Chapter 8

Assessment of Diagnostic Testing to Guide the Surgical Management of Chronic Thromboembolic Pulmonary Hypertension

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1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by organizing thrombotic obstructions in the pulmonary arteries by nonresolving thromboemboli, formation of fibrosis and remodeling of pulmonary blood vessels. It is defined as precapillary PH as assessed by right heart catheterization (mean pulmonary arterial pressure, mPAP ≥ 25 mmHg with a pulmonary arterial occlusion pressure, (PAOP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 3 wood units, in the presence of one or more mismatched segmental or larger perfusion defects by ventilation-perfusion lung scintigraphy, computerized tomography, and/or pulmonary angiography after at least 3 months of effective anticoagulation (Lang, 2010) (Table 1).

Although the incidence and prevalence of CTEPH have been a matter of debate, it represents one of the most prevalent forms of PH. Current data derived from registries suggest that CTEPH occurs at an incidence of 3-30 cases per million in the general population. Classical estimates of disease frequency refer to the number of CTEPH cases per survived pulmonary thromboembolic events and report cumulative incidences between 0.1% and 9.1% after a single episode of pulmonary embolism (median follow-up of 4-8 years) and 13.4% after recurrent venous thromboembolism. However, 25 to 40% of patients with CTEPH do not have a documented antecedent venous thromboembolic event (depending on prospective versus retrospective reports, respectively) (Pengo et al., 2004; Bonderman et al., 2009; Pepke-Zaba et al., 2011). Finally, CTEPH can be diagnosed if organized thrombi in main, lobar, segmental or

subsegmental pulmonary arteries can be visualized in a patient with precapillary pulmonary hypertension.

The final diagnosis of CTEPH is based on the presence of:
1. Symptomatic PH
2. mPAP ≥ 25 mmHg, PAOP ≤ 15 mmHg
3. With chronic/organized thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, or subsegmental level)
4. After at least three months of effective anticoagulation.

Table 1. Diagnostic criteria in CTEPH.

Hemodynamic failure and death occur in 20% of patients within 1 hour of acute pulmonary embolism (massive pulmonary embolism). Among the survivors, the natural evolution, in most cases, is the reabsorption of blood clots by local fibrinolysis with complete restoration of the pulmonary arterial bed. In some patients, reabsorption does not occur and the emboli evolves from an organized clot into fibrous tissue inside the pulmonary artery (PA). A latency period ("honeymoon") between the acute pulmonary embolus and the occurrence of symptoms of PH is common. The occurrence of dyspnoea after a symptom-free interval of several years is not due to recurrent emboli, but to development of local thrombosis and small vessels arteriopathy (Dartevelle et al., 2004).

Management decisions for patients with CTEPH should be made at an expert center based upon interdisciplinary discussion among internists, subspecialists, radiologists, and expert surgeons. Surgical pulmonary endarterectomy (PEA) is the therapy of choice for patients with CTEPH as it is a potentially curative treatment option, leading to a profound improvement in hemodynamics, functional class and survival (Wilkens et al., 2011; Pepke-Zaba, 2010). Selecting the candidates who will benefit from surgery is still a challenging task. Detailed pre-operative patient evaluation and selection, surgical technique and experience, and meticulous post-operative management are essential prerequisites for success after this intervention (Pepke-Zaba et al., 2011). Criteria for surgical suitability have been described but the decision to proceed with surgical intervention remains subjective (Jamieson et al., 2003; Condliffe et al., 2009; Skoro-Sajer et al., 2009; Freed et al., 2011). This is in agreement with a recent prospective CTEPH international registry, which showed a wide variation in non operability amongst participating countries (from 12 to 61%) (Mayer et al., 2011).

The aims of the present chapter are to evaluate the different preoperative diagnostic tools to assess the relative contribution of the extent of mechanical obstructions by organized thrombi and the distal small vessel disease. In addition, we analyze these tools to predict the hemodynamic improvement and early mortality after PEA.

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2. Pathogenesis of CTEPH

The pathogenesis of CTEPH is complex and is not fully understood. The most important pathobiological process is non-resolution of acute embolic thrombi which later undergo endothelialization and fibrosis, thus leading to narrowed or even obstructed pulmonary arteries.

Incomplete resolution occurs in a significant proportion of patients despite appropriate treatment, placing them at risk of developing CTEPH. Several studies have evaluated the resolution rate of acute PE and report divergent data. A meta-analysis of four prospective imaging studies found that more than 50% of patients with PE still have pulmonary perfusion defects 6 months after the primary diagnosis. A history of acute thromboembolism is not present in approximately 30% of patients presenting with CTEPH. Factors that appear to predispose to the development of CTEPH include recurrent embolic events, estimated systolic pulmonary pressure > 50 mmHg (on echocardiogram) at presentation of an acute pulmonary embolic event, and greater than 50% occlusion of the pulmonary vascular bed after a "single" embolic occurrence. Although CTEPH is commonly conceptualized as a thromboembolic disorder, neither coagulation cascade risk factors for venous thromboembolism nor defects in the fibrinolytic system have been identified in affected patients (Bonderman & Lang, 2012). For example, a deficiency of protein C, protein S, or antithrombin III, or the presence of factor V Leiden and factor II mutations, do not appear to be associated with a higher risk of CTEPH. Only the presence of a lupus anticoagulant (10%), elevated levels of antiphospholipid antibodies (20%), and elevated levels of factor VIII (39%), all well-known prothrombotic risk factors for venous thromboembolism, have been found in a significant proportion of CTEPH patients in a majority of studies (Wong et al., 2010). Other factors such as immunologic, inflammatory, or infectious mechanisms trigger pathological remodeling of major and small pulmonary vessels as a response to deranged thrombus resolution. Certain conditions are associated with an increased risk for CTEPH, including previous splenectomy, ventriculo-atrial shunt or pacemakers recipients with a history of device infection, and individuals with inflammatory bowel disease, myeloproliferative disorders, cancer, hypothyroidism treated with thyroid hormone replacement, non-0 blood types, and carriers of the fibrinogen Aα Thr312Ala polymorphism (Bonderman et al., 2009; Bonderman & Lang, 2012; Kim & Lang, 2012).

There are two main hypotheses explaining the pathologic process in CTEPH. In the classical *embolic hypothesis*, acute (single or recurrent) pulmonary emboli arising from sites of venous thrombosis are the initial event in developing CTEPH, but disease progression probably results from progressive vascular remodeling of the small vessels (Salisbury et al., 2011). The alternative *thrombotic hypothesis,* states that pulmonary vascular occlusions are caused by a primary arteriopathy and endothelial dysfunction and secondary *in situ* (local) thrombosis. Once vessel obliteration is sufficient to cause an increase in the pulmonary arterial pressure, self-perpetuated pulmonary vascular remodeling occurs and culminates in the development of PH (Jenkins et al., 2012b). This is supported by the fact that 1) unlike acute PE, there is no linear correlation between a compromised hemodynamic state and the mechanical obstruction of pulmonary

arteries; 2) PH progresses in the absence of recurrent thromboembolic events; and 3) PVR is still significantly higher in CTEPH patients than in acute PE patients with a similar percentage of vascular bed obstruction (Sacks et al., 2006).

