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Predictors of postoperative outcome after pulmonary endarterectomy from a 14-year experience with 279 patients☆

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Abstract

Objective: Postoperative outcome after pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) is difficult to predict. We sought to analyze specific preoperative findings to predict mortality, shorter mechanical ventilation, and hemodynamic improvement after PEA. **Methods:** A total of 279 patients with CTEPH (57 ± 14 years old, 57% male), who underwent PEA between 1995 and 2009, were reviewed retrospectively. Preoperative pulmonary hemodynamic parameters, spirometry data, laboratory data, cardiac co-morbidities, clinical stage, and number of desobliterated segments were analyzed using a logistic regression model to identify independent predictors for early mortality, shorter duration of mechanical ventilation, and hemodynamic improvement. **Results:** There were 31 early deaths (11.1%, last three years: 6.7%). Among 16 significant predictors for early mortality, preoperative arterial oxygenation was the only significant predictor in multivariate analysis ($P < 0.05$). A total of 147 patients (52.7%) could be extubated within 48 h postoperatively. Out of 16 significant predictors in univariate analysis for mechanical ventilation less than 48 h, only higher forced expiratory volume in 1 s FEV1.0 ($P < 0.05$) and higher preoperative cardiac index ($P < 0.05$) were significant in multivariate analysis. In 185 patients (66.3%), postoperative pulmonary vascular resistance (PVR) was reduced to lower than 400 dyn s^{-1} cm^{-5} at 48 h after PEA. Male gender ($P < 0.05$), lower preoperative mean pulmonary arterial pressure (PAP) ($P < 0.05$), and more intra-operative desobliterated segments ($P < 0.01$) were identified as significant predictors for this hemodynamic response with sensitivity of 77.5% and specificity of 67.9%. Using Pearson's correlation coefficient, PVR at 48 h after PEA could be estimated as PVR = 123.266 + 135.471 × creatinine − 22.053 × desobliterated segments + 3.248 × systolic PAP ($P < 0.01$, $R^2 = 0.401$, 95% confidence interval = 0.464 − 0.830). **Conclusions:** Preoperative factors can primarily predict postoperative outcome after PEA. Patients with underlying parenchymal lung disease will have increased risk for early mortality and prolonged mechanical ventilation. The extent of desobliterated segments as well as preoperative hemodynamic severity play a key role in predicting good hemodynamic responders.

Keywords: Chronic thromboembolic pulmonary hypertension; Pulmonary endarterectomy; Hemodynamic improvement; Predictors

1. Introduction

Pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) is a challenging and technically demanding operation, and is associated with a high mortality [1,2]. With experience and optimal patient selection, an operative mortality of 4% can be achieved [3]. These results, however, seem difficult to reproduce in other institutions, in part due to the long learning curve. Difficulty in preoperative decision making may lead to an unacceptably high mortality through surgical candidates, who will not benefit. Alternatively, surgery may not be offered to patients with somewhat increased risk, and they will die from right-heart failure, which could have been prevented by successful PEA. Exact prediction of operative risk and functional result is, therefore, essential.

Possible predictors for success of PEA are considered to be preoperative hemodynamics, preoperative radiological findings, and co-morbidities of patients [1,2]. The San Diego group classified the intra-operative anatomical findings into proximal and peripheral disease and showed that the latter is associated with worse outcome [4,5]. Recently, we published that angiographic characteristics may predict functional outcome [6]. However, more criteria are necessary for the assessment of the cumulative risk.

In this study, we have analyzed, mainly, the preoperative risk factors of 279 patients with CTEPH, who underwent PEA

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between 1995 and 2009, to identify independent predictors of mortality, shorter mechanical ventilation, and hemodynamic improvement.

2. Material and methods

2.1. Patients

Between December 1995 and December 2009, 279 patients with CTEPH underwent PEA performed by a single surgeon (HJS). The local ethics committee approved this retrospective investigation and waived the need for patient consent for the anonymous use of their data. Preoperative characteristics of patients and all parameters analyzed are demonstrated in Table 1. Their mean age was 57 ± 14 years and there was slight male predominance. Tricuspid valve regurgitation was seen in almost all patients. Concomitant cardiac operations were necessary in 53 patients (19.0%). Coronary artery bypass grafting was performed in 29 patients, closure of patent foramen ovale in 17 patients, aortic valve replacement in three patients, tricuspidal valve annuloplasty in three patients, mitral valve repair/replacement in two patients, and atrial electronical ablation in one patient (there are two overlaps).

Table 1. Characteristics of patients and all parameters analyzed.

