrovascular lesions are prevalent but not explaining residual PH, while we expected that distal vasculopathy is the most important factor in residual PH.

We used a prospective cohort of PEA patients with CTPA and magnetic resonance (MR) perfusion both before and 6 months after PEA to describe the prevalence of residual (sub)segmental vascular lesions on CTPA and parenchymal hypoperfusion on MR perfusion (as a marker of distal vasculopathy), and relate these imaging abnormalities to the presence or absence of residual PH after PEA.

Perfusion scans and CTPA are not part of standard follow-up after PEA and in general are only repeated by clinical indication. Therefore, the incidence of recurrent thrombosis and their relevance for residual PH is unknown. We hypothesized that recurrence of lesions is not a relevant factor in the majority of patients with regards to residual PH after PEA. A cohort of PEA patients with CTPA both before and 6 months after PEA was used to describe the incidence, morphology and clinical implications of recurrent thrombotic lesions after PEA, as described in **chapter 5**.

Considering potential therapeutic consequences of residual PH, is RHC 6 months after PEA a mandatory part of follow-up in all patients?
As illustrated in patient C, diagnosing residual PH is relevant because of consequences regarding morbidity and mortality and because of the availability of additional treatment options to prevent such long-term sequela in patients with substantial residual PH. Diagnosing residual PH requires RHC; structured follow-up with RHC in all patients is not always feasible. In **chapter 6** we analysed whether patients without residual PH can be identified based on non-invasive diagnostics (TTE and cardiopulmonary exercise testing (CPET)) in a safe and effective manner, to decrease the number of patients requiring re-RHC and enable a more focused approach towards patients with a higher probability of residual PH.

Despite normalised resting hemodynamics, exercise tolerance remains impaired in patient B: what explains the persistent exercise intolerance and could we have foreseen this before PEA, in order to manage patient expectations of the surgery?
Hemodynamic normalisation is the goal and primary outcome after PEA; however, the relation between hemodynamic outcome and exercise capacity in these patients is unknown, persistent exercise intolerance is probably frequent, and these outcomes do not always correspond, as illustrated in patient B: while hemodynamics at rest normalised, exercise capacity remained impaired. Exercise capacity as an outcome parameter after PEA is very relevant for patients, also when managing patient expectations before PEA. As a first step, we analysed the incidence of exercise intolerance and its relationship with (resting) hemodynamics and potential preoperative predictors in a prospective cohort of 68 CTEPH patients with RHC, CMR and CPET before and 6 months after PEA, with detailed analysis of CPET patterns to enable us to further hypothesize on the underlying mechanisms of persistent exercise intolerance **(chapter 7)**.

Conclusion

CTEPH is a devastating disease leading to severe limitations and considerable morbidity and mortality when remaining undiagnosed and/or left untreated. Therapeutic options with curative intent and favorable long-term results are available. Awareness for this disease is therefore crucial, just as the management of these patients in expert centres with the full treatment spectrum available to be able to offer each patient the most optimal treatment. PEA is the treatment of first choice in operable patients and the only potentially curative therapy. The outline of this thesis is highlighted in the previous paragraphs, with a focus on pathophysiology of CTEPH and RV function, mechanisms involved in residual PH after PEA, non-invasive diagnosis of (the absence of) residual PH after PEA, and the relation between exercise intolerance and hemodynamic outcomes after PEA.

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CHAPTER 2

2

Pathophysiology of acute pulmonary embolism

Dieuwertje Ruigrok and Anton Vonk Noordegraaf

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Abstract

Acute right ventricular (RV) failure and impaired gas exchange (mainly hypoxemia) can be two important issues clinicians are confronted with in patients with acute pulmonary embolism. An acute increase in RV afterload due to mechanical obstruction and vasoconstriction is the crucial factor starting a cascade with compensatory mechanisms, RV dilatation, RV ischemia and inflammation ultimately leading to RV dysfunction/failure. On the other hand, vascular occlusion leads to redistribution of pulmonary perfusion to regions with relative overperfusion causing profound hypoxemia. Less commonly, shunting occurs due to atelectasis or due to opening of a patent foramen ovale, causing refractory hypoxemia. Understanding these mechanisms is crucial in making the right treatment decisions when facing a patient with acute pulmonary embolism and hemodynamic or respiratory instability.

Acute pulmonary embolism (PE) is a relatively frequently occurring cardiovascular disorder, with a substantial mortality rate if untreated, especially within the first hours of presentation. The two main clinical issues faced in the emergency department are hemodynamic instability and hypoxemia. Understanding of the pathophysiological mechanisms leading to acute right ventricular (RV) failure and impaired gas exchange is pivotal in making treatment decisions regarding, for example, volume expansion and use of vasodilators.

Cardiovascular compromise

Acute PE is the second most frequent cause of acute RV failure (after acute RV failure due to left-sided heart failure) and the most important cause of acute RV pressure overload [1]. Acute RV dysfunction/failure in acute PE is the primary cause of death in acute PE [1-2]. The main pathophysiological mechanism leading to RV dysfunction and RV failure in acute PE is the sudden increase in afterload. Impaired contractility is an important contributing factor.

Afterload is acutely increased by pressure overload due to both mechanical obstruction of the pulmonary vasculature by emboli and by vasoconstriction under the influence of vasoactive mediators released by endothelial cells and platelets (among others thromboxane A2 and serotonin) [3-4]. In both animal studies and small patient series, hypoxic vasoconstriction appeared to be blunted in acute PE considering the lack of an oxygen effect on pulmonary vascular resistance (PVR) [5-6], possibly due to the counteracting effects of the vasoactive mediators, although the exact mechanism is not known.

The sudden increase in afterload and PVR leads to increased RV muscle stretch, increased wall tension, and RV dilatation, as reflected by increases in (N-terminal pro-) brain natriuretic peptide. Initially, compensatory mechanisms comprising increasing the contractility through autoregulation (Anrep effect) [7], the Frank-Starling mechanism, and inotropic and chronotropic stimulation (neurohormonal activation) [8] result in development of pulmonary hypertension thereby maintaining pulmonary and systemic blood flow [9]. However, a previously healthy non-hypertrophied RV can acutely generate a mean pulmonary artery pressure up to 40 mmHg [10]. With further increases in afterload a higher pulmonary artery pressure cannot be generated and further RV dilatation becomes maladaptive leading to RV failure.

The association between the degree of pulmonary vascular occlusion and hemodynamic compromise as well as an adverse clinical outcome remains a matter of debate. Earlier studies showed a correlation between the degree of angiographic obstruction and pulmonary artery pressure in patients without pre-existing cardiopulmonary disease, with increasing pulmonary artery pressure when angiographic pulmonary vascular

obstruction exceeded 30% [10]. This correlation was absent in patients with pre-existing cardiopulmonary disease [11]. When using computed tomography to quantify embolic burden, conflicting results have been reported regarding the correlation with RV dysfunction and short-term mortality [12-15]; two recent meta-analyses showed no correlation between obstruction index or thrombus load on computed tomography and short-term all-cause mortality; however, an association with PE-related mortality and adverse clinical outcomes was found [16-17].

Contractility becomes impaired by several factors. First, increased wall tension and increased myocardial transmural pressure compromise perfusion of the right coronary artery, thereby decreasing oxygen supply leading to regional ischemia [18-19]. Against the background of increased oxygen demand due to increased workload and tachycardia, a vicious circle results with myocardial ischemia, decreased RV contractility, decreased cardiac output and decreased oxygen supply, ultimately leading to RV dysfunction and failure.

Contractility is further reduced by inflammation. Knowledge about inflammation in RV damage following acute PE is limited. However, several studies showed extensive influx of inflammatory cells into the RV (mainly mononuclear cells and neutrophilic granulocytes) in post mortem samples after massive PE, coinciding with myocytolysis indicating myocarditis [20-22]. In a rat model, treatment with antibodies to a neutrophil chemoattractant CINC-1 resulted in suppression of neutrophilic accumulation in the RV and a reduction of the plasma concentration of troponin I [23].

Ventricular interdependence is the concept that size, shape and compliance of one ventricle affect these properties of the other ventricle by mechanical interactions [24]. Acute RV overload and RV dilatation lead to RV shape changes, a left-sided shift of the interventricular septum, and a constraining effect of the pericardium, compromising left ventricular diastolic function and cardiac output [1,25] (figure 1).

RV dilatation, subsequent tricuspid regurgitation and elevated pressures may trigger tachyarrhythmias, mainly atrial fibrillation and flutter, further compromising contractility and cardiac output.

To what extent the described mechanisms summarised in figure 2 occur, also depends on the presence of co-morbidities and pre-existing cardiovascular and pulmonary reserve.

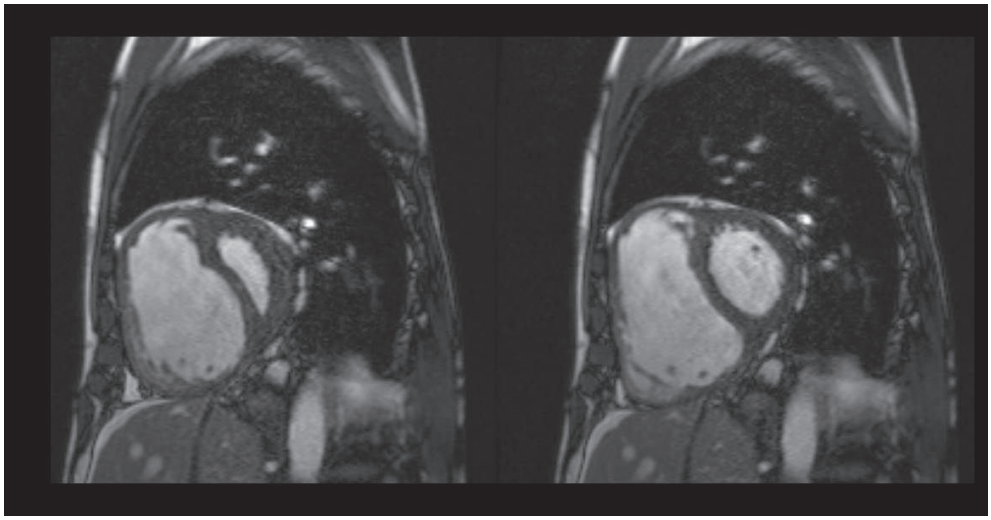

Figure 1: short-axis cardiac magnetic resonance images. Significant right ventricular dilatation leading to a left-sided shift of the interventricular septum, thereby compromising left ventricular function (left image, end-systolic; right image, end-diastolic).

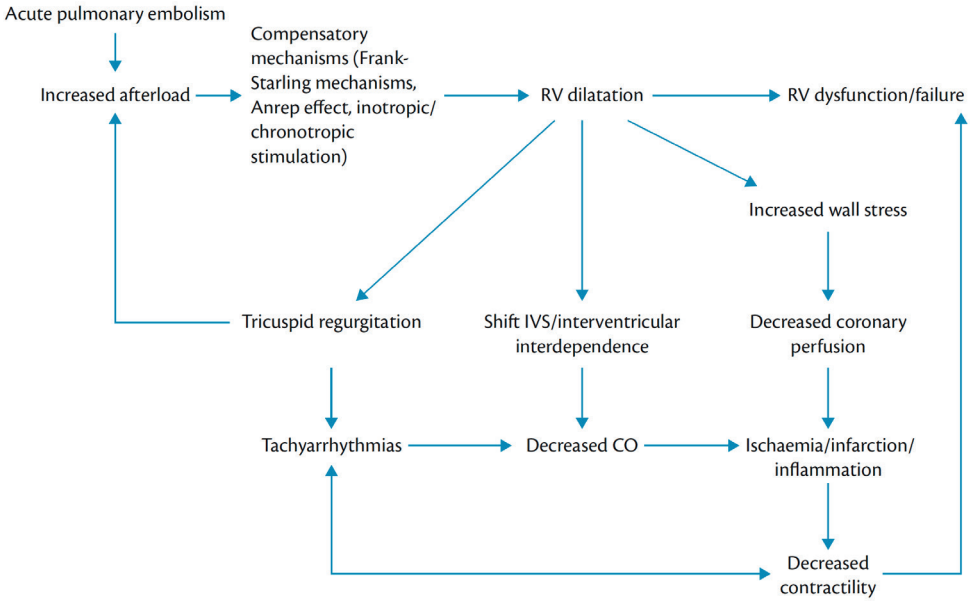

Figure 2: supposed mechanisms leading to cardiovascular compromise in acute pulmonary embolism. CO: cardiac output; RV: right ventricular; IVS: interventricular septum.

Hypoxemia

Hypoxemia is frequently occurring in acute pulmonary embolism [3,26-27], but a correlation with embolic load is absent [28] and the degree of hypoxemia is influenced by time, cardiac output, pre-existing conditions, compensatory ventilation and locations of the clots [3]. Also, the absence of hypoxemia does not rule out pulmonary embolism [29].

Several factors contribute to hypoxemia in acute PE (figure 3): ventilation/perfusion (V'/Q') mismatch, intrapulmonary shunting, and intracardiac right-to-left shunts [26].

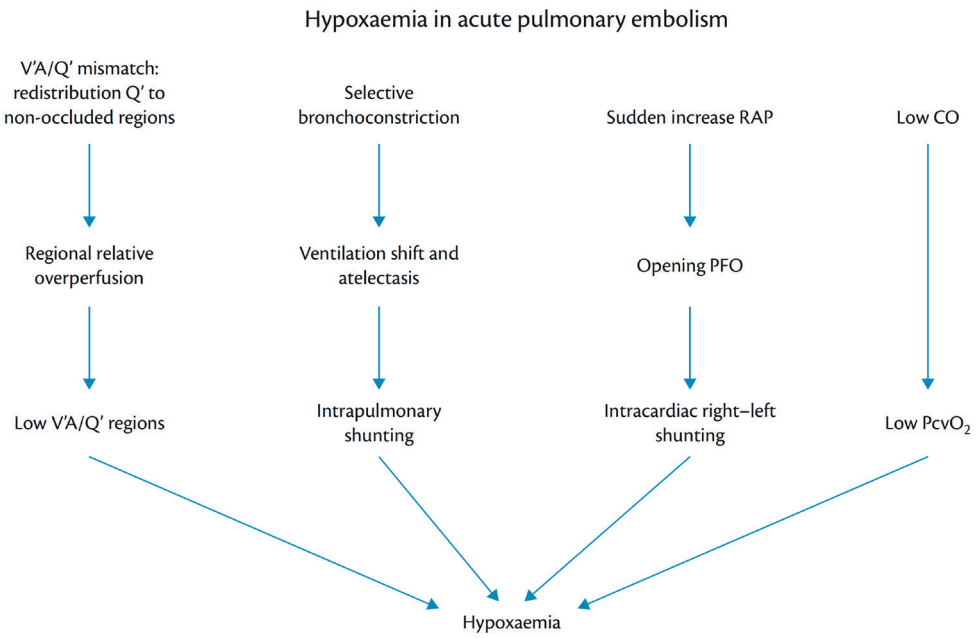

Figure 3: mechanisms leading to hypoxemia in acute pulmonary embolism. CO: cardiac output; $PcvO_2$: central venous oxygen tension; PFO: patent foramen ovale; RAP: right atrial pressure; V'A/Q': alveolar ventilation/perfusion.

The most important factor appears to be ventilation/perfusion mismatch: redistribution of perfusion away from occluded arteries leads to relative overperfusion of non-embolic regions, causing profound hypoxemia [3,26].

Selective bronchoconstriction and reduced parenchymal compliance (pneumoconstriction) can occur near embolic (hypoperfused) regions leading to ventilation shifts, atelectasis and intrapulmonary shunting. This has been related to

the frequently occurring atelectasis on chest X-ray [26,30], and is partly and temporally reversible through deep inhalation [28]. Spirometry in patients with acute PE showed evidence of bronchial obstruction [27]. The exact mechanism of this selective broncho/pneumoconstriction and atelectasis is unknown: alveolar hypocapnia (termed hypocapnic bronchoconstriction) [3,31], serotonin release from lysed platelets of the embolus [32], loss of surfactant [33] and splinting due to pleuritic pain [3] have been implicated.

Intracardiac right-left shunting due to opening of a patent foramen ovale has been described in up to 35% of patients with major pulmonary embolism [34].

It has been discussed that ventilation-perfusion mismatch and shunt are moderate and disproportionate relative to the size of hypoxemia. Low cardiac output and resulting low central venous oxygen tension is another factor contributing to hypoxemia [26]. However, increasing cardiac output could lead to worsening of hypoxemia due to further redistribution of pulmonary blood flow to non-embolic regions already overperfused relative to (decreased) ventilation [3].

Considerations for clinical practice

When translating this to clinical practice: excessive volume expansion to optimise RV preload can lead to decreased left ventricular cardiac output through the mechanism of ventricular interdependence and should be avoided. On the other hand, hypovolemia also has a negative impact on RV preload and cardiac output. Therefore, a delicate balance should be sought bearing in mind the above described pathophysiological mechanisms.

Vasodilators theoretically can be used to decrease pulmonary vascular resistance; however, their lack of specificity for the pulmonary circulation could lead to systemic hypotension when administered systemically, further compromising coronary perfusion.

Vasopressors/inotropes on the other hand can have a positive inotropic effect on the RV but increasing cardiac output will lead to increased pulmonary blood flow to non-occluded regions which are already overperfused, further aggravating hypoxemia.

Taking into consideration acute RV failure as the primary cause of death, early reperfusion remains the most important therapy in patients with hemodynamic instability/low cardiac output due to acute RV failure in acute PE, significantly decreasing mortality and leading to a favorable clinical response in over 90% of patients.

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CHAPTER 3

3

Right ventricular load and function in chronic thromboembolic pulmonary hypertension: differences between proximal and distal chronic thromboembolic pulmonary hypertension

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Abstract

Rationale: While location of chronic thromboembolic pulmonary hypertension (CTEPH) lesions does not seem to influence hemodynamic parameters, it may impact right ventricular (RV) function.

Objectives: Aim of this study was to determine the influence of proximal and distal vascular obstructions on RV afterload and function in patients with CTEPH.

Methods: Hemodynamic, RV function and loading parameters were analysed in 21 proximal and 25 distal CTEPH patients, prior to treatment by surgery or medication.

Measurements and main results: Patients with proximal and distal CTEPH had similar pulmonary vascular resistance and pulmonary arterial compliance. Despite the similarities in load, patients with proximal CTEPH had a more compromised RV function, as indicated by a lower RV ejection fraction (mean 34.1% vs 44.7%, p 0.015), and a higher RV end-diastolic volume index (mean 95.3 mL vs 80.5 mL, p 0.041) than patients with distal CTEPH.

Conclusions: RV ejection fraction as a measure of RV function is significantly compromised in proximal CTEPH compared to distal CTEPH. However, RV afterload, as described by pulmonary vascular resistance and compliance, did not explain the diminished RV function in proximal CTEPH.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a condition defined by the presence of pre-capillary pulmonary hypertension (PH) plus at least one (segmental) perfusion defect despite at least 3 months of effective anticoagulation therapy [1]. The clinical presentation of CTEPH ranges from more central pulmonary obstruction, due to non-resolving organised thrombus, to more peripheral obstruction and distal small vessel vasculopathy, due to redistribution of blood flow to non-obstructed areas and altered shear stress [2]. While the final common pathway in untreated proximal and distal CTEPH is right ventricular (RV) dysfunction and RV failure [3-4], the question remains unresolved whether RV function is affected by the localisation of the vascular lesions.

RV afterload is determined by both static components (pulmonary vascular resistance (PVR)) and pulsatile components (compliance of the pulmonary arteries and characteristic impedance of the proximal pulmonary arteries), assuming a three-element windkessel model [5-6]. In most forms of pulmonary hypertension, the relation between resistance and compliance was shown to be constant irrespective of aetiology, severity and treatment [7-9]. This fixed relation was confirmed in a cohort of CTEPH patients, showing similar PVR and compliance in proximal and distal CTEPH [10]. However, it was recently suggested that for a given resistance, a more proximal vascular obstruction is associated with a larger RV afterload [11]. Hypothetically, proximal CTEPH lesions could increase pulmonary arterial stiffening or increase characteristic impedance, leading to a greater RV afterload for a given resistance. The question we aimed to answer in this exploratory analysis was: do proximal and distal CTEPH have different effects on RV afterload and function? Answering this question would not only provide a better understanding of determinants of RV function in proximal and distal CTEPH but would also provide insights into the interplay of load and RV function in pulmonary hypertension in general.

Methods

Study subjects and design

In this retrospective analysis, patients with a diagnosis of CTEPH according to the current clinical guideline [1] were selected from the clinical registry of the VU University Medical Centre Amsterdam, an academic referral centre for pulmonary hypertension in the Netherlands. Patients who were operated or visited our PH-clinic for the first time between January 2010 and January 2018 were screened for the presence of at least a high-quality computed tomography pulmonary angiography (CTPA), right heart catheterisation (RHC) and cardiac magnetic resonance (CMR) imaging. All three investigations had to be performed before the start of any treatment, with a maximum interval of 6 months between investigations. Figure 1 illustrates patient selection and reasons for exclusion.

CTEPH was subtyped for each side separately (either as proximal or distal per side) based on CTPA. According to the newly proposed updated intraoperative classification from the University of California, San Diego [12], proximal disease was defined as level I or II disease with lesions starting in the main or lobar arteries (representative CT image in figure 2A) (comparable to type 1-2 disease in the previous Jamieson classification). Distal disease was defined as level III-IV disease with lesions starting in the segmental and subsegmental arteries (representative CT image in figure 2B) (comparable to type 3-4 disease in the previous Jamieson classification). To create uniform groups, patients with asymmetrical lesions (*i.e.* proximal on one side and distal on the other side; approximately one third of the total study population) were not included in the final analysis.

This retrospective study, based on available clinical data obtained for clinical purposes, did not fall within the scope of the Medical Research Involving Human Subjects Act, as confirmed by the Medical Ethics Review Committee of the VU University Medical Centre (2017.025).

