Residual pulmonary hypertension after pulmonary endarterectomy: A meta-analysis

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ABSTRACT

Objective: Chronic thromboembolic pulmonary hypertension is surgically treated through pulmonary endarterectomy. Although pulmonary endarterectomy is the treatment of choice for chronic thromboembolic pulmonary hypertension in terms of both functional outcomes and survival, many patients experience persistent pulmonary hypertension after pulmonary endarterectomy. The study objective was to calculate the pooled estimates of outcomes after pulmonary endarterectomy, including persistent pulmonary hypertension.

Methods: Meta-analyses were conducted on published studies reporting residual/persistent/recurrent pulmonary hypertension in 4868 patients with chronic thromboembolic pulmonary hypertension after pulmonary endarterectomy. The rate of persistent pulmonary hypertension and change in mean pulmonary artery pressure, pulmonary vascular resistance, and 6-minute walk distance after pulmonary endarterectomy were outcomes of interest.

Results: Twenty-five percent of patients with chronic thromboembolic pulmonary hypertension were diagnosed with persistent pulmonary hypertension after pulmonary endarterectomy. Pulmonary endarterectomy reduced mean pulmonary artery pressure and pulmonary vascular resistance by approximately 21 mm Hg (standardized mean difference, 1.75; 95% confidence interval, -1.62 to 1.88; $P < .00001$) and 561 dyn.s/cm⁵ (standardized mean difference, 1.64; 95% confidence interval, -1.58 to 1.70; $P < .00001$), respectively. Conversely, 6-minute walk distance increased by 96 m (standardized mean difference, -0.83; 95% confidence interval, -0.91 to -0.76; $P < .00001$) after pulmonary endarterectomy.

Conclusions: Pulmonary endarterectomy is the gold standard treatment for chronic thromboembolic pulmonary hypertension and provides immediate correction of hemodynamic parameters in most patients. However, in up to one quarter of operable cases, pulmonary hypertension persists after surgery. In those patients with persistent pulmonary hypertension, continued medical management with newer agents may be required to improve pulmonary hemodynamics and, therefore, patient outcomes. (J Thorac Cardiovasc Surg 2018;156:1275-87)

Forest plot of mPAP in patients with CTEPH after PEA.

Central Message

PEA is a common treatment for chronic PH and improved hemodynamic parameters and physical status. Medical management is required if PH persists.

Perspective

PEA is the current gold standard for treating CTEPH. Although PEA improves hemodynamic outcomes and physical condition, continued medical management is required in patients with persistent PH after PEA. Our study can help clinicians make a better evidence-based informed decision on treating patients with CTEPH.

See Editorial Commentary page 1288.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a pulmonary vascular disease resulting from the chronic obstruction of major pulmonary arteries. The disease typically results from unresolved thrombi that if

left untreated undergo fibrotic transformation, leading to mechanical obstruction of the pulmonary arteries.¹ Microvessel remodeling comparable to the arteriopathy seen in pulmonary arterial hypertension (PAH) is also believed to

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Abbreviations and Acronyms

CTEPH	= chronic thromboembolic pulmonary hypertension
df	= degrees of freedom
mPAP	= mean pulmonary artery pressure
PEA	= pulmonary endarterectomy
PH	= pulmonary hypertension
PVR	= pulmonary vascular resistance
RPH	= residual pulmonary hypertension
6MWD	= 6-minute walk distance
WHO	= World Health Organization

▶ Scanning this QR code will take you to a procedural video.

significantly contribute to CTEPH pathogenesis.² Pulmonary embolism (PE) is a common preceding condition to CTEPH, and, as such, CTEPH is typically thought of as a rare complication of PE. According to an international prospective registry report, approximately 80% of patients with CTEPH had a history of PE.³ In addition, recurrent venous thromboembolism and idiopathic PE were both found to be associated with an increased risk of CTEPH.⁴ Although the true prevalence and incidence of CTEPH are unknown, it is believed to occur in up to 5 individuals per million population per year or in up to 9.1% of patients within the first 2 years after an acute PE event.^{5,6}

The typical diagnostic criteria for CTEPH are mean pulmonary artery pressure (mPAP) of 25 mm Hg or more, pulmonary capillary wedge pressure of 15 mm Hg or less after 3 or more months of effective anticoagulation treatment in conjunction with chronic occlusive emboli or thrombi in the pulmonary arteries, and at least 1 segmental perfusion defect on ventilation/perfusion lung scans.^{7,8} One major clinical challenge is differentiating between CTEPH and PAH. However, CTEPH has several distinctive features compared with PAH, including nonhomogeneous distribution of the disease, an episodic disease course, and more frequent occurrence of hemoptysis. A definitive diagnosis can be established by conventional or computed tomography (CT), pulmonary angiogram, magnetic resonance angiography (MRA), and right heart catheterization.³

Occlusion of the pulmonary arteries can result in an increase in pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and subsequent right heart failure. Therefore, CTEPH is progressive and often fatal, with a median survival in severe untreated CTEPH reported

to be as low as 10% to 20% after 2 to 3 years.^{9,10} Early diagnosis is critical for the proper management of this disorder. Furthermore, CTEPH is potentially curable with pulmonary endarterectomy (PEA) surgery. This surgical procedure removes the impeding thromboembolic matter and can result in significant symptomatic and prognostic improvements in eligible patients.¹¹ The surgery is complex and requires a technically skilled and experienced surgeon. In addition, several important factors must be considered before a patient is deemed eligible for PEA, including comorbidities, advanced age, the accessibility of thromboembolic material, and the level of PVR.⁵ Patients with less than 50% in PVR post-PEA and with PVR greater than 1200 dyn.s/cm⁵ are ineligible for surgery.¹²⁻¹⁴ Expert centers tend to have excellent success rates, with periprocedural mortality rates of less than 2% to 5%.¹⁵

Although PEA is the gold standard treatment for CTEPH, the disease process is complex, and several patients present with persistent or residual pulmonary hypertension (RPH) after PEA.¹⁶⁻²⁰ This can be explained by the 2-compartment model proposed by Moser and Braunwald in 1973.²¹ In this model, patients with operable CTEPH may develop a distal, secondary, small-vessel arteriopathy in the nonobstructed vascular beds.²⁰ However, few centers have comprehensively evaluated these patients, and the estimates of the number of patients with RPH after PEA vary greatly from 5% to 35%.¹⁷⁻²⁰ Therefore, the current meta-analyses aimed to investigate the occurrence of RPH after PEA and compare changes in mPAP, PVR, and 6-minute walk distance (6MWD) after PEA.

MATERIALS AND METHODS**Data Sources and Search Terms**

The search strategy was designed to identify full-length publications reporting RPH in patients with CTEPH. PubMed was searched using Medical Sub-Heading terms using the term “pulmonary hypertension/surgery,” where “pulmonary hypertension” was defined as “increased vascular resistance in the pulmonary circulation, usually secondary to heart diseases or lung diseases.” Embase and Medline databases were searched through Embase using the Emtree terms “endarterectomy,” “pulmonary hypertension,” and “residual pulmonary hypertension.” Filters were applied to select only English language publications reported on human subjects to reduce publication bias because of potential misinterpretation of research findings. Reference lists of the reviews and research articles were manually screened to identify further articles. Inclusion criteria included (1) studies reporting residual/persistent/recurrent PH in patients with CTEPH after PEA and (2) studies reporting change in mean pulmonary artery pressure (mPAP), PVR, and 6MWD after PEA. Abstracts, conference proceedings, posters, case series/reports, reviews, editorials, and non-English publications were excluded, because these gray literature usually omit the reporting of many relevant outcomes and therefore might contribute to reduced generalizability of research findings because of incomplete reporting of essential information for the analyses conducted in this study.

Study Selection

Any duplicate articles were removed. The titles and abstracts of the remaining articles were reviewed by 2 independent investigators (Figure 1) (Kappa index: 0.932, 95% confidence interval [CI], 0.889-0.961;

FIGURE 1. PRISMA flow diagram of the steps followed in the selection of studies per the inclusion criteria (Kappa index: 0.932; 95% CI, 0.889-0.961; $P < .001$).

$P < .001$) who were responsible for determining whether the articles were eligible for inclusion. To address any inconsistencies, the investigators compared lists before they reviewed the full text of the studies identified as eligible. When the final list of articles was complete, a third investigator resolved final discrepancies.

Data Extraction and Meta-Analysis

A standardized custom Excel sheet (Microsoft Corp, Redmond, Wash) was used to extract all the relevant and specific data on study characteristics, patient characteristics, diagnostic methods, surgical interventions, and outcomes. These data were extracted independently by 2 investigators (Figure 1) (Kappa index: 0.932; 95% CI, 0.889-0.961; $P < .001$) and compared to resolve discrepancies. To calculate the rate of RPH after PEA and estimate the changes in mPAP, PVR, and 6MWD after PEA, 4 meta-analysis models were constructed: Model 1, estimation of the pooled event rate of residual PH after PEA; Model 2, post-PEA change in mPAP; Model 3, post-PEA change in PVR; and Model 4, post-PEA change in 6MWD.

Publication bias was qualitatively assessed via funnel plots and quantitatively evaluated by the Egger test. A qualitative estimate of statistical heterogeneity between studies was assessed using the Cochrane Q test. For the chi-square test, a P value of less than .05 was considered statistically significant. In the presence of significant heterogeneity, the I^2 statistic was used to quantify the level of heterogeneity. The I^2 value was interpreted on the basis of Hedges criteria, where 25%, 50%, and 75% correspond to low, medium, and high heterogeneity, respectively.²²

Statistical heterogeneity, Forest plots, and publication bias were conducted with Comprehensive Meta-analysis software (Biostat, Englewood, NJ). To accommodate between-study heterogeneity, the DerSimonian and Laird random-effects model was used for all meta-analysis models.²³ Effect size was represented by the standardized mean difference (SMD),²² which indirectly reflects the difference between the interventions, in all included studies, because these studies did not use the same outcome measures.

RESULTS

Study Selection and Characteristics of the Trials

The databases and manual search retrieved 1358 English language journal articles. The titles and abstracts of these

articles were screened to eliminate 1319 studies that were duplicates or abstracts, or studied different objectives. In the next phase, 39 full texts of articles were obtained and screened. Fourteen of these articles provided incomplete data and, not to impair the generalizability of research findings, were discarded from the articles assessed in this meta-analysis. The remaining 25 articles were included for meta-analysis.^{3,15,18-20,24-43} The flow chart of the studies evaluated is represented in Figure 1.

The characteristics of the included studies and their participants, along with the methods for diagnosing CTPEH, are summarized in Table 1. Six studies were conducted in Japan, 3 each in the United Kingdom, Canada, Italy, and Austria, 2 each in the Netherlands and China, and 1 each in the United States and Germany. One study had subjects from all over Europe. Twelve studies analyzed the patient records retrospectively, 3 studies did not report the study design clearly, and 10 studies recruited patients for a prospective analysis. A total of 4686 patients' data were available from these studies, with an average age range of 38 to 64 years with 22% to 85% male. Baseline and postsurgery measurements of the patients, along with follow-up times, are presented in Table 2.

Residual Pulmonary Hypertension After Pulmonary Endarterectomy

Eighteen studies reported RPH after PEA in patients with CTPEH. The heterogeneity between these studies was statistically significant (Cochran Q 300.4 [degrees of freedom [df] = 17]; I^2 94.3; $P < .00001$). A random effects model showed that 25% (95% CI, 0.18-0.34) of the patients experienced RPH after PEA (Figure 2).

The funnel plot showed a likelihood of publication bias, because more studies were plotted on the left side. Duvall and Tweedie's trim and fill imputed no possibly missing studies. Egger's test ($B_0 = -3.42$; 95% CI, -6.49 to -0.35 ; $t = 2.36$; $df = 16$; $P_{1-tailed} = .02$) showed that the publication bias was statistically significant.

Mean Pulmonary Artery Pressure Before and After Pulmonary Endarterectomy

Twenty-three studies reported changes in mPAP after PEA in patients with CTPEH. The heterogeneity between these studies was not statistically significant (chi-square 12.8 [df 11]; I^2 14%; $P = .31$). A random effects model showed that mPAP reduced by an average of 21.42 mm Hg after PEA (SMD, 1.75; 95% CI, 1.62-1.88). This reduction was statistically significant ($P < .00001$) (Figure 3).

The funnel plot showed a likelihood of publication bias, because all the studies were plotted on the right side of the plot. Duvall and Tweedie's trim and fill imputed no possibly missing studies. Egger's test of the intercept ($B_0 -0.74$; 95% CI, -3.85 to 2.37 ; $t = 0.49$; $df = 11$; $P_{1-tailed} .31$)

TABLE 1. Study and patient characteristics of the included articles

Study	Origin	Design	Subjects	Follow-up	Diagnostic methods	Criteria for RPH	Age (y)	Male (%)
Yin and colleagues, ²⁴ 1992	Chinese (with German data)	RTS	32	>12 mo	ABG, CXR, EKG	>30 mm Hg	38	46
D'Armini and colleagues, ²⁵ 2000	Italy	RTS	33	2 y	V/Q scan, CT, CTPA	NR	48	55
Nagaya and colleagues, ²⁶ 2002	Japan	NR	34	NR	ABG	NR	49	38
Zoia and colleagues, ²⁷ 2002	Italy	PRS	38	2 y	RHC, PFT, ABG	NR	51	50
Ogino and colleagues, ²⁸ 2006	Japan	RTS	88	5 y	V/Q scan, RHC, CTPA	NR	52	40
Bonderman and colleagues, ¹⁸ 2007	Austria	RTS	105	12 mo	CXR, EKG, PFT, ABG, RHC, V/Q scan, CT, CTPA	>25 mm Hg	52	47
Condliffe and colleagues, ¹⁹ 2008	United Kingdom	RTS	236	3 y	CTPA, RHC, EKG	NR	NR	NR
Ishida and colleagues, ²⁹ 2009	Japan	PRS	23	7-59 mo	RHC	NR	54	57
Song and colleagues, [*] 2010	China	RTS	15	≥2 y	V/Q scan, CTPA, CT, RHC	NR	42	80
van der Plas and colleagues, ³¹ 2010	Netherlands	RTS	54	1 y	CTPA, RHC	>25 mm Hg	51	39
Mayer and colleagues, ³ 2011	Europe	PRS	386		RHC, V/Q scan, CT, CTPA	>25 mm Hg	60	54
Freed and colleagues, ²⁰ 2011	United Kingdom	PRS	314		V/Q scan, CTPA	≥30 mm Hg	55	54
van der Plas and colleagues, ³³ 2011	Austria	NR	96	>12 mo	CTPA, RHC	>25 mm Hg	NR	NR
de Perrot and colleagues, ³² 2011	Canada	RTS	58	25 mo	V/Q scan, EKG, CTPA, RHC	>25 mm Hg	56	43
Madani and colleagues, ¹⁵ 2012	United States	RTS	1500	60 mo	CXR, EKG, V/Q scan, RHC, CT, CTPA	>25 mm Hg	51	
Li and colleagues, ³⁴ 2013	China	PRS	26	24 mo	EKG, RHC	>25 mm Hg	45	85
D'Armini and colleagues, ³⁵ 2014	Italy	RTS	331	49 mo	V/Q scan, CT, CTPA	>25 mm Hg	61	39
de Perrot and colleagues, ³⁷ 2015	Canada	PRS	120	6 mo	V/Q scan, EKG, CTPA, RHC	>25 mm Hg	54	53
Shimura and colleagues, ³⁸ 2015	Japan	RTS	9	NR	CT, V/Q scan, CTPA, ABG, PFT, EKG	(1) mPAP ≥25 mm Hg and (2) PVR ≥3.75 Wood units	54	22
Cannon and colleagues, ³⁹ 2016	United Kingdom	PRS	880	4.3 y	V/Q scan, CTPA	≥25 mm Hg	57	53
Jujo and colleagues, ³⁶ 2016	Japan	PRS	17	1-2 mo	RHC, V/Q scan, CTPA	NR	64	29

(Continued)

TABLE 1. Continued

Study	Origin	Design	Subjects	Follow-up	Diagnostic methods	Criteria for RPH	Age (y)	Male (%)
Richter and colleagues, ⁴¹ 2016	Germany	PRS	37	1 y	CXR, EKG, PFT, ABG, RHC, V/Q scan, CT, CTPA	>25 mm Hg and PVR >240 dyn.s/cm ⁵	61	54
Surie, ⁴³ 2016	Netherlands	PRS	55	NR	PFT, EKG, V/Q scan, CTPA	>25 mm Hg	52	35
Nierlich and Ristl, ⁴⁰ 2016	Austria	RTS	161	NR	V/Q scan, CT, RHC, CTPA, US, PFT	NR	NR	61
Leung and colleagues, ⁴² 2016	Canada	PRS	38	29	V/Q scan, CT, RHC, CTPA, US, PFT	>25 mm Hg	54	45

RPH, Residual pulmonary hypertension; RTS, retrospective; ABG, arterial blood gas; CXR, chest x-ray; EKG, electrocardiogram; V/Q, ventilation/perfusion; CT, computed tomography; CTPA, computed tomography pulmonary angiography; NR, not reported; PRS, prospective; RHC, right heart catheterization; PFT, pulmonary function testing; US, ultrasound. *Song G, Liu Y, Su P-x, Zhai Z-g, Yang Y-h, Wang C. Pulmonary andarterectomy for chronic thromboembolic pulmonary hypertension: preliminary exploration in China. *Chin Med J*. 2010;123:979-83.

showed that the publication bias was not statistically significant (Figure 3).

Pulmonary Vascular Resistance Before and After Pulmonary Endarterectomy

Nineteen studies reported change in PVR after PEA in patients with CTPEH. The heterogeneity between these studies was not statistically significant (chi-square 3.53 [df 9]; I² 0%; *P* = .94). A random effects model showed that PVR decreased by an average of 560.3 dyn.s/cm⁵ after PEA (SMD, 1.64; 95% CI, 1.58-1.70). This reduction was statistically significant (*P* < .00001) (Figure 4).

The funnel plot showed a likelihood of publication bias, because all the studies were plotted on the right side of the plot. Duvall and Tweedie’s trim and fill imputed 8 possibly missing studies. Egger’s test of the intercept (B0 4.19; 95% CI, −0.00 to 8.39; *t* = 2.11; *df* = 9; *P*_{1-tailed} .33) showed that the publication bias was not statistically significant (Figure 4).

Six-Minute Walk Distance Before and After Pulmonary Endarterectomy

Eleven studies reported improvements in 6MWD after PEA in patients with CTPEH. The heterogeneity between these studies was not statistically insignificant (chi-square 6.25 [df 6]; I² 4%; *P* = .40). A random-effects model showed that 6MWD increased by an average of 95.7 m after PEA (SMD = −0.83; 95% CI, −0.91 to −0.76). This decrease was statistically significant (Figure 5).

The funnel plot showed a likelihood of publication bias, because all the studies were plotted on the right side of the plot. Duvall and Tweedie’s trim and fill imputed 2 possibly missing studies. Egger’s test of the intercept (B0 0.43; 95% CI, −0.52 to 1.38; *t* = 1.03; *df* = 6; *P*_{1-tailed} .17) showed that the publication bias was not statistically significant (Figure 5).

New York Heart Association/World Health Organization III to IV Clinical Score Before and After Pulmonary Endarterectomy

Six studies reported a significant reduction in the number of patients with New York Heart Association/World Health Organization (WHO) III to IV clinical scores after PEA in patients with CTPEH. The heterogeneity between these studies was statistically significant (chi-square 40.0 [df 5]; I² = 88%; *P* < .00001). The DerSimonian and Laird random effects model indicated that the incidence of patients associated with New York Heart Association/WHO III-IV decreased by an average of 41.2 after PEA (95% CI, 9.2-184.6). This reduction was statistically significant (*P* < .00001) (Figure 6). The asymmetry in the funnel plot in Figure 6 (bottom) indicated a likelihood of publication bias, because most of the studies were plotted on the left side of the plot.

DISCUSSION

This study was conducted to estimate the incidence of RPH after PEA in patients with CTPEH. The methodology was limited to English language publications to reduce publication bias, perhaps at the cost of limiting the generalizability of the findings, despite the meta-analysis including 4686 patients with CTPEH. PEA aims to increase the PVR, improve the ventilation/perfusion, and alleviate right ventricular compromise. Although a curative operation for many, 16.7% to 35% patients experience PH after PEA.^{3,20,44} This persistence is mainly due to the failure to remove distal or chronic thromboemboli or to secondary vascular pathologies. Our analysis provides a similar estimate, because 25% of patients had RPH after PEA.¹⁹ Condliffe and colleagues¹⁹ investigated predictors of outcomes in CTPEH, reporting that approximately 92% of patients with associated medical conditions experienced RPH, whereas only 20% of patients who did not have associated medical conditions experienced RPH. In addition, RPH was

TABLE 2. Outcome characteristics of the included studies

Study	mPAP, mm Hg		PVR, dyn.s/cm ⁵		NYHA/WHO class III-IV (%)		6MWD, m		Time from surgery (mo)	RPH, (%)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Yin and colleagues, ²⁴ 1992	53 ± 12	17 ± 6	1045 ± 430	194 ± 75	100	43	NR	NR	NR	3
D'Armini and colleagues, ²⁵ 2000	50 ± 10	16 ± 3	1056 ± 0	182 ± 15	NR	NR	NR	NR	24	NR
Nagaya and colleagues, ²⁶ 2002	46 ± 2	19 ± 1	NR	NR	NR	NR	NR	NR	1	NR
Zoia and colleagues, ²⁷ 2002	50 ± 12	26 ± 10	1067 ± 0	335 ± 196	NR	NR	NR	NR	3, 12, 24	NR
Ogino and colleagues, ²⁸ 2006	NR	NR	1024 ± 10	320 ± 215	97	1	NR	NR	36, 60	11
Bonderman and colleagues, ¹⁸ 2007*	49 ± 13	25 ± 12	859 ± NR	269 ± 222	18	NR	NR	NR	12, 24	NR
Condliffe and colleagues, ¹⁹ 2008	48 ± 11	27 ± 10	1028 ± 120	464 ± 215	88	12	275 ± 275	380 ± 380	12, 36	35
Ishida and colleagues, ²⁹ 2009	47 ± 12	25 ± 10	925 ± 142	337 ± 260	60	14	NR	NR	7, 59	26
Song and colleagues, [†] 2010	49 ± 16	27 ± 11	939 ± 03	317 ± 153	100	0	308 ± 308	446 ± 446	12, 24	NR
van der Plas and colleagues, ³¹ 2010	43 ± 14	25 ± 8	769 ± NR	430 ± 175	NR	NR	401 ± 401	506 ± 506	12	32
Mayer and colleagues, ³ 2011	NR	NR	750 ± 5	247 ± 10	81	NR	366 ± 366	458 ± 458	12	17
Freed and colleagues, ²⁰ 2011	48 ± 12	26 ± 10	805 ± 0	301 ± 232		NR	269 ± 269	367 ± 367	3	31
van der Plas and colleagues, ³³ 2011‡	44 ± 11	25 ± 7	NR ± NR	NR ± NR	NR	NR	NR	NR	24, 36, 48, 60	NR
de Perrot and colleagues, ³² 2011	45 ± 10	25 ± 5	880 ± 408	320 ± 70	80	40	376 ± 376	480 ± 480	6, 23	93
Madani and colleagues, ¹⁵ 2012	46 ± 12	27 ± 9	790 ± N/A	274 ± 176	90	NR	NR	NR	60, 120	NR
Li and colleagues, ³⁴ 2013	55 ± 16	32 ± 15	944 ± 484	334 ± 78	78	48	NR	NR	3, 12, 24	5
D'Armini and colleagues, ³⁵ 2014	45 ± 11	23 ± 7	901 ± 00	273 ± 154	87	0	283 ± 283	395 ± 395	3, 12	5
de Perrot and colleagues, ³⁷ 2015	44 ± 13	25 ± 12	841 ± 4	NR	91		365 ± 365	430 ± 430	20, 60	38
Shimura and colleagues, ³⁸ 2015	50 ± 5	34 ± 3	NR	NR	100	22	NR	NR	6, 12	100
Cannon and colleagues, ³⁹ 2016	47 ± 11	27 ± 10	830 ± NR3	317 ± 239	NR	NR	260 ± 260	353 ± 353	3, 6, 12	NR
Jujo and colleagues, ³⁶ 2016	45 ± 11	26 ± 10	725 ± 2	319 ± 170	NR	NR	NR	NR	12	NR
Richter and colleagues, ⁴¹ 2016	43 ± 9	29 ± 8	606 ± 220	328 ± 241	73	22	405 ± 405	453 ± 453	12	57
Surie, ⁴³ 2016	42 ± 14	24 ± 7	644 ± 4	NR	87		397 ± 397	497 ± 497	3, 12	NR
Nierlich and Ristl, ⁴⁰ 2016	50 ± 13	32 ± 10	794 ± 9	303 ± 171	NR	NR	NR	NR	2, 6	NR

(Continued)

TABLE 2. Continued

Study	mPAP, mm Hg		PVR, dyn.s/cm ⁵		NYHA/WHO class III-IV (%)		6MWD, m		Time from surgery (mo)	RPH, (%)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Leung and colleagues, ⁴² 2016	50 ± 14	32 ± 7	1209 ± 132	500 (11 patients)	97	13	NR	NR	6, 24, 36, 48	8

mPAP, Mean pulmonary artery pressure; PVR, pulmonary vascular resistance; NYHA, New York Heart Association; WHO, World Health Organization; 6MWD, 6-minute walk distance; NR, not reported. *mPAP and PVR values were calculated by merging subgroup data. †Song G, Liu Y, Su P-x, Zhai Z-g, Yang Y-h, Wang C. Pulmonary andarterectomy for chronic thromboembolic pulmonary hypertension: preliminary exploration in China. *Chin Med J*. 2010;123:979-83. ‡Postsurgery mPAP and PVR values are for 86 patients.

reported in 35% of patients after PEA in a British study.⁴⁵ The increased morbidity and mortality associated with RPH were historically a significant problem; however, the overall perioperative mortality rate decreased from 27% between 1992 and 1995 to 15% between 1996 and 1999 and has been at 5% since 2004.¹⁸

Successful PEA surgery can result in near complete normalization of pulmonary hemodynamics, with immediate reductions seen in both mPAP and PVR and increases in 6MWD. The changes in mPAP, PVR, and 6MWD were quantified using a pooled estimate meta-analysis, mPAP and PVR of particular note because they are good predictors of postoperative hospital mortality in patients with CTEPH.⁴⁶

mPAP was reduced after PEA by approximately 21 mm Hg (SMD = 1.75; 95% CI, -1.62 to 1.88; *P* < .00001).

Large-scale studies have shown that a postoperative mPAP of greater than 46 mm Hg increases the probability of in-hospital mortality. Thus, an mPAP of 46 to 50 mm Hg has been considered a cutoff between high- and low-risk patients.^{46,47} Historically, the 3-year survival for patients with an mPAP of greater than 30 mm Hg was as low as 10%.¹⁰ However, the use of disease-modifying treatments such as bosentan has greatly increased post-PEA survival, with a 1-year survival of 96% achieved with bosentan in patients with persistent PH even with an mPAP of 51 mm Hg.⁴⁸

The average pooled estimate of reduction in PVR after PEA was 561 dyn.s/cm⁵ (SMD = 1.64; 95% CI, 1.58-1.70), from 883 dyn.s/cm⁵ presurgery to 309 dyn.s/cm⁵ postsurgery. A preoperative PVR greater than 1000 to 1150 dyn.s/cm⁵ increased hospital postoperative mortality,

FIGURE 2. Forest plot of residual PH after PEA in patients with CTPEH. Pooled event rates are estimated with a random effects model, which shows that 25% (95% CI, 0.18-0.34) of the patients experienced RPH after PEA.

FIGURE 3. Forest (top) and funnel (bottom) plot of standardized mean difference in mPAP in patients with CTEPH pre- and post-PEA. Standardized mean differences are estimated with a random effects model, which shows that mPAP decreased by an average of 21.42 mm Hg after PEA ($SMD = 1.75$; 95% CI, 1.62-1.88; $P < .00001$). The funnel plot shows a likelihood of publication bias, as all the studies are plotted on the right side of the plot, although this was not statistically significant by Egger's test of the intercept ($B_0 -0.74$; 95% CI, -3.85 to 2.37 ; $t = 0.49$; $df = 11$; $P_{1-tailed} 0.31$). mPAP, Mean pulmonary artery pressure; SD, standard deviation; CI, confidence interval; SE, standard error; SMD, standardized mean difference.

with a PVR of 645 dyn.s/cm^5 considered a preoperative cut-off between high- and low-risk patients.⁴⁶ Intervention with PEA typically will demonstrate a reduction in PVR of

approximately 400 to 500 dyn.s/cm^5 . Although preoperative high PVR is an important risk factor, postoperative PVR is more strongly linked to in-hospital mortality.

FIGURE 4. Forest (top) and funnel (bottom) plot of standardized mean difference of PVR in patients with CTEPH pre- and post-PEA. Raw differences in means are estimated with a random effects model, which shows that PVR reduced by an average of 560.3 dyn.s/cm⁵ after PEA (SMD = 1.64; 95% CI, 1.58-1.70; *P* < .00001). The funnel plot shows a likelihood of publication bias, as all the studies are plotted on the right side of the plot, although this was not statistically significant by Egger's test of the intercept (*B*₀ 4.19; 95% CI, -0.00 to 8.39; *t* = 2.11; *df* = 9; *P*_{1-tailed} 0.33). PVR, Pulmonary vascular resistance; SD, standard deviation; CI, confidence interval; SE, standard error; SMD, standardized mean difference.

Mortality rates were reported as 4% for patients with PVR less than 900 dyn.s/cm⁵, 10% for patients with a PVR between 900 and 1200 dyn.s/cm⁵, and 20% for patients with a PVR greater than 1200 dyn.s/cm⁵.¹² Our meta-analysis suggests that PEA drastically reduces the PVR. The reduction in PEA may increase the survival of patients.

The 6MWD is a useful test to assess functional outcome after PEA and is reported to correlate with the

hemodynamic severity of the disease.³³ The pooled average increase in 6MWD was 96 m, from 337 m presurgery to 433 m after surgery.

Until recently, there were no approved treatments for inoperable CTEPH or for patients with persistent PH. Instead, PAH-specific pharmacologic agents were used off-label. These drugs demonstrated variable clinical efficacy and included inhaled iloprost, epoprostenol,

FIGURE 5. Forest (top) and funnel (bottom) plot of mean difference in 6MWD in patients with CTEPH in pre- and post-PEA. Raw difference in means is estimated with a random effects model, which shows that 6MWD increased by an average of 95.7 m after PEA (SMD = -0.83; 95% CI, -0.91 to -0.76; $P < .00001$). The funnel plot shows a likelihood of publication bias, as all the studies are plotted on the right side of the plot, although this was not statistically significant by Egger's test of the intercept (B0 0.43; 95% CI, -0.52 to 1.38; $t = 1.03$; $df = 6$; P1-tailed 0.17). 6MWD, 6-minute walk distance; SD, standard deviation; CI, confidence interval; SE, standard error; SMD, standardized mean difference.

treprostinil, sildenafil, and bosentan.^{44,48-50} Recently, riociguat, a soluble guanylate cyclase stimulator, was approved by the US Food and Drug Administration for the treatment of RPH and inoperable CTEPH. Riociguat improves a range of hemodynamic parameters in both inoperable patients and patients post-PEA surgery with persistent PH, as supported by findings from recent clinical trials.⁵¹⁻⁵³ Riociguat provides a similar benefit to PEA in inoperable patients with CTEPH by improving PVR but not 6MWD.^{33,49,50} Although a promising therapy, riociguat does not remove the obstructive lesions, and its clinical benefit has not been ascertained in asymptomatic patients with RPH.⁵¹ As such, balloon pulmonary angioplasty represents an additional treatment option that uses

telescoping catheters, wires, and balloons to mechanically disturb chronic clot material. The efficacy of riociguat versus balloon pulmonary angioplasty as a therapy for non-operable CTEPH has not been reported; however, a clinical trial investigating precisely this is currently under way ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT02634203) NCT02634203). Although balloon pulmonary angioplasty seems to improve pulmonary hemodynamics in inoperable, symptomatic patients with CTEPH, further randomized controlled trials are needed to ascertain its clinical benefit.⁵³ There is currently no guideline on the optimal medical management of patients with CTEPH undergoing PEA to treat persistent PH.⁵² If completed, the results from this study will aid in the correct management of patients with persistent PH and inoperable CTEPH.

FIGURE 6. Forest (top) and funnel (bottom) plot of New York Heart Association/WHO III-IV clinical scores in patients with CTEPH pre- and post-PEA. Pooled event rates are estimated with a random effects model, which shows that the incidence of patients associated with New York Heart Association/WHO III-IV decreased by an average of 41.2 after PEA (95% CI, 9.2-184.6; $P < .00001$). The asymmetry in the funnel plot indicates a likelihood of publication bias, as most of the studies were plotted on the left side of the plot. SE, Standard error.

Recent findings demonstrate the effectiveness of novel pharmacologic treatments, including macitentan^{54,55} and subcutaneous treprostinil,^{56,57} in inoperable patients with CTEPH and patients with RPH in addition to PEA. Of note, a large randomized placebo-controlled clinical trial (“MERIT-1”⁵⁴) performed from 2014 to 2016 demonstrated that the use of macitentan led to a significant improvement in PVR in patients with inoperable CTEPH ($n = 80$).

Lang and colleagues⁵⁶ analyzed clinical outcomes from long-term subcutaneous therapy using treprostinil and found that it improved exercise capacity, hemodynamics, and symptoms in patients with inoperable CTEPH ($n = 23$), as well as contributing to increasing their long-term survival.⁵⁷ Skoro-Sajer and colleagues⁵⁷ confirmed these findings in patients with severe inoperable CTEPH

($n = 56$). Short-term venoarterial extracorporeal membrane oxygenation has been suggested as an additional strategy for the treatment of hemorrhage during PEA.⁵⁸⁻⁶⁰

One of the largest studies included in this article provided a detailed analysis of long-term follow-up in 198 patients with CTEPH who survived PEA.¹⁹ Data from this study provided a clear picture of outcomes after PEA. Of the 81% who survived PEA, 35% were diagnosed with persistent PH. These patients had a significantly higher mPAP (50.5 ± 9.4 mm Hg vs 46.5 ± 10.4 mm Hg) and PVR (1144 ± 475 dyn.s/cm⁵ vs 934 ± 344 dyn.s/cm⁵) scores compared with those showing recovery. The 1-year (98% vs 99%) and 3-year (94% vs 93%) survivals were comparable between recovered and persistent PH groups. Patients with persistent PH also showed improvements in terms of the proportion of WHO class I or II subjects, which

VIDEO 1. Pulmonary endarterectomy. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31258-3/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31258-3/fulltext).

increased from 4% at baseline to 82% at 3 months postsurgery. However, the proportion of patients receiving disease-modifying agents increased from 8% at 3 months to 18% at 2 years after surgery.

Study Limitations

The main limitation of this study lies in having assessed only findings from nonrandomized trials because of the lack of relevant data reported in the literature. Other limitations, as discussed in the **Materials and Methods** section, included the exclusion of gray literature and non-English studies, which might have led to discarding potentially relevant data and that, therefore, might have reduced the heterogeneity in the results. Moreover, the lack of a standardized definition of residual PH further contributes to impair the generalizability of the results. However, the results obtained in this study could be useful to help treat patients with residual PH if assessed similarly to the centers from the studies included in this meta-analysis.

Our analysis shows that a quarter of patients with CTEPH experience persistent PH after PEA. However, PEA provides drastic improvements in hemodynamic and exercise function (**Video 1**). The literature shows that, despite the high persistence of PH, PEA remains the best available option in patients with CTEPH.

CONCLUSIONS

Outcomes for patients with CTEPH have greatly improved over the last 20 years. PEA is still the treatment of choice in terms of both survival and functional improvements; however, patients with persistent PH after PEA are now also reported to have a good prognosis. In the current meta-analysis, RPH was reported in 25% of patients with CTEPH post-PEA surgery. In addition, PEA was seen to significantly reduce hemodynamic parameters and improve

the functional outcome as measured by an increase in 6MWD. Accurate diagnosis and assessment by experienced surgical staff are vital for the management of this disorder. For patients ineligible for surgery or with significant post-PEA RPH, riociguat and balloon pulmonary angioplasty represent viable therapeutic alternatives for symptomatic patients with RPH.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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