Variables analyzed	Mean ± SD (%)	Range
Age (years)	56.7 ± 13.6	11–84
Gender (male)	158 (56.6%)	
Body height (cm)	172.8 ± 12.8	79–196
Body weight (kg)	78.1 ± 16.8	42–168
Body surface area (m^2)	1.91 ± 0.21	1.32–2.68
Patent foramen ovale	39 (14.0%)	
Diabetes mellitus	11 (3.9%)	
Hyperlipidemia	48 (17.2%)	
History of smoking	58 (20.8%)	
Serum creatinine level (mg dl^{-1})	1.1 ± 0.3	0.6–3.5
Serum GOT level (IU l^{-1})	26.3 ± 18.1	4.0–137.0
Serum GPT level (IU l^{-1})	26.2 ± 20.9	1.0–194.0
Duration of symptom (month)	39.8 ± 42.0	2.0–216.0
NYHA functional class	3.1 ± 0.6	
PaO_2 (mmHg)	63.0 ± 12.2	30.0–100.0
$PaCO_2$ (mmHg)	31.6 ± 5.0	20.2–62.0
FEV1.0 (l)	2.6 ± 0.8	1.0–4.7
FEV1.0 (% of predicted value)	81.9 ± 18.9	22.0–129.0
VC (l)	3.4 ± 1.0	1.1–6.2
VC (% of predicted value)	87.7 ± 17.8	20.7–135.0
Systolic PAP (mmHg)	81.5 ± 17.5	31–128
Diastolic PAP (mmHg)	27.5 ± 8.8	10–60
Mean PAP (mmHg)	46.5 ± 10.8	10–80
Right atrial pressure (mmHg)	10.7 ± 5.7	2–42
PVR (dyn s^{-1} cm^{-5})	872.1 ± 458.1	133–3233
Cardiac output (l min^{-1})	3.8 ± 1.3	1.7–10.5
Cardiac index (l min^{-1} m^{-2})	2.1 ± 0.6	1.0–5.0
Left ventricle ejection fraction (%)	60.8 ± 15.2	10–92
Concomitant cardiac operation	53 (19.0%)	
Desobliterated segments (right)	7.5 ± 2.2	0–10
Desobliterated segments (left)	5.2 ± 2.4	0–9
Desobliterated segments (total)	12.7 ± 3.5	1–19

NYHA: New York Heart Association, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, PaO_2: partial arterial oxygen pressure, $PaCO_2$: partial arterial carbon dioxide pressure, FEV1.0: forced expiratory volume in 1 s, VC: volume capacity, PAP: pulmonary arterial pressure, PVR: Pulmonary vascular resistance, SD: standard deviation.

2.2. Angiographic and hemodynamic findings

All pulmonary angiograms were performed in our institution, unless those taken elsewhere had perfect quality. Pulmonary angiograms were performed through a right femoral vein approach with a standard technique in all patients. Two projections were obtained for each pulmonary artery with contrast material (30 ml per injection) given at 18 ml s^{-1} (Integris Allura™, Philips Medical Systems, Best, the Netherlands, films stored digitally). Prior to angiography, a complete hemodynamic assessment was performed. Mean preoperative systolic, diastolic, and mean pulmonary arterial pressure (PAP) were 82 ± 18 mmHg, 28 ± 9 mmHg, and 47 ± 11 mmHg, respectively. Mean pulmonary vascular resistance (PVR) was 827 ± 458 dyn s^{-1} cm^{-5}, and cardiac output was 3.8 ± 1.3 l min^{-1}.

2.3. Anesthesia and operative technique

All patients received general anesthesia using propofol and sufentanyl. Neither steroids nor mannitol was given routinely. Nitric oxide was not given during the study period. The Swan–Ganz catheter was used for continuous monitoring of pulmonary hemodynamics during the procedure and for at least 48 h postoperatively. Inhalation of nebulized iloprost (Ilomedin, Bayer Vital GmbH, Leverkusen, Germany) was administered with 20 μg h^{-1} intra-operatively.

The details of our routine technique of PEA have been described before [6,7]. Briefly, PEA was begun on the left side, followed by the right side after a brief period of systemic reperfusion. PEA was started at the level where the most proximal extent of scar tissue could be identified. In approximately a quarter of patients, this was at the level of the segmental arteries. The dissection plane was continued to the level of the subsegmental branches. Weaning from cardiopulmonary bypass was initiated at a core temperature of 34 °C using intravenous administration of norepinephrine in most cases to maintain adequate perfusion pressure. Volume was controlled carefully to maintain a mean PAP of less than 30 mmHg.

Mean operating, cardiopulmonary bypass, aortic cross-clamp, and circulatory arrest times were 211 ± 41 min, 131 ± 29 min, 66 ± 18 min, and 38 ± 20 min, respectively. The number of surgically desobliterated segments was 12.7 ± 3.5 per patient. Significantly more segments were desobliterated from the right lung (7.5 ± 2.2 segments) compared with the left lung (5.2 ± 2.4 segments, $P < 0.01$).

