Clinical worsening in Chronic Thromboembolic Pulmonary Hypertension

BASTIAAN E. SCHÖLZEL

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'To the world you might
be one person, but to
one person you might be
the world.'

— Voor Shaula, Thijn en Jeppe

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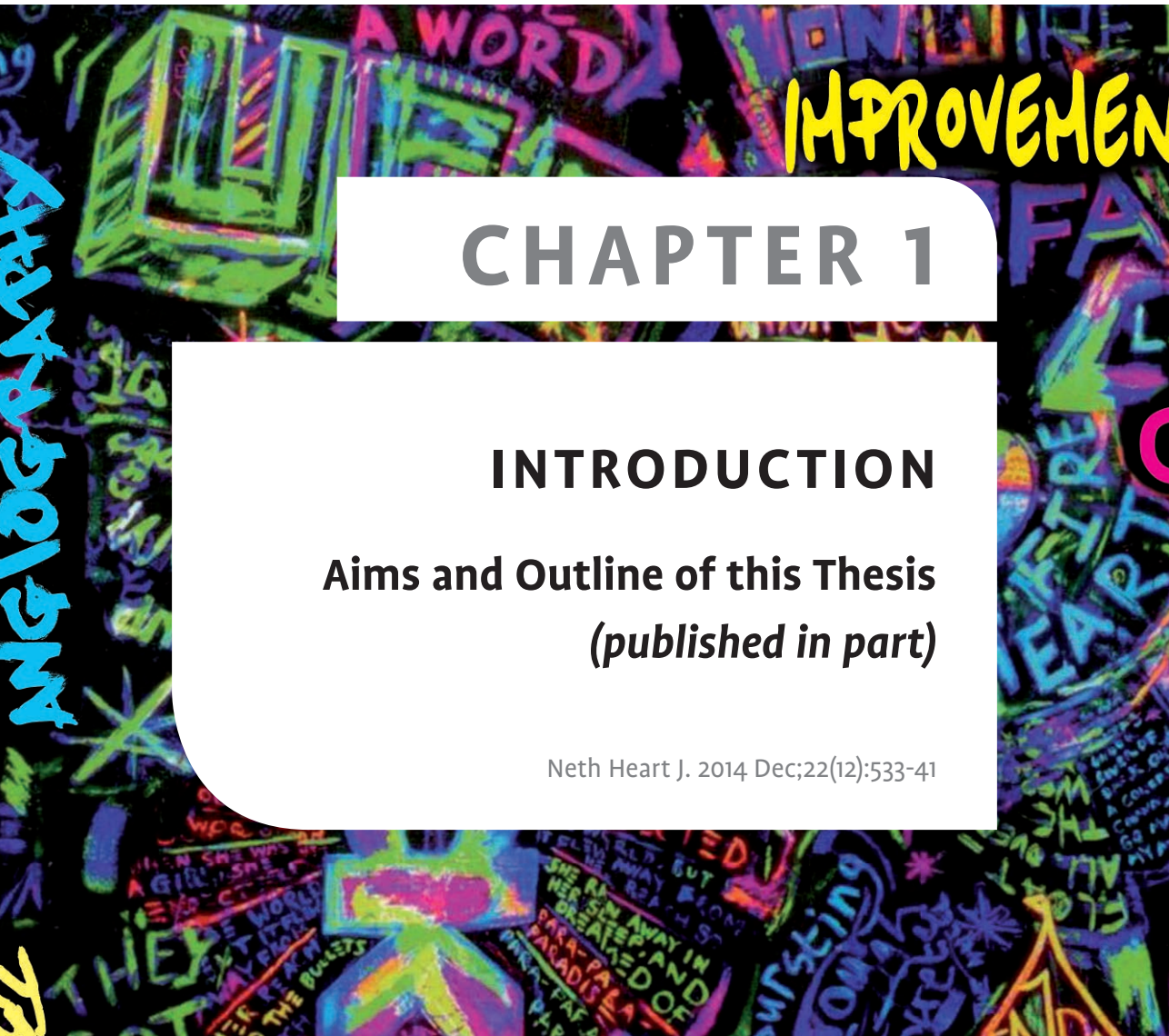
WIM J. MORSHUIS, MARTIJN C. POST



CHAPTER 1

INTRODUCTION

Aims and Outline of this Thesis *(published in part)*

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INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) results from obstruction of the pulmonary vascular bed by non-resolving thromboemboli.[1] Although anatomic resolution of acute embolism is often incomplete, sufficient resolution occurs in the majority of patients to restore normal pulmonary hemodynamics associated with return to a pre-embolism functional status.[2] Several prospective studies have reported that between 0.6% and 4.6% of acute pulmonary embolic survivors will develop symptomatic CTEPH.[3,4] However, previous reports have shown that 42% to 63% of patients with the established diagnosis of chronic thromboembolic disease have no previously documented acute venous thromboembolism.[5,6]

CTEPH is defined by the following observations after at least 3 months of effective anticoagulation: mean pulmonary artery pressure (PAP) >25 mmHg with a pulmonary capillary wedge pressure ≤15 mmHg and perfusion defects detected by appropriate imaging techniques.[7]

The incidence of acute pulmonary embolism (PE) is approximately 1:1000[8], and yearly diagnosed in about 16.000 patients in the Netherlands. The estimated cumulative incidence of CTEPH in the Netherlands is 0.5-1.5%.[3]

Historical data indicate, that if left untreated, CTEPH is associated with a poor five-year survival, ranging from 10% to 40% depending on pulmonary hemodynamics.[9] Pulmonary endarterectomy (PEA) is the procedure of choice in symptomatic patients with surgically accessible CTEPH.[1] After surgery, most patients experience a substantial hemodynamic improvement, which is associated with improvements in functional status and long-term survival.[1,10] The 30-days mortality rate after PEA ranges from less than 5% in the most experienced centres to 10% in others.[11,12] However, in 30-50% of patients a PEA is not possible (inoperable CTEPH) due to either distal pulmonary vascular obstruction or significant co-morbidities thought to be associated with unacceptably high risk.[13]

Furthermore, approximately 10% to 15% of operated patients suffer from persistent or recurrent pulmonary hypertension (PH).[14] For patients who are inoperable or suffering from residual pulmonary hypertension after PEA, treatment with PH-specific medication is widely available. Therefore, careful selection of the most appropriate treatment of CTEPH patients should be done in specialized centres.

PATHOPHYSIOLOGY AND RISK FACTORS OF CTEPH

Unlike pulmonary arterial hypertension (PAH) where vascular remodelling tends to occur in small pulmonary arteries, CTEPH is associated with prominent obstructions in larger vessels, combined with small vessel disease. The pathophysiology of CTEPH remains unclear. The embolic hypothesis suggests that CTEPH is the result of single or recurrent PE arising from sites of venous thrombosis.[15] The European CTEPH Registry has recently revealed that previous PE is detected in 74.8% of all CTEPH patients while previous deep venous thrombosis (DVT) is documented in 56.1% of patients.[16] Recently, a prior history of splenectomy, ventriculo-atrial shunt for the treatment of hydrocephalus, thyroid replacement therapy, a history of malignancy and chronic inflammatory disorders such as osteomyelitis and inflammatory bowel disease, were associated with an increased risk of CTEPH.[17] Regarding details of the acute embolic event, systolic PAP greater than 50 mmHg at the time of diagnosis of acute embolism or at hospital discharge, previous PE, and a larger degree of pulmonary vascular obstruction at the time of acute PE diagnosis have been identified as risk factors for CTEPH.[4,18,19]

According to current knowledge, CTEPH emerges as a "dual" pulmonary vascular disorder with thrombosis inducing major vessel vascular remodelling, combined with pulmonary arteriopathy (small pulmonary vessel disease) as a consequence of non-occluded area over-perfusion.[5,20,21] Lung biopsy findings obtained at the time of PEA surgery demonstrate pathohistological changes in the microvasculature, similar to those seen in other forms of small-vessel PH, distal to both obstructed and non-obstructed central arteries.[20] The arteriopathy is considered to be the cause of the hemodynamic and symptomatic decline over time by contributing to the elevated pulmonary vascular resistance (PVR), thereby adversely affecting cardiac function and eventually leading to the progressive hemodynamic instability and increased mortality observed in patients with CTEPH.[9]

Endothelin-1 (ET-1) is a potent endogenous vasoconstrictor and is considered to contribute to the increase in vascular tone and pulmonary vascular remodelling associated with PH.[22] It was demonstrated that endothelial signaling pathway components are upregulated in CTEPH.[23] Taken this into account, these observations indicate that ET-1 may play a role in the development of the secondary arteriopathy observed in CTEPH. Moreover, ET-1 levels were shown to significantly decrease after successful PEA.[24] Therefore, ET-1 has been considered a potential target for medical therapy in selected CTEPH patients.[25]

CLINICAL MANIFESTATIONS AND DIAGNOSTIC WORK-UP

Early in the course of the disease, the clinical presentation of CTEPH can be subtle, which may contribute to a delay in diagnosis (honeymoon period). The common complaint in patients with CTEPH is exertional dyspnea, the result of increased dead space ventilation as well as a limitation in cardiac output response to increased physiologic demand.[26] Progression of the disease and further limitation of cardiac output may lead to signs of right heart failure, exertion-related presyncope, and chest pain. The latter may be due to decreased right ventricular coronary flow related to increased right ventricular systolic pressure and mass.[27]

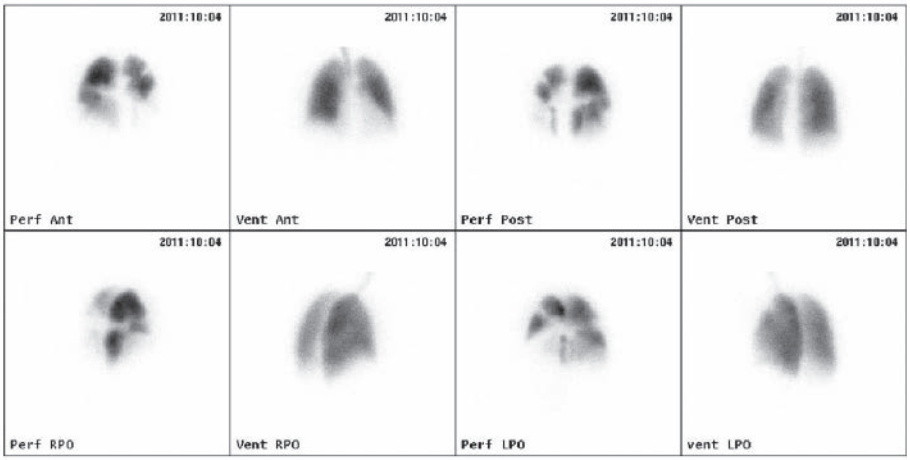
Physical examination findings early in the course of the disease may be entirely unremarkable, thereby contributing to diagnostic delay. As disease progression occurs, findings consistent with PH develop: prominence of the right ventricular impulse, a closely split second heart sound with accentuation of its pulmonic component, a right ventricular S4 gallop, and varying degrees of tricuspid regurgitation. With the onset of right ventricular failure, jugular venous distension, peripheral edema, hepatomegaly, ascites, a right-sided S3, and a widened split of the second heart sound may be present.

Symptoms of disease are nonspecific and often attributed to other cardio-respiratory disorders, deconditioning, or even psychogenic disorders. Recent registry data showed a median time-interval of 14.1 months between first symptoms and CTEPH diagnosis.[16] Indeed, CTEPH is associated with a poor prognosis unless an early diagnosis and treatment is made.[9]

Once the possibility of a pulmonary vascular disease has been considered, the diagnostic approach has three goals: first, to establish the presence and extent of PH, second, to determine its cause, and third to evaluate the therapeutic options.

Imaging studies are fundamental to establish the diagnosis and operability of CTEPH. Transthoracic echocardiography is sensitive for the detection of PH and right ventricular dysfunction, but is not specific for the diagnosis of CTEPH. Common echocardiographic findings include right ventricular hypertrophy, dilatation and impaired right ventricular systolic function. Furthermore, right atrial enlargement, right ventricular pressure overload and tricuspid regurgitation can be found. However, echocardiography is not able to distinguish acute from sub-acute and chronic PE.[29]

FIGURE 1. **Lung perfusion scan in CTEPH, showing homogeneous ventilation and segmental defects in the perfusion scan**

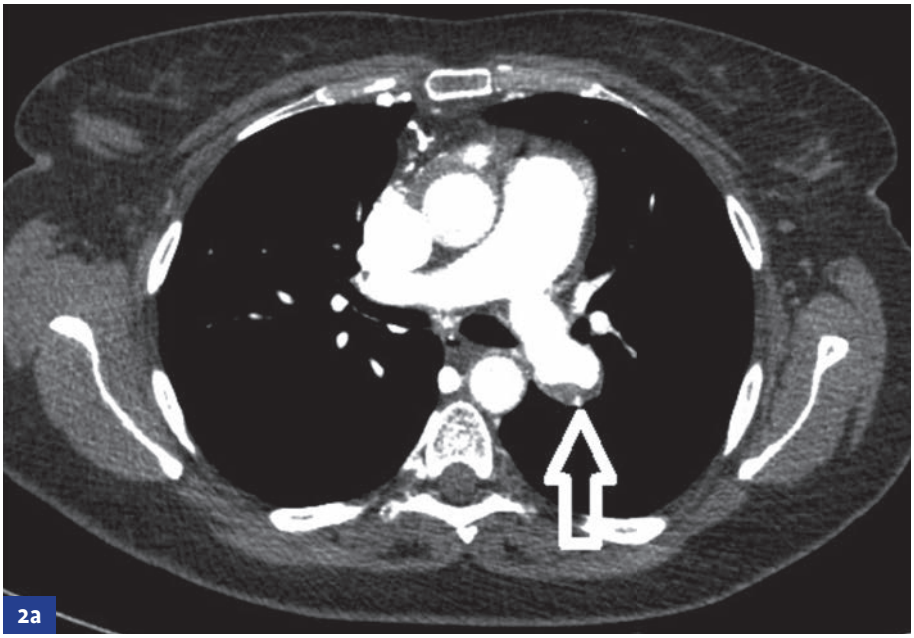


Previous echocardiographic studies in CTEPH patients showed the good effect of PEA on right-sided echocardiographic parameters.[30-32] In patients with idiopathic pulmonary hypertension, echocardiographic parameters like pericardial effusion, right atrial enlargement and septal displacement have been shown to be predictors of adverse outcome.[33] Hardziyenka et al. found TAPSE to be a pre-operative determinant of in-hospital mortality following PEA, although the pulmonary flow systolic notch appeared to be the strongest determinant.[32]

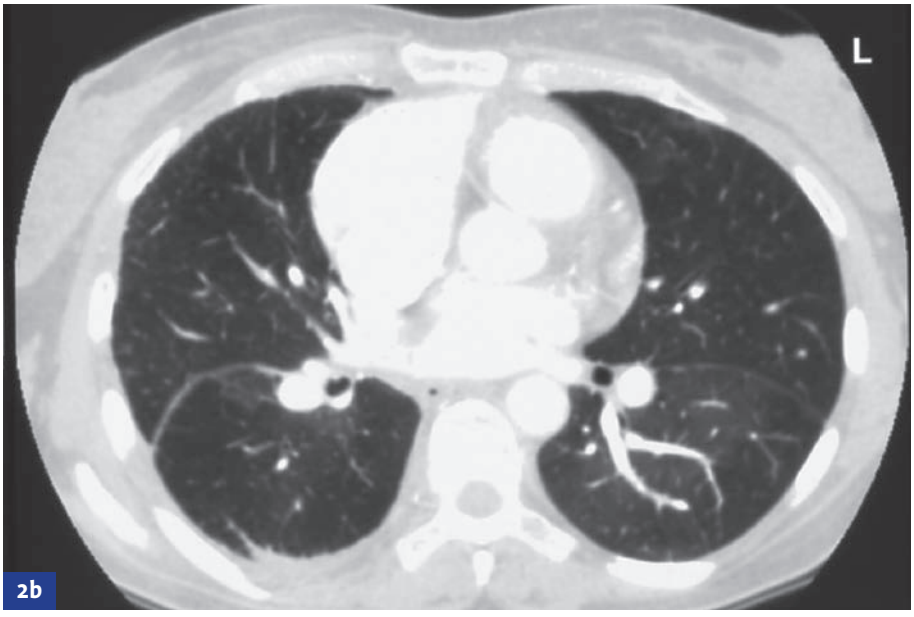
Newer echocardiographic imaging techniques might become to play a role in the diagnostic work-up in patients with CTEPH. Recently, three-dimensional (3D) echocardiography showed promising results for measuring RV volumes and function in comparison to cardiac magnetic resonance in pulmonary arterial hypertension,[34] but more experience is needed with this imaging modality in (chronic thromboembolic) pulmonary hypertension to determine the additional value in the diagnostic process.

Ventilation-perfusion (VP) lung scanning should always be performed in the diagnostic work-up of PH. In patients with CTEPH, the VP scan invariably demonstrates one or more mismatched, segmental or larger defects (figure 1).[35] Normal findings on VP lung scanning rule out the diagnosis CTEPH and other investigations to find the cause of PH should be performed.[29] VP lung scanning does not anatomically localize the extent of disease and cannot be used to determine surgical accessibility.[29]

FIGURE 2a & 2b.

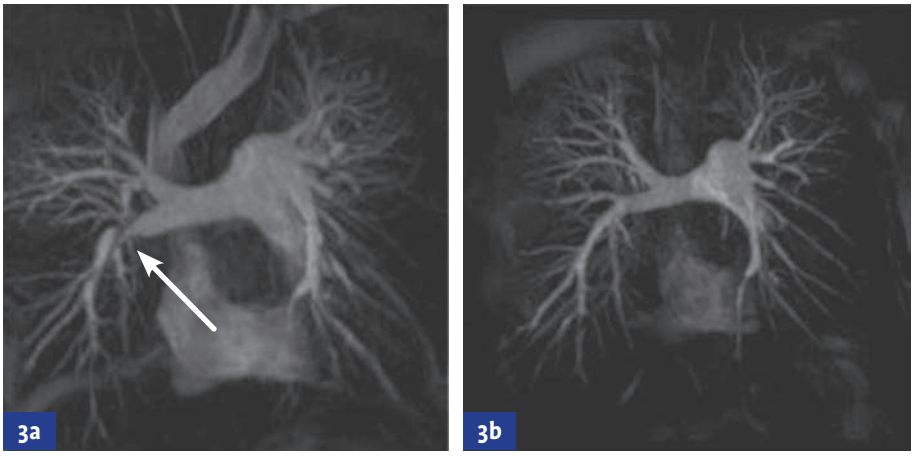


Contrast-enhanced chest CT in CTEPH shows eccentric thrombotic material within the left pulmonary artery (arrow)



Contrast-enhanced chest CT scan in CTEPH before PEA showing mosaic perfusion

FIGURE 3a & 3b. **MRA from a patient with CTEPH before (a) and after (b) PEA showing a normalization of the flow to the right lower lobe (arrow)**



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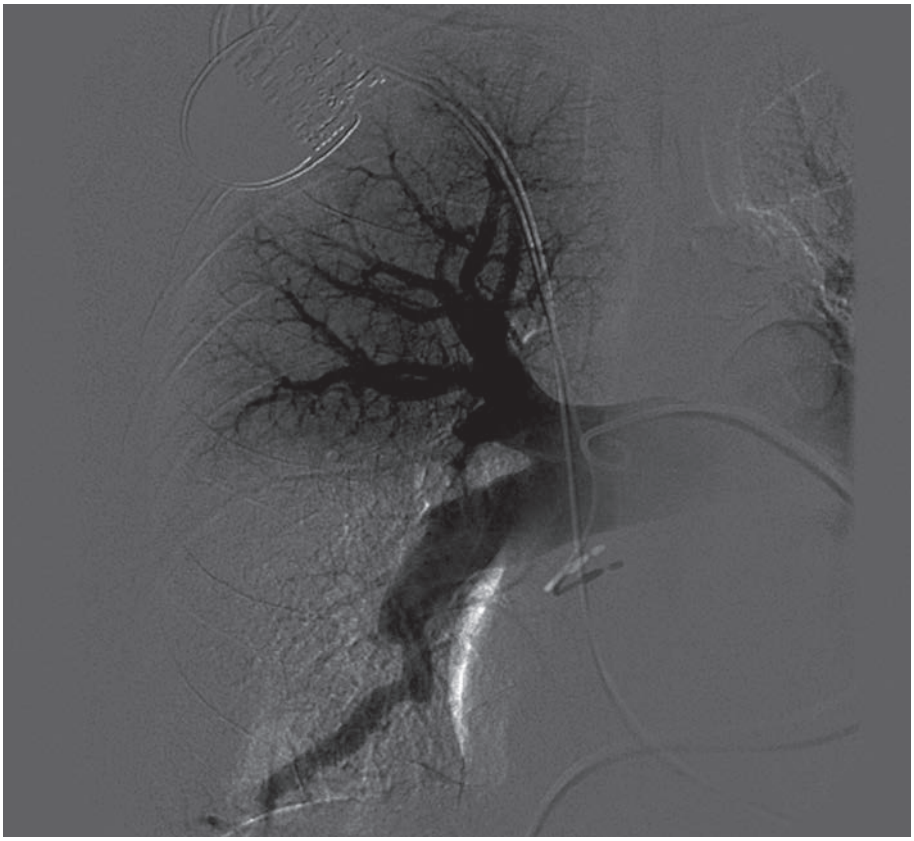
CT-angiography may demonstrate a variety of parenchymal, vascular, or mediastinal abnormalities in patients with CTEPH. These include a mosaic parenchymal perfusion pattern, parenchymal scars, enlargement of the right ventricle and/or central pulmonary arteries, asymmetry in the size and distribution of lobar and segmental vessels, intraluminal thrombus, organized thrombus lining the pulmonary vascular walls, arterial webs or bands, and mediastinal collateral vessels (figure 2a and 2b).[36] Accuracy of CT scanning has improved with technological advances, however, a negative CT scan does not rule out CTEPH.[37]

Magnetic resonance imaging (MRI) is a noninvasive technique with no radiation exposure and offers great potential in CTEPH diagnosis and risk stratification before PEA.[38] It can be used for morphological, anatomical and functional assessment of both the heart and pulmonary circulation. Both high-resolution pulmonary angiography and dynamic temporally resolved angiography can be performed, with the latter enabling the detection of perfusion defects (figure 3).[39]

Pulmonary angiography remains the gold standard. It establishes the diagnosis and assesses the operative resectability. Specific angiographic patterns that correlate with operative findings include pulmonary-artery webs or bands, intimal irregularities, abrupt stenosis or pouches of major pulmonary arteries, and obstruction of lobar or segmental arteries at their origins (figure 4).[40]

FIGURE 4. **Pulmonary substraction angiography of the right pulmonary artery showing a subsegmental branch occlusion of anterior trunk of the right upper lobe, an occlusion of the middle and lower lobe right pulmonary artery**



The final diagnosis of CTEPH requires right-sided heart catheterization and pulmonary angiography, which should be done in expert centres, where the best therapeutic approach for affected patients will be determined.

The pulmonary artery occlusion technique was developed to estimate pulmonary capillary pressure and most likely approximates pressure in the precapillary small pulmonary arteries (occlusion pressure; Poccl).[41-44] With Poccl, the pulmonary arterial resistance can be partitioned into larger arterial (upstream) and small arterial plus venous (downstream)

components. Recently, it was shown that patients with CTEPH who had predominantly proximal (large vessel) disease had a higher upstream resistance (R*up*), whereas CTEPH patients with significant concomitant small-vessel disease had lower R*up*.[45] Toshner et al. tested the hypothesis that the occlusion technique was able to discriminate large vessel organised thrombus from distal vasculopathy by performing occlusion pressures in patients with operable CTEPH, distal inoperable CTEPH and post-PEA residual CTEPH.[46] R*up* was found to be significantly increased in operable proximal CTEPH compared with inoperable distal CTEPH. Although ROC curves demonstrated good sensitivity, the specificity for distinguishing between operable and inoperable disease was much lower.[46] Therefore, new studies are necessary as these data do not support the clinical use of this technique in routine assessment.

SURGICAL TREATMENT OF CTEPH: PULMONARY ENDARTERECTOMY

The treatment of choice for symptomatic patients with CTEPH is PEA.[1,28,47] The principle and aim of the operation is the removal of obstructive material with an immediate reduction in pulmonary vascular resistance (PVR) (figure 5). The first successful true endarterectomy via sternotomy (with cardiopulmonary bypass standby) was performed in 1962 by Houk and colleagues.[48] Currently the PEA procedure involves median sternotomy, cardiopulmonary bypass and intermitted periods of hypothermic circulatory arrest to achieve a bloodless operative field and optimal exposure of the pulmonary artery.[49,50] Periods of circulatory arrest are limited to 20-minute intervals. In general, an entire unilateral endarterectomy can usually be accomplished within this time by an experienced surgeon. After each period of circulatory arrest, reperfusion is carried out until at least 10 minutes have passed. The right pulmonary artery is incised where it passes the aorta to the division of the lower lobe arteries. On the left, the incision extends from the main pulmonary artery to the origin of the left upper-lobe branch.[28] Pulmonary endarterectomy bears no resemblance to acute pulmonary embolectomy. The neo-intima in chronic thromboembolic disease is not easily recognizable as chronic thromboemboli and, thus, a true endarterectomy is necessary to restore pulmonary arterial patency. An endarterectomy plane is established between the intima and medial layer and so removing the fibrotic thromboembolic material. Considerable surgical experience with this procedure is required to identify the correct operative plane. A plane that is too deep will result in

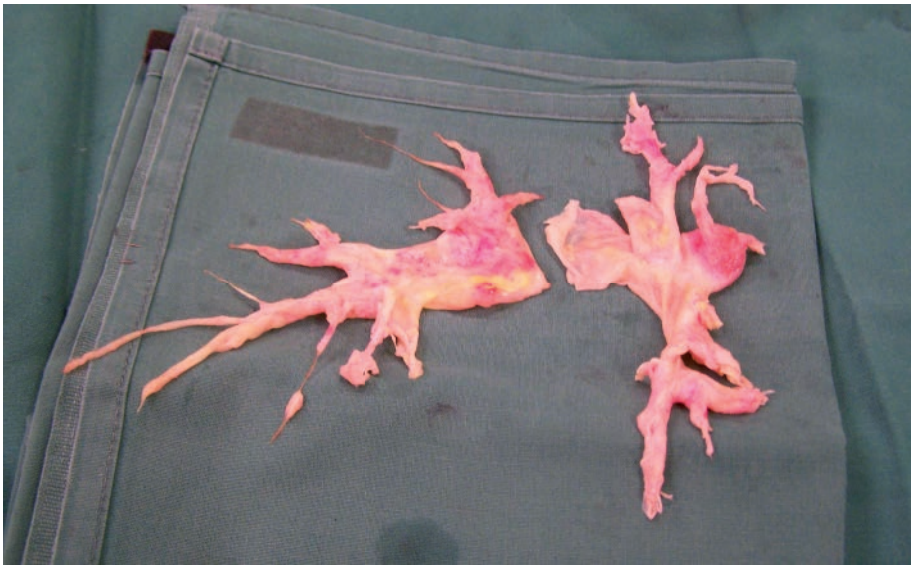
perforation of the vessel, while a plane that is too superficial will not result in an adequate endarterectomy.

Operability is based on the pre-operative estimate of surgical classification[51] and the pre-operative estimation of post-operative PVR, both of which determine risk of intervention and probable outcome.

Outcome after pulmonary endarterectomy

Successful PEA markedly improves the hemodynamics, symptoms and functional status.[11] In the majority of patients undergoing PEA, both the short- and long-term hemodynamic outcomes are favourable and may be regarded as permanent.[28] A dramatic and immediate post-operative reduction of the mean PAP and PVR occurs. The mean reduction in PVR has approximated 70% and a PVR in the range of 200 to 350 dyn·s·cm^{-5} can be achieved.[14] Patients in whom the post-operative PVR decreases by at least 50%, to a value of less than 500 dyn·s·cm^{-5}, have a more favourable prognosis after surgery than those

FIGURE 5. **The endarterectomy specimen showing a pouch in the right lower lobe and the removal of fibrotic chronic thromboembolic material in the distal sub-segmental branches**



who do not; 30-days mortality rate of 1.2% versus 5.7%.[49,50] The hemodynamic improvement is associated with improvement of symptoms and physical signs.