Several lines of evidence suggest that increased pulmonary arterial pressures in CTEPH are caused by both vascular obstruction by organized thrombi tightly attached to the pulmonary arterial medial layer in the elastic PA, replacing the normal intima, and remodeling of small distal pulmonary arterioles in non-occluded areas (including plexiform lesions), a pulmonary arteriopathy indistinguishable from idiopathic pulmonary arterial hypertension (Lang & Klepetko, 2008; Auger et al., 2010). Therefore, as proposed by Moser and Braunwald, CTEPH is considered a 'dual' pulmonary vascular disorder, consisting of a large vessel vascular remodeling process of thrombus organization combined with a small vessel vascular disease secondary to redistribution of blood flow within the pulmonary vasculature causing the development of overflow and postobstructive vasculopathy (Moser & Braunwald, 1973; Hoeper et al., 2006) (Fig. 1).

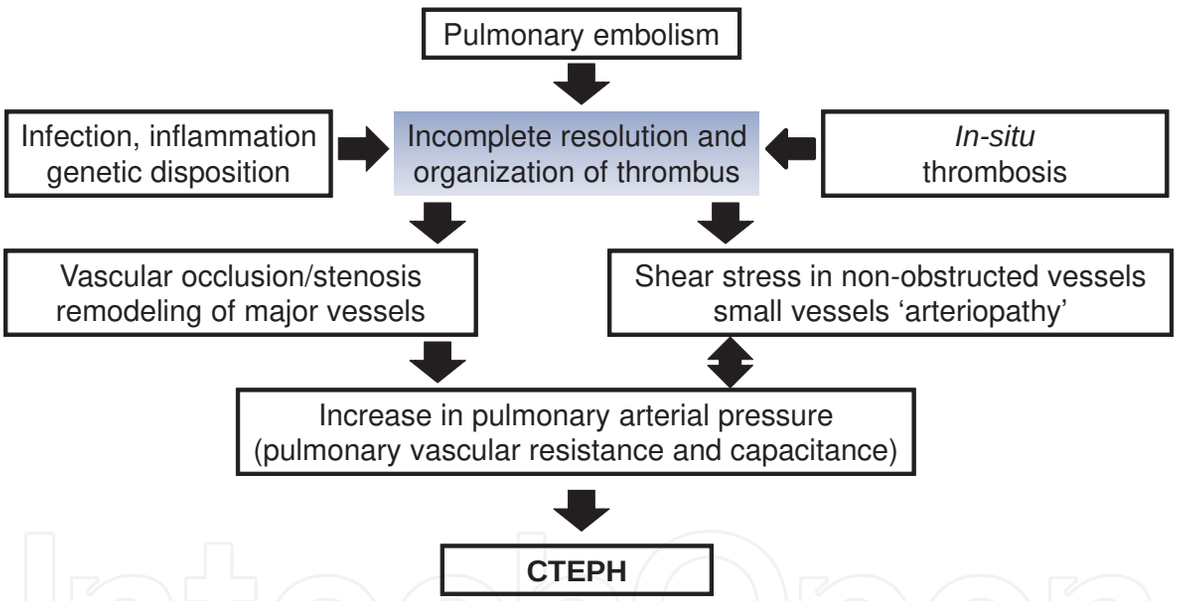

Figure 1. Current hypothesis for the pathogenesis of CTEPH.

Many fundamental questions persist about the risk factors and pathogenesis of CTEPH: 1) why many patients with PE do not develop CTEPH; 2) why many CTEPH patients have postoperative residual PH and; 3) whether patients with CTEPH who have poor postoperative outcome have cellular, molecular, and genetic abnormalities in the pulmonary vasculature similar to those in idiopathic PAH patients. Answering these questions poses a challenge for years ahead. However, a growing body of evidence suggests that in affected patients, minor o major thromboemboli do not resolve under conditions of concomitant inflammation, infection or malignancy, leading to fibrotic transformation of thrombus tissue (major vessel fibrosis) and small-vessel remodeling (Bonderman & Lang, 2012).

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3. Diagnostic evaluation

The diagnosis of CTEPH is often delayed because the onset of symptoms is insidious and the symptoms themselves are nonspecific. Like patients with other forms of PH, CTEPH patients suffer from symptoms of progressive right ventricular failure. At early stages, exertional dyspnoea, fatigue and rapid exhaustion are typical. At more advanced stages, signs and symptoms (resting dyspnoea and fluid retention) of overt right heart failure are predominant. In contrast to a progressive course of disease in PAH, CTEPH progresses episodically. Episodes of desaturation and deterioration occur, interrupting apparent health (so-called honeymoon period). Thus a high degree of suspicion is required to detect CTEPH. Symptoms are related to impaired cardiac output and RV failure due to obstruction of the PA by unresolved thrombus and associated vasculopathy (Hoeper et al., 2006). The 1-year untreated mortality rate in CTEPH ranges from 12-24% and is predicted by the PA pressure at diagnosis (Condliffe et al., 2008). In contrast to other subtypes of pre-capillary PH, CTEPH is amenable to surgery. With PEA, patient survival improves to 89% and 75% at 5 and 6 years, respectively. Therefore, the main goal of the diagnostic evaluation of patients with an established diagnosis of pre-capillary PH is to test for the presence of thrombotic obstructions in major PA and refer patients to specialized expert centres for this life-saving surgery (Ryan et al., 2011).

All patients with unexplained PH should be evaluated for the presence of CTEPH. Suspicion should be high when the patient presents with a history of previous venous thromboembolism. Patients who survive an episode of acute PE are treated with anticoagulants for at least 3 months as secondary prevention to avoid recurrence (Kearon et al., 2012). However, the optimal duration of anticoagulant therapy is still unclear. After a first episode of PE, three major problems need to be considered: the risk of recurrence when anticoagulation is stopped, the risk of bleeding when anticoagulation is continued, and the risk of CTEPH. CTEPH is a rare complication of PE but it is associated with severe morbidity and mortality. There is no generally accepted strategy of follow-up of acute PE survivors. This is related to the relatively low incidence of clinically relevant CTEPH after an embolic episode (1 to 4%) which is diagnosed early and adequately treated. Echocardiographic follow-up after discharge (usually 3-6 months) is certainly advisable in all survivors of acute PE who remain symptomatic or develop exercise limitation due to dyspnoea at any time during their hospital stay to determine whether or not PH has resolved (Torbicki, 2010). Few prospective data are available on the incidence of CTEPH after a first episode of PE (Table 2) (Poli et al., 2010).

The initial diagnosis of CTEPH is established by echocardiography and ventilation/perfusion (V/Q) scan. Evidence of PH on echocardiography associated with mismatched segmental perfusion defects on the V/Q scan provides enough information to warrant referral to a centre with expertise in PEA (Fig. 2). A V/Q lung scan is recommended to exclude CTEPH; it is more sensitive than pulmonary computed angiotomography (CT). A normal V/Q lung scan virtually excludes CTEPH, with few exceptions (Skoro-Sajer et al., 2004), while unmatched perfusion defects can also occur in other conditions, such as mediastinal fibrosis, pulmonary artery sarcoma, schistosomiasis, and non-thrombotic embolism. In clinical practice, an abnormal perfusion study alone is diagnostic for CTEPH, if pulmonary parenchymal disease is absent.