2.4. Postoperative care

In the intensive care unit, hyperventilation was applied to maintain a partial pressure of carbon dioxide of less than 35 mmHg. Inhaled iloprost (20 μg) was administered every 2 h, and mean PAP was kept at less than 30 mmHg, if possible. Fluids were adjusted to achieve a urine output of at least 1 ml kg^{-1} h^{-1}. Norepinephrine or vasopressin was given for systemic hypotension, if present. Intravenous heparin was initiated 6 h postoperatively with a partial thromboplastin time longer than 60 s. Oral coumadin (DuPont, Wilmington, DE, USA) therapy was resumed on the first postoperative day with a target prothrombin time–international normalized

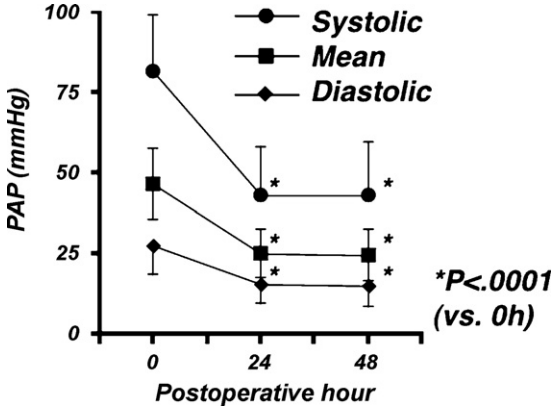

Fig. 1. Postoperative time course of pulmonary arterial pressure (PAP).

ratio between 3 and 3.5. In most patients, the pulmonary artery catheter was removed shortly after 48 h post PEA.

Compared with preoperative levels, PAP significantly decreased at 24 h postoperatively and remained low up to 48 h, at which time the Swan–Ganz catheter was removed in most patients (Fig. 1). PVR was also significantly decreased at 24 h postoperatively and sustained until 48 h after the operation (Fig. 2). Cardiac output was significantly increased 24 h postoperatively and remained so up to 48 h after surgery (Fig. 2). It was confirmed using a scattergram that they were distributed normally.

2.5. Statistical analysis

All values are expressed as mean ± standard deviation. Statistical analysis was performed using StatView™ 5.0 program (SAS Institute Inc., NC, USA) or Statistical Program for Social Sciences (SPSS) for Windows version 17.0 (SPSS, Chicago, IL, USA). A repeated-measures analysis of variance with the Scheffé *post hoc* test was used for comparison of the continuous variables between the groups. Forward stepwise multivariate logistic regression models for likelihood ratio were used to predict mortality, shorter duration of mechanical ventilation, and postoperative pulmonary hemodynamic improvement. A *P* value less than 0.05 in the univariate analysis was defined for selecting variables for entry into the multivariate analysis. Age and gender were always entered into the multivariate analysis, regardless of their *P* value. To examine multi-collinearity of the regression model, we calculated the variance inflation factor because a variance inflation factor exceeding 10 was defined as indicating that collinearity was problematic. We confirmed that none of them exceeded 10. A Pearson's correlation coefficient was used to select independent variables in a multiple regression analysis to evaluate the correlation of the clinical variables and postoperative PVR at 48 h after PEA. Then, a forward-backward stepwise selection was performed in the multiple regression analysis as well as in the logistic regression. A *P* value of less than 0.05 was considered statistically significant. Factors listed in Table 1 were entered into the analysis of predictors for early death, shorter duration of mechanical ventilation, and pulmonary hemodynamic improvement.

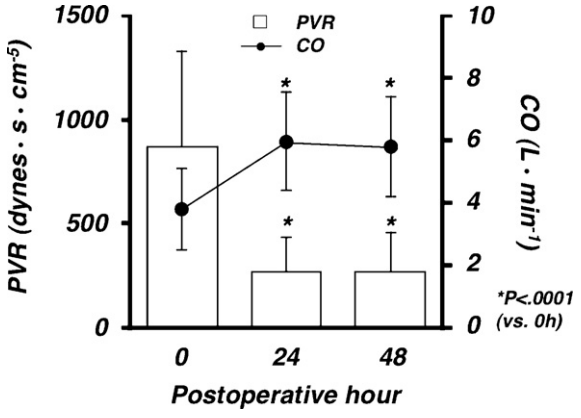

Fig. 2. Postoperative time course of pulmonary vascular resistance (PVR) and cardiac output (CO).

3. Results

3.1. Operative outcome

Thirty-one patients died within 30 days after the surgery resulting in an early mortality of 11.1%, with a recent mortality in the past three years of 6.7%. The most frequent cause of early death was multi-organ failure. We experienced no lethal right ventricle failure. Sixteen parameters proved to be significant predictors for early mortality in univariate analysis, but only preoperative arterial partial pressure of oxygen was significant ($P < 0.05$) in forward stepwise multivariate logistic regression models for likelihood ratio with sensitivity of 42.9% and specificity of 94.3% (Table 2).