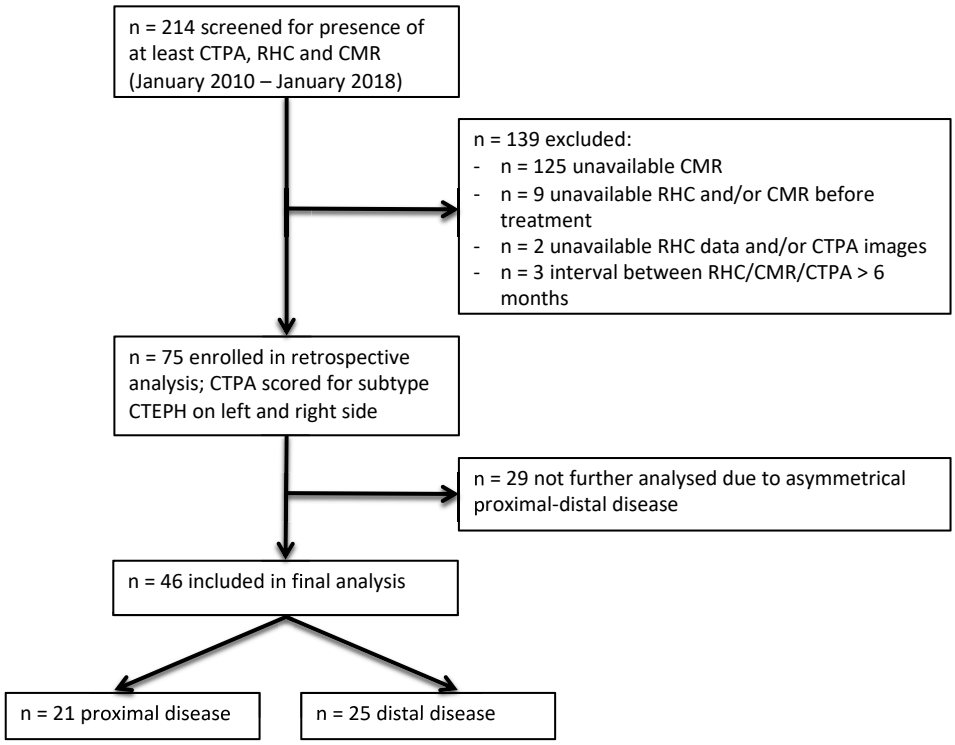

Figure 1: Flowchart of patient selection and inclusion into the retrospective analysis.
CTPA: CT-pulmonary angiography; RHC: right heart catheterisation; CMR: cardiac magnetic resonance; CTEPH: chronic thromboembolic pulmonary hypertension.

CTPA and CMR

Available CTPA were used for evaluation, with minimal requirement of a 64-slice multidetector CT. CTPA images were reviewed by 2 investigators (LJM and DR), subtyping the location of CTEPH lesions as indicated above; final evaluations were achieved by consensus.

All CMR images were acquired with a 1.5 Tesla MR Avanto scanner and analysed as previously described [13].

Figure 2: computed tomography pulmonary angiography (CTPA) illustrating proximal and distal CTEPH. Panel A: CTPA in axial view illustrating proximal disease: extensive thrombus in left main pulmonary artery. Panel B: CTPA in reconstructed coronal view illustrating distal disease: web in segmental posterobasal artery left lower lobe.

RHC, compliance and RC time constant

RHC was performed as previously described [13]. Pulmonary arterial compliance (C) was calculated as stroke volume divided by pulse pressure (C_{SVPP}, mL/mmHg). Stroke volume (SV) was derived from RHC, as cardiac output/heart rate (CO/HR). Pulse pressure (mmHg) was the difference between systolic pulmonary artery pressure (PAP) and diastolic PAP. For calculation of resistance-compliance (RC) time, PVR was recalculated from dynes·s·cm^{-5} to mmHg·s·mL^{-1} by multiplying with 0.75·10^{-3}. RC time was the product of PVR (mmHg·s·mL^{-1}) and C_{SVPP} (mL/mmHg).

Statistical analysis

Data are presented as mean (standard deviation, SD) or median (interquartile range, IQR). Differences were tested using unpaired t-test/Mann-Whitney test or Fisher's exact test/Chi-square test where appropriate. Values of $P < 0.05$ were considered to reflect statistical significance. Statistics were performed using IBM SPSS Statistics version 24 and GraphPad Prism version 7.0b (GraphPad Software, La Jolla, California, USA).

Results

We screened 214 eligible CTEPH patients for the presence of adequate CTPA and RHC. After excluding 139 patients for various reasons, 75 CTEPH patients were enrolled (figure 1). 29 patients with asymmetrical disease were excluded, while 21 patients with proximal disease and 25 patients with distal disease were included in the final analysis.

Baseline characteristics were comparable in both groups, except for more former or current smokers, a lower 6-minute walking distance (6MWD), higher N-terminal pro-brain natriuretic peptide (NT-proBNP) and lower transfer factor for carbon monoxide (T_{LCO}) in proximal CTEPH (table 1). The hemodynamic profile was comparable between groups except for a higher right atrial pressure (RAP) in proximal CTEPH (table 2). Confirming the findings of previous studies, no differences between groups were observed in either pulmonary arterial compliance (based on the C_{SVPP} method) (proximal CTEPH: median 1.11 (IQR 0.64-1.31) mL/mmHg; distal CTEPH: median 1.34 (IQR 0.80-1.89) mL/mmHg; p 0.098), the relationship between compliance and resistance, or the products of resistance and compliance (RC time) (proximal CTEPH mean 0.58 s (SD 0.13); distal CTEPH mean 0.58 s (SD 0.13); p 0.851) (figure 3).

Table 1: baseline characteristics

Variable	Proximal CTEPH *n = 21*	Distal CTEPH *n = 25*	P value
Age (years)	65 (50-70)	66 (52-73)	0.723
Male (n, %)	13 (62%)	11 (44%)	0.226
History of acute VTE	20 (95%)	23 (92%)	> 0.999
Smoker (current or former)	16 (89%) *n = 18*	10 (45%) *n = 22*	0.007*
NYHA class I-II vs III-IV (n, %)	6 (32%) vs 13 (68%) *n = 19*	13 (52%) vs 12 (48%)	0.176
6MWD (m)	339 (71) *n = 19*	445 (108) *n = 19*	0.001*
NT-proBNP (ηg/L)	1745 (549-4185)	446 (150-1360)	0.032
T_{LCO} (% predicted)	61.9 (13.8) *n = 18*	75.7 (13.5) *n = 19*	0.004*
Comorbidities			
Systemic hypertension	4 (19%)	9 (36%)	0.325
Malignancy in previous history	1 (5%)	2 (8%)	> 0.999
Diabetes mellitus	2 (10%)	2 (8%)	> 0.999
Obstructive lung disease	4 (19%)	3 (12%)	0.686
Known significant coronary artery disease	2 (10%)	1 (4%)	0.585
Thyroid replacement therapy	1 (5%)	2 (8%)	> 0.999

Data are presented as mean (standard deviation), median (interquartile range) or number of patients (%). Data apply to all 21 and 25 patients per group unless otherwise stated. Statistical tests: unpaired t test, Chi-square test, Fisher's exact test, Mann-Whitney test. Statistical significance indicated with an *.
CTEPH: chronic thromboembolic pulmonary hypertension; VTE: venous thromboembolism; NYHA: New York Heart Association; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; T_{LCO}: transfer factor for carbon monoxide.

Table 2: hemodynamic and cardiac magnetic resonance profile

Variable	Proximal CTEPH *n = 21*	Distal CTEPH *n = 25*	P Value
Right heart catheterisation			
mPAP (mmHg)	49.1 (12.3)	45.5 (10.2)	0.286
PAWP (mmHg)	9.7 (4.3)	11.8 (2.7)	0.058
PVR (dynes·s·cm^{-5})	740 (544-1011)	555 (419-775) *n = 24*	0.162
CI (L/min/m^2)	2.1 (0.4)	2.4 (0.6) *n = 24*	0.077
RAP (mmHg)	11.6 (5.3) *n = 18*	8.2 (2.9)	0.010*
PA pulse pressure (mmHg)	52.8 (15.8)	47.9 (11.6)	0.234
Stroke volume (mL)	54.8 (19.6)	64.3 (22.9) *n = 22*	0.150
Heart rate (beats/min)	80 (71-88)	73 (63-81) *n = 22*	0.088
Cardiac magnetic resonance			
RVEF (%)	34.1 (12.9)	44.7 (15.2)	0.015*
RVEDVI (mL/m^2)	95.3 (26.2)	80.5 (21.4)	0.041*
LVEF (%)	59.8 (9.3)	66.9 (10.1)	0.018*
LVEDVI (mL/m^2)	54.2 (14.4)	53.5 (13.6)	0.873
SVI (mL/m^2)	29.9 (6.1)	33.6 (9.1) *n = 24*	0.120

Data presented as mean (standard deviation) or median (interquartile range). Data apply to all 21 and 25 patients per group unless otherwise stated. Statistical tests: unpaired t test, Mann-Whitney test. Statistical significance indicated with an *.
CTEPH: chronic thromboembolic pulmonary hypertension; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; CI: cardiac index; RAP: right atrial pressure; PA: pulmonary artery; RVEF: right ventricular ejection fraction; RVEDVI: right ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVEDVI: left ventricular end-diastolic volume index; SVI: stroke volume index.

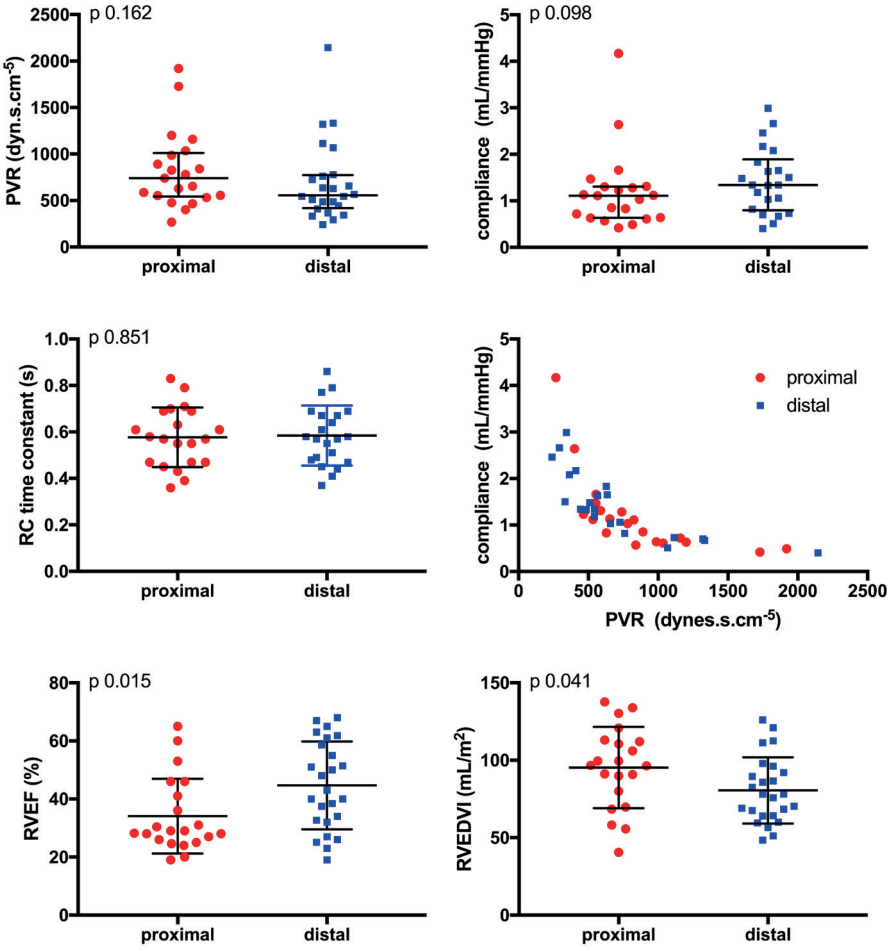

Figure 3: RV load parameters and CMR-based RV parameters in proximal versus distal CTEPH. Horizontal bars indicate mean with standard deviation (RC time, RVEF and RVEDVI; p value calculated with independent *t* test) or median with interquartile range (PVR and pulmonary arterial compliance; p value calculated with Mann-Whitney test).
RV: right ventricular; CMR: cardiac magnetic resonance; CTEPH: chronic thromboembolic pulmonary hypertension; PVR: pulmonary vascular resistance; RC time: resistance-compliance time; RVEF: right ventricular ejection fraction; RVEDVI: right ventricular end-diastolic volume index.

Despite the observed similarities in RV load, we found a significantly lower right ventricular ejection fraction (RVEF) in patients with proximal CTEPH compared to patients with distal CTEPH (mean 34.1% and 44.7% respectively, p 0.015) (table 2). Left ventricular ejection fraction (LVEF) was also significantly lower in proximal CTEPH (mean 59.8% and 66.9% respectively, p 0.018). Finally, a significantly higher right ventricular end-diastolic volume index (RVEDVI) indicated more RV dilatation in proximal CTEPH (figure 3).

Overall, LVEF and RVEF were significantly correlated (Spearman rho 0.665, $p < 0.001$). RV function of excluded patients with asymmetrical lesions was similar, as in the group with distal CTEPH.

Discussion

In this retrospective analysis we described RV load, as defined by PVR and compliance, as well as RV function assessed by CMR in a cohort of CTEPH patients with either proximal or distal lesions, prior to initiation of treatment. Although the site of vascular obstruction did not affect PVR or compliance, we observed a significantly lower RVEF and more RV dilatation, together with a lower LVEF, in patients with proximal CTEPH compared to distal CTEPH patients.

RV (systolic) function in the pressure-overloaded RV is determined by several components, both load-dependent and load-independent (intrinsic contractility). Pathogenesis is complex, but central is the increased load to the RV leading to increased contractility with homeometric adaptation (adaptive remodelling). At some point, heterometric maladaptive adaptation with RV dilatation (increased RVEDV) ensues, in order to maintain stroke volume [14]. One of the clinically used measures of RV function is RVEF, which is load-dependent and a reflection of (depressed) RV function and RV dilatation. Other potential measures of RV systolic function are tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC). In this analysis we used CMR-derived RVEF, which has already proven its prognostic value in pulmonary arterial hypertension (PAH) [13].

This analysis confirms earlier reports that proximal and distal CTEPH patients present with similar hemodynamics at baseline. However, previous comparisons were made solely based on mPAP and PVR [15-16] and not on pulsatile components of afterload or RV function. As described, RV function and afterload are determined by static components (PVR) and pulsatile components (pulmonary arterial compliance and characteristic impedance) [5-6]. Arterial compliance can be determined by different methods, either based on CMR data with flow measurements or based on RHC-derived SV and pulse pressure [7]. Although strong correlations exist between these different methods in PH patients, the SV/PP method gave a consistently higher compliance than CMR-based methods [7]. Resistance and compliance are inversely related, and the product of the two, also known as RC time, is constant [6-7]. The inverse relationship between resistance and compliance has been shown to be constant in non-PH and PH patients, irrespective of the cause of PH (with one exception: PH due to left heart disease, probably due to the higher pulmonary artery wedge pressure (PAWP) used in the definition of PVR) [7-9]. Additionally, the RC time of separate lungs in CTEPH has been shown to be constant, irrespective of extent or location of occlusion [17]. However, recent publications have questioned a constant relationship between resistance and compliance in proximal

CTEPH. An animal model simulating proximal CTEPH by banding of the proximal pulmonary artery, featured a decreased compliance, a changed relationship between resistance and compliance, and increased characteristic impedance [11]. The question is whether this is an appropriate model to mimic proximal CTEPH since central banding might also change the mechanical properties of the pulmonary artery. Also, RC time by itself is not a measure of afterload but an indicator of stiffness of the pulmonary arterial system for a given resistance. MacKenzie Ross *et al* compared proximal to distal CTEPH and found a slightly lower PVR in the proximal group despite similar compliance, indicating that overall load was not significantly different between proximal and distal CTEPH [10]. It has been hypothesized that proximal lesions could lead to a different distribution of compliance and increase in characteristic impedance. In our analysis both pulmonary arterial compliance and PVR were similar in proximal and distal CTEPH, just as the relation between these components (RC time) and their distribution along the inverse hyperbolic curve, further supporting previous results [17]. Also, RC times were comparable to those reported previously in another CTEPH cohort [18].

The observed difference in RVEF between proximal and distal CTEPH is currently unexplained, but several different mechanisms can be postulated.

First, the function of the RV in patients with proximal CTEPH may have been depressed because of its direct dependence on left ventricular (LV) function and a lower LV contraction, as shown by the lower LVEF and the significant correlation between RVEF and LVEF. When the RV is not pressure overloaded, it derives about 20-40% of its function directly from LV contraction [19]. The relationship between RVEF and LVEF can reverse when there is a pressure overload on the RV. The dilated RV then impairs LV diastolic filling and spuriously increases LVEF [20]. This then would make it less likely that the finding of a lower RVEF in proximal CTEPH is explained by a lower LVEF in the same patients.

Second, characteristic impedance may be a relevant additional component of afterload that was not accounted for in the current or any prior studies on load in CTEPH, which all focus on PVR and compliance. Characteristic impedance describes the interaction between the acceleration of blood mass and compliance in the proximal circulation [5]. As such, characteristic impedance reflects the dynamic properties of mainly the proximal pulmonary arteries. Unilateral proximal pulmonary artery occlusion in a rat model was recently shown to increase pulse pressure and the characteristic impedance, while leaving arterial compliance and peripheral resistance unchanged compared to baseline [21]. Additionally, characteristic impedance was increased in the animal model simulating proximal CTEPH by banding of the pulmonary artery [11], although it was unclear whether this finding was related to the location of the obstruction or to changed mechanical properties of the pulmonary artery. Characteristic impedance is difficult to quantify, as it requires measurements of (simultaneous) pressure and flow wave shapes.

At this time, conclusive evidence regarding the role of characteristic impedance in the depressed RV function of patients with proximal CTEPH is lacking.

Third, RV function in CTEPH may be critically dependent on proximal vascular properties and wave propagations, which are not reflected in the three component windkessel analysis. Although the proximal vascular properties could be different between proximal and distal CTEPH, we found no differences in total pulmonary arterial compliance. Saouti *et al* previously studied local/proximal compliance and found that area compliance and resistance were not different between the left and right main pulmonary arteries and did not vary with location of CTEPH lesions along the vascular tree [17]. In addition, the contribution of proximal compliance to overall pulmonary arterial compliance has been reported to be relatively small (19%) [17]. However, it is unknown how different distributions of compliance over the pulmonary arterial vasculature affect the RV. Wave reflections possibly better represent proximal vascular properties, but for a more detailed description on wave reflection, we refer to papers focusing on this topic [22-23].

A final explanation for the decreased RVEF in proximal CTEPH may lie in intrinsic differences in RV adaptation independent from load and possibly related to other clinical features, such as comorbidities. Although the prevalence of relevant comorbidities was similar in both groups, transfer factor for carbon monoxide (T_{LCO}) and LVEF were remarkably different.

The modest study size precludes analysis of relationships of our findings with known comorbidity and risk factors for CTEPH and outcome [4]. Since a significant number of patients not treated with PEA were included, classification of CTEPH type was based on CTPA. Inter-rater agreement, comparing blinded surgical classification by an experienced cardiothoracic surgeon performing PEA to radiological classification by an experienced thoracic radiologist, indicated good agreement (Cohen's kappa 0.7), indicating this CTPA-based classification can be regarded as reliable and creates the possibility to classify non-operated patients. A large prospective cohort underscores this correlation between radiological and surgical findings [24]. It is important to recognise that this classification of proximal or distal disease is an anatomical classification used for research purposes and does not imply any decisions regarding technical operability. The interval between CMR and RHC might constitute a limitation of the study. However, the median interval between investigations was 1 day, and like described before [25] heart rates during both CMR and RHC correlated well (Pearson's r 0.71, $p < 0.001$), supporting the assumption that this time interval did not have significant effects on our results. In addition, we performed a subgroup analysis of patients with a maximum interval of 30 days between CMR and RHC, which did not change the overall results.

In conclusion, although patients with proximal and distal CTEPH present with similar PVR and pulmonary artery compliance, we observed important differences in cardiac

function. RVEF was significantly lower and RV dilatation more pronounced in patients with proximal CTEPH. It remains to be determined whether these observed differences are related to differences in load that are not accounted for by quantifying resistance and compliance, or whether comorbidities, including a depressed LV systolic function, could explain these differences.

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CHAPTER 4

Pulmonary vascular imaging characteristics after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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Abstract

Background: Between 16 and 51% of patients with chronic thromboembolic pulmonary hypertension will have residual pulmonary hypertension (PH) after pulmonary endarterectomy (PEA). Whether residual PH is related to remaining (sub)segmental macrovascular lesions or to microvascular disease is unknown. New imaging techniques can provide detailed information about (sub)segmental pulmonary arteries and parenchymal perfusion. The aim of this study was to describe the prevalence after PEA of remaining (sub)segmental vascular lesions on electrocardiogram-gated computed tomography pulmonary angiography (CTPA) and parenchymal hypoperfusion on magnetic resonance imaging (MRI) and to relate these imaging abnormalities to the presence or absence of residual PH after PEA.

Methods: In a prospective cohort of patients with operable chronic thromboembolic pulmonary hypertension, hemodynamics, CTPA and lung perfusion MRI were performed before and 6 months after PEA. The percentage of (sub)segmental vascular lesions was calculated on CTPA and parenchymal hypoperfusion on lung perfusion MRI.

Results: PEA led to significant improvements in hemodynamics and a reduction of imaging abnormalities. Residual PH was present in 45% of patients after PEA, while remaining (sub)segmental vascular lesions and parenchymal hypoperfusion were present in 20% and 21% of the pulmonary vasculature, respectively. Patients with and without residual PH after PEA had similar percentages of remaining (sub)segmental vascular lesions (25% ± 14% vs. 17% ± 15%; p 0.16) and similar degrees of parenchymal hypoperfusion (20% ± 7% vs. 19% ± 6%; p 0.63).

Conclusions: After successful PEA, advanced imaging shows that around 20% of the pulmonary vasculature remains abnormal, independent of the presence of residual PH. This may suggest that microvascular disease, rather than residual macrovascular lesions, plays a prominent role in residual PH after PEA.

Introduction

Pulmonary endarterectomy (PEA) is the gold standard treatment for patients with chronic thromboembolic pulmonary hypertension (CTEPH) and results in hemodynamic and functional improvements. Although most patients benefit from PEA, residual pulmonary hypertension (PH) is present in 16 to 51% of post-PEA patients, which is associated with significant morbidity and mortality [1-3]. Although the exact cause of residual PH after PEA remains unknown, current treatment options include targeted medical therapy or balloon pulmonary angioplasty (BPA) [4], with BPA being increasingly performed over the last years.

Persistence of PH after PEA may result from residual macrovascular subsegmental lesions or from the presence of microvascular disease inaccessible to surgery. Because of a lack of prospective studies on systematic pulmonary vascular imaging after PEA, it is currently unknown which type of these two vascular lesions could explain residual PH after PEA. Such knowledge, however, is very relevant for managing this category of patients. If (sub) segmental macrovascular lesions are the culprit, BPA would be the treatment of choice, whereas microvascular disease is best treated with PH-specific medication.

Electrocardiogram (ECG)-gated computed tomography pulmonary angiography (CTPA) provides the best image quality for morphological assessment of central, segmental and subsegmental pulmonary arteries [5-7], whereas lung perfusion magnetic resonance imaging (MRI) has the ability to quantify parenchymal perfusion [8]. In this study, we used ECG-gated CTPA and lung perfusion MRI to provide a comprehensive description of the pulmonary vascular bed after PEA for CTEPH. The aim of this study was to describe the prevalence after PEA of remaining (sub)segmental vascular lesions on ECG-gated CTPA and parenchymal hypoperfusion on MRI, and to relate these imaging abnormalities to the presence of residual PH after PEA.

