ORIGINAL ARTICLE

Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy

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ABSTRACT

Background Chronic thromboembolic pulmonary hypertension is surgically curable by pulmonary endarterectomy (PEA). It is unclear whether PEA impacts primarily steady state right ventricular afterload (ie, pulmonary vascular resistance (PVR)) or pulsatile right ventricular afterload (ie, pulmonary arterial compliance (CPA)). Our objectives were to (1) quantify PEA specimens and measure the impact of PEA on PVR and CPA in a structure/function study and (2) analyse the effects of haemodynamic changes on long-term survival/freedom of lung transplantation in an outcome study.

Methods Thrombi were laid out, weighed, photographed and measured. PVR, CPA and resistance times compliance (RC-time) were assessed at baseline, within 4 days after PEA (immediately postoperative) and 1 year after PEA, in 110 consecutive patients who were followed for 34.5 (11.9; 78.3) months.

Results Lengths and numbers of PEA specimen tails were inversely correlated with immediate postoperative PVR (r=-0.566; p<0.0001, r=-0.580). PVR and CPA normalised immediately postoperatively while RC-time remained unchanged. Immediate postoperative PVR was the only predictor of long-term survival/freedom of lung transplantation (p<0.0001). Patients with immediate postoperative PVR<590 dynes.s.cm−5 had better long-term outcomes than patients with PVR≥590 dynes.s.cm−5 (p<0.0001, respectively).

Conclusions PEA immediately decreased PVR and increased CPA under a constant RC-time. However, immediate postoperative PVR was the only predictor of long-term survival/freedom of lung transplantation. Our study confirms the importance of a complete, bilateral surgical endarterectomy. Low PVR measured immediately postoperative predicts excellent long-term outcome.

INTRODUCTION

Pulmonary endarterectomy (PEA) is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH)1 with a peri-procedural mortality rate of <5% in Europe today,2 nearly normalised haemodynamics and substantial improvement in clinical symptoms in the majority of patients.1,4 Outcomes after PEA have been estimated on the basis of postoperative pulmonary vascular resistance (PVR) measurements, with a PVR of 500 dynes.s.cm−5 as a threshold of favourable outcome in several databases.1,2 Right ventricular (RV) afterload bears a steady component (represented by PVR) and an oscillatory component (the opposition that the ventricle encounters to maintain forward flow and pulsatile components of flow). Pulmonary arterial compliance (CPA) relates to oscillatory load with potentially greater prognostic importance than resistance.5,6 RV hydraulic load is determined by the dynamic interaction between PVR and CPA.7 The product of resistance (PVR) and CPA is consistently inversely related and remains unaltered at approximately 0.7 s in various types of pulmonary hypertension (PH).8 We have recently reported that patients with persistent exertional dyspnoea after successful PEA display an abnormal pulmonary haemodynamic response to exercise, characterised by increased PVR and decreased CPA.7 Because PEA mainly affects major vessels that are surgically accessible, and CPA appears to be determined by the larger vessel compartment,9 we hypothesised that PEA primarily increases CPA, which may then also be an important predictor of prognosis in CTEPH. Therefore, we quantified thrombus, measured the impact of PEA on haemodynamics in a structure/function study and analysed which RV afterload parameter (PVR, CPA or resistance times compliance (RC-time)) is the best predictor of long-term survival/freedom of lung transplantation in an outcome study.
Haemodynamic definitions
PVR was calculated by mean pulmonary arterial pressure (mPAP)—mean pulmonary capillary wedge pressure/cardiac output (CO) multiplied by 80 for dynes.s.cm\(^{-5}\). C\(_{PA}\) was calculated as stroke volume (CO/heart rate) divided by systolic PAP—diastolic PAP. The RC-time (product of resistance (R=PVR) and compliance (C\(_{PA}\))) was calculated as previously described\(^8\) and expressed in seconds.

