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ORIGINAL ARTICLE

Pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension: an institutional experience[†]

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Abstract

OBJECTIVE: Pulmonary endarterectomy (PEA) is the treatment of choice for patients with chronic thrombo-embolic pulmonary hypertension (CTEPH). The aim of this study was to review our initial experience since the implementation of our program.

METHODS: Data were collected prospectively on all patients who underwent PEA between March 2011 and March 2012.

RESULTS: Forty-nine patients (20 male, 29 female, mean age 47.7 years) underwent surgery. The preoperative New York Heart Association class distribution showed the majority to be in class III or IV ($n = 40$). Mortality rate was 14.2% ($n = 7$) and the morbidity rate was 26.5% ($n = 13$). After PEA, the durations of mechanical ventilation, intensive care stay and hospital stay before discharge were 49.7 ± 46.1 h, 6.5 ± 5.0 days and 12.9 ± 7.5 days, respectively. The systolic and mean pulmonary artery pressure (PAP) fell significantly from 87.0 ± 26.6 mmHg and 53.8 ± 14.5 before, to 41.5 ± 12.4 mmHg and 28.5 ± 10.5 after surgery ($P < 0.001$ and $P < 0.001$, respectively). Pulmonary vascular resistance (PVR) also improved significantly from 808 ± 352.0 to 308 ± 91 dyn•s•cm^{-5} ($P < 0.001$). Univariate analysis showed that preoperative systolic PAP, tricuspid annular plane systolic excursion, right atrial volume, right atrial pressure, forced expiratory volume in 1 s, forced vital capacity, preoperative PVR, postoperative PVR, the duration of circulatory arrest and postoperative use of extracorporeal membrane oxygenation were risk factors for mortality ($P < 0.05$). According to multivariate analyses, only prolonged mechanical ventilation was selected as predictive risk factor for morbidity ($P = 0.005$). After a median follow-up of 6.1 months, two patients died due to cerebrovascular disease and one patient needed targeted pulmonary hypertension therapy. The rest of the 39 patients showed marked improvements in their clinical status.

CONCLUSIONS: Starting a pulmonary endarterectomy program with acceptable mortality and morbidity rates and satisfactory early-term outcomes increases awareness of the CTEPH and surgery. Preoperative factors can primarily predict postoperative outcome after PEA. Identifying the risk factors in order to achieve a good result is important for the success of a PEA program. Therefore all patients diagnosed with CTEPH should be referred for consideration of PEA in a specialized centre.

Keywords: Chronic thrombo-embolic pulmonary hypertension • Pulmonary endarterectomy • Mortality • Outcome

INTRODUCTION

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is the non-resolution of acute pulmonary embolism (PE) that later undergoes fibrosis, leading to mechanical obstruction of the pulmonary vasculature. It is estimated that about 5% of patients with an acute symptomatic pulmonary embolus will go on to experience pulmonary hypertension [1, 2], not only as the result of pulmonary vascular obstruction, but also as a result of a pulmonary arteriopathy that develops in the unobstructed vascular bed [2]. Pulmonary endarterectomy (PEA) is the procedure of choice and potentially a curative option for patients with CTEPH [2–6]. The technical aspects of the surgery have been refined over the past 20 years and the procedure is currently performed with limited risk in experienced centres [2, 3, 6–8]. A PEA centre is defined as an institution that performs ≥20 PEA surgeries per year with a mortality rate <10% [5]. Despite the significant decrease in

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surgical mortality from as high as 40% to today's 1.3% (median 8%), PEA remains variable and centre- or expert-dependent [6, 7].

PEA was an uncommon procedure in Turkey and we elected to start a new program of pulmonary endarterectomy. This study aimed to evaluate the efficacy of PEA in treatment of CTEPH and to present our preliminary results. In addition, we attempted to determine the risk factors of mortality and morbidity.

MATERIALS AND METHODS

Patients

Between March 2011 and March 2012, 49 consecutive patients with diagnosis of CTEPH underwent pulmonary endarterectomy at our centre (Table 1). The mean age of 29 female and 20 male patients was 47 ± 13 mean ± standard deviation (SD) years, ranging from 14 to 72 years. Overall, the existence of symptoms ranged from a period of 3–300 months preoperatively, with an average period of 39.8 ± 48.9 months and all patients were in the World Health Organization/New York Heart Association (WHO/NYHA) functional class II ($n = 9$), III ($n = 35$) or IV ($n = 5$). Twenty-one patients (42.8%) presented with a history of pulmonary embolism, 14 patients (28.5%) had a history of deep venous thrombosis and 8 patients had some coagulation disorders associated with immunological disorders—comprising four cases with inherited deficiencies of protein C or protein S or Factor V Leiden mutation and four with antiphospholipid antibody syndrome or systemic lupus erythematosus. One patient had a diagnosis of Klippel-Trénaunay-Weber syndrome and hyperhomosistenemia. One patient, who had his primary operation at another institution, underwent a PEA reoperation. All patients had chronic symptoms of cardiopulmonary disease. Preoperatively, eight patients were on pulmonary arterial hypertension (PAH)-specific treatment, either sildenafil, or endotelin-receptor antagonist or inhaled iloprost or combinations of them. Nine patients had a history of diabetes, nine had chronic obstructive pulmonary disease (COPD) and 17 patients were smokers. CTEPH was diagnosed routinely by the presence of mismatched perfusion defects on the radioisotopic ventilation perfusion (V/Q) scan associated with evidence of pulmonary hypertension on transthoracic echocardiogram, despite adequate anticoagulation for at least 3 months. Evidence of CTEPH was then confirmed by high-resolution helical computed tomographic scanning (CT) of the pulmonary vasculature (i.e. pulmonary CT angiography) using maximal intensity projections (MIP) and right heart catheterization with measurements of the right atrial-, pulmonary artery- and pulmonary wedge pressures, at rest and under vasoactive stimulation. Cardiac output (CO) was determined by thermodilution, and pulmonary vascular resistance (PVR) was calculated. No patient underwent pulmonary angiography. Pulmonary hypertension (PH) was defined as mean pulmonary arterial pressure (mPAP) greater than 25 mmHg at rest. All tests demonstrated that the patients had main-, lobar- or proximal segmental-level defects, which had been generally characterized as proximal disease. We also examined the right heart by echocardiography to assess the right atrium and ventricular function. The parameters to be performed and reported included a measure of right atrial (RA) volume, RA pressure, right ventricular (RV) systolic function by tricuspid annular plane systolic excursion (TAPSE) with myocardial performance index (MPI) and systolic pulmonary artery pressure (sPAP) with estimate of RA pressure on the basis of the inferior vena cava. In addition, the degree of functional tricuspid regurgitation was reported as trivial–mild or moderate–severe.

