

# An Australian tertiary referral center experience of the management of chronic thromboembolic pulmonary hypertension

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## ABSTRACT

The objective of this study was to report the outcome of pulmonary endarterectomy (PEA) surgery performed for chronic thromboembolic pulmonary hypertension (CTEPH) at a single tertiary center. The prospective study consisted of 35 patients with surgically amenable CTEPH undergoing PEA between September 2004 and September 2010. The main outcome measures were Functional (New York Heart Association [NYHA] class, 6-Minute Walk Distance), hemodynamic (echocardiography, right heart catheterization, and cardiac MRI), and outcome data (morbidity and mortality). Following PEA, there were significant improvements in NYHA class (pre 2.9±0.7 vs. post 1.3±0.5,  $P < 0.0001$ ), right ventricular systolic pressure (pre 77.4±24.8 mmHg vs. post 45.1±24.9 mmHg,  $P = 0.0005$ ), 6-Minute Walk Distance (pre 419.6±109.4 m vs. post 521.6±83.5 m,  $P = 0.0017$ ), mean pulmonary artery pressure (pre 41.8±15.3 mmHg vs. post 24.7±8.8 mmHg,  $P = 0.0006$ ), and cardiac MRI indices (end diastolic volume pre 213.8±49.2 mL vs. post 148.1±34.5 mL,  $P < 0.0001$ ; ejection fraction pre 40.7±9.8 mL vs. post 48.1±8.9 mL,  $P = 0.0069$ ). The mean cardiopulmonary bypass time was 258.77±26.16 min, with a mean circulatory arrest time of 43.83±28.78 min, a mean ventilation time of 4.7±7.93 days (range 0.2-32.7), and a mean intensive care unit stay of 7.22±8.71 days (range 1.1-33.8). Complications included reperfusion lung injury (20%), persistent pulmonary hypertension (17.1%), slow respiratory wean (25.7%), pericardial effusion (11.4%), and cardiac tamponade (5.7%). 1-year mortality post-procedure was 11.4%. Pulmonary endarterectomy can be performed safely with relatively low mortality.

**Key Words:** chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, pulmonary vascular resistance, pulmonary vasodilator therapy, pulmonary artery sarcoma

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe form of pulmonary hypertension that has largely been under-diagnosed due to poor understanding and recognition of affiliated clinical symptoms. Although most patients who suffer an acute pulmonary embolism (PE) demonstrate complete thrombus resolution and normalization of pulmonary vascular hemodynamics within 30 days, 3.8% of these patients go on to develop CTEPH.<sup>[1]</sup> The true incidence of CTEPH may be significantly higher, given that most episodes of PE are asymptomatic, with up to 60% of patients having no clear history of an inciting venous thromboembolism.<sup>[2]</sup> In CTEPH, unresolved thrombotic

material becomes incorporated into the vessel intima, resulting in fibrosis, increased pulmonary vascular resistance, and ultimately, pulmonary hypertension. Patients may be asymptomatic for months to years after the initial event (the so-called honeymoon phase) before presenting with exertional dyspnea or overt right heart failure. Survival with CTEPH is strongly linked with the degree of pulmonary hypertension, with a 5-year survival of less than 10% in patients with a mean pulmonary artery pressure (mPAP) above 50 mmHg.<sup>[3]</sup>

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Pulmonary endarterectomy (PEA) remains the treatment of choice for CTEPH, with significant improvement in symptoms, pulmonary hemodynamic, and survival. The procedure is only performed at a handful of specialized centers across the world, with reported mortality rates ranging from 5% to 24%.<sup>[4]</sup> The purpose of this study was to report our experience with PEA at The Prince Charles Hospital (TPCH).

## MATERIALS AND METHODS

We undertook a prospective study at TPCH, a large tertiary cardiorespiratory referral center in Brisbane, Queensland. The study protocol was approved by the hospital's Human Research Ethics Committee.