Persistent/recurrent PH was defined as mPAP≥25 mmHg and PVR≥400 dynes.s.cm\(^{-5}\) at the routine 1-year FU RHC.\(^{11}\)

Analysis of PEA specimens
The Jamieson classification system\(^3\) was used to describe the four major types of CTEPH. Jamieson type I is semithermally or organised thrombosis that begins in the main or lobar arteries; type II is organised thrombus and intimal thickening proximal to segmental arteries; type III is intimal thickening and fibrosis in the distal segmental arteries; and type IV is distal arteriolar vasculopathy with no intraluminal disease. If there was a discrepancy in CTEPH type between left and right specimen, the most proximal thrombus determined the final classification.

Starting 2005, semiquantitative assessment of consecutive PEA specimens, labelled as ‘thrombi’, was performed. Thrombi were laid out, weighed and photographed (n=69). Organised small-vessel thrombus (‘thrombus tails’) was defined as white dissection, <2 mm in thickness and at least 2 mm in length. Thrombus tails were counted and measured in centimetres. Those analysing PEA specimens (GM and CG) were blinded to the case of skewed distributions, by medians (25% percentile; 75% percentile). Discrete data were presented as counts. Deltas (Δ) were calculated as the difference between values at the immediate postoperative RHC and baseline RHC, and were depicted as vectors for each patient.

RESULTS
Baseline characteristics
A total of 110 patients undergoing PEA between May 1994 and December 2010 were included in the study. Patients’ baseline characteristics are summarised in table 1.

All patients were on standard medical therapy consisting of oral anticoagulation (international normalised ratio 2.0–3.0), digoxin, diuretics and other supportive treatments including birth control and vaccinations. Five patients who were referred from other centres received preoperative pulmonary arterial hypertension (PAH)-specific therapies (sildenafil, bosentan, inhaled iloprost) that were terminated at the time of PEA. Patients underwent surgery 129±362 days after diagnosis. CTEPH types\(^4\) are listed in table 1.

### Table 1: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>110 (100%)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>56±14</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td></td>
<td>56/54</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>26±4</td>
</tr>
<tr>
<td>WHO functional class (II/III/IV)</td>
<td></td>
<td>5/76/29</td>
</tr>
<tr>
<td>6-MWD (m)</td>
<td></td>
<td>390±119</td>
</tr>
<tr>
<td>Time from first symptoms to diagnosis (months)</td>
<td></td>
<td>26±36</td>
</tr>
<tr>
<td>Time to PEA (days)</td>
<td></td>
<td>129±362</td>
</tr>
<tr>
<td>Medical treatment prior to PEA (n=number of patients)</td>
<td></td>
<td>5 (0.05)</td>
</tr>
<tr>
<td>CTEPH types II/III/IV</td>
<td></td>
<td>32/55/158</td>
</tr>
</tbody>
</table>

The data are presented as means ± SD. Discrete data are presented as counts. 6-MWD, 6-min walking distance; BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.
Analysis of PEA specimens
In all, 11±3 thrombus tails were counted per surgical specimen, measuring 19±5 cm in total length. Figure 1 shows two representative examples of surgical specimen analyses. Total numbers and lengths of thrombus tails were inversely correlated with immediate postoperative PVR (r=−0.58, p<0.0001; r=−0.57, p<0.0001; figure 2A,B) and Δ CPA (from baseline to immediately postoperative, r=0.44, p=0.002; and to 1 year FU, r=0.44, p=0.002). Thrombus weights varied widely and did not correlate with haemodynamic parameters (data not shown).

Haemodynamic changes as a consequence of PEA
Haemodynamic assessment within 4 days after PEA (2±2 days) was performed in 104 patients, with left atrial pressures serving to assess postoperative PVRs. The remaining six patients are #19, #22, #42, #43 (operated in 1996), #72 (operated in 2004) and #81. Immediate postoperative data of these patients were not available because left atrial catheters were pulled before a final haemodynamic evaluation.