All patients completed their assessments with a 6 min walking test, pulmonary function tests, duplex scanning of the lower extremities and arterial blood gas test. Surgical candidates older than 45 years underwent a coronary angiography as part of their assessment. Severe coronary artery disease was defined as disease requiring coronary artery bypass graft (CABG), or disease that precluded PEA (i.e. left ventricular ejection fraction <30%). At our centre, the only surgical contra-indication was underlying severe parenchymal lung disease. Three patients had a history of previous insertion of inferior vena cava filter. All data were collected prospectively and entered into a database. For the early cases, our indications for PEA surgery were as follows: PVR greater than 300 dyn•s•cm^{-5}, mPAP greater than 25 mmHg, NYHA functional class greater than II and absence of significant comorbidities and pulmonary CT angiographic or scintigraphic evidence of obstruction of the pulmonary arterial tree, despite 3 months of anticoagulation and exclusion of other causes of PH [6]. But later we operated on patients with CTEPH with the evidence of chronic thromboembolic disease localized in the segmental arteries or more proximally, regardless of the degree of right ventricular dysfunction or the severity of the PVR [2]. Surgical candidates underwent PEA according to the standardized technique previously described [2, 3]. In brief, surgery was performed under general anaesthesia through a median sternotomy and using extracorporeal circulation with periods of circulatory arrest under deep hypothermia (18–20°C) for the right and left pulmonary arteries. The endarterectomy specimen was circumferentially followed down to the segmental and subsegmental branches in each lobe, until a complete

Table 1: Preoperative characteristics of patients

Characteristics	Value or *n*
Age (years)	47.7 ± 13.6 (14–72)
Gender	
Male (*n*)	20 (40.8%)
Female (*n*)	29 (59.2%)
BSA (m^2)	1.8 ± 0.1 (1.4–2.2)
First diagnosis (months)	39.8 ± 48.9 (3–300)
NYHA	
Class II	9
Class III	35
Class IV	5
6-min walking test (metres)	221.7 ± 162.5 (0–500)
FEV_1 (% predicted)	82.8 ± 16.4 (43–111)
FVC (% predicted)	86.7 ± 18.0 (60–117)
FEV_1/FVC (% predicted)	79.4 ± 11.3 (51–109)
PAP (mmHg)	
Systolic	87.0 ± 26.6 (32–150)
Mean	53.8 ± 14.5 (30–109)
TAPSE (mm)	14.7 ± 4.4 (1–28)
MPI (ms)	0.57 ± 0.27 (0.23–1.5)
Right atrial volume (ml/m^2)	22.8 ± 7.3 (10–40)
Right atrial pressure (mmHg)	11.7 ± 4.0 (5–20)
Cardiac index (l/min/m^2)	2.2 ± 0.7 (1–4.1)
Cardiac output (l/min)	3.8 ± 1.0 (1.7–5.7)
Preoperative PVR (dyn•s•cm^{-5})	808.0 ± 352.0 (243–2035)

BSA: body surface area; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MPI: myocardial performance index; ms: millisecond; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; TAPSE: tricuspid annular plane systolic excursion.

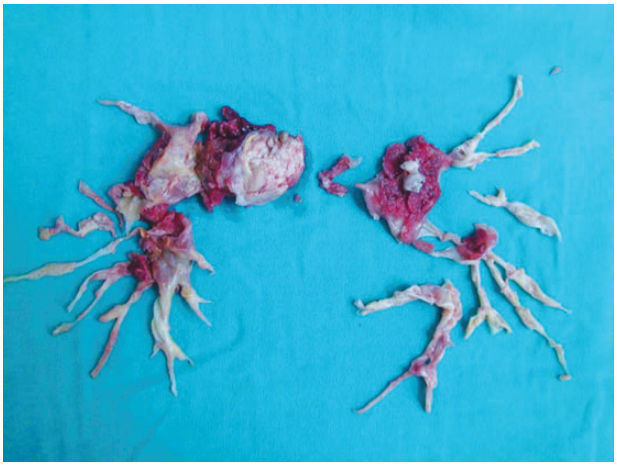

Figure 1: Type I thrombo-embolic specimen removed from both right and left pulmonary artery.

endarterectomy of the pulmonary vascular bed was achieved (Fig. 1). When tricuspid regurgitation of more than moderate degree was present—particularly in high-risk patients with severe pulmonary hypertension due to distal disease—sutured tricuspid annuloplasty was performed using DeVega's technique. Weaning from cardiopulmonary bypass (CPB) was performed with care, since haemodynamics were unstable as a result of residual PH arising from hypothermia, CPB and reperfusion injury of the lungs, even after successful pulmonary endarterectomy. For patients in whom weaning was unsuccessful due to hypotension or hypoxia (or both) resulting from residual PH or pulmonary bleeding, percutaneous extracorporeal membrane oxygenation (ECMO) was performed using femorofemoral circuit. Patients were tested for weaning when clearing of interstitial oedema commenced on radiograph. Acceptable PaO_2 (>60 mmHg), $PaCO_2$ (<50 mmHg) and stable pH for a period of 2–3 h with the reduced device support represented an indication for removal of the device.

The operation was performed on both lungs and under complete circulatory arrest. A true endarterectomy was accomplished and, when it was completed on both sides, circulation with warming was restarted. Any additional procedure was performed during this phase of the operation.

Patients were kept anaesthetized and sedated postoperatively in the intensive care unit. Extensive ventilatory and circulatory monitoring were continuously performed, including online measurement of pulmonary artery pressure with an oxymetric Swan-Ganz catheter (Edwards LifeSciences, Irvine, CA, USA), cardiac output, mixed venous oxygen saturation and arterial blood gases. Patients were placed in pressure-controlled mechanical ventilation with a positive end-expiratory pressure (PEEP) of 6 cm H_2O and tidal volume of 8 ml/kg. Inhaled nitric oxide at doses of 15–20 ppm were given for the first 4 h postoperatively and gradually withdrawn. Cautious fluid- and vasoactive drug administration and aggressive diuresis were provided as long as necessary for the patient to recover. Following extubation, inhaled iloprost at doses of 2.5 μg, six times per day was started. Most patients were extubated on the first or second postoperative day. Anticoagulation with unfractionated heparin was resumed at a low dose within 4–6 h after the end of the surgery and progressively increased to full anticoagulation within 24 h. Oral Coumadin was usually started after 48–72 h, targeting an international normalized ratio (INR) of around 2.5. Transthoracic echocardiography was performed on the day of the patient's discharge from the hospital. Patients were followed up and reviewed in the PEA outpatients' clinic at 1, 3 and 6 months. Patients were classified functionally according to the WHO/NYHA functional class and assessed with a 6 min walking test and echocardiogram at each follow-up visit.

Operative mortality was defined as death in hospital or within 30 days of surgery. Deterioration in WHO/NYHA functional class was determined by a worsening of at least one class, compared with the best class achieved after PEA. Repeat right heart catheterization was performed when patients experienced deterioration in WHO/NYHA functional class or remained in functional class III after PEA.

Statistical analysis

Data are summarized as mean ± standard deviation for continuous variables and as number (or percentage) for categorical variables. Follow-up was 100% complete. We retrospectively reviewed the overall outcome of PEA and investigated risk factors for early mortality and morbidity using univariate comparisons between the two groups using the chi-squared test or Fisher's exact test for categorical variables and the unpaired Student' *t*-test for continuous variables. Then, for significant risk factors, multivariate logistic regression analysis was performed. With regard to 27 preoperative factors and six peri-/postoperative factors, a statistical analysis was performed regarding mortality and the same 27 preoperative factors and another seven peri-/postoperative factors were analysed for the morbidity. Comparison between pre- and postoperative variables was performed for continuous variables using the paired two-tailed Student's *t*-test and, for categorical variables, McNemar χ^2 test was used. All statistical analyses were performed using SPSS version 16 software (SPSS Inc., Chicago, IL), with *P*-values of less than 0.05 considered significant.

Approval for this study was granted by the Institutional Review Board of the Kartal Koşuyolu Training and Research Hospital.

RESULTS

All 49 patients underwent pulmonary endarterectomy. The preoperative and intra- and postoperative characteristics of patients are presented in Tables 1 and 2, respectively. Eleven patients underwent concomitant surgery (Table 2). Venoarterial ECMO was used in six patients (12.2%). Of these, three required the technique intraoperatively, including two patients with residual pulmonary hypertension, one of whom had massive pulmonary bleeding. Our approach for patients with massive pulmonary haemorrhage following PEA has been reported elsewhere [9]. Put briefly, following PEA surgery, the patient presented severe pulmonary haemorrhage when separation from CPB was performed. Bleeding from the right lower lobe bronchi of the tracheobronchial tree was observed by fibre-optic bronchoscopy. The right lower lobe bronchus was occluded with a Fogarty balloon catheter and a peripheral veno-arterial ECMO was instituted because of hypoxia and haemodynamic instability. She was successfully weaned from ECMO on the fourth postoperative day. On postoperative day (POD) 7, she was weaned off ventilation and was later discharged.

Two patients were put on ECMO on POD 3 for reperfusion lung injury and right heart failure. ECMO was used in one patient on POD 7, due to cardiac tamponade and progressive right heart

Table 2: Intra- and postoperative characteristics of patients

Characteristics	Value or *n*
Cardiopulmonary bypass (min)	164.0 ± 44.2 (102–376)
Aortic cross-clamp (min)	107.6 ± 26.0 (55–182)
Total circulatory arrest (min)	21.4 ± 7.2 (6–36)
Concomitant surgery	11
PFO closure and DeVega's tricuspid annuloplasty	3
PFO closure	2
Coronary artery bypass graft	2
Removal of right atrial thrombus	2
Mitral valve replacement for severe mitral valve regurgitation	1
Left lower lobe bullectomy	1
ECMO	6
Mechanical ventilation time (hours)	49.7 ± 46.1 (12–168)
ICU (days)	6.5 ± 5.0 (2–24)
Hospital discharge (days)	12.9 ± 7.5 (7–39)
Postoperative PAP (mmHg)	
Systolic	41.5 ± 12.4 (25–85)
Mean	28.5 ± 10.5 (18–55)
Postoperative PVR (dyn•s•cm^{-5})	308.7 ± 91.4 (150–510)
NYHA class I + II or III (*n*)	39 *vs* 1

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; PFO: patent foramen ovale.

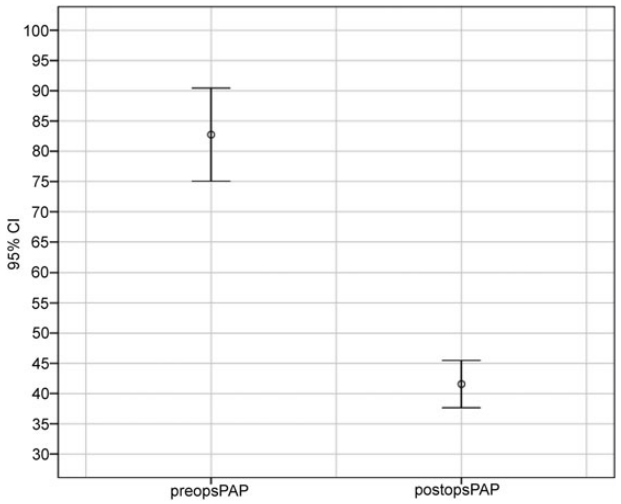

Figure 2: Preoperative systolic pulmonary artery pressure was decreased from 87.0 ± 26.6 to 41.5 ± 12.4 mmHg following pulmonary endarterectomy ($P < 0.0001$). (Preop sPAP: preoperative systolic pulmonary artery pressure; Postop sPAP: postoperative systolic pulmonary artery pressure) (points are the mean pressures and lines the 95% confidence intervals for the mean).

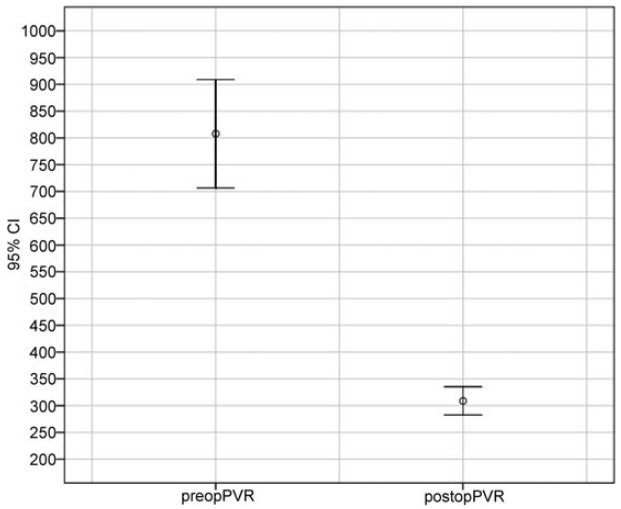

Figure 3: Preoperative pulmonary vascular resistance was decreased from 808.0 ± 352.0 to 308.7 ± 91.4 dyn•s•cm^{-5} following pulmonary endarterectomy ($P < 0.0001$). (Preop PVR: preoperative pulmonary vascular resistance; Postop PVR: postoperative pulmonary vascular resistance) (points are the mean resistance and lines the 95% confidence intervals for the mean).

failure. Of six patients on ECMO, three of them survived. The mean duration of ECMO was 3.6 ± 1.7 days for all patients and 2.6 ± 0.5 days for those who survived.

The in-hospital mortality rate was 14.2% ($n = 7$). Causes of death were massive pulmonary reperfusion injury and persistent pulmonary hypertension in five patients, cardiac tamponade in one and cardiac arrest secondary to pneumothorax under non-invasive mechanical ventilation in one.

Thirteen patients (26.5%) had postoperative complications, three with reperfusion pulmonary oedema, three with re-exploration for bleeding, three with organic brain syndrome, pneumonia in one, massive pulmonary haemorrhage in one, sternal dehiscence in one and atrial fibrillation in one.

Haemodynamic parameters

Immediate pre- and postoperative haemodynamic measurement was taken in all patients and compared to the preoperative values. Following PEA, the systolic and mean PAPs fell significantly from 87.0 ± 26.5 mmHg and 52.7 ± 16.3 before to 41.5 ± 12.4 mmHg (Fig. 2) and 28.5 ± 10.5 after surgery, respectively ($P < 0.001$, $P < 0.001$). Pulmonary vascular resistance also improved significantly, from 807.9 ± 352.0 to 308.7 ± 91.4 dyn•s•cm^{-5} (Fig. 3) ($P < 0.001$).

We analysed risk factors for mortality and morbidity. Among factors that were investigated, those showing a significant effect on mortality in the univariate analysis were preoperative sPAP ($P = 0.004$), TAPSE ($P = 0.001$), right atrial volume ($P = 0.003$), right atrial pressure ($P = 0.001$), FEV_1 ($P = 0.03$), FVC ($P = 0.004$), preoperative PVR ($P = 0.02$), postoperative PVR ($P = 0.001$), the duration of circulatory arrest time ($P = 0.02$) and postoperative use of ECMO ($P = 0.03$) (Table 3). On the other hand, no statistically significant risk factor was identified within the multivariate analysis.

Similarly, risk factors to predict morbidity were analysed for the 42 survivors. Only postoperative PVR ($P = 0.03$) and mechanical ventilation time ($P = 0.008$) was identified as a significant risk factor in the univariate analysis (Table 4). Multivariate regression analysis of all variables showed that the main predictor for morbidity after PEA in this study was prolonged mechanical ventilation time ($P = 0.005$; 95% CI,1.00–1.04).

After a median follow-up of 6.1 months (0–12 months), two patients had died due to cerebrovascular disease at two and three months, respectively, following PEA surgery. All but one patient improved to WHO/NYHA functional class I and II at follow-up

Table 3: Univariate analyses of factors to predict mortality following pulmonary endarterectomy