Mean intensive care unit stay was 5.2 ± 6.4 days (median: 3 days), mean duration of mechanical ventilation was 70 ± 107 h (median: 30 h), and 147 patients (52.7%) could be extubated within 48 h postoperatively. We experienced only two cases with severe reperfusion lung injury and one case with postoperative hemoptysis. No postoperative extracorporeal circulation support was used. In the patients, who required mechanical ventilation for more than 48 h, mortality increased up to 21.2%, whereas it was only 3.0% in patients extubated earlier ($P < 0.01$). Sixteen parameters proved to be significant predictors for mechanical ventilation of less than 48 h, in univariate analysis. Only higher forced expiratory volume (FEV1.0) ($P < 0.05$) and higher cardiac index ($P < 0.05$) were significant in forward stepwise multivariate logistic regression models for likelihood ratio with sensitivity of 49.0% and specificity of 84.4% (Table 3).

3.2. Pulmonary hemodynamics

In 185 patients (66.3%), postoperative PVR was reduced to lower than 400 dyn s^{-1} cm^{-5} at 48 h after PEA. These patients were defined as good hemodynamic responders. Early mortality was 32.1% in cases with PVR at 48 h post PEA higher than 400 dyn s^{-1} cm^{-5}, whereas it fell to 5.9% in cases with lower PVR ($P < 0.01$). Out of 13 significant predictors in univariate analysis, forward stepwise multivariate logistic regression models for likelihood ratio identified male gender, lower preoperative mean PAP, and more total desobliterated segments as predictors for good hemodynamic response with

Table 2. Positive predictors for early mortality.

Positive predictors	Univariate *P*-value	Multivariate *P*-value	Early mortality ($n = 21$)	OR	95% CI
Lower PaO_2 (mmHg)	<0.01	<0.05	Yes 54.7 ± 15.2 No 64.1 ± 11.4	0.910	0.830–0.998
Higher age	<0.05	0.06			
Lower body height	<0.05	0.97			
Smaller body weight	<0.05	0.42			
Smaller BSA	<0.01	0.50			
Higher creatinine	<0.01	0.78			
Higher NYHA class	<0.05	0.28			
Lower FEV1.0 (l)	<0.01	0.30			
Lower FEV1.0 (%)	<0.05	0.69			
Lower VC (l)	<0.05	0.27			
Higher diastolic PAP	<0.01	0.79			
Higher PVR	<0.01	0.71			
Lower cardiac output	<0.01	0.32			
Lower cardiac index	<0.05	0.34			
Fewer desobliterated segment (right)	<0.01	0.99			
Fewer desobliterated segment (total)	<0.05	0.98			

PaO_2: arterial partial pressure of oxygen, BSA: body surface area, NYHA: New York Heart Association, FEV1.0: forced expiratory volume in 1 s, VC: volume capacity, PAP: pulmonary arterial pressure, PVR: Pulmonary vascular resistance, OR: odds ratio, CI: confidence interval.

Table 3. Positive predictors for need of mechanical ventilation less than 48 h.

Positive predictors	Univariate *P*-value	Multivariate *P*-value	Mechanical ventilation < 48 h ($n = 147$)	OR	95% CI
Higher FEV1.0 (%)	<0.01	<0.05	Yes 86.0 ± 16.5 No 76.7 ± 20.5	1.037	1.003–1.073
Higher cardiac index	<0.05	<0.05	Yes 2.19 ± 0.74 No 1.88 ± 0.47	5.351	1.216–23.557
Younger age	<0.01	0.10			
Higher body weight	<0.01	0.26			
Larger BSA	<0.05	0.60			
Higher PaO_2	<0.01	0.46			
Higher FEV1.0 (l)	<0.01	0.42			
Higher VC (l)	<0.01	0.58			
Higher VC (%)	<0.05	0.31			
Lower diastolic PAP	<0.05	0.46			
Lower mean PAP	<0.05	0.61			
Lower PVR	<0.01	0.48			
Higher cardiac output	<0.05	0.49			
More desobliterated segment (right)	<0.05	0.42			
More desobliterated segment (left)	<0.05	0.27			
More desobliterated segment (total)	<0.01	0.25			

BSA: body surface area, PaO_2: arterial partial pressure of oxygen, NYHA: New York Heart Association, FEV1.0: forced expiratory volume in 1 s, VC: volume capacity, PAP: pulmonary arterial pressure, PVR: Pulmonary vascular resistance, OR: odds ratio, CI: confidence interval.

Table 4. Positive predictors for good hemodynamic response such as pulmonary vascular resistance (PVR) at 48 h after pulmonary endarterectomy less than 400 dyn s^{-1} cm^{-5}.

Positive predictors	Univariate *P*-value	Multivariate *P*-value	48 h PVR<400 ($n = 185$)	OR	95% CI
Male gender	<0.01	<0.05	Yes 62.2% No 7.3%	0.130	0.017–0.989
Lower mean PAP (mmHg)	<0.05	<0.05	Yes 45.6 ± 10.1 No 49.8 ± 11.7	0.896	0.818–0.980
More desobliterated segment (total)	<0.01	<0.01	Yes 13.0 ± 3.0 No 9.6 ± 3.6	1.493	1.122–1.988
Higher body height	<0.05	0.67			
More body weight	<0.01	0.99			
Larger BSA	<0.01	0.71			
Higher FEV1.0 (l)	<0.05	0.93			
Lower diastolic PAP	<0.01	0.79			
Lower PVR	<0.01	0.88			
Higher cardiac output	<0.01	0.28			
Higher cardiac index	<0.05	0.09			
More desobliterated segment (right)	<0.01	0.89			
More desobliterated segment (left)	<0.01	0.89			

PAP: pulmonary arterial pressure, BSA: body surface area, FEV1.0: forced expiratory volume in 1 s, OR: odds ratio, CI: confidence interval.

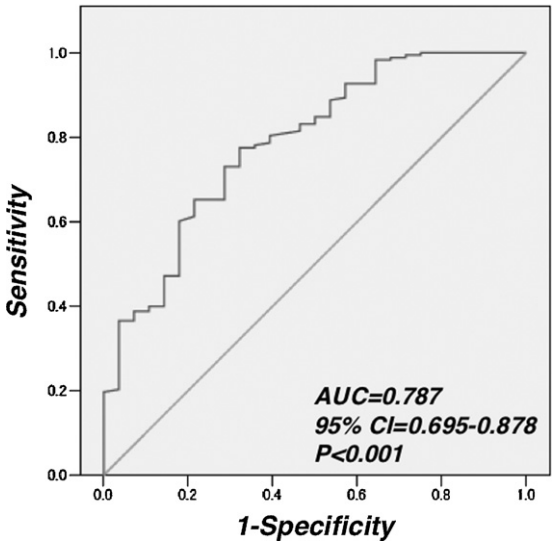

Fig. 3. The receiver operating characteristic curve to predict postoperative pulmonary vascular resistance lower than 400 dyn s^{-1} cm^{-5} at 48 h after pulmonary endarterectomy. AUC: area under the curve, CI: confidence interval.

sensitivity of 77.5% and specificity of 67.9% (Table 4). Using the following equation, we could predict good hemodynamic responders preoperatively:

$$\text{Predictive score } [48\,\text{h PVR} < 400] = \frac{1}{[1+\exp(-X)]}$$

$X = 4.348 - 2.037 \times \text{Gender} + 0.401 \times \text{Expected total desobliterated segments} - 0.11 \times \text{Mean PAP}$ (Gender: male = 1, female = 0).

When predictive score is lower than 0.5, PEA may not reduce PVR to less than 400 dyn s^{-1} cm^{-5}. When this score is greater than 0.5, PVR will be reduced to less than 400 dyn s^{-1} cm^{-5}. The receiver operating characteristic curve analysis of this prediction (Fig. 3) resulted in a high probability with an area under the curve of 0.787 ($P < 0.01$, 95% confidence interval = 0.695–0.878).

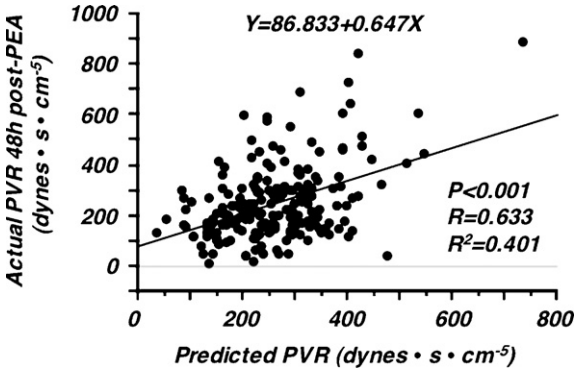

Fig. 4. Correlation between predicted and actual pulmonary vascular resistance (PVR) at 48 h after pulmonary endarterectomy (PEA).

Using Pearson's correlation coefficient, PVR at 48 h after PEA could be estimated using the following equation:

$$\begin{aligned}\text{PVR 48 h post PEA} &= 123.266 + 135.471 \times \text{Creatinine} - 22.053 \\ &\times \text{Expected total desobliterated segments} + 3.248 \\ &\times \text{Systolic PAP}\end{aligned}$$

Predicted value correlated with actual value with R^2 of 0.401 ($P < 0.01$, 95% confidence interval = 0.464–0.830) as shown in Fig. 4.