Materials and methods

Study subjects

Consecutive CTEPH patients undergoing PEA in the VU University Medical Centre between October 2014 and July 2016 were included in this prospective observational study. CTEPH was diagnosed according to the most recent guideline [4] by using pulmonary angiography, right heart catheterisation and ECG-gated CTPA. As part of routine care all patients had pulmonary function and exercise testing and lung perfusion MRI. Treatment success was evaluated 6 months after PEA using right heart catheterisation, CTPA and lung perfusion MRI. Patients with missing CTPA or lung perfusion MRI 6 months after PEA were excluded from this analysis. Post-PEA patients were classified into the following two groups: patients with residual PH (mean pulmonary artery pressure (mPAP) ≥ 25mmHg) and patients without residual PH (mPAP < 25 mmHg). This study

did not fall within the scope of the Medical Research Involving Human Subjects Act, since the follow-up diagnostic procedures were performed for clinical purposes. This was confirmed by the Medical Ethics Review Committee of the VU University Medical Centre (2017.313).

Assessment of operability and surgery

Treatment options were carefully assessed by a multidisciplinary CTEPH expertise team, consisting of an experienced PEA surgeon, pulmonologists, (interventional) radiologists and (interventional) cardiologists. Operability was assessed according to the criteria as described by Madani *et al* with, among others, an assessment of the extent and level of obstruction correlated to the severity of PH [9]. Guided by the preoperative imaging studies, a surgical endarterectomy was performed in all patients. To ensure adequacy of the endarterectomy, every segment was checked for residual lesions before closing the pulmonary artery. Anticoagulation with unfractionated heparin (activated partial thromboplastin time 60-80 seconds) was started three hours postoperatively, and switched to low-molecular-weight heparin (LMWH) the next day. Before discharge, vitamin K antagonists were resumed and LMWH was discontinued upon establishing stable therapeutic oral anticoagulation.

Diagnostics

Right heart catheterisation

Hemodynamic assessment was performed using a fluid-filled balloon-tipped 7F Swan-Ganz catheter (131HF7, Baxter Healthcare Corp, Deerfield, IL). During continuous electrocardiographic monitoring, mPAP and pulmonary artery wedge pressure (PAWP) were recorded and mixed venous oxygen saturation was measured. Cardiac output (CO) was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index). Pulmonary vascular resistance (PVR) was calculated as 80 x ([mPAP - PAWP]/CO).

CT pulmonary angiography

CTPA was performed on a 256-MDCT scanner (Brilliance iCT 256, Philips Healthcare) with retrospective ECG triggering with 0.625 slice thickness and 0.27 seconds/rotation. The tube voltage was set at 100 kV and the tube current was set at 600 mA, with dose modulation to reduce radiation exposure. The injection protocol consisted of administration of 85 mL of non-ionic contrast agent (iobitridol, Xenetix 300, Guerbet, Villepinte, France) through an antecubital vein at a flow rate of 5 mL per second followed by injection of 40 mL saline solution. Automatic bolus tracking was applied with the region of interest positioned in the truncus pulmonalis, and a threshold for triggering data acquisition was set at 115 HU. The acquisition was performed during inspiration. The CT images were reconstructed at 75% of the R-R interval with 1.5 slice thickness at 1.0 mm intervals. The CT images were digitally stored and analysed at a dedicated workstation.

Vascular morphology was assessed post-hoc using a scoring model designed to evaluate 31 pulmonary arteries including 5 mediastinal, 6 lobar and 20 segmental arteries in every patient [10]. Each artery was scored as normal, containing thrombus, web(s) or early tapering (*i.e.* pouching defect) (figure 1). Affected pulmonary arteries were defined as arteries containing thrombi, webs or tapering. Morphological pulmonary artery characteristics were presented as percentage of the total pulmonary arterial vasculature. Two investigators, including an experienced cardiothoracic radiologist with expertise in CTEPH, reviewed the images and were blinded for PH status, and final evaluation was achieved by consensus.

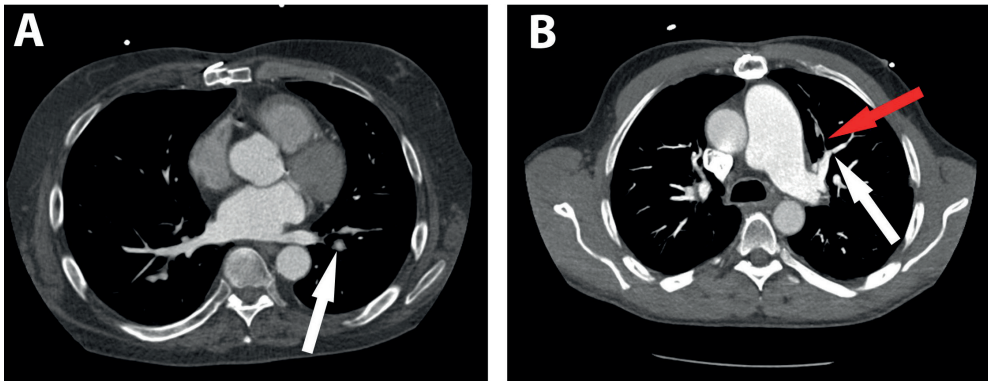

Figure 1: Vascular morphology 6 months after PEA on CTPA. A: thrombus. B: web (white arrow) and tapered pulmonary artery (red arrow). PEA: pulmonary endarterectomy; CTPA: computed tomography pulmonary angiography.

Lung perfusion MRI

Lung perfusion MRI was performed at 1.5T (Avanto, Siemens Healthcare, Erlangen, Germany). CTEPH-related changes in regional lung perfusion were evaluated by means of three-dimensional delayed contrast enhancement time-resolved angiography with stochastic trajectories, using a 16-channel torso phased array coil and the following MRI parameters: echo time 0.88 msec; repetition time 2.49 sec; flip angle 25; acquisition matrix 256 x 256; coronal field of view 500 mm; grappa parallel imaging; voxel size 2.0 x 2.0 x 2.0 mm; 0.5 mmol/ml dotarem, 3 mL/kg with 2 mL intravenous application; and 16 series in time of 80 reconstructed coronal sections covering the whole lung.

Parenchymal hypoperfused areas were quantified post-hoc using Medis Suite 3.0.18.0. To make sure bronchial circulation was excluded from the analysis, the series containing contrast in the pulmonary arteries but without contrast in the aorta was selected.

Total lung volume was quantified via a three-dimensional reconstruction of the lung by obtaining the contour of the entire lung in every 8 sections, including the first and

last section (figure 2A). To quantify parenchymal hypoperfusion volume, hypoperfused areas were manually traced in every section (figure 2B). Parenchymal hypoperfusion was expressed as the percentage hypoperfused volume relative to total lung volume (figure 2C).

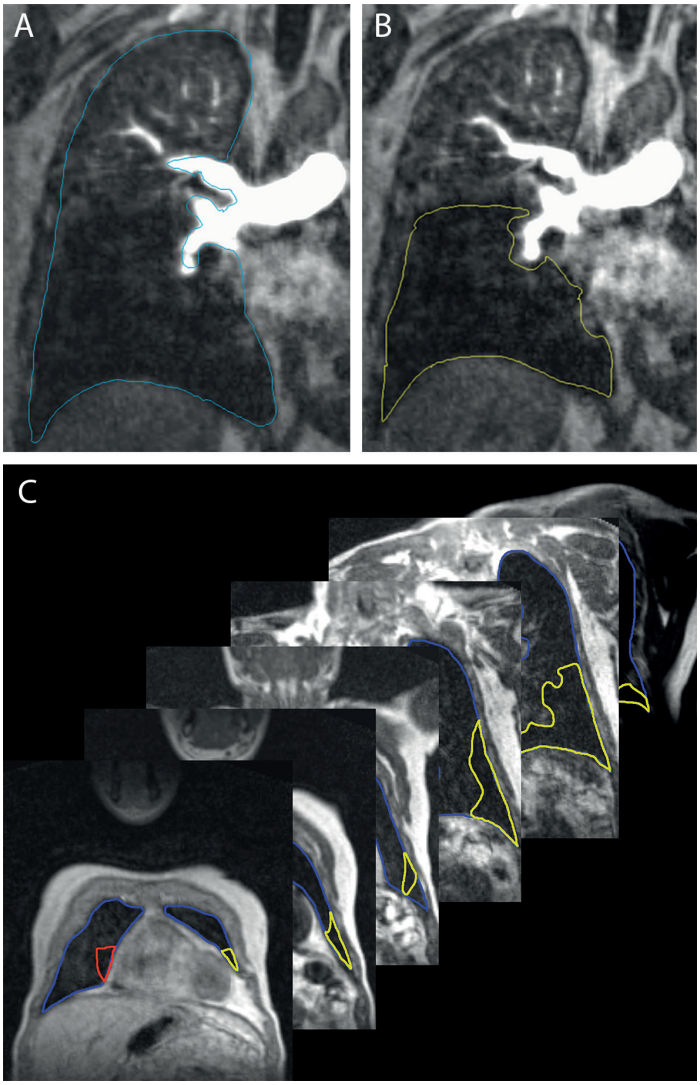

Figure 2: Pulmonary perfusion quantification on lung perfusion MRI before pulmonary endarterectomy. A: Entire right lung contour. B: Area of pulmonary hypoperfusion. C: three-dimensional reconstruction of the parenchymal hypoperfused areas (in red and yellow). MRI: magnetic resonance imaging.

Statistical analysis

Data are presented as mean (standard deviation), median (25^{th}-75^{th} percentiles), or number of patients (%). All variables were tested for normal distribution by carefully assessing the mean, median and standard deviation. N-terminal pro-brain natriuretic peptide (NT-proBNP) failed the normal distribution and was log-transformed for analysis. Comparison of baseline characteristics before and 6 months after PEA was performed using dependent *t*-test for normally distributed continuous variables, Wilcoxon signed-rank test for non-parametric data and McNemar test for proportions. Comparison of characteristics between patients with and without residual PH was performed using independent *t*-test and odds ratio for normally distributed variables, Mann-Whitney U test for non-parametric variables and chi-square test for proportions. Percentage affected pulmonary arteries and parenchymal perfusion was correlated with mPAP using Pearson correlation whereas percentage of tapered pulmonary arteries was correlated with mPAP using Spearman correlation. Missing data were not imputed. Values of $p < 0.05$ were considered to reflect statistical significance. Statistical analysis was performed using GraphPad Prism version 7.0b (GraphPad Software, La Jolla, CA) and IBM SPSS Statistics version 24.

Results

Baseline characteristics

As indicated in the flow chart (figure 3), 42 patients with CTEPH underwent PEA between October 2014 and July 2016. Successful surgical endarterectomy was performed in all patients as confirmed by the surgeon upon close perioperative evaluation of the surgical specimen in all patients. None of the patients received PH medication until the evaluation 6 months after PEA, and all patients continued oral anticoagulant therapy with vitamin K antagonists, aiming for a target international normalised ratio 2.0-3.0. According to the per-protocol analysis, 11 patients were excluded because of missing hemodynamics or ECG-gated CTPA. Complete hemodynamic assessment and CTPA were available in 31 patients, whose baseline characteristics are presented in table 1. PEA led to significant improvements in hemodynamics and functional status (table 1). After PEA, residual PH was present in 14 patients (45%) with a mean mPAP of 29 ± 6 mmHg (table 2). Patients with residual PH had higher levels of NT-proBNP, higher PVR and lower oxygen uptake than patients without residual PH (table 2), even though preoperative functional and hemodynamic status had not been different (supplementary table S1).

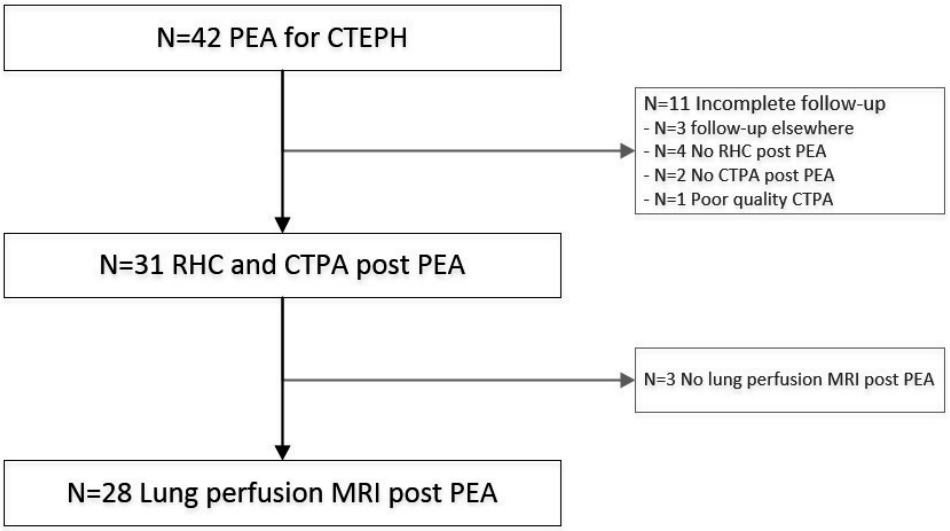

Figure 3: Flowchart of study participants. PEA: pulmonary endarterectomy; CTEPH: chronic thromboembolic pulmonary hypertension; RHC: right heart catheterisation; CTPA: computed tomography pulmonary angiography; MRI: magnetic resonance imaging.

Affected pulmonary arteries on CTPA

Figure 4A represents the prevalence of the different types of vascular lesions (thrombi, webs, and tapered pulmonary arteries) and the percentage of affected pulmonary arteries before and after PEA. All morphological lesions (thrombi, webs, and tapered pulmonary arteries) decreased significantly after PEA. As a consequence, the percentage of affected pulmonary arteries decreased significantly from 51% ± 21% before PEA to 20% ± 15% after PEA (mean difference -31%; 95% confidence interval (CI) -40 to -22; $p < 0.001$).

Figure 4B represents the prevalence of the different morphological types of lesions (thrombi, webs, and tapered pulmonary arteries) and the affected pulmonary arteries as a percentage of the total pulmonary vasculature for patients with and without residual PH. They had similar percentages of affected pulmonary arteries on CTPA after PEA (25% ± 14% vs. 17% ± 15%, respectively, mean difference -8%; 95% CI -18 to 3; p 0.16). Furthermore, affected pulmonary arteries did not correlate with mPAP after PEA (R^2 0.027, p 0.38). Patients with residual PH had significantly more tapered pulmonary arteries than patients without residual PH (odds ratio 1.13; 95% CI 1.01-1.26; $p < 0.05$). In addition, percentage of tapered pulmonary arteries correlated with mPAP after PEA (ρ 0.431, $p < 0.05$).

Table 1: Baseline characteristics

	N	Before PEA	6 months after PEA	Mean difference (95% CI)	P-value
Demographics					
Age (years)	*31*	60 (11)			
Male, n (%)	*31*	20 (64.5%)			
BMI (kg/m^2)	*31*	27 (4)			
Functional status					
NYHA class I, n (%)	*31*	0 (0%)	17 (55%)		<0.001
6MWD (m)	26	421 (113)	478 (111)	58 (24-91)	<0.01
Max VO_2/kg (mL/min/kg)	*25*	15 (4)	18 (4)	3 (1-5)	<0.01
NT-proBNP (ng/L)	*30*	253 (119-1051)	212 (106-365)		NS
Hemodynamics					
mPAP (mmHg)	*31*	39 (7)	24 (7)	-16 (-12 to -19)	<0.001
PVR (dynes·s·cm^{-5})	*29*	519 (237)	185 (94)	-334 (-232 to -436)	<0.001
SvO_2 (%)	*27*	66 (10)	70 (5)	5 (1-8)	<0.05
Cardiac index (L/min/m^2)	*29*	2.5 (0.6)	3.2 (0.6)	0.7 (0.3-1.0)	<0.001

Data are presented as mean (SD), median (interquartile range) or n (%). Statistical tests: *t*-test or Wilcoxon Signed-Rank test (numeric variables) and McNemar test (proportions). N: number of patients; PEA: pulmonary endarterectomy; CI: confidence interval; BMI: body mass index; NYHA: New York Heart Association; 6MWD: six-minute walking distance; VO_2: oxygen consumption; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation; NS: not significant.

In an additional analysis on preoperative CTPA morphology, percentage of tapered pulmonary arteries was equally present in patients who would subsequently present with or without residual PH after PEA (16% ± 11% vs. 13% ± 15%, respectively; mean difference -3%; 95% CI -7 to 13; p 0.56). However, preoperative percentage of affected pulmonary arteries was lower in patients with residual PH than in patients without residual PH (41% ± 11% vs. 60% ± 23%, mean difference 18%; 95% CI 5-32; p < 0.01).

Table 2: Functional and hemodynamic status after PEA in patients with and without residual pulmonary hypertension.

Characteristic	No residual PH N=17	Residual PH N=14	Mean difference (95% CI)	P-value
Functional status				
NYHA class I, n (%)	10 (59%)	7 (50%)		NS
6MWD (m)	506 (63)	446 (146)	-51 (-34 to 135)	NS
Max VO_2/kg (mL/min/kg)	20 (4)	16 (4)	-4 (0 to -7)	<0.05
NT-proBNP (ng/L)	196 (103 – 224)	364 (114 – 649)		<0.05
Hemodynamics				
mPAP (mmHg)	19 (3)	29 (6)	-10 (-7 to -14)	<0.001
PVR (dynes·s·cm^{-5})	128 (45)	255 (91)	-127 (-74 to -180)	<0.001
SvO_2 (%)	70 (5)	70 (4)	0 (-4 to 3)	NS
Cardiac index (L/min/m^2)	3.4 (0.6)	3.0 (0.6)	0.3 (-0.1 to 0.8)	NS

Data are presented as mean (SD), median (interquartile range) or n (%). Statistical tests: independent *t*-test or Mann-Whitney U test (numeric variables) and chi-square (proportions) to compare between patients with and without residual PH. PEA: pulmonary endarterectomy; PH: pulmonary hypertension; CI: confidence interval; NYHA: New York Heart Association; 6MWD: six-minute walking distance; VO_2: oxygen uptake; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation.

Parenchymal hypoperfusion on lung perfusion MRI

In 21 patients a lung perfusion MRI before and after PEA was available, and overall, pulmonary hypoperfusion significantly decreased from 29% ± 9% to 21% ± 5% after PEA (mean difference -8%, 95% CI -4 to -12; p < 0.001; figure 5A).

Of the 28 patients subjected to lung perfusion MRI after PEA, 13 patients (46%) had residual PH 6 months after PEA. Parenchymal hypoperfusion was similar in patients with and without residual PH after PEA (20% ± 7% vs. 19% ± 6%, respectively, mean difference -1%, 95% CI -6 to 4; p 0.63; figure 5B) and did not correlate with mPAP after PEA (R^2 0.007, p 0.67).

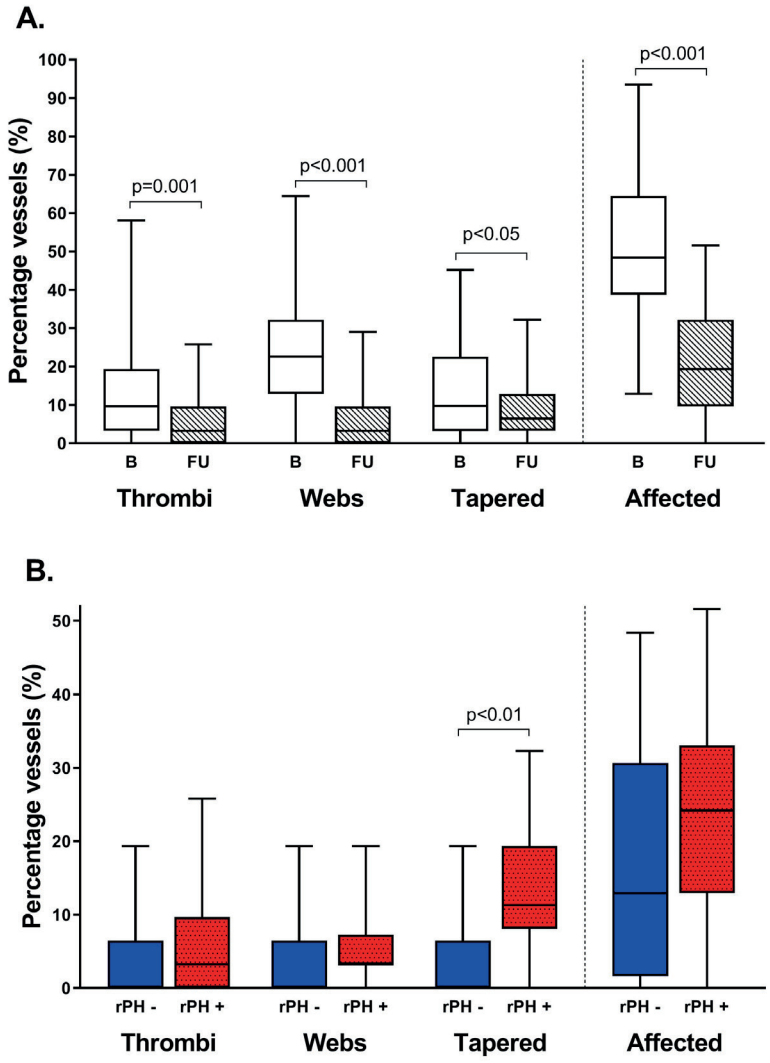

Figure 4: Pulmonary morphological characteristics on CTPA.
A: Pulmonary morphological characteristics on CTPA before and 6 months after pulmonary endarterectomy. Data are presented as median percentage (interquartile range) of the total pulmonary vasculature.
B: Pulmonary morphological characteristics on CTPA 6 months after PEA in patients without residual PH (n = 17; rPH -) and patients with residual PH (n = 14, rPH +). Data are presented as median percentage (interquartile range) of the total pulmonary vasculature.
CTPA: computed tomography pulmonary angiography; PH: pulmonary hypertension.

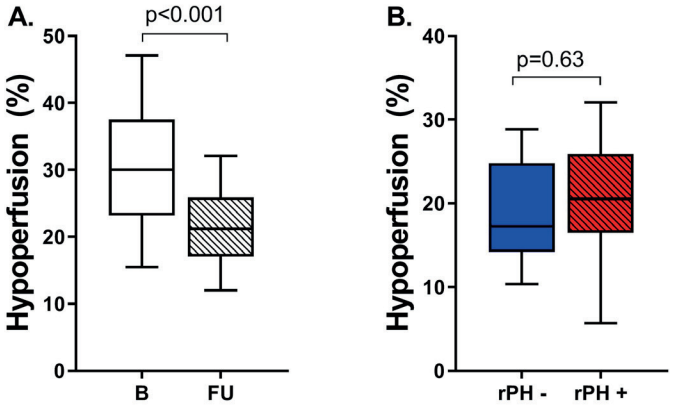

Figure 5: Percentage of parenchymal hypoperfusion on lung perfusion MRI.
A: Percentage parenchymal hypoperfusion on lung perfusion MRI before and 6 months after PEA. Data are presented as median percentage (interquartile range) of the total pulmonary vasculature. B = baseline (before PEA); FU = follow-up (6 months after PEA).
B: Pulmonary hypoperfusion on MRI 6 months after PEA in patients without residual PH (n=15, rPH-) and patients with residual PH (n=13, rPH+) after PEA. Data are presented as median (interquartile range).
MRI: magnetic resonance imaging; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

Discussion

This is the first prospective imaging study in patients with CTEPH treated by PEA, providing a comprehensive description of pulmonary vascular imaging characteristics on both CTPA and lung perfusion MRI after PEA. We found that 6 months after successful PEA, around 20% of the pulmonary arteries remained abnormal, which was independent of the presence of residual PH. This would suggest that microvascular disease plays a more significant role in residual PH after PEA.

The contribution of visible residual (sub)segmental affected pulmonary arteries to residual PH after PEA has, to our knowledge, never before been investigated. Previous studies have focused on preoperative pulmonary artery characteristics in relation to residual PH after PEA and showed that patients with more central and segmental disease have a greater decrease in PVR after PEA than patients with distal disease [11,12]. Besides visualising central and segmental pulmonary arteries, ECG-gated CTPA can accurately visualise subsegmental pulmonary arteries located beyond the field of view of the PEA surgeon. Residual PH can sometimes result from incomplete PEA because of surgical inexperience [13]. This does not appear to be the case in our patient study population, because patients were operated by an experienced PEA surgeon who confirmed complete endarterectomy. In addition, our results show a comparable improvement in hemodynamics to what is reported by high-volume centres [3,14,15]. Moreover,

incomplete surgery would not explain why the decrease in affected pulmonary arteries after PEA as visualised by CTPA is comparable in patients with and without residual PH. Surgery significantly diminished parenchymal hypoperfusion, as was also reported by Schoenfeld *et al* [8]. In the latter study, no comparison was made between patients with or without residual PH. Here, we showed that the percentage of hypoperfusion was not different between patients with and without residual PH after PEA.

Although this study did not prove directly that residual PH is solely caused by microvascular disease and not by incomplete PEA, several studies have suggested that microvascular disease may play a crucial role in the origin of residual PH [3,16]. Indeed, patients with perioperative segmental and distal disease have greater postoperative PVR than patients with proximal affected pulmonary arteries [17]. Signs of microvascular disease in CTEPH were demonstrated using histological examination of lungs of piglets with experimental CTEPH [18]. By showing that (sub)segmental affected pulmonary arteries are less present before PEA in residual PH and are equally present after PEA in patients with and without residual PH, our data suggests that residual PH after PEA is mainly explained by microvascular disease. Targeting microvascular disease with riociguat, a soluble guanylate cyclase stimulator, is currently the only medical therapy for residual PH after PEA with proven benefit in a randomised placebo-controlled trial [19].

Patients with residual PH had a higher percentage of residual tapered pulmonary arteries after PEA. This is in line with a previous observation in patients undergoing BPA for residual PH after PEA, where a sudden narrowing distal to the end of the endarterectomy segment was frequently observed [20]. This sudden narrowing (*i.e.* pouching defect or tapered pulmonary artery) leads to a complete occlusion of the vessel. Opening such an occluded tapered vessel is particularly challenging and carries a high risk of lung bleeding [21]. In addition, compared with other morphological lesions, a complete occlusion offers the lowest chance for successful passage of the guidewire across the lesion and delivery of the balloon catheter to the lesion [22,23]. Despite the lower chance of success and higher risk of complications, a Japanese study of Shimura *et al* found a significant improvement in hemodynamics after BPA treatment for residual PH in a small group of 9 patients [20]. Apart from performing BPA in patients with residual PH, another treatment option is a combined approach with medical therapy. The study of Araszkiewicz *et al* [24] was the first European study to investigate the effect of combined medical therapy and BPA in patients with residual PH after PEA. The authors found a significant decrease in hemodynamics after combined medical therapy and BPA treatment. Whether this decrease in hemodynamics was due to medical therapy or BPA is unknown.

A proposed mechanism for residual PH after PEA is presented in figure 6. Obviously, microvascular disease likely explains residual PH in patients without detectable lesions (figure 6A). However, the absence of a relation between residual PH and detectable vascular lesions suggests that microvascular disease is also responsible for most of the

hemodynamic impairment in patients with detectable lesions after successful PEA, where residual tapered pulmonary arteries might only partly explain the hemodynamic impairment (figure 6B). Future studies investigating treatment with BPA and/or PH medication in patients with residual PH and residual macroscopic lesions are warranted.

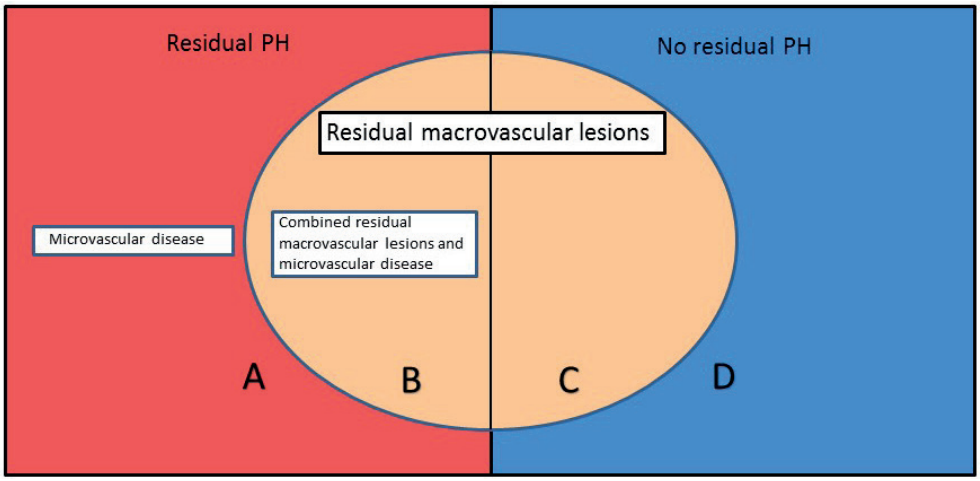

Figure 6: Proposed mechanism for residual PH after PEA. After successful PEA, residual subsegmental macrovascular lesions are equally present in patients with and without residual PH. We therefore propose that residual PH in patients with residual subsegmental macrovascular lesions is mainly caused by microvascular disease, not by residual macroscopic lesions (B). Residual PH in patients without residual subsegmental macrovascular lesions is most likely caused by microvascular disease (A). Patients without residual PH can either show residual macrovascular lesions (without affecting pulmonary pressures) (C), or no residual macrovascular lesions (D).
PH: pulmonary hypertension; PEA: pulmonary endarterectomy.

This study used CTPA to analyse vessel morphology. The results of vessel morphology in residual PH patients might have been different when assessed with pulmonary angiography instead of ECG-gated CTPA [5-7]. Furthermore, this study is limited by its relatively small sample size. Our centre is one of the two CTEPH expert centres in the Netherlands and performs around 20 PEA procedures per year, which is less than reported in other high-volume centres [3,25]. Previous studies have reported that patients with a high preoperative PVR (>1000 dynes·s·cm^{-5}) are at risk of developing residual PH [14,16]. Compared with these patients, patients with CTEPH in our cohort showed only a modest PVR elevation, with a mean PVR of 554 dynes·s·cm^{-5} before PEA. Although CTEPH patients in our cohort had less severe CTEPH prior to PEA than patients in other centres, we have shown excellent hemodynamic and functional improvement after PEA. Notably, 45% of patients had residual PH after PEA, which is comparable with what other centres reported (35%-51%) [3,14,15]. Despite our small sample size, we consider that the observations

derived from this structured prospective comprehensive imaging study in residual PH may be of help to better understand the mechanism of residual PH.

In conclusion, CTPA shows that, after PEA, approximately one quarter of the segmental and subsegmental pulmonary arteries remain abnormal. However, persistent vascular abnormalities poorly correlated to the presence of residual PH. This may suggest that microvascular disease, rather than residual macrovascular lesions, plays a prominent role in residual PH after PEA.

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Supplement

Table S1: Functional and hemodynamic status before PEA in patients with and without residual pulmonary hypertension.

	No residual PH *N=17*	Residual PH *N=14*	Mean difference (95% CI)	P-value
Functional status				
NYHA class I, n (%)	0 (0%)	0 (0%)		NS
6MWD (m)	415 (101)	435 (122)	20 (-66 to 107)	NS
Max VO_2/kg (mL/min/kg)	14 (3)	15 (6)	1 (-3 to 5)	NS
NT-proBNP (ng/L)	316 (164-1051)	219 (119-1246)		NS
Hemodynamics				
mPAP (mmHg)	40 (8)	39 (7)	0 (-6 to 5)	NS
PVR (dynes·s·cm^{-5})	554 (275)	461 (166)	94 (-84 to 270)	NS
SvO_2 (%)	65 (12)	65 (6)	0 (-8 to 8)	NS
Cardiac index (L/min/m^2)	2.4 (0.6)	2.6 (0.7)	0.1 (-0.6 to 0.3)	NS

Data are presented as mean (SD), median (interquartile range) or n (%). Statistical tests: independent *t*-test or Mann-Whitney U test (numeric variables) and chi-square (proportions) to compare between patients with and without residual PH. PEA: pulmonary endarterectomy; PH: pulmonary hypertension; CI: confidence interval; NYHA: New York Heart Association; 6MWD: six-minute walking distance; VO_2: oxygen uptake; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation.

CHAPTER 5

5

Dynamic vascular changes in chronic thromboembolic pulmonary hypertension after pulmonary endarterectomy

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Abstract

Residual pulmonary hypertension is an important sequela after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Recurrent thrombosis or embolism could be a contributor to this residual pulmonary hypertension, but the potential extent of its role is unknown, in part because data on incidence are lacking.

We aimed to analyse the incidence of new intravascular abnormalities after pulmonary endarterectomy and determine hemodynamic and functional implications.

A total of 33 chronic thromboembolic pulmonary hypertension patients underwent routine computed tomography pulmonary angiography (CTPA) before and six months after pulmonary endarterectomy, together with right heart catheterisation and exercise testing. New vascular lesions were defined as 1) a normal pulmonary artery before pulmonary endarterectomy and containing a thrombus, web, or early tapering six months after pulmonary endarterectomy, or 2) a pulmonary artery already containing thrombus, web, or early tapering at baseline, but increasing six months after pulmonary endarterectomy.

Nine of 33 (27%) chronic thromboembolic pulmonary hypertension patients showed new vascular lesions on CTPA six months after pulmonary endarterectomy. In a subgroup of patients undergoing CTPA 18 months after pulmonary endarterectomy, no further changes in lesions were noted. Hemodynamic and functional outcomes were not different between patients with and without new vascular lesions.

New vascular lesions are common after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension; currently their origin, dynamics and long-term consequences remain unknown.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by incomplete resolution of pulmonary embolism (PE) leading to organised thrombus, secondary remodelling of the distal vasculature, and microvascular disease [1-2]. If left untreated, chronic pressure overload will ultimately lead to right ventricular failure and death. CTEPH distinguishes itself from other groups of pulmonary hypertension (PH) by the possibility of potential curation through a pulmonary endarterectomy (PEA) in approximately 60% of patients [3-4]. Despite the excellent results and long-term survival after PEA [4], residual PH after PEA is an important sequela occurring in 30-50% of patients [5]. Little is known about the mechanism and predictors of residual PH. Residual lesions, distal pulmonary vasculopathy, recurrent embolism, and *in situ* thrombosis (despite anticoagulation) after PEA could all contribute to residual PH. Large follow-up studies on recurrent perfusion defects after PEA have not been performed. Accurate estimations of the incidence of new thrombotic or embolic lesions after PEA are unavailable, although a recent cohort study showed recurrent PE in 6 of 356 patients after PEA [5]. Notably, all these six patients had a vena cava inferior (VCI) filter in situ and four had antiphospholipid syndrome, suggesting that new vascular lesions were caused by the intervention/surgery or resulted from *in situ* thrombosis. In the study, postoperative computed tomography pulmonary angiography (CTPA) were only performed in symptomatic patients [5] and therefore the true incidence of new vascular lesions may have been underestimated.

Several relevant questions remain currently unanswered. First, how often can new (thrombotic) lesions be identified when CTPA is performed routinely after PEA? Second, which patients are at risk for recurrent lesions after PEA? And third, what are the clinical consequences of new vascular lesions, particularly with respect to the presence of residual PH?

In the current study, we evaluated a cohort of CTEPH patients who were routinely subjected to electrocardiogram (ECG)-triggered CTPA six months after PEA. Our objective was to describe the incidence, morphology, and clinical implications of recurrent thrombotic lesions after PEA.

Methods

Study subjects

Patients with CTEPH undergoing PEA in the VU University Medical Centre between October 2014 and July 2016 were screened for inclusion in this observational analysis. Inclusion criteria consisted of a diagnosis of CTEPH, and performance of ECG-triggered CTPA both before and six months after PEA (as part of standard clinical care). Patients with chronic thromboembolic disease without pulmonary hypertension were excluded.

According to our centre's clinical protocol at that time, all patients had a VCI filter implanted before PEA unless contraindicated and were permanently anticoagulated. Postoperatively, intravenous heparin was started as soon as the chest tube production was < 50 mL/hour for 3 hours. After the initial postoperative period, patients were restarted on vitamin K antagonists (VKA).

At the time of six-month follow-up after PEA, six-minute walking test (6MWT) and cardiopulmonary exercise testing (CPET) were performed in addition to CTPA, as well as right heart catheterisation (RHC). These tests were also performed before PEA in all patients.

This study did not fall within the scope of the Medical Research Involving Human Subjects Act, since a retrospective 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

All CT-scans were obtained on a 256-MDCT scanner (Brilliance 256, Philips Healthcare) with retrospective ECG triggering with 0.625 slice thickness and 0.27 s/rotation. The tube voltage was set at 100 kV and the tube current was set at 600 mA with dose modulation to reduce radiation exposure. The injection protocol consisted of administration of 85 mL of non-ionic contrast agent (iobitridol, Xenetix 300, Guerbet) through an antecubital vein at a flow rate of 5 mL per sec followed by injection of 40 mL saline solution. Automatic bolus tracking was applied with the region of interest positioned in the truncus pulmonalis and a threshold for triggering data acquisition was set at 115 HU. The acquisition was performed during inspiration. The CT images were reconstructed at 75% of the R-R interval with 1.5 slice thickness at 1.0 mm intervals using standard algorithm. The CT images were digitally stored and analysed at a dedicated workstation.

Changes in vascular morphology on ECG-triggered CTPA six months after PEA were assessed post-hoc using a scoring model designed to evaluate 31 pulmonary arteries including five mediastinal, six lobar and 20 segmental arteries in every patient [6]. Each artery was scored as normal, containing thrombus, web(s), or early tapering before and six months after PEA. New vascular lesions were defined as 1) a normal pulmonary artery before PEA and containing a thrombus, web, or early tapering six months after PEA, or 2) a pulmonary artery already containing thrombus, web, or early tapering at baseline which had increased six months after PEA. Early tapering is the early narrowing of arteries on CTPA, comparable to subtotal lesions on angiography. Two investigators, including an experienced cardiothoracic radiologist with expertise in CTEPH, reviewed the images and final evaluations were achieved by consensus. Due to the nature of this analysis, inter-observer variability regarding the CTPA evaluation was not analysed.

6MWT was performed according to the 2002 ATS statement [7]. CPET consisted of a symptom-limited maximal incremental exercise test using a cycle ergometer [8].

RHC was performed using a fluid-filled balloon-tipped 7F Swan-Ganz catheter inserted via the jugular vein under local anaesthesia, with positioning under continuous electrocardiographic monitoring, and recording of the following variables: pulmonary artery pressures (PAP), right atrial pressures, pulmonary artery wedge pressure (PAWP), and heart rate. Cardiac output (CO) was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index). Pulmonary vascular resistance (PVR) was calculated from (80 x [mPAP - PAWP]/CO).

Study design and statistical analysis

Primary objective of this observational retrospective study was analysis of the incidence of new vascular (recurrent thrombotic or thromboembolic) lesions six months after PEA. The secondary objective was an analysis of clinical (hemodynamic and functional) implications of new vascular lesions.

The corresponding author had full access to all the study data and takes responsibility for its integrity and data analysis. Data are presented as mean (standard deviation (SD)), median (interquartile range (IQR)) or number of patients (%). Based on the number of patients, non-parametric testing was performed, using Mann-Whitney test or Fisher's exact test where appropriate, to compare patients with or without new vascular lesions. Changes in CT morphology were assessed using Wilcoxon matched-pairs signed-rank test. Missing data were not imputed. Values of $P < 0.05$ were considered to reflect statistical significance. Correlation analysis regarding the association between abnormal arteries and hemodynamic parameters were performed using Pearson correlation in data normally distributed and using Spearman correlation in data not normally distributed. Statistical analysis was performed using GraphPad Prism version 7.0b (GraphPad Software, La Jolla, California, USA) and IBM SPSS Statistics version 24.

Results

As indicated in the flow chart (figure 1), 43 CTEPH patients underwent PEA in the time period between October 2014 and July 2016. After excluding 10 patients with absent or incomplete follow-up data, 33 patients with CTPA before and six months after PEA were included in this observational analysis. Patient characteristics and baseline (hemodynamic) parameters are shown in the first column of table 1.

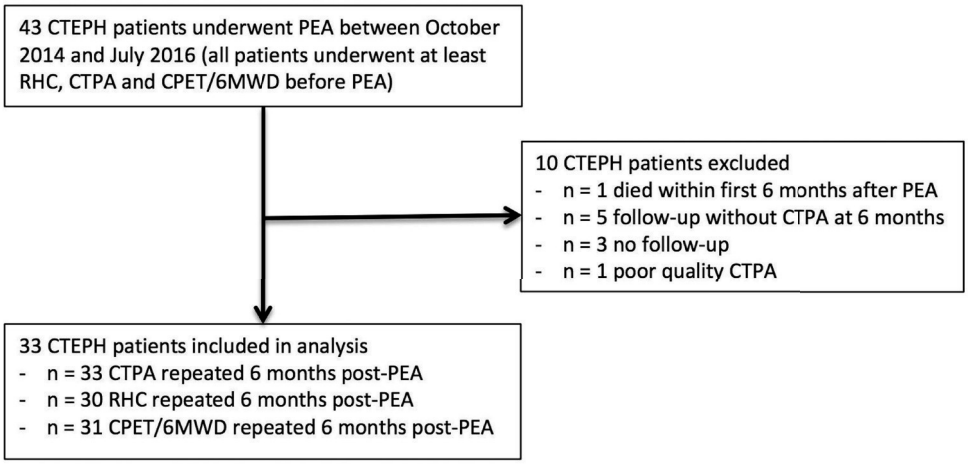

Figure 1: flowchart of included patients and reasons for exclusion.
CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy; RHC: right heart catheterisation; CTPA: computed tomography pulmonary angiography; CPET: cardiopulmonary exercise testing; 6MWD: six-minute walking distance.

Primary outcome

Nine out of 33 patients (27%) were found to have new vascular lesions on CTPA six months after PEA. New vascular lesions mainly consisted of new or increased thrombus and early tapering of mainly the segmental pulmonary arteries (table 2). Examples of new vascular lesions in different patients are shown in figure 2.

The mean percentage of normal vessels increased from 48% (SD 20%, range 6-87%) pre-PEA to 88% (SD 9.8%, range 68-100%) six months post-PEA; the percentages of arteries with thrombus, webs, or tapering all significantly decreased (figure 3).

Table 1: subject characteristics and comparison of characteristics at baseline (before PEA)

Variable	Overall baseline characteristics for total cohort of 33 patients	Group 1: with new vascular lesions on CTPA 6 months post-PEA (9 patients)	Group 2: without new vascular lesions on CTPA 6 months post-PEA (24 patients)
Age at PEA (years)	63 (range 22-79)	65 (range 45-78)	62.5 (range 22-79)
Male gender (n, %)	21 (64%)	6 (67%)	15 (63%)
Time CTEPH diagnosis to PEA (days)	154 (109-254)	153 (94-472)	154 (119-260)
BMI at baseline (kg/m^2)	26.4 (24.3-29.8)	25.4 (22.8-27.4)	26.6 (24.4-30.4)
Acute VTE in previous history	30 (91%)	8 (89%)	22 (92%)
DVT in previous history	9 (27%)	1 (11%)	8 (33%)
Blood group non-O	23 (70%)	5 (56%)	18 (75%)
Myeloproliferative disease (n, %)	1 (3%)	0 (0%)	1 (4%)
Diabetes mellitus (n, %)	2 (6%)	2 (22%)	0 (0%)
Obstructive lung disease (n, %)	3 (9%)	2 (22%)	1 (4%)
Systemic hypertension (n, %)	12 (36%)	6 (67%)	6 (25%)
Splenectomy (n, %)	2 (6%)	1 (11%)	1 (4%)
Known significant coronary artery disease (n, %)	0 (0%)	0 (0%)	0 (0%)
Known thyroid disease/thyroid replacement therapy (n, %)	1 (3%)	1 (11%)	0 (0%)
Current or former smoker (n, %)	18 (69%) (n=26)	4 (80%) (n=5)	14 (67%) (n=21)
Baseline hemodynamic parameters			
mPAP pre-PEA (mmHg)	39 (34-48)	39 (33-46)	40 (35-48)
PVR pre-PEA (dynes·s·cm^{-5})	469 (346-690) (n=32)	503 (346-720) (n = 8)	469 (338-638)
PAWP pre-PEA (mmHg)	11 (9-13) (n=32)	9.5 (6.8-11.8) (n=8)	12 (9.3-13)
CI pre-PEA (L/min/m^2)	2.5 (2.0-3.1) (n=32)	2.8 (1.9-3.1) (n=8)	2.4 (2.0-3.1)
Other parameters pre-PEA			
PAH-specific medication pre-PEA	11 (33%)	3 (33%)	8 (33%)
VCI-filter pre-PEA in situ	31 (94%)	9 (100%)	22 (92%)
NT-proBNP (ng/L)	489 (114-1305)	316 (119-1003)	725 (112-1715)
NYHA class III-IV (n, %)	15 (48%) (n=31)	3 (33%)	12 (55%) (n=22)
6MWD (m)	449 (363-511) (n=30)	482 (439-560)	416 (321-480) (n=21)
T_{LCO} (% predicted)	66.5 (61.3-78.3) (n=28)	70.5 (65-80.5) (n=8)	65.5 (61-76) (n=20)

Data presented as median (interquartile range) or absolute number of patients (%) unless otherwise stated. Data apply to all 33 (9 plus 24) patients unless otherwise stated. Statistical tests: Mann-Whitney test (numeric variables) and Fisher's exact test (categorical variables).
CTPA: computed tomography pulmonary angiography; PEA: pulmonary endarterectomy; BMI: body mass index; VTE: venous thromboembolism; DVT: deep vein thrombosis; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; CI: cardiac index; PAH: pulmonary arterial hypertension; VCI: vena cava inferior; NYHA: New York Heart Association; 6MWD: six-minute walking distance. T_{LCO}: transfer factor for carbon monoxide.

Table 2: description of new vascular lesions on CTPA in nine patients six months after PEA

Patient number	Location new lesion	Preoperative CTPA	CTPA 6 months after PEA
1	Superior segmental artery left lower lobe (segment A6)	normal	tapering
2	Superior segmental artery lingula (segment A4) (fig 2E)	normal	tapering
3	Superior segmental artery lingula (segment A4) (fig 2A)	normal	tapering
4	Superior segmental artery right lower lobe (segment A6)	tapering	increase in tapering
	Anterobasal segmental artery right lower lobe (segment A8) (fig 2F)	normal	thrombus
5	Anterobasal segmental artery right lower lobe (segment A8) (fig 2D)	normal	thrombus
	Lateral segmental artery middle lobe (segment A4)	tapering	increase in tapering
6	Lingula	thrombus	increase in thrombus
	Superior segmental artery left lower lobe (segment A6)	normal	thrombus
	Left lower lobe artery (fig 2C)	normal	thrombus
7	Lateral segmental artery middle lobe (segment A4) (fig 2B)	normal	web
	Superior segmental artery left lower lobe (segment A6)	normal	web
8	Posterior segmental artery left upper lobe (segment A10)	normal	tapering
9	Apical segmental artery right upper lobe (segment A1)	normal	thrombus

CTPA: computed tomography pulmonary angiography; PEA: pulmonary endarterectomy

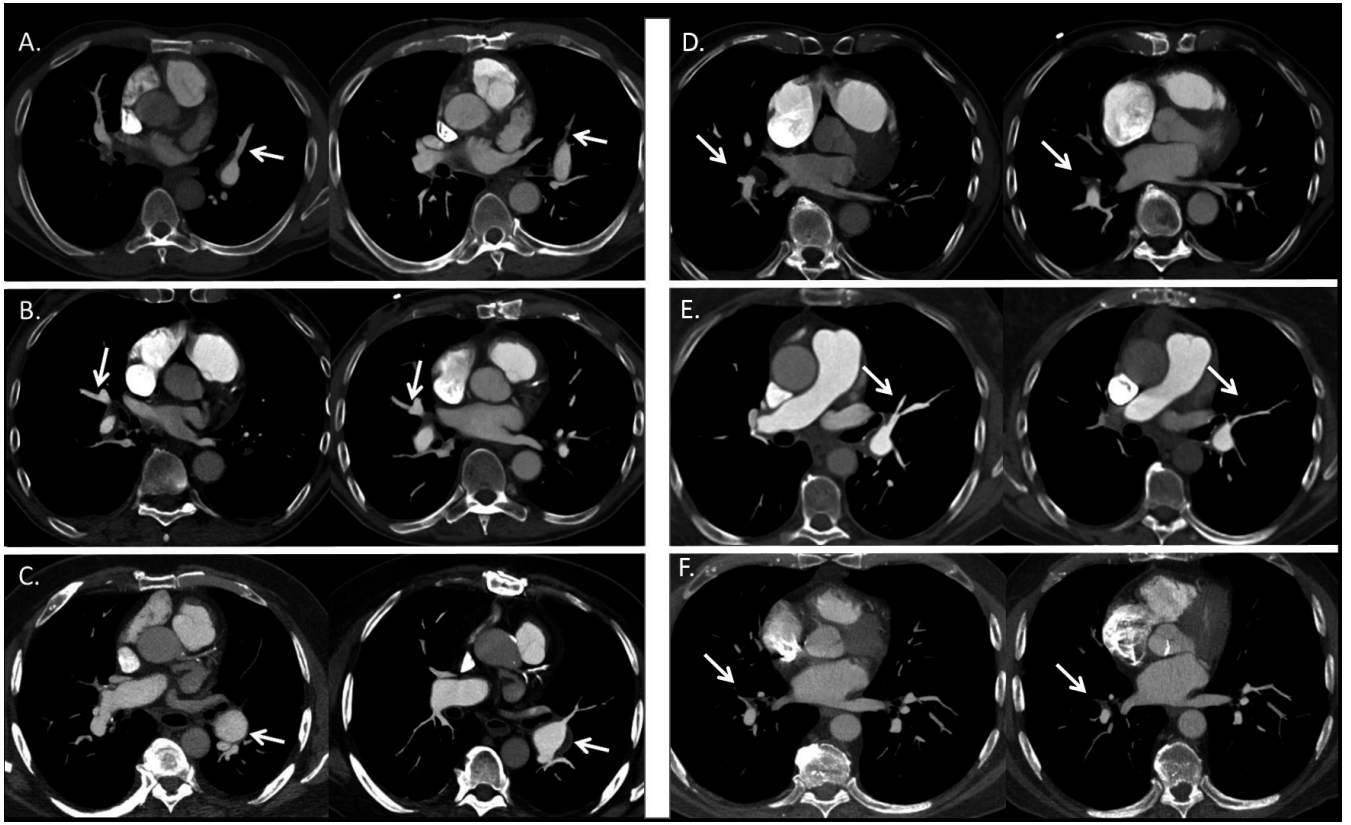

Figure 2: examples of new vascular lesions six months after pulmonary endarterectomy (PEA).
A. Superior segmental artery lingula (segment A4): normal before PEA (left panel), tapering six months after PEA (right panel). **B**. Lateral segmental artery middle lobe (segment A4): normal before PEA (left panel), new web six months after PEA (right panel). **C**. Left lower lobe artery: normal before PEA (left panel), new thrombus six months after PEA (right panel). **D**. Anterobasal segmental artery right lower lobe (segment A8): normal before PEA (left panel), new thrombus six months after PEA (right panel). **E**. Superior segmental artery lingula (segment A4): normal before PEA (left panel), tapering six months after PEA (right panel). **F**. Anterobasal segmental artery right lower lobe (segment A8): normal before PEA (left panel), thrombus six months after PEA (right panel).

Secondary outcomes

Correlations between number of remaining abnormal arteries and postoperative mean PAP (mPAP) and PVR were absent (Spearman correlation r 0.32 (p 0.08) and Pearson correlation r 0.18 (p 0.32), respectively).

Subject characteristics and baseline hemodynamic and exercise parameters of nine patients with new lesions on CTPA (group 1) and 24 patients without new lesions (group 2) were comparable (table 1), except for a higher prevalence of systemic hypertension in patients with new lesions.

The incidence of residual PH (as defined by mPAP ≥ 25 mmHg) six months after PEA was not different between patients with or without new vascular lesions (29% versus 48% in groups with and without new lesions on CTPA, respectively, Fisher's exact test p 0.43) and hemodynamic and functional outcomes were similar (table 3 and supplementary table A).

Anticoagulation parameters such as time to start of heparin after ICU admission and time to first adequate activated partial thromboplastin time (APTT) were similar in both groups (supplementary table A). It can be noticed that the median time to the first adequate APTT was 11-12 hours in both groups with a large range indicating an interval of suboptimal anticoagulation during which thrombus formation could occur. Direct oral anticoagulant (DOAC) instead of VKA was used in only two patients, both in the group without new lesions on CTPA.

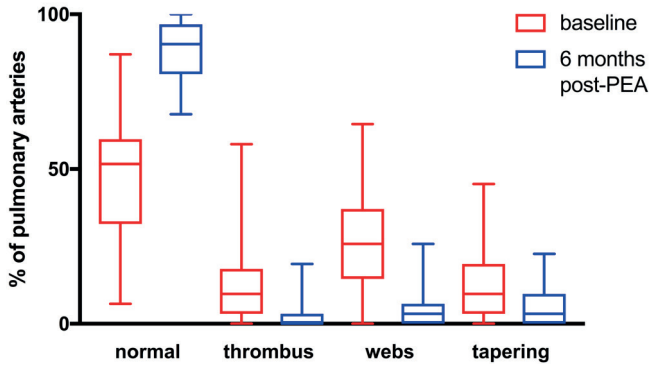

Figure 3: changes in vascular morphology of pulmonary arteries before and after PEA. Boxplots of percentages of (ab)normal pulmonary arteries for 33 patients. Red boxplots indicate data at baseline, blue boxplots indicate data six months after PEA. Changes in all morphological groups (normal, thrombus, webs, and tapering) between baseline and six months after PEA were statistically significant ($p < 0.001$, Wilcoxon matched-pairs signed-rank test).
PEA: pulmonary endarterectomy.

In a non-selective subgroup of 19 patients, CTPA was performed 18 months after PEA. This subgroup included seven patients with new lesions six months after PEA and in all these patients, lesions remained unchanged 18 months after PEA.

Table 3 comparison of hemodynamic outcomes six months post-PEA

Hemodynamic parameter six months post-PEA	Group 1: with new vascular lesions on CTPA six months post-PEA 9 patients	Group 2: without new vascular lesions on CTPA six months post-PEA 24 patients	P-value
mPAP (mmHg)	22 (16-31) (n=7)	24 (18-27) (n=23)	0.857
PVR (dynes·s·cm^{-5})	216 (154-283) (n=7)	160 (99-227) (n=23)	0.156
PAWP (mmHg)	6 (4.8-12.5) (n=6)	11 (8-12) (n=23)	0.256
CI (L/min/m^2)	2.9 (2.5-3.4) (n=7)	3.2 (2.7-3.7) (n=23)	0.292

Data presented as median (IQR). Data apply to the number of patients stated per variable. Statistical test: Mann-Whitney test.
CTPA: computed tomography pulmonary angiography; PEA: pulmonary endarterectomy; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; CI: cardiac index.

Discussion

This is the first report on the results of a structured follow-up with CTPA after PEA. In this observational study, 27% of patients had new vascular lesions on CTPA six months after PEA. Morphology of new vascular lesions after surgery varied from new or increased thrombus to new webs or new/increased tapering (this consisted of at least one completely new abnormality in all nine patients, with three patients with an additional increase in thrombus or tapering). Hemodynamic and functional outcomes after PEA were not influenced by these lesions, and had no effect on the incidence of residual PH.

Few studies have addressed recurrent thromboembolism after PEA. Most studies on the role of CTPA in residual PH after PEA used preoperative CT imaging to predict hemodynamic results after PEA [9-10]. One case series from almost two decades ago performing follow-up CT in 21 patients within three months to one year after PEA, described complete absence of new vascular lesions [11]. At the time of that study, CTPA imaging quality was inferior compared to imaging accuracy in the current era [12-13]. A recent large prospective cohort study reported recurrent thromboembolic lesions in 1.7% of patients after PEA [5]. However, only symptomatic patients underwent CTPA, while our cohort is unique because CTPA was performed in all patients irrespective of symptoms. This explains the large difference in incidence of new vascular lesions between the two cohorts (27 vs 1.7%).

Although the timing of new lesion development cannot be firmly established on the basis of our data, the fact that no new lesions developed after six months in a subset of 19 patients who underwent CTPA 18 months after surgery suggests that new lesions

probably developed in the early postoperative period. The dissected pulmonary endothelium and media layer can be considered very prone to platelet aggregation and *in situ* thrombus formation in the early postoperative phase, after removal of the endothelial and intimal layer of the vessel, is likely to occur. Superimposed on this are (short) time periods of suboptimal anticoagulation especially in the early postoperative phase where new thrombus formation can occur. Second, besides the formation of new thrombus, this study also illustrated that some vessels showed increased tapering after surgery, possibly explained by residual intimal flaps and local disruptions of the media layer directly related to surgery. To our knowledge, the exact mechanism of tapering has not been described before and might also be a consequence of mechanical stimulation/ injury eliciting a vasoconstrictive response of the vascular smooth muscle. Recurrent venous thromboembolism is less likely unless suboptimal anticoagulation is present but cannot be excluded by the presence of VCI filters since small thrombi may pass the filters, as illustrated by two prospective trials indicating recurrent PE in 3% of patients despite retrievable VCI filters [14-15]. In only one patient, new webs were found, making it difficult to hypothesize on the origins of new webs in this single patient.

Importantly, new vascular lesions were not associated with the hemodynamic outcome after PEA in this cohort. Because only one patient died before CTPA was performed, it seems unlikely that a survival bias explains the lack of correlation between new vascular lesions and the presence of residual PH. However, the relatively small number of patients might under power the detection of a potential hemodynamic effect. Additionally, we observed no symptomatic or functional consequences of new vascular lesions. Our findings are in line with the current hypothesis that residual PH is caused by either incomplete removal of more distal thrombi and/or concomitant small-vessel disease, while recurrent PH is thought to be rare and presumed to be associated with new thrombus [16]. Possibly the potential negative hemodynamic effects of new thromboembolic lesions are too small in relation to the major vascular improvements made after surgery (the mean percentage of remaining abnormal arteries decreased from 52% to 12%). Correlation between number (or fraction) of remaining abnormal arteries and PVR (or its fractional delta) was absent, similar to the absent relation in previous studies between pulmonary vascular obstruction (based on perfusion scintigraphy) and total pulmonary resistance in untreated CTEPH [17]. Incomplete resection of removable chronic thromboembolic lesions is unlikely or at least no more likely than in other centres since hemodynamic and functional outcomes are comparable to other PEA centres, and the PEA surgeon checked every segment for residual lesions before closing the pulmonary artery, to ensure complete endarterectomy.

Lack of power represents the main limitation of this study, together with its retrospective nature resulting in some missing data, especially regarding thrombophilia factors. However, since structured follow-up after PEA is often limited by logistical issues (such as travel distance), and CTPA is only rarely part of follow-up programs, larger patient

numbers are probably not to be expected. The exclusion of 23% of eligible patients, mainly because of missing follow-up CTPA, represents a potential source of bias. Unfortunately, the quality of long-term anticoagulation and time in the therapeutic range (TTR) of vitamin K antagonist therapy could not be quantified; however, the current system of local thrombosis services in the Netherlands offers high quality and adequacy of vitamin K anticoagulant treatment, and therefore major differences in TTR are not expected to be a relevant determinant of our main outcome. And last, classification of new vascular lesions was based on the occurrence of new lesions or an increase of pre-existing abnormalities according to the information provided by CTPA; this is in contrast to a more detailed classification of lesions based on pulmonary angiography, such as proposed by Kawakami *et al* [18].

Based on the quite high incidence of new lesions and lack of hemodynamic consequences in this cohort, we do not recommend follow-up CTPA after PEA in CTEPH as part of standard clinical care unless new symptoms occur. Potentially the remaining abnormal arteries after PEA, whether old or new, represent new therapeutic targets for balloon pulmonary angioplasty in the case of significant remaining symptoms or residual PH.

In conclusion, we showed new vascular lesions on CTPA six months after PEA in 27% of patients despite anticoagulation and VCI filters. These findings should be regarded as hypothesis generating: the origin, dynamics, and long-term outcome of these vascular changes after PEA are currently unknown, although the time course suggests a relation with the surgical procedure.

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Supplement

Table A: comparison of anticoagulation, functional and other parameters (six months) post-PEA

Variable	Group 1: with new vascular lesions on CTPA six months post-PEA 9 patients	Group 2: without new vascular lesions on CTPA six months post-PEA 24 patients	P-value
Anticoagulation parameters post-PEA			
Time to start heparin after ICU admission (hours)	3.5 (3.1-4.1)	4.0 (3.2-5.8)	0.203
Time to first adequate APTT after ICU admission (hours)	11.3 (8.9-31.2)	12.1 (10.2-27.9)	0.619
Anticoagulation post-PEA with VKA (compared to DOAC)	9 (100%)	22 (92%)	> 0.999
Functional parameters at 6 months post-PEA			
6MWD (m)	523 (482-571) (n = 8)	486 (444-536)	0.298
CPET peak VO_2 (mL/min)	1440 (1132-2031)	1492 (1152-1727) (n = 23)	0.657
CPET O_2 pulse (mL)	11.9 (9.2-15.1)	10.6 (8.7-13.2) (n=23)	0.160
CPET V_E/VCO_2 at anaerobic threshold	31.1 (28.9-34.1) (n=8)	33.2 (30.4-37.2) (n=22)	0.374
CPET SpO_2 at maximal exercise (%)	90 (87-95)	95 (91-97) (n=23)	0.119
Other markers at 6 months post-PEA			
NT-proBNP (ng/L)	192 (115-256) (n=7)	204 (99-402) (n=23)	0.811
NYHA class I	5 (63%) (n = 8)	10 (56%) (n = 18)	> 0.999
VCI filter 6 months post-PEA in situ	7 (78%)	21 (88%)	0.597
Use of PAH-specific medication at six months	0 (0%)	0 (0%)	n.a.
Use of PAH-specific beyond six months	1 (11%)	1 (4%)	0.477

Data presented as median (interquartile range) or absolute number of patients (%). Data apply to all 9 or 24 patients unless otherwise stated. Statistical tests: Mann-Whitney test (numeric variables) and Fisher's exact test (categorical variables).
CTPA: computed tomography pulmonary angiography; PEA: pulmonary endarterectomy; ICU: intensive care unit; APTT: activated partial thromboplastin time; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; 6MWD: six-minute walking distance; CPET: cardiopulmonary exercise test; VO_2: oxygen consumption; O_2: oxygen; V_E/VCO_2: ventilatory equivalent for carbon dioxide; SpO_2: peripheral oxygen saturation; n.a.: not applicable; NYHA: New York Heart Association; VCI: vena cava inferior; PAH: pulmonary arterial hypertension.

CHAPTER 6

Assessing hemodynamic success of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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Submitted

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 6-month follow-up assessment including NT-proBNP, TTE and CPET. After dichotomization and univariate analysis, sensitivity, specificity, positive predictive value and negative predictive value (NPV) were calculated.

Results: Eleven out of 51 included patients had residual PH six months after PEA (22%). Correlations between early postoperative and 6-month follow-up mean pulmonary artery pressure and pulmonary vascular resistance were moderate (Pearson R^2 0.260 and 0.269, respectively; both $p < 0.001$). Early hemodynamics did not predict late success. NT-proBNP > 300 ng/L had insufficient NPV to exclude residual PH. Probability for PH on TTE had a high NPV for residual PH. Peak VO_2 < 80% predicted on CPET had the highest NPV for residual PH. Only cases with mild residual PH without need for treatment would be missed based on NT-proBNP, TTE and CPET.

Conclusions: TTE and CPET 6 months after PEA 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 highest 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 to distinguish between patients with a low vs. intermediate to high probability of residual PH on the basis of early postoperative hemodynamics and non-invasive data at follow-up (N-terminal pro-brain natriuretic peptide (NT-proBNP), CPET and TTE). We asked the question whether the existence of residual PH can be safely excluded on the basis of either early hemodynamics, NT-proBNP, TTE and/or CPET.

Methods

Study subjects

Patients undergoing PEA between October 2014 and September 2019 were enrolled in this observational analysis if they had data available from the postoperative intensive care unit (ICU) time period and 6-month follow-up RHC and CPET. As per clinical protocol, NT-proBNP, CPET, six-minute walking testing (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, 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 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, pulmonary artery wedge pressure (PAWP) measurements were not performed in the ICU. Therefore, pulmonary vascular resistance (PVR) in the ICU was calculated by replacing PAWP with central venous pressure.

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]. 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) > 20 mmHg and PVR ≥ 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 [10].

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; log-transformation was performed when distribution was not normal. 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 remained not normal despite log-transformation. In the setting of comparing multiple time-points with paired data, ANOVA or mixed-model effects 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 Pearson 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, 11-12]. 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 patients was small, multivariate logistic regression analysis was not performed. Instead, testing characteristics (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)) were determined for all parameters with $p < 0.10$ in univariate logistic regression analysis.

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 October 2014 and September 2019, 98 patients underwent PEA in our centre. All patients with full data available from TTE, RHC and CPET 6 months after PEA were selected. Four patients died within 6 months after PEA; one patient underwent lung transplantation after PEA. Forty-two patients were excluded because of incomplete or missing data. Altogether, 51 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. Twelve percent of patients used PH-specific medication before PEA. Residual PH 6 months post-PEA was present in 11 patients (22%). Forty patients without residual PH were comparable to 11 patients with residual PH regarding gender, age and BMI; preoperative NT-proBNP was significantly higher in those with residual PH.

None of the analysed patients were started on or continued PH-specific medication after PEA based on early hemodynamics in the ICU. In 3 patients (all of them with mPAP ≥ 30 mmHg) PH-specific medication was started after the 6-months' re-evaluation. Three other patients with mPAP ≥ 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.

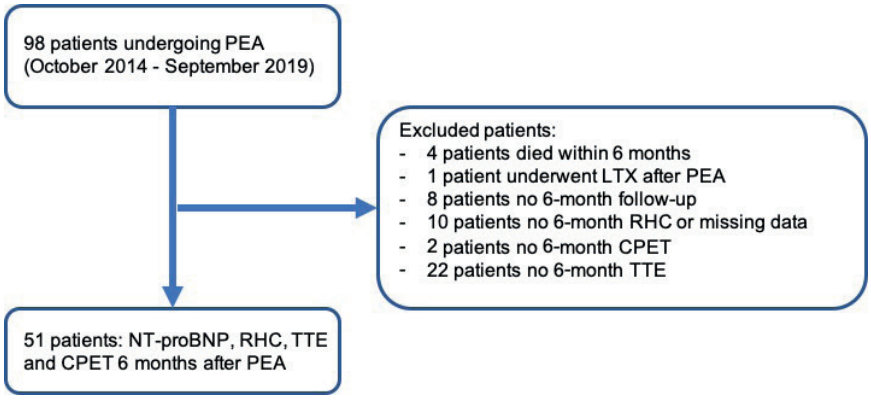

Figure 1: flowchart of patient selection
PEA: pulmonary endarterectomy; LTX: lung transplantation; RHC: right heart catheterisation; CPET: cardiopulmonary exercise testing; TTE: transthoracic echocardiography; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 1: cohort characteristics

Parameters before PEA	Total (n = 51)	Patients without residual PH after PEA (n = 40)	Patients with residual PH after PEA (n = 11)
Age at PEA (years)	65 (range 17-79)	64 (range 26-79)	68 (range 17-74)
Women (%)	20 (39%)	14 (35%)	6 (55%)
BMI (kg/m^2)	26.7 (24.5-30.4)	27.0 (24.6-30.6)	25.6 (17.9-26.8)
Use of PH-specific medication before PEA	6 (12%)	3 (8%)	3 (27%)
NYHA class I/II/III/IV (%)	2/39/51/8%	2.5/37.5/50/10%	0/44/56/0%
6MWD (m)	423 (113) *n=34*	428 (372-531) *n=27*	414 (298-474) *n=7*
NT-proBNP (ng/L)	299 (109-1455)	263 (80-1083)	1606 (446-3201)
Comorbidities			
Ischemic heart disease	2 (4%)	1 (2.5%)	1 (9%)
Obstructive lung disease	6 (12%)	6 (15%)	0 (0%)
Diabetes mellitus	3 (6%)	3 (7.5%)	0 (0%)
Systemic hypertension	19 (37%)	15 (38%)	4 (36%)
Malignancy	4 (8%)	4 (10%)	0 (0%)
Thyroid disease	5 (10%)	2 (5%)	3 (7.5%)

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.