PVR, Cpa, RC-time and stroke volume
PVR decreased from preoperative 770.4 (583; 1011) to 368 (251; 516) dynes.s.cm⁻⁵ immediate postoperative (p<0.001, figure 3A). The change of PVR between immediate postoperative and 1-year FU was not significant (p=0.22). CPA changed significantly from baseline to immediate postoperative, without further changes to 1-year FU (figure 3B). On average, RC-time decreased after PEA, albeit not significantly: RC-time=0.72±0.71 s (baseline), RC-time=0.60±0.3 s (immediate postoperative) and RC-time=0.59±0.34 s (1-year FU; figure 3C; paired t test: p=0.13 from baseline to immediate postoperative, and p=0.32 from baseline to 1-year FU). The change of RC-time was not different between patients with persistent/recurrent PH compared with patients with no PH (immediately postoperative p=0.81, at 1 year p=0.64).

Haemodynamic parameters at baseline, immediate postoperative and at 1-year FU are listed in table 2.
Stoke volume increased from baseline to 1-year FU, while it did not change significantly from baseline to immediate postoperative (figure 3D).

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Immediate postoperative</th>
<th>1-year FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR (dynes.s.cm(^{-5}))</td>
<td>770 (583; 1011)</td>
<td>368 (251; 516)**</td>
<td>280 (186; 472)**</td>
</tr>
<tr>
<td>CPA (mL/mm Hg)</td>
<td>1.0 (0.8; 1.4)</td>
<td>2.2 (1.5; 3.2)**</td>
<td>2.7 (1.4; 3.8)**</td>
</tr>
<tr>
<td>RC-time (s)</td>
<td>0.72±0.71</td>
<td>0.60±0.3</td>
<td>0.59±0.34</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>58.4±16.8</td>
<td>61.1±20.9</td>
<td>71.6±18.6**</td>
</tr>
</tbody>
</table>

PVR and CPA are presented as medians (25% percentile; 75% percentile), RC-time and SV as means±SDs.

**p<0.001.

CPA, pulmonary arterial compliance; FU, follow-up; PVR, pulmonary vascular resistance; RC-time, resistance times compliance; SV, stroke volume.

Vector diagram indicating the change in both R and C between catheterisations

Figure 4 depicts vectors from the origin that indicate the change (A) in both PVR and CPA between catheterisations at baseline and immediate postoperative to discriminate poor ‘PVR-responders’ from poor ‘CPA-responders’. The majority of vectors (n=78, 75%) point to the top-left quadrant indicating that if PVR decreases, CPA increases concordantly. The five vectors ending in the top-right quadrant (‘PVR non-responders’) represent five patients with persistent/recurrent PH, with one patient dying from right heart failure. In the left-bottom quadrant (concordant decreases of PVR and CPA) are 21 vectors representing predominantly female patients, of whom 14 patients (67%) had persistent/recurrent PH, with seven deaths (33%). In this group were three patients with ventriculo-atrial (VA) shunts (out of a total of four patients with VA shunts among the 110 patients).

**Survival**

Overall survival showed 1-, 3- and 5-year cumulative rates of 92%, 89%, 85% and 61% at 10 years.
Perioperative inhospital death occurred in five patients (three female patients, 5%) at 11±14 days after PEA (table 3) due to right heart failure. Deceased patients had higher baseline PVRs (1090±502 dynes.s.cm⁻⁵) and higher immediate postoperative PVRs (821±501 dynes.s.cm⁻⁵). Three further patients died within the first year (163±117 days postoperatively). Mean immediate postoperative PVR was 587±147 dynes.s.cm⁻⁵ in these cases.

Predictors of outcome

During the observation 21 events occurred. Two patients died from malignancies and were excluded from the analyses of disease-specific survival. Baseline PVR>1000 dynes.s.cm⁻⁵ was a weak predictor of 1-, and 3- year survival (Fisher’s exact test p=0.05, p=0.06).