Risk factors	Survivors (n = 42)	Non-survivors (n = 7)	Univariate P-value
Age (year)	47.5 ± 14.0	49.4 ± 12.0	0.73
Gender (M/F)	16/26	4/3	0.42
BSA (m^2)	1.80 ± 0.1	1.84 ± 0.1	0.62
Duration of the symptoms (months)	37.7 ± 50.7	52.2 ± 35.7	0.47
PAH-specific treatment	6	2	0.32
NYHA functional class (II vs III vs IV)	7/31/4	2/4/1	0.66
History of pulmonary embolism	17	4	0.68
History of deep venous thrombosis	13	1	0.65
History of coronary artery disease	2	2	0.10
History of hypertension	15	4	0.41
History of diabetes	7	2	0.60
History of COPD	9	0	0.32
Smoking	14	3	0.68
Preoperative sPAP (mmHg)	82.7 ± 24.6	113.1 ± 23.5	0.004
TAPSE (mm)	15.4 ± 3.7	9.7 ± 4.7	0.001
MPI (ms)	0.53 ± 0.2	0.69 ± 0.1	0.27
[a]Tricuspid regurgitation (mild vs severe)	22/20	1/6	0.28
Right atrial volume (ml/m^2)	21 ± 0.5	31 ± 0.9	0.003
Right atrial pressure (mmHg)	11 ± 4.0	15 ± 2.0	0.001
FEV_1 (%)	85.2 ± 16.4	68.6 ± 6.1	0.03
FVC (%)	89.5 ± 17.6	70.0 ± 9.2	0.004
FEV_1/FVC (%)	78.3 ± 11.3	89.5 ± 3.5	0.19
6 min walking test (metres)	222 ± 172	218 ± 144	0.96
mPAP (mmHg)	53 ± 15	53 ± 7	0.94
Cardiac index ($l/min/m^2$)	2.17 ± 0.67	2.06 ± 0.29	0.71
Cardiac output (l/min)	3.73 ± 1.0	3.79 ± 0.3	0.82
Preoperative PVR ($dyn{\cdot}s{\cdot}cm^{-5}$)	763 ± 351	1075 ± 225	0.02
Cardiopulmonary bypass (min)	157 ± 30.6	217 ± 91	0.15
Aortic cross-clamp (min)	105 ± 24	120 ± 31	0.21
Circulatory arrest time (min)	20 ± 6.6	27 ± 8.6	0.02
Postoperative PVR ($dyn{\cdot}s{\cdot}cm^{-5}$)	286 ± 76	442 ± 48	0.001
Concomitant surgery	9	2	0.64
ECMO	3	3	0.03

[a]Defined degree of functional tricuspid regurgitation as trivial–mild or moderate–severe; BSA: body surface area; COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; F: female; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; M: male; mPAP: mean pulmonary artery pressure; MPI: myocardial performance index; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

Table 4: Univariate analyses of factors to predict morbidity following pulmonary endarterectomy in 42 survivors.

Risk factors	Uneventful cases (n = 29)	Morbidity (n = 13)	Univariate P-value
Age (year)	47.6 ± 12.2	47.0 ± 18.0	0.89
Gender (M/F)	10/19	6/7	0.51
BSA (m^2)	1.81	1.70	0.42
Duration of the symptoms (months)	32.4 ± 31.9	49.5 ± 78.6	0.31
PAH-specific treatment	4	2	0.90
NYHA functional class (II vs III vs IV)	5/22/2	2/10/1	0.94
History of pulmonary embolism	9	8	0.09
History of deep venous thrombosis	9	4	0.93
History of coronary artery disease	1	1	0.53
History of hypertension	11	4	0.73
History of diabetes	6	1	0.39
History of COPD	6	3	0.91
Smoking	8	6	0.30
Preoperative sPAP (mmHg)	81.8 ± 25.4	84.6 ± 23.5	0.74
TAPSE (mm)	15.7 ± 3.9	14.7 ± 3.1	0.41
MPI (ms)	0.56 ± 0.32	0.48 ± 0.11	0.56
[a]Tricuspid regurgitation (mild vs severe)	15/21	8/5	0.42
Right atrial volume (ml/m^2)	21.5 ± 6.2	20.4 ± 4.9	0.65
Right atrial pressure (mmHg)	11.0 ± 4.2	11.4 ± 3.7	0.84
FEV_1 (%)	88.2 ± 15.7	79.5 ± 17.0	0.17
FVC (%)	89.8 ± 16.9	89.0 ± 19.7	0.90
FEV_1/FVC (%)	78.2 ± 13.1	78.5 ± 6.3	0.97
6 min walking test (meters)	225 ± 166	207 ± 293	0.38
mPAP (mmHg)	52 ± 11	57 ± 14	0.32
Cardiac index ($l/min/m^2$)	2.2 ± 0.7	2.0 ± 0.4	0.62
Cardiac output (l/min)	3.5 ± 0.9	4.2 ± 1.2	0.09
Preoperative PVR ($dyn{\cdot}s{\cdot}cm^{-5}$)	713 ± 356	874 ± 324	0.17
Cardiopulmonary bypass (min)	155 ± 33	161 ± 25	0.56
Aortic cross-clamp (min)	106 ± 27	103 ± 20	0.66
Circulatory arrest time (min)	20 ± 7	21 ± 5	0.59
Postoperative PVR ($dyn{\cdot}s{\cdot}cm^{-5}$)	269 ± 76	323 ± 66	0.03
ECMO	1	2	0.22
Concomitant surgery	7	2	0.69
Mechanical ventilation time (hours)	34 ± 30	85 ± 56	0.008

[a]Defined degree of functional tricuspid regurgitation as trivial–mild or moderate–severe; BSA: body surface area; COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; F: female; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; M: male; mPAP: Mean pulmonary artery pressure; MPI: myocardial performance index; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

after surgery. One patient who underwent re-surgery suffered a deterioration in their WHO/NYHA functional class and was started on PH therapy.

DISCUSSION

CTEPH is a common cause of pulmonary hypertension and is associated with a significant mortality rate, with a median two- to three-year survival rate of as low as 10–20% in untreated patients with severe CTEPH [5]. It has become established that PEA surgery is the treatment of choice for CTEPH. Pulmonary endarterectomy is associated with low morbidity, low mortality, and significant improvement in pulmonary haemodynamics and right heart function [5–7].

The median age of patients with CTEPH is approximately 60 years in most large series, suggesting that the incidence of the disease is particularly high in the elderly population [6, 7]. However, in the present study, mean age was 47 ± 13. CTEPH should be actively looked for regardless of the age of the patients, in order not to delay diagnosis and appropriate treatment. The surgery is typically associated with major improvement in WHO/NYHA functional class in patients [6, 7].

In experienced hands, peri-operative (30-day) mortality ranges from 4–10%, with the most common cause of early death related to persistent PH [2, 3, 7, 8, 10, 11]. Increasing surgical experience, technical refinements and better patient selection probably explain the improvements in peri-operative mortality during the past 20 years. However, the purported benefits of PEA suffer from potential publication bias and outcomes may vary significantly from centre to centre, depending on experience and surgical expertise. In the present study, the mortality rate was 14.2%. The most common cause of death was massive pulmonary reperfusion injury and persistent pulmonary hypertension (5/7 patients; 71%). On the other hand, 13 patients (26.5%) had postoperative complications. One may argue that this mortality rate, although acceptable, is quite high. The operative mortality rate was 17% even in the early San Diego series, and a reduction was observed over the course of time, across the whole patient cohort that they reviewed [2]. In this study, on postoperative evaluation of the survivors, mean pulmonary artery pressure and pulmonary vascular resistance also significantly declined. Our favourable surgical results are similar to those reported by the other centres [1–3, 7, 8, 12].

The surgical indications for PEA were modified by experience in the PEA centres. It was well documented by Dartevelle *et al.* [3] that patients with increased PVR have higher mortality rates than those with PVR <900 dyn•s•cm^{-5}. A higher postoperative mortality rate occurs if PEA surgery cannot reduce the pulmonary resistance by 50% [3]. Although the degree of right ventricular dysfunction is not a critical issue for PEA indication, it is known that the discrepancy between PVR and vascular obstruction is of critical importance. We agree with Hoeper *et al.* [13] that indication for PEA has to take into account the balance between proximal obstruction, distal obstruction and distal vasculopathy: the more pronounced the distal vascular changes are, the higher is the risk of surgery and the less likely is haemodynamic improvement after surgery. Although, the incidence of bilateral type III disease is increased, the mortality rate following PEA for this group of patients is decreased [2]. Therefore, patients with high preoperative PVR undergo the operation and no patient is now considered inoperable if the origin of the disease is thrombo-embolic. On the other hand, patients who have evidence of significant thrombo-embolic disease but have a relatively low PVR, with NYHA functional class II, became candidates for PEA surgery to increase their exercise tolerance and eliminate dead space ventilation and to prevent the development of secondary pulmonary arteriopathy and hypertension [2]. In this study, patients with preoperative PVR <300 dyn•s•cm^{-5} also underwent surgery without mortality. It is obvious that selection of patients and early referral for consideration of PEA at a specialized centre are important in decreasing postoperative mortality.

The accepted and well-established technique for PEA surgery is through a median sternotomy using central cannulation with cardiopulmonary bypass and deep hypothermic circulatory arrest (DHCA). In this study, it was found that patients in the mortality group had significantly increased circulatory arrest time, compared with the survivors (27 ± 8.6 min *vs* 20 ± 6.6 min, respectively). Although prolonged circulatory arrest could indicate a more distal disease, resulting in higher postoperative mortality, we believe that this incidental finding may be explained by the fact that this incidental finding may be explained by the fact that our cohort was very small. On the other hand, multivariate analysis did not identify any risk factor for the mortality for our initial experience. Although there has been vigorous debate over the need for DHCA—and proposed alternative methods to replace DHCA—the recent PEA and cognition study (PEACOG) by the Papworth Group has shown no benefit of cerebral perfusion over hypothermia in PEA, suggesting circulatory arrest as the optimum modality for patients undergoing surgery [14–16]. We also agree that PEA should be performed under deep hypothermic circulatory arrest to optimize visualization and the quality of the pulmonary artery dissection [2, 3].

Patients with CTEPH benefit from PEA, which results in an immediate and sustained decrease in PVR and right ventricular (RV) afterload. The outcome of the operation depends mainly on the reduction in PVR and preoperative and postoperative severity of RV dysfunction [13]. In the present study, assessment of the right atrium and -ventricle showed that increased RA volume and RA pressure, decreased TAPSE and higher sPAP were found to be significant risk factors for the early mortality in the univariate analysis. It has been previously reported that patients with pulmonary hypertension had higher RA size and a TAPSE of less than 18 mm was associated with poor prognosis [17,18]. Although we did not identify any risk factor for mortality in multivariate analysis, patients who undergo PEA surgery should be well assessed preoperatively for the right heart function.

The Jamieson classification describes four major types of pulmonary occlusive disease based on anatomy and location of thrombus and vessel wall pathological change [2]. Type 1 refers to fresh thrombus in the main-lobar pulmonary arteries; type 2 refers to intimal thickening and fibrosis proximal to the segmental arteries; type 3 refers to disease within distal segmental arteries only and type 4 refers to distal arteriolar vasculopathy without visible thrombo-embolic disease. This intraoperative classification of disease allows the prediction of patient outcome after PEA. The San Diego Group [19] reported that patients with distal thrombo-embolic disease (types 3 and 4) had a higher peri-operative mortality rate, compared with the mortality rate in patients with types 1 and 2 disease. In this study, we did not assess the effect of the Jamieson classification system on the prediction of early patient outcome after pulmonary endarterectomy.

Any additional procedure, such as CABG, valvular repair or replacement, or closure of an atrial septal defect, is performed during the re-warming phase of the operation [2]. Although there is no data in respect of patent foramen ovale (PFO) closure at the

time of PEA, it is accepted practice to close a PFO, especially if there is a history of paradoxical embolism. However, if residual pulmonary hypertension is expected for those patients with very high PVR and more distal disease, then some surgeons would avoid closure. This allows better cardiac output secondary to left ventricular filling, but at the expense of more hypoxia. At the extremes, hypoxia is better tolerated than low cardiac output. Septostomy is still regarded as a treatment for pulmonary hypertension [5]. If the patient has a true atrial septal defect, rather than PFO, then closure is usually necessary, but this situation is quite rare as any moderate-sized defect would result in significant shunting when right-sided pressures rose as a result of CTEPH. Five patients underwent PFO closure in our study. Our patients had high PVR values (857 ± 230 dyn•s•cm^{-5}, range 480–1051) and proximal diseases; four of them had Jamieson type 1 and one had type 2 disease. Since we did not expect residual pulmonary hypertension following PEA, we performed PFO closure.

Although concomitant surgery was not a significant risk factor, mortality was observed in our two cases. The reasons for death were reperfusion lung injury in one, who underwent concomitant DeVega's tricuspid annuloplasty, and cardiac tamponade in one, who underwent CABG. In patients with CTEPH, functional tricuspid regurgitation tends to develop owing to long-standing severe pulmonary hypertension, which induces dilatation of the right ventricle and tricuspid annulus. Right ventricular function also deteriorates with severe pulmonary hypertension, resulting in progressive right heart failure. The presence of these changes can significantly affect the outcome of CTEPH surgery. Since functional tricuspid regurgitation improved in 70% of patients, with large reduction of pulmonary artery pressure after successful PEA, some authors do not recommend simultaneous performance of tricuspid annuloplasty with PEA [20, 21]. However, tricuspid annuloplasty for high-risk patients with severe PH due to distal pulmonary artery disease was recommended by Ogino *et al.* [12]. The San Diego group has reported that 30% of their patients had persistent, unresolved tricuspid regurgitation due to residual pulmonary hypertension, even after PEA surgery [2]. Patients with persistent severe tricuspid regurgitation had a 12-fold greater incidence of atrial fibrillation than those exhibiting improvement of tricuspid regurgitation. Distal Jamieson's type 3 disease was proposed to be more prevalent among patients with persistent severe tricuspid regurgitation. In our early cases, tricuspid annuloplasty was performed in three patients who had severe tricuspid regurgitation. We did not take the risk of unresolved tricuspid regurgitation due to residual pulmonary hypertension after PEA surgery. However, as our experience increased, we began not to perform tricuspid annuloplasty, even in patients with severe tricuspid regurgitation. All patients but one were successfully weaned from CPB without ECMO after effective tricuspid annuloplasty.

We found that lower FEV_1 and FVC were found to be significant risk factors for mortality in univariate analysis. This is similar to the recent report by Kunihara *et al.*, who have shown that patients with underlying parenchymal lung disease would have increased risk of early mortality and prolonged mechanical ventilation [11]. Therefore, patients with low FEV_1 and FVC representing parenchymal lung disease should be carefully managed for possible death or long mechanical ventilation.

Preoperative PVR levels, as well as postoperative PVR measurements, correlate with postoperative mortality in the present study. As our surgical experience has increased, we have also been able to identify high-risk patients preoperatively, according to PVR values and predicting a 50% reduction in PVR postoperatively.

Veno-venous ECMO is indicated when inadequate gas exchange occurs after pulmonary endarterectomy [22] whereas veno-arterial ECMO (VA-ECMO) is indicated if the patient needs a cardiovascular circulatory support following PEA [23]. In our cases, support for both blood oxygenation and cardiac pump function was required. Therefore, we performed VA-ECMO. Although postoperative use of ECMO was found as a risk factor for morbidity, the role of ECMO is well known, especially in high-risk patients with severe PH due to distal disease, when weaning from CPB is difficult in the presence of hypotension and hypoxia. The San Diego and Papworth groups have reviewed their experience with use of ECMO for patients who underwent PEA [22, 23]. Twenty patients (1.12%) in the San Diego group and seven patients (5.5%) in the Papworth group required ECMO support due to extreme cardiorespiratory compromise in the immediate postoperative period. Survival was 30 and 73%, respectively. ECMO was used in our six patients (12%), with a 50% survival that is quite similar to these experienced centres. All six patients presented with Jamieson type 2 disease. Although complete PEA surgery was performed, ECMO was used as a bridge to recovery in four cases with persistent pulmonary hypertension due to pulmonary oedema. We did not use ECMO as a bridge to transplantation for those patients with endarterectomy failure. In fact, we considered transplantation for one young case with reperfusion injury but, due to morbid obesity of the patient, we did not attempt the operation. The other two patients had no indication for lung transplantation because of their ages. On the other hand, this is one of the reasons to concentrate CTEPH surgery in skilled surgical centres where lung and heart-lung transplantations can be performed, even after failure of PEA surgery.

When we analysed possible risk factors for morbidity, prolonged mechanical ventilation time in survivors was found to be a significant risk factor in the multivariate analysis, as it was reported that early extubation on the first and second postoperative days is important for patients who underwent PEA [7]. Recently we started to extubate our patients as soon as possible, when their haemodynamics were stable. At our centre, following PEA, inhaled nitric oxide (NO) is started intraoperatively. NO is generally administered to improve right ventricular function if the PVR is not yet back to normal. However, we used NO even if the PVR was normal because we could not predict the incidence of reperfusion injury in our very early cases. Since iloprost (a stable analogue of prostacyclin) is known to reduce residual postoperative pulmonary hypertension, decrease right ventricular afterload and may facilitate the early postoperative management after PEA, we started administering inhaled iloprost following extubation of the patients [24]. Currently, as our surgical expertise has increased, inhaled iloprost is no longer used in the absence of persistent pulmonary hypertension.

Pulmonary angiography is known as the 'gold standard' for the diagnosis of thrombo-embolic pulmonary hypertension [2, 3]. However, multiplanar digital subtraction imaging, showing the exact localization of pulmonary artery obstructions, is also used to assess operability [5]. Specific experience is required for the interpretation of angiograms. At the beginning of our PEA program, lack of this experience led us to perform CT both for diagnosis of CTEPH and assessment of operability. Pulmonary CT angiography detects the distribution of obstructive pulmonary artery lesions at the main, lobar and segmental levels and a mosaic pattern of lung attenuation as a sign of regional perfusion differences. Currently, if there is no doubt about the diagnosis and operability for CTEPH, we do not use pulmonary angiography. Recently Madani *et al.* [2]

also reported that, at the San Diego centre, pulmonary angiography is used if CT angiography of the chest is non-diagnostic. On the other hand, the V/Q scan is used routinely to diagnose CTEPH. The persistence of mismatched segmental perfusion defect after 3 months of adequate anticoagulation is diagnostic of chronic thrombo-embolic disease. It is our protocol that all newly diagnosed patients with pulmonary hypertension undergo a V/Q scan to rule out CTEPH.

In contrast to the University of California at San Diego (UCSD) PEA group [2], we have not routinely used inferior vena cava filter peri-operatively in our program, owing to the lack of evidence supporting the use of inferior vena cava (IVC) filters in CTEPH, and their potential side effects in the long term [1, 3].

Patients with residual PH after surgery are at higher risk of postoperative complications. However, these patients can still benefit from surgery and demonstrate major and long-standing clinical improvement. In some situations, the residual pulmonary hypertension can also improve for several months after the surgery due to the reverse remodelling of the vasculopathy located in the pulmonary microvasculature. If residual pulmonary hypertension is suspected, patients should undergo repeat right heart catheterization to confirm the presence of residual pulmonary hypertension, because the diagnosis of pulmonary hypertension on echocardiogram may not be accurate. The effect of PEA on patients with residual PH after surgery was recently documented in a study from the Papworth group [25]. They demonstrated that the 5-year survival was close to 90% in patients with residual PH after PEA and the outcome was not significantly different to the group of patients who normalized their pulmonary pressures immediately postoperatively, as long as they survived the operation. In the present study, only one patient presented with residual pulmonary hypertension following PEA. A PEA centre is defined as an institution which performs ≥20 PEA surgeries per year with a mortality rate <10% [5]. Currently, fewer than 5000 PEA surgeries have been performed in 15–20 expert centres worldwide [6]. We have developed our PEA program to become a PEA centre in Turkey. We are currently performing more than 40 PEA operations per year. We are very sure that, based on a multidisciplinary team and a high level of surgical experience, we will have more favourable outcomes in the near future. As patients with pulmonary embolus are often treated by a wide variety of specialists, it is important that more is done across the medical spectrum to draw attention to this situation and increase awareness of the availability of PEA surgery.

In conclusion, our experience demonstrates that PEA can be performed with limited risk and result in a favourable early outcome. Preoperative factors can predict postoperative outcome after PEA. Increased risk factors for early mortality were higher preoperative sPAP, decreased TAPSE, increased right atrial volume and right atrial pressure showing depressed right heart function, decreased FEV_1 and FVC showing underlying parenchymal lung disease, higher preoperative and postoperative PVR, longer duration of circulatory arrest and postoperative use of ECMO. Prolonged mechanical ventilation was the only predictive risk factor for morbidity. Patients diagnosed with CTEPH should be referred to experienced centres without delay, to confirm the diagnosis and determine the best therapeutic options.

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Conflict of interest: Bedrettin Yıldızeli has given presentations for Bayer and Actelion.

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APPENDIX. CONFERENCE DISCUSSION

Dr P. Dartevelle *(Le Plessis Robinson, France)*: The authors have developed a centre for pulmonary endarterectomy in Turkey. It's never easy to develop such a centre, and the results are acceptable because they are initial results.

My first question is about the first patients you operated on before this series, which is a series of one year. What were the results before this series—the results at the initial procedures? My second question is about preoperative pulmonary angiogram, because CT scan is not sufficient to assess the quality of the indication in this disease.

My third question is about the technique you have used to treat major intraoperative pulmonary bleeding after pulmonary artery perforation. You speak of this complication in your manuscript. What did you do for perforation of the pulmonary artery?

Dr Yildizeli: Professor Dartevelle was one of my teachers and we spent a couple of years together.

I just want to say that, as I told you, there are fewer than 20 centres (approximately) in the world that perform as high-volume centres. In addition to outstanding surgeons and anaesthesiologists, a successful PEA program requires collaboration between different groups of physicians and nurses, particularly because there are many problems that may occur in the postoperative period. Assembling such a team is like assembling a puzzle for me, and it requires time and patience.

As you know, I came back from Marie Lannelongue Hospital and we waited more than a year to start the PEA program. During that time we have talked together often, even considering our patients with you. With your help we started our PEA program. And over a year we operated on 22 patients with a mortality of 3. After that our hospital has changed; we needed to move to another hospital. During that time the hospital administration didn't support us very well, so I joined another team. And with the new dedicated team we have so far operated on more than 70 patients in less than 2 years. We are trying to decrease our mortality to less than 10%; we are trying to become a better centre.

Regarding your second question about pulmonary angiograph, I couldn't say anything except that it is the 'gold standard' for assessment of the operability and diagnosis of chronic thrombo-embolic pulmonary hypertension. However, we need to have specific expertise for interpreting the pulmonary angiogram. Besides, the pulmonary angiogram should be taken in the anterolateral, posterolateral and oblique views. At that time I couldn't find any radiologists in Turkey that could interpret and perform this pulmonary angiogram. So we performed pulmonary CT angiogram with multiplanar digital subtraction imaging. With this we can reconstruct all the images in the 3-D oblique lateral and so we use those scanners for the assessment. I am sure that if we have any problems we could have a pulmonary angiography right now. I know that I can call you any time, you answer many times, so I have the feeling that I am very comfortable about CT scan because of you.

And the last question about the patient with massive pulmonary haemorrhage; that occurred after the endarterectomy patient had sudden haemoptysis. At that time the patient was still on cardiopulmonary bypass and we just performed a bronchoscopy and the bleeding was coming from the right lower lobe bronchus, so we re-intubated the patient with a double lumen tube and occluded the right lower lobe bronchus with a Fogarty catheter. Our aim was to embolize the patient, but the patient's haemodynamic position wasn't enough to wean the patient from cardiopulmonary bypass so we put the patient on ECMO. On the third day of ECMO we didn't observe any bleeding from the bronchial system, so we stopped the ECMO, weaned the patient, cleared all the secretions, and then the patient was extubated in two days without any problem. I think it was our chance to recover the patient with ECMO from this massive pulmonary haemorrhagic complication.

Dr Dartevelle: It is the right solution.

Dr K. Athanassiadi *(Athens, Greece)*: I was trained with the Hannover group, who transect the vena cava and they are still doing it. Do you mobilize it or do you transect it?

Dr Yildizeli: We just mobilize the superior vena cava. We don't need to transect it. Because transection causes other problems, such as re-thrombosis, plus the superior vena cava is just good enough for you to perform the operation. Plus Prof Dartevelle would not give me any permission for that.