doi: 10.5761/atcs.oa.10.01653

Original Article

Pulmonary Thromboendarterectomy for Chronic Thromboembolic Pulmonary Hypertension : A Systematic Review

Mohammad Rahnavardi, MD,[1,2] Tristan D Yan, BSc (Med), MBBS, PhD,[1,2]
Christopher Cao, BSc (Med), MBBS,[1,2] Michael P Vallely, MBBS, PhD,[1,2]
Paul G Bannon, MBBS, PhD,[1,2] and Michael K Wilson, MBBS[1,2]

Purpose: Pulmonary thromboendarterectomy (PTE) is a treatment option for patients with chronic thromboembolic pulmonary hypertension (CTEPH). The present systematic review was performed to assess the safety and efficacy of PTE for CTEPH.
Methods: A systematic review was performed, and six electronic databases were searched for published studies from January 1999 to February 2010. All articles that presented morbidity and mortality data, survival data or preoperative and postoperative pulmonary hemodynamic indices were included. The primary outcome measures extracted were early morbidity and mortality, pulmonary hemodynamic and functional outcome indices prior to and after the operation, and survival data.
Results: Of the 654 publications retrieved, 19 relevant papers (total number of 2729 patients) representing the most recent and complete data set from each institute, were included for appraisal and data extraction. No randomized controlled trials or matched comparative studies were identified. Thirty-day mortality ranged from 1.3% to 24% (median 8%). Residual pulmonary hypertension was reported in 11%–35% of patients after PTE. Pulmonary artery pressure and pulmonary vascular resistance significantly decreased after PTE in all studies. Before PTE, 60%–100% of patients were in NYHA functional class III or IV. This percentage decreased to 0%–21% after PTE. Five-year survival ranged from 74% to 89%.
Conclusions: The current literature suggests that PTE for patients with CTEPH is associated with acceptable perioperative morbidity and mortality rates and improved hemodynamic indices and survival when viewed against the prognosis associated with historical controls using medical therapy.

Keywords: pulmonary, lung, thromboendarterectomy and endarterectomy

[1]*Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, The University of Sydney, Sydney, Australia*
[2]*The Baird Institute for Applied Heart and Lung Surgical Research, Sydney, Australia*

Received: December 12, 2010; Accepted: February 4, 2011
Corresponding author: Mohammad Rahnavardi, MD. Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, The University of Sydney, Missenden Road, Camperdown, Sydney, Australia
Email: rahnavardi@gmail.com

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is estimated to develop in 3.8% of patients who survive an acute pulmonary embolic event.[1] CTEPH is characterized by intraluminal thrombus organization, fibrous stenosis of pulmonary artery, and subsequent vascular remodeling in small unobstructed vessels resulting in pulmonary hypertension and progressive right heart failure.[2] Riedel et al.[3] followed a series of 26 patients for up to 15 years and showed that those with a mean pulmonary artery pressure (mPAP) >50 mmHg had a 2-year survival of less than 20%. In another study, 90% of CTEPH patients with a mPAP of >30 mmHg who were only treated with anticoagulants died within three years of follow-up.[4] Pulmonary thromboendarterectomy (PTE) is a treatment option for patients with CTEPH.[5] Optimal patient selection, adequate preoperative work-up, meticulous surgical technique, and careful postoperative management are essential for the success of PTE.[5, 6]

PTE is performed in several specialist centers around the world. The procedure can be associated with relatively high morbidity and mortality, especially before the treating surgeons or centers overcome their initial learning curves. To date, there is a paucity of robust clinical data in the form of randomized controlled trials (RCTs) on the safety and efficacy of PTE. The last systematic review on the topic was reported in 2001 and included studies from 1996 to 2000.[7] Within the last decade, some modifications to the surgical technique have been applied, and some longer-term follow-up results have become available. We performed the present systematic review to objectively assess the safety and efficacy of PTE for CTEPH based on the studies published from 1999 to early 2010.

Materials and Methods

Literature search strategy

A systematic review was performed, and six electronic databases including MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systemic Reviews, and Database of Abstracts of Review of Effectiveness were searched for original published studies from January 1999 to February 2010. Search keywords were “pulmonary” OR “lung” AND “thromboendarterectomy” OR “endarterectomy.” The reference lists of all relevant, retrieved studies were manually search for further identification of potentially relevant studies.

Selection criteria

Studies selected for appraisal were either retrospective or prospective, presenting results of PTE in CTEPH patients. All articles that presented morbidity and mortality data, survival data or preoperative and postoperative pulmonary hemodynamic indices were included. Case studies, editorials, review articles, and studies involving less than 20 operated patients were excluded to allow consistent results. Papers that presented data within defined subgroups of PTE patients were included only if they presented perioperative data for the whole study population. All studies selected were human trials and in the English language. When a paper separately presented data regarding isolated PTE and combined PTE with other heart operations, only data regarding isolated PTE was included.

Data extraction and critical appraisal

Two reviewers (M.R. and T.D.Y.) independently appraised each included study, using a standard form, and extracted data on methodology, quality criteria, and outcome measures. All data were extracted and tabulated from the relevant articles’ texts, tables, and figures. The quality of studies was assessed using criteria recommended by the National Health Service Centre for Reviews and Dissemination case series quality assessment criteria (University of York, Healington, United Kingdom).[8]

Study population

All included patients had CTEPH and were considered suitable for PTE. Clinical guidelines from the American College of Chest Physicians recommend the following four criteria to be met: 1) New York Heart Association (NYHA) class III or IV symptoms, 2) preoperative pulmonary vascular resistance (PVR) of >300 dynes-sec-cm^{-5}, 3) surgically accessible thrombus (in the main, lobar, or segmental pulmonary arteries), and 4) no significant comorbidities.[9] CTEPH patients may be classified as having Type 1 (fresh or organized clot in the main or lobar pulmonary artery), Type 2 (intimal thickening and fibrosis without visible thrombus proximal to the segmental arteries), Type 3 (fibrosis, intimal webbing and thickening in segmental and subsegmental arteries only- no visible thrombus), or Type 4 (microscopic distal arteriolar vasculopathy- not directly related to pulmonary embolism) disease.[5, 10]

Interventions and outcome measures

The current common technique of PTE is pioneered by surgeons at the University of California, San Diego (UCSD). The procedure was well described by Jamieson and colleagues, who reported the largest surgical volume of PTE to date.[5, 6] The major outcome measures extracted from selected studies were early (30-day; procedure-related) morbidity and mortality, pulmonary hemodynamic and functional outcome indices prior to and after the operation, and survival data.

Results

Quantity of evidence

After removing duplicates, a total of 654 publications were retrieved for screening. Review of the title and abstract of these publications identified 74 potentially relevant articles. Review of the reference lists of these 74 publications identified four additional relevant studies. When the inclusion and exclusion criteria were applied to these 78 publications, 40 papers[6, 10–48] were selected for evaluation (**Table 1**). Serial publications reporting accumulating numbers of patients or increased length of follow-up were identified. Only the most recent publications with the most complete data set from each institute were retained. As a result, 19 studies[6, 15, 21, 22, 25, 26, 29, 30, 33, 35, 36, 38, 40, 42–44, 46–48] with a total number of 2729 patients were included for appraisal and data extraction (**Table 2**).

Quality of evidence

There were no randomized controlled trials or matched comparative studies. Four prospective studies were identified,[30, 38, 40, 46]; other studies were either clearly retrospective[6, 15, 22, 25, 29, 35, 42, 44, 47, 48] or not specified.[21, 26, 33, 43] Two studies presented results in a series of CTEPH patients treated surgically and medically[40, 47]; others included only series of surgically treated patients. There was one retrospective study from Austria that compared hemodynamic indices between PTE and non-PTE patients with a 1-year follow-up, but could not be included in the current review due to insufficient data to meet the inclusion criteria.[49] Criteria to consider PTE in CTEPH patients was explicitly stated in a few papers only.[25, 29, 33, 42]

With the exception of one multicenter study from the UK[40] and another study from Germany including two centers,[36] other studies were from single tertiary referral centers.[6, 15, 21, 22, 25, 26, 29, 30, 33, 35, 38, 42–44, 46–48] The largest series included 988 patients who underwent isolated PTE from 1997 to 2007 at UCSD.[6] Seven series had more than 100 patients,[6, 15, 25, 38, 40, 44, 47] five had between 50 and 100 patients (range 50–88),[22, 29, 30, 35, 43] and the other seven series had less than 50 patients each (range 23–41).[21, 26, 33, 36, 42, 46, 48] The surgical technique was clearly described in one study,[6] and some modifications to Jamieson's technique were described in two studies.[21, 36]

Thirty-day mortality was reported by all studies.[6, 15, 21, 22, 25, 26, 29, 30, 33, 35, 36, 38, 40, 42–44, 46–48] Morbidity was reported in 12 series.[6, 22, 25, 26, 29, 30, 36, 40, 44, 46–48] Scattered surgical complications were reported from different series, making direct comparisons between studies impossible. The details of adverse events were presented in four articles.[6, 22, 29, 44] Survival data was reported in eight articles.[15, 22, 25, 29, 38, 40, 43, 47] One study presented separate survival data for proximal and distal types of CTEPH,[47] and another study presented hemodynamic results and mortality rate for each thromoembolic class.[6] All series but three[6, 33, 35] had a minimum follow-up of six months (range 6–130 months). Some studies analyzed risk factors for mortality[22, 29, 35, 47] and hemodynamic outcomes.[15, 35]

Assessment of morbidity and mortality

Thirty-day mortality ranged from 1.3% to 24% (median 8%) and does not appear to be associated with the number of patients operated on at each center (**Table 2**). The reported mortality from UCSD was 4% in a series of 988 patients who underwent isolated PTE from 1997 to 2007.[6] This study reported a mortality rate of less than 4% in the last 200 patients. A multicenter study from UK reported an overall mortality rate of 16%, with 11.5% in the subgroup diagnosed from 2003 and 5.4% for patients who underwent surgery in 2006.[40] Another report from Japan showed a decrement of mortality from 15.3% before 2000 to 4.8% after 2000.[22] Additionally, Bonderman et al.[49] reported a gradual decline in mortality after PTE from 27% (1992–1995), to 15% (1996–1999), to 6% (2000–2004), and to 5% (2004–2006) over years of performing the operation in a single center in Vienna. These data suggest that there is a significant learning curve associated with this procedure.

Residual pulmonary hypertension was reported in 11.4%–35% of patients after PTE, although definition was not similar in all of the studies (**Table 2**).[22, 26, 30, 40] Thirty-five percent of the 162 patients who survived PTE to discharge and had a repeat right heart catheter had persistent pulmonary hypertension (mPAP ≥25 mmHg and PVR ≥240 dynes-sec-cm^{-5}) in one multicenter study.[40] In a series from Austria, persistent pulmonary hypertension occurred in 92% of patients who had comorbidities, compared to just 20%for patients without comorbidities.[49] Reperfusion edema was the single most frequent complication reported in 15.6% of PTE patients of the UCSD series.[6] The incidence of respiratory failure or reperfusion edema ranged from 5.5% to 19.3% (**Table 2**). Bleeding requiring a reoperation was reported in 3.1%–4.5% of patients (**Table 2**).

Assessment of hemodynamic outcomes

Pulmonary artery pressure (PAP) and PVR significantly

Table 1 Screened 39 studies on pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension

Center	First author	Reference	Year	No. of patients	Follow-up	Survival	Morbidity	Mortality	Hospital stay	Functional outcome findings	Prognostic factors	Echocardio graphic	Pulmonary hemodynamics
San Diego, USA	Thistlethwaite	6	2008	988			+	+	+	+		+	+
San Diego, USA	Jamieson	10	2003	500				+	+		+		+
San Diego, USA	Archibald	11	1999	308	3.3Y	+				+			+
San Diego, USA	Bergin	12	2000	39							+		+
San Diego, USA	Thistlethwaite	13	2002	202		+	+	+		+	+	+	+
San Diego, USA	Thistlethwaite	14	2006	956		+	+	+	+	+		+	+
Pavia, Italy	Corsico	15	2008	157	4Y	+	+	+		+	+		+
Pavia, Italy	Petrucci	16	2007	22						+	+		+
Pavia, Italy	Piovella	17	2006	134	3Y	+	+	+		+			+
Pavia, Italy	D'Armini	18	2005	134	3Y	+	+	+		+			+
Pavia, Italy	Zoia	19	2002	38	2Y			+		+			+
Pavia, Italy	D'Armini	20	2000	33	2Y	+	+	+		+	+		+
Bologna, Italy	Mikus	21	2008	30	6m		+	+		+			+
Osaka, Japan	Ogino	22	2006	88	5Y	+	+	+	+	+	+	+	+
Osaka, Japan	Iwase	23	2001	21	4m			+					+
Osaka, Japan	Ando	24	1999	24			+	+		+			+
Suita, Japan	Matsuda	25	2006	102	0–130m	+	+	+		+			+
Chiba, Japan	Ishida	26	2009	23	7–59m		+	+		+			+
Chiba, Japan	Yoshimi	27	2008	40	1-3Y	+		+		+	+		+
Chiba, Japan	Masuda	28	2001	50	10Y	+	+	+					+
Nieuwegein, The Netherlands	Saouti	29	2009	72	4Y	+	+	+		+	+		+
Amsterdam, The Netherlands	Van der Plas	30	2010	54	1Y					+			+
Amsterdam, The Netherlands	Reesink	31	2007	42	1Y					+			+
Amsterdam, The Netherlands	Hardziyenka	32	2007	58	3m			+		+	+	+	+
Mainz, Germany	Menzel	33	2002	24						+		+	+
Mainz, Germany*	Kramm	34	1999	22	72m					+	+		+
Homburg, Germany	Tscholl	35	2001	69				+		+	+		+
Hannover, Germany	Macchiarini	36	2006	30	18m		+	+		+			+
Hannover, Germany	Hagl	37	2003	30	29m		+	+		+			+
Cambridge, UK	Freed	38	2008	229	1Y	+		+		+			+
Cambridge, UK	Suntharalingam	39	2007	105	3m			+		+			+
UK	Condliffe	40	2008	236	3Y	+		+		+			+
UK	Thomson	41	2008	151	1Y		+	+	+	+			+
Belgium	Puis	42	2005	40	673d			+					+
Skejby hospital, Denmark	Mellemkjaer	43	2006	50	3Y	+	+	+		+			+
Ontario, Canada	Rubens	44	2007	106			+	+	+			+	+
Ontario, Canada	Rubens	45	2000	21			+	+				+	+
Bangalore, India	Narayana	46	2010	41	6m		+	+		+			+
Beijing, China	Gan	47	2009	360	8Y	+					+		
Beijing, China	Ji	48	2006	30	37m		+	+		+			+

Table 2 Perioperative morbidity and mortality

Study	Study period6	No. of patients	ICU stay, day	Hospital stay, day	Early mortality	Pericardial condition*	Residual pulmonary hypertension	Neurologic dysfunction	Respiratory failure/reperf	Bleeding requiring re-operation usion edema
6	1997–2007	988	6.7	13.6	4%	0.6%		0.3%	15.6%	3.1%
15	1994–2006	157			11.5%					
21	2004–2007	30			6.6%					
22	1995–2004	88	5	51**	8.0%	8.0%	11.4%	6.8%	8.0%	4.5%
25	1995–2005	102			7.8%	3.9%			7.8%	4.9%
26	2002–2008	23			4.3%		26%		8.7%	
29	1998–2007	72			6.9%	15%		7%	5.5%	
30		54			7.4%		31.5%			
33	1996–1998	24								
35	1995–2000	69	5.5 ± 3.2		10.1%					
36	2004–2005	30	6.6 ± 8.5		3%			10%		
38	1997–2006	229			1.3%					
40	2001–2006	236			16%		35%			
42	1999–2003	40			15%					
43	1994–2004	50			24%					
44	1995–2006	106	10.9 ± 13.6	19 ± 15	9.4%	17.3%		4.8%	18.3%	
46	2008–2009	41	11.2		12%				19.3%	
47	1989–2008	360			4.4%				9.4%	
48	1997–2005	30						10%		

* including pericarditis, pericardial effusion, cardiac tamponade
** included rehabilitation period
ICU: intensive care unit

decreased after PTE in all 17 studies that presented these indices (**Table 3**). Cardiac output, cardiac index, and/or arterial oxygenation improved significantly postoperatively (**Table 3**). In the largest series, Thistlethwaite et al.[6] reported that systolic PAP dropped by 29 ± 20 mmHg and PVR by 567 ± 392 dynes-sec-cm^{-5} after PTE.

Menzel et al.[33] assessed left and right ventricular performance using Doppler-derived indices in a series of 24 patients undergoing PTE. Both right ventricle (RV) and left ventricle (LV) myocardial performance indices improved after the operation. Two-dimensional echocardiography showed a decrease in end-diastolic and end-systolic RV sizes. Furthermore, the abnormally low LV end-diastolic chamber size enlarged after PTE. RV ejection fraction increased significantly after PTE in a series of 106 patients (21 ± 10 vs. 30 ± 8, p <0.0001).[44] There was a mean decrease of 1.1 ± 0.8 M/s in tricuspid regurgitant velocity amongst 988 patients who underwent isolated PTE in the UCSD series.[6]

Assessment of functional outcomes

There was a significant reduction in the percentage of patients who were classified as NYHA or World Health Organization (WHO) class III or IV after PTE. Compared to 60%–100% of patients who were in NYHA/WHO class of III or IV preoperatively, only 0%–21% remained in these functional classes after PTE, with the exception of reporting from one study (**Table 4**).[15] Congruently, significant improvement in the 6-min walk distance (6MWD) after PTE was observed in different series (**Table 4**). Major improvement in 6MWD results were observed during the first year after PTE with minimal change thereafter.[25, 38, 40]

Matsuda et al.[25] measured several respiratory function tests and showed that diffusing capacity of lung for carbon monoxide (D_{LCO}) and percentage of vital capacity worsened one month after the operation, but returned to the baseline values one year after PTE. They observed significant improvements in 6MWD, peak oxygen uptake (V_{O2}), and ventilator response to carbon dioxide production (V_E-V_{CO2}) slope, as early as one month after PTE, which continued to improve during the first year postoperatively but reached a plateau thereafter. PTE resulted in a reduction in the percentage of patients requiring oxygen therapy from 94% preoperatively to 21% five years after the operation in one series,[25] and from 100% to 41% in another series with a mean follow-up of 34 months.[26]

Assessment of survival

Five-year survival ranged from 74% to 88.7% (**Table 4**). Gan et al.[47] reported the longest survival data in a series of 360 PTE patients and 144 non-surgically treated CTEPH patients from China. Separate actuarial survival data was presented for patients with proximal (thrombus found in the main or left or right pulmonary artery and their lobular branches on echocardiography, CT angiography

Table 3 Pulmonary hemodynamic indices before and after the operation

Study reference	Mean/median age	No. of patients	mPAP, mmHg		PVR, dynes-sec-cm-5		CO, L/min		CI, L/min/m²		Pa_{O2}, mmHg	
			Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
6	50 ± 15	988	76 ± 19/29 ± 10*	↓by 29 ± 20/10 ± 10**	863 ± 442	↓by 567 ± 392**	3.9 ± 1.4	↑by 1.5 ± 1.6**				
15	55 ± 16	157	48 ± 13	24 ± 11	1,140 ± 517	327 ± 238	3.3 ± 1.0	5.1 ± 1.3			65.4 ± 10.4	
21	62	30	48 ± 10	26	791 ± 278	280			2.3 ± 0.4			
22	52 ± 13	88			1,024 ± 400	320 ± 215						
25	52 ± 13	102	46 ± 9	21 ± 11	1072 ± 448	386 ± 300			2.0 ± 0.6	2.6 ± 0.6	59.9 ± 9.6	69.0 ± 13.7
26	54 ± 12	23	47 ± 12	25 ± 10	925 ± 342	337 ± 260			2.2 ± 0.5	2.7 ± 0.6	57.7 ± 7.7	64.2 ± 11.6
29	56 ± 14	72	42 ± 11	22 ± 7	572 ± 31							
30	51 ± 14	54	43 ± 14	25 ± 8	769 ± 425	430 ± 175					68.5 ± 11.0	79.6 ± 10.8
33	54 ± 14	24	46 ± 10	25 ± 6	839 ± 332	281 ± 148						
35	55 ± 15	69	50 ± 12	28 ± 7	988 ± 554	322 ± 188	3.6 ± 1.2	5.5 ± 1.3				
36	55 ± 12	30	57 ± 18	25 ± 7	1,110 ± 192	279 ± 98			1.7 ± 0.3	2.9 ± 0.4		
38	55	229	47 ± 14	25 ± 14	800 ± 494	244 ± 253			1.9 ± 0.7	2.5 ± 0.6		
40	58 ± 16	236	48 ± 11	27 ± 10	1028 ± 421	464 ± 215			2.1 ± 0.6	2.5 ± 0.4		
42	57 ± 18	40	50 ± 11	38 ± 10	1246 ± 482	515 ± 294			1.5 ± 0.5	2.6 ± 0.7		
43	59	50	50	37	819	373			1.8	3.1		
44	51 ± 15	106	47 ± 12	28 ± 19	814 ± 429	224 ± 145			2.0 ± 0.7	3.2 ± 0.7		
46	41	41	41 ± 9	24 ± 7	418 ± 96	142 ± 36			2.0 ± 0.2	3.3 ± 0.6		
47	44 ± 13	360	81 ± 17		18.9 ± 6.5***						61.8 ± 6.4	
48	46 ± 11	30	91 ± 22!	48 ± 11!					1.6 ± 0.5	2.6 ± 0.5	56.2 ± 8.6	88.9 ± 6.0

* systolic/diastolic pulmonary pressure presented in the original paper[6)]

** Postoperative change from preoperative value rather than exact figure available in the original paper[6)]

*** unit in wood

!Systolic PAP

mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CO: cardiac output; CI: cardiac index; Pa_{O2}: arterial oxygen pressure; Preop: preoperative figure; Postop: postoperative figure

Table 4 Functional outcomes and survival data

Study reference	No. of patients	NYHA/WHO class III-IV		6MWD, m		Survival				
		Preop	Postop	Preop	Postop	1-year	3-year	5-year	10-year	15-year
6	988	88%	18%							
15	157	97%	85%	95 ± 148	342 ± 276	96%		88%		
21	30	100%		371 ± 109	483 ± 114***					
22	88	97%	1%				90.7%	86.4%		
25	102			358 ± 102	433 ± 105		90.9%	84.0%		
26	23	60%	14%							
29	72	97%		359 ± 124	518 ± 117	93.1%	91.2%	88.7%		
30	54			401 ± 120	506 ± 98					
33	24	79%	12%							
35	69									
36	30	100%	0%							
38	229	88%	13%	269 ± 123	375 ± 104		74.6%	72.7%	69.3%	
40	236	88%	12%	275 ± 125	380 ± 103	98%–99%*	93%–94%*			
42	40									
43	50	100%	21%					74%		
44	106									
46	41	61%								
47	360	100%							71.8–94.6**	29.6–91.0**
48	30	100%	4%							

* First and second presented rates represent survival among patients with and without persistent pulmonary hypertension, respectively
** range represent survival for the distal and proximal types of CTEPH, respectively
*** results from 6-month follow-up
NYHA: New York Heart Association; WHO: World Health Organization; 6MWD: 6-minute walk distance

or MRI) and distal (no thrombus found in echocardiogram) types of the disease. In patients with proximal type CTEPH, the surgical group had a significantly higher 10-year (94.6% vs. 81.4%) and 15-year (91.0% vs. 56.4%) survival when compared with the non-surgical group. However, for the distal type CTEPH, the results were not significantly different with a 10-year survival of 71.8% in the surgical group and 69.8% in the non-surgical group and a 15-year survival of 29.6% in the surgical group and 32.6% in the non-surgical group. Condliffe et al.[40] reported a 1-year and 3-year survival of 99% and 94% for those with and 98% and 93% for those without persistent pulmonary hypertension.

Discussion

The present systematic review included 19 most complete studies from different specialist centers around the world. All studies analyzed were based on observational cohorts. However, it should be acknowledged the difficulties of performing RCTs given the collective evidence on the efficacy of PTE in selected CTEPH patients. The current review revealed homogenous data across different studies on the efficacy of PTE in terms of lowering pulmonary artery pressure and PVR and thus improving cardiac output, arterial oxygenation, and functional status of CTEPH patients. In experienced centers, hospital mortality was less than 5% with 1- and 5-year survival of 95% and 85%, respectively. Persistent pulmonary hypertension after the operation was observed in as high as 35% of patients in a multicenter study. However, even these patients had a reasonable improvement in their functional status (*i.e.* proportion in WHO class I/II increased from 4% to 82% at 3 months and 1- and 3-year survival of those with or without persistent pulmonary hypertension were not significantly different.[40] Medical management in patients with surgically 'accessible' disease resulted in a higher mortality[49] and was associated with a markedly reduced long-term survival.[47] In a multicenter study, nonsurgical patients had a 1-year and 3-year survival of 82% and 70% from the date of diagnosis which were significantly lower than those treated with PTE (1-year survival 88%, 3-year survival 76%, log-rank test $p = 0.023$).[40]

Jamieson's technique is followed in many centers. Insertion of the inferior vena cava filter preoperatively, a median sternotomy approach, cardiopulmonary bypass, deep hypothermia, cold cardioplegia while not in circulatory arrest, right followed by left PTE, institution of circulatory arrest when bronchial back bleeding obscures visualization, limitation of circulatory arrest to 20-minute intervals, and performance of additional procedures during the rewarming period are standard in this technique.[10] Hagl et al.[37] introduced some modification to this technique.

They inserted an aortic balloon catheter into the ascending aorta and directed it to the descending aorta beyond the left subclavian artery to reach the level of the previously CT established takeoff of the bronchial artery (ies) inflated when back-bleeding from these arteries obscures visualization. Cross-clamping Boyden artery on the right side and postponing its endarterectomy to the end to avoid back-bleeding, complete transection of the proximal left pulmonary artery from the pulmonary trunk, left lung hyperinflation, and end-to-end anastomosis after left PTE were other modifications introduced. Early mortality in this series was 10% (3/30).[37] Mikus et al.[21] performed PTE with some modifications aiming to avoid deep hypothermia and subsequent circulatory arrest by using moderate hypothermia at 26°C. They attempted to minimize bronchial back-bleeding by placing a 18 F cannula in the left ventricle through the right upper pulmonary vein which is then connected to a reservoir inside which a negative pressure is created by a vacuum device. The cardiopulmonary bypass pump flow was adjusted to the lowest rate, able to maintain a mixed venous oxygen saturation of 65% or above and endarterectomy of the Boyden branch was selectively done last. Early mortality was 6.6% in this series.[21]

Ogino et al.[22] performed a multivariate analysis and showed that age greater than 60 years was the only significant independent risk factor for hospital mortality (odds ratio, 22.6; 95% CI, 2.1–243.1). Mortality was higher in patients who underwent concomitant PTE and valve surgery (16.7%) or PTE and coronary artery bypass grafting (9.6%) compared to isolated PTE (4.0%) for patients in the UCSD series. More distal disease was shown to be associated with a higher mortality (16.7% in Type 4, 6.3% in Type 3, 4.7% in Type 2, and 3.9% in Type 1 CTEPH).[6] In another study, higher baseline PVR was the only factor associated with increased risk of death.[29] Tscholl et al.[35] demonstrated that right atrial pressure (odds ratio, 1.34 /mmHg, $p = 0.002$) and female gender (odds ratio, 5.54, $p = 0.007$) were independent risk factors for inadequate hemodynamic improvement (PVR ≥500 dynes-sec-cm^{-5}) after PTE.

Distal type of CTEPH (odds ratio, 3.57; 95% CI, 1.19-11.91), no usage of deep hypothermic circulatory arrest (DHCA) (odds ratio, 5.23; 95% CI, 1.78–17.62), PVR >15 wood (odds ratio, 4.42; 95% CI, 1.34–13.51) and systemic SaO_2 <85% (odds ratio, 3.87; 95% CI, 1.19–13.28) were independent risk factors for in-hospital mortality obtained from multivariate analysis in a series from China.[47] Non-surgical therapy (odds ratio, 9.35; 95% CI, 4.12–31.36), distal type of CTEPH (odds ratio, 4.83; 95% CI, 1.49–15.96), and no usage of DHCA (odds ratio, 3.83; 95% CI, 1.32–11.45) were independent risk factors for late death in the same series.[47] Bonderman et al.[49] showed that PTE surgery (hazard ratio, 0.14; 95% CI, 0.05–0.41), comorbidities (hazard ratio, 3.17; 95% CI, 1.70–5.92), and baseline PVR (hazard ratio, 1.02; 95% CI, 1.00–1.04) were predictors of survival in CTEPH patients.

Selection criteria for PTE have been published by the American College of Chest Physicians.[9] In centers like UCSD with the largest reported PTE experience, patients were not deemed illegible for the operation based on the severity of pulmonary hypertension or age.[6] Higher baseline PVR was an independent risk factor for mortality in several studies.[29, 47, 49] Jamieson et al.[10] in an earlier report from UCSD reported a mortality rate of 10.1% (18/179) in patients with preoperative PVR >1000 dynes-sec-cm^{-5} and 1.3% (4/309) in those with baseline PVR <1000 dynes-sec-cm^{-5} ($p < 0.0001$). Dartevelle et al.[50] reported a series of 275 patients underwent PTE at a center in France from 1996 to 2003. The mortality rate was 4% when preoperative PVR was less than 900 dynes-sec-cm^{-5} but increased to 10% in those with PVR between 900 and 1,200 dynes-sec-cm^{-5} and to 20% in those with a higher PVR. The risk of mortality was high only in those with a very high PVR and a low anatomic obstruction, but was low in patients with similarly high PVR and with proximal anatomic obstruction.[50] A high PVR, out of proportion to the angiographic findings, signifies secondary vasculopathy probably at the arteriolar-capillary bed level. This is a pre-terminal condition and PTE may not benefit these patients.[10] Further improvements in pulmonary wave-form analysis, MRI and CT scan could help identify patients with secondary vasculopathic changes and thus exclude them from surgery.[6, 51, 52] Some investigators withheld surgery when PVR exceeded 1,100 dynes-sec-cm^{-5}.[49] However, Puis et al.[42] reported an early mortality rate of 15% after PTE in patients with mean preoperative PVR of 1,246 ± 482 dynes-sec-cm^{-5}. Although a high PVR (*i.e.* >1000 dynes-sec-cm^{-5}) is not an absolute contraindication for PTE, it should be considered as a relative contraindication in the presence of a high suspicion for secondary vasculopathic changes.

More distal types of CTEPH were associated with a higher mortality.[6, 47] Long-term survival of patients with distal type CTEPH was similar in surgical and non-surgical groups in one study.[47] Surgical accessibility was a selection criterion, and it usually indicates the presence of thrombus in the main, lobar, segmental pulmonary arteries,[9] and subsegmental pulmonary arteries with advanced endarterectomy techniques.[6)] Although some investigators suggested re-evaluating the relative merit between the surgical and medical management for distal type CTEPH,[47)] others do not consider any patients as having surgically inaccessible disease, if the embolism is the origin of pulmonary hypertension.[6)] However, the latter group admits that patients with Type 4 disease and evidence of arteriolar-capillary vasculopathy do not benefit from the operation and thus should be excluded.[6)] Only one study identified age as an independent risk factor for mortality.[22)] Older age may be associated with significant comorbidities but has not been recognized as a significant independent risk factor for mortality in a number of studies.[29, 35, 47, 49)]

The American College of Chest Physicians suggested that PTE should be offered to CTEPH patients who have 1) NYHA class III or IV symptoms, 2) preoperative PVR of >300 dynes-sec-cm^{-5}, 3) surgically accessible thrombus (in the main, lobar, or segmental pulmonary arteries) and 4) no significant comorbidities. Based on the collective evidence in this systematic review, PTE can still be considered for CTEPH patients with PVR >1000 dynes-sec-cm^{-5}, provided there is no evidence suggesting arteriolar-capillary vasculopathy. The decision should be individualized considering comorbidities, age, level of surgical expertise available, and the patient's and surgeon's preferences. Lung transplantation can be considered in patients with advanced small vessel disease. Three potential options can be considered in patients who are deemed nonsurgical or high-risk surgical candidates: medical therapy, balloon pulmonary angioplasty, and long transplantation.[9)]

PTE requires a high level of training and expertise to optimize safety and long-term outcome for patients. It is important to realize that the results achieved by surgical specialists may not be replicated in routine clinical practice and concentration of the services may improve the outcome for these patients. High quality prospective observational data collection will be extremely important, as it may offer more accurate estimates of safety and efficacy for the procedure, in addition to information on potential prognostic factors associated with favorable outcomes. More importantly, outcomes must be recorded on an intention-to-treat basis. Many centers report outcomes only in patients who received PTE. Although this may be predictive of outcome, it only applies to selected patients, usually with favorable prognostic features. This is not useful in terms of patient selection. Ideally, establishment of a multi-institutional registry requiring a minimum data set for all patients and recording treatment outcomes regardless of the intervention they received would provide more reliable estimates of outcomes for patients receiving different therapies over a longer term. It is possible that this approach to observational data collection may also provide some information on prognostically similar patients undergoing different management pathways, thereby providing more robust evidence for a comparison between different treatment options. The UCSD has the largest single center experience and demonstrated excellent clinical results. Such a centralized system is important, as it allows a specialist treatment center to maintain expertise and is likely to have a safety advantage. In addition, this may provide efficiencies in terms of staff skills and costs and provide a center for further data collection to address uncertainties regarding the effectiveness, safety and harm of the procedure.

In conclusion, this systematic review evaluated 19 most recent observational studies. To date, no RCTs have been completed. The current literature suggests that PTE for patients with CTEPH is associated with acceptable perioperative morbidity and mortality rates and improved hemodynamic indices and survival when viewed against the prognosis associated with historical controls using medical therapy.

References

1) Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004; **350**: 2257-64.
2) Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993; **103**: 685-92.
3) Riedel M, Stanek V, Widimsky J, et al. Longterm follow-up of patients with pulmonary thromboembolism Late prognosis and evolution of hemodynamic and respiratory data. Chest 1982; **81**: 151-8.
4) Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 2001; **119**: 818-23.
5) Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. Curr Probl Surg 2000; **37**: 165-252.
6) Thistlethwaite PA, Kaneko K, Madani MM, et al. Technique and outcomes of pulmonary endarterectomy surgery. Ann Thorac Cardiovasc Surg 2008; **14**: 274-82.
7) Pulmonary thromboendarterectomy for chronic thrombembolic pulmonary hypertension (Structured abstract) Database of Abstracts of Reviews of Effects

2010; **2**: 2.
8) Dissemination NCfRa Undertaking Systemic Reviews of Research on Effectiveness: CRD's Guidance for Those Carrying Out or Commissioning Reviews—CRD Report 4 2ed York, United Kingdom: NHS Centre for Reviews and Dissemination 2001.
9) Doyle RL, McCrory D, Channick RN, et al. Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; **126** (1 Suppl): 63S-71S.
10) Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003; **76**: 1457-62.
11) Archibald CJ AW, Fedullo PF, Channick RN, et al. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 1999; **160**: 523-8.
12) Bergin CJ, Sirlin C, Deutsch R, et al. Predictors of patient response to pulmonary thromboendarterectomy. AJR Am J Roentgenol 2000; **174**: 509-15.
13) Thistlethwaite PA, Mo M, Madani MM, et al. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. J Thorac Cardiovasc Surg 2002; **124**: 1203-11.
14) Thistlethwaite PA, Madani M, Jamieson SW. Outcomes of pulmonary endarterectomy surgery. Semin Thorac Cardiovasc Surg 2006; **18**: 257-64.
15) Corsico AG, D'Armini AM, Cerveri I, et al. Long-term outcome after pulmonary endarterectomy. Am J Respir Crit Care Med 2008; **178**: 419-24.
16) Petrucci L, Carlisi E, Ricotti S, et al. Pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension: short-term functional assessment in a longitudinal study. Eura Medicophys 2007; **43**: 147-53.
17) Piovella F, D'Armini AM, Barone M, et al. Chronic thromboembolic pulmonary hypertension. Semin Thromb Hemost 2006; **32**: 848-55.
18) D'Armini AM, Zanotti G, Vigano M. Pulmonary endarterectomy: the treatment of choice for chronic thromboembolic pulmonary hypertension. Ital Heart J 2005; **6:** 861-8.
19) Zoia MC, D'Armini AM, Beccaria M, et al. Mid term effects of pulmonary thromboendarterectomy on clinical and cardiopulmonary function status. Thorax 2002; **57**: 608-12.
20) D'Armini AM, Cattadori B, Monterosso C, et al. Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension: hemodynamic characteristics and changes. Eur J Cardiothorac Surg 2000; **18**: 696-701.
21) Mikus PM, Mikus E, Martin-Suarez S, et al. Pulmonary endarterectomy: an alternative to circulatory arrest and deep hypothermia: mid-term results. Eur J Cardiothorac Surg 2008; **34**: 159-63.
22) Ogino H, Ando M, Matsuda H, et al. Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg 2006; **82**: 630-6.
23) Iwase T, Nagaya N, Ando M, et al. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. Heart 2001; **86**: 188-92.
24) Ando M, Okita Y, Tagusari O, et al. Surgical treatment for chronic thromboembolic pulmonary hypertension under profound hypothermia and circulatory arrest in 24 patients. J Card Surg 1999; **14**: 377-85.
25) Matsuda H, Ogino H, Minatoya K, et al. Long-term recovery of exercise ability after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg 2006; **82**: 1338-43.
26) Ishida K, Masuda M, Tanaka H, et al. Mid-term results of surgery for chronic thromboembolic pulmonary hypertension. Interact Cardiovasc Thorac Surg 2009; **9**: 626-9.
27) Yoshimi S, Tanabe N, Masuda M, et al. Survival and quality of life for patients with peripheral type chronic thromboembolic pulmonary hypertension. Circ J 2008; **72**: 958-65.
28) Masuda M, Nakajima N. Our experience of surgical treatment for chronic pulmonary thromboembolism. Ann Thorac Cardiovasc Surg 2001; **7**: 261-5.
29) Saouti N, Morshuis WJ, Heijmen RH, et al. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. Eur J Cardiothorac Surg 2009; **35**: 947-52.
30) van der Plas MN, Reesink HJ, Roos CM, et al. Pulmonary endarterectomy improves dyspnea by the relief of dead space ventilation. Ann Thorac Surg 2010; **89**: 347-52.
31) Reesink HJ, van der Plas MN, Verhey NE, et al. Six-minute walk distance as parameter of functional outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 2007; **133**: 510-6.
32) Hardziyenka M, Reesink HJ, Bouma BJ, et al. A novel echocardiographic predictor of in-hospital mortality and mid-term haemodynamic improvement after pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension. Eur Heart J 2007; **28**: 842-9.
33) Menzel T, Kramm T, Mohr-Kahaly S, et al. Assessment of cardiac performance using Tei indices in patients undergoing pulmonary thromboendarterectomy. Ann Thorac Surg 2002; **73**: 762-6.
34) Kramm T, Mayer E, Dahm M, et al. Long-term results after thromboendarterectomy for chronic pulmonary embolism. Eur J Cardiothorac Surg 1999; **15**: 579-83.
35) Tscholl D, Langer F, Wendler O, et al. Pulmonary thromboendarterectomy--risk factors for early survival and hemodynamic improvement. Eur J Cardiothorac Surg 2001; **19**: 771-6.
36) Macchiarini P, Kamiya H, Hagl C, et al. Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: is deep hypothermia required? Eur J Cardiothorac Surg 2006; **30**: 237-41.