All consecutive patients referred to the Queensland Centre for Pulmonary Transplantation and Vascular Diseases between September 2004 and September 2010 with suspected CTEPH were enrolled. Following a baseline 2D echocardiogram, all patients with pulmonary hypertension were screened for the presence of CTEPH using ventilation-perfusion (VQ) scanning as per the Papworth diagnostic algorithm shown in Figure 1.<sup>[5]</sup> The presence of CTEPH was defined as having a single, large perfusion defect or multiple perfusion defects on VQ scanning, together with echocardiographic evidence of pulmonary hypertension (right ventricular systolic pressure [RVSP] greater than or equal to 35 mmHg, right ventricular dilatation, and/or right ventricular systolic dysfunction). Patients with suspected CTEPH underwent computerized tomography of the pulmonary arteries (CTPA), together with pulmonary magnetic resonance angiography (MRA), and gold-standard pulmonary angiography to determine the surgical suitability of their disease. All patients with CTEPH underwent right heart catheterization (RHC) to confirm the presence and severity of pulmonary hypertension (defined as an mPAP greater than or equal to 25 mmHg at rest), cardiac magnetic resonance imaging (MRI) to calculate right ventricular hemodynamic parameters, and a 6-Minute Walk Test (6MWT) to determine their exercise capacity. Selected patients also underwent coronary angiography to assess for concurrent coronary artery disease. The functional severity of right ventricular failure was defined according to those definitions proposed by the New York Heart Association (NYHA).<sup>[6]</sup>

### CTEPH diagnostic algorithm

Patients with operable disease (defined as thromboembolic disease confined to the proximal pulmonary arterial tree) were referred for PEA if they met the following criteria: (1) NYHA Class III or IV symptoms; (2) pulmonary vascular resistance (PVR) greater than 300 dynes/s/cm<sup>5</sup>; (3) surgically accessible thrombus in the main, lobar, or

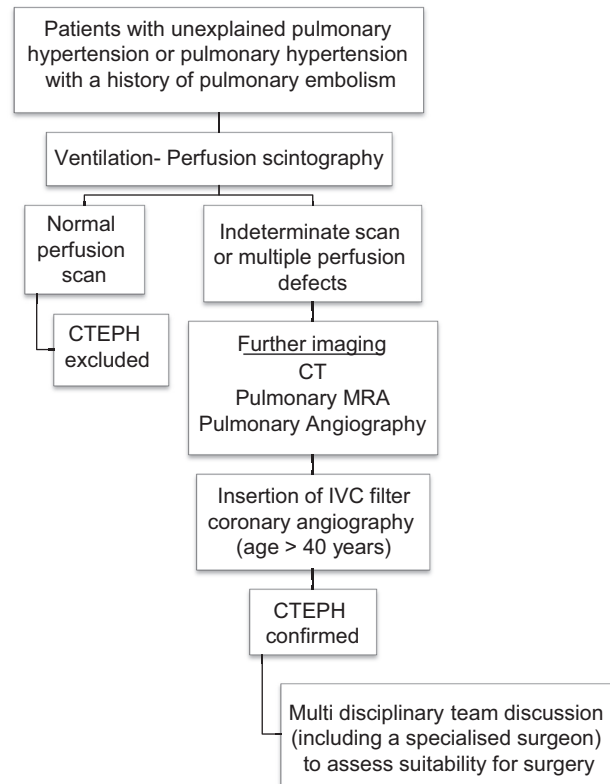


Figure 1: CTEPH diagnostic algorithm.

segmental pulmonary arteries; and (4) without other significant comorbidities. Patients with Class II symptoms were referred for surgery if there were abnormalities in their pulmonary hemodynamic parameters. The procedure was performed using the technique described by Jamieson and Kapilanski,<sup>[7]</sup> and all operative specimens were sent for histopathology to exclude malignancy such as pulmonary sarcoma. A pulmonary artery catheter and nasogastric tube was routinely placed perioperatively. Patients were mechanically ventilated in the intensive care unit (ICU) using synchronized intermittent mandatory ventilation or volume control mode with pressure support. Tidal volume was set as 10 mL/kg, with a respiratory rate of 16 breaths per minute, positive end-expiratory pressure (PEEP) of 10 cm H<sub>2</sub>O, and pressure support of 10 cm H<sub>2</sub>O above PEEP. Patients were sedated for a minimum of 12 h postoperatively to avoid agitation and ventilator dyssynchrony.

Intravenous frusemide was commenced on the day of surgery at 20 mg QID for the first six doses (and reduced thereafter), together with esomeprazole (40 mg IV daily), and ceftriaxone (2 g IV BD until extubation). Intravenous heparin was also commenced on the day of surgery if no bleeding was present (defined as less than 25 mL/h for the preceding two consecutive hours), followed by warfarin at 10 mg on the first postoperative day if no bleeding was present. Further doses of warfarin were adjusted according to the INR (with a target range of 2.5–3.5).

Sodium nitroprusside or glyceryl tri-nitrate was used to control systemic hypertension (defined as a systolic blood pressure of 100–140 mmHg or a mean arterial pressure of 65–95 mmHg). Fluid therapy was directed toward a negative daily fluid balance to reduce the risk of reperfusion injury (RLI) and pulmonary edema. Only 4% saline solutions were used to maintain ventricular filling pressures and cardiac output. Blood products were used to maintain hemoglobin above 100 g/L and hematocrit greater than 30%.

Weaning from mechanical ventilation was initiated on the first post-operative day. The  $\text{FiO}_2$  was gradually reduced by 10% every two hours to a nadir of 40% while maintaining  $\text{PaO}_2$  above 100 mmHg at all times. Surgical drains were left in situ for a minimum of 48 hours, and removed when requested by the surgeon and depending on whether a pericardial window was performed. Pulmonary arterial catheters remained in situ until the patient was extubated or the third postoperative day. For patients who remained intubated by the evening of the second postoperative day, enteral feeding was commenced as per the Australian and New Zealand Intensive Care Society Enteral Feeding Algorithm.<sup>[8]</sup>

For patients with persistent pulmonary hypertension (PPHT), nitric oxide and intravenous prostacyclin infusions were initiated only after consultation with the surgical and pulmonary vascular teams. Following discharge from hospital, patients were reviewed in the pulmonary hypertension outpatients' clinic at 1 month, 3 months, 6 months, 12 months, 24 months, and 36 months. Repeat echocardiography and 6MWT was performed prior to each clinic review, with a repeat MRI and MRA being performed at 6 months.

Patients with inoperable disease or inadequate surgical clearance were commenced on monotherapy with compassionate access to either bosentan or sildenafil. Combination therapy was commenced if there was further evidence of disease progression or a decline in functional capacity during follow-up.

Patients who were not found to have CTEPH at the time of initial screening were excluded from the study, as were patients failing to meet the criteria for surgery who elected to have PEA in other Australian states. Patients who were lost to follow-up or were followed up in other states were not included in the final analysis.

Data collected included patient demographics, preoperative data (NYHA functional class, 6MWT, echocardiography, MRI, and RHC results), postoperative data (ICU length of stay, ventilation hours, and morbidity), and follow-up data (mortality, NYHA functional class, 6MWT, echocardiography, MRI, and RHC results). The data are expressed as mean  $\pm$  standard deviation, with an independent sample *t* test

used to compare results pre- and post-PTE. A *P* value of less than 0.05 was considered to be statistically significant (Fig. 1).

## RESULTS

There were 720 pulmonary hypertension referrals to our unit between September 2004 and September 2010. CTEPH was confirmed in 55 of these patients (7.6% of all referrals), with 14 patients having inoperable disease. Forty-one patients had surgically amenable disease, with four patients referred for surgery elsewhere in Australia (three in Sydney and one in Perth). Two patients were diagnosed with pulmonary sarcoma (Fig. 2).

### Study flowchart

Of the 35 patients who underwent PEA for CTEPH at our institution, four were excluded from the long-term analysis as they relocated to other Australian states for analysis or declined to attend follow-up appointments. There were 19 females and 12 males, with a mean age of  $51.8 \pm 15.8$  years (range 16–77 years). They had moderate-to-severe exercise limitation, with 42.9% of patients with NYHA functional Class III and 20% of patients with Class IV symptoms (25.7% Class II, 0% Class I). Severe right ventricular (RV) dysfunction was seen in 25.7% of patients ( $n=9$ ), with

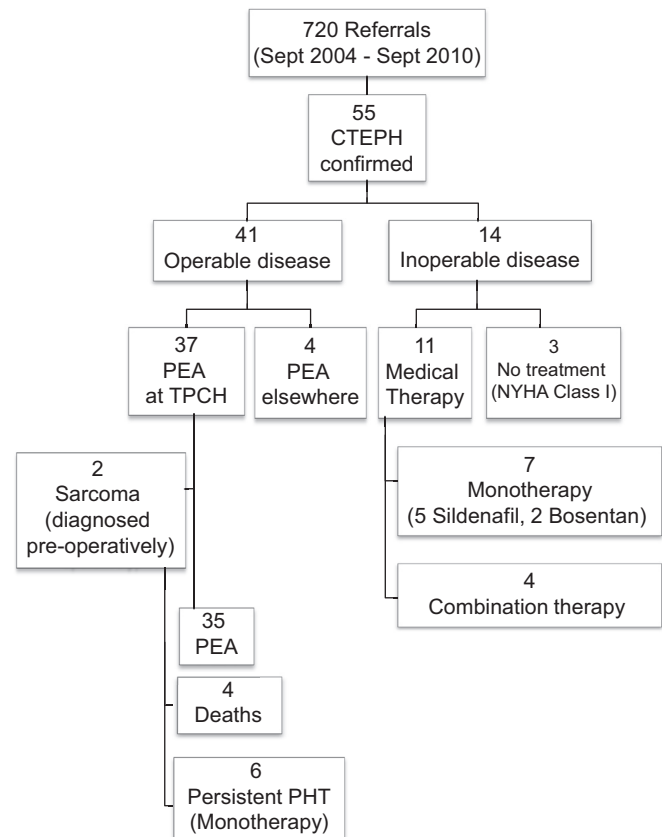


Figure 2: Study flowchart.

moderate dysfunction in 20% ( $n=7$ ), and mild dysfunction in 34.3% ( $n=11$ ) of patients. Approximately 9% of patients had normal RV function at the time of initial assessment, but developed RV dysfunction following a period of observation. Thrombophilia was identified in four patients (two anti-phospholipid syndrome, one protein C deficiency, and one prothrombin gene mutation). Of the 17 patients who received preoperative vasodilator therapy, six received monotherapy with either sildenafil or bosentan, seven received combination therapy, and four received triple therapy with the addition of intravenous prostacyclin targeting a minimum dose of 8-10 ng/kg/min. One patient required intra-aortic balloon pump support pre-operatively.

At baseline, the mean RVSP was  $77.4 \pm 24.8$  mmHg, with an mPAP of  $41.8 \pm 15.3$  mmHg and a mean PVR of  $575.0 \pm 404.8$  dynes/s/cm<sup>5</sup> (Table 1). The mean cardiopulmonary bypass time was  $258.77 \pm 26.16$  min, with a mean combined circulatory arrest time of  $43.83 \pm 28.78$  min. Patients were mechanically ventilated for an average of  $4.7 \pm 7.93$  days (range 0.2-32.7 days), and remained in ICU for  $7.22 \pm 8.71$  days (range 1.1-33.8 days).

### Functional, echocardiographic, and hemodynamic variables at baseline and at 6 months following PEA

At 6 months post-PEA, there were significant improvements in NYHA functional class, 6MWT parameters, RVSP, mPAP, and cardiac MRI indices, as outlined in Table 1.

RLI and PPHT necessitating prolonged mechanical ventilation were the commonest complications following surgery (Table 2).

### Morbidity following PEA in $n=35$ patients

There were four deaths during the study period, all occurring within seven days of surgery (12-month mortality rate 11.4%). Case 1 was a 25-year-old female with a baseline PVR of 1454 dynes/s/cm<sup>5</sup> who developed RLI and PPHT intraoperatively, and was found to have pulmonary veno-occlusive disease and isolated cardiac sarcoidosis at autopsy.

Case 2 was a 75-year-old male non-smoker who underwent PEA for CTEPH with a baseline PVR of 1050 dynes/s/cm<sup>5</sup>. He developed RLI and PPHT intraoperatively, and at autopsy was found to have metastatic adenocarcinoma of the lung within organized and recanalized pulmonary artery thrombi.

Case 3 was a 40-year-old female who underwent PEA for CTEPH on a background of anti-phospholipid syndrome (PVR 937 dynes/s/cm<sup>5</sup>). She developed RLI in the setting of a postoperative antiphospholipid crisis that was refractory to treatment. Extensive pulmonary hemorrhage, diffuse alveolar damage, and CTEPH were noted at autopsy.

Case 4 was a 27-year-old man who underwent a redo PEA for CTEPH and died intraoperatively from uncontrolled pulmonary hemorrhage with similar findings at autopsy.

Two patients were diagnosed with pulmonary artery sarcoma in our program, with a survival time of 6 and 21 months, respectively.

## DISCUSSION

This prospective study demonstrates that PEA significantly improves the functional status, hemodynamic variables, and outcome data for patients with CTEPH, and remains the treatment of choice in this condition. As such, all patients with suspected CTEPH should be referred to an experienced center for consideration for PEA as soon as the diagnosis is suspected.

The first successful PEA was performed by Allison in 1960,<sup>[9]</sup> and more than 4,000 operations have been performed worldwide since then. The PEA program at the University of California San Diego (UCSD) is globally recognized for its expertise in this field, having performed more than 2,500 procedures with the lowest reported mortality rate of 4.4%.<sup>[10]</sup> Postoperative mortality rates from other centers vary between 5% and 24%, depending on the level of surgical experience at the reporting institution.<sup>[4,11]</sup>

**Table 1: Functional, echocardiographic, and hemodynamic variables at baseline and at 6 months following pulmonary endarterectomy**

	Variable	Pre-PTE	Post-PTE	P value
NYHA Functional Class		2.9±0.7	1.3±0.5	<0.0001
6MWT	Distance (m)	419.6±109.4	521.6±83.5	0.0017
	Resting saturations (%)	95.1±2.5	96.4±2.0	0.1517
	Lowest saturations (%)	85.6±7.3	89.7±7.3	0.0758
	Borg score	4.2±1.9	2.8±1.4	0.0123
Echocardiography	RVSP (mmHg)	77.4±24.8	45.1±24.9	0.0005
Right heart catheter	mPAP (mmHg)	41.8±15.3	24.7±8.8	0.0006
	PVR (dynes/s/cm <sup>5</sup> )	573.0±404.8	—	—
Cardiac MRI	RV end-diastolic volume (mL)	213.8±49.2	148.1±34.5	<0.0001
	RV ejection fraction (mL)	40.7±9.8	48.1±8.9	0.0069

**Table 2: Morbidity following pulmonary endarterectomy in n = 35 patients**

Complication	N	Percent
Prolonged mechanical ventilation	9	25.7
2° to	2	
Reperfusion lung injury (RLI) alone	5	
RLI + Persistent pulmonary hypertension	1	
Airways disease	1	
Pneumonia		
Circulatory shock	2	5.7
Pericardial effusion	4	11.4
Pericardial tamponade	2	5.7
Pleural effusion	1	2.9
Pulmonary hemorrhage	1	2.9

The 12-month mortality in our series was 11.4%, which compares favorably with data from similar-sized programs. Zoia and colleagues reported a 10% in-hospital mortality rate with 38 patients,<sup>[12]</sup> Mellekjaer et al. reported 24% mortality with 50 patients,<sup>[13]</sup> and Tscholl et al. reported 10.1% with 69 patients.<sup>[14]</sup>

A large number of institutions report a learning curve with the procedure,<sup>[15,16]</sup> with mortality rates declining as surgical skill and expertise improve. The majority of PEA procedures in our program were performed by the same surgeon who, having performed more than 200 procedures elsewhere, had considerable skill and experience in the field. Furthermore, the deaths in our program did not arise directly from recognized complications of PEA such as RLI or PPHT. One possible explanation for our low mortality rate is the preoperative management of high-risk patients. Severe pulmonary hypertension (defined as a preoperative PVR greater than 1,100 dynes/s/cm<sup>5</sup> and an mPAP greater than 50 mmHg) has been shown to increase operative mortality by almost six and five times, respectively.<sup>[17]</sup> A high PVR in the absence of significant proximal perfusion defects reflects concomitant secondary small vessel arteriopathy, which increases the risk of PPHT in the postoperative period.<sup>[18]</sup> Despite the paucity of randomized controlled trials in this area, many centers use specific pulmonary arterial hypertension therapies (such as endothelin receptor antagonists, prostacyclins, and phosphodiesterase-5 inhibitors) in an attempt to optimize pulmonary hemodynamics prior to PEA.<sup>[19]</sup> There were only five patients in our program who had a PVR greater than 900 dynes/s/cm<sup>5</sup>, all of whom received single or combination pulmonary vasodilator therapy in the preoperative period. Despite these measures, PPHT was noted in four of the five, with three patients dying in the immediate postoperative period. This highlights the difficulty of diagnosing disease states that can often radiologically and hemodynamically mimic CTEPH even in experienced tertiary centers (such as concomitant pulmonary veno-occlusive disease, large vessel arteritis, and metastatic carcinoma). Lastly, improvements in the

postoperative intensive care may have resulted in lower mortality rates. We have developed a highly specialized protocol for all patients undergoing PEA at our institution based on the experience of our surgical team and the knowledge gained from the perioperative management of patients at the Papworth Hospital and UCSD. To conclude, patients with a PVR greater than 900 dynes/s/cm<sup>5</sup> are high risk and warrant careful multidisciplinary, preoperative assessment.

When assessing patients with CTEPH, consideration should always be given to excluding pulmonary artery sarcoma, a rare malignancy that frequently mimics CTEPH both clinically and radiologically. MRI is useful in differentiating sarcoma from CTEPH as T1-weighted images demonstrate an intraluminal mass, with T2-weighted images resulting in a mild increase in signal intensity and significant enhancement with gadolinium, indicating the vascular nature of such tumors<sup>[20]</sup> as seen in our cohort.

Eleven of the 14 patients with distal thromboembolic disease, or those who failed to meet the surgical criteria at our institution, were offered pulmonary vasodilator therapy for CTEPH; five of these patients received sildenafil, two received bosentan, and four received combination therapy. Three patients were not commenced on therapy as they had functional Class I symptoms at the time of diagnosis and were observed without medical therapy. The mean NYHA functional class at baseline was 3.23±0.73 (vs. 3.00±0.96 at 6 months following treatment, *P* = 0.2631) with a mean RVSP of 77.64±15.45 mmHg (vs. 80.56±21.91 mmHg, *P* = 0.6597), and a mean 6MWT distance of 328.64±116.84 m (vs. 397.75±172.51 m, *P* = 0.4363). The baseline mPAP was 40.00±6.50 mmHg, with a mean PVR of 542.42±353.34 dynes/s/cm<sup>5</sup>.

PEA is considered curative, with significant and sustained improvements in functional and hemodynamic parameters in the majority of patients with CTEPH as shown in our small series. Multidisciplinary assessment of pulmonary hemodynamics (particularly the PVR) is an important determinant of perioperative mortality and clinical outcome. Advanced pulmonary vasodilator therapies such as prostacyclin, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors may be beneficial preoperatively to improve pulmonary hemodynamics and for patients with inoperable disease. However, further clinical studies are required.

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