4. Comment

In 2001, we published that in patients, who underwent PEA, preoperative severity of disease apparently determines postoperative mortality and hemodynamic improvement [7]. Specifically, age, right atrial pressure, New York Heart Association (NYHA) functional class, cardiac output, creatinine, and the number of angiographically involved segments were significant predictors for early death in univariate analysis. Inadequate hemodynamic improvement (postoperative PVR > 500 dyn s^{-1} cm^{-5}) was predicted by age, right atrial pressure, and female gender in multivariate analysis. Recently, we also found that angiographic variables could predict good hemodynamic responders with high sensitivity [6]. Namely PVR < 400 dyn s^{-1} cm^{-5} at 48 h after PEA could be predicted by higher number of pouch or membrane segments, shorter duration of symptoms, greater number of involved segments, and lower serum creatinine level. With increased experience of over 14 years, we decided to repeat the analysis of predictors for early death, shorter mechanical ventilation, and pulmonary hemodynamic improvement. The emphasis was placed again on preoperative clinical parameters; in addition, we analyzed the number of desobliterated segments, as we could not provide angiographic data for all patients.

To reproduce acceptable outcome after PEA, exact predictors for mortality and precise cutoff values for selecting suitable candidates, who will benefit from PEA, should be established. A number of clinical parameters have been analyzed and proposed [1]. Many of these, however, are medically interrelated, requiring careful statistical verification. The multivariate analysis of predictor for mortality has been performed infrequently. Auger and colleagues have stated in their review that NYHA class IV, age older than 70 years, the severity of preoperative PVR, the presence of right-ventricular failure, morbid obesity, and the duration of CTEPH have been reported to affect postoperative survival [1]. Recently, two multivariate analyses identified age over 60 years [8] or gas transfer of the lung for carbon monoxide and exercise capacity [9] as independent risk factors for mortality after PEA. Our current analysis identified many factors, such as worse respiratory and hemodynamic function and extent of disease, as predictors for mortality after PEA in univariate analysis. Unexpectedly, preoperative hypoxia was the only significant risk factor in multivariate analysis. The implication of our result is difficult to interpret; however,

approximately 15% of our patients had relevant obstructive lung disease (FEV1.0 < 70% of predicted value), which might contribute to impaired gas exchange. This is similar to previous findings [3,9]. Interestingly, higher age had a tendency to affect both early mortality ($P = 0.06$) and prolonged mechanical ventilation ($P = 0.10$), next to the significant factors in multivariate analysis, although it was not significant.

The second aspect to play an important role in postoperative outcome after PEA is hemodynamic response. One of the frequent causes of death after PEA is right ventricular failure as a consequence of residual pulmonary hypertension [1,2]. It has been realized that a discrepancy between angiographic findings and the degree of pulmonary hypertension has been the most important risk factor for impaired recovery [3–5,10,11]. Dartevelle and colleagues emphasized that overall operative mortality of 10.9% dramatically dropped to 5% after exclusion of distal disease [12]. The presence of distal vasculopathy may prevent restoration of blood flow to the distal segments beyond those by PEA, and may fail in reduction in right ventricular afterload and an augmentation in cardiac output. Our current results partially reflect this concept. In good hemodynamic responders, an average of 13 segments was desobliterated, whereas only an average of 9.6 segments was desobliterated in poor hemodynamic responders. Interestingly, this tendency was more pronounced in the right lung. The number of desobliterated segments from the right lung was a significant predictor for early mortality in univariate analysis ($P < 0.01$), but those from the left lung was not ($P = 0.37$). The number of expected desobliterated segments from the right lung might reflect better predictability of complete desobliteration of the right lower lobe, while complete desobliteration of the left lower lobe may be difficult. This laterality was also confirmed by Brauwet and colleagues with 92 desobliterated specimens [13]. Ventilation/perfusion scintigrams might further help confirm our result; however, this investigation was applied to only limited cases. We believe pulmonary angiography can provide the best quality to estimate the number of expected desobliterated segments. In the same way, lower mean PAP proved to be an independent predictor for good hemodynamic responders. This is in line with a previous report indicating that higher PAP is associated with inferior PVR improvement and accelerated risk of mortality [10]. As we already emphasized, severity of the disease may primarily determine postoperative hemodynamic improvement [7]. Interestingly, female gender was a significant risk for postoperative residual PVR higher than 400 dyn s^{-1} cm^{-5} at 48 h in the current analysis, which was in line with our previous analysis [6,7]. In the San Diego series, type III disease (fibrosis, intimal webbing, and thickening with or without organized thrombus within distal segmental arteries only) predominated in women [5,14]. In the Mayo clinic experience, all five patients with type III disease were women [13]. Furthermore, idiopathic pulmonary arterial hypertension has female predominance, whereas CTEPH does not [15]. Therefore, the surgeon should take special care of female patients to distinguish CTEPH from idiopathic pulmonary arterial hypertension that might, in part, be included in our patients who underwent PEA.

Difficulty of management in intensive care had a central role in the multidisciplinary approach to PEA. The main cause of mortality after PEA has been reperfusion lung injury [1,2]. It has been reported that 16.2% of patients develop reperfusion lung edema and approximately 1% of extreme cases require extracorporeal support [3,16,17]. We experienced only two cases (0.7%) with lung reperfusion injury but no case with extracorporeal support after PEA up to now. The main reason of this rather different incidence may be due to the definition of lung reperfusion injury. Others have defined lung reperfusion injury as prolonged mechanical ventilation more than 24 h post PEA [3], whereas we have defined it as high vascular permeability that leads to alveolar edema. There are two possible underlying mechanisms in prolonged mechanical ventilation except reperfusion lung injury. One may be hypoxemia and increased dead space ventilation as a consequence of the marked ventilation–perfusion mismatch [18], which was the main reason in almost all of our patients; the other may be hemodynamic instability due to combination with postoperative residual pulmonary hypertension and systemic hypotension. In the current study, we found obstructive lung disease and lower cardiac index as significant predictors for prolonged mechanical ventilation in multivariate analysis. The former may reflect accelerated risk of ventilation–perfusion mismatch, while the latter may reflect severity of right heart failure caused by parenchymal lung disease. These findings seem consistent with previous reports that recognized a marked increase of risk in the presence of severe underlying parenchymal lung disease [1–3]. The most frequent cause of early death in our series was neither reperfusion lung injury nor right ventricle failure but multi-organ failure. We carefully evaluated postoperative right ventricle function using transesophageal echocardiography as well as hemodynamic data obtained through a Swan–Ganz catheter. Adequate and aggressive dosage of catecholamine preserved the right ventricle function sufficiently in most cases in spite of residual pulmonary hypertension. However, on the other hand, a high dosage of catecholamine increased peripheral vascular resistance, which led to non-occlusive mesenteric ischemia. As is well known, it was associated with increased intestinal permeability and translocation of endotoxin/Gram-negative bacteria that caused multi-organ failure. That was the typical postoperative course of our non-survivors after PEA.

4.1. Limitations

Several limitations of this study deserve to be discussed. First, this is not a prospective but a retrospective study of early outcome with consecutive cases. The selection process included a bias; approximately a quarter of referred patients were not accepted for PEA mainly because less than 10 segments were angiographically involved in spite of mean PAP greater than 50 mmHg. Further, many patients were not referred to us by the judgment of the internist alone. A prospective study with a larger cohort and long-term follow-up with decision making for or against PEA using our calculation by a multidisciplinary team including pulmonologists, cardiologist, radiologists, and surgeons will be essential to confirm the core of this article. Second, the definition of 'good hemodynamic responder' is highly

variable. The majority of reports have consistently used postoperative PVR of 500 dyn s^{-1} cm^{-5} as a cutoff value for a good hemodynamic responder. It has been reported that mortality rose up to 25.5% in cases with postoperative PVR higher than 500 dyn s^{-1} cm^{-5}, whereas it was only 2.7% in cases with lower PVR [16]. In the current study, postoperative PVR was reduced to lower than 500 dyn s^{-1} cm^{-5} in 200 patients (71.7%); hence, we set this criterion more strictly to 400 dyn s^{-1} cm^{-5} so that 185 patients (66.3%) matched this criterion. Indeed, an intensive review between 2000 and 2006 revealed that postoperative mean PVR was less than 400 dyn s^{-1} cm^{-5} in 14 reports out of 18 [16]. In the current study, early mortality was 32.1% in cases with PVR at 48 h post PEA higher than 400 dyn s^{-1} cm^{-5}, whereas it decreased to 5.9% in cases with lower PVR, which seemed quite similar to previous findings. Third, variables to predict postoperative outcome are multifactorial. Some intra-operative factors such as cardiopulmonary bypass time or myocardial ischemic time might also influence postoperative outcome. However, this study was primarily designed to identify suitable candidates for PEA preoperatively. Therefore, we used only preoperative factors except desobliterated segments. Ideally, preoperative angiographic findings should be analyzed, but it was impossible in this retrospective analysis over 14 years. Nevertheless, intra-operative desobliterated segments can be estimated by preoperative angiographic findings. Thus, we believe our equation to predict postoperative PVR can help select optimal candidates for PEA. Fourth, in the same way, pre- and post-treatment with prostanoids, endothelin-receptor antagonists, or phosphodiesterase-5 inhibitors might potentially modify our results. Several previous reports have already shown that these agents can improve pulmonary hypertension significantly [19–23]. However, we have administered either sildenafil (n = 14) or bosentan (n = 9) to only a small subset of high-risk patients preoperatively since 2007. The effects of these pretreatments at present should be carefully observed and reassessed when more data are available.

In conclusion, preoperative factors primarily can predict postoperative outcome after PEA. Especially, underlying lung disease is associated with higher early mortality and prolonged mechanical ventilation. The extent of desobliterated segments as well as preoperative hemodynamic severity play a key role in predicting good hemodynamic responders. These novel findings may greatly help identify suitable candidates with CTEPH for PEA and eliminate unnecessary surgical intervention.

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Appendix A. Conference discussion

Dr J. Dunning (*Cambridge, United Kingdom*): Since this operation was popularized by the work of Stuart Jamieson and his team in San Diego, there have been concerted efforts to mirror their success. It is acknowledged that there is a learning curve associated with the procedure, both in terms of the technical aspects that are required during the operation itself, and perhaps more importantly for the institution in terms of their preoperative preparation and assessment of patients and their postoperative care in the intensive care unit.

The experience of Dr Schäfers' team mirrors that seen elsewhere, i.e. that the perioperative mortality is reduced in a stepwise manner with time, in this case to around 6% over the last 3 years. In our own experience at Papworth, which now totals over 600 cases in a 14-year period, we have seen the mortality come down to less than 4% over the same period.

Now, your paper identifies underlying parenchymal disease as a predictor of poor outcome, but from my reading of the paper, it is based largely on spirometry. It is our own practice at Papworth to use CT scanning as a second imaging modality in the assessment of all patients, and most of our patients now receive both pulmonary angiography, or MR angiography, supported by CT scanning. If the CT does not demonstrate significant parenchymal disease, then we are less concerned about the spirometric parameters.

You have emphasized that a good hemodynamic response with a reduction in pulmonary vascular resistance to 400 dyn or less is a predictor of reduced mortality in the postoperative period. This is true, but using adjunctive therapy with pulmonary vasodilators and indeed with ECMO, it is also possible to manage patients who do not have such favorable hemodynamic responses in an effective manner.

The clinical stage, the duration of the procedure, and segments cleared, which you have also identified as important predictors, are only available, unfortunately, after the operation has been completed and may therefore be less helpful in deciding which patients should move forward to surgery. We believe that the angiographic findings are probably the most important predictors of outcome from this operation and they have greater relevance than the presence of co-morbidities, including other cardiac conditions.

My questions for you are as follows: First of all, have your selection criteria changed in the last 3 years to explain your improvements in outcome, or is this simply a reflection of the learning curve? Secondly, do you routinely assess lung parenchyma with other imaging modalities or do you rely solely on spirometric and respiratory function tests?

You have commented that you have had no lethal cases of right heart failure, but I wonder if the multi-organ failure that has accounted for many of the deaths in the series is actually a manifestation of right heart failure occurring in the postoperative period. I'm staggered that you have only had two cases of severe reperfusion pulmonary edema, and I wonder if this reflects a selection bias in that one-quarter of patients referred for surgery were turned down. Finally, do you think that using ECMO and selective pulmonary vasodilators may help you to further improve your results?

Dr Kunihara: First, regarding our indications for selecting patients, we have recognized that these patients, as I showed, for example, female with high pressure but fewer angiographic findings, were excluded for many years, but now we try to improve this cohort with preoperative treatment with, for example, bosentan. So the criteria have changed a little bit. But we currently only have a small number with these preoperative variables and did not analyze these factors.

Dr Schäfers: I would like to comment on the selection bias question.

Principally, as in all therapeutic decisions, selection bias cannot be completely ruled out. We have intentionally tried to expand the initial very strict criteria in order to allow the application of the procedure to more patients, knowing that this will increase morbidity/mortality for the whole group, but then simply expand the potential candidates. So while there is a selection bias in it, this bias is the end result of careful expansion and testing of hypothesis.

Dr Aubrey A Almeida, (*Melbourne*, *Australia*): Thank you for that clarification. Would you care to answer the other two questions, please?

Dr Kunihara: The second question is to test for the underlying lung diseases, right?

Dr Dunning: Other imaging modalities for lung disease. Do you use CT scanning to assess the condition of the lung parenchyma?

Dr Kunihara: Yes, both of them, and we repeat angiography in our hospital if the other image is not good, but with only CT scan it is difficult to differentiate this underlying parenchymal disease, and sometimes if the patient requires preoperative oxygen therapy, it is difficult to cut this patient out of the surgical intervention. I'm sorry, but it's difficult to answer it.

Dr Almeida: In the interests of time, the final question was the question of postoperative support with ECMO and vasodilators and the impact of that. If you could comment on that, please.

Dr Schäfers: We have not used ECMO in the whole series. My personal feeling is minimal chance of recovery and lung transplantation is the only ultimate outcome. We are very aggressive with pulmonary vasodilators on an empiric basis, with inhalative iloprost, bosentan, and a combination treatment also with sildenafil. This is all instituted in the patients who do not respond well to the operation. So they first come out of the operating room naked, we observe pulmonary vascular resistance for the first 8 to 12 hours, and, if necessary, aggressive pulmonary vasodilation is instituted.