Role of early hemodynamics

The median time between PEA and the last hemodynamic profile in the ICU was 2 days (range 0-7). The complete hemodynamic 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 (ANOVA $p < 0.001$), mPAP overall did not change between the early postoperative period and 6 months after PEA (Tukey's multiple comparisons test p 0.056). The correlation between mPAP in the ICU and after 6 months was moderate (Pearson R^2 0.260, 95% confidence interval (CI) 0.273-0.689, $p < 0.001$), and the same was true for PVR (R^2 0.269, 95% CI 0.281-0.697, $p < 0.001$). The slope of the regression line (0.617 for mPAP and 0.786 for PVR) 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 6 months (R^2 0.007, 95% CI -0.212-0.365, p 0.582).

Four out of 11 patients with residual PH 6 months after PEA had no residual PH in the ICU. Five out of 12 patients with apparent residual PH in the ICU had normal pulmonary (resting) hemodynamics 6 months after surgery. Sensitivity and specificity of early hemodynamics for a diagnosis of residual PH at 6 months were 0.64 and 0.88, respectively, with a PPV and NPV of 0.58 and 0.90, respectively. Using the absence of residual PH in the ICU as the criterium to determine whether patients should have RHC 6 months after PEA would reduce the "number-needed-to-catheterise" from 51 to 12/51 (24%); this would lead to missing 4/11 (36%) of residual PH cases, including one case of residual PH started on PH-specific medication after the 6-month re-evaluation (supplementary table B).

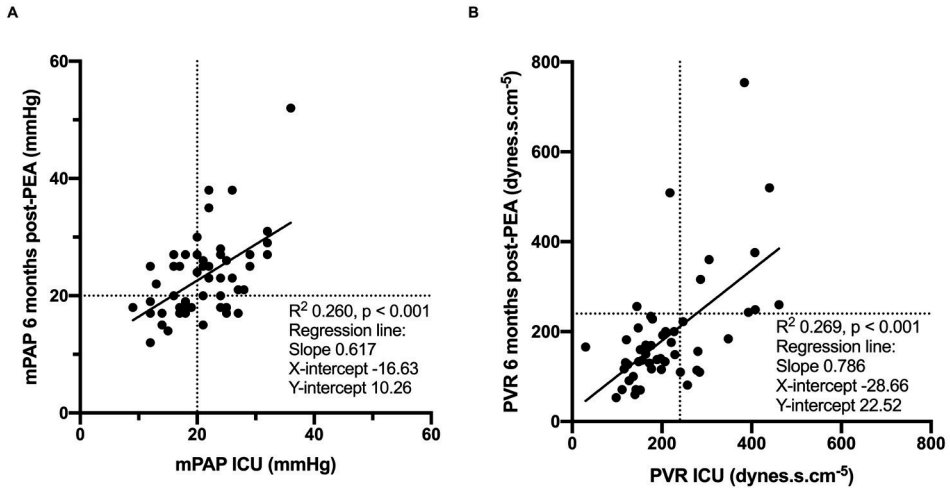

Figure 2: correlation analysis of mPAP and PVR between ICU and 6-months re-evaluation after PEA
Pearson correlation performed (after log-transformation for PVR)
mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; ICU: intensive care unit; PEA: pulmonary endarterectomy.

Role of NT-proBNP 6 months post-PEA

NT-proBNP was determined in 45 patients 6 months after PEA (median 238 ng/L, IQR 106-399 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) 5.7, 95% CI 1.32-24.54, p 0.020). Sensitivity and specificity were 0.64 and 0.76, respectively. PPV and NPV were 0.47 and 0.87, respectively. 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 15/45 (33%), at the expense of 4 missed cases of residual PH (36% of residual PH patients) (supplementary table B).

Role of echocardiography 6 months post-PEA

TTE 6 months after PEA with concurrent RHC were available in all 51 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 6.750, 95% CI 1.286-35.416, p 0.024). Twenty-five TTEs were classified as either intermediate- or high probability for PH; in 9 patients residual PH was confirmed with RHC, while in 16 patients no residual PH was present. Twenty-six TTEs were classified as low probability for PH. In 2 of those patients, however, residual PH was present. Following from these data, sensitivity of intermediate/high PH probability TTE for residual PH was 0.82, while specificity was 0.60; PPV and NPV were 0.36 and 0.92, respectively. 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 25/51 (49%), at the expense of 2

missed cases of residual PH. These two cases with false-negative TTE were characterised by mild hemodynamic abnormalities, not requiring additional treatment (supplementary table B).

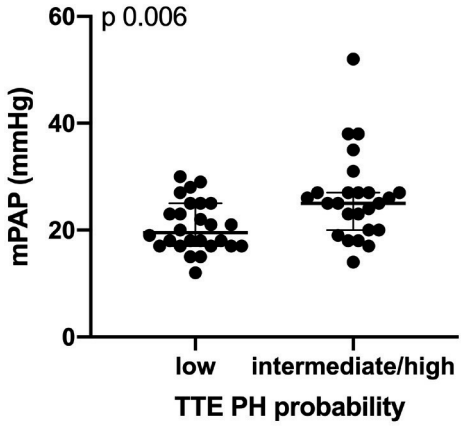

Figure 3: mPAP distribution according to TTE PH probability
Unpaired t-test performed.
mPAP: mean pulmonary artery pressure; TTE: transthoracic echocardiography; PH: pulmonary hypertension.

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

Parameter	OR	95% CI	P value
Peak load < 80% predicted	> 100	0.000 - ∞	0.998
Peak VO_2 < 80% predicted	7.391	0.862-63.396	0.068
VO_2/WR < 8.4 mL/min/Watt	6.000	1.092-32.979	0.039
O_2 pulse < 80% predicted	3.164	0.800-12.511	0.101
$P_{ET}CO_2$ max exercise < 4.0 kPa	3.259	0.753-14.116	0.114
V_E/VCO_2 AT ≥ 34.0	6.000	1.125-31.989	0.036
SpO_2 max exercise ≤ 94%	4.071	0.780-21.265	0.096

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.

Role of cardiopulmonary exercise testing 6 months post-PEA

CPET 6 months after PEA with concurrent RHC was available in 51 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. Two circulatory and two gas exchange parameters with $p < 0.100$ (indicating at least a trend towards an association) were further analysed for their testing characteristics regarding diagnosing residual PH (table 3). Based on NPV/false-negative rates, peak VO_2 < 80% predicted was the most appropriate parameter to use, reducing

the number-needed-to-catheterise to 33/51 (65%), while missing only 1/11 cases (9%) with residual PH. The case missed based on peak $VO_2 \geq 80\%$ corresponded to case 1 who would have been missed based on ICU hemodynamics, low PH probability on TTE and NT-proBNP ≤ 300 ng/L, with mild hemodynamic abnormalities not requiring treatment (supplementary table B).

Table 3: test characteristics of CPET parameters for residual PH

Parameter	Sensitivity	Specificity	PPV	False-positive rate	NPV	False-negative rate	Number-needed-to-catheterise
Peak VO_2 < 80% predicted	10/11 (0.91)	17/40 (0.43)	10/33 (0.30)	23/33 (0.70)	17/18 (0.94)	1/18 (0.06)	33/51 (0.65)
VO_2/WR < 8.4 mL/min/Watt	7/9 (0.78)	24/38 (0.63)	7/21 (0.33)	14/21 (0.67)	24/26 (0.92)	2/26 (0.08)	21/51 (0.41)
V_E/VCO_2 AT ≥ 34	8/10 (0.80)	24/40 (0.60)	8/24 (0.33)	16/24 (0.67)	24/26 (0.92)	2/26 (0.08)	24/51 (0.47)
$SpO_2 \leq 94\%$ (max exercise)	9/11 (0.82)	19/40 (0.48)	9/30 (0.30)	21/30 (0.70)	19/21 (0.90)	2/21 (0.10)	30/51 (0.59)

CPET: cardiopulmonary exercise testing; PH: pulmonary hypertension; PPV: positive predictive value; NPV: negative predictive value; VO_2: oxygen consumption; WR: work rate; V_E/VCO_2: ventilatory equivalent for carbon dioxide; AT: anaerobic threshold; SpO_2: peripheral oxygen saturation.

Discussion

In this observational analysis, TTE and CPET appeared very useful for the exclusion of residual PH, thereby safely reducing the number of patients needing to undergo re-RHC after PEA to diagnose residual PH. However, based on the number of false-positives, a diagnosis of residual PH should not be based on TTE or CPET alone. Data from the early postoperative ICU period should not be used to diagnose 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 [13]. 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 [2,14]. 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 [15]. This reflects the persistence of an abnormal pulmonary vascular response to exercise [16-17]. 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 [18]. 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, 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 diagnose residual PH, since this would lead to an inappropriate number of missed cases of residual PH including one case 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 [19]. 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. Irrespective of the method of analysis, the importance of postoperative PVR as a predictor for mortality does not change. 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.* 6 months after PEA) hemodynamics.

NT-proBNP 6 months after PEA was associated with residual PH. NT-proBNP cut-off > 300 ng/L provided high 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 four cases of residual PH (36%). Reassuringly, none of these patients required additional treatment. 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 high NPV for excluding residual PH. However, due to the number of false-positive

TTE results, RHC remained necessary in 49% of our cohort to diagnose the 22% with 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 TAPSE and systolic tricuspid annular velocity; it remains to be determined whether these parameters, which correlate with pulmonary hemodynamics in CTEPH [20-21] 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 [20,22].

It was previously shown that exercise stress testing with cycle ergometry provides a very efficient evaluation of the RV and pulmonary circulation [23]. 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, except for O_2 pulse and $P_{ET}CO_2$, were associated with the presence of residual PH and especially peak VO_2 provided excellent discriminatory value in selecting patients with a very low probability of residual PH. Unexpectedly, while O_2 pulse and $P_{ET}CO_2$ were different between patients with or without residual PH, no association was found between residual PH and O_2 pulse and $P_{ET}CO_2$ in the univariate analysis. This was probably related to the cut-off chosen.

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, a large number of patients was excluded because of missing follow-up data. Since we wanted to be able to compare the different modalities regarding their diagnostic/predictive properties we aimed for a cohort with complete data and therefore accepted the exclusion of a considerable number of patients because one or more of the modalities was missing. Second, PVR was not calculated based on real-time PAWP or left atrial pressure, as is practiced in some centres. Third, due to the limited number of patients with residual PH we 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. However, we think despite this limitation, the data provide a strong signal indicating the value of CPET and TTE 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 [24].

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

TTE (low PH probability) and CPET (peak VO_2 ≥ 80% predicted) 6 months after PEA can be used to select patients with a very 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, although validation of this strategy in a larger cohort is needed. Our study illustrates that TTE and CPET retain their diagnostic properties after PEA. Whether one of them or both TTE and CPET are used in follow-up after PEA can be decided on local availability and preference. 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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Supplement

Table A: hemodynamics before and after PEA

	Baseline	ICU post-PEA	6 months post-PEA	P-value
mPAP (mmHg)	41.5 (11.2)	21.2 (6.1)	23.3 (7.1)	< 0.001[a]
PAWP (mmHg)	10.7 (3.2)		10.1 (3.3)	0.143[b]
CI (L/min/m^2)	2.6 (0.7)	2.7 (0.6)	3.0 (0.5)	0.006[c]
PVR (dynes·s·cm^{-5})	476 (290-712)	189 (147-278)	155 (117-224)	< 0.001[c]
RAP (CVP in ICU)	7 (5-10)	7 (4-11)	5 (3-6)	< 0.001[c]

Statistical tests used: [a] ANOVA, [b] paired t-test, [c] mixed-effects model. PVR and RAP were analysed after log-transforming data and confirming normal distribution. 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 6 months post-PEA	PVR 6 months post-PEA	NT-proBNP 6 months post-PEA	Additional PH-specific treatment
1	ICU hemodynamics, NT-proBNP, TTE, CPET	30 mmHg	249 dynes·s·cm^{-5}	161 ng/L	no
2	ICU hemodynamics, NT-proBNP, TTE	27 mmHg	243 dynes·s·cm^{-5}	73 ng/L	no
3	ICU hemodynamics	27 mmHg	256 dynes·s·cm^{-5}	363 ng/L	no
4	ICU hemodynamics	52 mmHg	509 dynes·s·cm^{-5}	1150 ng/L	yes
5	NT-proBNP	38 mmHg	360 dynes·s·cm^{-5}	234 ng/L	no
6	NT-proBNP	31 mmHg		253 ng/L	no

Overview of residual PH cases missed (false-negatives) based on early hemodynamics (mPAP in ICU ≤ 20 mmHg and PVR < 240 dynes·s·cm^{-5}), NT-proBNP (≤ 300 ng/L), TTE (low PH probability) or CPET (peak VO_2 ≥ 80% predicted), with their respective mPAP, PVR and NT-proBNP 6 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.

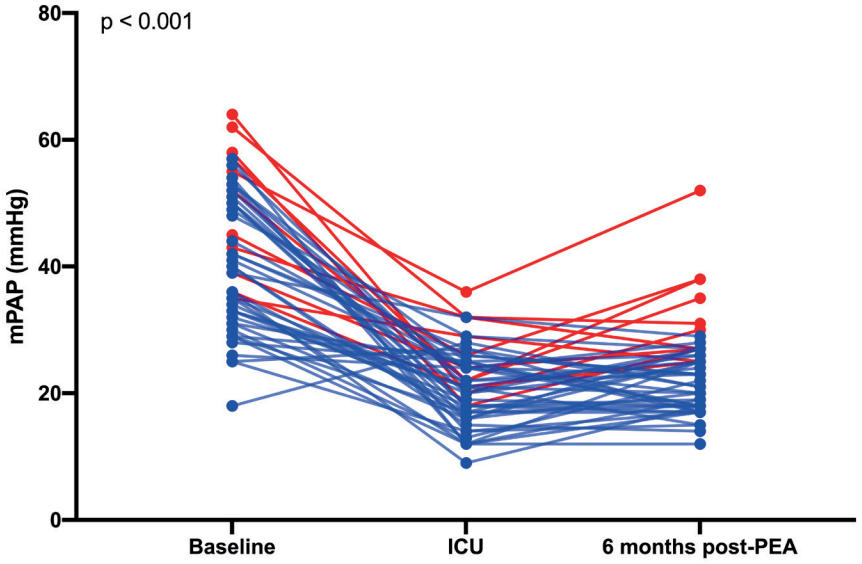

Figure A: individual evolution of mPAP before and after PEA. Indicated in red: cases with residual PH 6 months post-PEA; indicated in blue: cases without residual PH 6 months post-PEA. Statistical test used: ANOVA.
mPAP: mean pulmonary artery pressure; PEA: pulmonary endarterectomy; ICU: intensive care unit

CHAPTER 7

Persistent exercise intolerance after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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Abstract

Aim: Hemodynamic normalisation is the ultimate goal of pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH). However, whether normalisation of hemodynamics translates into normalisation 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 catheterisation (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 (T_{LCO}) was the only predictor of exercise intolerance after PEA.

Conclusions: The majority of CTEPH patients have exercise intolerance after PEA, often despite normalisation of resting hemodynamics. Not all exercise intolerance after PEA is explained by the presence of residual PH, and lower preoperative T_{LCO} 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 right ventricular (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 (CMR) imaging 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 catheterisation (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, pulmonary artery wedge pressure (PAWP), heart rate (HR), and central venous oxygen saturation. Cardiac output (CO) was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index). 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 ≥ 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 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 calculations of dead space to tidal volume ratio 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), 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 American Thoracic Society (ATS) statement [21].

Single-breath carbon monoxide uptake, *i.e.* transfer factor of the lung for carbon monoxide (T_{LCO}), was determined before surgery according to the 2005 joint European Respiratory Society (ERS)/ATS statement [22].

Baseline tests (RHC, CMR, CPET, 6MWT and T_{LCO}) 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

The 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 RV function parameters.

Data are presented as mean (standard deviation), 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 body mass index (BMI) at time of diagnosis was 26.5 kg/m^2 (IQR 24.3-29.3). At the time of CTEPH diagnosis 6% of patients were in New York Heart Association (NYHA) class I, 37% were in NYHA class II, 51% were in NYHA class III, and 6% in NYHA class IV. The proportions and changes in NYHA class after PEA are shown in supplementary figure A. 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 supplementary table A).

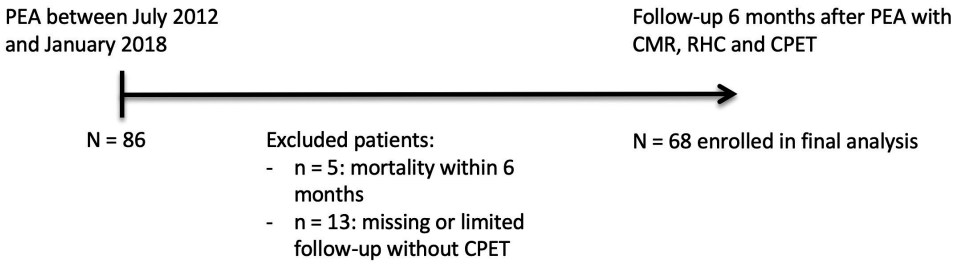

Figure 1: timeline and flow chart of patient selection
PEA: pulmonary endarterectomy; CPET: cardiopulmonary exercise testing; CMR: cardiac magnetic resonance; RHC: right heart catheterisation

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

	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 catheterisation; 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.

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* [20], 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 normalised 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 N-terminal pro-brain natriuretic peptide (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), 6-minute walking distance (6MWD) was significantly higher in patients with normalised peak VO_2 post-PEA (539 (72) meters versus 454 (84) meters, $p < 0.001$).

Residual PH (mPAP > 20 mmHg and PVR ≥ 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 normalised 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 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). Supplementary figure B illustrates that exercise intolerance can persist after PEA despite normalisation of resting hemodynamics.

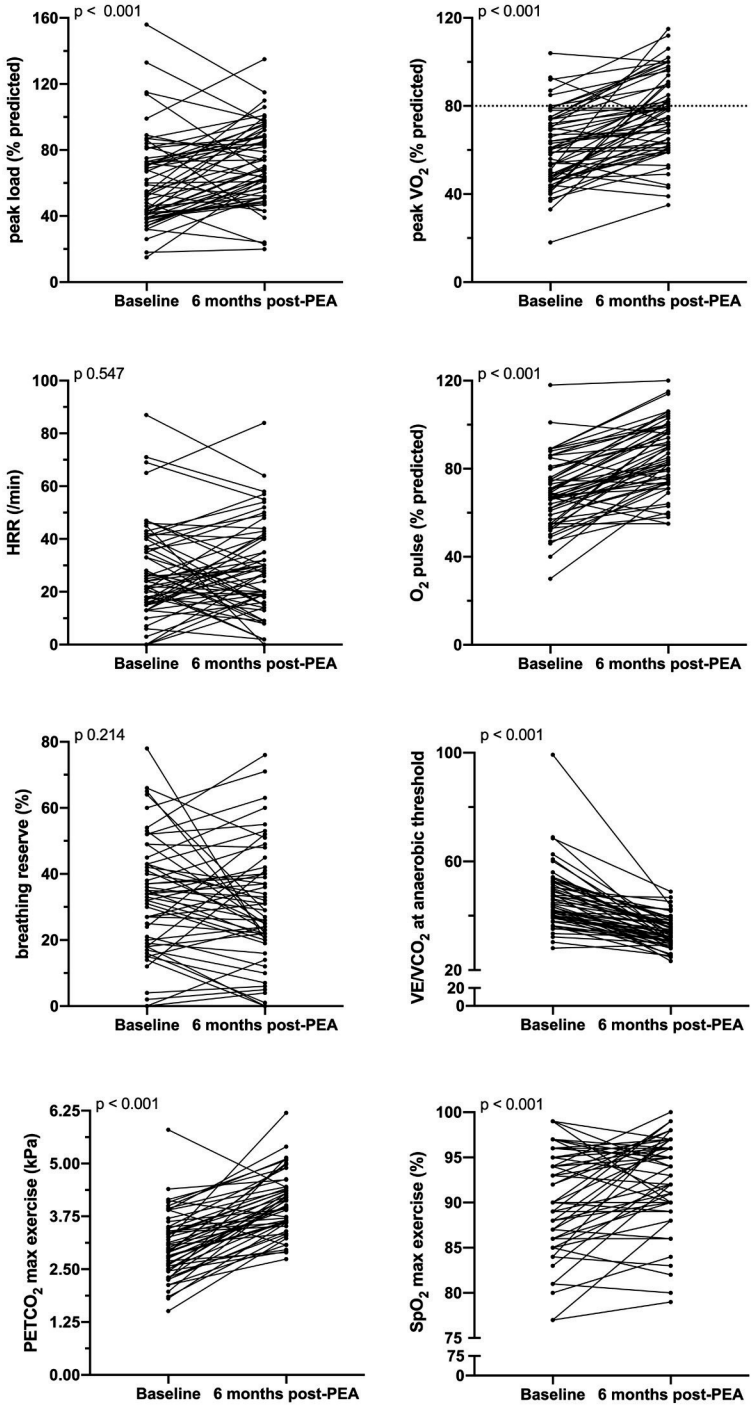

Figure 2: CPET parameters pre-PEA compared to 6 months post-PEA
CPET: cardiopulmonary exercise test; PEA: pulmonary endarterectomy; VO_2: oxygen consumption; HRR: heart rate reserve; V_E/V_{CO2}: ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; SpO_2: peripheral oxygen saturation.

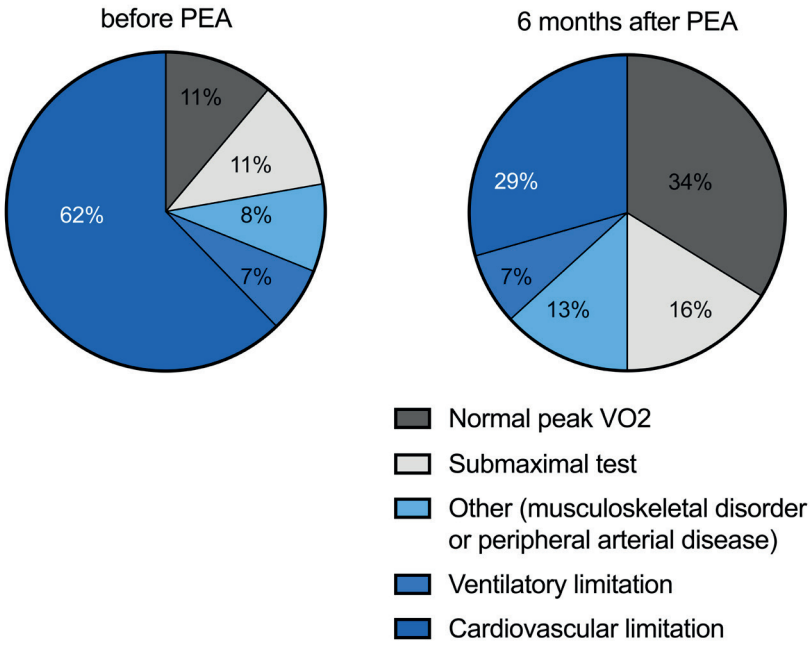

Figure 3: pie charts indicating main determinants of exercise limitation
PEA: pulmonary endarterectomy; VO_2: oxygen consumption

In a large UK cohort, the start of PH-specific medication was associated with a mPAP ≥ 30 mmHg after PEA [2]. Seven patients in our cohort fulfilled the criterium of mPAP ≥ 30 mmHg; none of these patients had a normalised 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 RV ejection fraction (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 V_E/VCO_2 at the anaerobic threshold and $P_{ET}CO_2$ 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).

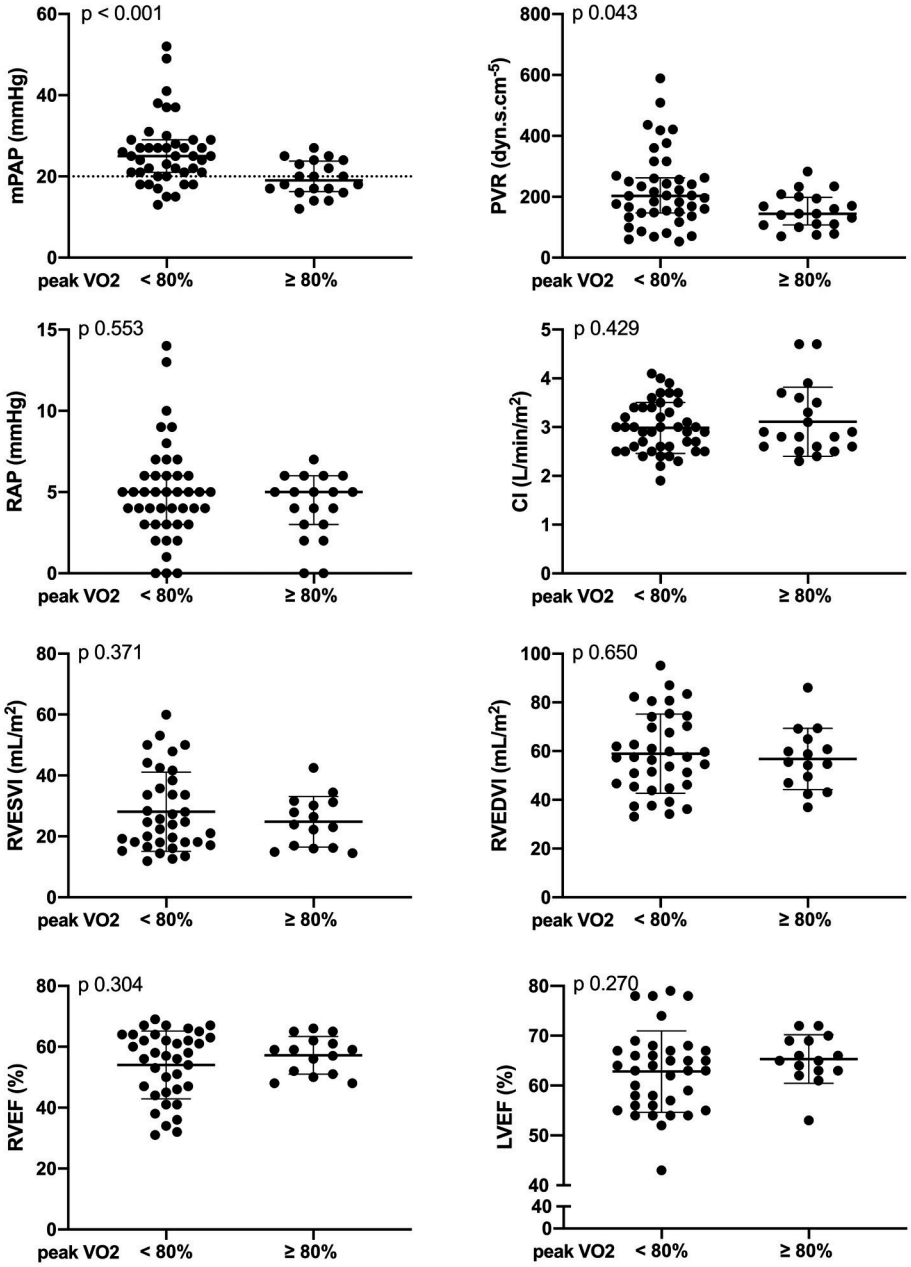

Figure 4: comparison of RHC and CMR parameters 6 months post-PEA between those with or without persistent exercise intolerance 6 months post-PEA. Horizontal bars indicate median and interquartile range (mPAP, PVR, RAP) or mean and standard deviation (CI, RVESVI, RVEDVI, RVEF and LVEF). Statistical test used: unpaired t-test (after log-transformation of non-normal distributed data). RHC: right heart catheterisation; 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.

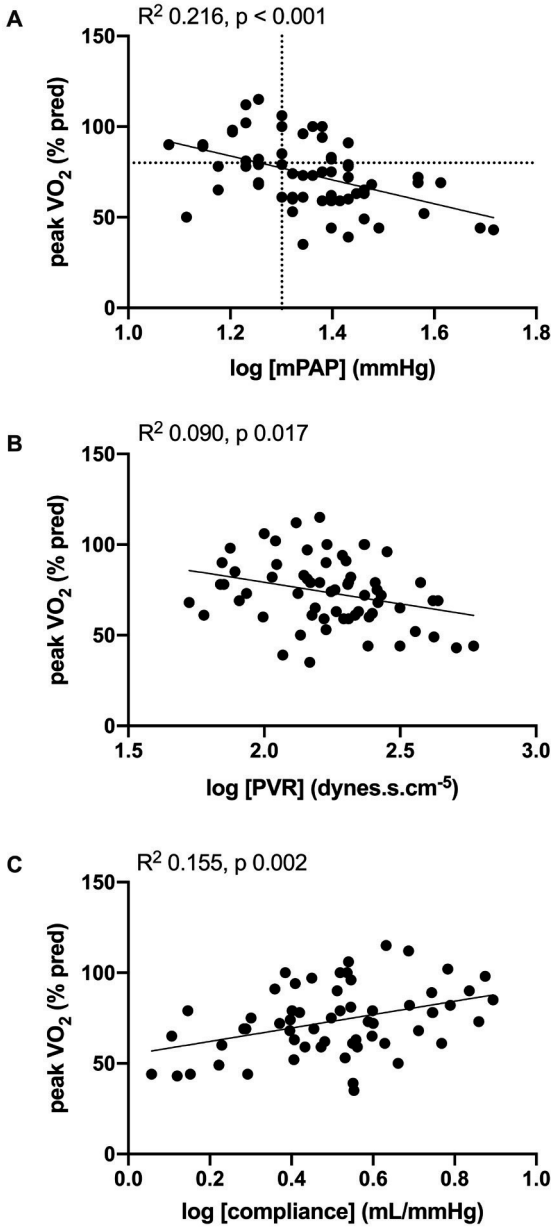

Figure 5: correlation between mPAP/PVR/pulmonary arterial compliance post-PEA and peak VO_2 post-PEA
A: correlation between log-transformed mPAP and peak VO_2. The vertical dotted line indicates mPAP 20 mmHg; the horizontal dotted line indicates peak VO_2 80% of predicted. B: correlation between log-transformed 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.

Patients with persistent exercise intolerance after PEA were characterised before surgery with more frequent treatment with PH-specific medication, a higher NYHA class, a lower 6MWD and a lower T_{LCO} (supplementary table B). 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 (supplementary table C). Pre-surgical T_{LCO} 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 T_{LCO} at baseline compared to the patients without obstructive lung disease.

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 T_{LCO} (% 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; T_{LCO}: transfer factor of the lung for carbon monoxide.

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 T_{LCO} 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 m 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, as follows.

A likely explanation for persistent exercise intolerance is that even when resting hemodynamics normalise, exercise hemodynamics may remain abnormal post-PEA. Although we did not perform 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 T_{LCO} predicts persistent exercise intolerance after PEA is interesting in this context. T_{LCO} 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. In contrast, in patients with CTED significant improvements in exercise RHC and normalised 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, RV ejection fraction was only weakly correlated with peak VO_2 (comparable to previous research in PAH [35]). RV end-diastolic volume index or RV end-systolic volume

index 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], it is likely that this 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 V_E/VCO_2 at the anaerobic threshold (a marker of ventilatory efficiency) was only weakly correlated with peak VO_2. Surprisingly, $P_{ET}CO_2$ 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 left ventricular ejection fraction (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 left ventricular 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 T_{LCO} 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 T_{LCO} and outcomes after PEA in CTEPH. In a French cohort, pre-PEA T_{LCO} 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 T_{LCO}/alveolar

ventilation ratio 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 T_{LCO} and hemodynamic response, we add evidence of an association between pre-PEA T_{LCO} and the functional response after PEA. T_{LCO} 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-thirds 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-thirds 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 T_{LCO} serves as a strong predictor of persistent exercise intolerance after PEA. T_{LCO} 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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Supplement

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
O_2 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/VCO_2 at AT	44.0 (39.7-51.6)	33.5 (30.4-37.2)	< 0.001*‡
SpO_2 at max exercise (%)	90 (86-95)	93 (90-96)	< 0.001*

Data presented as mean (standard deviation), median (interquartile range) 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/VCO_2: ventilatory equivalent for carbon dioxide; SpO_2: peripheral oxygen saturation.

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

Parameter	Peak VO_2 < 80% post-PEA N = 45	Peak VO_2 ≥ 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‡
SvO_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*
T_{LCO} (% 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 catheterisation; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index; RAP: right atrial pressure; SvO_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; T_{LCO}: transfer factor of the lung for carbon monoxide.

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

	Peak VO_2 < 80% post-PEA N = 45	**Peak VO_2 ≥ 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/VCO_2 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
SpO_2 rest (%)	94 (3) *n = 33*	96 (2) *n = 22*	0.006*
SpO_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_EVCO_2: ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; SpO_2: peripheral oxygen saturation

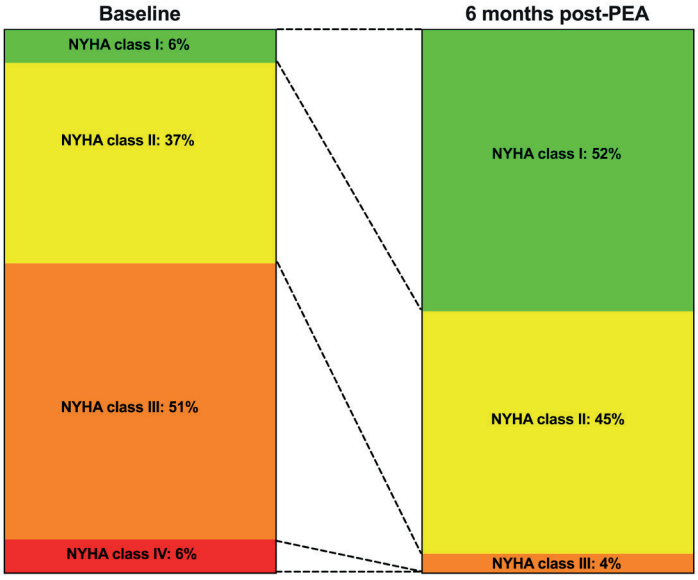


Figure A: NYHA class distribution at baseline (at time of CTEPH diagnosis) and 6 months after PEA
NYHA: New York Heart Association; CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy.

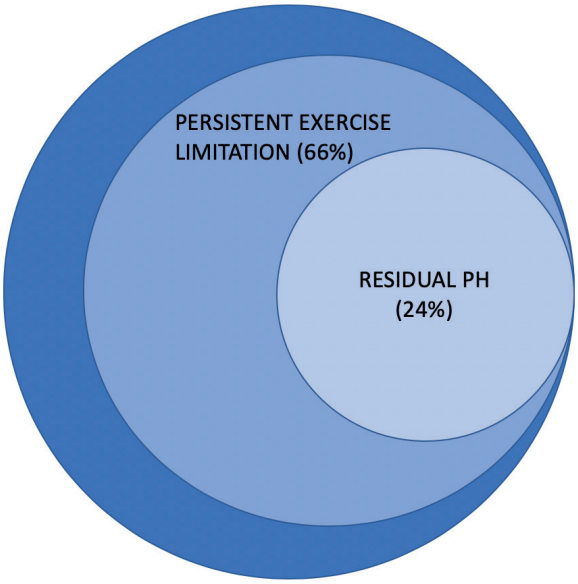
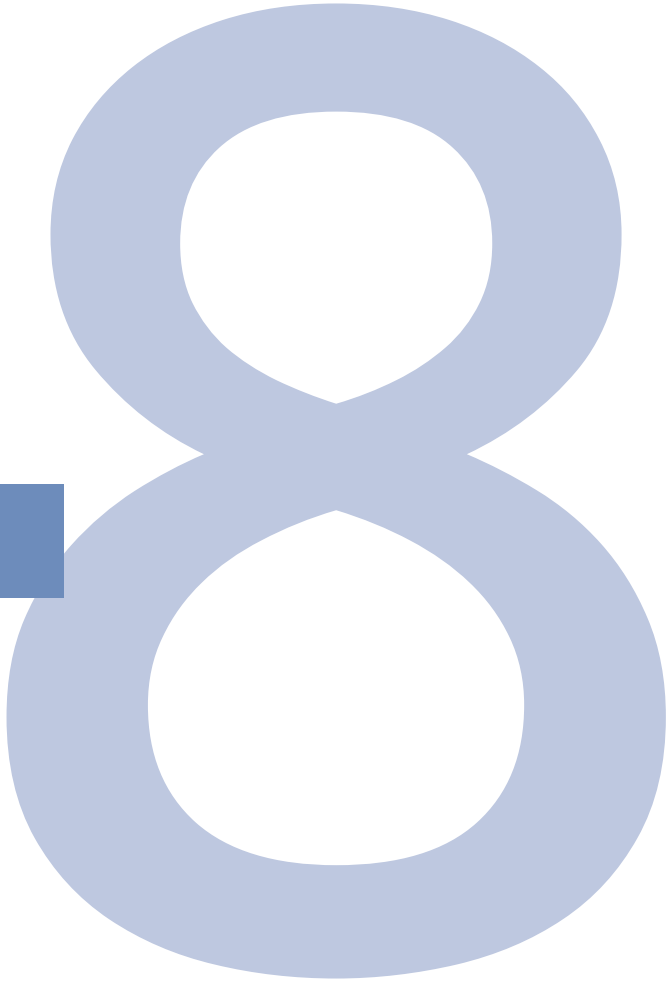


Figure B: Venn diagram indicating the relation between persistent exercise intolerance and residual pulmonary hypertension (PH).
The dark blue circle indicates the whole cohort; the smallest lightest blue circle indicates the patients with residual PH; the middle blue circle indicates the patients with persistent exercise intolerance after PEA.
Residual PH defined by mPAP > 20 mmHg and PVR ≥ 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.



CHAPTER 8

General discussion and future perspectives

Conclusions of the research described in this thesis:

1. Patients with proximal and distal chronic thromboembolic pulmonary hypertension (CTEPH) present with similar resistance and compliance, but right ventricular ejection fraction is significantly lower and right ventricular dilatation more pronounced in patients with proximal CTEPH (chapter 3).

2. After successful pulmonary endarterectomy (PEA) approximately 20% of the pulmonary vasculature remains abnormal on imaging, independent of the presence of residual pulmonary hypertension (PH). This may suggest that microvascular disease, rather than residual macrovascular lesions, plays a prominent role in residual PH after PEA (chapter 4).

3. New vascular lesions are common after PEA for CTEPH (in 27% of patients). Their origin, dynamics, and long-term consequences remain currently unknown, although a relation with the surgical procedure seems likely (chapter 5).

4. Echocardiography and cardiopulmonary exercise testing 6 months after PEA can be used to exclude residual PH, thereby safely reducing the number of patients needing to undergo right heart catheterisation after PEA (chapter 6).

5. Two-thirds of CTEPH patients have exercise intolerance after PEA, often despite normalisation of resting hemodynamics. Not all exercise intolerance after PEA is explained by the presence of residual PH, and a lower preoperative T_{LCO} was a strong predictor of exercise intolerance 6 months after PEA (chapter 7).

In this thesis several aspects of the pathophysiology of chronic thromboembolic pulmonary hypertension (CTEPH), both before and after pulmonary endarterectomy (PEA), are discussed. Three clinical cases, described in the introduction of this thesis, served as the outline of this thesis and serve again as the outline of this discussion.

Despite the more severe pulmonary hemodynamic abnormalities in patient A, right ventricular (RV) function was more compromised in patient B. What determines pulmonary hemodynamics and RV function in CTEPH and how can the differences between these two patients be explained?

In chapter 2, I described the pathophysiology of acute pulmonary embolism (PE) in general, which includes both cardiovascular compromise and mechanisms of hypoxemia. Just as in acute PE, increased RV afterload is central in the pathophysiology of CTEPH. Traditionally, resistance and compliance, which are inversely related, are considered as the primary determinants of afterload. Characteristic impedance is a third component of afterload, but is in clinical practice difficult to quantify and therefore its importance remains unknown. Pulmonary artery pressures (PAP) are the resultant of afterload and

contractility. RV function and imaging abnormalities are highly variable in CTEPH, as illustrated in case A and B. This led to my hypothesis that the location of vascular lesions explains these differences. In chapter 3, we analysed RV afterload and function in 21 patients with proximal CTEPH (lesions starting in the main and lobar pulmonary arteries) and 25 patients with distal CTEPH (lesions starting at the (sub)segmental level). mean PAP (mPAP), pulmonary vascular resistance (PVR) and compliance were similar. However, RV ejection fraction (RVEF) was more compromised and RV dilatation more pronounced in the patients with proximal CTEPH. In other words, the site of vascular obstruction did affect RV function while it did not influence PVR or compliance. In chapter 3 several potential explanations for these findings were considered: 1) other components of load that were not accounted for (*i.e.* characteristic impedance), 2) intrinsic properties of the RV, or 3) wave reflections. Subsequent analyses indicated that characteristic impedance did not explain the differences in RV function; however, in proximal CTEPH, pressure waves returned earlier to the RV in patients with proximal CTEPH leading to more RV wall stress [1], serving as the most probable explanation for our findings.

Although patients with proximal CTEPH are likely candidates for PEA and these findings do not preclude operability, being aware of earlier wave reflections and as a result a more compromised RV function provides essential knowledge during the perioperative care of these patients. This is of particular importance when cardiac magnetic resonance (MR) analysis is not part of the preoperative work-up and quantitative analysis of RV function is not routinely available.

What determines residual pulmonary hypertension (PH) after PEA for CTEPH?

Prognosis after PEA is generally excellent, but residual PH is frequent and its pathophysiology is less well known. Four potential determinants of residual PH are 1) (very) distal vasculopathy, 2) macrovascular lesions near the subsegmental level beyond the reach of the surgeon, 3) recurrent thromboembolism, and 4) residual lesions in the setting of a technically insufficient PEA. Assuming proper preoperative selection in a multidisciplinary discussion setting and performance of PEA in experienced centres makes the latter explanation unlikely.

In chapter 4 we focused on the first two potential determinants, namely distal vasculopathy (pathological changes in pulmonary arteries/arterioles with a diameter below 500 µm) and remaining (sub)segmental macrovascular lesions. In a cohort of 31 PEA patients computed tomography pulmonary angiography (CTPA) and MR perfusion were performed 6 months after PEA, and compared to CTPA and MR perfusion before PEA. Approximately 20% of the pulmonary arteries remained abnormal after PEA, but these were not associated with residual PH. Parenchymal perfusion as determined by MR perfusion improved after PEA, but was not different between patients with or without residual PH. Evidence for distal vasculopathy/microvascular disease as the major determinant of residual PH was indirect: the preoperative extent of abnormalities on

CTPA was less pronounced in those with residual PH after PEA, indicating the potential role of more distal vasculopathy in those patients. In addition, residual PH was also present in patients without residual macrovascular lesions on CTPA.

This adds to a recent publication from the Vienna group providing evidence regarding the role of small vessel disease in residual PH: in histomorphometric analysis of lung biopsies taken during PEA, residual PH and mortality were associated with increased medial and intimal thickness, indicating more microvascular disease [2].

In chapter 5 we focused on recurrent thrombosis as a potential mechanism of residual PH after PEA. In a large UK cohort analysis [3], it was already suggested that recurrent thromboembolism occurs only in a very small number of patients. However, this analysis was restricted to patients with recurrent PH after initial hemodynamic normalisation or worsening residual PH over time, and structured follow-up with either ventilation-perfusion scans or CTPA was not performed. In chapter 5, we analysed 33 patients with CTPA 6 months after PEA, comparing this CTPA with the preoperative CTPA. New vascular lesions were seen on CTPA 6 months after PEA in 27% of patients, mainly consisting of new or increased thrombus and early tapering. The presence of new vascular lesions was not associated with hemodynamic outcomes or the presence of residual PH. Although our analysis was insufficiently powered to provide firm conclusions regarding the role of recurrent thrombosis, it does provide a signal that, although new intravascular lesions are quite frequent, their hemodynamic consequences remain limited in the context of the major vascular improvements accomplished during PEA.

Altogether, microvascular disease is the most probable determinant of residual PH after PEA, with contribution of residual macrovascular lesions or recurrent thrombosis in selected patients. This is essential since more knowledge regarding the mechanisms involved in residual PH provides a more informed therapeutic strategy in those needing additional treatment.

Considering potential therapeutic consequences of residual PH, is right heart catheterisation (RHC) 6 months after PEA a mandatory part of follow-up in all patients?

The current guideline advises follow-up after PEA in CTEPH centres with at least one hemodynamic assessment to be considered 6-12 months after PEA [4]. This hemodynamic assessment focuses on residual PH which requires invasive RHC. The question is whether all patients need follow-up RHC. Alternatively, early postoperative hemodynamics or non-invasive diagnostic modalities can perhaps be used to exclude residual PH, thereby reducing the number of re-RHC without clinical consequences in the follow-up after PEA.

In chapter 6 we described our analysis of early postoperative hemodynamics, and 6-month follow-up transthoracic echocardiography (TTE), cardiopulmonary exercise

testing (CPET) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in 51 CTEPH patients after PEA. This analysis indicated that TTE (low PH probability) and CPET (peak oxygen consumption (VO_2) ≥ 80% predicted) 6 months after PEA could be used to exclude residual PH. Using either of these parameters would lead to a reduction of up to two-thirds of RHCs, which equals to a considerable reduction of resources needed, without missing clinically relevant cases of residual PH.

When interpreting these results, some considerations require further attention.

First, the definition of residual PH is not well established. Different hemodynamic definitions have been used, although most studies describe residual PH as mPAP ≥ 25 mmHg at some point after PEA, analogous to the definition in the current guideline [4]. Many distinguish residual PH from clinically relevant PH. This is well illustrated in the study performed by Cannon *et al*, where two additional categories are described: clinically significant residual PH (mPAP ≥ 30 mmHg) indicating patients at risk for deterioration in functional status and triggering initiation of pulmonary vasodilator therapy, and residual PH associated with a higher risk of death because of CTEPH (mPAP ≥ 38 mmHg and PVR ≥ 425 dynes·s·cm^{-5}) [3]. The writing of this thesis coincides with a discussion regarding the hemodynamic definitions of PH, started at the 6th World Symposium on Pulmonary Hypertension in Nice in 2018. The current ESC/ERS guideline uses mPAP ≥ 25 mmHg and pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg to define pre-capillary PH [4]. The upcoming guidelines are expected to use the new proposed hemodynamic definition for pre-capillary pulmonary hypertension: mPAP > 20 mmHg, PAWP ≤ 15 mmHg and PVR ≥ 240 dynes·s·cm^{-5} [5]. In chapters 6 and 7 this new proposed hemodynamic definition was used. Although we want to stay away from a substantive discussion regarding this new proposed definition, we do think that this definition might select more relevant residual PH, especially due to the addition of the PVR criterium. This is important since (left ventricular) diastolic dysfunction may account for a substantial number of patients falling in the "grey zone" mPAP between 20 and 25 mmHg with normal PVR. It is also important to emphasise that this definition is not synonymous with clinically significant residual PH as defined by Cannon *et al* [3]. However, it does help to reduce the number of re-RHC in the follow-up to provide more focus towards the patients with potential clinically relevant residual PH.

Second, there is little evidence to guide treatment of (clinically relevant) residual PH. In the evaluation of the patient with symptomatic residual PH after PEA, the same treatment algorithm as in new CTEPH patients applies [4], which is geared towards selection of the treatment with the highest potential for improvement, considering the location of the abnormalities. In patients with significant (re)occlusions in the lobar and (sub)segmental arteries within reach of the surgeon, re-do endarterectomy can be considered, taking in to account the reasons for failure of the primary PEA. Data on re-do PEA are, however, scarce [6-8]. The most recently published series consists of 12 patients undergoing re-

do PEA with a mean interval of 6.3 years between the primary and re-do PEA [6]. In this highly selected group (12 patients over a 20-year time period in a large national reference centre), significant improvements in both hemodynamic and functional outcomes were seen with acceptable in-hospital mortality (8.3%) [6].

Balloon pulmonary angioplasty (BPA) is a potential treatment option in patients with residual symptomatic PH and significant lesions at the segmental and subsegmental level. Again, data are scarce and observational. The largest series of sequential BPA after PEA consists of 15 patients with residual PH after PEA undergoing BPA (patient selection based on mPAP ≥ 25 mmHg, PAWP < 15 mmHg, PVR ≥ 300 dynes·s·cm^{-5}, and WHO functional class ≥ II 3-6 months after PEA) [9]. Substantial improvement in pulmonary hemodynamics, NT-proBNP and 6-minute walking distance (6MWD) were shown after BPA in patients with quite severe residual PH (mPAP mean 48.5 (standard deviation 9.6) mmHg and PVR mean 700 (standard deviation 207) dynes·s·cm^{-5}) before BPA, while being safe with a relatively low complication rate and no periprocedural mortality [9].

Medical therapy is the only additional treatment option explicitly mentioned in the current guideline for patients with residual PH after PEA [4]. Based on the pathophysiology of residual PH, and assuming distal vasculopathy as the culprit in the majority of patients with residual PH, this is also the most logical treatment. Both the BENEFIT (bosentan) [10] and CHEST (riociguat) [11] trials included patients with residual PH after PEA in randomised placebo-controlled trials with these respective drugs. In both trials, a mPAP ≥ 25 mmHg and PVR ≥ 300 dynes·s·cm^{-5} was required for inclusion. With these criteria, a substantial number of patients would qualify for drug therapy after PEA, even though in routine practice only few would normally be considered for medical therapy [3]. The BENEFIT trial reported similar effects of 16 weeks of bosentan treatment on PVR (significant improvement) and 6MWD (no improvement) in the subgroup analysis of patients with residual PH after PEA (28%) as in the whole cohort [10]. The CHEST-1 trial included 72/261 with residual or recurrent PH after PEA [11]. While in the inoperable group 6MWD (primary outcome) significantly improved, the predefined subgroup analysis of persistent/recurrent PH after PEA did not shown a significant effect on 6MWD after 16 weeks of riociguat [11]. A separate detailed analysis of the subgroup with persistent/recurrent PH after PEA indicated significant changes in PVR and mPAP after 16 weeks of riociguat [12].

Based on this study, the current guidelines recommend riociguat for symptomatic patients with persistent/recurrent PH after PEA (class I, level B recommendation) [4]. In clinical practice however, not every symptomatic residual PH patient will be treated accordingly. In the majority of patients, residual PH has no therapeutic consequences. This is also illustrated by Cannon *et al* with only 28% of patients with mPAP ≤ 20 mmHg despite significant improvements in functional class maintained in the long-term and excellent survival [3].

Third, possibly more important than the absolute values is the change in pulmonary hemodynamics after PEA. A NYHA I class patient with a mPAP of 30 mmHg and PVR of 300 dynes·s·cm^{-5} 6 months post-PEA, who was in NYHA class 4 with a mPAP of 50 mmHg and a PVR of 1200 dynes·s·cm^{-5} before PEA, would be considered a surgical success in the setting of a properly adapted right heart. However, a patient with a mPAP of 24 mmHg and PVR of 240 dynes·s·cm^{-5} after PEA would not per se be classified as a surgical success if these were 28 mmHg and 280 dynes·s·cm^{-5} before PEA. Analysing changes in hemodynamics over time is difficult, while RV function and adaptation are probably even more important than hemodynamic parameters per se. These considerations fuel ongoing discussions regarding proper outcome parameters in PH research. While the focus in current CTEPH research after PEA is on resting hemodynamics, this does not tell the whole story.

Despite normalised resting hemodynamics exercise tolerance remains impaired in patient B: what explains the persistent exercise intolerance and could we have foreseen this before PEA, in order to manage patient expectations of the surgery?
As mortality and residual PH after PEA are the most commonly reported outcome measures after PEA, less attention has been paid to persistent exercise intolerance after PEA. In chapter 7 we analysed the incidence of persistent exercise intolerance after PEA, and its determinants and relation with resting hemodynamics. 68 CTEPH patients with cardiac MR imaging, RHC and CPET 6 months after PEA were enrolled. Persistent exercise intolerance, defined as peak VO_2 < 80% predicted 6 months after PEA, was present in 66% of patients, despite substantial hemodynamic improvements. Not all exercise intolerance could be explained by the presence of residual PH, as illustrated by the discrepancy between the incidence of persistent exercise intolerance and residual PH. Three possible explanations for the high incidence of exercise intolerance and the discrepancy between exercise intolerance and resting hemodynamics are discussed in chapter 7:

1. Exercise hemodynamics remain abnormal after PEA due to the persistence of increased afterload (*i.e.* remaining distal vasculopathy and/or impaired pulmonary arterial compliance).

2. Low exercise stroke volume due to afterload-independent right ventricular dysfunction (incomplete reverse remodelling of the RV).

3. Impaired peripheral oxygen extraction due to peripheral muscle dysfunction or deconditioning.

Several papers on this topic have been published in the last year and provide additional insights into the pathophysiology of persistent exercise intolerance after PEA.

The same signal of reduced exercise capacity in patients with normalised resting hemodynamics was seen after BPA [13]. Although the level of vascular involvement differs between patients eligible for PEA (main, lobar, segmental and subsegmental arteries) and BPA (segmental and subsegmental arteries), the Japanese origin of this study indicates substantial overlap in disease characteristics. However, this does not change the large difference in endovascular treatment effect between surgical and percutaneous interventions. Of 249 analysed patients with normalised resting hemodynamics after BPA, 116 patients qualified as exercise PH (mPAP/cardiac output slope > 3 mmHg/L/min and/or mPAP > 30 mmHg at cardiac output 10 L/min) with significantly higher NYHA class and lower 6MWD and peak VO_2 compared to those without exercise PH. Already after leg raise, the increase in cardiac output was less in the exercise PH group, resulting in increased PVR after leg raise. This response to increased venous return can be regarded as a clue towards increased afterload and/or persistent RV dysfunction as an explanation for exercise intolerance despite normalised resting hemodynamics.

The Aarhus group performed a prospective analysis of exercise hemodynamics in 20 CTEPH patients before and 3 and 12 months after PEA, compared to a group of 15 healthy controls [14]. After initial significant improvements in pulmonary hemodynamics after PEA, no further changes were seen between 3 and 12 months after PEA. Although a structured rehabilitation was not described as part of the program, one would expect some improvement between 3 and 12 months if peripheral muscle dysfunction or deconditioning was a critical factor. In addition, only 50% of patients had a mPAP/cardiac output slope < 3 mmHg/L/min 12 months after PEA. Cardiac output and pulmonary arterial compliance both at rest and during exercise improved after PEA, but remained significantly lower compared to healthy controls. Again, these findings point towards increased afterload and/or persistent RV dysfunction as an explanation for exercise intolerance despite normalised resting hemodynamics.

Prospective evaluation of a structured and early rehabilitation program in 45 CTEPH patients starting 3 weeks after PEA showed ongoing RV reverse remodelling and increasing exercise capacity between 3 and 22 weeks after PEA [15]. These findings indicate that both deconditioning and RV reverse remodelling are relevant factors in the initial exercise limitation present after PEA. If distal vasculopathy was the only factor, no improvement in peak VO_2 between 3 and 22 weeks after PEA would be expected. Unfortunately, the initial plan for a randomised controlled trial was not possible. Therefore, the magnitude of the effect of deconditioning cannot be determined based on these data.

Altogether, based on the findings described in chapter 7, the papers discussed in chapter 7 and the new data published, it appears that the explanation for persistent exercise limitation despite normalised resting hemodynamics is multifactorial. Increased afterload due to distal vasculopathy, incomplete reverse remodelling of the RV and peripheral

muscle dysfunction should all be considered. The relative importance of each of these factors differs between patients and in time.

Another question is whether persistent exercise intolerance can be predicted upfront. In chapter 7 we described our findings from univariate and multivariate logistic regression analysis, indicating that hemodynamics and imaging before PEA did not predict persistent exercise intolerance, while a lower preoperative transfer factor for carbon monoxide (T_{LCO}) was a strong predictor. T_{LCO} probably reflects distal vasculopathy and these findings underline distal vasculopathy as an important factor in the pathophysiology of persistent exercise intolerance after PEA.

Future perspectives

Although not covered in this thesis, important challenges are faced in the follow-up of patients after acute PE. On the one hand, there is a high incidence of persistent symptoms and incomplete recovery after acute PE ("post-PE syndrome") [16-17], and on the other hand there is a significant diagnostic delay [18] and possibly underdiagnosis of CTEPH. Considering the large difference between the high incidence of "post-PE syndrome" and the relatively low incidence of CTEPH [19], there is a need for diagnostic tools adequately separating these groups in a safe and effective manner. Clinical decision rules such as the In-Shape algorithm are very helpful in detecting patients at higher risk for CTEPH [20], while reducing the number of echocardiography studies needed to screen all patients after acute PE. The downside of a clinical decision rule is that it helps selecting high(er)-risk patients, but does not explain persistent complaints after acute PE if CTEPH is ruled out. And that is where CPET has major advantages, since it can help in uncovering the underlying pathophysiology of exercise intolerance. Now that the role of CPET in CTEPH after PEA has been shown, it would also be of interest to evaluate the role of CPET in the evaluation of persistent symptoms after acute PE. For example, is echocardiography still needed in the setting of exercise intolerance after acute PE and a completely normal CPET? The diagnostic role of CPET in CTEPH patients with normal echocardiography has already been illustrated in a retrospective series [21], but requires further prospective confirmation. Another discussion is the role of CPET in the diagnosis of chronic thromboembolic disease (CTED). Currently, the jury is still out on the exact definition of CTED, but including CPET into its diagnostic criteria seems inevitable.

Residual PH is the most commonly used outcome parameter after PEA in CTEPH. However, its clinical relevance is inconclusive, as already discussed here. Many questions remain currently unanswered regarding the therapeutic consequences of residual PH. What is the impact of additional treatment on long-term outcome, in terms of survival benefit, hemodynamic improvements but also relief of exercise intolerance and improvement of quality of life? Exactly which patients will benefit from additional treatment after PEA? Will selected patients with exercise intolerance and normal resting hemodynamics also

benefit from additional treatment? Also, the potential of hybrid therapeutic approaches combining PEA, BPA and/or medical therapy, upfront or in the setting of residual PH after initial PEA, remains to be determined.

Essential in these future studies is the use of sophisticated imaging modalities, since the impact of the different treatment options is also highly dependent on the location of residual disease and underlying pathophysiology.

After the initial studies with superior sensitivity of ventilation-perfusion scintigraphy compared to CTPA in detecting CTEPH [22], major improvements in the diagnostic accuracy of CTPA have been made [23]. CTPA provides a detailed analysis of the pulmonary vasculature. ECG-gated multidetector CTPA, as practiced in the research described in this thesis, has already significantly improved diagnostic accuracy, especially at the segmental level [24-25]. Dual-energy CTPA provides additional information on peripheral perfusion of the lung parenchyma [26]. Using these improved imaging modalities enables more effective patient selection in treatment trials, based on level of (residual) disease.

Conclusion

In this thesis, a comparison was made of RV function between patients with proximal or distal CTEPH. Despite similar hemodynamics, RV function was more severely decreased in patients with proximal CTEPH. CT-pulmonary angiography and MR perfusion studies after PEA provided additional insights into the determinants of residual PEA, indicating that microvascular disease is the major determinant, while new vascular lesions after PEA are frequent but probably less important. Echocardiography and CPET can be used in the follow-up after PEA to exclude residual PH after PEA in a non-invasive manner. Two-thirds of patients have exercise intolerance after PEA, often despite normalised resting hemodynamics, most likely due to the combination of increased afterload due to distal vasculopathy, incomplete RV reverse remodelling and/or deconditioning.

In the research described in this thesis several diagnostic modalities were described. For the near future it would be of interest to evaluate the role of CPET in post-PE syndrome and CTEPH/CTED diagnosis, and also to refine patient selection for different treatment options based on disease level and underlying pathophysiology using advanced imaging modalities. The ultimate goal is and will remain to provide the best possible treatment for each individual CTEPH patient in the changing treatment landscape.

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Summary

Summary

After a general introduction on chronic thromboembolic pulmonary hypertension (CTEPH), three clinical cases are described in **chapter 1**. The questions raised based on these clinical vignettes served as the outline for the research described in this thesis.

In **chapter 2** an overview of the pathophysiology of acute pulmonary embolism (PE) is given, focusing on the hemodynamic consequences of acute PE and factors involved in explaining hypoxemia. Central in the pathophysiology of acute PE is an acute right ventricular (RV) pressure overload, leading to adaptive and ultimately maladaptive responses of the RV, with RV failure as the final common pathway. CTEPH has many similarities with acute PE, although the hemodynamic compromise is acute in the setting of acute PE and chronic in the setting op CTEPH.

The response of the RV to an increased RV afterload, with pulmonary vascular resistance (PVR) and compliance as the main determinants of afterload, differs between CTEPH patients. In **chapter 3** we hypothesized that location of CTEPH lesions explains the differences in RV function between patients. We analysed RV afterload and function in 21 patients with proximal CTEPH and 25 patients with distal CTEPH. While mean pulmonary artery pressure, PVR and compliance were similar, RV ejection fraction was more severely compromised and RV dilatation more pronounced in the patients with proximal CTEPH. It was concluded that the site of vascular obstruction did affect RV function while it did not influence PVR nor compliance. Subsequent research by Fukumitsu *et al* has taught us that this difference in RV function was explained by earlier return of wave reflections in proximal CTEPH leading to more RV wall stress.

Chapters 4 and 5 focused on the determinants of residual pulmonary hypertension (PH). Residual PH after pulmonary endarterectomy (PEA) is relatively frequent. However, the pathophysiology of residual PH is less well understood. It is assumed in general that distal vasculopathy is the major determinant of residual PH, although evidence regarding other potential contributors is lacking. In **chapter 4** we analysed the role of residual (sub)segmental macrovascular lesions. In 31 patients computed tomography pulmonary angiography (CTPA) and magnetic resonance (MR) perfusion were performed 6 months after PEA, and compared to CTPA and MR perfusion before PEA. Although 20% of the pulmonary arteries remained abnormal after PEA, no association was found with residual PH. In addition, residual PH was also present in patients without residual macrovascular lesions on CTPA, leading to the conclusion that remaining (sub)segmental macrovascular lesions are a contributor at most but not a major determinant of residual PH. Parenchymal perfusion as determined by MR perfusion improved after PEA, but no differences were seen between patients with residual PH and those without residual PH. In **chapter 5** the role of recurrent thrombosis was analysed. In 33 patients with CTPA before and 6 months after PEA, new vascular lesions were seen on CTPA 6 months after PEA in 27% of patients.

These new lesions mainly consisted of new or increased thrombus and early tapering, and their presence was not associated with hemodynamic outcomes or the presence of residual PH. It was concluded that although new vascular lesions are quite frequent after PEA, their hemodynamic consequences are limited, especially when put into context with the major vascular improvements accomplished with PEA. Their origin, dynamics, and long-term consequences however, remain unknown for now.

A diagnosis of residual PH after PEA requires right heart catheterisation (RHC). As RHC is an invasive procedure, with risk of complications and logistical issues, and the majority of patients will not have residual PH, an analysis was performed to evaluate the role of postoperative early hemodynamics and non-invasive diagnostic procedures (NT-proBNP, echocardiography and cardiopulmonary exercise testing (CPET)) in identifying patients who do not require repeat RHC because of a very low likelihood of residual PH. In **chapter 6** the analysis of 51 CTEPH patients after PEA was described: early hemodynamics after PEA should not be used to define hemodynamic success, and NT-proBNP 6 months after PEA (cut-off 300 ng/L) had insufficient negative predictive value. Echocardiography (low PH probability) and CPET (peak $VO_2 \geq 80\%$ predicted) 6 months after PEA could be used to exclude residual CTEPH. Using either of these parameters would lead to a reduction of the number of repeat RHC to 49-65%, without missing clinically relevant cases of residual PH.

An important focus of research after PEA is on residual PH, despite the limited clinical consequences of residual PH in general, and the many unknowns regarding treatment consequences. Less attention has been directed towards exercise intolerance after PEA. In **chapter 7** the incidence of persistent exercise intolerance after PEA and its determinants and relation with resting hemodynamics was analysed in 68 CTEPH patients. Persistent exercise intolerance, defined as peak $VO_2 < 80\%$ predicted 6 months after PEA, was present in 66% of patients, despite substantial hemodynamic improvements. Not all exercise intolerance could be explained by the presence of residual PH, as illustrated by the discrepancy between the incidence of persistent exercise intolerance and residual PH. Lower preoperative T_{LCO} was a strong predictor of exercise intolerance 6 months after PEA. Based on available evidence from other research discussed in **chapter 7** and the general discussion in **chapter 8**, the explanation of persistent exercise limitation despite normalised resting hemodynamics is likely multifactorial: increased afterload due to distal vasculopathy, incomplete reverse remodelling of the RV and peripheral muscle dysfunction.

Appendices

List of publications

This thesis:

Ruigrok D and Vonk Noordegraaf A. Pathophysiology of acute pulmonary embolism. Book chapter in: *ESC CardioMed* 3rd edition, 2018, edited by Camm JA, Lüscher TF, Maurer G and Serruys PW.
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Curriculum vitae

Dieuwertje Ruigrok was born on January 15th 1983 in Katwijk, The Netherlands. She finished atheneum *cum laude* at the Andreas College (Katwijk), and started medical school in 2001 at the University of Leiden/Leiden University Medical Centre (LUMC). After the doctoral exam (*cum laude*) in 2005, she became a medical doctor in 2007. Between 2007 and 2009 she worked as an intern at the pulmonology department in the Diakonessenhuis Leiden. In February 2009 she started her training to become a pulmonologist, first as a resident in internal medicine in the Rijnland Ziekenhuis Leiderdorp (supervisor dr. M.J.F.M. Janssen), later as a pulmonary resident in the LUMC (supervisor dr. L.N.A. Willems) and Kennemer Gasthuis Haarlem (supervisor dr. H.B. Kwa), ending with a 6-month training in severe asthma and interstitial lung diseases in the Academic Medical Centre (AMC) Amsterdam (supervisor dr. R.E. Jonkers).

Since January 2015 she is registered as a pulmonologist, working in the Vrije Universiteit Medical Centre (VUmc, Amsterdam) in 2015 and between 2016 and 2018, and in the University Medical Centre Utrecht (UMC Utrecht) in 2015-2016 and from September 2018 onward. In 2016 she started working on the research described in this thesis.

Since September 2018 she is working in the UMC Utrecht, with focus on lung transplantation, interstitial lung diseases and pulmonary vascular diseases.

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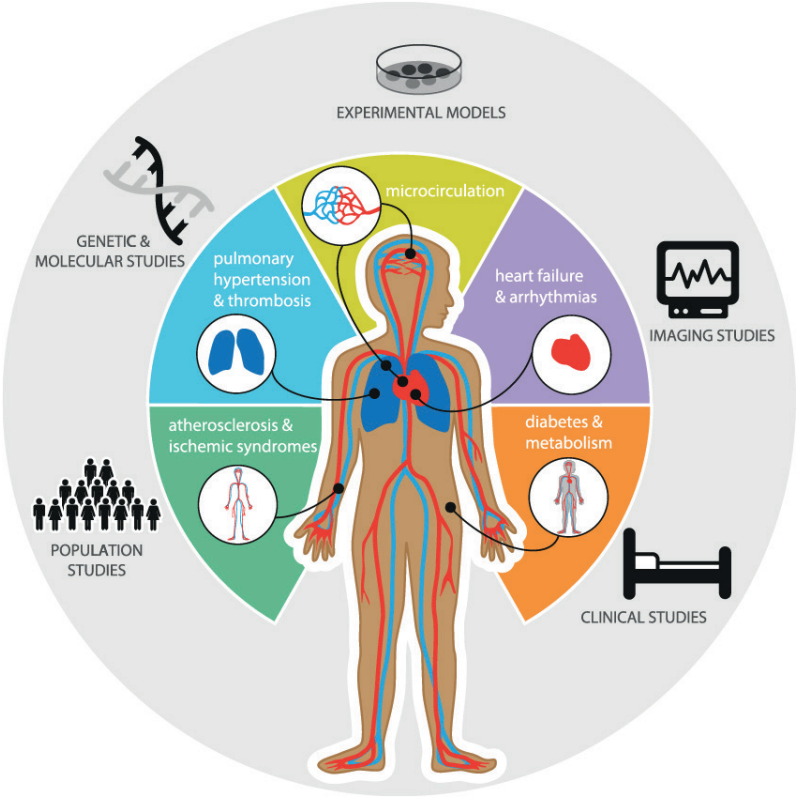

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