Overall 30-days mortality rate ranges from less than 5% in the most experienced centres to 10% in others.[11-13] A mortality rate of 1.3% has been reported in patients at low risk based on their pre-operative hemodynamic profile.[28] Potentially contributing to the improved outcome is a better understanding of the natural history of the disease, earlier and more selective surgical referral, improved diagnostic techniques, and advances in post-operative care.[2]

Patients undergoing PEA are subject to many of the same post-operative complications as other cardiothoracic surgical procedures, like atelectasis, pleural or pericardial effusion, diaphragmatic dysfunction and arrhythmias. However, reperfusion edema and residual or persistent PH are unique complications seen in the PEA patient and are associated with increased mortality.[2]

Reperfusion edema occurs in 10-40% of patients, depending on the definition used. It is a high permeability edema that occurs in regions that have been endarterectomised and reperfused.[51,52] Reperfusion edema is an early post-operative complication with 60% of cases presenting immediately after surgery, 30% developing within the first 48 hours post-operatively and the minority (10%) occurring later during the hospitalisation (> 48 hours).[47] Severity of pre-operative PH and the presence of residual PH are associated with an increased risk of developing reperfusion pulmonary edema.[53]

Mortality due to CTEPH is low among patients who survive three months post-endarterectomy. Reported five-year survival rates vary between 72% and 93%.[11-13]

Residual or persistent PH after PEA may result from incomplete endarterectomy, inaccessible chronic thromboemboli or small-vessel arteriopathy. The reported rates vary from 5% to 35%, depending on the definition.[54-56] Although it is associated with a higher risk of late post-operative adverse events[11], functional improvement might be achieved and the survival seems to be equivalent to those without PH after PEA.[54] This may indicate that the amount of PVR reduction matters, rather than the final PVR.[2]

Residual PH and reperfusion lung injury are often present in combination, and when severe, conventional therapy has been proved ineffective. Extracorporeal membrane oxy-

genation (ECMO) can be helpful as a supportive measure for patients with severe post-endarterectomy complications and should be a standard of care in PEA centres.[57]

Recently, clinical worsening (CW) has been used as a composite endpoint in pulmonary arterial hypertension trials, as described by McLaughlin.[58] It is a combination of mortality and different parameters which describe morbidity after the initiation of specific PH therapy. In recent reports, CW in CTEPH patients was defined as the combination of death, need for initiation of PH-specific medication after PEA or a 15% decrease in 6-minute-walking-distance (6-MWD) without improvement in New York Heart Association (NYHA) functional class. Until now, the prevalence of CW in patients with CTEPH is unclear.

Predictors of outcome after pulmonary endarterectomy

After a hemodynamically successful PEA the NYHA functional class improves and life expectancy increases.[10] Possible pre-operative predictors for successful PEA are considered to be PVR, 6-MWD, radiological findings and co-morbidities of the patients.[1,6,13] Several studies have associated high pre-operative PVR (i.e. >900-1100 dyn·s·cm^{-5}) with increased mortality after PEA.[13,28,59] The post-operative PVR is also strongly related to mortality, and a decrease to less than 500 dyn·s·cm^{-5} has been reported as optimal.[3] Tscholl et al. demonstrated that age, right atrial pressure, NYHA functional class, cardiac output, creatinine and the number of angiographically involved segments were significant predictors for early death in univariate analysis. Age, right atrial pressure and female gender were identified as risk factors for unfavourable hemodynamic outcome after PEA.[60] Bonderman and associates demonstrated that the presence of associated medical conditions (i.e. splenectomy, inflammatory bowel disease and osteomyelitis) predicted increased operative risk and worse long-term outcome in CTEPH (i.e. higher mortality rates and more frequent occurrence of residual PH).[55]

In a large prospective registry of Mayer et al., PVR three to five days after PEA and 6-MWD at diagnosis were identified as independent risk factors for in-hospital death.[13] Survivors had a higher 6-MWD and a lower PVR at diagnosis than non-survivors. The one-year mortality rate increased with increasing values of PVR at diagnosis to 12.8% for those with a PVR exceeding 1200 dyn·s·cm^{-5}.[13]

MEDICAL TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

All patients with CTEPH should receive lifelong anticoagulation adjusted to a normalized target ratio between 2.0 and 3.0. The rationale is to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism.

Consideration about commencing medical therapy for CTEPH patients should only occur following surgical assessment, as the currently available drugs are not alternatives to PEA.[47]

Primary medical therapy and pre-treatment with medical therapy prior to PEA in patients who appear to have surgically accessible chronic thromboembolic disease that seems proportionate with the degree of PH are currently not recommended by the international guidelines. Patients with "out of proportion" elevated PVR prior to surgery, persisting/residual PH following PEA, due to distal obstructive thrombotic lesions situated beyond the sub-segmental level but also to arteriopathy, and inoperable CTEPH are often considered for management with PAH targeted therapies, despite the fact these medications are not approved for the treatment of CTEPH.[25,61]

A substantial number of patients (operable and inoperable CTEPH) are currently being treated off-label. In the International CTEPH Registry, 38% of all patients were treated with at least one PH-targeted drug at diagnosis.[16] Most of the studies investigating the use of PH-targeted therapies in the management of patients with distal CTEPH show beneficial effects.[62,63] The BENEFiT study is a large randomized controlled trial that has been performed in patients with inoperable CTEPH (n=157).[25] This study demonstrated a positive treatment effect of bosentan (a dual endothelin receptor antagonist) on hemodynamics in this patient population without improvement of exercise capacity.[25]

In the recent CHEST-1 study, the efficacy and side-effect profile of riociguat (soluble guanylate cyclase stimulators) was evaluated in patients with inoperable CTEPH and patients with persistent or recurrent pulmonary hypertension after PEA.[64] Riociguat significantly improved exercise capacity and PVR in patients with CTEPH compared with placebo.[64]

Selected patients with a predicted higher risk for post-operative mortality may benefit from pre-operative medical treatment, especially those with a severely increased PVR or

signs of right heart failure.[63] These patients include those in NYHA functional class IV, those with a mean PAP greater than 50 mmHg, cardiac index less than 2 $L \cdot min^{-1} \cdot m^{-2}$ and/or PVR greater than 1200 $dyn \cdot s \cdot cm^{-5}$.[65] Whether improving pulmonary hemodynamics with pre-operative PH treatment also improves surgical outcome is unknown and remains largely speculative.[66] In a retrospective analysis of 9 patients who were treated with continuous intravenous epoprostenol (a prostacyclin analogue) before surgery, Bresser et al. found substantial improvements in cardiac index, mean PAP and total pulmonary resistance in all patients after PEA. However, impact on post-PEA morbidity and mortality could not be established.[65] In a prospective randomized study by Reesink et al., pulmonary hemodynamics and functional capacity were analysed in 25 PEA candidates treated with or without bosentan.[67] After treatment of 16 weeks, significant improvements were observed in mean PAP, total pulmonary resistance and 6-MWD in the bosentan group compared to controls. However, the outcome after PEA was similar in both groups.[67]

Jensen et al. retrospectively analysed the medical treatment of the CTEPH patients referred to their centre for PEA.[68] Although the use of PAH-specific medication before surgery had significantly increased, there was no significant improvement in pre-operative pulmonary hemodynamics and post-operative outcome.[68]

The increased use of medications in operable patients could possibly delay referral of patients for PEA. Selection of suitable candidates for bridging therapy should be carefully carried out in expert centres.[68]

AIMS AND OUTLINE OF THE THESIS

This thesis concerns the outcome of patients with operable and inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Chapter 2 concerns the incidence of clinical worsening in patients with inoperable CTEPH in a single centre population and in chapter 3 we describe the occurrence of clinical worsening in patients with CTEPH who underwent pulmonary endarterectomy (PEA). Chapter 4 and chapter 5 provide us the important role of cardiovascular imaging modalities like echocardiography and computed tomography in the pre-operative prediction of outcome after PEA. Finally, in chapter 6 the upstream pulmonary artery resistance measured by the pulmonary artery occlusion technique is evaluated as a predictor of outcome after PEA.

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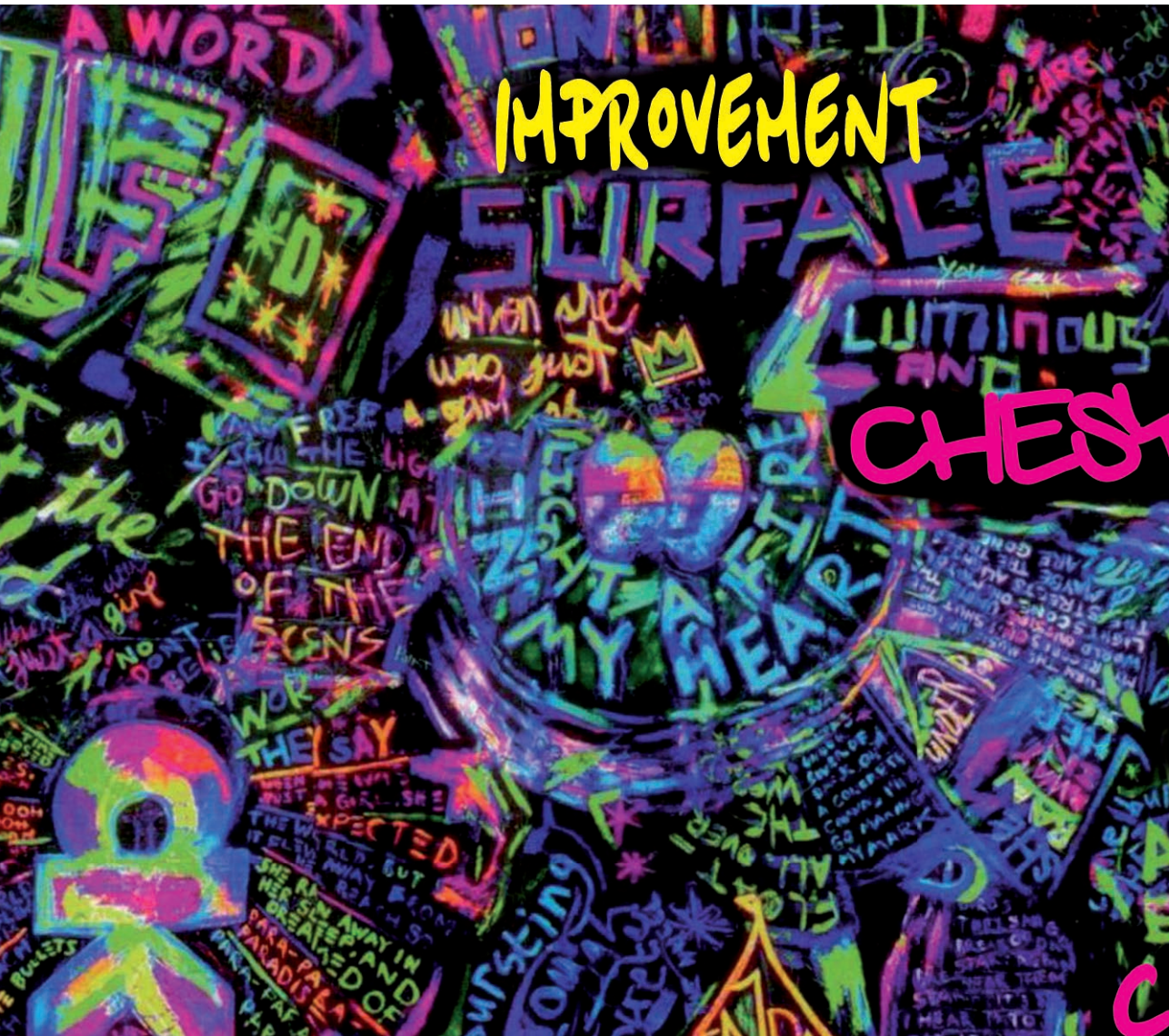
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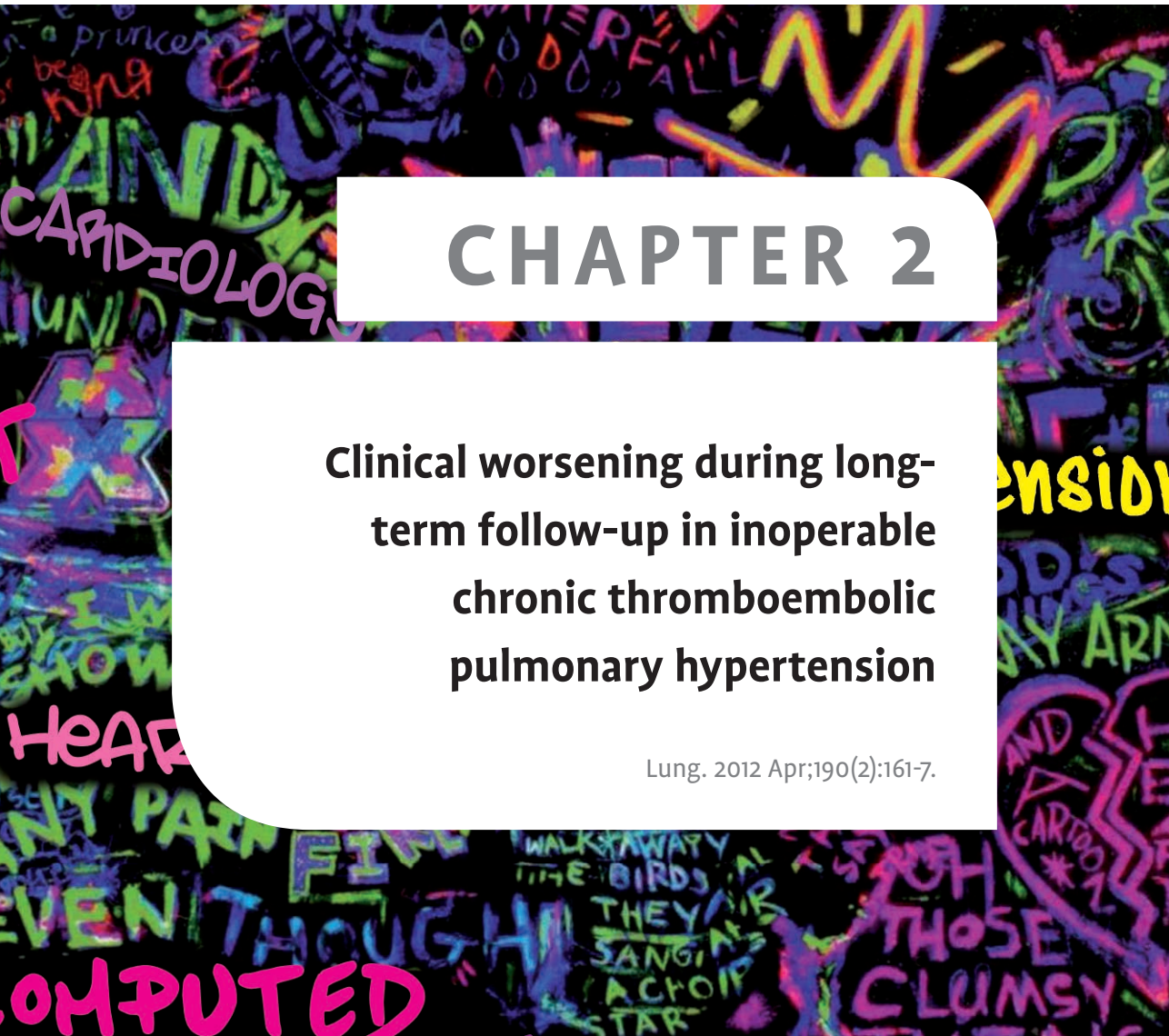


CHAPTER 2

Clinical worsening during long-term follow-up in inoperable chronic thromboembolic pulmonary hypertension

Lung. 2012 Apr;190(2):161-7.

ABSTRACT

Background

Pulmonary endarterectomy is the treatment of choice in chronic thromboembolic pulmonary hypertension (CTEPH). Specific pharmacological therapy is used in patients with an inoperable disease. These modern pulmonary vaso-active medication (i.e. endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostacyclins) improved prognosis. We evaluate mortality and time to clinical worsening (TtCW) in inoperable CTEPH patients during long-term follow-up.

Methods

All 32 patients with inoperable CTEPH were enrolled between June 2002 and January 2009. TtCW was defined as the combination of death, need for intravenous pulmonary arterial hypertension (PAH) medication or 15% decrease in six-minute walk distance (6-MWD) without improvement in functional class. The Cox proportional Hazard regression was used to identify predictors.

Results

During a mean follow-up of 3.4 years (0.2 – 10.2 years) 11 patients died (34%). The one- and three-year survival rates were 87% and 77%, respectively. Baseline functional class, 6-MWD, mean pulmonary artery pressure, and pulmonary vascular resistance were predictors for survival. Clinical worsening occurred in 16 patients (50%). The one- and three-year rates of freedom from clinical worsening were 74% and 60%, respectively. The only predictor for clinical worsening was the baseline 6-MWD.

Conclusion

Despite the improvement in medical treatment of inoperable CTEPH, the mortality rate is still high, and clinical worsening occurred in a substantial number of patients during a follow-up of more than three years.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious complication of pulmonary embolism and is associated with important morbidity and mortality.[1] Obstruction of the pulmonary arteries by organised fibrotic clot formation leads to pathophysiological changes in the distal pulmonary vascular bed, and a significant rise in pulmonary vascular resistance (PVR). Finally, this might result in dysfunction of the right ventricle. Approximately 1.5 to 4% of the patients who survive an acute pulmonary thromboembolic event will develop CTEPH within the first two years following an acute pulmonary embolus.[2,3] Untreated, CTEPH has a poor prognosis, with over one-half of patients with mean pulmonary arterial pressure (mPAP) of 50 mmHg not surviving beyond 1 year after diagnosis.[4]

The gold standard in treatment for patients with surgically accessible CTEPH is surgical pulmonary endarterectomy (PEA).[5] Experience with PEA-surgery is well documented and excellent outcomes can be achieved for most patients deemed surgical candidates.[6] However some patients are not suitable for surgical treatment due to the distal location of pulmonary thromboemboli or severe co-morbidity. In addition, approximately 10% of patients who undergo PEA obtain no relief and maintain a pulmonary hypertensive state.[7] Modern specific pulmonary vaso-active medication (i.e. endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostacyclins) seems to improve the functional status and hemodynamics in patients with inoperable CTEPH at short term follow-up.[8-17] However, limited data are available concerning the survival rate and time to clinical worsening in this patient population since “modern” vaso-active treatments like endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostacyclins were introduced.

The aim of this study was to describe the long-term follow-up in inoperable CTEPH and to identify predictors of mortality and time to clinical worsening.

METHODS

Patient selection

The present study was conducted at the Pulmonary Hypertension Unit of the St Antonius Hospital in Nieuwegein. This centre is one of the largest referral centres for surgical treatment of CTEPH in the Netherlands. The diagnosis of CTEPH was based on a standardised assessment of all patients including ventilation-perfusion scanning, CT-angio of the chest, chest radiography, transthoracic echocardiography, pulmonary angiography and right-sided heart catheterization, and arterial blood gas analysis at rest and exercise. Other aetiologies for pulmonary hypertension were excluded. A multidisciplinary panel including pulmonologists, radiologists, cardiologists, and cardiothoracic surgeons reviewed each case.

CTEPH was judged inoperable because of peripheral localization of thrombotic material (according to pulmonary angiography). Patients with a distal involvement of pulmonary vessels (chronic thromboembolic lesions only at the segmental and/or subsegmental level) or patients with a high PVR compared with the level of pulmonary obstruction were also considered inoperable. The presence of severe co-morbidity was another reason for inoperability. The local Institutional Review Board approved the study design.

Study design

This is a retrospective observational cohort study of patients with inoperable CTEPH. All consecutive patients were enrolled between June 2002 and January 2009. Cohort entry was defined as the time/date of the first outpatient clinic visit.

Follow-up

At baseline (i.e. cohort entry) and during follow-up all patients underwent a 6-minute walk distance (6-MWD), assessment of the New York Heart Association (NYHA) functional class, and blood samples were obtained for assessment of liver function, anticoagulation, and N-terminal-pro brain natriuretic peptide (NT-proBNP). In addition to oral anticoagulation (adjusted to a target international normalised ratio between 2.0 and 3.0), the patients also received pulmonary arterial hypertension (PAH)-specific medications. The pharmacological treatment varied among patients (see table 2). Patients were evaluated on an outpatient basis at four weeks, 12 weeks and thereafter every four months. Safety was assessed by monitoring liver enzymes, vital signs, and adverse events.

Endpoints

The primary endpoint was defined as all-cause mortality. The secondary endpoint was time to clinical worsening (TtCW), defined as death, need for intravenous PAH medication or 15% decrease in 6-MWD without improvement in functional class.

Statistical analysis

The data are expressed as mean and standard deviation if normal distribution was present and as median with range in the absence of normal distribution. Changes from baseline were evaluated with a paired *t* test for continuous variables and with a Wilcoxon Rank-Sum test or χ^2 test for ordinal variables if appropriate. Time to event data are presented as Kaplan-Meier curves and Cox proportional Hazard regression. Significance was determined at $p<0.05$; all reported p values were two tailed. All statistical analyses were performed by using SPSS software (SPSS Inc., version 17.0 for Windows; Chicago, IL).

RESULTS

Patient characteristics

Thirty-two consecutive patients (mean age 61.8±12.7 years, 50% female) were enrolled in this study. The patient baseline characteristics are summarized in table 1. At baseline, 31 patients were in NYHA functional class III or higher. The mean pulmonary artery pressure (mPAP) was 43.0±2.4 mmHg with a mean PVR of 575.7±316.7 dyn·s·cm^{-5} (range 200-1552 dyn·s·cm^{-5}).

Follow-up

The mean follow-up was 3.4±2.2 years (range 0.22-10.17). Bosentan was in most of the cases the first choice of treatment (23 patients [71.8%], see table 2). During follow-up combination therapy was initiated in 14 patients (42.8%). In seven patients (21.8%) administration of intravenous PAH-medication was needed because of deterioration of the clinical condition. In six patients there was a decrease in 6-MWD.

Survival

During follow-up 11 patients (34.4%) died. Within the first year after study enrollment, 4 patients died, 3 patients died in the second year after study enrollment and the other 4 patients died more than 3 years after inclusion in the study. The 1-year survival rate was

87.5%; the 3-year survival rate was 77.0%. The Kaplan-Meier curve for overall survival is shown in figure 1. At baseline, the survivors were significantly younger, had a higher walking distance, a lower mPAP and PVR compared to non-survivors. These data are summarized in table 3. The NYHA functional class, 6-MWD, and pulmonary hemodynamics were predictors for survival. In table 4 the data of the univariate Cox proportional hazards regression analysis are shown.

Clinical worsening

During follow-up, clinical worsening occurred in 16 patients (50%). The one- and three-year rates of freedom from clinical worsening were 74% and 60%, respectively. Figure 2 shows the Kaplan-Meier curve for freedom of clinical worsening. A comparison of baseline characteristics of patients with and without the occurrence of clinical worsening is outlined in table 5. The baseline 6-MWD was a predictor for clinical worsening (table 6), the baseline functional class tended to be a predictor (Hazard ratio 2.87; 95% Confidence Interval 0.96 – 8.55, p = 0.06).

TABLE 1. Baseline characteristics

Number	32
Age (years)	61.8±12.7
Gender	
Female (%)	16 (50.0)
Male (%)	16 (50.0)
BMI (kg/m^2)	27.5±5.1
NYHA FC (I/II/III/IV)	0/1/25/6
6-MWD (m)	348±162
NT-proBNP (pg/mL)	2723±3746
Creat (mmol/L)	97.8±20.7
Right-sided heart catheterization	
PAP mean (mmHg)	43.0±12.4
PVR (dyn·s·cm^{-5})	575.7±316.7
CO (L/min)	5.2±1.5
VC (L)	3.4±1.3
FEV1 (%)	86.1±19.1
pO2 (kPa)	8.5±2.0
Saturation (%)	91.7±8.2

BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; NT-proBNP = N-terminal pro brain natriuretic peptide; Creat = creatinine; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure

TABLE 2. Follow-up

FU (year)	3.4±2.2
First treatment	
Bosentan	23 (71.8)
Sildenafil	2 (6.3)
Epoprostenol	3 (9.4)
None	4 (12.5)
Treatment during FU	
Bosentan only	9 (28.1)
Sildenafil only	2 (6.3)
Bosentan and Sildenafil	10 (31.3)
Epoprostenol only	3 (9.4)
Epoprostenol and Bosentan	2 (6.3)
Epoprostenol, Bosentan and Sildenafil	2 (6.3)
None	4 (12.5)
Endpoints	
Death	11 (34.4)
IV PH medication	7 (21.9)*
6-MWD worsening without improvement in NYHA FC	6 (18.8)**
Combination	16 (50.0)

FU = Follow-up; IV PH medication = intravenous pulmonary hypertension medication; 6-MWD = six minute walk distance; NYHA FC = New York Heart Association Functional Class

* 5 of them died during FU

** 2 of them died and 1 needed IV PH medication.

Data are presented as mean ± standard deviation or number (with percentage)

TABLE 3. **Comparison of baseline characteristics of survivors and non-survivors in inoperable CTEPH**

	Survivors	Non-survivors	p
Number	21	11	
Age (years)	58.2±13.2	68.6±8.6	0.03
Gender (n (%))			0.71
Female	10 (52.4)	5 (45.5)	
Male	11 (47.6)	6 (54.5)	
BMI (kg/m^2)	28.3±5.6	25.9±3.8	0.22
NYHA FC (I/II/III/IV)	0/1/18/2	0/0/7/4	0.06
6-MWD (m)	413±146	209±96	0.001
NT-proBNP (pg/mL)	1950±3043	4462±4758	0.12
Creat (mmol/L)	96.6±20.3	100.2±22.4	0.65
Right-sided heart catheterization			
PAP mean (mmHg)	38.9±11.4	50.9±10.5	0.007
PVR (dyn·s·cm^{-5})	491.8±213.6	764.5±434.3	0.04
CO (L/min)	5.3±1.5	4.7±1.6	0.46
VC (l)	3.7±1.4	3.0±1.0	0.15
FEV1 (%)	87.9±18.3	82.6±21.6	0.52
pO2 (kPa)	8.7±2.3	8.2±1.5	0.55
Saturation (%)	91.1±9.7	92.7±5.1	0.67
Follow-up (year)	4.1±2.2	2.0±1.7	0.01
Therapy follow-up			0.005
Oral mono therapy	11 (52.4)	0	
Oral dual therapy	7 (33.3)	3 (27.3)	
IV therapy	2 (9.5)	5 (45.5)	
None	1 (4.8)	3 (27.3)	

Table footnote on next page

CTEPH = Chronic Thrombo-Embolic Pulmonary Hypertension; BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; NT-proBNP = N-terminal pro brain natriuretic peptide; Creat = creatinine; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure.
Data are presented as mean ± standard deviation or number (with percentage).

TABLE 4. Predictors for death during follow-up

	HR (univariate)	p	HR (multivariate)	p
Male	0.90 (0.27-2.97)	0.86		
BMI	0.96 (0.83-1.11)	0.60		
Age	1.06 (1.00 – 1.12)	0.07	0.94 (0.82-1.09)	0.42
NYHA FC	6.36 (1.69-23.9)	0.006	1.81 (0.09-37.7)	0.70
6-MWD	0.99 (0.99-1.00)	0.002	0.98 (0.96-1.00)	0.02
Mean PAP	1.10 (1.03-1.17)	0.004	1.05 (0.93-1.19)	0.45
PVR	1.00 (1.00-1.01)	0.01	1.00 (0.99-1.00)	0.23
CO	0.79 (0.39-1.69)	0.55		
Creat	1.01 (0.98-1.04)	0.61		
NT-proBNP	1.00 (1.00-1.00)	0.28		
VC	0.67 (0.36-1.24)	0.20		
FEV1	0.98 (0.95-1.02)	0.34		
pO2	0.91 (0.68-1.23)	0.55		
Saturation	1.02 (0.94-1.11)	0.60		

HR = Hazard ratio; BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; Mean PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; Creat = creatinine; NT-proBNP = N-terminal pro brain natriuretic peptide; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure

TABLE 5. Baseline characteristics of patients with clinical worsening and patients without clinical worsening

	Clinical worsening	No clinical worsening	p
Number	16	16	
Age (years)	65.2±12.0	58.3±12.8	0.13
Gender (n (%))			0.29
Female	10 (62.5)	6 (37.5)	
Male	6 (37.5)	10 (62.5)	
BMI (kg/m^2)	28.0±5.9	27.0±4.3	0.60
NYHA FC (I/II/III/IV)	0/0/12/4	0/1/13/2	0.24
6-MWD (m)	257±136	426±143	0.004
NT-proBNP (pg/mL)	3550±4292	2116±3312	0.35
Creat (mmol/L)	93.6±21.9	102.1±19.3	0.25
Right-sided heart catheterization			
PAP mean (mmHg)	56.6±14.0	40.5±10.4	0.25
PVR (dyn·s·cm^{-5})	667.2±391.6	484.3±193.8	0.14
CO (L/min)	4.8±1.4	5.5±1.5	0.25
VC (l)	2.9±1.1	4.0±1.4	0.04
FEV1 (%)	81.6±19.3	90.6±18.9	0.24
pO2 (kPa)	8.4±2.0	8.6±2.2	0.84
Saturation (%)	91.9±7.0	91.5±9.7	0.89
Follow-up (year)	1.6±1.6	3.3±1.6	0.005
Therapy follow-up			0.005
Oral mono therapy	2 (12.5)	9 (56.3)	
Oral dual therapy	4 (25.0)	6 (37.5)	
IV therapy	7 (43.8)	0	
None	3 (18.8)	1 (6.3)	

Table footnote on next page

BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; NT-proBNP = N-terminal pro brain natriuretic peptide; Creat = creatinine; RHC = right heart catheterization; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure.

TABLE 6. **Predictors for clinical worsening during follow-up**

	HR (univariate)	p	HR (multivariate)	p
Male	0.58 (0.21-1.60)	0.29		
BMI	1.05 (0.96-1.16)	0.28		
Age	1.02 (0.98-1.06)	0.38		
NYHA	2.87 (0.96-8.55)	0.06	0.27 (0.03-2.21)	0.22
6-MWD	0.99 (0.99-1.00)	0.008	0.99 (0.98-1.00)	0.006
Mean PAP	1.04 (0.99-1.09)	0.16	0.96 (0.89-1.03)	0.27
PVR	1.00 (1.00-1.00)	0.14	1.00 (0.99-1.00)	0.55
CO	0.85 (0.52-1.39)	0.52		
Creat	0.98 (0.95-1.01)	0.18		
NT-proBNP	1.00 (1.00-1.00)	0.73		
VC	0.67 (0.41-1.09)	0.10		
FEV1	0.97 (0.94-1.00)	0.07		
pO2	0.99 (0.77-1.28)	0.95		
Saturation	1.02 (0.95-1.08)	0.60		

HR = Hazard ratio; BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; Mean PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; Creat = creatinine; NT-proBNP = N-terminal pro brain natriuretic peptide; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure

FIGURE 1. Free of death

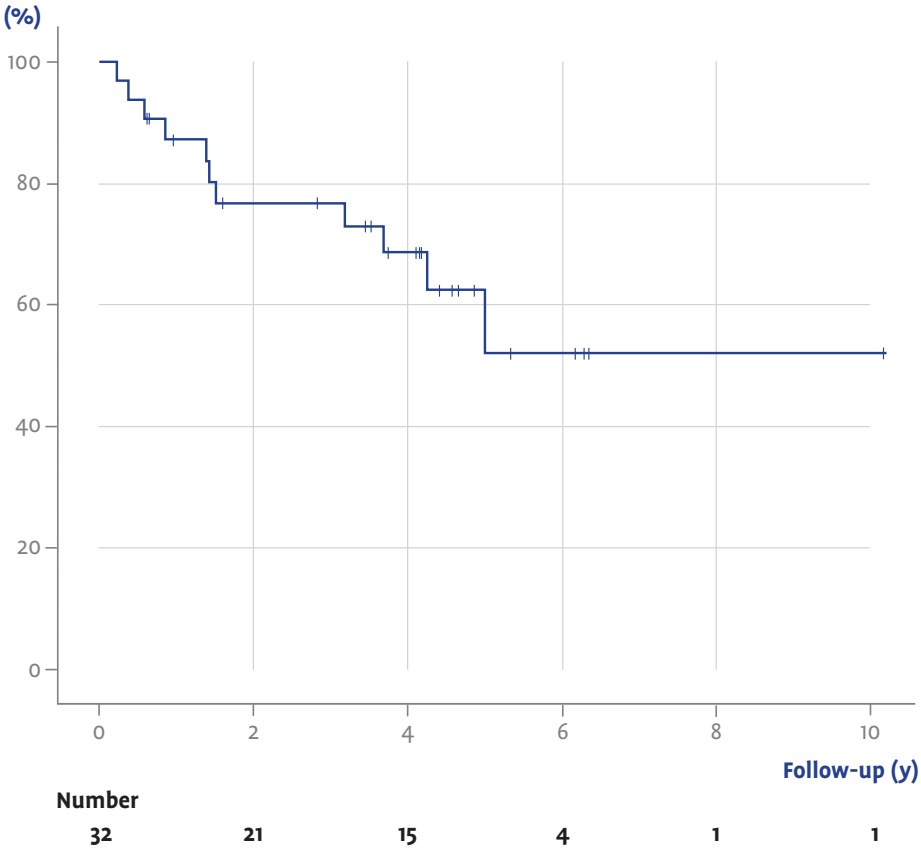
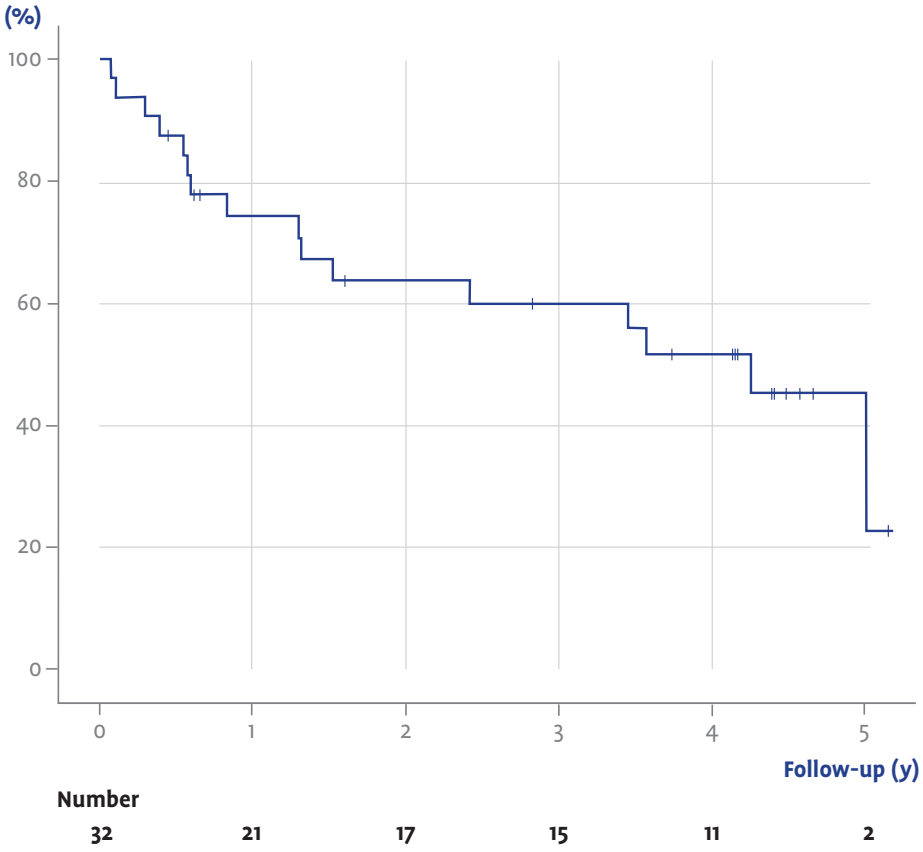


FIGURE 2. Free of clinical worsening (Combination of Death, need for IV therapy and decrease in 6-MWT)



DISCUSSION

This study is the first study describing the time to clinical worsening during long-term follow-up in patients with inoperable CTEPH. It demonstrates that, despite modern pulmonary vaso-active medication, 23% of the patients died and clinical worsening occurred in 40% of the patients within three years after diagnosis.

Untreated, CTEPH has a poor prognosis, with a survival rate of 50% five years after diagnosis. The survival rate decreases with an increase in pulmonary artery pressure.[4] However, after the modern pulmonary vaso-active therapy, like endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostacyclins, became available the survival rate seems to improve at short- and mid-term follow-up. Seyfarth and colleagues compared survival data from 50 CTEPH patients treated with specific vaso-active therapy with two previously reported patient groups without specific vaso-active treatment.[14] Patients receiving specific vaso-active therapy showed a significantly improved survival, compared with both historical groups, which suggests a beneficial effect of a specific vaso-active treatment on overall survival in inoperable CTEPH patients. The three years survival rate was around 90%. Other studies described the use of sildenafil in inoperable CTEPH patients.[15,16] In both studies sildenafil therapy led to significant and sustained long-term functional and hemodynamic improvement. The one-year survival rates were 94% and 100% respectively. Cabrol et al. described the administration of epopostenol in patients with inoperable CTEPH[17], suggesting that epoprostenol infusion leads to a significant improvement in hemodynamics with clinical benefits in terms of NYHA functional class and exercise capacity. The one- and three-year survival rate were 73% and 41%, respectively.

In the BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) trial, patients with either inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA were included and randomized to treatment with Bosentan or placebo. The study demonstrated a positive treatment effect of Bosentan on hemodynamics over placebo in this patient population during follow-up of 16 weeks.[13] Other studies report one-year survival rates of 95% in patients with inoperable CTEPH treated with Bosentan.[10,12]

In our study we found a one year survival rate of 87% and a three year survival rate of 77%. This is comparable with survival rates reported by other studies[18,19], however some reports describe higher survival rates.[10,20] Presumably this difference is the result of selection of a different study population. For example most of the patients included in our study were in NYHA functional class III or IV (97%) which differs from the other studies. In the non-survivor group three patients died before medical therapy could be initiated.

Several studies were conducted in search for predictors of mortality in patients with inoperable CTEPH. An association between mPAP at baseline and mortality has been described frequently.[4,20-21] Saouti and colleagues reported an association between baseline mPAP, PVR, right atrial pressure and 6-MWD with mortality. The 6-MWD was the only independent predictor of survival.[20] Miyamoto et al. identified the 6-MWD as a strong independent factor associated with mortality in patients with idiopathic pulmonary arterial hypertension.[22] In this present study NYHA functional class, 6-MWD, mPAP and PVR were identified as predictors for mortality during follow-up. Multivariate analysis however showed that the 6-MWD was the only independent predictor of mortality. This is in agreement with the results of the studies mentioned above.

Because of the low event rate in recent PH studies, mortality alone has not been an adequately powered endpoint. Therefore, a composite endpoint, time to clinical worsening, has been developed. However, different definitions of TtCW have been used in different trials, making comparison difficult. Recently an article of McLaughlin and colleagues was published concerning endpoints and clinical trial design in pulmonary hypertension.[23] A more uniform definition was proposed, including all-cause mortality, non-elective hospital stay for PAH (usually for initiation of intravenous prostanoids, lung transplantation or septostomy) and disease progression. In our study clinical worsening was defined as the composite endpoint of death, need for intravenous PAH-medication or 15% decrease in 6-MWD with no improvement of functional class.

The endpoint clinical worsening has been mostly used in clinical trials in patients with pulmonary arterial hypertension. No studies are available describing the rate of clinical worsening in patients with inoperable CTEPH.

Clinical worsening in our study population was seen in 26% after one year and 40% after three years. After one year the endpoint of clinical worsening was mainly reached because of death, but after three years clinical worsening was mainly caused by need for

intravenous PH medication or a decrease in 6-MWD in our study. The only predictor for clinical worsening during long-term follow-up which was identified in our study was the 6-MWD at baseline. The NYHA functional class at baseline tended to be a predictor. No data from other studies are available to confirm these results.

The main limitation of this study is its retrospective observational design. Another limitation is the small study population and small number of events, therefore the results should be interpreted with caution. This study only included inoperable CTEPH patients, therefore these results cannot be applied to operable CTEPH patients.

CONCLUSION

Despite the improvement in medical treatment of inoperable CTEPH, the mortality rate is still high, and clinical worsening occurred in a substantial number of patients during a follow-up of more than three years. Finally, it has to be mentioned that patients with CTEPH should be referred to centres with excellence in the management of CTEPH and PEA-surgery, and the decision of inoperability should be made at these centres.

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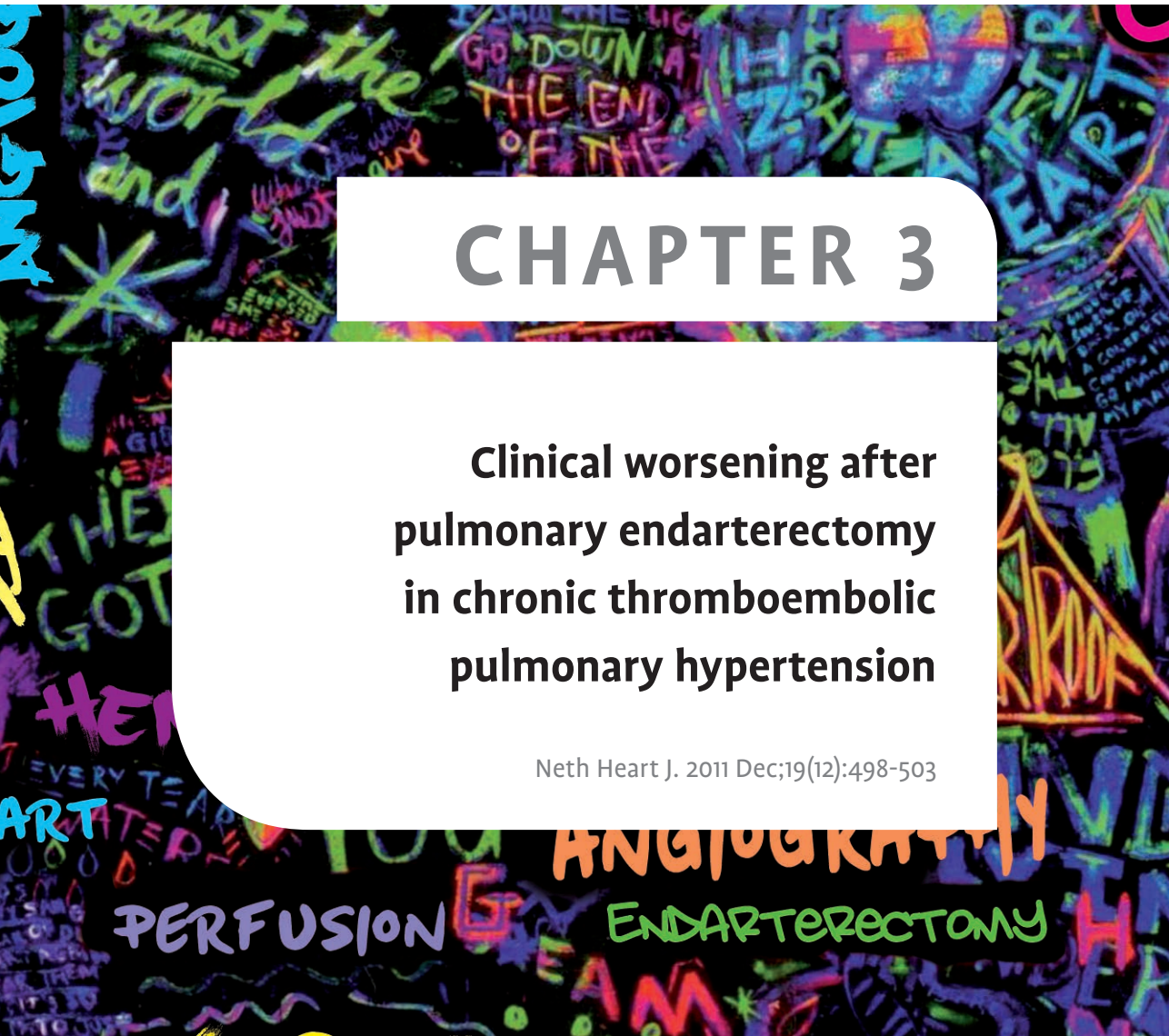
CLINICAL WORSENING
PULMONOLOGY

BASTIAAN E. SCHÖLZEL, REPKE J. SNIJDER,
WIM J. MORSHUIS, NABIL SAOUTI,
H.W. THIJS PLOKKER, MARTIJN C. POST



CHAPTER 3

Clinical worsening after pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension

Neth Heart J. 2011 Dec;19(12):498-503

ABSTRACT

Introduction

Pulmonary endarterectomy (PEA) is the most effective treatment for chronic thromboembolic pulmonary hypertension (CTEPH). The aim of this study is to evaluate long-term survival and freedom from clinical worsening after PEA.

Methods

All patients who underwent PEA in our hospital between May 2000 and August 2009 were included. Follow-up parameters were all-cause mortality and time to clinical worsening (CW), defined as combination of death, need for pulmonary hypertension specific medication or 15% decrease in six-minute walk distance without improvement in functional class. The Cox proportional Hazard regression was used to identify predictors.

Results

Seventy-four consecutive patients (mean age 55.9±13.8 years, 51% female) underwent PEA. Prior to surgery, 55 patients were in NYHA functional class III or higher. The mean pulmonary artery pressure was 41.3±11.9 mmHg with a mean pulmonary vascular resistance of 521±264 dyn·s·cm^{-5} (range 279–1331 dyn·s·cm^{-5}). Five patients (6.8%) died in-hospital. Out of hospital, 5 out of 69 patients (7.2%) died during a median follow-up of 3.7±2.2 years (range 0.1-8.5 years). The one and five years survival rates were 93% and 89%, respectively. During follow-up, CW occurred in 13 out of 69 patients (18.8%). The one and five year rates of freedom from CW were 94% and 72%, respectively. The baseline NT-proBNP level tended to be a predictor for occurrence of CW.

Conclusion

Pulmonary endarterectomy is associated with good long-term survival in patients with CTEPH. However, CW occurred in a substantial number of patients at long-term follow-up.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) has been estimated to occur in up to 3.8% two years following an episode of confirmed pulmonary embolism.[1,2] It is characterized by intraluminal thrombus organization which causes stenosis or complete obliteration of the pulmonary arteries[3], resulting in an increased pulmonary vascular resistance (PVR), pulmonary hypertension (PH) and progressive right heart failure. Although obstruction of pulmonary arteries is recognized as the inciting event, small-vessel arteriopathy is believed to appear in the course of the disease and to contribute to its progression.[4]

Pulmonary endarterectomy (PEA) is the treatment of choice, offering immediate hemodynamic benefits and providing a potential cure for many patients.[5-7] However, 10 to 50% of CTEPH patients are inoperable, due to either distal pulmonary vascular obstruction that is surgically inaccessible or significant co-morbidities thought to be associated with unacceptable high risk.[8] The direct post-operative mortality rates of PEA range from 5% in most experienced centres to 10%.[5,6,9]

However, limited data are available concerning clinical worsening (CW) after PEA. The aim of this study is to describe CW during long-term follow-up in CTEPH patients who underwent PEA.

METHODS

Patient selection

The present study was conducted at the Pulmonary Hypertension Unit of the St. Antonius Hospital in Nieuwegein. This centre is one of the two centres for surgical treatment of CTEPH in the Netherlands. The diagnosis of CTEPH was based on a standardized assessment of all patients including ventilation-perfusion scanning, CT-angio of the chest, chest radiography, transthoracic echocardiography, pulmonary angiography and right-sided heart catheterization, and arterial blood gas analysis at rest and exercise. Other aetiologies for pulmonary hypertension were excluded. A multidisciplinary panel including pulmonologists, radiologists, cardiologists, and cardiothoracic surgeons reviewed each case.

Patients were considered suitable for surgery when they were symptomatic, had an elevated pulmonary vascular resistance (PVR) (>250 dyn·s·cm^{-5}), segmental or more proximal lesions and no severe co-morbidity. Severity of hemodynamic disease was not a reason to decline a patient for surgery. At the beginning of our PEA program severely compromised hemodynamic patients were pre-operatively treated with prostacyclin. Since 2003 high-risk patients with PVR >1000 dyn·s·cm^{-5} were treated with oral disease modifying therapy consisting of phosphodiesterase-5 inhibitors (PDE-5 inhibitors) and/or endothelin receptor antagonist (ERA).

Study design

This is a retrospective observational cohort study of patients with operable CTEPH. All consecutive patients were enrolled between May 2000 and August 2009. Cohort entry was defined as the date of the PEA. All patients were consistently operated by one surgeon (WM) using standardized technique discussed elsewhere.[10,11] The study design was approved by the local ethical committee.

Follow-up

Follow-up of the patients was performed 8 weeks after discharge from the hospital followed by visits to the outpatient clinic after 3 months and every half-year thereafter. Investigations consisted of clinical examination by means of assessing the NYHA functional class, transthoracic echocardiography if appropriate, six-minute walk distance (6-MWD), assessing the NT-proBNP value and right-sided heart catheterization was performed when PH was suspected on echocardiography. Residual or recurrent CTEPH was

defined as a mPAP >25 mm Hg with a pulmonary wedge pressure <15 mmHg and a PVR >250 dyn·s·cm^{-5}.

Endpoints

The primary endpoint was time to CW, defined as the combination of death, need for PH-medication initiated after PEA or 15% decrease in 6-MWD without improvement of functional class during follow-up.

Statistical analysis

The data are expressed as mean and standard deviation if normal distribution was present and as median with range in the absence of normal distribution. Changes from baseline were evaluated with a paired *t* test for continuous variables and with a Wilcoxon Rank-Sum test or χ^2 test for ordinal variables if appropriate. Time to event data are presented as Kaplan-Meier curves and Cox proportional Hazard regression. Significance was determined at $p<0.01$; all reported p values were two tailed. All statistical analyses were performed by using SPSS software (SPSS Inc., version 17.0 for Windows; Chicago, IL).

RESULTS

Patient characteristics

Seventy-four consecutive patients (mean age 55.9±13.8 years, 51% female) were enrolled in this study. The patient baseline characteristics are summarized in table 1. At baseline, 55 patients (74%) were in NYHA functional class III or higher. The mean pulmonary artery pressure (mPAP) was 41.3±11.9 mmHg with a mean PVR of 521±264 dyn·s·cm^{-5} (range 279 -1331 dyn·s·cm^{-5}). The mean 6-MWD at baseline was 389±130 meters.

In hospital

Within three days after the PEA, the mean pulmonary artery pressure decreased to 25.2± 11.2 mmHg (p=0.001). During the post-operative period, five patients out of 74 (6.8%) died in the hospital. Three patients died as a consequence of reperfusion pulmonary edema of which one was treated with extracorporeal membrane oxygenation. The fourth patient died as a consequence of respiratory failure after septic pneumonia. The fifth patient died after multi organ failure.

Follow-up

The mean follow-up was 3.7±2.2 (range 0.1-8.5) years. One year after the PEA, the mean 6-MWD increased to 480±141 meters (p <0.001). There was also an improvement in NYHA functional class, 91.4% of the patients were in NYHA class I or II (p <0.001). During long-term follow-up, another five patients (out of 69) died (7.2%). Of these patients, only one patient died as the consequence of progressive residual PH. The overall one-, three- and five-year survival rates, with exclusion of the patients who died in-hospital, were 93%, 91% and 89%, respectively.

Clinical worsening

After the initial hospitalization, CW occurred in 13 out of 69 patients (18.8%) during follow-up. In 8 patients initiation of PH specific medication was needed during follow-up (table 2). The one-, two-, four-, six- and eight-year rates of freedom from CW were 94%, 90%, 81%, 68% and 57%, respectively. Figure 1 shows the Kaplan-Meier curve for freedom of CW. A comparison of the baseline characteristics of patients with and without CW is outlined in table 3. There were no significant differences between the two groups. The baseline NT-proBNP level tended to be the only predictor for the occurrence of CW (table 4).

TABLE 1. **Baseline characteristics**

Number of patients	74
Age (years)	55.9±13.8
Female (n (%))	35 (50.7)
BMI (kg/m2)	27.8±4.7
Systolic bloodpressure (mmHg)	129.9±21.2
Diastolic bloodpressure (mmHg)	80.1±13.7
NYHA functional class (I/II/III/IV)	2/12/48/7
6-MWD (m)	389±130
NT-proBNP (pg/mL)	1265±1346
Creatinine (µmol/L)	96.7±63.8
Right-sided heart catheterization	
PAP mean (mmHg)	41.3±11.9
PVR (dyn·s·cm^{-5})	521±264
CO (L/min)	4.7±1.2
VC (L)	3.7±1.1
FEV1 (%)	88.4±18.1
pO2 (kPa)	9.1±2.1
Saturation (%)	93.6±4.5
Follow-up (years)	3.7±2.2 (range 0.1-8.5)

BMI = Body Mass Index; NYHA = New York Heart Association; 6-MWD = six minute walk distance; NT-proBNP = N-terminal pro brain natriuretic peptide; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure

TABLE 2. Follow-up

Treatment during FU	
ERA only	3 (4.3)
PDE-5 inhibitor only	3 (4.3)
Combination of ERA and PDE-5 inhibitor	2 (2.9)
None	61 (88.5)
Endpoints	
Death	5 (7.2)
PH medication	8 (11.6)*
6-MWD worsening without improvement in NYHA FC	3 (4.3)**
Combination	13 (18.8)

FU = Follow-up; ERA = Endothelin receptor antagonist; PDE-5 inhibitor = phosphodiesterase type-5 inhibitor; PH medication = pulmonary hypertension medication; 6-MWD = six minute walk distance; NYHA FC = New York Heart Association Functional Class

* 2 of them died during FU, ** in 1 PH medication was initiated

TABLE 3. Baseline characteristics of patients with or without CW

	No CW	CW	p
Number in follow-up	56	13	
Age (years)	55.1±14.3	59.6±11.3	0.29
Female (n (%))	27 (51.8)	8 (61.5)	0.39
BMI (kg/m2)	27.9±4.9	27.4±3.7	0.78
Systolic bloodpressure (mmHg)	130.4±21.5	127.7±20.7	0.69
Diastolic bloodpressure (mmHg)	80.3±14.3	79.6±11.2	0.88
NYHA functional class (I/II/III/IV)	2/9/39/6	0/3/9/1	0.88
6-MWD (m)	393±138	374±89	0.68
NT-proBNP (pg/mL)	1092±1132	2648±2177	0.19
Right-sided heart catheterization			
PAP mean (mmHg)	41.9±12.1	38.5±11.0	0.36
PVR (dyn·s·cm^{-5})	534±264	467±269	0.48
CO (L/min)	4.7±1.2	5.0±1.2	0.51
VC (L)	3.7±1.0	3.7±1.4	0.83
FEV1 (%)	87.8±17.0	90.4±22.3	0.66
pO2 (kPa)	9.2±2.3	9.0±1.2	0.77
Saturation (%)	93.4±4.9	94.1±1.6	0.70
Follow-up (years)	3.4±2.2	5.1±1.8	0.02

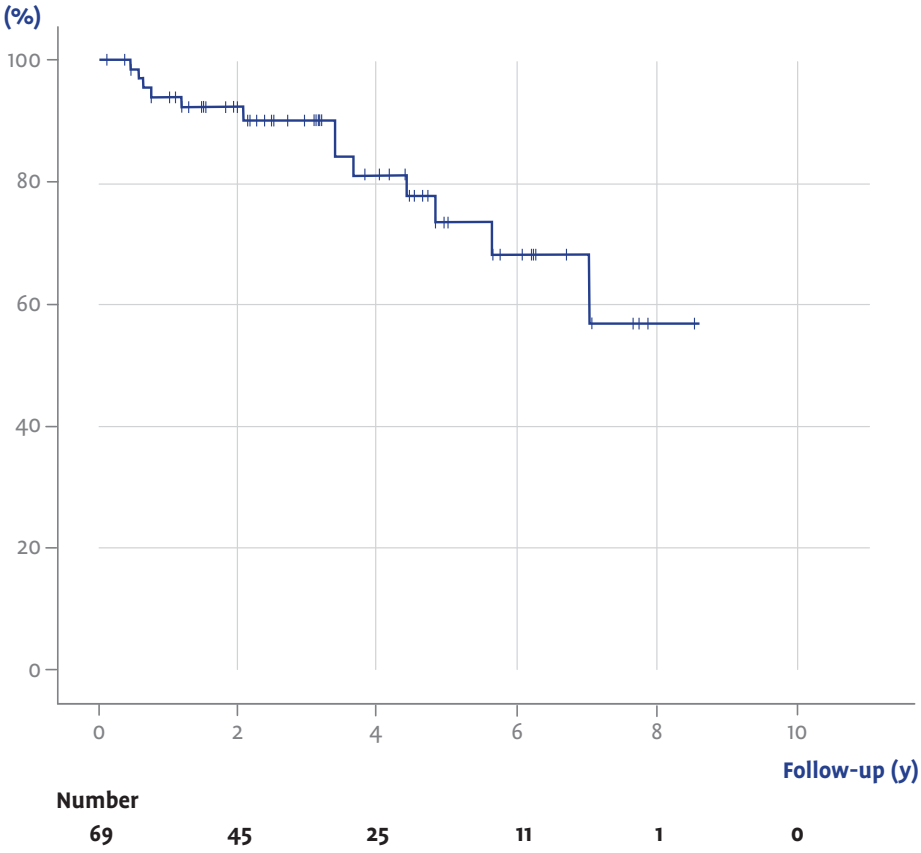
CW=Clinical worsening; BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; NT-proBNP = N-terminal pro brain natriuretic peptide; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure

TABLE 4. **Predictors for clinical worsening during follow-up using Cox proportional hazards**

	HR (univariate)	p
Male	0.54 (0.18-1.68)	0.29
BMI	1.02 (0.89-1.16)	0.80
Age	1.03 (0.98-1.08)	0.23
NYHA FC	0.73 (0.32-1.65)	0.45
6-MWD	1.00 (1.00-1.00)	0.79
PAP mean	0.98 (0.94-1.03)	0.47
PVR	1.00 (1.00-1.00)	0.36
CO	1.69 (0.89-3.32)	0.13
NT-proBNP	1.00 (1.00-1.00)	0.04
VC	0.92 (0.58-1.47)	0.73
FEV1	1.01 (0.98-1.05)	0.53
pO2	0.95 (0.72-1.26)	0.73
Saturation	1.04 (0.88-1.23)	0.64

HR = Hazard ratio; BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; NT-proBNP = N-terminal pro brain natriuretic peptide; VC = vital capacity; FEV1 = Forced Expiratory Volume in 1 second; pO2 = O2-pressure

FIGURE 1. Free of death



DISCUSSION

A PEA is thought to provide a potential cure for patients with CTEPH. However, the development of CW had never been described in patients who underwent a PEA. We found that CW occurred in almost 19% of the patients within four years after the surgical treatment. With increasing institutional and surgical experience, most centres report improved in-hospital survival as case volume increases. Jamieson et al. described the decline in peri-operative mortality over the years from 17% to 4.4% after changes in the operative technique.[5] In 2006, Matsuda and colleagues reported an in-hospital mortality rate of 7.8% after PEA (n=102) and a three- and five-year survival rate of 91% and 84%, respectively.[12]

We found an in-hospital mortality rate after PEA of 6.8%. The overall one-, three- and five-year survival rates were 93%, 91% and 89%, respectively. These results are comparable to the results mentioned in the studies above.

Residual PH after PEA has been described in several reports. The reported rates vary from 5% to 35%, depending on the definition.[13-16] It is believed that a substantial component of persistent post-operative PH is related to distal pulmonary vasculopathy in small precapillary vessels both in the occluded and non-occluded pulmonary vascular bed.[17-18] The extent and type of microvascular disease in CTEPH have a strong influence on the likelihood of a successful outcome in PEA.[19] Freed et al. described the survival of a study cohort of 314 CTEPH patients who underwent PEA and suffered from residual PH. Surprisingly, in this study residual PH after PEA did not have a significant effect on survival. In 8% of the patients, PH specific medication was started after PEA.[13] A report by Reesink et al. described initiation of PH specific medication in 3 of 38 patients (8%) who underwent PEA and of whom follow-up data were available.[21] In our study, initiation of PH specific medication after PEA was needed in 8 (in two patients it was initiated immediately after surgery) of 69 patients (11.5%) within 1.8 years (range 0-5.6 years) after PEA, which is in agreement with the rates mentioned above.

Another frequently used endpoint in clinical trials is NYHA functional class. Freed et al. reported an improvement in NYHA functional class among 229 patients with CTEPH who underwent PEA. At baseline 88% of the patients were in NYHA class III or IV. Three months after PEA, 87% of the patients were in NYHA class I or II. One year after PEA 91% of the patients were in NYHA functional class I or II.[20] Corsico and associates described

the long-term outcome after PEA in 157 patients.[22] At baseline 97% of the patients were in NYHA functional class III or IV. One year after PEA only 12% of the patients were in NYHA class III or IV. Post-operative NYHA class III or IV appeared to be associated with the highest risk of late events (i.e. death related to CTEPH or PEA, lung transplant or PEA redo between 3 months and 5 years after PEA). In our present study 55 patients (74%) were in NYHA functional class III or IV at baseline. One year after PEA, 91% of the patients were in NYHA class I or II, in accordance with the results of other reports.

The 6-MWD is another frequently used parameter to evaluate the effect of PEA. Reesink et al. demonstrated that the 6-MWD correlated with parameters reflecting clinical and hemodynamic severity of disease in CTEPH. A PEA performed in 42 patients resulted in a significant increase in the 6-MWD, one year after surgery.[21] In our study, at baseline the mean 6-MWD was 389 meters and increased to 480 meters at one year follow-up. This is comparable with the results from other reports.[20,21]

Recent pivotal trials in pulmonary arterial hypertension have used time to CW as a composite endpoint as described by McLaughlin and associates.[23] It is a combination of mortality and different parameters which described morbidity after the initiation of specific pulmonary hypertension therapy. The definition most frequently used is a combination of all-cause mortality, non-elective hospital stay for PH to initiate intravenous prostanoid or lung transplantation, and disease progression defined as a reduction from baseline in 6-MWD distance by 15%.[23] In our CTEPH patients we defined the composite endpoint time to CW as the combination of death after discharge from the hospital after PEA, initiation of pulmonary hypertension specific medication, or a decrease in 6-MWD by 15% without improvement in functional class. Because CTEPH is potentially a curable disease, in almost all patients the PH-specific medication is discontinued shortly after PEA. The need to initiate PH-specific medication after surgery reflects deterioration of the clinical situation in this specific group of patients.

In our study, although post-operative values regarding mortality, residual PH, NYHA functional class, and 6-MWD were comparable to other studies, CW occurred in 13 patients (19%) during long-term follow-up, with a five year rate of freedom from CW of 72%. The initiation of PH-specific medication was the main reason for CW, whereas in 12% PH-specific medication was started because of residual PH.

In our study we could not find a significant predictor at baseline for CW during long-term follow-up. This might be due to the small number of patients included in our study. Data from other studies to verify our results are lacking.

The main limitation of this study is its retrospective observational design. Another limitation is the small study population and small number of events, therefore the results should be interpreted with caution.

CONCLUSION

Pulmonary endarterectomy is associated with a good long-term survival in patients with CTEPH. However, CW occurred in a substantial number of patients after long-term follow-up.

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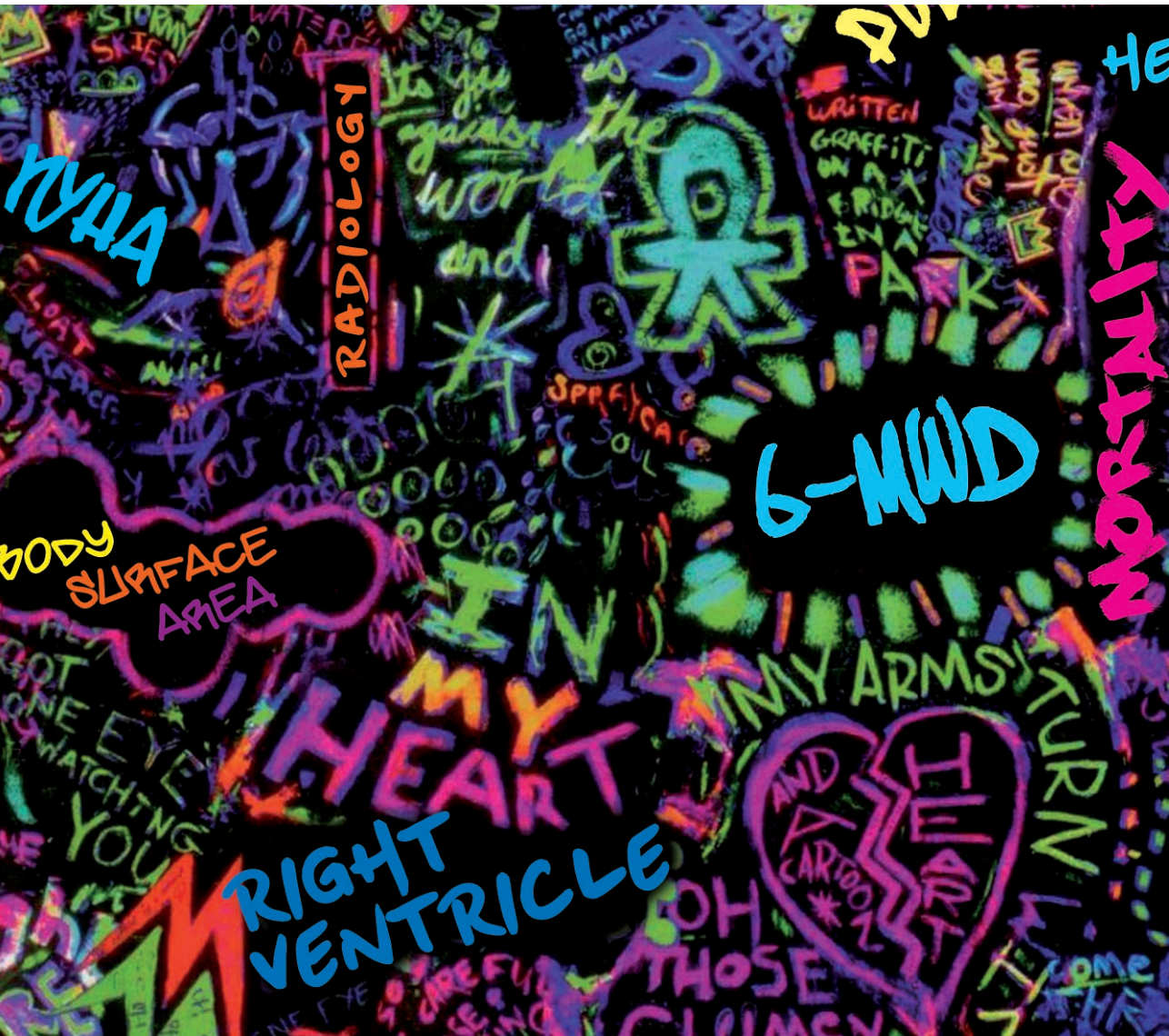
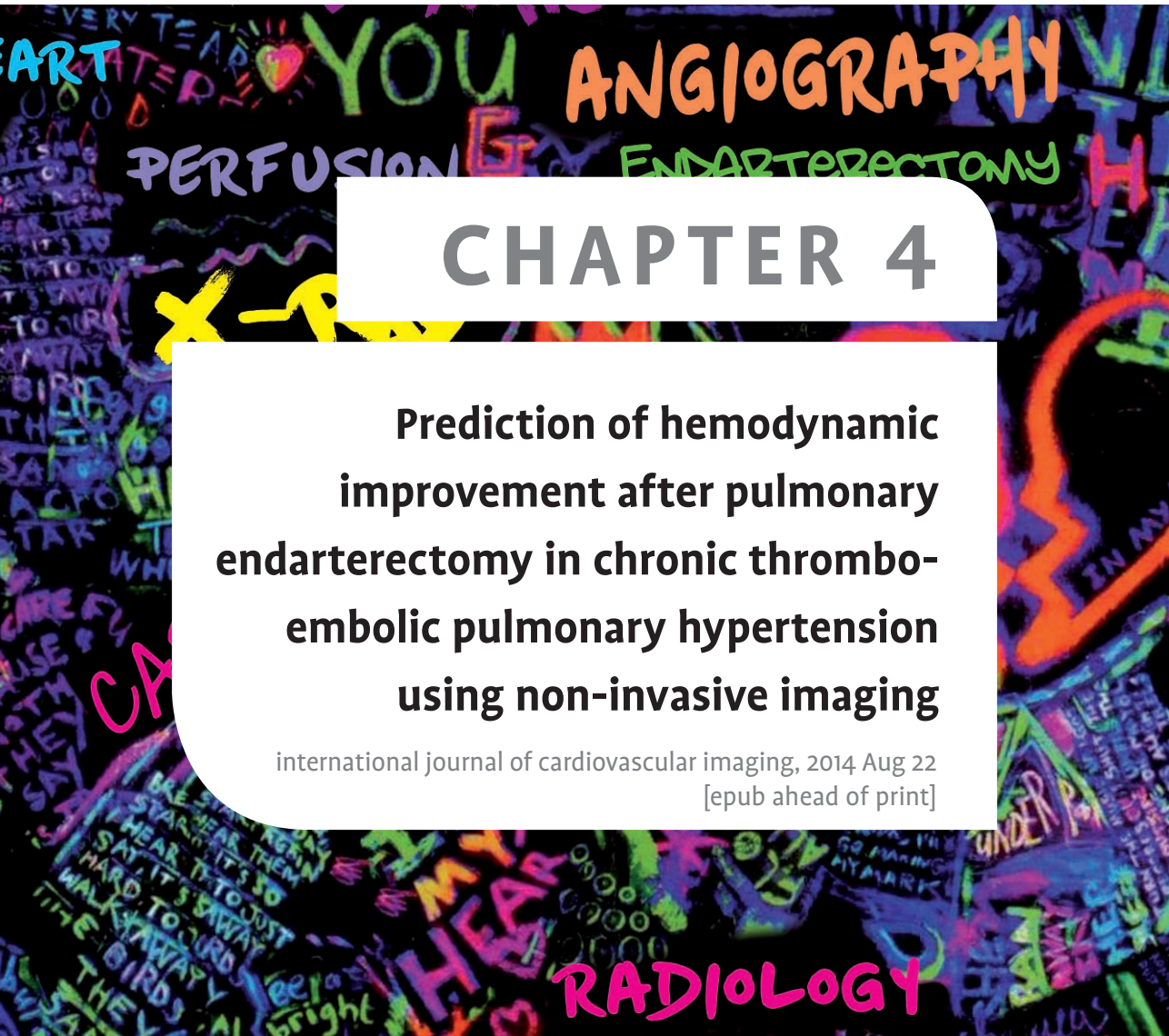

RADIOLOGY
WRITTEN GRAFFITI ON A BRIDGE IN A PARK
6-MWD
MORTALITY
BODY SURFACE AREA
IN MY HEART
RIGHT VENTRICLE
AND A CARTOON HEART
OH THOSE

BASTIAAN E. SCHÖLZEL, MARTIJN C. POST,
ALEXANDER VAN DE BRUAENE, WIM WUYTS,
STEVEN DYMARKOWSKI, BART MEYNS,
WERNER BUDTS, MARION DELCROIX



CHAPTER 4

Prediction of hemodynamic improvement after pulmonary endarterectomy in chronic thrombo-embolic pulmonary hypertension using non-invasive imaging

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ABSTRACT

Purpose

Pulmonary endarterectomy (PEA) is the recommended treatment in chronic thromboembolic pulmonary hypertension (CTEPH). Prediction of outcome after PEA remains challenging. In search for pre-operative predictors we evaluated non-invasive parameters measured by chest CT-scan and echocardiography.

Methods

Between May 2004 and January 2009, 52 consecutive patients with CTEPH who underwent PEA (59.6% female, mean age 58.9±13.4 years) were included. Prior to surgery, pulmonary artery (PA) diameter indices were calculated by chest CT scan and different echocardiographic measurements to evaluate pulmonary hypertension were obtained. Hemodynamic improvement after PEA was defined as a pulmonary vascular resistance (PVR) <500 dyn·s·cm^{-5} and a mean pulmonary artery pressure (PAP) <35 mmHg three days after PEA. Mortality was evaluated at day 30.

Results

Mean PAP at baseline was 40.1±8.5 mmHg, with a PVR of 971±420 dyn·s·cm^{-5}. Persistent pulmonary hypertension was observed in 15 patients (28.8%). Gender, pre-operative mean PAP, PA diameter indices, and TAPSE were all predictors for hemodynamic improvement after PEA. The indexed PA diameter on CT was the only independent predictor for hemodynamic improvement: 19.4±2.4 mm/m^2 versus 22.9±4.9 mm/m^2 in those without improvement (OR 0.76; 95% CI 0.58-0.99; p=0.04).

All patients who died within 30 days (9.6%) had persistent pulmonary hypertension, with a post-operative mean PAP of 51.6±14.1 mmHg and PVR of 692±216 dyn·s·cm^{-5}.

Conclusion

The pre-operative PA diameter indexed for body surface area was the only independent predictor for hemodynamic improvement after PEA in CTEPH patients. In all patients who died within 30 days after PEA, persistent pulmonary hypertension was present.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) might develop within two years after an initial pulmonary thromboembolic event in approximately 1.5 to 3.8%.[1,2] The preferred treatment for CTEPH is a surgical pulmonary endarterectomy (PEA). However, in 30-50% of the patients who developed CTEPH, PEA cannot be performed.[3-5] Crucial for determining the operability is the surgical accessibility of the thrombus and the concordance between mechanical obstruction and level of pulmonary hypertension. Despite a careful selection procedure, the peri-operative mortality rate is still high, between 5 and 10% in experienced centres.[6-9] Important predictors for mortality after PEA surgery are the pre-operative and post-operative pulmonary vascular resistance (PVR).[8-10] A correlation between the main pulmonary artery (PA) diameter and pulmonary hemodynamic parameters before PEA have been described in CTEPH patients,[11] however it has never been correlated to hemodynamic outcome after PEA. We evaluated whether pre-operative non-invasive parameters, like PA diameter indices on CT scan, and also echocardiographic parameters, were able to predict post-operative pulmonary hemodynamics and mortality.

METHODS

Patients

All consecutive CTEPH patients who underwent contrast-enhanced chest CT scan and transthoracic echocardiography (TTE) prior to PEA in the University Hospitals of Leuven between May 2004 and January 2009 were included in this retrospective study. Before surgery all patients underwent a right-sided heart catheterization (RHC) and pulmonary angiography. Survival at day 30 was recorded. A multidisciplinary panel including a pulmonologist, a radiologist, and a cardiothoracic surgeon reviewed each case. Patients were considered suitable for surgery when they were symptomatic, had an elevated PVR (>250 dyn·s·cm^{-5}), segmental or more proximal lesions and no severe co-morbidity. Hemodynamic severity was not a reason to reject a patient for surgery. The study was approved by the local ethical committee.

Right-sided heart catheterization

Pre-operatively, within a time frame of 3 months, a RHC through the right jugular vein was done in all patients. The pulmonary artery (PAP) and pulmonary artery occlusion (PAOP) pressures were measured. Cardiac output (CO) was recorded using the thermodilution technique, and PVR was calculated as (mean PAP-PAOP) x 80/CO. This procedure was repeated three days after PEA in 52 patients (98%) with measurement of left atrial pressure in place of PAOP. Pre-operative New York Heart Association (NYHA) functional class and six-minute walk distance (6-MWD) were recorded within 3 days of the pre-operative RHC.

Transthoracic echocardiogram

Echocardiographic examinations were performed pre-operatively following international guidelines on echocardiographic assessment of the right heart in adults.[12] The examinations were stored digitally for off-line analysis. Echocardiographic measurements consisted of right ventricular (RV) area, left ventricular/RV area ratio, right atrium (RA) area, PA acceleration time, RV ejection time, RV Tei contractility index, vena cava inferior diameter, tricuspid annular plane systolic excursion (TAPSE), RV to RA pressure gradient, mitral valve E/E' velocity ratio and the presence of pericardial effusion.

CT scan of the chest

A helical CT scan of the chest was performed pre-operatively using either a 16- or 64 slice MDCT scanner and standard preset procedures. Images were acquired at a fixed delay of

40 seconds after the start of injection of contrast material. This allowed for clear opacification of both the pulmonary arteries and the thoracic aorta. Vascular enhancement was achieved by injecting 120 ml of non-ionic intravenous contrast material (Xenetix 350, Guerbet) at a rate of 3 ml/s using a power injector (Envision CT Injector, Medrad, Pittsburgh, PA, USA). Transverse and coronal slices of 3 mm were reconstructed and interpreted by a single radiologist, blinded to the surgical outcome and pre- and post-operative hemodynamic measurements.

According to the study by Heinrich et al., the widest diameters of the ascending aorta (Ao) and the widest diameter of the main pulmonary artery perpendicular to its long axis were measured at the level of the bifurcation of the pulmonary artery (figure 1). The ratio of the PA and the Ao diameters was calculated[11]. The PA diameter was indexed by body surface area (BSA).

Clinical outcome

Hemodynamic improvement after PEA was defined as a PVR <500 dyn·s·cm^{-5} and a mean PAP <35 mmHg three days after PEA[3,10]. The 30-days mortality rate was mentioned.

Statistical analysis

Descriptive statistics were used where applicable. Continuous variables were reported as mean ± standard deviation. Proportions were given by numbers and corresponding percentages. Differences between groups were analyzed by paired or unpaired Student's *t* test for continuous variables, and χ^2 test was done for nominal variables. Univariate logistic regression was used to determine risk factors for hemodynamic improvement. Following univariate analysis, variables with a p-value of less than or equal to 0.05 were entered into a multivariate logistic regression model. The Odds ratios (OR) with their 95% confidence intervals (CI) were calculated. The OR's for 6-MWD and PVR were calculated per 10 meters and 10 dyn·s·cm^{-5}, respectively. The cut-off value for PA diameter to predict hemodynamic improvement was determined by receiver operating characteristics (ROC) curve analysis. All tests were two-sided and the level of significance was set at $p<0.05$. Statistical analysis was performed with the SPSS software version 17.0 (Chicago, IL) for Windows XP.

RESULTS

Patient characteristics

In total, 102 CTEPH patients were screened for operability. Fourty-eight patients were not suitable for PEA (inoperable CTEPH). Eventually, 54 patients (52.9%) underwent a PEA in our hospital. One patient was excluded because the CT scan of the chest was performed in another hospital. Another patient was excluded because no hemodynamic data after PEA were available. Therefore, 52 patients (59.6% female, mean age of 58.9±13.4 years) could be included in the study. Thirty-seven patients (71.2%) suffered a known pulmonary embolism in the past. The median time between the first episode of pulmonary embolism and the pulmonary endarterectomy was 1.5 years (range 0.3-28.7 years). In two patients the PEA was combined with coronary artery bypass grafting surgery and in one patient with the closure of a patent foramen ovale. The median stay at the intensive care unit was 6 days (range 2-35 days). All baseline characteristics are summarized in table 1. Fifty patients (96.2%) were in sinus rhythm at the moment of PEA. In 8 patients treatment with PH specific medication was initiated in the months before PEA (prostacyclins) and in one patient shortly after surgery (endothelin-receptor antagonist).

At the moment of screening, the inoperable patients had a mean age of 65.4±14.3 years, a PVR of 699±380 dyn·s·cm^{-5}, a mean PAP of 41.0±11.8 mmHg and a 6-MWD of 294±152 meters.

Hemodynamic changes after PEA

Before PEA, mean PAP was 40.1±8.5 mmHg, and PVR was 971±420 dyn·s·cm^{-5} (range 242-2062). Three days after surgery the mean PAP decreased to 33.8±11.9 mmHg and PVR was 328±163 dyn·s·cm^{-5} ($p<0.001$ for both, compared to baseline) [figure 2 and 3]. Incomplete hemodynamic improvement occurred in 15 patients (28.8%, 87% female, mean age 59.3±14.0 years). The characteristics of the patients with and without hemodynamic improvement are summarized in table 2. In 9 patients the PVR was >500 dyn·s·cm^{-5} with a mean PAP >35 mmHg. In the other 6 patients the PVR was <500 dyn·s·cm^{-5}, but the mean PAP was >35 mmHg and therefore they did not meet the criteria for hemodynamic improvement.

Predictors of improved outcome

Univariate logistic regression identified male gender (OR 6.86: 95% CI 1.36-34.7, p=0.02), lower mean PAP (OR 0.85: 95% CI 0.77-0.94, p=0.001), lower PA diameter on CT (OR 0.86:

95% CI 0.76-0.97, p=0.01), lower PA diameter indexed for BSA (OR 0.75: 95% CI 0.61-0.93, p=0.008), and higher TAPSE (OR 1.22: 95% CI 1.02-1.46, p=0.03) as predictors for hemodynamic improvement. By multivariate analysis the indexed PA diameter was the only independent pre-operative predictor of hemodynamic improvement after PEA, 19.4±2.4 mm/m^2 in patients with versus 22.9±4.9 mm/m^2 in patients without hemodynamic improvement (OR 0.76: 95% CI 0.58 - 0.99, p=0.04). These data are summarized in table 2. The area under the ROC curve for PA/BSA was 0.69, and the optimal cut-off value to predict hemodynamic improvement after PEA was 19.2 mm/m^2, yielding a sensitivity and specificity of 80% and 45.9%, respectively.

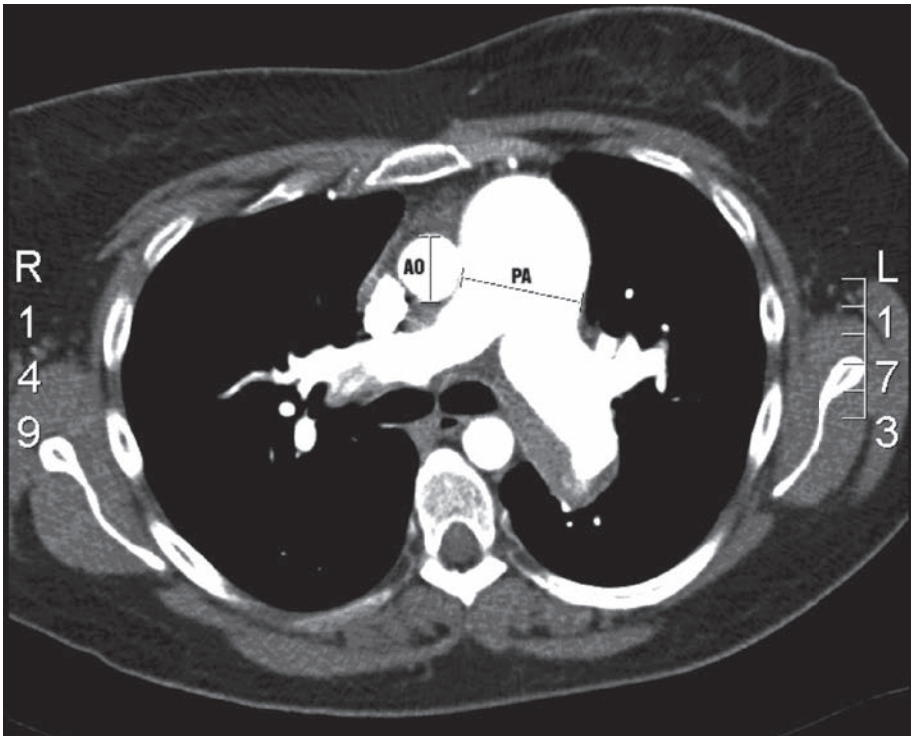
When we would define hemodynamic improvement only based on a mean PAP <35 mmHg (n=37), univariate analysis identified gender, systolic PAP, diastolic PAP, mean PAP, PVR, PA diameter, PA/BSA and TAPSE at baseline as predictors. Unfortunately, we did not identify an independent predictor for hemodynamic improvement.

For hemodynamic improvement based on a PVR <500 $dyn{\cdot}s{\cdot}cm^{-5}$ (n=43), systolic PAP, diastolic PAP, mean PAP, PA diameter, PA/BSA and RV-RA gradient at baseline were identified as predictors. Again, we were not able to identify an independent predictor for hemodynamic improvement in multivariate analysis.

Mortality

Within 30 days after PEA, 5 patients (9.6%) died (100% female, mean age 54.9±15.9 years). The mean AP/BSA ratio for these patients was 23.1±4.8 mm/m^2. Two patients died due to right ventricle failure, one patient due to thoracic bleeding, ARDS and systemic inflammatory response syndrome (SIRS). In all, hemodynamic improvement was incomplete or absent, with a post-operative mean PAP of 51.6±14.1 mmHg and PVR of 692±216 $dyn{\cdot}s{\cdot}cm^{-5}$ in patients who died, compared to a post-operative mean PAP of 32.2±10.1 mmHg and PVR of 302±141 $dyn{\cdot}s{\cdot}cm^{-5}$ in patients who survived.

FIGURE 1. **Contrast-enhanced CT-scan of a patient with CTEPH**



The widest diameter of the aorta (AO) and the widest diameter of the main pulmonary artery (PA) perpendicular to its long axis were measured at the level of the bifurcation of the pulmonary artery.

FIGURE 2. **Mean pulmonary artery pressure before and three days after surgery for all patients**

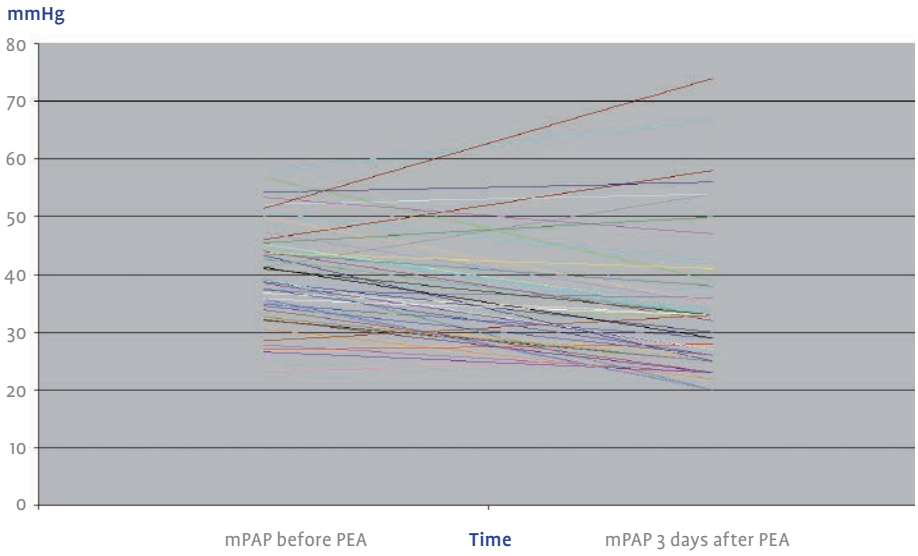


FIGURE 3. **Pulmonary vascular resistance before and three days after surgery for all patients**

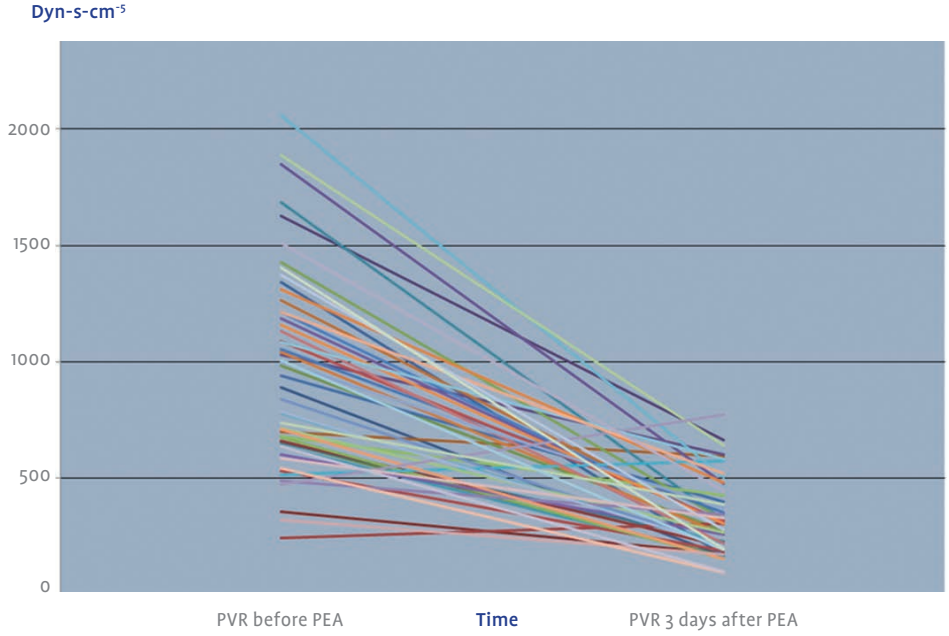


TABLE 1. Pre-operative characteristics of all included patients

	Operable CTEPH
Number	52
Gender, n (%)	
Male	21 (40.4)
Female	31 (59.6)
Age (years)	58.9±13.4
BMI, kg/m^2	26.9±5.2
BSA (m$^{2)}$	1.87±0.20
FEV_1 (%)	84.4±21.4
NYHA	2.8±0.6
6-MWD (m)	352±114
Heartrate (beats/min)	80±15
Right-sided heart catheterization	
RA pressure (mmHg)	8.9±5.0
Systolic PA pressure (mmHg)	83.8±16.8
Diastolic PA pressure (mmHg)	31.7±10.0
Mean PA pressure (mmHg)	40.1±8.5
PAOP (mmHg)	8.9±4.2
PA O_2-saturation, %	60.1±10.9
CO, l·min^{-1}	3.7±1.0
PVR, dyn·s·cm^{-5}	971±420 (range 242-2061)
CT scan	
Ao (mm)	33.5±4.4
PA (mm)	37.9±6.0
PA/Ao	1.14±0.17
PA/BSA (mm/m$^{2)}$	20.4±3.6

Echocardiography	
RA area ($cm^{2)}$	19.8±6.0
RV diastolic area ($cm^{2)}$	30.8±7.2
LV/RV area ratio	0.81±0.19
PA acc time (ms)	67.6±13.9
RV ejection time (ms)	303±43.0
Tei index	0.60±0.23
TAPSE (mm)	16.8±5.1
RV-RA pressure gradient (mmHg)	78.0±18.8
VCI diameter (mm)	10.9±7.0
MV E/E'	5.9±2.8
Pericardial effusion (%)	44.4

N = number; BMI = body mass index; BSA = body surface area; FEV1 = Forced expiratory volume in 1 second; NYHA = New York Heart Association functional class; min = minutes; 6-MWD = six-minute walk distance; RA = right atrium; PA = pulmonary artery; PAOP = pulmonary artery occlusion pressure; CO = cardiac output; PVR = pulmonary vascular resistance; Ao = aorta, RV = right ventricle; LV = left ventricle; PA acc time = pulmonary artery acceleration time; TAPSE = tricuspid annular plane systolic excursion; VCI = vena cava inferior; MV = mitral valve

TABLE 2. Hemodynamic improvement after pulmonary endarterectomy

	Improvement		Univariate			Multivariate		
	No	Yes	OR	CI (95%)	p	OR	CI (95%)	p
Number	15 (28.8)	37 (71.2)	–	–	–	–	–	–
Gender, n (%)			6.86	1.36-34.7	0.02	3.82	0.48-30.3	0.21
Female	13 (86.7)	18 (48.6)						
Male	2 (13.3)	19 (51.4)						
Age (years)	59.3±14.0	58.8±13.3	1.00	0.95-1.04	0.90			
BMI (kg/m$^{2)}$	26.6±2.9	27.0±5.9	1.02	0.90-1.14	0.81			
BSA, m^2	1.8±0.2	1.9±0.2	3.50	0.17-73.7	0.42			
FEV_1 (%)	78.8±22.5	86.7±20.8	1.02	0.99-1.05	0.23			
NYHA FC	2.9±0.5	2.7±0.6	0.44	0.13-1.44	0.17			
6-MWD (m)	326±156	358±104	1.02*	0.97-1.08	0.39			
Heart rate (beats/min)	79.9±14.2	79.8±15.7	1.00	0.96-1.04	0.98			
Right-sided heart catheterization								
RA pressure (mmHg)	9.1±4.3	8.8±5.3	0.99	0.88-1.12	0.88			
Systolic PA pressure (mmHg)	87.9±15.8	82.1±17.1	0.98	0.94-1.02	0.26			
Diastolic PA pressure (mmHg)	35.2±9.3	30.2±10.0	0.95	0.89-1.01	0.11			
Mean PA pressure (mmHg)	46.8±8.1	37.5±7.1	0.85	0.77-0.94	0.001	0.93	0.82-1.04	0.19

PAOP (mmHg)	7.7±3.2	9.4±4.5	1.12	0.95-1.31	0.20			
PA O_2-saturation (%)	61.4±11.4	59.7±10.8	0.99	0.93-1.04	0.61			
CO ($l \cdot min^{-1}$)	3.6±1.0	3.7±1.0	1.16	0.63-2.13	0.64			
PVR ($dyn \cdot s \cdot cm^{-5}$)	1105±468	917±393	0.99†	0.98-1.00	0.15			
CT scan								
Ao (mm)	34.8±4.2	33.0±4.4	0.91	0.79-1.05	0.18			
PA (mm)	41.6±8.0	36.4±4.2	0.86	0.76-0.97	0.01			
PA/Ao	1.2±0.2	1.1±0.2	0.07	0.002-2.3	0.13			
PA/BSA (mm/m^2)	22.9±4.9	19.4±2.4	0.75	0.61-0.93	0.008	0.76	0.58-0.99	0.04
Echocardiography								
RA area (cm^2)	19.5±4.7	19.9±6.4	1.01	0.90-1.13	0.84			
RV diastolic area (cm^2)	30.2±9.0	31.1±6.6	1.02	0.93-1.11	0.70			
LV/RV-ratio	0.76±0.21	0.83±0.19	6.45	0.23-183	0.28			
PA acc time (ms)	69.3±13.5	66.9±14.1	0.99	0.94-1.03	0.58			
RV ejection time (ms)	291±32	308±46	1.01	0.99-1.03	0.28			
RV Tei index	0.63±0.30	0.58±0.20	0.34	0.02-5.21	0.44			
VCI diameter (mm)	14.0±5.7	9.8±7.2	0.91	0.83-1.01	0.08			
TAPSE (mm)	14.2±4.1	17.9±5.2	1.22	1.02-1.46	0.03	1.11	0.89-1.39	0.36
RV-RA gradient (mmHg)	83±20	76±18	0.98	0.95-1.01	0.23			
MV E/E'	6.2±3.3	5.8±2.6	0.95	0.75-1.21	0.69			

Table footnote on next page

BMI = body mass index; BSA = body surface area; FEV1: Forced expiratory volume in 1 second; NYHA FC = New York Heart Association functional class; 6-MWD = six-minute walk distance; min = minutes; RA: right atrium; PA = pulmonary artery; PAOP = pulmonary artery occluded pressure; CO = cardiac output; PVR = pulmonary vascular resistance; Ao = aorta; RV = right ventricle; LV = left ventricle; PA acc time = pulmonary artery acceleration time; TAPSE = tricuspid annular plane systolic excursion; VCI = vena cava inferior, MV = mitral valve; OR = odds ratio; CI = confidence interval.

DISCUSSION

The present study is the first demonstrating the pulmonary artery diameter indexed for BSA as an independent pre-operative non-invasive predictor for in-hospital hemodynamic improvement after pulmonary endarterectomy for CTEPH.

The only definite treatment in patients with CTEPH is a PEA, with a benefit in symptoms, hemodynamics and survival.[11] However, this major surgical procedure is not without risk, the peri-operative mortality rate varies between 5% and 10%.[3,6-9,13] The 30-days mortality rate in our study was 9.6%, which is in agreement with the studies mentioned above. Several studies have associated high pre-operative PVR (i.e. >900-1100 dyn·s·cm^{-5}) with increased mortality after PEA.[8-10,14,15] The post-operative PVR is also strongly related to mortality, and a decrease to less than 500 dyn·s·cm^{-5} has been reported as optimal.[3,10] Residual pulmonary hypertension after PEA may result from incomplete endarterectomy, inaccessible chronic thromboemboli or small-vessel arteriopathy and is associated with a higher risk on late post-operative adverse events.[16] The reported rates of persistent post-operative pulmonary hypertension vary from 5% to 35%, depending on the definition.[9,13,17,18] Absence of hemodynamic improvement (i.e. residual pulmonary hypertension) was found in 28.8% of the patients in our study. This is in agreement with the results from other reports.[13,17] It should be mentioned that all deaths within 30 days after PEA in our study were patients who were suffering from residual pulmonary hypertension.

Several studies have identified predictors of residual pulmonary hypertension. Tscholl et al. identified age, right atrial pressure and female gender as risk factors for absence of hemodynamic improvement, defined as a PVR ≥ 500 dyn·s·cm^{-5}.[19] A study by Bonderman

et al. described that the incidence of residual pulmonary hypertension was higher in patients with CTEPH and associated medical conditions such as splenectomy, ventriculoatrial shunt for the treatment of hydrocephalus, permanent central intravenous lines, inflammatory bowel disease and osteomyelitis.[18] The correlation between non-invasive imaging techniques and pre-operative hemodynamics have been reported earlier.[11] The association between PA indices measured by chest CT scan and pulmonary hemodynamic characteristics in operable CTEPH have been described by Heinrich et al.[11] In this retrospective study the PA diameter and the ratio of the PA and aortic diameters correlated with the pre-operative hemodynamics in 60 patients who underwent a PEA.[11] However, these parameters did not correlate with post-operative improvement. A study by Schmidt et al. also demonstrated a positive correlation between the diameter of the PA on CT and the mean PAP and PVR in patients with CTEPH.[20] Ng et al. showed that in patients with a wide range of pulmonary and cardiovascular diseases the PA was influenced by the BSA.[21] Therefore we indexed the PA diameter for BSA in our study. We identified female gender, an increased mean PAP, a lower TAPSE and larger PA diameter indices as predictors of unfavourable hemodynamic outcome. However, the pulmonary artery diameter indexed for BSA was the only independent pre-operative predictor for hemodynamic improvement, i.e. the larger the indexed PA diameter, the higher the risk for unfavourable hemodynamic outcome after PEA. This might be explained by the presence of a more extensive disease in patients with higher PA diameters. The dilation of the PA reflects both the degree and the duration of the presence of increased pulmonary artery pressure. The modified compliance of the pulmonary artery is an important factor in the relationship between the PA diameter and the increased pulmonary artery pressure. Earlier studies provided evidence that structural changes in elastin and collagen of the PA vessel wall in the presence of an increased PAP might eventually become a cause of PA dilatation.[22,23] Furthermore, altered flow in pulmonary hypertension affects wall shear stress and eventually matrix properties of the vessel wall that may contribute to PA dilatation.[24]

Previous echocardiographic studies in CTEPH patients showed the good effect of PEA on right-sided echocardiographic parameters.[25-27] In patients with idiopathic pulmonary hypertension, echocardiographic parameters like pericardial effusion, right atrial enlargement and septal displacement have been shown to be predictors of adverse outcome.[28] Hardziyenka et al. found TAPSE to be a pre-operative determinant of in-hospital mortality following PEA, although TAPSE did not appear to be the strongest determinant.[27] In the present study, a lower TAPSE was associated with poor post-operative hemodynamics. However, it was not identified as an independent predictor for hemodynamic improvement after PEA.

Newer echocardiographic imaging techniques might become to play a role in the diagnostic work-up in patients with CTEPH. Recently, three-dimensional (3D) echocardiography showed promising results for measuring RV volumes and function in comparison to cardiac magnetic resonance in pulmonary arterial hypertension,[29] but more experience is needed with this imaging modality in (chronic thromboembolic) pulmonary hypertension to determine the additional value in the diagnostic process.

The pre-operative non-invasively measured PA diameter indices might be valuable additives in predicting the hemodynamic outcome prior to PEA. However, every patient with CTEPH should be referred to a CTEPH centre with an experienced surgeon regardless of prognostic indices. Studies with larger study population are necessary to verify these results.

Some limitations of our study have to be mentioned. First, it is a retrospective study which might imply incomplete data. However, PEA is an uncommon surgical procedure and all patients underwent a similar pre-operative work-up, and a standardized post-operative follow-up. Early post-operative hemodynamic data were only missing in one patient. Secondly, it is a single centre study, therefore a selection bias might be present. Thirdly, we had to deal with a small sample size. This might have led to non-significant analysis because of lack of statistical power. However, the low number of patients might affirm the significance of our findings.

In conclusion, this is the first study showing that the pre-operative PA/BSA ratio was an independent predictor for hemodynamic outcome after PEA. Therefore, we have to consider that the PA diameter indices might be valuable additives in predicting the hemodynamic outcome prior to PEA.

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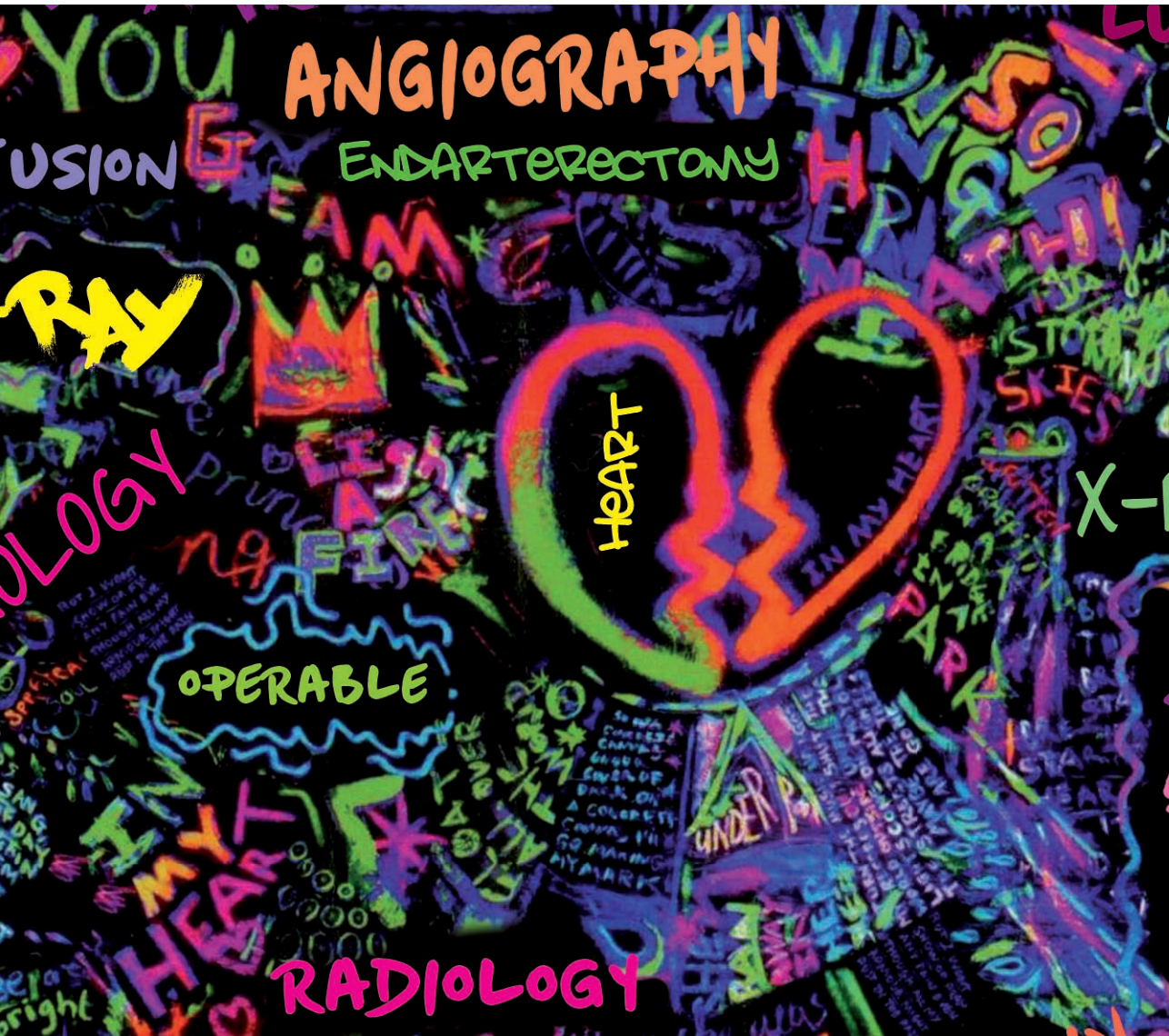
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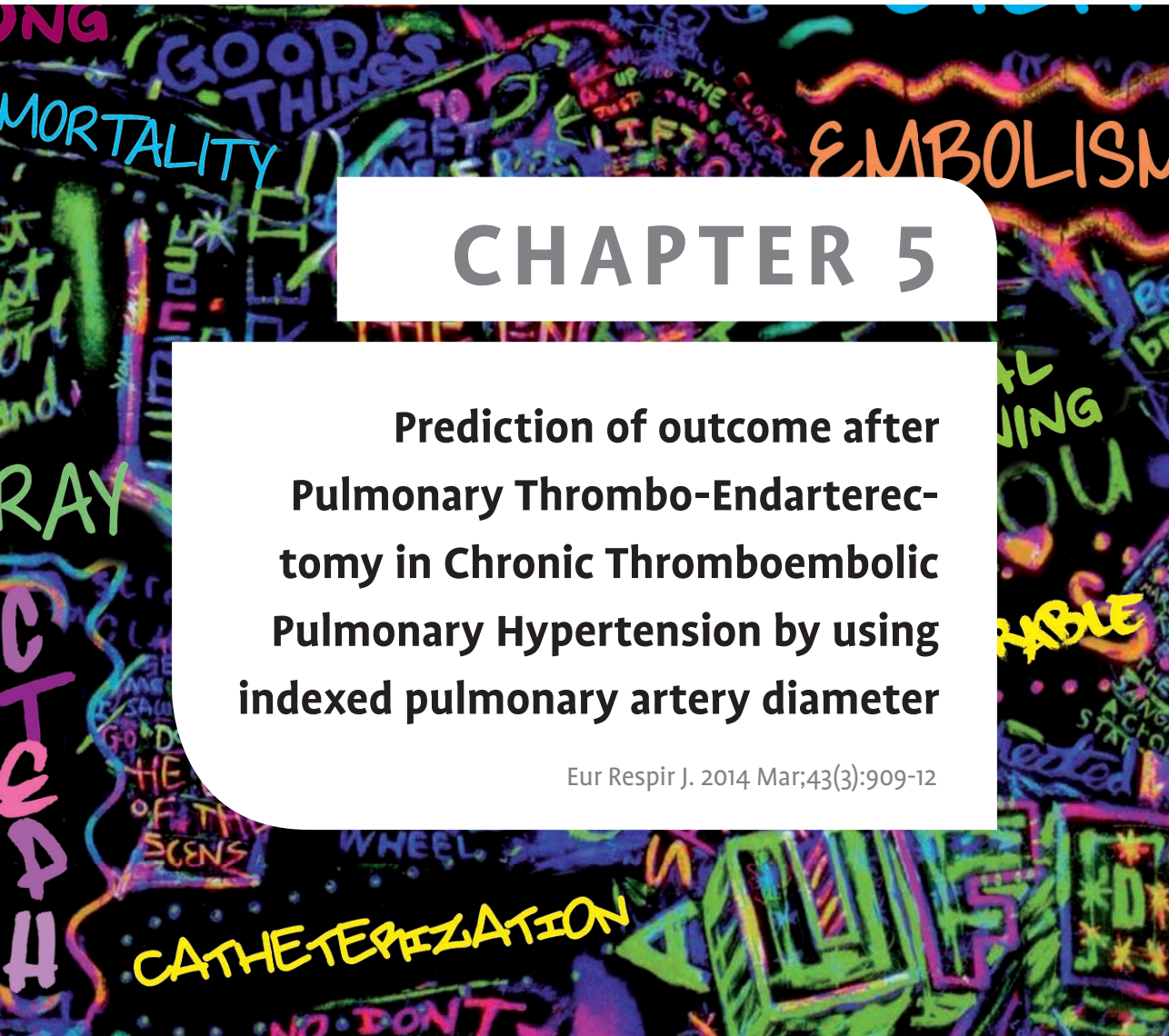

CHAPTER 5

Prediction of outcome after Pulmonary Thrombo-Endarterectomy in Chronic Thromboembolic Pulmonary Hypertension by using indexed pulmonary artery diameter

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INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is associated with considerable morbidity and mortality.[1] It occurs in 2-4% of patients after acute pulmonary embolism (PE).[2] Pulmonary endarterectomy (PEA) is the treatment of choice to relieve pulmonary artery obstruction in patients with CTEPH and has been remarkably successful.[3] However, in 10-50% of the patients PEA is not possible due to either distal pulmonary vascular obstruction that is surgically inaccessible or significant comorbidities thought to be associated with unacceptably high risk.[4] Therefore, careful selection of operable candidates is paramount. A correlation between the main pulmonary artery (PA) diameter and pulmonary hemodynamic parameters before PEA have been described in CTEPH patients.[5] We evaluated whether pre-operative PA diameter indices could predict the occurrence of mortality and clinical worsening after PEA.

METHODS

A multidisciplinary panel including pulmonologists, radiologists, cardiologists, and cardiothoracic surgeons reviewed each case. Patients were considered suitable for surgery when they were symptomatic, had an elevated pulmonary vascular resistance (PVR) (>250 dyn·s·cm^{-5}), segmental or more proximal lesions and no severe co-morbidity. Before surgery all patients underwent standardized work-up as described earlier.[4] The study was approved by the local ethical committees.

According to the study by Heinrich et al., the widest diameters of the ascending aorta (Ao) and the widest diameter of the main PA perpendicular to its long axis were measured at the level of the bifurcation of the PA. The ratio of the PA and the Ao diameters was calculated[5]. The PA diameter was indexed by body surface area (BSA).

Clinical worsening (CW) was defined as the combination of death, need for pulmonary arterial hypertension (PAH) medication initiated after PEA in the presence of persistent or residual pulmonary hypertension (PH) or 15% decrease in 6 minute walk distance (6-MWD) in comparison with the best post-operative value, without improvement in NYHA functional class during follow-up. CW was determined by the event which was first reached.

Persistent or residual PH after PEA was defined as mean pulmonary artery pressure (PAP) >25 mmHg by right-sided heart catheterization or systolic PAP >40 mmHg by echocardiography.[4]

RESULTS

A pre-operative chest CT-scan was available for analysis in 114 (mean age of 56.9±13.8 years, 57.9% female) of the 161 patients who underwent a PEA in the two centres (61 patients in Nieuwegein and 53 patients in Leuven) between June 2000 and November 2010. Ninety-two patients (80.7%) suffered a known pulmonary embolism (PE) in the past. The median time between the first episode of PE and the PEA was 2.0 years (range 0.2-51.7 years). Eleven patients (9.6%) had a previous medical history of malignancy. The baseline characteristics are summarized in table 1. There were no significant differences in baseline characteristics between patients with or without available pre-operative CT-scan for analysis.

Seven patients died within 30 days after PEA (6.1%), due to right ventricular failure in two patients, thoracic bleeding in two patients, reperfusion edema in two patients and multi-organ failure in one patient. By multivariate analysis the indexed PA-diameter and mean PAP were the only independent pre-operative predictors of 30-days mortality after PEA (OR 1.35: 95%CI 1.01-1.81, p=0.04 and OR 1.21: 95%CI 1.03-1.42, p=0.02, respectively). The immediate post-operative mean PAP in patients who died within 30 days after PEA was 45.6±11.9 mmHg, versus 30.2±11.6 mmHg in patients who survived, and was a predictor for the occurrence of 30-days mortality (OR 1.11: 95%CI 1.02-1.20, p=0.01). The post-operative PVR in non-survivors was 764±202 dyn·s·cm^{-5} versus 367±211 dyn·s·cm^{-5} in survivors, and was also a predictor for mortality within 30 days after surgery (OR 2.11: 95%CI 1.23-3.61, p=0.007).

During a mean follow-up of 3.2 years (range 0.01-7.8 years), 8 out of 107 patients (7.5%) who survived surgery died. Only one patient died as the consequence of progression of PH. The other patients died because of sepsis, sudden death, leukemia, stroke and an overdose, respectively. In two patients the cause of death was unknown. CW occurred in 24 out of 107 patients (22.4%). History of malignancy was present in one out of these 24 patients (4.2%). In 4 out of these 24 patients CW occurred as the result of death, in 11 patients as a consequence of initiation of PAH specific medication and in 9 patients due to the combination of a 15% decrease in 6-MWD without improvement in NYHA functional class.

Indexed PA-diameter (HR 1.20: 95%CI 1.04-1.39, p=0.01), age (HR 1.06: 95%CI 1.01-1.11, p=0.02) and LVEF (HR 1.05: 95%CI 1.01-1.10, p=0.03) were independent pre-operative predictors for the occurrence of CW during follow-up (table 1).

The immediate post-operative mean PAP (37.3±12.0 mmHg versus 28.0±10.6 mmHg; HR 1.07: 95%CI 1.03-1.10, p<0.001) and the post-operative PVR (452±231 dyn·s·cm^{-5} versus 323±188 dyn·s·cm^{-5}; HR 1.29: 95%CI 1.05-1.59, p=0.01) were predictors for the occurrence of CW.

TABLE 1. **Baseline characteristics and predictors for clinical worsening during follow-up after PEA using Cox proportional Hazards**

Variables	Baseline	HR (univariate)	p	HR (multivariate)	p
Number	114	107			
Age (years)	56.9±13.8	1.05 (1.01-1.09)	0.008	1.06 (1.01-1.11)	0.02
Male (n[%])	48 (42.1)	0.94 (0.42-2.13)	0.89		
BSA (m^2)	1.9±0.2	0.98 (0.96-1.00)	0.02*		
SBP (mmHg)	128.3±19.8	1.00 (0.98-1.02)	0.98		
DBP (mmHg)	81.6±12.7	0.99 (0.96-1.02)	0.45		
NYHA FC (I/II/III/IV)	2/25/79/8	0.94 (0.44-2.03)	0.88		
6-MWD (m)	369±128	1.01 (0.97-1.04)	0.73		
Cardiac evaluation					
PAP mean (mmHg)	41.2±10.2	1.01 (0.97-1.05)	0.68		
PVR (dyn·s·cm^{-5})	759±422	1.09 (0.98-1.21)	0.10		
CO (l/min)	4.1±1.2	0.60 (0.38-0.95)	0.03	0.85 (0.52-1.39)	0.52
HR (beats/minute)	77.1±14.9	0.98 (0.95-1.01)	0.18		
LVEF (%)	62.2±9.4	1.05 (1.01-1.09)	0.02	1.05 (1.01-1.10)	0.03
VC (l)	3.6±0.9	0.84 (0.39-1.85)	0.67		
FEV1 (l)	2.6±0.8	0.67 (0.25-1.82)	0.43		
O2-Saturation (%)	94.3±2.6	0.93 (0.80-1.09)	0.36		
CT-scan					
PA diameter (mm)	35.7±6.0	1.09 (1.02-1.16)	0.02		
Ao diameter (mm)	32.0±4.7	1.09 (1.00-1.18)	0.06		
PA/Ao	1.1±0.2	1.06 (0.10-11.4)	0.96		
PA/BSA (mm/m^2)	19.0±3.9	1.29 (1.14-1.46)	<0.001	1.20 (1.04-1.39)	0.01

BSA = Body Surface Area; SBP = systolic blood pressure; DBP = diastolic blood pressure; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; HR = heart rate; CT = computed tomography; PA = pulmonary artery; Ao = aorta; * per 0.1 m^2

DISCUSSION

The present study demonstrates that the PA diameter indexed for BSA, is an independent predictor for the occurrence of mortality within 30 days after PEA and for the occurrence of CW during follow-up in patients with operable CTEPH.

The 30-days mortality rate in our study was 6.1%, which is in agreement with earlier studies.[6] Known pre-operative predictors for peri-operative mortality are a pre-operative increased PAP, ethnicity, pre-operative PVR, and 6-MWD.[3,7] Interestingly, in our study, the mean PAP and indexed PA-diameter at baseline were the only independent pre-operative predictors for 30-days mortality after PEA.

Recently, CW has been used as a composite endpoint in PAH trials, as described by McLaughlin.[8] During follow-up, CW occurred in 22% of patients, mainly driven by the initiation of PAH specific therapy. In search for pre-operative predictors for CW, we identified age, left ventricular ejection fraction and the indexed PA-diameter as independent predictors for the occurrence of CW.

The dilation of the main PA is a common finding in patients with PH. Several studies identified an increased main PA diameter as a reliable predictor of PAH, especially when the ratio of the main PA and Ao diameter is used.[9,10]

The association between PA diameter indices and outcome after PEA might be explained by the presence of a more extensive disease in patients with higher PA diameters. The dilation of the PA reflects both the degree and the duration of the presence of increased PAP. The reduced compliance of the PA is an important factor in the relationship between the PA diameter and the increased PAP.

Some limitations of our study have to be mentioned. First, it is a retrospective study which might implement lack of data. In 47 patients there was no CT-scan available for retrospective analysis because these were performed in a referring hospital. Furthermore, the study was conducted in two tertiary referral centres, therefore selection bias might be present.

In conclusion, the non-invasive measured PA diameter indices might be a valuable additive in predicting the outcome prior to PEA. However, every patient with CTEPH should

be referred to centres with excellence in the management of CTEPH and PEA-surgery regardless of prognostic indices.

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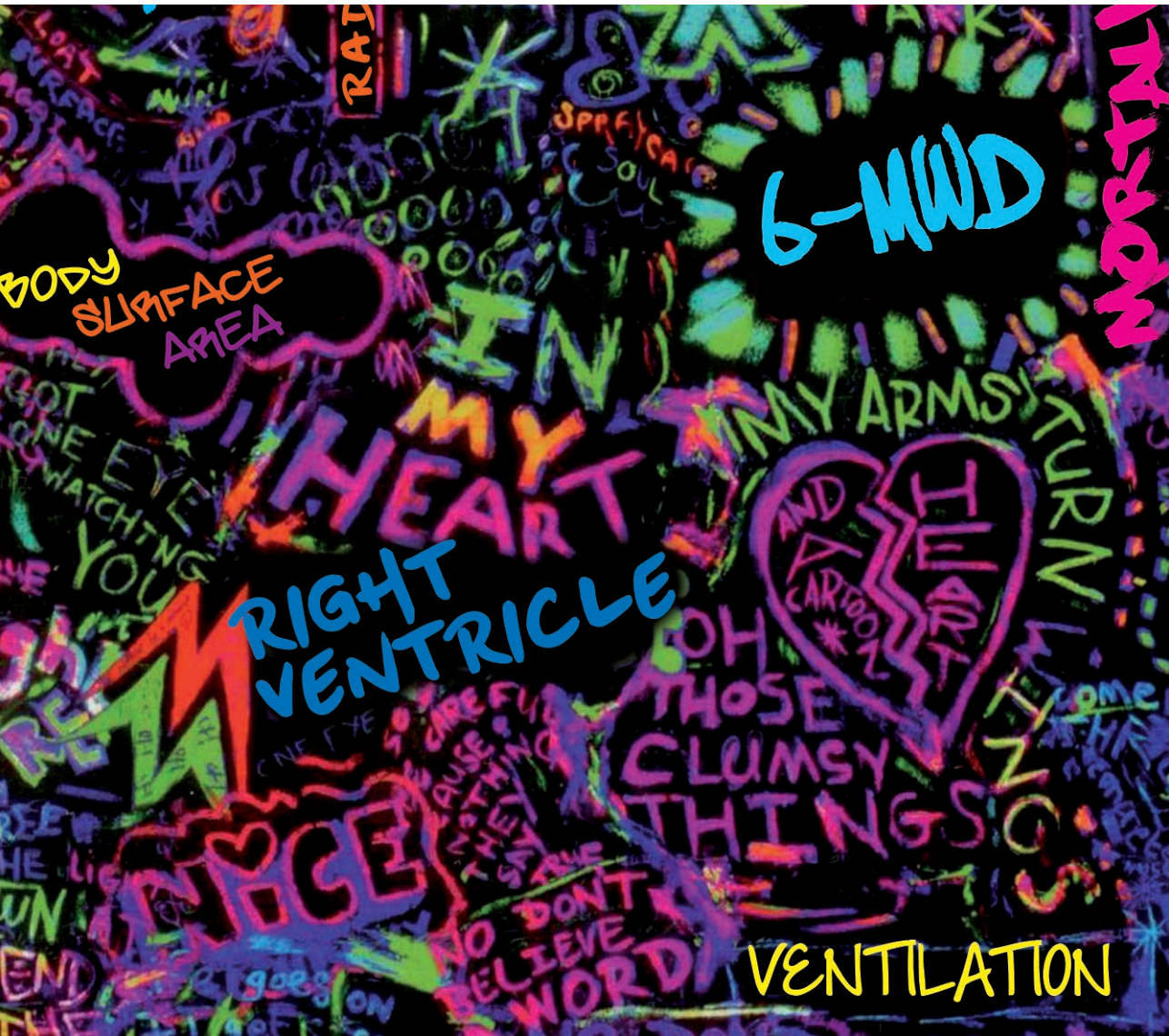
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MORTALITY
IN MY HEART
MY ARMS TURN
RIGHT VENTRICLE
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NO DON'T BELIEVE WORDS
VENTILATION

BASTIAAN E. SCHÖLZEL, MARTIJN C. POST,
PIERRE FESLER, ALEXANDER VAN DE BRUAENE,
STEVEN DYMARKOWSKI, WIM WUYTS, BART MEYNS,
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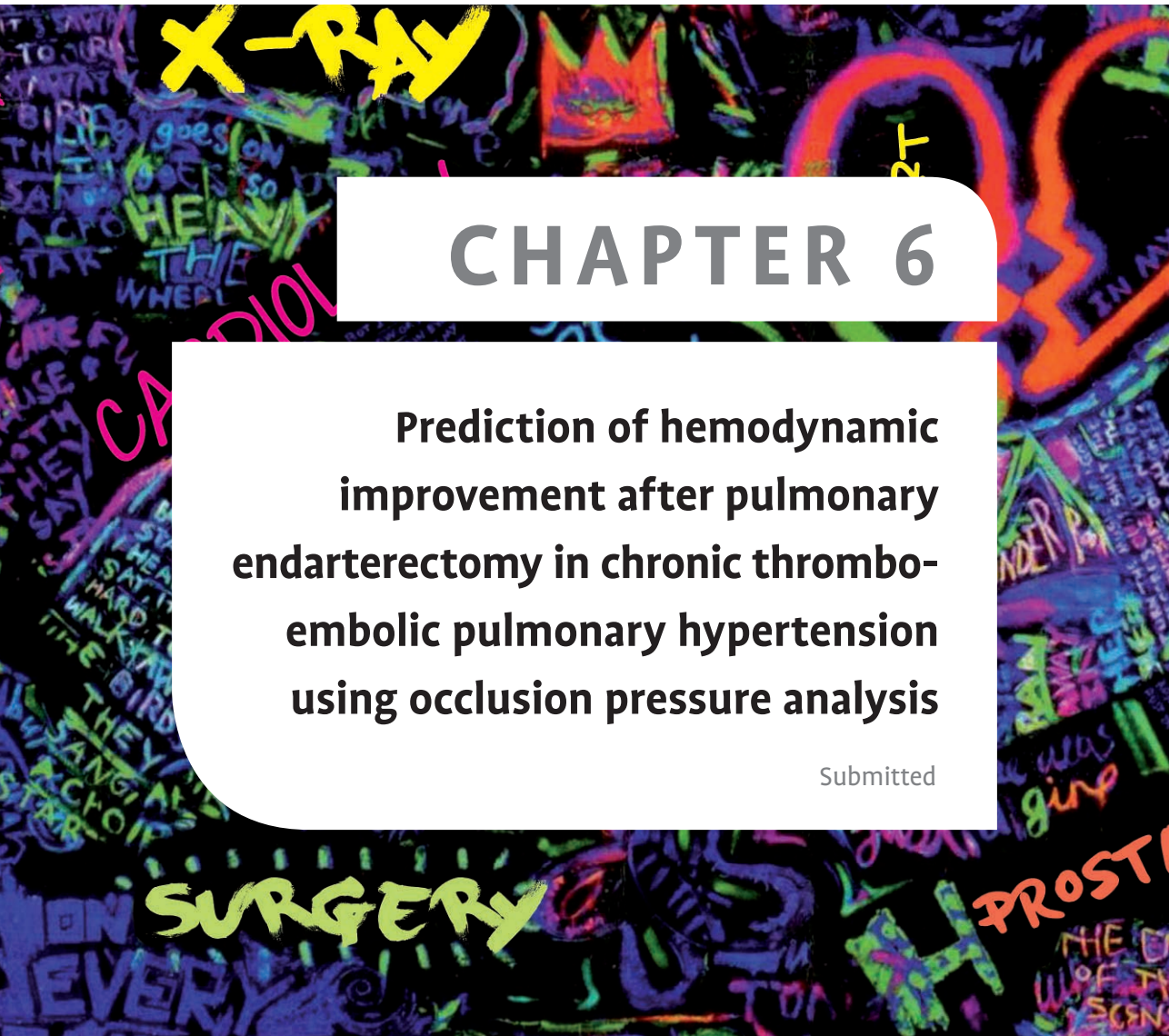

CHAPTER 6

Prediction of hemodynamic improvement after pulmonary endarterectomy in chronic thrombo-embolic pulmonary hypertension using occlusion pressure analysis

Submitted

ABSTRACT

Background

Pulmonary endarterectomy (PEA) is the only potential cure for chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary occlusion pressure (Poccl) analysis might predict outcome by differentiating proximal from distal small vessel disease. We evaluated whether upstream resistance (R*up*) could predict occurrence of 30-days mortality and hemodynamic outcome after PEA.

Methods and results

Forty-two CTEPH patients (54.8% female, mean age 59.1±14.1 years) who underwent PEA were included. Prior to surgery, right-sided heart catheterization was obtained including the pulmonary occlusion technique. Hemodynamic improvement (HI) after PEA was defined as a pulmonary vascular resistance (PVR) <500 dyn·s·cm^{-5} and a mean pulmonary artery pressure (mPAP) <35 mmHg three days after PEA. Mortality was evaluated at day 30.

At baseline, mPAP was 40.1±8.6 mmHg and PVR 961±427 dyn·s·cm^{-5}. Incomplete HI was observed in 13 patients (31.0%). Pre-operative mPAP was the only independent predictor for HI after PEA. R*up* in patients with HI was 77.7±13.4% versus 74.3±16.3% in patients with unfavourable hemodynamic outcome, and was no predictor for HI (OR 1.02: 95% CI 0.97-1.07, p=0.48).

All five patients who died within 30 days (11.9%) had persistent pulmonary hypertension, with post-operative mPAP of 51.6±14.1 mmHg and PVR of 692±216 dyn·s·cm^{-5}. Mean R*up* in these patients was 73.8±13.5%. The mPAP was the only independent pre-operative predictor for 30-days mortality after PEA. R*up* was no predictor for 30-days mortality (OR 0.99: 95% CI 0.93-1.05, p=0.71).

Conclusion

R*up* was not a predictor for 30-days mortality or HI after PEA in CTEPH.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) may develop in up to 4% of patients within the first two years after acute pulmonary embolism,[1] and retrospective studies have described preceding venous thromboembolism in up to 69% of cases.[2] Left untreated, the disease has a poor prognosis, proportional to the severity of pulmonary hypertension.[3]

The only potentially curative treatment is surgical removal of the obstructive material by pulmonary endarterectomy (PEA).[4] However, a substantial percentage of patients with CTEPH are not operable.[5,6] Concomitant small vessel arteriopathy is often present to varying degrees in CTEPH .[7] In these patients, pulmonary hypertension persists despite the removal of proximal material. Up to 15% of operated patients suffer from persistent pulmonary hypertension.[8]

The pulmonary artery occlusion technique was developed to estimate pulmonary capillary pressure and most likely approximates pressure in the precapillary small pulmonary arteries (occlusion pressure; Poccl).[9-12] With Poccl, the pulmonary arterial resistance can be partitioned into larger arterial (upstream) and small arterial plus venous (downstream) components. Recently, it was shown that patients with CTEPH who had predominantly proximal (large vessel) disease had a higher upstream resistance (R*up*), whereas CTEPH patients with significant concomitant small-vessel disease had lower R*up*.[13]

In this study we evaluated whether R*up* could predict the occurrence of 30-days mortality and hemodynamic outcome after PEA.

METHODS

Patients

Between May 2004 and January 2009, pulmonary artery occlusion pressures (PaOP) during right-sided heart catheterization (RHC) were recorded in 43 patients with CTEPH before PEA. All patients also underwent contrast-enhanced chest CT scan, pulmonary angiography and transthoracic echocardiography (TTE) prior to PEA in the University Hospitals of Leuven. The study was approved by the local ethical committee.

Right-sided heart catheterization

Pre-operatively, within a time frame of 3 months, a RHC through the right jugular vein was done in all patients. The pulmonary artery (PAP) and PaOP (Pulmonary artery Occlusion Pressure) were measured. Cardiac output (CO) was recorded using the thermodilution technique, and PVR was calculated as (mean PAP-PaOP) x 80/CO. This procedure was repeated three days after PEA in 42 patients (98%) with measurement of left atrial pressure in place of PaOP. Pre-operative New York Heart Association (NHYA) functional class and six-minute walk distance (6-MWD) were recorded within 3 days of the pre-operative RHC.

Occlusion pressure technique and analysis

A 7F, flow-directed, balloon-tipped Swan-Ganz catheter (131HF7; Baxter Healthcare Corp) was inserted in an internal jugular vein after administration of local anesthetic. Under fluoroscopic and continuous pressure monitoring, the catheter was positioned into a pulmonary artery. Hemodynamic measurements were obtained at endexpiration after zeroing the transducer at mid-chest. The pressure data were collected using a disposable transducer (Namic; Boston Scientific) connected to a hemodynamic and electrocardiographic monitoring system (Mac-Laboratory 7000, General Electric Medical Systems). The vascular pressure signals were sampled at 200 Hz with the use of an analogue-to-digital converter (DAQCard-AI-16XE-50, National Instruments) and displayed and stored on a personal computer. Cardiac output was recorded by using thermodilution technique as an average of at least 3 measurements. After single inflation of the pulmonary artery catheter, occlusion waveforms were recorded during breath-holding for 8 seconds at end-expiration. Measurements were performed in triplicate. The pulmonary vascular pressure signals were filtered using a 2-pole digital low-pass filter with a cutoff at 18 Hz. A separate, blinded investigator performed a biexponential fitting of the pressure decay curve between the moment of occlusion and the PaOP, with normalization to the mPAP.

This has been previously described and is used here to derive occlusion pressure (Poccl).[12,13] R*up* (upstream pressure) was calculated as follows: R*up* % = 100 x (mPAP - Poccl) / (mPAP - PaOP).

Clinical outcome

Hemodynamic improvement after PEA was defined as a PVR <500 dyn·s·cm^{-5} and a mean PAP <35 mmHg three days after PEA.[14,15] The 30-days mortality rates were mentioned.

Statistical analysis

Descriptive statistics were used where applicable. Continuous variables were reported as mean ± standard deviation. Proportions were given by numbers and corresponding percentages. Differences between groups were analyzed by paired or unpaired Student's *t* test for continuous variables, and χ^2 test was done for nominal variables. Univariate logistic regression was used to determine risk factors for hemodynamic improvement. Following univariate analysis, variables with a p-value of less than 0.05 were entered into a multivariate logistic regression model. The Odds ratios (OR) with their 95% confidence intervals (CI) were calculated. The OR's for 6-MWD and PVR were calculated per 10 meters and 10 dyn·s·cm^{-5}, respectively. All tests were two-sided and the level of significance was set at p<0.05. Statistical analysis was performed with the SPSS software version 17.0 (Chicago, IL) for Windows XP.

RESULTS

Patient characteristics

Fifty-two CTEPH patients underwent a PEA in our hospital between May 2004 and January 2009. Pulmonary occlusion pressures during right-sided heart catheterization were recorded in 43 patients. Post-operative hemodynamic data were available in 42 patients. Therefore, 42 patients (54.8% female, mean age of 59.1±14.1 years) could be included in the study. All baseline characteristics are summarized in table 1.

Hemodynamic changes after PEA

Before PEA, mPAP was 40.1±8.6 mmHg, and PVR was 961±427 dyn·s·cm^{-5} (range 242-2062). Three days after surgery the mPAP decreased to 34.0±12.6 mmHg and PVR was 330±171 dyn·s·cm^{-5} ($p<0.001$ for both, compared to baseline). Incomplete hemodynamic improvement occurred in 13 out of 42 patients ([31.0%], 77% female, mean age 58.6±14.9 years). The mean R*up* in patients with favourable hemodynamic outcome was 77.7±13.4%; in patients with incomplete hemodynamic improvement, the mean R*up* was 74.3±16.3%. The characteristics of the patients with and without hemodynamic improvement are summarized in table 2.

Predictors of improved outcome

Univariate logistic regression identified gender (OR 0.13: 95% CI 0.02-0.69, p=0.02) and mPAP (OR 0.86: 95% CI 0.78-0.95, p=0.004) as predictors for hemodynamic improvement. This is summarized in table 2. By multivariate analysis the mPAP was the only independent pre-operative predictor of hemodynamic improvement after PEA (OR 0.88: 95% CI 0.79-0.98, p=0.02). R*up* did not appear to be a predictor for occurrence of hemodynamic improvement (OR 1.02: 95% CI 0.97-1.07, p=0.48).

Mortality

Within 30 days after PEA, 5 out of 42 patients (11.9%) died (100% female, mean age 54.9±15.9 years). Two patients due to right ventricle failure, one patient each due to thoracic bleeding, ARDS and systemic inflammatory response syndrome. In all, hemodynamic improvement was incomplete or absent, with a post-operative mPAP of 51.6±14.1 mmHg and PVR of 692±216 dyn·s·cm^{-5}, compared to a post-operative mPAP of 32.0±10.4 mmHg and PVR of 300±147 dyn·s·cm^{-5} in patients who survived.

Univariate logistic regression identified PVR (calculated per 10 dyn·s·cm^{-5}; OR 1.03: 95% CI 1.00-1.05, p=0.04) and mPAP (OR 1.38: 95% CI 1.08-1.78, p=0.01) as predictors for 30-days mortality. By multivariate analysis the mPAP was the only independent pre-operative predictor for 30-days mortality after PEA (OR 1.44: 95% CI 1.07-1.94, p=0.02). R*up* was not a predictor for the occurrence of mortality within 30 days after PEA (OR 0.99: 95% CI 0.93-1.05, p=0.71). This is summarized in table 3. The mean R*up* value of these five patients was 73.8±13.5%.

TABLE 1. Baseline characteristics

Number	42
Age (years)	59.1±14.1
Gender (n[%])	
Female	23 (54.8)
Male	19 (45.2)
BMI (kg/m^2)	26.7±5.0
Arterial bloodpressure	
Systolic (mmHg)	128.5±20.0
Diastolic (mmHg)	83.8±11.7
Heart rate (beats per minute)	78.7±15.2
O_2 Saturation (%)	94.0±2.8
NYHA FC (I/II/III/IV)	0/12/28/2
6-MWD (m)	354±123
Right-sided heart catheterization	
PAP syst (mmHg)	82.4±15.3
PAP diast (mmHg)	31.1±9.3
PAP mean (mmHg)	40.1±8.6
PVR (dyn·s·cm^{-5})	961±427
CO (l/min)	3.7±1.1
R*up* (%)	76.6±14.3

BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; RHC = right-sided heart catheterization; PAP syst = pulmonary artery pressure systolic; PAP diast = pulmonary artery pressure diastolic; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; R*up* = upstream resistance

TABLE 2. **Baseline characteristics of patients with and without hemodynamic improvement after PEA**

	HD improvement	No HD improvement	OR	p
Number	29	13		
Age (years)	59.3±13.9	58.6±14.9	1.00 (0.96-1.05)	0.89
Gender (n)			0.13 (0.02-0.69)	0.02
Female	13	10		
Male	16	3		
BMI (kg/m^2)	26.9±5.7	26.3±3.0	1.03 (0.90-1.18)	0.68
Bloodpressure				
Systolic (mmHg)	130.5±21.6	124.2±15.4		0.36
Diastolic (mmHg)	86.0±11.2	78.8±11.8		0.06
Heart rate (beats per minute)	79.6±15.1	78.3±15.5	0.99 (0.95-1.04)	0.80
NYHA FC (I/II/III/IV)	0/2/10/1	0/10/18/1	0.41 (0.10-1.59)	0.20
6-MWD (m)	358±111	344±149	1.01 (0.96-1.07)*	0.74
Pre-operative right-sided heart catheterization				
PAP mean (mmHg)	37.2±7.0	46.6±8.6	0.86 (0.78-0.95)	0.004
PVR (dyn·s·cm^{-5})	890±376	1119±504	0.99 (0.97-1.00)*	0.12
CO (l/min)	3.8±1.1	3.6±1.1	1.22 (0.65-2.28)	0.54
R*up* (%)	77.7±13.4	74.3±16.3	1.02 (0.97-1.07)	0.48

BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; RHC = right-sided heart catheterization; PAP mean = pulmonary artery pressure mean; PVR = pulmonary vascular resistance; CO = cardiac output; R*up* = upstream resistance

* OR for 6-MWD calculated per 10 meters

* OR for PVR calculated per 10 dyn·s·cm^{-5}

TABLE 3. **Predictors for 30-days mortality after PEA using Cox proportional hazards**

	OR (univariate)	p	OR (multivariate)	p
Age	0.98 (0.91-1.05)	0.51		
Female	0.49 (0.35-0.68)	0.05		
BMI	1.02 (0.85-1.22)	0.83		
Heart rate	0.98 (0.92-1.05)	0.58		
NYHA FC	2.86 (0.40-20.5)	0.30		
6-MWD*	0.92 (0.84-1.00)	0.06		
Mean PAP	1.38 (1.08-1.78)	0.01	1.44 (1.07-1.94)	0.02
PVR*	1.03 (1.00-1.05)	0.04	0.99 (0.96-1.02)	0.56
CO	0.72 (0.29-1.83)	0.49		
R*up*	0.99 (0.93-1.05)	0.71		

PEA = Pulmonary Endarterectomy; OR = Odds ratio; BMI = Body Mass Index; NYHA FC = New York Heart Association Functional Class; 6-MWD = six minute walk distance; Mean PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; R*up* = upstream resistance

* OR for 6-MWD calculated per 10 meters

* OR for PVR calculated per 10 dyn·s·cm^{-5}

DISCUSSION

The present study demonstrates that R*up* was unable to predict 30-days mortality or short-term hemodynamic improvement after pulmonary endarterectomy in patients with CTEPH.

The only potentially curative treatment for patients with CTEPH is surgical removal of the obstructive material by PEA.[4,15] However, this major surgical procedure is not without risk, the peri-operative mortality rate varies between 5% and 16%.[14,16-19] The 30-days mortality rate in our study was 11.6%, which is in agreement with the studies mentioned above.

Despite this potential curative treatment, a substantial percentage of patients with CTEPH are not operable, and 5 to 35% of operated patients suffer from persistent pulmonary hypertension, depending on the definition.[6,8,19-21] Residual pulmonary hypertension after PEA may result from incomplete endarterectomy due to inaccessible distal chronic thromboemboli or irreversible small-vessel arteriopathy and is associated with a higher risk on late post-operative adverse events.[22] Incomplete hemodynamic improvement (i.e. residual pulmonary hypertension) was found in 13 out of 42 (31%) patients in our study. This is in agreement with the results from other reports. It should be mentioned that all in-hospital deaths in our study were patients who suffered residual pulmonary hypertension.

Previous reports showed that the pulmonary artery occlusion technique might be able to estimate the pre-capillary pressure.[9-11] Kim et al. recently reported results in a cohort of patients with CTEPH undergoing PEA. They suggest that the occlusion technique was able to effectively partition resistance into small and large vessel compartments. A strong correlation between occlusion derived partition of resistance and immediate post-operative hemodynamics was found. A flow-directed R*up* of <60% was demonstrated to be a significant risk factor for mortality.[13] Toshner et al. tested the hypothesis that the occlusion technique was able to discriminate large vessel organised thrombus from distal vasculopathy by performing occlusion pressures in patients with operable CTEPH, distal inoperable CTEPH and post-PEA residual CTEPH. R*up* was found to be significantly increased in operable proximal CTEPH compared with inoperable distal CTEPH.[23] In line with the previous study we hypothesized that R*up* would be able to predict in-hospital clinical outcome after PEA in patients with operable CTEPH. However, R*up* did not appear to be a predictor for 30-days mortality nor hemodynamic improvement.

There was no significant difference in mean R*up* between patients with and without hemodynamic improvement. Interestingly, Toshner et al. reported that flow-directed R*up* was also not able to discriminate patients with significant post-operative pulmonary hypertension[23], which is in agreement with our findings. In contrast to the results reported by Kim et al.[13], the mean R*up* in patients with favourable hemodynamic outcome did not differ from the mean R*up* in patients with incomplete hemodynamic improvement in our study. It should be mentioned that there was no statistical analysis performed in the study by Kim et al.[13] A possible explanation for the difference in results between our study and the study of Kim et al. could be patient selection and the size of the study population (26 versus 42 patients). The mean R*up* in our population of patients with operable CTEPH was 76.6%, versus 72.3% in the study of Kim[13] and 87.3% in the study of Toshner.[23] Furthermore, we were not able to perform pulmonary occlusion technique in all consecutive patients in this present study, which could have encouraged selection bias.

Some limitations of our study have to be mentioned. First, it is a retrospective study which might imply incomplete data. Secondly, it is a single centre study, therefore a selection bias might be present. Finally, we had to deal with a small sample size. This might have led to non-significant analysis because of lack of statistical power.

In conclusion, R*up* was not found to be a predictor for 30-days mortality or unfavourable hemodynamic outcome after PEA in patients with CTEPH.

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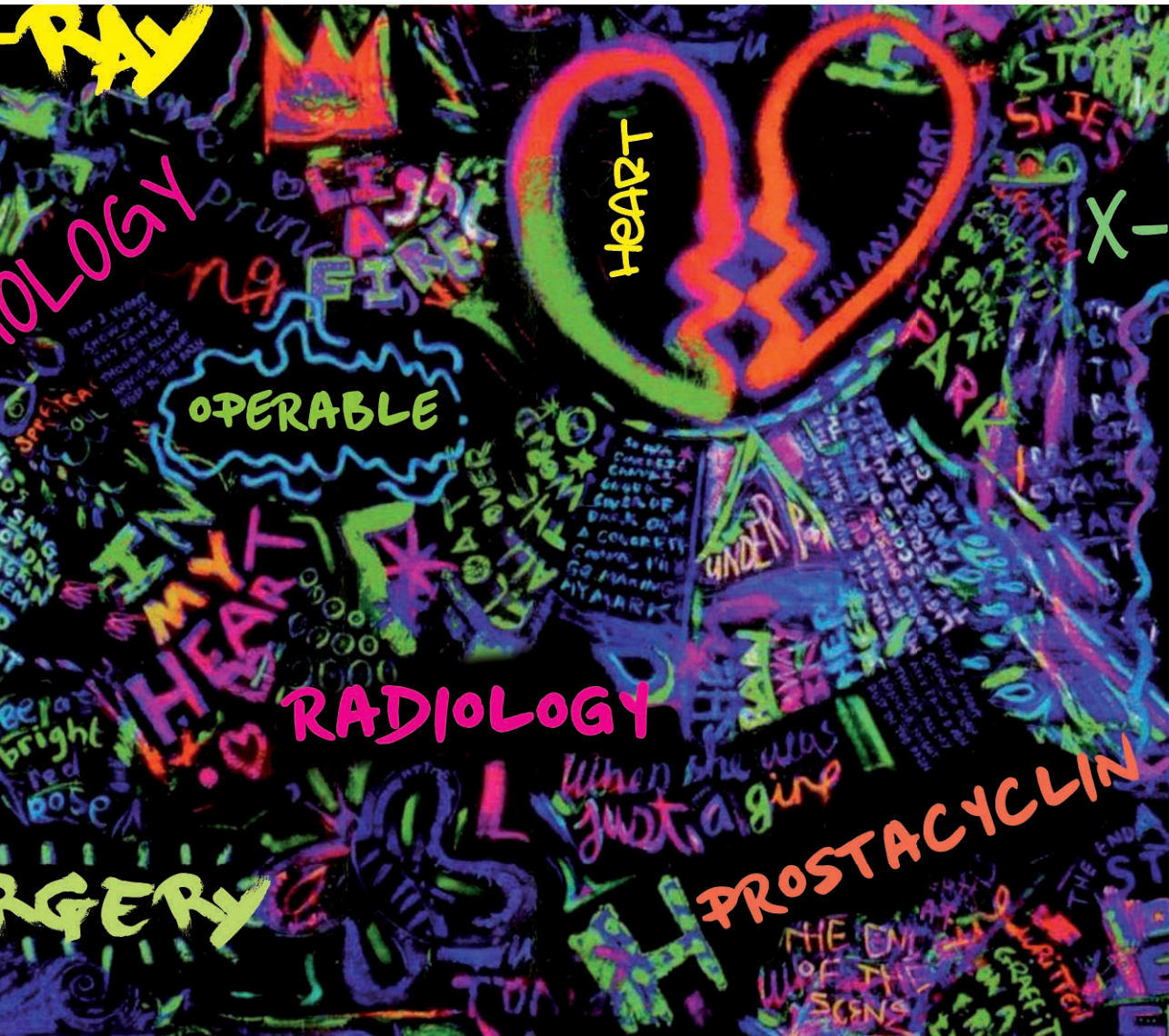
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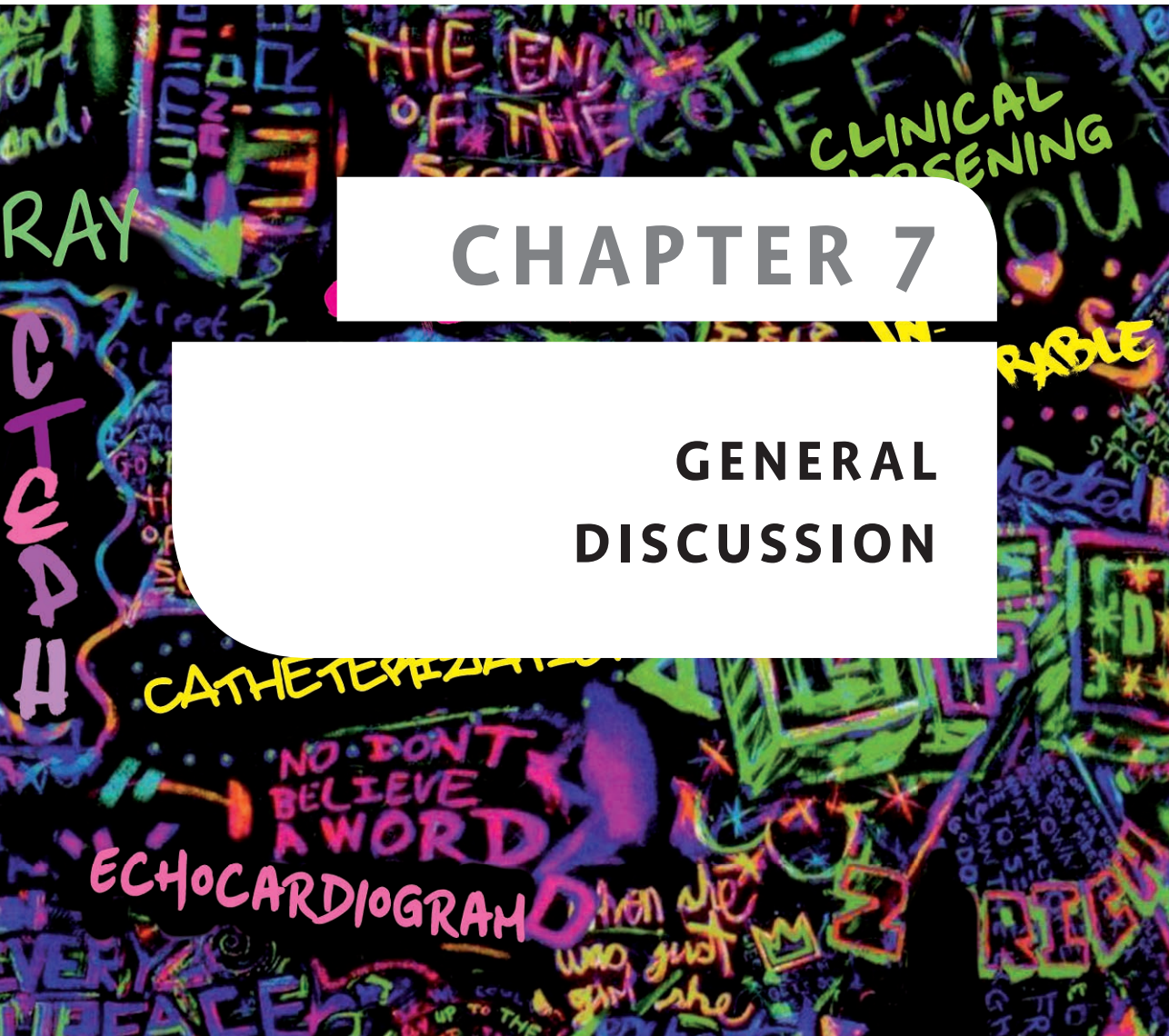


CHAPTER 7

GENERAL DISCUSSION

INTRODUCTION

Because of the low event rate in recent pulmonary hypertension (PH) studies, mortality alone has not been an adequately powered endpoint. Therefore, a composite endpoint, time to clinical worsening (CW), has been developed. However, different definitions have been used in different trials, making comparison difficult. In 2009, an article by McLaughlin et al. was published concerning endpoints and clinical trial design in PH.

A more uniform definition was proposed, including all-cause mortality, non-elective hospital stay for pulmonary arterial hypertension (PAH) (usually for initiation of intravenous prostanoids, lung transplantation, or septostomy), and disease progression.[1]

The endpoint CW has been used mostly in clinical trials in patients with PAH. There are no studies describing the rate of CW in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

This thesis addresses the outcomes of our studies on the occurrence of CW in patients diagnosed with operable and inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Amongst others, the contribution of transthoracic echocardiography and chest computed tomography scan for the prediction of outcome after pulmonary endarterectomy (PEA) was explored.

Symptomatic CTEPH will develop in 0.57% to 4.6% of acute pulmonary embolic survivors.[2-4] Left untreated, CTEPH has a poor prognosis, leading to right heart failure and death.[5]

PEA remains the treatment of choice in symptomatic patients with surgically accessible CTEPH.[6] A substantial hemodynamic improvement occurs in most patients, which is associated with improvements in functional status and long-term survival.[2,7] The 30-days mortality rate after PEA ranges from less than 5% in the most experienced centres to 10% in other centres.[8,9] However, in 30-50% of patients a PEA is not possible (inoperable CTEPH) due to either distal pulmonary vascular obstruction or significant co-morbidities thought to be associated with unacceptably high risk.[10]

OUTCOME IN INOPERABLE CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

In chapter 2 of this thesis we describe the occurrence of CW in patients with inoperable CTEPH. CW was defined as the combination of death, need for intravenous PAH medication, or 15% decrease in 6-minute walk distance (6-MWD) without improvement in functional class.[11] It demonstrated that despite modern pulmonary vasoactive medication, like endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclins, 23% of the patients died and CW occurred in 40% of the patients within 3 years after diagnosis.[11]

CW in our study population was seen in 26% after 1 year and 40% after 3 years. After 1 year the endpoint of CW was mainly reached because of death, but in the second and third year after inclusion, CW was mainly caused by need for parenteral PAH medication or a decrease in 6-MWD. This emphasizes the importance of a composite endpoint in this patient group. If the endpoint mortality was used, a substantial number of the inoperable CTEPH patients would have been considered as patients with a good follow-up. Several reports have shown that after modern pulmonary vasoactive therapy became available, the survival rate of patients with inoperable CTEPH seems to improve at short- and mid-term follow-up. Several open-label studies have been performed with prostanoids, endothelin receptor antagonists, PDE-5 inhibitors and soluble guanylate cyclase stimulator in patients with non-operable CTEPH and/or with persistent pulmonary hypertension after PEA. Most of them showed significant improvement in NYHA functional class, exercise capacity and/or hemodynamics.[12-15] Further randomized placebo controlled trials are needed to confirm these findings.

In the BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) trial, patients with either inoperable CTEPH or persistent/recurrent PH after PEA were included and randomized to treatment with bosentan or placebo. During follow-up of 16 weeks, the study demonstrated a significant positive treatment effect of bosentan over placebo on pulmonary vascular resistance (PVR [-24,1% of baseline]), total pulmonary resistance (-193 $dyn \cdot s \cdot cm^{-5}$) and cardiac index (0.3 $l \cdot min^{-1} \cdot m^{-2}$). However, this hemodynamic improvement did not translate into a favourable effect on exercise capacity.[16] A possible explanation for the discrepancy could be the relatively old age of the study population. Furthermore, the duration of the study could have been not long enough to demonstrate improvement in exercise capacity as measured by 6MWD.[16]

Ghofrani et al. recently presented the results of the CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1) trial which investigated the efficacy and safety of riociguat in patients with inoperable CTEPH.[17] There was a significant improvement in 6-MWD (+ 39m) in patients treated for 16 weeks with riociguat compared with placebo. Riociguat also showed significant improvement in PVR (-226 dyn·s·cm^{-5}), NT-proBNP level and NYHA functional class.[17]

Because there is no experts' agreement on the criteria defining operability, it is difficult to characterise the CTEPH patients who might benefit from medical therapies. In future studies it will be necessary to clearly describe the patients who may benefit from PAH-targeted therapies and to define meaningful endpoints which are specific for CTEPH, like for example CW.

OUTCOME AFTER PULMONARY ENDARTERECTOMY IN PATIENTS WITH CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

In chapter 3 we focus on the incidence of CW after PEA in patients with operable CTEPH. In our CTEPH patient population, we defined the composite endpoint time to CW as the combination of death, initiation of PH specific medication after PEA, or a decrease in 6-MWD by 15% without improvement in functional class. Because of the fact that CTEPH is potentially curable with PEA, usually PH specific medication is discontinued after surgery. The need to (re-) start with PH specific medication after PEA reflects deterioration of the clinical situation in this specific group of patients. We found that CW occurred in about 20% of the CTEPH patients within five years after the surgical treatment.[18] CW was predominantly determined by the initiation of PH-specific medication during follow-up. It could be hypothesized that CW may have occurred in patients with more distal disease. Therefore the endarterectomy in this subset of patients may have been incomplete. Furthermore, there is a possibility that CW is secondary to recurrent pulmonary emboli and vessel obstruction that occurred after surgery, although all patients were treated with lifelong coumadin.

The 30-days mortality rate was around 7%, the one- and five-year survival rates were 93% and 89%, respectively. These findings are in agreement with rates from other studies.[9,10,19-21]

Residual or persistent PH after PEA may result from incomplete endarterectomy, inaccessible chronic thromboemboli or small-vessel arteriopathy. The reported rates vary from 5% to 35%, depending on the definition.[22-24] However, long-term information as to what level of residual PH negatively affects functional status and survival is lacking.[22,23] In our study, PH-specific medication was initiated in 8 patients (11,5%), which is in agreement with previous reports.[22-24]

Furthermore we searched for pre-operative predictors for unfavourable (i.e. mortality and CW) outcome after PEA.

Possible predictors for successful PEA are considered to be pre-operative PVR, pre-operative 6-MWD, pre-operative radiological findings and co-morbidities of the patients.[6,10,23] Unfortunately, the definition of a successful PEA differs between the studies. Bonderman et al. demonstrated that the presence of associated medical conditions like sple-

nectomy, ventriculoatrial shunt, inflammatory bowel disease and osteomyelitis predicts the increased operative risk and worse long-term outcome in CTEPH.[23] Despite technically successful surgery, patients with associated medical conditions had worse outcomes with higher peri-operative mortality (24% versus 9%) and an increase incidence of post-operative PH. The mechanism of worse outcome in patients with associated medical conditions remain undefined.[23] Corsico et al. reported the long-term outcome after PEA in 157 patients. At 4 years 74% of the patients were in NYHA functional class I and none was in class IV. However, 25% of survivors still had moderate to severe hypoxemia or persistent PH; they were significantly older and were more frequently in NYHA class III-IV 3 months after PEA compared to the others.[21] In a study by Dartevelle et al, the mortality rate was 4% in patients with a PVR <900 dyn·s·cm^{-5}, 10% in patients with a PVR between 900 and 1200 dyn·s·cm^{-5}, and 20% with a higher PVR, in a total of 275 PEA procedures.[25] Auger and colleagues have stated in their review that NYHA class IV, age older than 70 years, the severity of pre-operative PVR, the presence of right ventricular failure, morbid obesity and the duration of CTEPH have been reported to affect post-operative survival.[26] Kunihura et al. studied 279 CTEPH patients who underwent PEA. Pre-operative arterial oxygenation was identified as the only independent predictor for 30-days mortality after PEA. Male gender, lower pre-operative mean pulmonary artery pressure (PAP) and more intra-operative desobliterated segments were identified as predictors for favourable hemodynamic outcome (i.e. PVR <400 dyn·s·cm^{-5} at 48 hours after PEA).[27] Mayer et al. reported the results from an international prospective registry concerning the surgical management and outcome of 679 CTEPH patients of whom 386 underwent PEA.[10] PVR at the end of intensive care was identified as an independent risk factor for in-hospital death and for death at 1 year. The 6-MWD was also an independent risk factor for death at 1 year. Survivors had a higher 6-MWD and a lower PVR at diagnosis than non-survivors.[10] We were not able to identify an independent predictor for the occurrence of CW.

PREDICTION OF OUTCOME AFTER PULMONARY ENDARTERECTOMY IN PATIENTS WITH CTEPH USING NON-INVASIVE IMAGING MODALITIES

The association between the diameter of the main pulmonary artery (PA) and the ratio of the PA and ascending aorta diameter measured by chest CT scan and pulmonary hemodynamic characteristics in operable CTEPH have been described by Heinrich et al.[28] In this retrospective study the PA diameter and the ratio of the PA and aortic diameters correlated with the pre-operative hemodynamics in 60 patients who underwent a PEA. However, these parameters did not correlate with post-operative improvement.[28] A study by Schmidt et al. also demonstrated a positive correlation between the diameter of the PA on CT and the mean PAP and PVR in patients with CTEPH.[29] Zylkowska and colleagues evaluated the prognostic significance of main PA dilatation in patients with PAH and patients with inoperable CTEPH.[30] PA dilatation emerged as an independent risk factor for death, unexplained by right ventricular failure or comorbidities. Possible mechanisms include the consequences of left main coronary artery compression or dissection with cardiac tamponade.[30] It could be hypothesized that higher PA diameters reflects more extensive disease in patients with CTEPH and therefore could also have prognostic value in patients with operable CTEPH regarding post-operative outcome. The dilation of the PA reflects both the degree and the duration of the presence of increased PAP. The modified compliance of the PA is an important factor in the relationship between the PA diameter and the increased PAP. Earlier studies provided evidence that structural changes in elastin and collagen of the PA vessel wall in the presence of an increased PAP might eventually become a cause of PA dilatation.[31,32] Furthermore, altered flow in PH affects wall shear stress and eventually matrix properties of the vessel wall that may contribute to PA dilatation.[33]

Ng et al. showed that in patients with a wide range of pulmonary and cardiovascular diseases the PA was influenced by the BSA.[34] Therefore we indexed the PA diameter for BSA in our study.

Previous echocardiographic studies in CTEPH patients showed the good effect of PEA on right-sided echocardiographic parameters.[35-37] Casaclang-Verzosa et al. studied the echocardiographic changes in CTEPH patients at 3 months and 1 year after PEA.[34] Within 3 months after PEA there was a significant decrease in end-systolic and –diastolic area, as well as a significant decrease in right ventricular systolic pressure. There was also a significant improvement of tricuspid regurgitation. These findings were unchanged at 12

months after PEA.[35] Blanchard and colleagues evaluated the utility of tissue Doppler-derived right ventricular (RV) Tei (or myocardial performance) index in patients with CTEPH before and after PEA.[36] They demonstrated a correlation between RV Tei index and right heart hemodynamics (particularly PVR) in CTEPH.[36] In patients with idiopathic PH, echocardiographic parameters like pericardial effusion, right atrial enlargement and septal displacement have been shown to be predictors of adverse outcome.[38] Hardziyenka et al. found TAPSE to be a pre-operative determinant of in-hospital mortality following PEA, although the pulmonary flow systolic notch appeared to be the strongest determinant.[37]

In chapter 5 of this thesis we focus on the predictive value of echocardiographic and CT parameters on the short-term hemodynamic improvement after PEA. We identified female gender, an increased mean PAP, a lower TAPSE and larger PA diameter indices as predictors of unfavourable hemodynamic outcome. However, the PA diameter indexed for BSA was the only independent pre-operative non-invasive predictor for in-hospital hemodynamic improvement after PEA for CTEPH, defined as PVR <500 dyn·s·cm^{-5} and a mean PAP <35 mmHg three days after PEA (i.e. the larger the indexed PA diameter, the higher the risk for unfavourable hemodynamic outcome after PEA).[39,40]

In chapter 6 we evaluated whether PA diameter indices could predict clinical outcome after PEA.[41] Univariate logistic regression identified baseline 6-MWD, mean PAP, PVR, PA-diameter and PA-diameter indexed for BSA as predictors for 30-days mortality. By multivariate analysis the indexed PA-diameter and mean PAP were the only independent pre-operative predictors of 30-days mortality after PEA. During follow-up CW occurred in 24 out of 107 patients (22.4%). History of malignancy was present in one out of these 24 patients (4.2%). In 4 out of these 24 patients CW occurred as the result of death, in 11 patients as a consequence of initiation of PAH specific medication and in 9 patients due to the combination of a 15% decrease in 6-MWD without improvement in NYHA functional class. By univariate logistic regression: pre-operative age, cardiac output, left ventricular ejection fraction (LVEF), PA-diameter and PA-diameter indexed for BSA were found to be pre-operative predictors for CW. After multivariate analysis, PA-diameter indexed for BSA, age and LVEF were independent pre-operative predictors for the occurrence of CW during follow-up.[41]

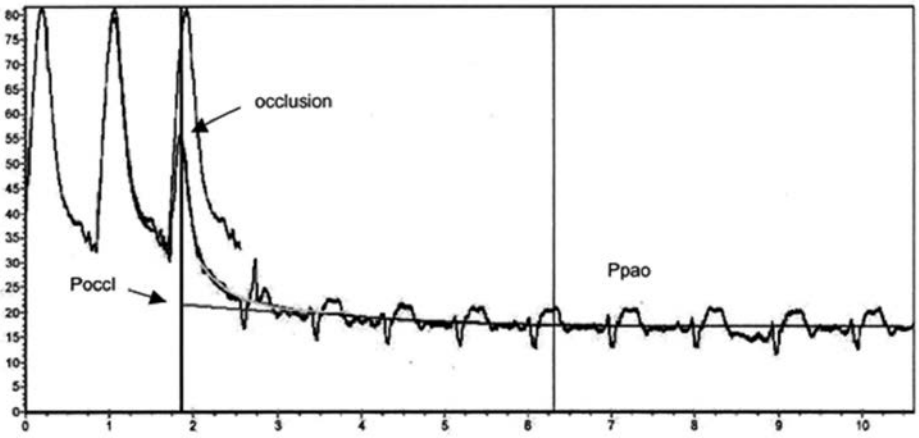
Therefore we think that the non-invasive measured PA diameter indices might be a valuable additive in predicting the short-term hemodynamic and long-term clinical outcome after PEA.

PREDICTION OF OUTCOME AFTER PULMONARY ENDARTERECTOMY IN PATIENTS WITH CTEPH BY USING INVASIVE TECHNIQUES

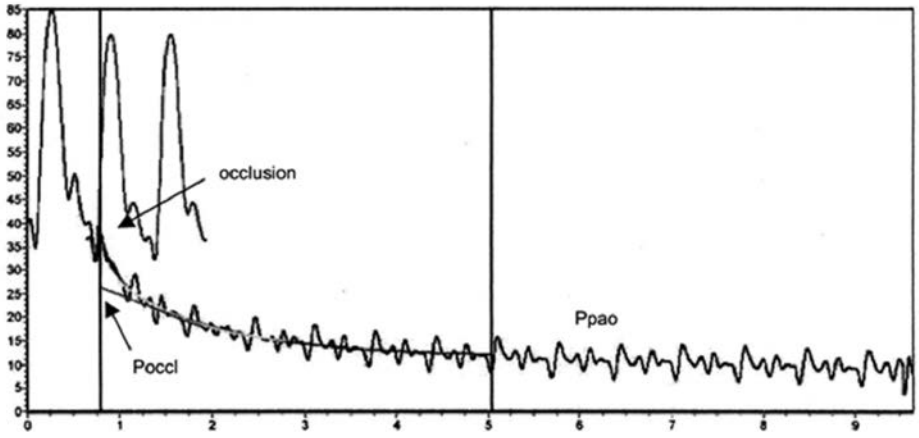
In CTEPH the ability to discriminate the contribution of small vessel vasculopathy from organised thrombus in large vessels is critical for treatment decisions. Distal disease, whether vasculopathic or small vessel thrombotic, is a major risk factor for poorer outcome.[42,43] Additional discriminators to identify those at risk of poor outcome are therefore desirable. The analysis of pressure decay curves after occlusion of the PA by the Swan-Ganz catheter was developed to estimate true pulmonary capillary pressure and most probably approximates pre-capillary pressure.[44,45] These curves consist of a first, fast component that reflects the stop of flow through arterial resistance, and a second, slower component, which corresponds to the emptying of compliant capillaries through a venous resistance. From the intersection of these two components, one calculates an upstream resistance, essentially determined by the resistive properties of the large pulmonary arteries, and the other a downstream resistance, determined by the cumulated resistance of small arterioles, venules and capillaries (figure 1).[46,47] Kim et al. reported results from a cohort of patients undergoing PEA that suggest that PA occlusion pressure waveform analysis may identify CTEPH patients at risk for persistent PH and poor outcome after PEA.[24] The occlusion derived partition of resistance correlated strongly with immediate post-operative results and additionally demonstrated promise in identifying those at high operative risk regardless of PVR.[24] A recent report of Toshner et al. evaluated whether the occlusion technique was able to distinguish small from large vessel disease. They studied 59 patients with CTEPH, idiopathic PAH and connective tissue disease-associated PAH. With fitting of the pressure decay curve, PVR was partitioned into downstream (small vessels) and upstream (large vessels, R*up*). The R*up* was significantly higher in the operable subjects than in the two predominantly distal vasculopathic groups.[48]

In chapter 7 of this thesis we evaluated whether upstream resistance (R*up*) could predict occurrence of 30-days mortality and hemodynamic outcome after PEA. Prior to surgery, patients underwent right-sided heart catheterization including the pulmonary occlusion technique. Hemodynamic improvement after PEA was defined as a PVR <500 dyn-s-cm^{-5} and a mean PAP of <35 mmHg three days after PEA. Mortality was evaluated at day 30. Unfortunately, R*up* was not identified as a predictor for hemodynamic outcome after PEA, nor as a predictor for the occurrence of 30-days mortality. It seems that PVR partitioning is technically challenging, requiring a perfect position of the Swan-Ganz catheter

FIGURE 1. **Pulmonary artery occlusion in two patients**



1a



1b

a) primarily upstream resistance with a rapid drop in pressure to pulmonary arterial occlusion pressure (Ppao) or ''wedge''

b) significant downstream resistance with a longer time needed for the pressure to reach Ppao. Poccl: pulmonary capillary pressure after occlusion

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with regular pressure decay after occlusion. Interestingly, Toshner et al. reported that flow-directed R*up* was also not able to discriminate patients with significant post-operative PH[48], which is in agreement with our findings. In contrast to the results reported by Kim et al.[24], the mean R*up* in patients with favourable hemodynamic outcome did not differ from the mean R*up* in patients with incomplete hemodynamic improvement in our study. It should be mentioned that there was no statistical analysis performed in the study by Kim et al.[24] A possible explanation for the difference in results between our study and the study of Kim et al. could be patient selection and the size of the study population (26 versus 42 patients). The mean R*up* in our population of patients with operable CTEPH was 76.6%, versus 72.3% in the study of Kim[24] and 87.3% in the study of Toshner.[48] Furthermore, we were not able to perform pulmonary occlusion technique in all consecutive patients in this present study, which could have encouraged selection bias. Finally, our study is a retrospective analysis, which might imply incomplete data.

Therefore, it remains unclear whether the PA occlusion technique could be the key to operability in CTEPH patients. However, the occlusion technique could be in a unique position to offer more objective assessment in an otherwise subjective discipline of operability determination. Future prospective studies are necessary to confirm its value in the pre-operative work-up in CTEPH.

CONCLUSION

PEA is associated with a good long-term survival in patients with CTEPH. However, CW occurred in a substantial number of patients after long-term follow-up. This knowledge will help us to give our patients better information about the outcome after PEA.

Furthermore we identified the pre-operative PA-diameter indexed for BSA as a predictor for short-term and long-term outcome after PEA. Therefore it should be considered as a valuable additive in predicting the short-term hemodynamic and long-term clinical outcome after PEA**.** It is definitely not the case that these patients at higher risk should not be operated, but it will be helpful to identify these patients pre-operatively and give them appropriate information before surgery. Further studies are needed to investigate whether these patients at risk could benefit from additional pre-operative treatment.

For an optimal assessment, all patients with suspected CTEPH, should be referred to specific PAH centres who perform PEA operations.

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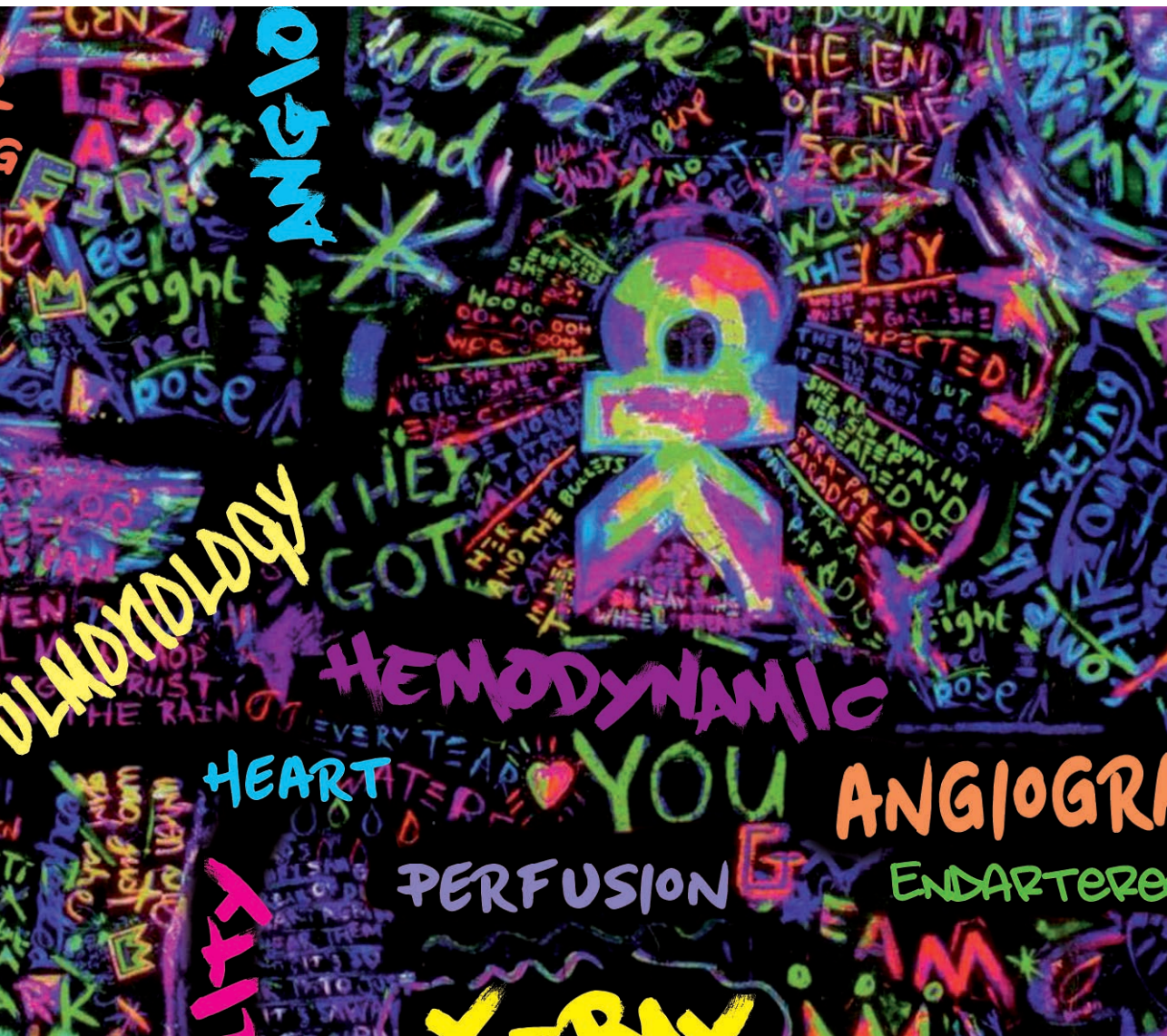
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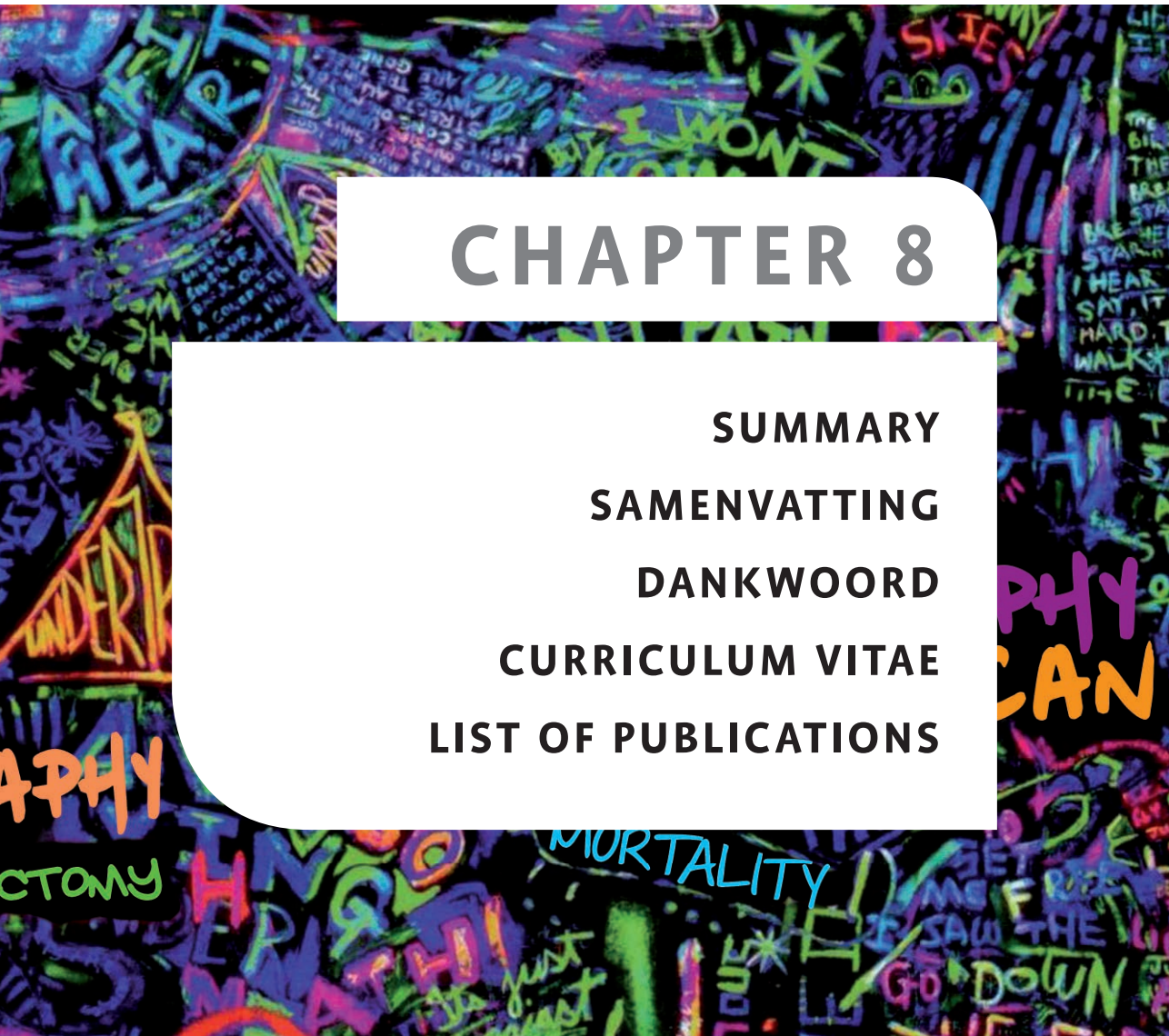

CHAPTER 8

SUMMARY

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a raised mean pulmonary artery pressure (of at least 25 mmHg at rest) caused by persistent obstruction of pulmonary arteries after pulmonary embolism that has not resolved despite at least 3 months of therapeutic anticoagulation.[1]

Non-resolving acute pulmonary embolism is the most common cause of CTEPH, and can occur after one or multiple episodes. CTEPH might occasionally develop owing to in-situ pulmonary artery thrombosis, which could be associated with inflammation of the vessel walls.[2] The estimated prevalence of CTEPH two years after acute pulmonary embolism is 0.1-4.0%.[3–7] Pulmonary endarterectomy (PEA) is the treatment of choice, offering immediate hemodynamic benefits and providing a potential cure for many patients.[8] However, PEA is not possible for about 50% of patients (inoperable CTEPH), due to either distal pulmonary vascular obstruction that is surgically inaccessible or significant comorbidities thought to be associated with unacceptably high risk.[9] Furthermore, in CTEPH patients with disease amenable to surgery, approximately 10% to 15% of patients have residual pulmonary hypertenion (PH, mean pulmonary arterial pressure [mPAP] >25 mmHg)[10] after PEA (persistent/recurrent post-operative PH).[11] In these situations, medical treatment might be useful.

Recently, clinical worsening (CW) has been used as a composite endpoint in pulmonary arterial hypertension (PAH) trials, as described by McLaughlin.[12] It is a combination of mortality and different morbidity parameters described after the initiation of specific PH therapy. The definition most frequently used is a combination of all-cause mortality, non-elective hospital stay for PH to initiate intravenous prostanoid or lung transplantation, and disease progression defined as a reduction from baseline in six-minutes walking distance (6-MWD) by 15%.[12]

Until now, the prevalence of CW in patients with CTEPH is unclear. This thesis concerns the outcome of patients with inoperable and operable CTEPH. Furthermore, we describe the prevalence of CW in these populations and try to identify predictors for the occurrence of CW after PEA.

In **chapter 2** we describe the long-term outcome of 32 consecutive patients (mean age 61.8±12.7 years, 50% female, mean PVR at baseline of 575.7±316.7 dyn s cm^{-5} [range 200-1,552 dyn s cm^{-5}]) with inoperable CTEPH at the St. Antonius Hospital Nieuwegein. Clinical worsening was defined as a combination endpoint of death, need for intravenous PAH medication, or 15% decrease in 6-MWD without improvement in functional class.

During a mean follow-up of 3.4 years, 11 patients died. The 1- and 3-years survival rates were 88% and 77%, respectively.

Clinical worsening occurred in 16 patients (50%). The 1- and 3-year rates of freedom from CW were 74% and 60%, respectively. The baseline 6-MWD was a predictor for the occurrence of CW.

Chapter 3 concerns the outcome of 74 consecutive patients (mean age 55.9±13.8 years, 51% female, PVR at baseline of 521±264 dyn·s·cm^{-5} [range 279-1331 dyn·s·cm^{-5}]) with CTEPH who underwent a PEA between May 2000 and August 2009 in the St. Antonius Hospital Nieuwegein. Clinical worsening was defined as the combination of death, need for PH medication initiated after PEA or 15% decrease in 6-MWD without improvement of functional class during follow-up. Within 3 days after the PEA, the mPAP decreased to 25.2±11.2 mmHg (p=0.001). During the post-operative period, five patients out of 74 (6.8%) died in the hospital.

During a mean follow-up of 3.7 years another 5 patients out of 69 (7.2%) died. The overall one-, three- and five-year survival rates after hospital discharge were 93%, 91% and 89%, respectively.

Clinical worsening occurred in 13 out of 69 patients (19%) during follow-up. In 8 patients initiation of PH-specific medication was needed during follow-up. We were not able to identify a significant predictor at baseline for the occurrence of CW during long-term follow-up.

In **chapter 4** we evaluated whether pre-operative non-invasive imaging modalities like chest computed tomography (CT) scan and echocardiography were able to predict post-operative pulmonary hemodynamics. According to the study by Heinrich et al.,[13] perpendicular to its long axis, the widest diameters of the ascending aorta (Ao) and the main pulmonary artery (PA) were measured at the level of the bifurcation of the PA. The ratio

of the PA and the Ao diameters was calculated. The PA diameter was indexed by body surface area (BSA).

Hemodynamic improvement after PEA was defined as a PVR <500 dyn s cm^{-5} and a mean PAP <35 mmHg 3 days after PEA.[14,15]

Fifty-two patients (mean age of 58.9±13.4 years, 59.6 % female, mean PAP at baseline 40.1±8.5 mmHg with a mean PVR at baseline of 971±420 dyn·s·cm^{-5}) with CTEPH underwent a PEA in the University Hospitals Leuven. Three days after surgery the mean PAP decreased to 33.8±11.9 mmHg and PVR was 328±163 dyn s cm^{-5} (both p<0.001, compared to baseline). Incomplete hemodynamic improvement occurred in 15 patients (29%, 87% female, mean age 59.3±14.0 years). Univariate logistic regression identified male gender, lower mean PAP, smaller PA diameter indexed for BSA and higher TAPSE as pre-operative predictors for hemodynamic improvement. The indexed PA diameter was the only independent pre-operative predictor of hemodynamic improvement after PEA, 19.4±2.4 mm/m2 in patients with versus 22.9±4.9 mm/m2 in patients without hemodynamic improvement (OR 0.76: 95 % CI 0.58–0.99, p = 0.04).

Within 30 days after PEA, 5 patients (9.6 %) died (100 % female, mean age 54.9±15.9 years). In all, hemodynamic improvement was absent, with a post-operative mean PAP of 51.6±14.1 mmHg and PVR of 692±216 dyn·s·cm^{-5} in patients who died, compared to a post-operative mean PAP of 32.2±10.1 mmHg and PVR of 302±141 dyn·s·cm^{-5} in patients who survived.

In conclusion, this is the first study showing that the pre-operative PA/BSA ratio was an independent predictor for hemodynamic outcome after PEA. Therefore, we have to consider that the PA diameter indices might be valuable additives in predicting the hemodynamic outcome prior to PEA.

In **chapter 5** we evaluated whether pre-operative PA diameter indices, measured on chest CT-scan, were able to predict the occurrence of mortality and CW after PEA. Persistent or residual PH after PEA was defined as mean PAP >25 mmHg by right heart catheterization or systolic PAP >40 mmHg by echocardiography.[16]

We studied 114 patients (mean age 56.9±13.8 years, 58% female, mean PAP at baseline 41.2±10.2 mmHg with a mean PVR at baseline of 759±422 dyn·s·cm^{-5}) with CTEPH who

underwent a PEA in the St. Antonius Hospital Nieuwegein or the University Hospitals Leuven. Seven (6.1%) patients died within 30 days after PEA. By multivariate analysis the indexed PA diameter and mean PAP were the only independent pre-operative predictors of 30-day mortality after PEA (OR 1.4, p=0.04; and OR 1.2, p=0.02, respectively). During a mean follow-up of 3.2 years, eight (7.5%) out of 107 patients who survived surgery died. Only one patient died as the consequence of progression of PH. Clinical worsening occurred in 24 (22%) out of 107 patients. Indexed PA diameter (HR 1.2, p=0.01), age (HR 1.1, p=0.02) and LVEF (HR 1.1, p=0.03) were all independent pre-operative predictors for the occurrence of CW during follow-up. In conclusion, the noninvasively measured PA diameter indices might be a valuable addition in predicting the post-operative CW prior to PEA.

The pulmonary artery occlusion technique was developed to estimate pulmonary capillary pressure and most likely approximates pressure in the pre-capillary small pulmonary arteries (occlusion pressure; Poccl).[17-20] With Poccl, the pulmonary arterial resistance can be partitioned into larger arterial (upstream) and small arterial plus venous (downstream) components. Recently, it was shown that patients with CTEPH who had predominantly proximal (large vessel) disease had a higher upstream resistance (R*up*), whereas CTEPH patients with significant concomitant small-vessel disease had lower R*up*.[21]

In **chapter 6** we evaluated whether R*up* could predict the occurrence of 30-days mortality and hemodynamic outcome 3 days after PEA. We studied 42 patients (mean age of 59.1±14.1 years, 54.8% female, mPAP at baseline was 40.1±8.6 mmHg with a PVR at baseline of 961±427 dyn·s·cm^{-5}) who underwent a PEA in the University Hospitals Leuven between May 2004 and January 2009. Hemodynamic improvement was defined as a PVR of <500 dyn·s·cm^{-5} and mean PAP <35 mmHg. Incomplete hemodynamic improvement occurred in 13 out of 42 patients ([31.0%], 77% female, mean age 58.6±14.9 years). The mean R*up* in patients with favourable hemodynamic outcome was 77.7±13.4%; in patients with incomplete hemodynamic improvement, the mean R*up* was 74.3±16.3%. The mean PAP was the only independent pre-operative predictor of hemodynamic improvement after PEA (OR 0.9, p=0.02). R*up* did not appear to be a predictor for occurrence of hemodynamic improvement (OR 1.0, p=0.48).

Within 30 days after PEA, 5 out of 42 patients (11.9%) died (100% female, mean age 54.9±15.9 years). In all, hemodynamic improvement was incomplete or absent, with a post-operative mean PAP of 51.6±14.1 mmHg and PVR of 692±216 dyn·s·cm^{-5}, compared to a post-operative mean PAP of 32.0±10.4 mmHg and PVR of 300±147 dyn·s·cm^{-5} in pa-

tients who survived. By multivariate analysis the mean PAP was the only independent pre-operative predictor for 30-days mortality after PEA (OR 1.4, p=0.02). R*up* was not a predictor for the occurrence of mortality within 30 days after PEA (OR 1.0, p=0.71).

In conclusion, R*up* was not found to be a predictor for 30-days mortality or unfavourable hemodynamic outcome after PEA in patients with CTEPH.

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SAMENVATTING

Chronische trombo-embolische pulmonale hypertensie (CTEPH) is gedefinieerd als een verhoogde gemiddelde druk in de arteria pulmonalis (AP) van tenminste 25 mmHg in rust, die ontstaat als een (groot) deel van de longcirculatie wordt afgesloten door niet of onvolledig geresorbeerde stolsels na een doorgemaakte longembolie, ondanks drie maanden van therapeutische antistolling.[1]

Het niet of onvolledig verdwijnen van een acute longembolie is de meest voorkomende oorzaak van CTEPH en kan optreden na een of meedere episoden. In sommige gevallen kan CTEPH echter ook ontstaan door het plaatselijk optreden van trombose in de arteria pulmonalis, hetgeen geassocieerd kan zijn met ontsteking van de vaatwand.[2] De geschatte prevalentie van CTEPH twee jaar na een doorgemaakte acute longembolie is 0.1-4.0%.[3-7]

De pulmonalis-endarteriëctomie (PEA) is de therapie van eerste keuze bij patiënten met CTEPH. Bij de meeste patiënten leidt de ingreep tot normalisatie van de pulmonale hemodynamiek en tot een permanente oplossing.[8] Echter, bij ongeveer 50% van de patiënten is een PEA niet mogelijk (inoperabele CTEPH) ten gevolge van te distale obstructie van het pulmonale vaatbed hetgeen chirurgisch niet benaderbaar is, of de aanwezigheid van belangrijke co-morbiditeit hetgeen leidt tot een onacceptabel hoog operatierisico.[9] Daarnaast is er bij ongeveer 10-15% van de patiënten die een PEA hebben ondergaan sprake van recidief of persisterende pulmonale hypertensie (PH, gemiddelde druk in arteria pulmonalis [mPAP] >25 mmHg).[10,11] In deze gevallen kan medicamenteuze behandeling worden overwogen.

Recent is het eindpunt klinische verslechtering geïntroduceerd als een samengesteld eindpunt in pulmonale arteriële hypertensie studies, zoals beschreven door McLaughlin.[12] Het is een samengesteld eindpunt bestaande uit mortaliteit en verschillende morbiditeit parameters die beschreven worden na het starten van PH-specifieke therapie. De meest gebruikte definitie is een combinatie van overlijden, ongeplande ziekenhuisopname vanwege PH voor starten van intraveneuze behandeling met een prostacycline analoog of longtransplantatie, of progressie van ziekte die werd gedefinieerd als een afname van de 6-minuten looptest afstand (6-MWD) met 15% ten opzichte van baseline.[12]

Tot nu toe is de prevalentie van klinische verslechtering bij patiënten met CTEPH onbekend. In dit proefschrift worden de uitkomsten van patiënten met inoperabele en operabele CTEPH beschreven. Daarnaast wordt de prevalentie van klinische verslechtering in deze patiëntengroepen beschreven en wordt getracht voorspellers voor het optreden van klinische verslechtering na PEA te identificeren.

In **hoofdstuk 2** worden de lange termijns uitkomsten beschreven van 32 opeenvolgende patiënten (gemiddelde leeftijd 61.8±12.7 jaar, 50% vrouw, gemiddelde pulmonale vaatweerstand [PVR] bij baseline van 575.7±316.7 dyn s cm^{-5}) met inoperabele CTEPH uit het St. Antonius ziekenhuis te Nieuwegein. Klinische verslechtering werd gedefinieerd als een samengesteld eindpunt van overlijden, noodzaak tot starten van intraveneuze PH-specifieke medicatie, of een 15% daling in 6-MWD zonder verbetering van functionele klasse. Tijdens een gemiddelde follow-up van 3.4 jaar overleden 11 patiënten. Na 1 jaar was 88% van de patiënten nog in leven. Na 3 jaar 77%.

Klinische verslechtering trad op bij 16 patiënten (50%). Na 1 jaar was 74% van de patiënten vrij van klinische verslechtering. Na 3 jaar 60%. De 6-MWD bij baseline was een voorspeller voor het optreden van klinische verslechtering tijdens follow-up.

In **hoofdstuk 3** worden de uitkomsten beschreven van 74 opeenvolgende patiënten (gemiddelde leeftijd 55.9±13.8 jaar, 51% vrouw, mean PAP 41.3±11.9 mmHg met een PVR bij baseline van 521±264 dyn·s·cm^{-5}) met CTEPH die tussen mei 2000 en augustus 2009 een PEA ondergingen in het St. Antonius ziekenhuis te Nieuwegein. Klinische verslechtering werd gedefinieerd als een combinatie eindpunt van sterfte, noodzaak tot starten van PH-specifieke medicatie na de PEA, of een 15% daling van de 6-MWD zonder verbetering van functionele klasse tijdens follow-up. Drie dagen na de PEA was de mPAP gedaald naar 25.2±11.2 mmHg (p=0.001). Tijdens de post-operatieve periode in het ziekenhuis overleden 5 patiënten (6.8%).

Tijdens een gemiddelde follow-up van 3.7 jaar overleden nog 5 van de nog in leven zijnde 69 patiënten (7.2%). Eén jaar na het ontslag uit het ziekenhuis was 93% van de patiënten nog in leven. Na 3 en 5 jaar was dit respectievelijk 91% en 89%.

Bij 13 van de 69 patiënten (19%) was sprake van klinische verslechtering tijdens follow-up. Bij 8 patiënten was het starten van PH-specifieke medicatie noodzakelijk. Het bleek niet mogelijk een pre-operatieve voorspeller te vinden voor het optreden van klinische verslechtering tijdens follow-up.

In **hoofdstuk 4** wordt onderzocht of niet-invasieve beeldvormingstechnieken zoals CT-scan en echocardiografie in staat zijn om de directe post-operatieve hemodynamische uitkomst te voorspellen. Analoog aan de studie van Heinrich[13] werden de grootste diameters van de aorta en AP gemeten ter hoogte van de bifurcatie van de AP. De verhouding hiervan werd berekend. Tevens werd de diameter van de AP geïndexeerd voor lichaamsoppervlak (BSA). Hemodynamische verbetering werd gedefinieerd als een PVR <500 dyn·s·cm^{-5} en een mPAP <35 mmHg 3 dagen na PEA.[14,15]

Tweeënvijftig patiënten met CTEPH (gemiddelde leeftijd 58.9±13.4 jaar, 59.6 % vrouw, mPAP bij baseline 40.1±8.5 mmHg met een PVR bij baseline van gemiddeld 971±420 dyn·s·cm^{-5}) ondergingen een PEA in het Gasthuisberg Universitair Ziekenhuis te Leuven. Drie dagen na operatie waren de mPAP en PVR respectievelijk gedaald naar 33.8±11.9 mmHg en 328±163 dyn s cm^{-5}. Bij 15 patiënten was geen sprake van hemodynamische verbetering. Met univariate logistische regressie analyse werden mannelijk geslacht, lagere mPAP, kleinere geindexeerde diameter van de AP en een hogere TAPSE geidentificeerd als pre-operatieve voorspellers voor het optreden van hemodynamische verbetering na PEA. De geïndexeerde AP diameter bleek echter de enige onafhankelijke voorspeller.

In **hoofdstuk 5** wordt onderzocht of de voor lichaamsoppervlak geïndexeerde AP diameter gemeten op CT-scan, ook in staat is om het optreden van mortaliteit en klinische verslechtering na PEA tijdens follow-up te voorspellen. Recidief of persisterende pulmonale hypertensie na PEA werd gedefinieerd als een mPAP >25 mmHg gemeten bij rechtscatheterisatie of een geschatte rechter ventrikel systolische druk >40 mmHg bij echocardiogram.[16] Wij onderzochten 114 patiënten (gemiddelde leeftijd 56.9±13.8 jaar, 58% vrouw, mPAP bij baseline 41.2±10.2 mmHg en een PVR bij baseline van gemiddeld 759±422 dyn·s·cm^{-5}) met CTEPH die een PEA ondergingen in het St. Antonius ziekenhuis te Nieuwegein of het Gasthuisberg Universitair ziekenhuis Leuven. Zeven patiënten (6.1%) overleden binnen 30 dagen na PEA. De geïndexeerde AP diameter en de mPAP waren de enige onafhankelijke pre-operatieve voorspellers voor 30 dagen mortaliteit. Tijdens een gemiddelde follow-up van 3.2 jaar overleden nog 8 patiënten (7.5%). Slechts één patiënt overleed aan progressie van de pulmonale hypertensie. Klinische verslechtering trad bij 24 patiënten (22%) op. De geïndexeerde AP diameter (HR 1.2, p=0.01), leeftijd (HR 1.1, p=0.02) en linker ventrikel ejectiefractie (HR 1.1, p=0.03) waren allen onafhankelijke voorspellers voor het optreden van klinische verslechtering tijdens follow-up.

De AP occlusie techniek werd ontwikkeld om de pulmonale capillaire druk te schatten en benadert in de meeste gevallen de druk in de kleine pre-capillaire pulmonaal arterieën (Poccl).[17-20] Met Poccl kan de weerstand in de pulmonaal arterieën worden onderverdeeld in een component van de grote arterieën (upstream) en een kleine arterieën plus veneuze component (downstream). Uit een recente studie blijkt dat patiënten met CTEPH bij wie met name proximale ziekte (grote vaten) aanwezig is, een hogere "upstream" weerstand (R*up*) hebben, in tegenstelling tot patiënten met meer distale ziekte die een lagere R*up* hebben.[21]

In **hoofdstuk 6** wordt onderzocht of R*up* een voorspeller is voor 30 dagen mortaliteit en voor hemodynamische verbetering 3 dagen na PEA.

We onderzochten 42 patiënten (gemiddelde leeftijd 59.1±14.1 jaar, 54.8% vrouw, mPAP bij baseline 40.1±8.6 mmHg met een PVR bij baseline van 961±427 dyn·s·cm^{-5}) die een PEA ondergingen in het Gasthuisberg Universitair ziekenhuis Leuven tussen mei 2004 en januari 2009. Hemodynamische verbetering werd gedefinieerd als PVR < 500 dyn·s·cm^{-5} en mPAP < 35 mmHg. Er trad geen hemodynamische verbetering op bij 13 van de 42 patiënten (31%). Bij deze patiënten was de gemiddelde R*up* 74.3±16.3%; bij patiënten bij wie sprake was van hemodynamische verbetering was dit 77.7±13.4%. De mPAP was de enige onafhankelijke pre-operatieve voorspeller voor hemodynamische verbetering na PEA (OR 0.9, p=0.02). R*up* bleek geen voorspeller voor hemodynamische verbetering.

De 30 dagen mortaliteit bedroeg 11.9%. Bij allen was er geen sprake van hemodynamische verbetering na de PEA. De post-operatieve mPAP bedroeg gemiddeld 51.6±14.1 mmHg met een gemiddelde PVR van 692±216 dyn·s·cm^{-5} versus 32.0±10.4 mmHg en 300±147 dyn·s·cm^{-5} bij de patiënten die in leven bleven. De mPAP bleek de enige onafhankelijke pre-operatieve voorspeller voor 30 dagen mortaliteit na PEA (OR 1.4, p=0.02). R*up* bleek ook hier geen voorspellende waarde te hebben (OR 1.0, p=0.71).

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 18 december 1977 te Dordrecht. Hij is getrouwd met Shaula Nuijts en is vader van Thijn (2011) en Jeppe (2014). In 1996 werd het diploma Voorbereidend Wetenschappelijk Onderwijs behaald aan de Regionale Scholengemeenschap Hoeksche Waard te Oud-Beijerland. In datzelfde jaar begon hij aan de studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Tijdens zijn afstudeeronderzoek "Coarctatio aortae en aortakleplijden" onder begeleiding van mw. Dr. J.W. Roos-Hesselink werd zijn interesse voor de cardiologie gewekt. In 2003 studeerde hij af en startte hij als arts-assistent-niet-in-opleiding op de afdeling cardiologie in het Amphia ziekenhuis. Na eerst nog een jaar op de afdeling cardiologie in het Erasmus MC te hebben gewerkt, werd in 2005 de overstap gemaakt naar het St. Antonius ziekenhuis te Nieuwegein. In 2006 werd de opleiding tot cardioloog aangevangen (opleider: Dr. W. Jaarsma). In 2007 werd de overstap weer gemaakt naar het Amphia ziekenhuis voor de vooropleiding interne geneeskunde (opleider: Dr. C. van Guldener). In 2009 werd de opleiding cardiologie vervolgd in het St. Antonius ziekenhuis (opleiders: Dr. W. Jaarsma en Dr. J.M. ten Berg). In 2010 werd onder begeleiding van Dr. M.C. Post gestart met het klinisch wetenschappelijk onderzoek dat uiteindelijk heeft geresulteerd in dit proefschrift. In november 2011 werd de opleiding tot cardioloog voltooid en aansluitend werd gestart met het fellowship interventiecardiologie in het St. Antonius ziekenhuis (opleider: Dr. J.A.S. van der Heyden). Per 1 januari 2013 trad hij toe tot de maatschap cardiologie in het Amphia ziekenhuis te Breda.

LIST OF PUBLICATIONS

1 Schölzel BE, Snijder RJ, Mager JJ, van Es HW, Plokker HW, Reesink HJ, Morshuis WJ, Post MC. Chronic thromboembolic pulmonary hypertension. Neth Heart J. 2014 Aug 29. [Epub ahead of print]

2 Schölzel BE, Post MC, van de Bruaene A, Dymarkowski S, Wuyts W, Meyns B, Budts W, Delcroix M. Prediction of hemodynamic improvement after pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension using non-invasive imaging. Int J Cardiovasc Imaging. 2014 Aug 22. [Epub ahead of print]

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