Author (year)	Patients (n)	Screening method for CTEPH	Diagnostic method for CTEPH	Median follow-up (months)	Incidence of CTEPH (%)
Pengo et al. (2004)	223	Transthoracic echocardiography	V/Q lung scan. Pulmonary angiography	94.3	3.8
Miniati et al. (2006)	320	Perfusion lung scanning, TTx echocardiography	Right heart catheterization	25.2	1.3
Becattini et al. (2006)	259	Transthoracic echocardiography	Perfusion lung scan. Pulmonary angiography	46	0.8
Dentali et al. (2009)	91	Transthoracic echocardiography	Perfusion lung scan. TTx echocardiography	12	8.8
Klok et al. (2010)	866	Transthoracic echocardiography	Perfusion lung scintigraphy and right heart catheterization	34	0.57

Table 2. Summary of studies examining the incidence of CTPH after pulmonary embolism

Recent data from a CTEPH registry showed that 98.7% of patients had abnormal perfusion scans and 19% had abnormal ventilation scans (Pepke-Zaba et al., 2011). Such findings should be followed by further diagnostic studies since V/Q scanning might underestimate the burden of vascular obstruction. Furthermore, although V/Q scanning is a functional technique, it has limited spatial resolution.

The confirmation of the diagnosis and the determination of the best therapeutic options rely on the hemodynamics and morphological data provided by invasive pulmonary angiography and computed tomography pulmonary angiography (Pepke-Zaba, 2010). CT pulmonary angiography can accurately define the nature and extent of disease in CTEPH, and provide multi-planar and three-dimensional reconstructions of the vascular tree. It may reveal organised thrombi lining the proximal pulmonary vessels, abrupt tapering or amputation of vessels or subtle intraluminal fibrous webs (Castañer, 2009). Enlarged bronchial artery collaterals may be also seen and are considered a good prognostic sign in operable patients. Other findings include pouch defects, bands, scarring and a mosaic perfusion pattern (Willemink et al., 2012).

Pulmonary angiography is still considered to be the gold standard diagnostic procedure for defining the extent and distribution of disease in CTEPH with a relatively good safety profile. Findings typically include dilatation of the pulmonary artery, vascular obstructions, vascular webs, post-obstructive dilatations and poorly perfused areas of the lung. Pulmonary angiography is often performed in conjunction with right heart catheterisation that provides accurate prognostic information (Jenkins et al., 2012b).

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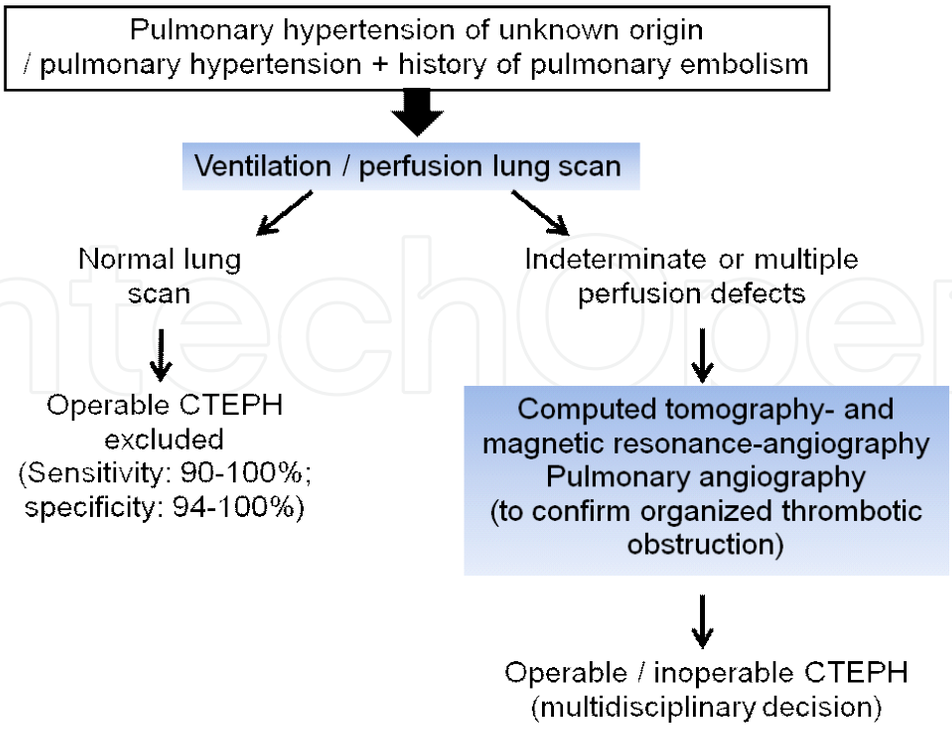

Figure 2. Diagnostic algorithm for CTEPH (modified from Hoeper M et al., 2006).

In summary, the reference standard for the diagnosis and determination of surgical accessibility remains combined right heart catheterization (to quantify the hemodynamic impairment) and conventional pulmonary angiography (to determine the extent and proximal location of chronic thromboembolic obstruction) (Fedullo et al., 2011). Vasodilator testing does not appear to be useful or necessary in determining operability, although preliminary data in a small cohort of patients suggest that preoperative vasodilator responsiveness (> 10.4% reduction in mPAP) is associated with an improved long-term hemodynamic outcome in patients who subsequently undergo PEA (Skoro-Sajer et al., 2009).

4. Surgical selection

Ultimately, the evaluation of patients with suspected CTEPH culminates in a decision regarding candidacy for PEA, since it is a realistic option for cure. Left untreated, CTEPH has a poor prognosis, proportional to the severity of PH. The 5-year survival is estimated to be approximately 30% if the mPA is greater than 30 mmHg and 10% if the Pm is greater than 50 mmHg (Riedel et al., 1982). When PH is established, the disease will progress despite adequate anticoagulation and eventually lead to right heart failure and death. Despite a strong rationale to administer vasodilator drugs in affected patients, current evidence from randomised controlled trials does not support the use of PAH-targeted pharmacotherapy. Still, compassionate use may be justified in cases considered inoperable, as a therapeutic bridge to PEA, in patients with persistent or recurrent PH after PEA, or when surgery is contra-indicated due

to comorbid conditions (Wilkens et al., 2011). Despite disappointing study results, a significant proportion of real world CTEPH patients are managed with vasodilator treatment. In a recent international prospective registry, 37.9% initiated at least one PAH-targeted therapy (28% of operable and 54% of inoperable patients) including prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors (Pepke-Zaba et al., 2011).