37) Hagl C, Khaladj N, Peters T, et al. Technical advances of pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Eur J Cardiothorac Surg 2003; **23**: 776-81.
38) Freed DH, Thomson BM, Tsui SS, et al. Functional and haemodynamic outcome 1 year after pulmonary thromboendarterectomy. Eur J Cardiothorac Surg 2008; **34**: 525-9.
39) Suntharalingam J, Goldsmith K, Toshner M, et al. Role of NT-proBNP and 6MWD in chronic thromboembolic pulmonary hypertension. Respir Med 2007; **101**: 2254-62.
40) Condliffe R, Kiely DG, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008; **177**: 1122-7.
41) Thomson B, Tsui SS, Dunning J, et al. Pulmonary endarterectomy is possible and effective without the use of complete circulatory arrest--the UK experience in over 150 patients. Eur J Cardiothorac Surg 2008; **33**: 157-63.
42) Puis L, Vandezande E, Vercaemst L, et al. Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Perfusion 2005; **20**: 101-8.
43) Mellemkjaer S, Ilkjaer LB, Klaaborg KE, et al. Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension Ten years experience in Denmark. Scand Cardiovasc J 2006; **40**: 49-53.
44) Rubens FD, Bourke M, Hynes M, et al. Surgery for chronic thromboembolic pulmonary hypertension—inclusive experience from a national referral center. Ann Thorac Surg 2007; **83**: 1075-81.
45) Rubens FD, Sabloff M, Wells PS, et al. Use of recombinant-hirudin in pulmonary thromboendarterectomy. Ann Thorac Surg 2000; **69**: 1942-3.
46) Narayana Iyengar RM, Hegde D, Chattuparambil B, et al. Postoperative management of pulmonary endarterectomy and outcome. Ann Card Anaesth 2010; **13**: 22-7.
47) Gan HL, Zhang JQ, Bo P, et al. The actuarial survival analysis of the surgical and non-surgical therapy regimen for chronic thromboembolic pulmonary hypertension. J Thromb Thrombolysis 2010; **29**: 25-31.
48) Ji B, Liu J, Wu Y, et al. Perfusion techniques for pulmonary thromboendarterectomy under deep hypothermia circulatory arrest: a case series. J Extra Corpor Technol 2006; **38**: 302-6.
49) Bonderman D, Skoro-Sajer N, Jakowitsch J, et al. Predictors of outcome in chronic thromboembolic pulmonary hypertension. Circulation 2007; **115**: 2153-8.
50) Dartevelle P, Fadel E, Mussot S, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2004; **23**: 637-48.
51) Kim NH, Fesler P, Channick RN, et al. Preoperative partitioning of pulmonary vascular resistance correlates with early outcome after thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Circulation 2004; **109**: 18-22.
52) Kreitner KF, Kunz RP, Ley S, et al. Chronic thromboembolic pulmonary hypertension - assessment by magnetic resonance imaging. Eur Radiol 2007; **17**: 11-21.