In all, 28 patients (26%) had a PVR>1000 dynes.s.cm⁻⁵ and a high risk for postoperative mortality. Of these, eight patients (29%) died within the observation period, with immediate postoperative PVRs of 765±237 dynes.s.cm⁻⁵.

Cox regression analysis revealed immediate postoperative PVR as the strongest independent predictor of long-term survival/freedom of lung transplantation (HR 1.005; 95% confidence limits 1.003 to 1.006; p<0.0001). Immediate postoperative PVR≥590 dynes.s.cm⁻⁵ can predict death/lung transplantation in patients after PEA (figure 5).

Patients with immediate postoperative PVR<590 dynes.s.cm⁻⁵ had a better long-term outcome than patients with PVR≥590 dynes.s.cm⁻⁵ (p<0.0001; figure 6A). The absolute value of immediately postoperative PVR predicted survival. Patients with immediate postoperative PVR<290 dynes.s.cm⁻⁵ had a better survival than patients with PVR between 292 and 450 dynes.s.cm⁻⁵, and those with immediate postoperative PVR>450 dynes.s.cm⁻⁵ (figure 6B). None of the patients with

<table>
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<th>Table 3 Haemodynamic variables of patients with early mortality (within 31 days after PEA), at baseline and immediately postoperative</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>PVR (dynes.s.cm⁻⁵)</td>
</tr>
<tr>
<td>Cpa (mL/mm Hg)</td>
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<tr>
<td>SV (mL)</td>
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</table>

The data are presented as means±SDs. Cpa, pulmonary arterial compliance; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; SV, stroke volume.
an immediate postoperative PVR<290 dynes.s.cm$^{-5}$ died or underwent lung transplantation within the observation period.

The numbers and lengths of thrombus tails were predictors of survival/freedom of lung transplantation (HR 0.81, p=0.02; HR 0.9; p=0.01, respectively).

Neither $C_{PA}$ nor RC-time showed a significant influence on survival.

**Predictors of persistent/recurrent PH**

No baseline haemodynamic parameter, but only immediate postoperative PVR (HR 1.004; 95% CI confidence limits: 1.0032 to 1.0056; p<0.0001) was an independent predictor of persistent/recurrent PH.

The numbers and lengths of thrombus tails were predictors of persistent/recurrent PH (n=25; Log OR 0.74, p=0.0026; Log OR 0.86, p=0.002, respectively).

**DISCUSSION**

Our data show that (i) PEA immediately decreased PVR and increased $C_{PA}$, under a constant RC-time. However, (ii) immediate postoperative PVR was the only predictor of persistent/recurrent PH.

The relationship between PVR and $C_{PA}$ is presented in figure 4, which is in concordance with findings of patients under PAH-specific treatments. Searching for cases in whom proximal compliance improved more than resistance, we chose to represent individual cases as vectors from the origin. The majority of vectors point to the top-left quadrant of figure 4, confirming that if PVR decreases, $C_{PA}$ increases concordantly, indicating a significant contribution of major vessel disobliteration to the improvement of vascular compliance in CTEPH.

Those patients in whom PVR and $C_{PA}$ are dissociated appear to experience worse outcomes (100% persistent/recurrent PH in the right upper quadrant of figure 4, and 67% persistent/recurrent PH in the left lower quadrant of figure 4). Causes may be a stiff and obstructed distal microcirculatory compartment or residual thrombus.