With experience and optimal patient selection, experienced centres may achieve a PEA operative mortality as low as of 4%. However, these results, are difficult to reproduce in different institutions, in part due to a long peri-operative and surgical management learning curve. Recent calculations based on delegates to the CTEPH association Cambridge meeting in June 2011 indicated that there were currently about 26 PEA centres worldwide, but many have a low volume of cases (Jenkins et al., 2012a). A centre can be considered to have sufficient expertise in this field if it performs at least 20 PEA operations per year with a mortality rate < 10% (Wilkens et al., 2011). If it were possible to organise treatment facilities, the ideal plan might be one centre geographically situated within a catchment area of 50 million individuals and performing > 75-100 cases per year (perhaps with a minimum of 50 cases per year) to achieve optimal outcomes. Exact prediction of operative risk and functional result is therefore, essential. PEA of major, lobar, and segmental pulmonary arterial branches is recognized as the standard treatment for CTEPH in most patients. The procedure involves the removal of fibrous obstructive tissue from the pulmonary arteries during circulatory arrest under deep hypothermia. The subsequent degree of relief of PH is variable, but in many cases may be total with restoration of pulmonary hemodynamics to normal or near normal (Wilkens et al., 2011). However, it has been recognized that the disorder may be accompanied by small-vessel pulmonary arteriopathy that is associated with perioperative death, postoperative persistent PH, or recurrence of disease. The decision whether PEA is feasible for specific patients must be made at a specialized centre. Operability is clearly a centre-specific assessment with large centre-to-centre variability. CTEPH is considered inoperable in 20-40% of cases, with the proportion of patients deemed inoperable differing between countries and specialist centres. The number of patients rejected from surgery due to distal obstructive disease decreases significantly with increasing expertise of the surgical centre (Mayer et al., 2011). In a contemporary registry, inoperability (37%) was due to surgical inaccessibility of the occlusions in almost half of patients, imbalance between PVR and the amount of accessible occlusions in 10%, PVR greater than 1500 dyn.s.cm^{-5} in 2.5%, advanced age in 2%, comorbidities in 13.4% and other reasons in 23% of patients. (Pepke-Zaba et al., 2011). The majority of patients selected for surgery are in New York Heart Association (NYHA) functional class III or IV and have dyspnea at low levels of exertion or at rest. Surgery may also be considered in patients in NYHA functional class II and with close to normal PVR at rest, if PVR increases significantly with exertion. In these patients, PEA will improve the ventilation-perfusion balance. Treatment of the disease at a relatively mild stage may, in time, help to minimise the development of secondary pulmonary arteriopathy. In 5-30% of patients with CTEPH, PEA may not be successful, because of residual PH (formal definition: mPAP ≥ 25 mmHg and PVR ≥ 240 dynes.s.cm^{-5}) Which is also the most common cause of perioperative mortality at many centres (Freed et al., 2011).

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Selecting the candidates who will benefit from surgery is still a challenging task, and currently there is no reliable preoperative risk stratification classification system. Some functional and hemodynamic variables have been associated with perioperative survival. A PVR > 1200 dyn.s.cm^{-5}, mPAP > 50 mmHg, transfer coefficient of the lung for carbon monoxide < 70% and a low fractional pulse pressure (fPp) have a higher likelihood of operative mortality, while higher CI and six minute walk distance, and a decrease of mPAP by at least 10% after administration of inhaled nitric oxide have been associated with better perioperative survival (Skoro-Sajer et al., 2009). Expert opinion consensus (Cambridge meeting, 2011) has concluded that major factors for any risk score system should include PVR, NYHA class, 6 min walk distance, presence of indwelling catheters, medical pretreatment and the amount of disease on imaging studies. The only risk factors that affected in-hospital mortality in the European CTEPH registry were presence of PH specific drug treatment, time from last PE, PVR value at diagnosis, 6 min walk distance at diagnosis, and PVR at discharge from the ICU (Pepke-Zaba et al., 2011).

At the time of operation, the major predictors of outcome after PEA are the endarterectomy specimens categorized according to location and property of thrombus and vessel wall pathology (Jamieson et al., 2003). Type I refers to clot burden in the proximal main and lobar branches with evidence of fresh or subacute thromboembolic material (about 25% of cases). Type II refers to more chronic and fibrotic disease in the proximal branches with no fresh clot (about 40% of cases). Patients with type III present with disease in the segmental and subsegmental branches only, making the procedure much more challenging, as the plane of the dissection has to be developed individually in each of the segmental and subsegmental branches. It may represent CTEPH with reabsorption of the proximal clot burden (about 30% of cases). Type IV refers to distal arteriolar vasculopathy with no visible thromboembolic disease (<5% of cases) (Thistlethwaite et al., 2002; Jamieson et al., 2003). Because this classification is based upon the operative determination of lesions as proximal or distal, it is not useful before PEA.

To improve outcomes after PEA, accurate predictors of operative success and surgical mortality should be established. The optimal characterization of the contribution of large vessel and small vessel disease to the increase in right ventricular afterload and severity of hemodynamic derangement is crucial for the preoperative assessment and outcome prediction of PEA. Different methods to analyze the various components contributing to pulmonary vascular afterload have been investigated. We will discuss first possible preoperative hemodynamic, angiographic, and echocardiographic predictors for PEA success, and finally we will review efforts to partition pulmonary vascular afterload in order to predict outcome after PEA.

4.1. Classical hemodynamic features

Among the criteria defining patient operability, the pre-operative assessment of the relative contribution between proximal and distal small-vessel disease is crucial. Both processes determine a wide spectrum increase of dynamic (steady and pulsatile) afterload in CTEPH patients. The extent of vascular obstruction and associated vasculopathy are the major determinants of PVR. However, a more proximal occlusive site causes greater PA stiffness and

an earlier and bigger wave reflection (pulsatile afterload) with a lower pulmonary vascular capacitance (Cp).

It is well known that high preoperative PVR is associated with higher short- and long-term postoperative mortality, especially in the absence of substantial chronic thromboembolic disease on the angiogram. This was supported by Dartevelle et al., and Condliffe et al. (Dartevelle et al., 2004; Condliffe et al., 2008) (Fig. 3). Dartevelle and colleagues reported that when the PVR was <900 dyn.s.cm^{-5}, the mortality rate was 4%, and increased to 10% in patients with PVR between 900-1200 dyn.s.cm^{-5}, and to 20% for PVR >1200 dyn.s.cm^{-5}. Condliffe and coworkers reported that total PVR (tPVR = input impedance) ≥900 dyn.s.cm^{-5} was associated with a PEA mortality above 10%, reaching 30% when total PVR was ≥1500 dyn.s.cm^{-5}. Patients with PVR in the range of 700 to 1100 dynes.sec.cm^{-5} are typically referred to surgical centres and many of these individuals will still benefit from surgical endarterectomy (Grignola, 2011). More detailed analysis revealed that the mortality is related to the degree of anatomic obstruction rather than to the resistance. Indeed, a patient with very high PVR and a low anatomic obstruction is at high risk, whereas one with the same PVR but with proximal anatomic obstruction presents with a low risk (Dartevelle et al., 2004).

Recent studies suggest that Cp, measured by stroke volume over pulse pressure (pPAP), may be a better prognostic marker of outcome than PVR in patients with idiopathic PAH. This observation may be of particular importance in CTEPH because the disease may predominantly affect the Cp rather than the resistance of the pulmonary vascular system (Naeije & Huez, 2007). De Perrot et al, have demonstrated that Cp is severely and rapidly affected in patients with CTEPH and does not always normalize three months after PEA despite a reduction in tPVR to <500 dynes.s.cm^{-5}. Cp improvement after PEA correlated with improvement in functional and exercise capacity, suggesting that Cp is an important parameter of the hemodynamic severity of CTEPH (De Perrot et al., 2011).

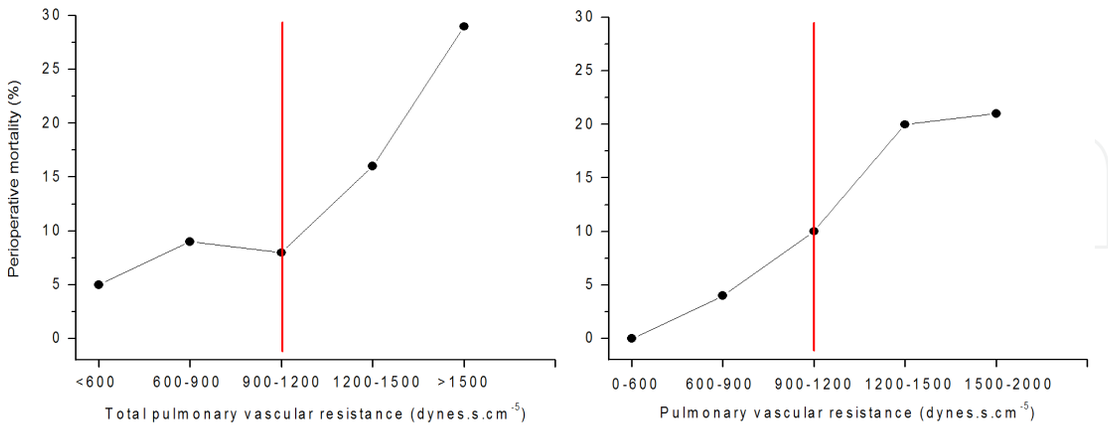

Figure 3. Perioperative mortality according to the pulmonary resistance (modified from Dartevelle et al, 2004 and Condliffe et al, 2009).

We also demonstrated that PEA improves long-term dynamic RV afterload. It is noteworthy that the postoperative increase of Cp is accompanied by a higher slope of the relationship

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between Cp and Pm with respect to preoperative values (Fig. 4). This observation allowed us to consider an improvement of the arterial cushioning function irrespective of mPAP decrease. However, some patients had persistent PH one year after PEA. These patients showed a significant lower improvement of Cp (2.0±0.8 vs. 3.9±1.1 ml/mmHg) and pPAP (38±11 vs. 18±6 mmHg), despite similar preoperative values (1.02±0.6 vs. 1.07±0.4 ml/mmHg and 58±15 vs. 58±16 mmHg). This lower increase in Cp at the expense of a reduced decrease in pPAP, associated with persistent PH could be related to a persistent impairment of the vessel wall viscoelastic properties secondary to vascular remodeling distal of the occluded major pulmonary artery and in vascular territories free of clot (Grignola et al., 2009a).

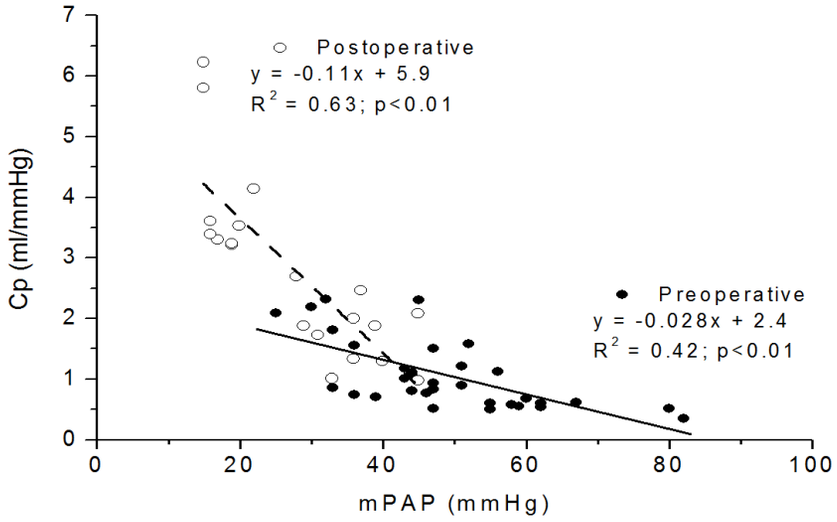

Figure 4. Correlation between mean PAP and Cp preoperative and one year post PEA.

In order to correlate functional hemodynamics with the anatomical lesions of CTEPH, we compared the multidetector pulmonary computed tomography angiography (MDCT) findings and the steady and pulsatile components of RV afterload in ten operable CTEPH patients (6 men; 50±11 years) who underwent PEA. Right-side catheterization and MDCT were performed preoperatively and one year after PEA. PVR and tPVR as steady components and Cp as the pulsatile component (viscoelastic properties of pulmonary arteries) were calculated. MDCT vascular (PA score), parenchymal (mosaic attenuation pattern score, MPP) and main PA diameter changes were evaluated. PA score was obtained by assigning every affected lobar or segmental PA n points (×2 if completely obstructed) according to the number of branches that originate from it (max score = 40). MPP was quantified (0-20) by giving 1 point to every parenchyma segment with a mosaic pattern (Ruiz-Cano et al., 2009). There was a significant improvement in the steady (PVR, tPVR) and pulsatile (Cp) components of the hemodynamic RV afterload after PEA along with a significant improvement of the parameters that assess the anatomical (PA score, PA diameter) and functional (MPP) changes in the lungs (Table 3).

	mPAP (mmHg)	PVR (dyn.s.cm^{-5})	tPVR (dyn.s.cm^{-5})	Cp (ml/mmHg)	PA diameter (mm)	PA score (%)	MPP
Preoperative	47±13	683±121	874±198	1.1±0.4	41±4.6	44±19	9.2±5
Postoperative	26±10§	323±210*	437±203*	2.6±1.1*	35±4.6§	24±18§	3.3±4*

Mean ± SD. *p<0.01; §p<0.001

Table 3. Preoperative and postoperative pulmonary hemodynamic (functional) and computed angio-tomography (anatomical) data.

Linear regression analysis demonstrated a significant correlation between changes in Cp and PA diameter (r = -0.63), between PVR and PA score (r = 0.58) and between PVR and MPP score (r = 0.6) (Fig. 5).

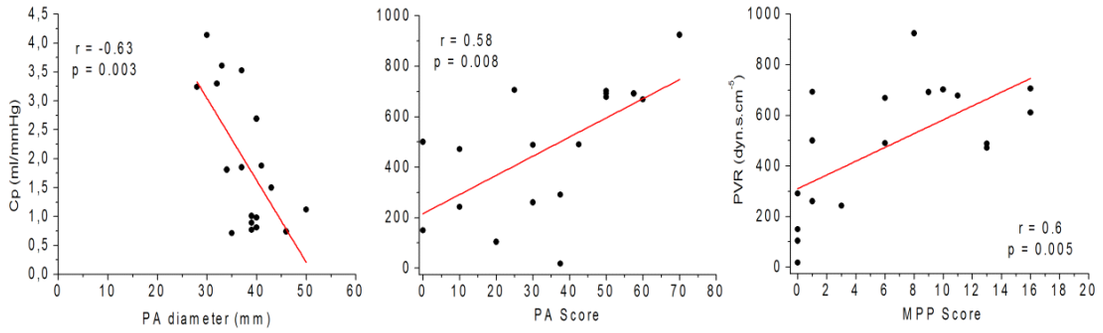

Figure 5. Correlations between pulmonary capacitance (Cp) and pulmonary arterial (PA) diameter and pulmonary vascular resistance (PVR) with PA score and mosaic attenuation pattern (MPP) score.

Further studies will be necessary to demonstrate that, vascular and parenchymal radiologic changes after PEA reflect the modification of the steady and pulsatile components of RV afterload.

Nakayama et al. showed that fPp (pPAP/mPAP) was useful for the differential diagnosis between CTEPH and idiopathic PAH (Nakayama et al., 1997). Accordingly, Tanabe et al. reported that fPp was higher in operable CTEPH than in idiopathic PAH and that it might be useful in predicting for the outcome of surgery, especially in patients with severe hemodynamic impairment (Tanabe et al., 2001). They proposed that both, increased characteristic impedance of PA and early and increased reflection wave could accentuate pPAP and fPp in CTEPH. Therefore, the assessment of fPp as well as the angiographic findings could be useful to determine the surgical accessibility to thrombi: high PVR with low fPp might be related to secondary PH change and/or distal thrombi, resulting in high operative mortality.

4.2. Echocardiographic findings

Patients with PH present with a pulmonary pressure wave with a huge pulse pressure, and a flow wave with a shortened time to peak velocity and a late or midsystolic deceleration

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(pulmonary flow systolic notch) secondary to systolic partial closure of the pulmonary valve. This midsystolic notching is caused by the negative effect of an early returned reflected wave on the forward wave. Wave reflection also explains a shorter time to notching on pulmonary arterial flow waves in embolic PH when compared with PAH. Clinical and experimental studies have provided evidence that an early notch signifies a proximal obstruction to pulmonary flow, whereas a late notch suggests that the obstruction site is more distal. All these changes are largely determined by wave reflections (Naeije & Huez, 2007). While a proximal site of reflection is an obvious determinant for an earlier return of a reflected wave, this can also be caused by an increased pulse wave velocity (PWV). PA wall distension with decreased compliance as a consequence of high pressures increases PWV. This explains why we also see a midsystolic deceleration of pulmonary flow in patients with severe PAH, in spite of the peripheral site of resistance in the PA tree and wave reflection. Recently, Hardziyenka et al. proposed that the so-called pulmonary flow systolic notch may distinguish proximally located obstruction in the pulmonary vascular bed. They defined a time to notching expressed as a notch ratio (NR), or the ratio of time from the onset of flow to maximum flow deceleration to time from maximum flow deceleration to end of flow (Fig. 6) (Hardziyenka et al., 2007).

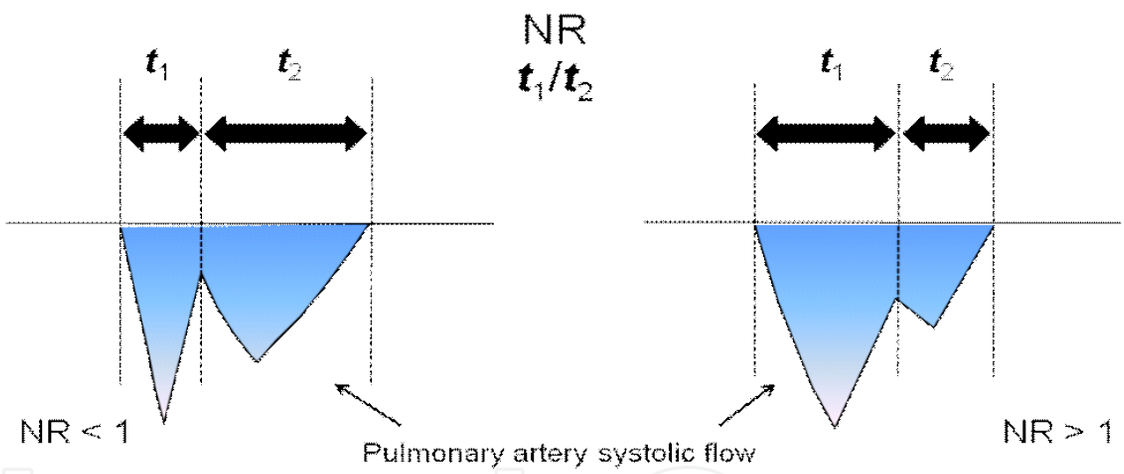

Figure 6. Schematic illustration of the method to calculate pulmonary flow systolic notch ratio (NR).

The timing of such a notch within the cardiac cycle is an excellent predictor of peri-operative mortality and functional improvement after PEA, with a lower mortality risk in patients with NR < 1. This optimal cutoff point (NR = 1) showed a sensitivity of 100% but a relative low specificity of 77% (confidence interval, 65-88%). Unfortunately, a preoperative notch was not observed in up to 12% of patients (Hardziyenka et al., 2007).

4.3. Angiographic assessment

As we mentioned before, the anatomic classification into proximal and distal lesions proposed by Jamieson et al is based on intraoperative findings and thus not useful to facilitate a decision before PEA. Also, interest should be focused on which patients with peripheral disease may

still benefit from surgical intervention. Thus, the need for more detailed interpretation of angiographic findings of the peripheral pulmonary vascular tree appears evident. The typical angiographic findings of CTEPH are characterized as irregular intimal surface, vascular webs or bandlike narrowings, pouch-like termination of segmental branches, abrupt and angular narrowing of the central vessels, and obstruction of pulmonary vessels (Castañer, 2009). Recently, Kunihara et al, proposed a quantitative analysis of the pulmonary angiogram in conjunction with hemodynamic data to predict mortality and hemodynamic improvements after PEA (Kunihara et al., 2010). The proximal 2 cm of a segmental artery was classified into three categories: A, occlusion; B, pouch or membrane but preserved distal perfusion or C, delayed perfusion. They showed that the extent of angiographically involved segments played an important role in conjunction with preoperative hemodynamic severity of the disease in estimating postoperative outcome. Above all, segments with obstruction but preserved peripheral perfusion (type B lesion) seemed to have a higher impact on postoperative improvement after PEA than occluded segments (Kunihara et al., 2010). These novel findings may greatly help to identify suitable candidates with CTEPH for PEA.

4.4. Composite hemodynamic method of pulsatile and steady right ventricular afterload assessment

An approach to identify distal vasculopathy in CTEPH is the analysis of pressure decay curves after pulmonary arterial occlusion (between the moment of occlusion and the pulmonary artery occluded pressure, PAOP). Such curves consist of an initial fast component, which corresponds to the reduction of flow through arterial resistance, and a subsequent lower component, which corresponds to the emptying of compliant capillaries through a venous resistance. This biexponential fitting of the pressure decay curve allows identification of an inflection point (Poccl), from which one calculates an upstream resistance (Rup), essentially determined by the resistive properties of the large pulmonary arteries, and a downstream resistance determined by the cumulated resistance of small arterioles, capillaries and venules. Rup is calculated as follows: Rup (%) = 100×(mPAP-Poccl)/(mPAP-PAOP). A study on a small series of CTEPH patients referred for PEA showed excellent predictive values of residual PH and associated mortality by a relative increase in Rup (Kim et al., 2004). Patients with CTEPH and Rup value < 60% appear to be at the greatest risk for significant distal, small-vessel disease.

Some concerns can be made about the validity of this technique: the size of vessel that partitioning segregates, and the reliability of a single flow-directed measurement in a heterogeneous disease. To test the hypothesis that the occlusion technique is able to discriminate large vessel organized thrombus from distal vasculopathy, Toshner et al. performed occlusion pressures on patients with operable CTEPH, distal inoperable CTEPH and post-PEA residual CTEPH (Toshner et al., 2012). They also undertook measurements in patients with idiopathic or connective tissue associated PAH, where distal vasculopathy is traditionally accepted as the predominant process. The authors found that Rup measured by the occlusion technique is increased in operable predominantly proximal CTEPH when compared with inoperable CTEPH and idiopathic PAH. It is noteworthy they determined a higher Rup cutoff value compared to Kim et al: 79% (sensitivity 100%, specificity 57%) versus 60% (sensitivity and

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specificity 100%). They proposed that the occlusion technique would not interrogate the correct range of vessel caliber and would mislabel a significant portion of resistance in these small vessels as upstream. They did not explain the differences in the Rup values, including the values of the two patients who died postoperatively (68 and 73%). This is supported by the fact that the idiopathic PAH and inoperable CTEPH cohorts had a much higher Rup than would be expected if resistance had been accurately partitioned into clinically relevant small and large vessels (Toshner et al., 2012). Finally, they proposed multiple measurements using a wire directed catheter in conjunction with the flow-directed one, in order to provide additional information on disease heterogeneity in CTEPH.

Surgical operability depends on surgical accessibility rather than the extent of small vessel arteriopathy. Surgical accessibility depends on the presence of distal obstructions which are defined by the surgeon's technical ability and experience. The best surgical results are achieved with complete endarterectomy and early postoperative reduction of PVR to < 500 dynes.s.cm^{-5} (6.25 wood units). A more proximal occlusive site of the pulmonary circulation causes a higher PA stiffness and an earlier and greater wave reflection which increases systolic PAP (sPAP) and especially decreases diastolic PAP (dPAP), so called "ventricularization" of the PAP curve, with non-significant changes in mPAP and PAOP (Wittine & Auger, 2010). Cp a component of pulsatile afterload, is inversely proportional to pPAP (pPAP = sPAP-dPAP). Considering that mPAP = (sPAP+2dPAP)/3, then mPAP-dPAP is proportional to 1/Cp. Furthermore, the difference between mPAP and PAOP (transpulmonary gradient) is proportional to PVR (steady component of afterload).

We studied Zup, a novel hemodynamic index that is calculated by (mPAP-dPAP) x100/(mPAP-PAOP) (Fig. 7). mPAP is the time-averaged PA pressure throughout cardiac cycle length and it is accurately described by cardiac output, tPVR and right atrial pressure. Previous studies have established a link between the steady and pulsatile component of PA pressure by estimating mPAP from sPAP and dPAP ('two-pressure model') (Kind et al., 2010; Saouti et al., 2010). The geometric mean of sPAP and dPAP was the most precise estimate of mPAP ($mPAP^2 = sPAP \times dPAP$). sPAP and dPAP mainly depend on tPVR and PA stiffness and wave reflection. Increasing tPVR causes both sPAP and dPAP to increase while increasing PA stiffness and wave reflection generate a wider pPAP without significant mPAP change. The negative contribution of arterial stiffness to sPAP and dPAP may have been canceled when one multiplies sPAP by dPAP, thus unmasking the remaining influence of tPVR (Chemla et al, 2009). The extent of vascular obstruction and associated vasculopathy are the major determinants of mPAP. A more proximal occlusive site by the fibrotic organized thromboembolic material incorporated into the native vascular intima causes a higher PA stiffness. Stiffening of proximal PAs could increase characteristic impedance and wave reflection (higher upstream afterload), increasing tPVR but with a lower dPAP, a faster pressure decay profile and Zup increase. The balance between mPAP and dPAP provides a rapid tool to describe the functional afterload status of CTEPH patient, since their absolute contributions on Zup value are higher than PAOP.

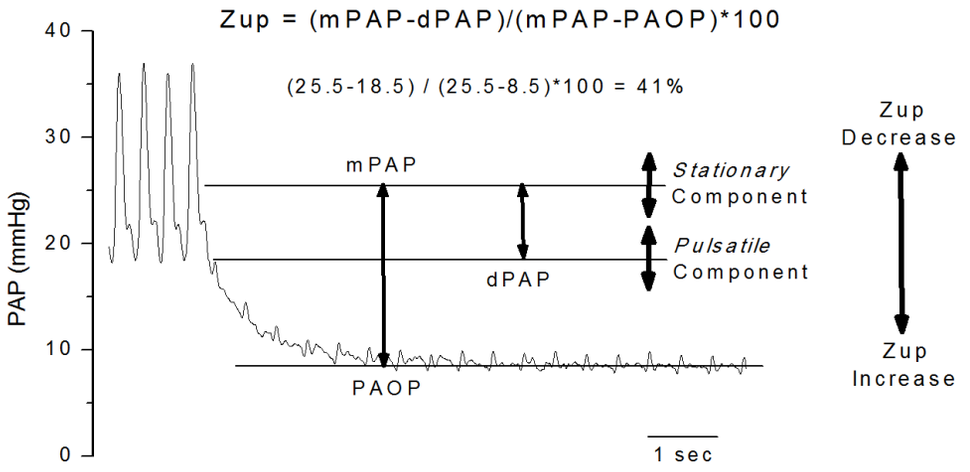

Figure 7. Example of the pulmonary artery decay curve showing the calculus of Zup index (mPAP and dPAP: mean and diastolic pulmonary arterial pressure, respectively; PAOP: pulmonary arterial occluded pressure).

Unlike the partition method described by Kim et al, (Kim et al., 2004) Zup index can be obtained directly from hemodynamic data without assumptions or fitting, and is affected by the extent and localization of anatomic obstruction, vascular remodeling and microvascular disease, setting a wide spectrum of dynamic afterload (steady and pulsatile components) (Ruiz-Cano et al., 2012).

Zup is inversely proportional to Cp, heart rate and PVR and it evaluates pulsatile and steady afterload components simultaneously (Fig. 7). A more important 'ventricularization' of PA pressure curve due to a higher proximal component of the afterload due to the lower dPAP and faster pressure decay profile would determine a higher Zup. Inversely, we hypothesized that preoperative Zup might be low in patients with CTEPH with inaccessible distal thrombi and/or secondary pulmonary hypertensive changes, resulting in a high operative mortality (Ruiz-Cano et al., 2010, 2012).

Total in-hospital mortality was 9.8% (6/61). According to the univariate analysis, lower preoperative Zup (OR 0.90, 95%CI 0.84–0.98, p=0.04) and CI (OR 0.004, 95%CI 0.001–0.67, p=0.03), and higher preoperative PVR (OR 1.3, 95%CI 1.08–1.64, p=0.007) had a significant association with early mortality after PEA. A low Zup value (cut-off point < 47%) predicted mortality after PEA with a sensitivity of 100% and a specificity of 78% [area under the curve (AUC)=0.86, p=0.006]. The AUC of ROC curves obtained for Zup and PVR showed no differences (p=0.4). When we analyzed the subgroup of 23 patients with higher preoperative PVR (>9 wood units, median of the cohort) Zup was a mortality risk predictor with sensitivity of 100% and specificity of 86% [AUC=0.86, p=0.013] for a cut-off point of 46.5%. On the other hand, PVR lost its capacity to predict mortality in this group [AUC=0.66, p=0.25]. Interestingly, in the population with the highest mortality risk according to the preoperative PVR (>9 wood units), Zup <46.5% could identify non-survivors more accurately with a sensitivity of 100% and a specificity of 86%. In this population, Zup >46.5% identified 7 patients who had successfully PEA operations even though they were very high risk based upon their pre-operative PVR (>15 wood units). The PVR and Cp of these patients were similar to the values of the patients who died. Thus, Zup might be an index

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of PA pressure 'ventricularization', that distinguishes proximal from distal disease in patients with the same pulmonary vascular RC constant. Concomitantly, PVR lost its ability to predict mortality in this population (Ruiz-Cano et al., 2012).

Finally, while it is likely that the functional adaptation of the pulmonary circulation to disease processes is generally monotonous (any change in PVR is associated with proportional changes in compliance and wave reflections), CTEPH is characterized by more predominant wave reflection as a cause of a disproportionate increase of sPAP and decrease of dPAP. We analyzed the behavior of Zup, fPp and Cp between idiopathic PAH and operable CTEPH in age and sex-matched cohort of patients with isobaric steady component of RV load and its effect on RV remodeling (Table 4) (Grignola et al., 2009b).

CTEPH patients were 53±14 years old and 58% were men, and IPAH patients were 56±5 years and 57% were men. Cardiac index and heart rate were similar in both groups. Isobaric steady component analysis permitted differentiation of the pulsatile component of IPAH and CTEPH cohorts, Table 4. The dynamic RV afterload in CTEPH patients was higher than in the IPAH patients. The lower Cp and fPp of operable CTEPH would be related to different vascular wall remodeling (thrombus organization and small vessel arteriopathy) and would explain the higher RV diastolic diameter (RVDd). The lower Zup in IPAH patients is in agreement with a more homogeneous distribution of the RV afterload.

	sPAP (mmHg)	dPAP (mmHg)	mPAP (mmHg)	pPAP (mmHg)	PVR (dyn.s.cm^{-5})	Cp (ml/mmHg)	fPp	Zup (%)	RVDd (mm)
CTEPH (n = 40)	83±21	27±8	48±12	56±18	744±350	1.17±0.6	1.19±0.2	57±15	49±7
IPAH (n = 44)	73±15*	32±10*	47±10	42±10§	760±370	1.5±0.7*	0.9±0.2§	43±15§	42±9§

Mean ± SD. *p<0.05; §p<0.01. (sPAP, dPAP, mPAP, pPAP: systolic, diastolic, mean and pulse pulmonary arterial pressure, respectively; PVR: pulmonary vascular resistance; Cp: pulmonary vascular capacitance; fPp: fractional pulse pressure; RVDd: right ventricle diastolic diameter).

Table 4. Steady (PVR) and pulsatile (Cp) afterload, hemodynamic data, Zup and RV diastolic diameter in idiopathic PAH and CTEPH patients.

To understand the hemodynamics of the pulmonary circulation in PAH, PVR and Cp have been measured. Lankhaar et al. showed that resistance and compliance in the pulmonary circulation are inversely related by a hyperbolic function (Lankhaar et al., 2008). They also showed, that the product, *i.e.* the RC-time, in the pulmonary circulation remains the same in healthy individuals and in patients with PAH. Clinical consequences of the constant RC-time are that CO can be increased more when a resistance decrease is accompanied by a compliance increase, than when resistance alone decreases with only a very small increase in compliance. Even when they included ten CTEPH patients in the analysis, six of them had inoperable CTEPH and they had different PVR.

Figure 8 shows the RC curve of our IPAH and CTEPH patients. The data show an inverse Cp-PVR relationship which reflects the coupling of these two components of RV afterload. However, the CTEPH curve is displaced down and leftward with respect to the IPAH curve. For patients with the same PVR (isobaric steady afterload), preoperative operable CTEPH showed a lower Cp, reflecting a higher pulsatile afterload component. These results disagree with the findings of Lankhaar et al and might expose a different RC coupling in operable CTEPH (Grignola et al., 2009b).

Finally, we analyzed Zup in operable and inoperable CTEPH patients (Ruiz-Cano et al., 2010). Among operable patients with good outcomes one year after PEA, lower Zup is predictive of persistent PH (PVR ≥ 240 dyn.s.cm^{-5}), which is associated with a lower improvement of Cp and pPAP. The lower Zup in inoperable CTEPH patients is in agreement with a more diffuse distribution of RV afterload seen in IPAH and would be related to different vascular wall remodeling (thrombus organization and small vessel arteriopathy).

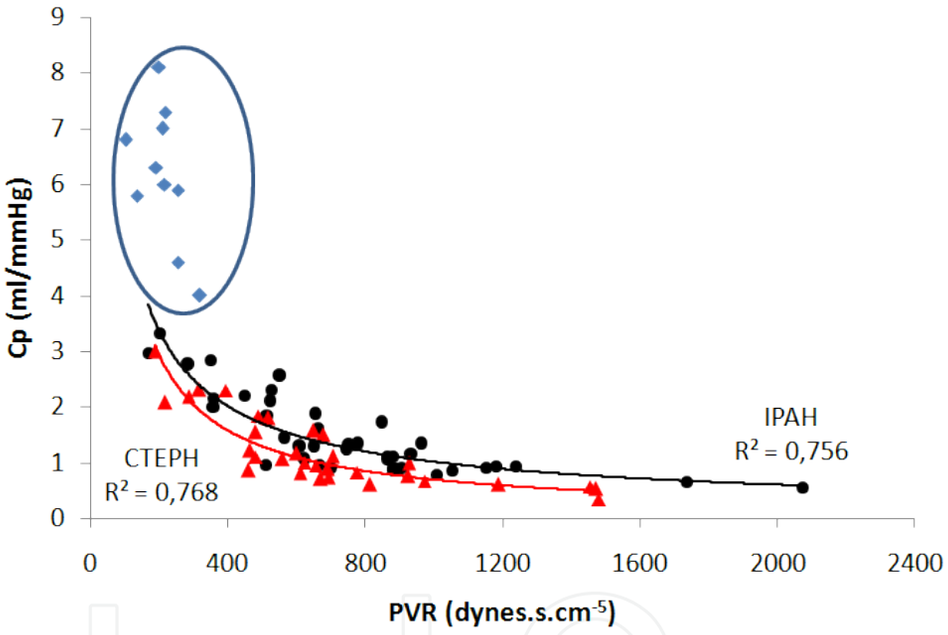

Figure 8. PVR-Cp (pulmonary vascular resistance-capacitance) plot of CTEPH and idiopathic PAH patients (fill diamonds represent ten normal subject without pulmonary hypertension) (Grignola et al., 2009b).

5. Conclusions

Substantial advances have occurred over the past quarter century in the diagnostic and therapeutic approach to CTEPH. In terms of management, surgery (PEA) is likely to remain the mainstay of therapy for patients with CTEPH. Further studies are necessary to obtain reliable long-term data on the effect of medical therapies in patients with CTEPH. It would be beneficial to have more objective definitions of what is considered to be operable and inoper-

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able disease based on anatomic and functional variables. At the present time, this is a purely subjective determination made at centres with varying levels of experience, surgical expertise, and postoperative hemodynamic expectations. Recent data would suggest that the risk of some element of persistent postoperative PH should not serve as a contraindication to PEA (Freed et al., 2011). However, criteria have not been defined to determine when the risk of PEA outweighs its potential benefit. This determination requires the development of diagnostic techniques or algorithms capable of more objectively partitioning the central, surgically correctable component of the PVR from the peripheral component. The relative contribution of large vessel and small distal vessel disease to the elevation of RV afterload remains part of the art of the PEA evaluation. We propose a novel hemodynamic index, Zup, that considers both steady (PVR) and pulsatile (Cp) components of the RV afterload simultaneously and would predict mortality shortly after PEA as accurately as PVR for the global population with CTEPH who are suitable for surgery. In patients with higher PVR, Zup < 47% provided better identification of the population with the highest risk for early postoperative mortality. Zup could therefore be a complementary tool to improve risk assessment for PEA in patients with CTEPH. Larger and prospective studies will be necessary to validate the different predictors that have been presented as indexes to evaluate operative risk in CTEPH patients.

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