In the outcome study we analysed the effects of haemodynamic changes on long-term survival/freedom of lung transplantation. CTEPH is a dual vascular disorder, with a major vessel disease component that can be addressed by surgical PEA as well as a microvascular disease (secondary vasculopathy). Secondary vasculopathy of CTEPH is indistinguishable from

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**Figure 6** (A) Kaplan–Meier survival curves in patients with operated chronic thromboembolic pulmonary hypertension (CTEPH) and immediate postoperative pulmonary vascular resistance (PVR)≥590 dynes.s.cm$^{-5}$ compared with patients with immediate postoperative PVR<590 dynes.s.cm$^{-5}$. Patients with immediate postoperative PVR<590 dynes.s.cm$^{-5}$ had a better long-term outcome than patients with PVR≥590 dynes.s.cm$^{-5}$ (p<0.0001). (B) Kaplan–Meier survival curves in patients with operated CTEPH by tertiles of immediate PVR (p<0.001, respectively).
pulmonary vascular lesions seen in PAH and affects pulmonary arteries measuring less than 200 μm in diameter, contributing to higher PVR and increased postoperative mortality. It has been difficult to compartmentalise resistance prior to PEA, that is, to predict which proportion of PVR is due to major vessel obstruction and which is due to small vessel disease. A preoperative PVR above 1000 dynes.s.cm⁻¹⁻¹ has generally been labelled as an important clinical risk factor, underlying a mortality rate of 10.1%, and is possibly a marker for significant small vessel disease. In the international prospective CTEPH registry, patients presenting with baseline PVR between 800 and 1000 dynes.s.cm⁻¹⁻¹ had mortality rates (in-hospital and 1-year) of 14.4% (15 of 104 patients), while patients with PVR>1200 dynes.s.cm⁻¹⁻¹ had mortality rates of 23.4%. While a baseline PVR>1000 dynes.s.cm⁻¹⁻¹ was a weak predictor of survival, preoperative PVR as a continuous variable did not appear as a multivariate predictor of 1-year-survival, similar to what was seen in the CTEPH registry. Furthermore, more recent studies have documented a significant reduction in post-PEA mortality even in patients with PVR>1000 dynes.s.cm⁻¹⁻¹ at baseline. By contrast, PVR measured immediately postoperative had a significant influence on long-term outcome (p<0.0001), at a threshold of 590 dynes.s.cm⁻¹⁻¹. Similar cut-offs (500 dynes.s.cm⁻¹⁻¹) were predictive of 30-day outcomes (p<0.001) in the study by Jamieson and coworkers. Our data demonstrate that patients with immediate postoperative PVR<290 dynes.s.cm⁻¹⁻¹ had excellent outcomes beyond 10 years FU.

Limitations

The relatively small study size and the single-centre design count as limitations. In addition, PEA specimens were not available from all patients and assessments were semi-quantitative. Outcomes were influenced by a centre-specific ‘learning curve’ that is significant in this technically difficult surgical procedure. Furthermore, we did not systematically assess residual thrombus by postoperative imaging.

CONCLUSIONS

The data support the value of a complete and bilateral surgical endarterectomy, and the need for a final haemodynamic assessment in the intensive care unit prior to removal of the Swan-Ganz catheter to assess postoperative PVR. PVR is the key haemodynamic parameter for predicting prognosis in CTEPH patients undergoing PEA. The outcome of operable CTEPH is best predicted immediately after PEA, based on PVR and the characteristics of the surgical specimen.

Contributors NS-S and IML designed the protocol, submitted ethics application, included patients and treated patients. RS-K collected the database. ST, PN and WK performed pulmonary endarterectomy. GM and CG performed the analysis of PEA specimens. GH and CG prepared statistical analyses and the graphs. NS-S and IML drafted the work.

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Competing interests Irene Marthe Lang and Nika Skoro-Sajer have relationships with drug companies including AOPPharm Pharmaceuticals, Actelion, Bayer, Astra-Zeneca, Servier, Cordis, Medtronic, GSK, Novartis, Pfizer and United Therapeutics. In addition, Irene Marthe Lang is an investigator in trials involving these companies, with relationships including consultancy service, research grants and membership of scientific advisory boards.

Patient consent Obtained.

Ethics approval IRB Committee Name: Ethik Kommission der Medizinischen Universität Wien.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES