Přílohy disertační práce

Články in extenso

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Residual pulmonary hypertension after pulmonary endarterectomy: A meta-analysis

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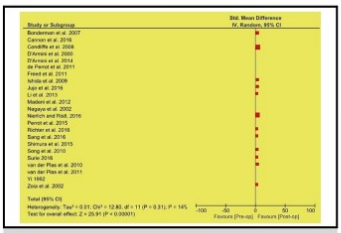
ABSTRACT

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/cm^5 (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

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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/cm^5 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 CTPEH. 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 CTPEH 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;

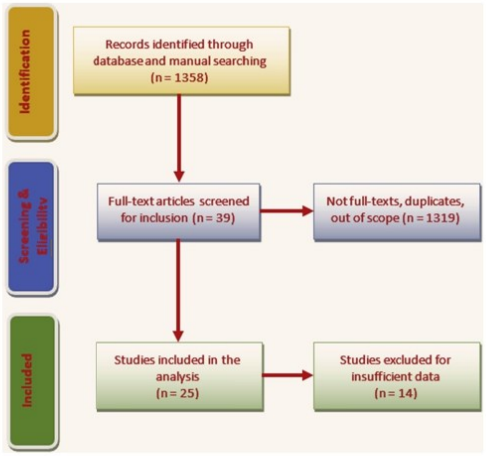


FIGURE 1. PRISMA flow diagram of the steps followed in the selection of studies per the inclusion criteria (Kappa index: 0.932; 95% CI, 0.889-0.961; $P < .001$).

$P < .001$) 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 (B0 = −3.42; 95% CI, −6.49 to −0.35; t = 2.36; df = 16; $P_{1\text{-tailed}} = .02$) 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 (B0 −0.74; 95% CI, −3.85 to 2.37; t = 0.49; df = 11; $P_{1\text{-tailed}}$ .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, 2015[37]	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]; I^2 0%; $P = .94$). A random effects model showed that PVR decreased by an average of 560.3 dyn.s/cm^5 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; $P_{1\text{-tailed}}$ .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]; I^2 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; $P_{1\text{-tailed}}$ .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]; $I^2 = 88\%$; $P < .00001$). 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 CTEPH. 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 CTEPH. 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 colleagues[19] investigated predictors of outcomes in CTEPH, 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	RPH, (%)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	(mo)	
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/cm^5 (SMD = 1.64; 95% CI, 1.58-1.70), from 883 dyn.s/cm^5 presurgery to 309 dyn.s/cm^5 postsurgery. A preoperative PVR greater than 1000 to 1150 dyn.s/cm^5 increased hospital postoperative mortality,

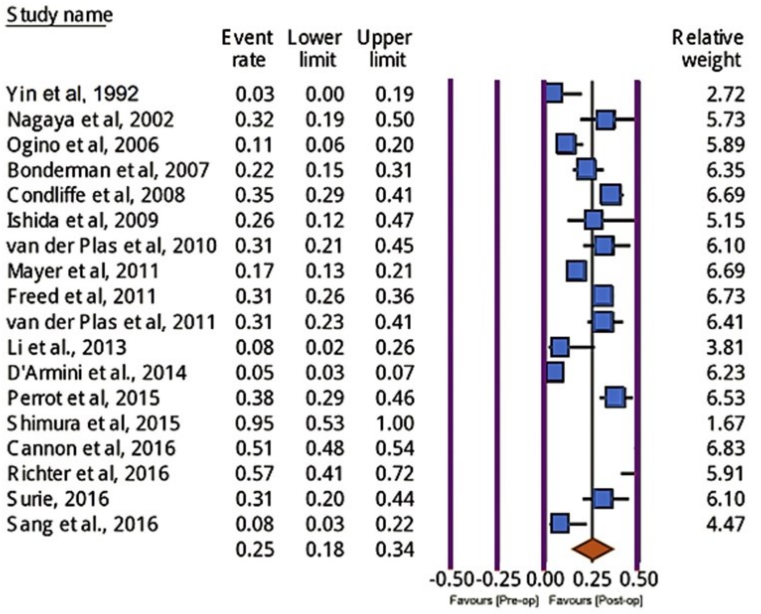
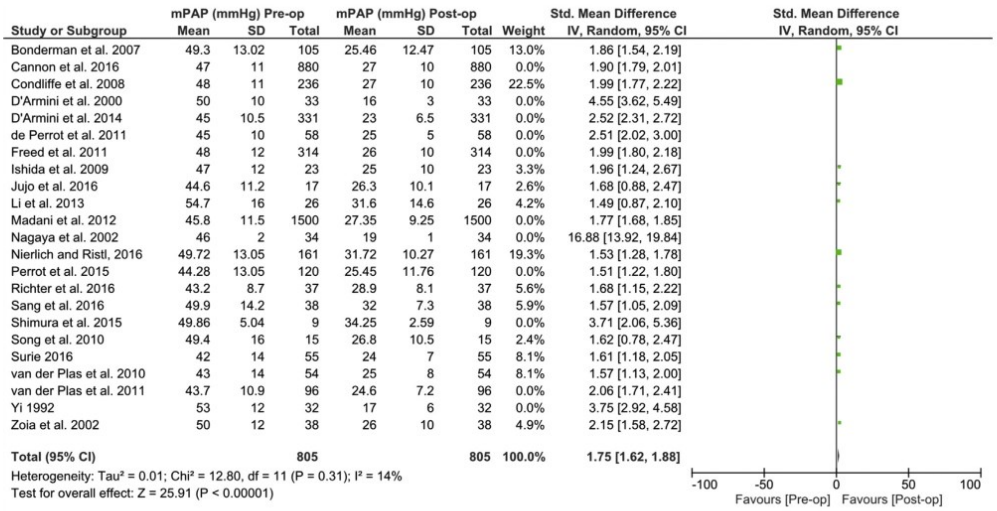


FIGURE 2. Forest plot of residual PH after PEA in patients with CTPEH. Pooled event rates are estimated with a random effects model, which shows that 25% (95% CI, 0.18-0.34) of the patients experienced RPH after PEA.



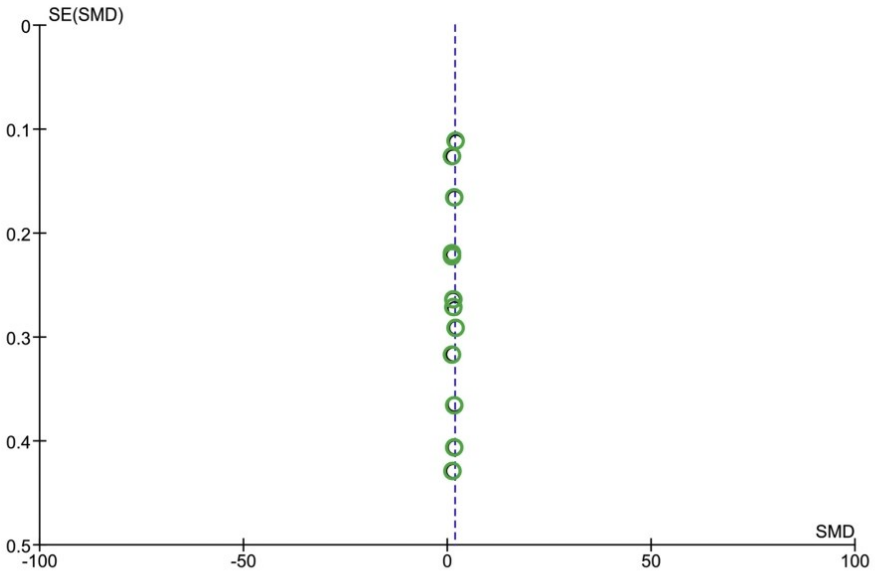


FIGURE 3. Forest (*top*) and funnel (*bottom*) plot of standardized mean difference in mPAP in patients with CTEPH pre- and post-PEA. Standardized mean differences are estimated with a random effects model, which shows that mPAP decreased by an average of 21.42 mm Hg after PEA (SMD = 1.75; 95% CI, 1.62-1.88; $P < .00001$). 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; $P_{1\text{-tailed}}$ 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.

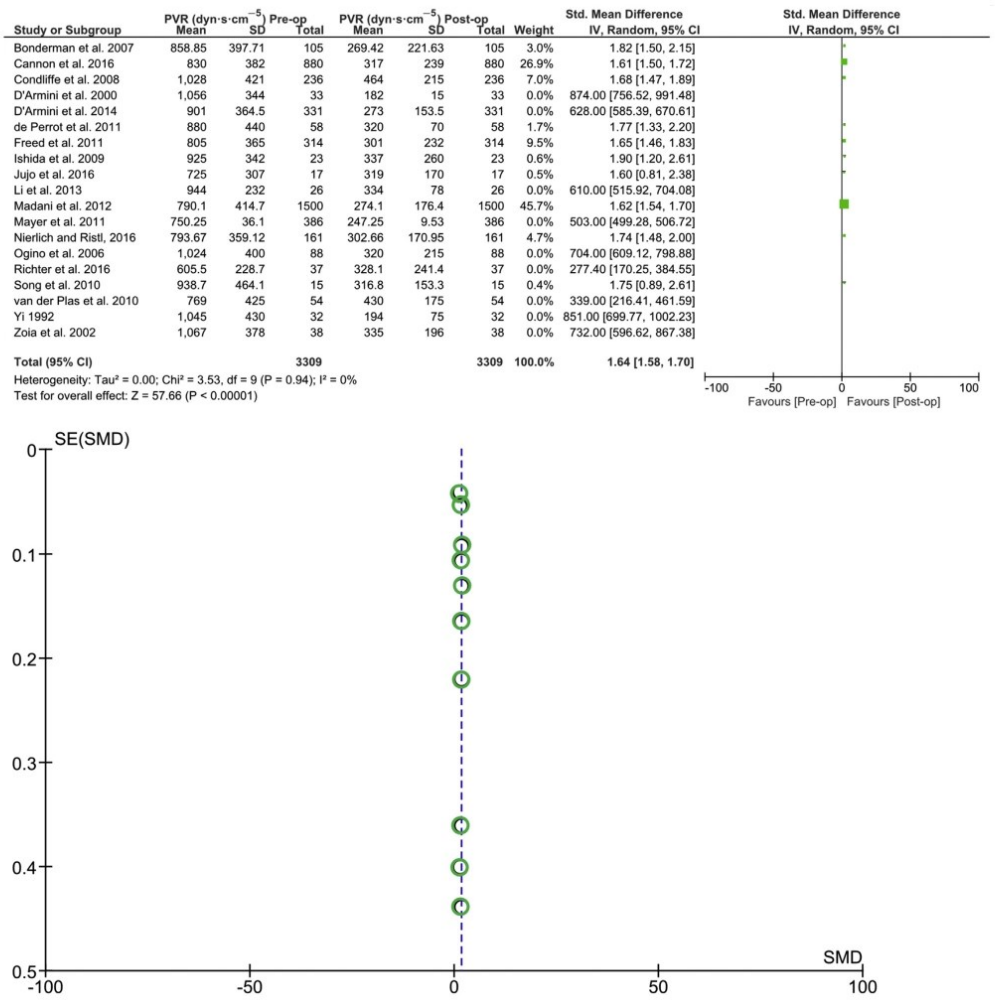


FIGURE 4. Forest (*top*) and funnel (*bottom*) plot of standardized mean difference of PVR in patients with CTEPH pre- and post-PEA. Raw differences in means are estimated with a random effects model, which shows that PVR reduced by an average of 560.3 dyn.s/cm^5 after PEA (SMD = 1.64; 95% CI, 1.58-1.70; $P < .00001$). 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; $P_{1\text{-tailed}}$ 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/cm^5, 10% for patients with a PVR between 900 and 1200 dyn.s/cm^5, and 20% for patients with a PVR greater than 1200 dyn.s/cm^5.[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,

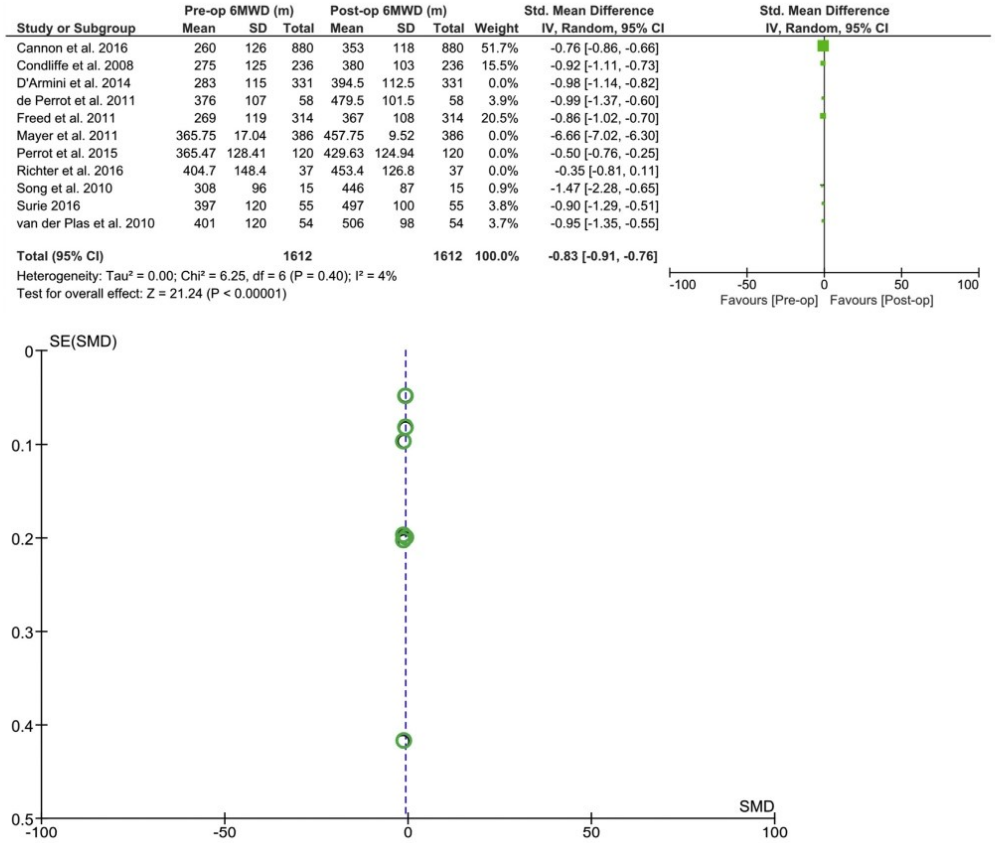


FIGURE 5. Forest (*top*) and funnel (*bottom*) plot of mean difference in 6MWD in patients with CTEPH in pre- and post-PEA. Raw difference in means is estimated with a random effects model, which shows that 6MWD increased by an average of 95.7 m after PEA (SMD = −0.83; 95% CI, −0.91 to −0.76; $P < .00001$). 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 nonoperable CTEPH has not been reported; however, a clinical trial investigating precisely this is currently under way (Clinicaltrial.gov 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.

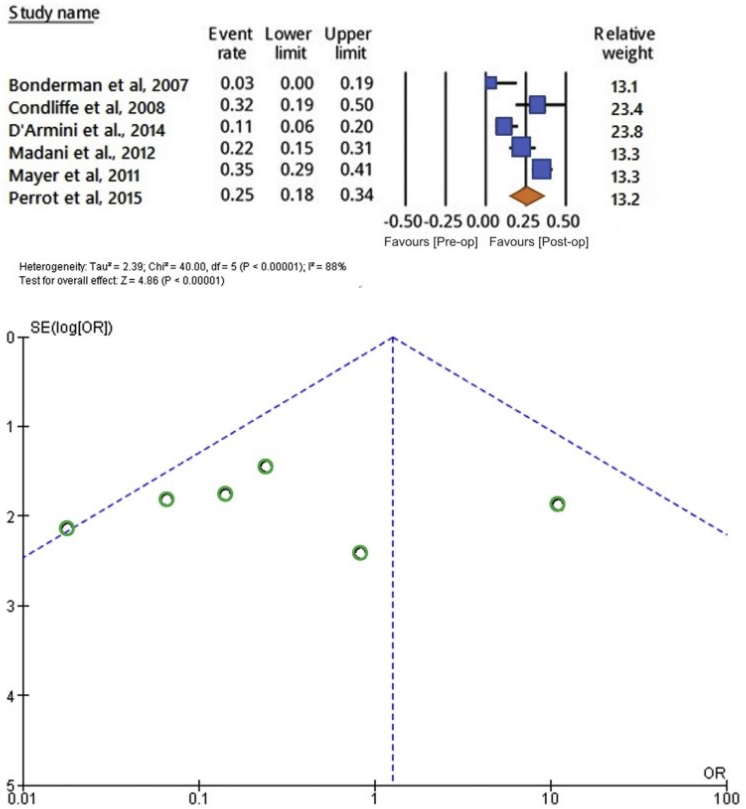
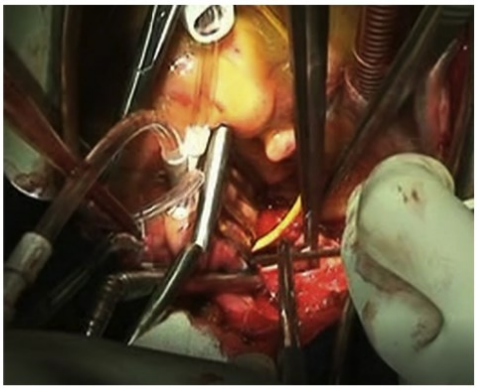


FIGURE 6. Forest (*top*) and funnel (*bottom*) plot of New York Heart Association/WHO III-IV clinical scores in patients with CTEPH pre- and post-PEA. Pooled event rates are estimated with a random effects model, which shows that the incidence of patients associated with New York Heart Association/WHO 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 colleagues[56] 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 colleagues[57] 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/cm^5 vs 934 ± 344 dyn.s/cm^5) 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.

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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Key Words: chronic thromboembolic pulmonary hypertension, mean pulmonary artery pressure, pulmonary endarterectomy, pulmonary thromboendarterectomy, pulmonary vascular resistance

Chirurgická léčba chronické tromboembolické plicní hypertenze

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Souhrn
Chronická tromboembolická plicní hypertenze (CTEPH) je onemocnění charakterizované vzestupem středního tlaku v plicním řečišti ≥ 25 mm Hg na podkladě intraluminálně organizovaných trombů, stenóz a uzávěrů jednotlivých větví plicnice a periferní cévní remodelace. Jedná se o chronickou komplikaci akutní plicní embolie. Důsledkem obstrukce plicnice je vzestup plicní cévní rezistence (Pulmonary Vascular Resistance – PVR) vedoucí k zatížení pravé komory srdeční a k pravostrannému srdečnímu selhání. Metodou volby v léčbě pacientů s CTEPH je chirurgická endarterektomie plicnice (PEA), výkon prováděný v hluboké hypotermii, v cirkulační zástavě. Jediným centrem specializujícím se na chirurgickou léčbu pacientů s CTEPH v ČR je Kardiocentrum VFN a 1. LF UK v Praze, na němž bylo v letech 2004–2017 operováno 314 pacientů (včetně 50 pacientů ze Slovenské republiky, kde tato léčba dostupná není). Pacienti s periferním typem postižení, u nichž nález není operabilní, a zároveň pacienti po PEA s reziduální plicní hypertenzí, jsou indikováni ke specifické vazodilatační terapii. V indikovaných případech se v léčbě pacientů uplatňuje také balonková angioplastika a transplantace plic.

Klíčová slova: balonková plicní angioplastika – chirurgická technika – chronická tromboembolická plicní hypertenze – možnosti léčby – plicní endarterektomie – riociguat

Surgical treatment of chronic thromboembolic pulmonary hypertension

Summary
Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease characterized by a mean pulmonary artery pressure that exceeds 25 mm Hg and is caused by intraluminal thrombi organisation, stenosis and occlusions of pulmonary artery and its branches and peripheral vascular remodelation. It is a chronic complication of acute pulmonary embolism. The obstruction of pulmonary artery branches increases pulmonary vascular resistance (PVR) and this leads to the right ventricular overload and right-sided heart failure. The treatment of choice is surgical pulmonary endarterectomy (PEA), a procedure that is performed in deep hypothermic cardiac arrest. The only center that specializes into the surgical treatment of patients with CTEPH in the Czech Republic is the Complex Cardiovascular Centre at the General Teaching Hospital in Prague. Between years 2004–2017 there were 314 patients operated (including 50 patients from Slovakia, where this treatment is not available). Patients with peripheral type of CTEPH, who are not indicated for operation and also patients with residual pulmonary hypertension after PEA can be indicated for specific vasodilatation therapy. In indicated cases the treatment may involve the balloon angioplasty or lung transplantation.

Key words: balloon angioplasty – chronic thromboembolic pulmonary hypertension – pulmonary endarterectomy – riociguat – surgical technique – treatment options

Úvod

Chronická tromboembolická plicní hypertenze (Chronic Thromboembolic Pulmonary Hypertension – CTEPH) je onemocnění charakterizované vzestupem středního tlaku v plicním řečišti ≥ 25 mm Hg a je třetí nejčastější příčinou chronické plicní hypertenze. Jedná se o chronickou komplikaci akutní plicní embolie u pacientů, u kterých trombolytická anebo antikoagulační terapie nevede ke kompletnímu rozpuštění trombotických hmot a dochází k jejich intraluminální organizaci s následným vznikem stenóz a uzávěrů jednotlivých větví plicnice. Zároveň dochází k periferní cévní remodelaci a oba tyto mechanizmy vedou k vzestupu plicní vaskulární rezistence. Metodou volby v léčbě pacientů s CTEPH je chirurgická endarterektomie plicnice (Pulmonary EndArterectomy – PEA). Důležitým kritériem

pro indikaci k PEA je lokalizace obstrukce plicního řečiště. Zatímco proximálně lokalizované stenózy a uzávěry jsou chirurgické léčbě přístupné a pomocí PEA tedy dobře řešitelné, periferně lokalizované léze (distálně od subsegmentárních větví) chirurgicky přístupné nejsou a pacienti s tímto nálezem jsou proto považováni za technicky inoperabilní.

Patofyziologie, epidemiologie

Patofyziologie CTEPH souvisí s akutní plicní embolií, tento vztah nicméně zatím nebyl zcela objasněn. Absence rozpuštění embolizovaných trombotických hmot, ke kterému jinak dochází u většiny pacientů po plicní embolii, není totiž jediným vysvětlením vzniku onemocnění. Anamnéza plicní embolie není přítomna u více než 20 % nemocných s CTEPH [1]. Teorie opakovaných embolizací do plic rovněž nejsou spolehlivým vysvětlením vzniku CTEPH, jelikož za recidivy plicní embolie jsou často mylně považovány epizody dušnosti, což je většinou v rozporu se stacionárním nálezem na plicní perfuzní scintigrafii.

Je tedy zřejmé, že v patofyziologii vzniku CTEPH se musí kromě embolizačního mechanizmu uplatňovat i mechanizmus neembolizační, a to je rozvoj remodelačních změn v oblasti zejména malých plicních cév. Akutní plicní embolie zde figuruje zřejmě jako iniciátor kaskády dalších dějů, u kterých se uplatňují lokální zánět, sekundární in situ trombóza, či genetická dispozice. U pacientů s CTEPH je známý vyšší výskyt prokoagulačních stavů (např. vyšší hladina antifosfolipidových protilátek, přítomnost lupus antikoagulans).

Incidence CTEPH není přesně známa, a to z důvodu již zmíněného nejasného vztahu s akutní plicní embolií. Uvádí se, že CTEPH se rozvíjí u 2–4 % pacientů po prodělané embolizaci do plic [2].

CTEPH je 3. nejčastější příčinou chronické plicní hypertenze a v klasifikaci plicní hypertenze se řadí do 4. skupiny (4.1), do níž jsou zahrnuty i další příčiny obstrukce plicních cév (4.2.1 angiosarkom, 4.2.2 jiné intravaskulární tumory, 4.2.3 arteriitidy, 4.2.4 vrozené stenózy plicnice, 4.2.5 parazitární onemocnění – hydatidóza) [1,3].

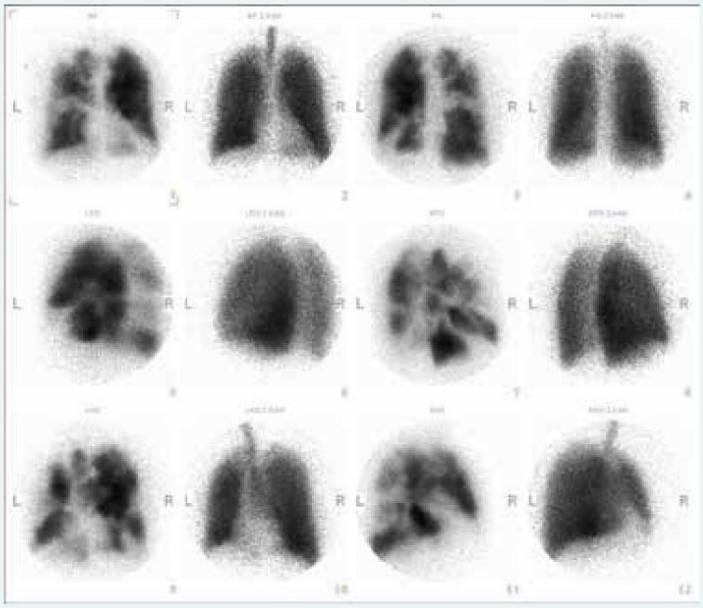
Klinický obraz

Příznaky CTEPH se u pacientů po prodělané akutní plicní embolii typicky začínají projevovat po bezpříznakovém období, které může trvat měsíce až roky. U pacientů bez anamnézy plicní embolie jsou to právě tyto příznaky, které by měly vést k podezření na onemocnění a k dovyšetření. Symptomatologie pacientů s CTEPH je identická jako u jiných forem chronické plicní hypertenze a zahrnuje zejména progredující námahovou dušnost, únavu, presynkopy až synkopy, sníženou fyzickou výkonnost. Mohou se objevit i bolesti na hrudi. V pokročilém stadiu onemocnění dochází k otokům dolních končetin, zvýšené náplni krčních žil a k cyanóze.

Diagnostika

Základní vyšetřovací metodou vedoucí k podezření na CTEPH je echokardiografické vyšetření, které prokáže známky plicní hypertenze. Echokardiografie by měla být provedena u všech pacientů na konci hospitalizace pro akutní plicní embolii. Při průkazu plicní hypertenze

Obr. 1. Ventilační a perfuzní scintigrafie plic u nemocného s chronickou tromboembolickou plicní hypertenzí zobrazující četné defekty v přítomnosti radiofarmaka na perfuzních scanech oboustranně



je nutno nemocného opět vyšetřit během 3–6 měsíců. Pokud nález plicní hypertenze není vysvětlitelný srdečním nebo plicním onemocněním, měl by pacient podstoupit ventilačně-perfuzní scintigrafii plic (obr. 1), jejíž negativní nález diagnózu CTEPH prakticky vylučuje [4]. V opačném případě by měl být pacient referován do centra zabývajícího se diagnostikou a léčbou plicní hypertenze k dovyšetření. Podrobná vyšetření se provádějí po nejméně 3měsíční antikoagulační léčbě. Aktivní vyhledávání CTEPH u asymptomatických pacientů po plicní embolii není obecně doporučeno.

V rámci definitivního vyšetření ve specializovaném centru pacient podstupuje konvenční angiografii plicních tepen (obr. 2), která je nezbytná pro posouzení lokalizace obstrukcí a stenóz plicního řečiště, a tedy i pro posouzení vhodnosti pacienta k chirurgickému řešení. Angiografie se provádí současně s pravostrannou srdeční katetrizací k posouzení hemodynamických parametrů. Nezbytná je rovněž angiografie koronárních tepen. Konvenční angiografii doplňuje CT angiografie (obr. 3), která umožňuje víceprojekční zobrazení plicního řečiště včetně rekonstrukcí. Pacienti dále podstupují podrobné echokardiografické vyšetření k posouzení ev. přidružených kardiochirurgicky řešitelných komorbidit, bodypletyzmografii, USG krčních tepen, vyšetření infekčních fokusů a podrobné interní vyšetření včetně genetického vyšetření prokoagulačních stavů.

Indikační kritéria

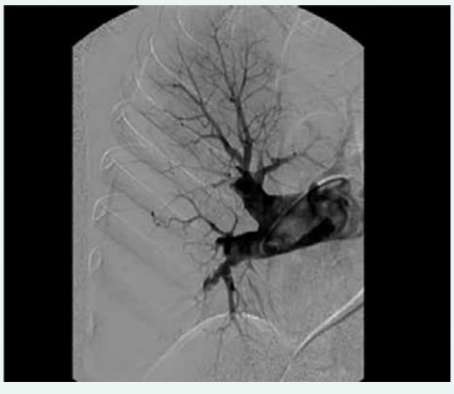
U pacientů s diagnostikovanou CTEPH je indikována dlouhodobá antikoagulační terapie. Pokud v průběhu 3 měsíců od nasazení antikoagulace dojde ke zlepšení hemodynamických parametrů a funkční třídy, je u oligosymptomatických a asymptomatických pacientů bez plicní hypertenze nebo s hraničními tlaky v plicnici indikován většinou konzervativní postup a pravidelná echokardiografická a klinická monitorace. V opačném případě prochází pacient indikačním seminářem, na kterém je na základě výsledků vyšetření hodnocena vhodnost pacienta ke kauzální terapii – k chirurgickému řešení [5]. Zásadní je lokalizace obstrukce plicního cévního řečiště a tedy chirurgická dostupnost lézí, dále odhad přítomnosti periferních remodelačních změn, které i po úspěšně provedené endarterektomii plicních tepen mohou vést k významné reziduální plicní hypertenzi. Důležitý je rovněž biologický stav pacienta a přítomnost případných komorbidit.

Technicky operabilních je asi 60 % pacientů [6]. Hlavní příčiny inoperability jsou chirurgická nedostupnost trombotických obstrukcí, komorbidity a odmítnutí chirurgického výkonu ze strany pacienta [7].

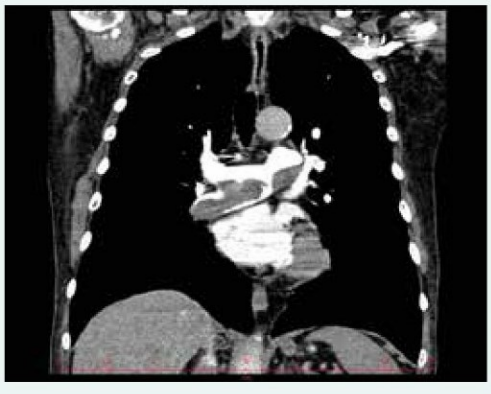
Chirurgická technika

Operační výkon je prováděn v celkové anestezii, u pacientů je kromě standardní peroperační monitorace sledován také tlak v plicnici pomocí Swanova-Ganzova katétru a saturace ve frontálních lalocích mozku pomocí NIRS (Near Infra Red Spectroscopy). Operačním přístupem je střední sternotomie. Pacient je napojen na mimotělní oběh (MO): arteriální kanyla do ascendentní aorty, 2 samostatné žilní kanyly do horní a dolní duté žíly, venty do kmene plicnice a cestou pravé horní plicní žíly do levé síně. Po spuštění MO je pacient uveden do hluboké hypotermie, referenční je teplota v močovém měchýři, v němž dosahuje 16–18 °C. Teplota je dále monitorována i z čidel v rektu a v jícnu. Doba chlazení je individuální, závisí na hmotnosti a tělesné konstituci pacienta, většinou se pohybuje kolem 45–60 min. Dodržuje se protokol chlazení pacienta s 10stupňovým teplotním gradientem. Na chlazení se kromě mimotělního oběhu podílí i nižší teplota na operačním sále, termopodložka s cirkulující tekutinou uložená pod pacientem a selektivně je chlazena také hlava a srdce pomocí speciálního obložení s cirkulující tekutinou. Po zchlazení pacienta je na ascendentní aortu naložena příčná svorka a do kořene aorty pomocí Cooleyho jehly aplikována studená krystaloidní

Obr. 2. Angiogram zobrazující anatomicky operabilní nález u nemocného s chronickou tromboembolickou plicní hypertenzí



Obr. 3. CT angiogram zobrazující objemný obtékaný trombus v pravé větvi plicnice u nemocného s chronickou tromboembolickou plicní hypertenzí



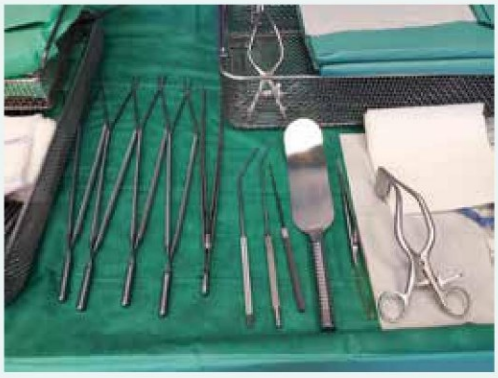
kardioplegie (Custodiol) [8]. Začíná se endarterektomií vpravo. Pomocí speciálního rozvěráčku (obr. 4) je odtažena horní dutá žíla od aorty a je vypreparována viditelná část pravé větve plicnice k hraně perikardu (obr. 5). Je provedena podélná tomie tepny a zahájena endarterektomie ve viditelném rozsahu.

Podstatou výkonu je skutečná endarterektomie, nikoliv embolektomie. V průběhu endarterektomie je totiž odstraněna intimální vrstva tepny s organizovanými trombotickými hmotami, na rozdíl od embolektomie, u které se zpravidla odstraňují čerstvé tromby. Provedení kompletní endarterektomie (obr. 5) ve správné vrstvě je základní podmínkou pro úspěšnost operace [9,10]. Vzhledem k bohatému zastoupení kolaterál v bronchiálním oběhu plic je operační pole znepřehledňováno neustálým zaplavováním krví, z toho důvodu je nevyhnutelná celková cirkulační zástava. Bezpečnost tohoto postupu je zachována díky hluboké hypotermii, která snižuje metabolické nároky tkání, včetně mozku, a době trvání zástavy. Ta by neměla překročit 30 min. Zároveň je monitorována saturace kyslíkem ve frontálních lalocích pomocí NIRS, jehož hodnota by neměla klesnout pod 40 % – v opačném případě musí být oběh obnoven a pokračovat lze až po krátké reperfuzi.

Po zastavení MO je pomocí několika manuálních dechových exkurzí vytlačena reziduální krev z plicního řečiště. V nyní již přehledném operačním poli může proběhnout samotná endarterektomie. Ta se provádí everzní technikou pomocí speciálního mikroraspatoria, chirurgicky dostupné jsou většinou lobární, segmentární a částečně subsegmentární větve plicnice. Vzhledem ke kalibru tepen a hloubce, ve které se nacházejí, je potřeba používat speciální pinzety s kloubem, umožňující otevření branží i v úzkém prostoru.

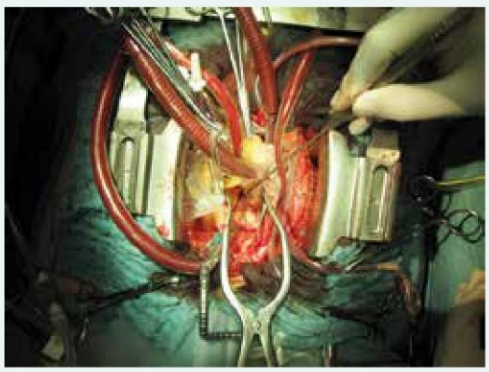
Po ukončení endarterektomie je znovu spuštěn MO za účelem reperfuze, která trvá zpravidla 10–15 min. V průběhu reperfuze je provedena sutura arteriotomie pomocí 6/0 polypropylenového stehu. Místo sutury je zpevněno pomocí tkáňového lepidla.

Obr. 4. Speciální instrumentárium používané v průběhu plicní endarterektomie



Následuje endarterektomie vlevo, srdce se rotuje pomocí speciálního retraktoru, aby se vizualizovala levá větev plicnice, která je podélně otevřena k okraji perikardu. Obdobně jako vpravo se začíná bez zástavy oběhu v rozsahu, který závisí na přehlednosti operačního pole. Ta je udržována 2 odsávačkami odsávajícími krev přitékající z větví plicnice. Po zástavě oběhu pokračuje endarterektomie standardním způsobem, dokud není kompletní (obr. 6). Následně je spuštěn MO, je zahájeno ohřívání pacienta, v průběhu kterého je provedena sutura tepny stejnou technikou jako na pravé straně. Ohřívání trvá 1,5–2násobek doby chlazení za dodržení teplotních gradientů. V průběhu ohřívání pacienta je zároveň prostor pro kombinované kardiochirurgické výkony, jako jsou aortokoronární bypassy, výkony na srdečních chlopních, MAZE, či sutura defektu septa síní. Následně je odstraněna svorka z ascendentní aorty a zahájena reperfuze srdce společně s reperfuzí plic za trvalého odlehčení průtoku odsáváním plicnicovým ventem. Časně je zahájena šetrná tlaková ventilace s nízkou frekvencí a dechovými

Obr. 5. Operační pole v průběhu plicní endarterektomie. Nástroj směřuje do otevřené obturované pravé větve plicnice



Obr. 6. Endarterium odstraněné u nemocného s těžkou tromboembolickou plicní hypertenzí při plicní endarterektomii (typ postižení I)

objemy s PEEP. Tato opatření snižují riziko reperfuzního edému plic, který může vést i ke krvácení do dýchacích cest.

Po ohřátí pacienta na 36 °C jsou zavedeny 2 síňové a 2 komorové dočasné stimulační elektrody, postupně je ukončen a dekanylován MO. Dříve užívaný levosíňový katétr k podávání noradrenalinu se v současnosti již nepoužívá. Následuje úprava koagulace, stavění krvácení, do hrudníku je zaveden retrokardiální a retrosternální drén, v případě otevření pleury také silastikový drén do pleurální dutiny. Je provedena sutura sternotomie po anatomických vrstvách a pacient je transportován na pooperační oddělení. Zde je 4–6 hod po operačním výkonu v případě přiměřených krevních ztrát zahájena antikoagulace heparinem, pacient je extubován standardně po 12–16 hod. V průměru 3.–6. pooperačního den je pacient přeložen na standardní oddělení, na němž je zahájena intenzivní rehabilitace. Po odstranění elektrod a drénu je pacient převeden na perorální antikoagulaci, preferenčně na warfarin s cílovou hodnotou INR 2,5–3,0.

Další možnosti léčby

Specifická farmakoterapie ovlivňující plicní cévní remodelaci je indikována u inoperabilních pacientů a u pacientů s reziduální plicní hypertenzí po PEA [11]. V současné době jsou jedinou skupinou léků specificky zasahujících do remodelačních změn u CTEPH stimulátory guanylátcyklázy. Mechanizmus působení je v zesílení účinku oxidu dusnatého na guanylátcyklázu a zároveň ve zvýšení senzitivity guanylátcyklázy na nízkou hladinu NO. Jediným registrovaným přípravkem pro léčbu inoperabilní CTEPH nebo reziduální plicní hypertenze je perorální preparát riociguat. Jeho účinnost a bezpečnost byla ověřena v randomizované multicentrické placebem kontrolované klinické studii CHEST-1 [12] a v navazující studii CHEST-2 [13].

Balonková plicní angioplastika (BPA) je metoda, která se v léčbě CTEPH začala uplatňovat od roku 1988 [14], zpočátku pouze sporadicky, a ani v dnešní době nicméně není zcela běžnou léčebnou metodou a rozhodně není alternativou PEA. Metoda nedosahuje takového zlepšení hemodynamiky jako u PEA. Jsou nutné opakované intervence na řadě segmentů. BPA je rovněž zatížena řadou komplikací, jako je krvácení či reperfuzní edém. Nezanedbatelná je také radiační zátěž spojená s výkonem [15]. BPA by měla být indikována v přísně selektovaných případech u pacientů nevhodných k PEA pro vysoké riziko operace nebo v případě chirurgicky nedosažitelného, nicméně k BPA vhodného nálezu. BPA může být rovněž kombinována s PEA, a to jak formou hybridního, tak sekvenčního výkonu.

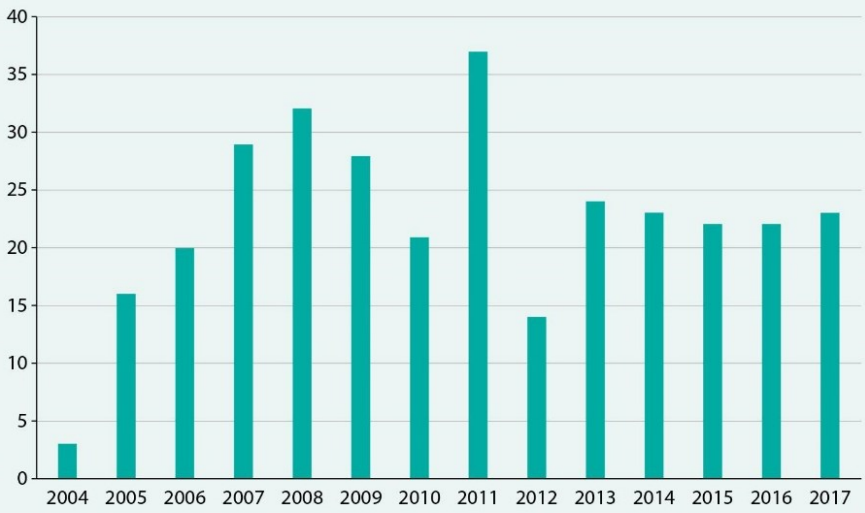
Transplantace plic přichází v úvahu u nemocných nevhodných k PEA po vyčerpání možností léčby pomocí farmakoterapie a BPA. Další indikací je selhání PEA. Dlouhodobé přežití po transplantaci plic je horší než po PEA.

Výsledky

V kardiocentru VFN v Praze bylo od zahájení programu chirurgické léčby CTEPH v roce 2004 do konce roku 2017 provedeno 314 endarterektomií plicnice, z toho 50 odoperovaných pacientů bylo ze Slovenské republiky (graf). Průměrný věk pacienta byl 59,7 let (nejmladší pacientce bylo 22 let, nejstaršímu 80 let), bylo odoperováno celkem 119 žen a 195 mužů. Průměrná délka operace byla 380 min, délka cirkulační zástavy 33 min (17 min vpravo, 16 min vlevo) při tělesné teplotě 17,1 °C.

U 90 pacientů byla PEA kombinována s dalším kardiochirurgickým výkonem (sutura foramen ovale patens 34krát, aortokoronární bypass 32krát, MAZE 16krát, implantace

Graf. Počet plicních endarterektomií provedených v Kardiocentru VFN v Praze



kardiostimulátoru 7krát, náhrada aortální chlopně 6krát, výkon na mitrální chlopni 2krát, plastika trikuspidální chlopně 1krát, korekce anomálního vyústění plicních žil 1krát). Ze závažných komplikací se u pacientů po PEA nejčastěji vyskytují: reperfuzní edém (5,5 %), krvácení/srdeční tamponáda s nutností chirurgické revize (4,5 %), krvácení do plic (4,1 %), neurologické komplikace (3,1 %), infekce operační rány (2,4 %). Časná mortalita se pohybuje do 5 %. Kardiocentrum VFN v Praze je jedním z 27 center zapojených do Evropského registru CTEPH a výsledky kardiocentra jsou dlouhodobě srovnatelné se souhrnnými výsledky registru [16].

Jednoleté přežití u operovaných pacientů je 89 %, 3leté 87 %, 5leté 82 % a 10leté 75 %. Naproti tomu ve skupině inoperabilních nemocných je přežívání výrazně horší a závisí na výši tlaku v plicnici [17,18].

Závěr

CTEPH je relativně vzácná chronická komplikace akutní plicní embolie s nepříznivou prognózou u neléčených pacientů. V diagnostice pacientů s podezřením na CTEPH hraje klíčovou roli echokardiografické vyšetření a ventilačně perfuzní scintigrafie plic. Metodou volby v terapii CTEPH je endarterektomie plicnice, která je pro většinu pacientů kurativní léčbou. Prognosticky nejvýznamnějším faktorem pro časnou i pozdní mortalitu je hemodynamicky významný pokles plicní cévní rezistence (Pulmonary Vascular Resistance – PVR) po operaci. U inoperabilních pacientů a u pacientů s reziduální plicní hypertenzí po PEA je indikována specifická léčba ovlivňující plicní cévní remodelaci. Další možností léčby u inoperabilních pacientů a u nemocných s reziduální plicní hypertenzí po PEA je v selektovaných případech balonková angioplastika. V případě selhání těchto léčebných postupů přichází v úvahu transplantace plic.

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Computed tomography angiographic parameters of pulmonary artery as prognostic factors of residual pulmonary hypertension after pulmonary endarterectomy

Matus Niznansky[1], Jan Kavan[2], Petra Zemankova[3], Tomas Prskavec[1], David Ambroz[4], Pavel Jansa[4] and Jaroslav Lindner[1]

Abstract

Objectives: This study aimed to retrospectively assess using computed tomography pulmonary angiography (CTPA) for predicting residual pulmonary hypertension (RPH) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary endarterectomy (PEA).

Methods: We retrospectively analyzed data of 131 patients with CTEPH who underwent PEA in our center (2008–2015). We measured several diameters of the pulmonary artery and thoracic aorta preoperatively. We evaluated the relationship between these measurements (and their indices) and signs of RPH represented by pulmonary artery systolic pressure (PASP) estimated by echocardiography.

Results: Significant correlations were observed between the aortopulmonary index and prediction of any residual hypertension and moderate/severe hypertension 1 year after PEA, and any residual hypertension and severe hypertension 2 years after PEA. The aortopulmonary index

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was significantly related to a reduction in PASP 1 year after the operation. A lower aortopulmonary index ($\leq$0.88 for the ascending aorta and $\leq$0.64 for the descending aorta) predicted lower RPH.

Conclusions: Preoperative CTPA parameters can be used to assess the risk of RPH after PEA. The aortopulmonary index has significant predictive value for RPH and a reduction in PASP after PEA. Lower values of the aortopulmonary index suggest a better outcome after PEA.

Keywords

Chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, computed tomography angiography, residual pulmonary hypertension, aortopulmonary index, pulmonary artery systolic pressure

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease characterized by a pulmonary artery mean pressure (PAMP) that exceeds 25 mmHg. CTEPH is caused by organization of intraluminal thrombi, stenosis and occlusions of the pulmonary artery and its branches, and peripheral vascular remodeling. CTEPH is a chronic complication of acute pulmonary embolism. Obstruction of pulmonary artery branches increases pulmonary vascular resistance (PVR), and this leads to right ventricular overload and right-sided heart failure. The treatment of choice for indicated patients is surgical pulmonary endarterectomy (PEA), which is performed in deep hypothermic cardiac arrest.[1,2] A total of 25% of patients with CTEPH are diagnosed with residual pulmonary hypertension (RPH) after PEA.[3] RPH is defined by the presence of increased pulmonary artery pressure and PVR 6 months after PEA. RPH is a predictor of an unfavorable outcome after surgical treatment in the early postoperative period during the first year of follow-up and it also increases the risk of periprocedural complications. Prediction of RPH may play a major role in the indication of patients to undergo PEA or to provide them with some additional treatment after PEA.[4]

This study aimed to determine an easy, non-invasive tool to predict RPH after PEA, represented by pulmonary artery systolic pressure (PASP) estimated by echocardiography, by using computed tomography pulmonary angiography (CTPA) images of the pulmonary artery and its branches. Some previous studies described the use of CTPA in association with pulmonary hypertension[5–9] and even proposed some scoring systems,[10] but none of these systems has been accepted into broader practice yet.

Patients and methods

Study population

This retrospective study included consecutive patients from the Czech Republic who underwent PEA in our center between May 2008 and December 2015. The PEA program started in our center in 2004, and

since then, 393 patients were operated on with an overall 30-day mortality rate of 7.6%. Since 2018, the 30-day mortality rate was 3.8%. The 5-year survival of patients who are operated on in our center is 82.2%.[11] We excluded patients from other countries owing to a lack of detailed follow-up data and patients who died within the first 6 months after surgery because they did not have any required follow-up data. The study was approved by the General University Hospital Ethics Committee (Protocol No. 1141/20 S-IV). Informed consent was not required because of the retrospective nature of the study. All patients were indicated to have a surgical procedure by a multidisciplinary team (pulmonary hypertension specialist, cardiac or thoracic surgeon experienced in PEA, and radiologist) after undergoing a cardiovascular examination with clinical, functional, and hemodynamic assessment. This assessment included echocardiography, a ventilation-perfusion lung scintigraphy scan, right-sided heart catheterization, conventional pulmonary angiography, and CTPA.

Data sampling

Clinical and hemodynamic data were collected retrospectively from our database. We collected data on the patients' age, weight, height, body mass index (BMI), body surface area (BSA), preoperative New York Heart Association (NYHA) functional class, 6-minute walking test (6-MWT) distance, and PASP estimated by echocardiography. Continuous wave Doppler of the tricuspid regurgitation (TR) trace was used to measure the difference in pressure between the right ventricle and right atrium. The simplified Bernoulli equation $P = 4[TRmax]^2$ was used to calculate this pressure difference using peak TR velocity. PASP was then calculated by adding the estimated right atrial pressure.[12] Additionally, the following right heart catheterization preoperative data were collected: PASP, PAMP, PVR, and the cardiac index (CI). The follow-up data included PASP estimated by echocardiography, which was recorded at 1, 2, and 3 years after the operation.

A CTPA scan was performed in all patients as a standard examination before PEA. Multidetector computed tomography (CT) scans with multiplanar reconstruction and the volume rendering technique were performed from 2008 to 2012 using the Siemens Somatom Sensation 16 Cardiac CT scanner (Siemens AG, Munich, Germany). CTPA was obtained with the patient in the supine position after intravenous injection of 80 mL of contrast medium (Optiray 350; Guerbet, Princeton, NJ, USA or Iomeron 350, Bracco Imaging Deutschland GmbH, Konstanz, Germany). Contrast medium was administered into the antecubital vein at a rate of 4.0 mL/using a mono-syringe power injector (EnVision CT EDU 700; MedRad, Pittsburg, PA, USA). Scanning was automatically started with a postinjection delay of 6 s by bolus tracking in the main pulmonary artery (PA) with a threshold of 100 HU. One rotation was per 0.5 s. CT scans were obtained with the setting of 100 mAs and 120 kV. CT images were performed using the reconstruction kernel B20f or B30f. From 2012 to 2015, multidetector CT scans were performed on the Philips Brilliance iCT 256 Essential Cardiac CT scanner (Koninklijke Philips Electronics N.V., Amsterdam, The Netherlands). The protocol used was similar to that used in 2008 to 2012 with only a few of the following differences: there was a lower volume of contrast medium applied (50–60 mL), and contrast medium was administered at a rate of 4.0 mL/s, followed by 60 mL of saline

solution at a rate of 5.0 mL/s, using a double-syringe power injector (Stellant; MedRad). The bolus tracking threshold was 130 HU. The tube voltage was 100 kV and the planned tube time-current was 180 mAs. CT images were reconstructed using filter B and the iterative reconstruction technique iDose at level 6.

CT images were analyzed using Dicompass Gateway WebViewer software (Medoro Ltd., Pardubice, Czech Republic) by a single surgeon from our CTEPH team who was trained in CTPA analysis. Images were then reanalyzed in random order by two experienced radiologists, who were blinded to the patients' clinical and hemodynamic data, but were aware of the patients' diagnosis of CTEPH. Discrepancies were resolved by consensus.

We measured the diameter of the main pulmonary artery (PA), right pulmonary artery (RPA) and left pulmonary artery (LPA), and the ascending (Ao) and descending (DAo) aorta. We also calculated the following indices using these measurements: Ao/PA, DAo/PA, PA/BSA, PA/BMI, RPA/BSA, RPA/BMI, LPA/BSA, and LPA/BMI.

The diameter of the PA was measured at the level of its bifurcation, perpendicular to its long axis, on an axial slice. The diameter of the Ao was also measured at the level of the bifurcation of the pulmonary trunk (Figure 1) and the diameter of the DAo was measured at the diaphragmatic hiatus (Figure 2A). RPA and LPA diameters were measured at their widest part after bifurcation of the pulmonary trunk (Figure 2B and 2C respectively).

Data analysis

We analyzed the relationships between the diameters of the PA, RPA, and LPA or their indices (indexed to the diameter of the Ao and DAo, BMI, and BSA) and RPH characterized by PASP. We analyzed the postoperative data of patients at 1, 2, and 3 years after the operation.

RPH was defined by a value of PASP $>$ 35 mmHg as estimated by echocardiography. We divided patients into four groups on the basis of their RPH depending on postoperative PASP estimated by echocardiography (group 0 [G0]: no hypertension, G1: mild hypertension, G2: moderate hypertension, and G4: severe hypertension) (Table 1). We then used the Cox regression model to compare the effect of CT measurements/indices on pulmonary hypertension. We attempted to evaluate whether we could predict any residual hypertension (PASP $>$ 35 mmHg) by comparing G0 with G1 + G2 + G3. We also wished to determine whether we could predict moderate and severe hypertension (PASP $>$ 45 mmHg) by comparing G1 + G2 with G2 + G3, and whether we could predict severe hypertension only (PASP $>$ 60 mmHg) by comparing G0 + G1 + G2 with G3.

Because the Ao/PA and DAo/PA indices appeared to be significant in several of the tests, we decided to set cut off values for risk stratification regarding RPH. The cut off values were set by the distribution of data (lower quartile, median, and upper quartile). We analyzed the distribution of patients with and without RPH 1 year after PEA within these intervals. We used the chi-square test to analyze the distribution of cut off values.

Statistical methods

All statistical analyses were performed using STATISTICA 12 software (StatSoft CR Ltd., Prague, Czech Republic). Two-tailed p values of <0.05 were considered statistically significant. Summary statistics (mean ± standard deviation) were calculated. The Cox regression model of proportional risks for investigating the effect of several variables on the

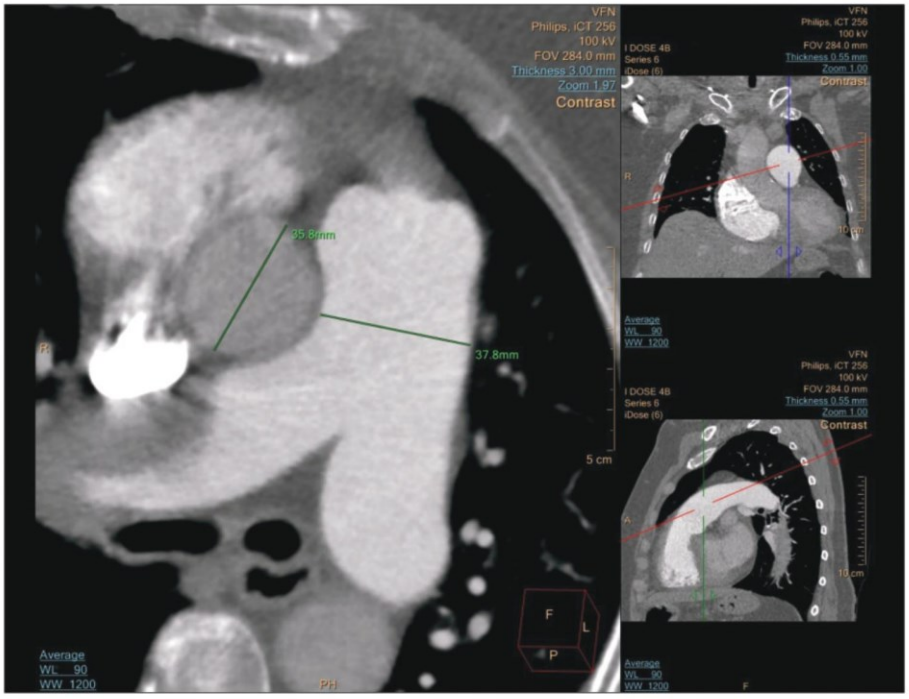

Figure 1. Computed tomography images showing measurement of the diameters of the main pulmonary artery and ascending aorta.

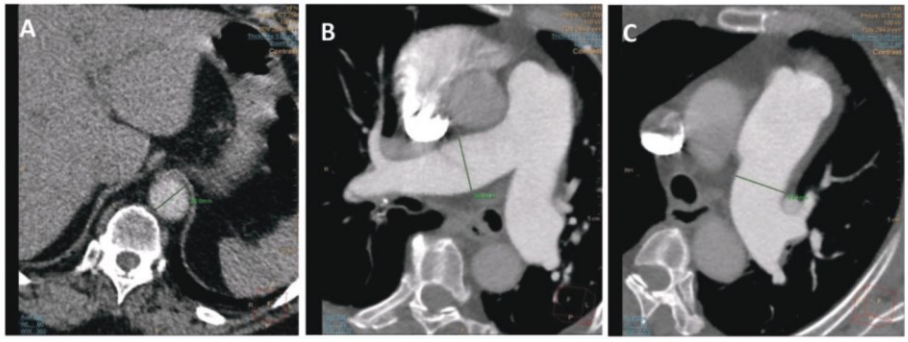

Figure 2. Computed tomography images showing measurement of the a) descending aorta diameter, b) right pulmonary artery diameter, and c) left pulmonary artery diameter.

time a specified event takes to occur was used to analyze the effect CT measurements/indices on postoperative PASP. Scatter plot graphs were used to evaluate the relationships between the Ao/PA and DAo/PA indices and the difference between preoperative and postoperative PASP.

Table 1. Residual pulmonary hypertension groups

Group	Pulmonary hypertension	PASP (mmHg)
G0	None	≤35
G1	Mild	36–45
G2	Moderate	46–60
G3	Severe	>60

PASP, pulmonary artery systolic pressure.

Table 2. Patient preoperative characteristics

Patient characteristics	(n = 131)
Age (years)	61 ± 11
Male sex	78 (60)
Weight (kg)	83 ± 15
Height (cm)	172 ± 9
BMI (kg/m^2)	28 ± 4
BSA (m^2)	2.0 ± 0.2
Right-sided heart catheterization:	
PASP (mmHg)	83 ± 17
PAMP (mmHg)	50 ± 11
PVR (dyn.s.cm^{-5}	766 ± 290
CI (L/minute/m^2)	2,2 ± 0,5
NYHA functional classification	2,9 ± 0,4
NYHA class I	0 (0)
NYHA class II	17 (13)
NYHA class III	106 (81)
NYHA class IV	8 (6)
6-MWT (m)	370 ± 116
PASP – estimated by ECHO (mmHg)	82 ± 20

Data are mean ± standard deviation or n (%).
BMI, body mass index; BSA, body surface area; PASP, pulmonary artery systolic pressure; PAMP, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; CI, cardiac index; NYHA, New York Heart Association; 6-MWT, 6-minute walking test; ECHO, echocardiography.

Table 3. Characteristics of CT measurements

CT measurements	n = 131
Main PA (mm)	37.2 ± 5.4
RPA (mm)	29.2 ± 3.9
LPA (mm)	28.1 ± 3.3
Ao (mm)	34.0 ± 4.3
DAo (mm)	26.0 ± 3.6

Data are mean ± standard deviation.
CT, computed tomography; PA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery; Ao, ascending aorta; DAo, descending aorta.

Results

Patient characteristics

The study included 78 men and 53 women, with a mean age of 61 ± 11 years (range: 29–80 years). Details of the patient characteristics are shown in Table 2. CT measurements are shown in Table 3.

The postoperative hemodynamic characteristics at 1, 2, and 3 years after PEA are shown in Table 4. The mean NYHA functional class was 1 5 ± 0.5 at 1 and 2 years after PEA and 1.6 ± 0.6 3 years after PEA. The mean 6-MWT distance is also shown in Table 4.

PASP analysis

There was a significant relationship between the Ao/PA index and postoperative PASP. Therefore, we were able to predict the presence of any RPH (PASP > 35 mmHg) 1 year after the operation ($p = 0.033$), the presence of moderate and severe hypertension (PASP > 45 mmHg) 1 year after the operation ($p = 0.032$), and severe hypertension (PASP > 60 mmHg) 2 years after the operation ($p = 0.033$). There was also a significant relationship between the DAo/PA index and postoperative PASP, where we could predict any RPH 1 year after the operation ($p = 0.010$), moderate and severe hypertension 1 year after the operation ($p = 0.044$), and any RPH ($p = 0.025$) and severe hypertension ($p = 0.026$) 2 years after the operation. Furthermore, the PA/BMI index showed a significant predictive

Table 4. Postoperative hemodynamic and clinical characteristics

	One year after PEA	Two years after PEA	Three years after PEA
PASP $\leq$ 35 mmHg	54 (48)	49 (54)	41 (64)
PASP 36–45 mmHg	25 (22)	20 (22)	10 (16)
PASP 46–60 mmHg	19 (17)	9 (10)	8 (12)
PASP $>$ 60 mmHg	15 (13)	12 (13)	5 (8)
NYHA functional class	1.5 ± 0.5	1.5 ± 0.6	1.6 ± 0.6
6-MWT (m)	483 ± 100	478 ± 139	481 ± 96

Data are mean $\pm$ standard deviation or n (%).
PEA, pulmonary endarterectomy; PASP, pulmonary artery systolic pressure; NYHA, New York Heart Association; 6-MWT, 6 minute walking test.

Table 5. Prediction of PASP at 1, 2, and 3 years after the operation

	One year			Two years			Three years		
PASP	>35 mmHg	>45 mmHg	>60 mmHg	>35 mmHg	>45 mmHg	>60 mmHg	>35 mmHg	>45 mmHg	>60 mmHg
PA	0.199	0.216	0.443	0.559	0.832	0.096	0.726	0.781	0.408
Ao/PA	**0.033**	**0.032**	0.210	0.137	0.320	**0.033**	0.601	0.507	0.072
DAo/PA	**0.010**	**0.044**	0.330	**0.025**	0.416	**0.026**	0.737	0.840	0.193
PA/BSA	0.312	0.495	0.638	0.648	0.208	0.283	0.621	0.810	0.331
PA/BMI	0.981	0.577	0.335	0.194	**0.021**	0.728	0.302	0.366	0.765

Data are shown as p values.
PASP, pulmonary artery systolic pressure; PA, main pulmonary artery; Ao, ascending aorta; DAo, descending aorta; BSA, body surface area; BMI, body mass index.

value of moderate or severe hypertension 2 years after the operation ($p = 0.021$, Table 5).

We did not aim to evaluate the presence or degree of RPH only, but also wished to determine the effect of the operation on a reduction in PASP, regardless of its exact value. We used scatter plot graphs to evaluate the relationships between the Ao/PA and DAo/PA indices (which were significant in the previous evaluation) and the difference between preoperative and postoperative PASP estimated by echocardiography. There were significant negative correlations between the difference in PASP before and after the operation and the Ao/PA index ($p < 0.001$, Figure 3) and with the DAo/PA index ($p < 0.001$, Figure 4).

Aortopulmonary index analysis

The cut off values of the Ao/PA and DAo/PA indices were set by the distribution of data (lower quartile, median, and upper quartile). The chi-square test showed a significant distribution of the cut off values of the Ao/PA index ($p = 0.0098$), but not for the DAo/Pa.

The lower quartile values of the aortopulmonary index (≤ 0.88 for the Ao and ≤ 0.64 for the DAo) were related to a lower PASP after PEA (72.3% for Ao/PA and 68.3% for DAo/PA as shown by no RPH 1 year after the operation) (Table 6).

Discussion

PEA is the method of choice for treating CTEPH because it is the only curative

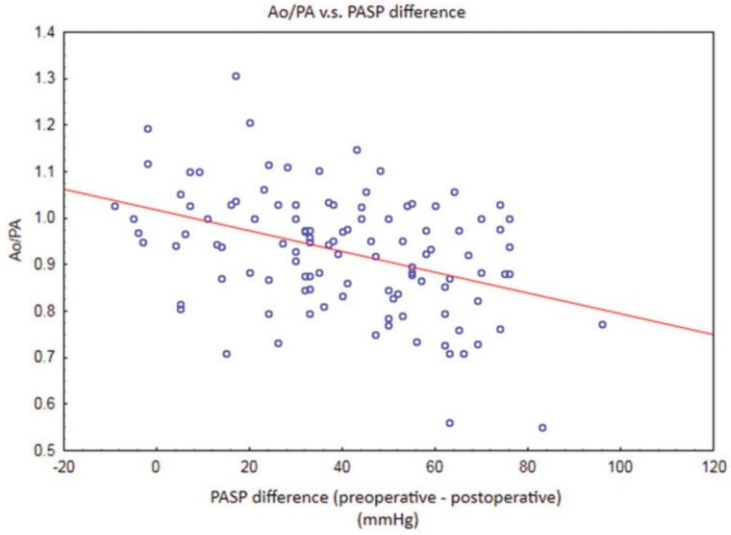

Figure 3. Relationship between the aortopulmonary index (Ao/PA) and the difference in PASP preoperatively and postoperatively. $p < 0.001$
PASP, pulmonary artery systolic pressure; Ao, ascending aorta; PA, main pulmonary artery.

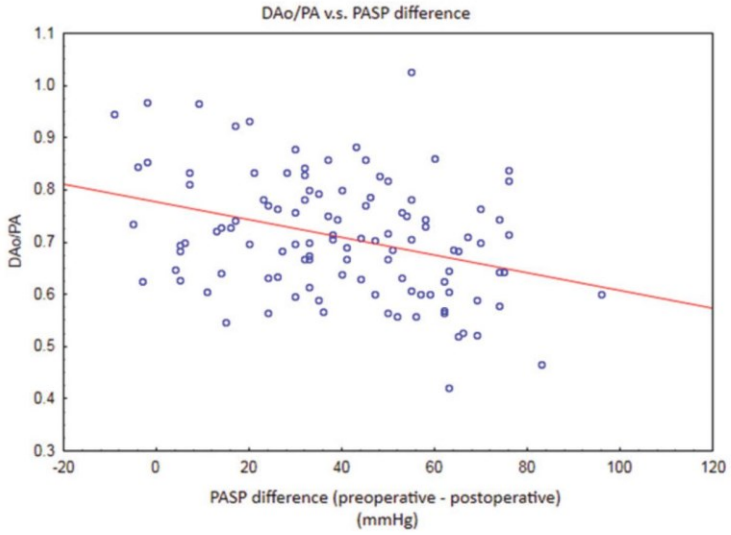

Figure 4. Relationship between the aortopulmonary index (DAo/PA) and the difference in PASP preoperatively and postoperatively. $p < 0.001$
PASP, pulmonary artery systolic pressure; DAo, descending aorta, PA, main pulmonary artery.

Table 6. Aortopulmonary index (Ao/PA and DAo/PA) cut off values

	Without residual hypertension n (%)	With residual hypertension n (%)
Ao/PA interval (p = 0.0098)		
Ao/PA $\leq$ 0.88	34 (72.3)	13 (27.7)
Ao/PA > 0.88 and $\leq$1.03	26 (43.3)	34 (56.3)
Ao/PA > 1.03	12 (50)	12 (50)
DAo/PA interval (p = 0.08)		
DAo/PA $\leq$ 0.64	28 (68.3)	13 (31.7)
DAo/PA > 0.64 and $\leq$0.82	34 (51.5)	32 (48.5)
DAo/PA > 0.82	10 (41.7)	14 (58.3)

Ao, ascending aorta; PA, main pulmonary artery; DAo, descending aorta.

option for operable patients that provides improvement in survival, symptoms, and hemodynamic parameters.[1,13–15] Prediction of surgical success in the individual patient is still challenging. There are some methods that can be used to predict RPH, but they are either invasive (right-sided heart catheterization and analysis of pulmonary artery pressure and pulmonary capillary wedge pressure curves, and vasodilatation testing) or are not sufficiently accurate (e.g., echocardiography). Several studies focused on prediction of hemodynamic improvement after PEA using non-invasive imaging. Schölzel et al.[16] analyzed data of 52 patients with CTEPH and found that the preoperative PA diameter indexed for BSA was the only independent predictor for hemodynamic improvement after PEA. Heinrich et al.[17] reported that the diameter of the PA and the ratio of the PA and the diameter of the Ao were correlated with preoperative PAMP. Postoperative PVR was negatively correlated with the presence and extent of central thrombi and dilated bronchial arteries observed on preoperative CT scans. Leone et al.[10] performed detailed radiological evaluation of 145 patients with CTEPH. These authors proposed a new CT score, which included distribution of disease, diameter of the PA, the presence of mosaic perfusion, and the degree of tricuspid regurgitation.

We analyzed data of patients in our center to evaluate the possibility of using a non-invasive imaging method to predict the outcome of patients after PEA. Our study showed that CTPA was useful for not only in preoperative anatomical description of the pulmonary arteries, but also in providing a predictive value for RPH after PEA.

As an outcome parameter, we chose PASP estimated by echocardiography because this is monitored once a year during the follow-up period for all patients in our center. With an increasing time after PEA, there was a higher incidence of missing follow-up data and this is why we chose a 3-year follow-up. The most complete follow-up data were in the first year after PEA. This might be one reason for fewer significant results being obtained in the second and third years.

This study has some limitations. Incomplete follow-up data was one of the main limitations of this study (PASP was recorded in 86% of patients 1 year after PEA, in 69% of patients 2 years after PEA, and in 48% of patients 3 years after PEA). Further limitations are the retrospective nature of the study, the limited number of patients, and the monocentric form of this research.

The aortopulmonary index, including the Ao/PA and DAo/PA, appears to be the best predictor of outcome after PEA. Although there has been considerable improvement in understanding of the natural history of CTEPH post-PEA,[18] the clinical relevance of RPH remains unclear. This lack of clarity is why we chose to use the Cox regression model to test for three different degrees of hypertension (>35 mmHg, >45 mmHg, and >60 mmHg). The aortopulmonary index showed a significant predictive value not only for RPH, but also for a decrease in PASP, regardless of the absolute value. This finding is important for the assessment of surgical success in patients who have an extremely high or low PASP before PEA. This is because the degree of residual hypertension after PEA does not provide an adequate answer to whether the procedure was successful in these patients, and therefore, whether the indication for their operation was appropriate (mild residual hypertension is a perfect result for a patient who has a preoperative PASP of 120 mmHg, but questionable for a patient who has a PASP of 45 mmHg).

In our study, lower quartile values of the aortopulmonary index corresponded to a lower PASP after PEA. This finding suggests that patients with dilatation of the PA before PEA have a better outcome after the operation. Dilatation of the PA is generally considered as a risk factor for patients with pulmonary hypertension.[19–21] However, this is mainly an issue in patients with primary pulmonary hypertension and inoperable CTEPH, where the risk is associated with compression of the left main coronary artery, or rupture or dissection of the PA with cardiac tamponade. One of the explanations for a better result of PEA in patients with dilatation of PA is as follows. Dilatation of the PA might be associated with more proximal disease due to organization of thrombotic materials in the central part of the pulmonary artery. However, patients with more peripheral disease, who typically have a poorer outcome, do not develop such dilatation. This possibility requires further research and we are already investigating the relationship of histological characteristics of pulmonary thromboendarterectomy specimens with dilatation of the PA.

Despite the promising role of the aortopulmonary index as a predictor of outcome after PEA, we are aware that this is only one factor in a complex situation in patients with CTEPH. We would like to emphasize that all characteristics and results of patients with CTEPH should be considered and that all patients should be evaluated by surgeons and teams with expertise in PEA.

RPH remains a challenge for those who treat patients with CTEPH. With the promising results of specific medical therapy for patients with CTEPH,[4,22,23] efforts for predicting RPH are no longer focused only on the appropriate indication for PEA, but also to properly identify patients who might requires some additional therapy after PEA and to follow these patients closely. Apart from specific pharmacotherapy, balloon pulmonary angioplasty [24,25] and the developing method of pulmonary denervation are also methods for treating RPH.[26] Despite these methods of RPH treatment, its prediction will remain important because of the association of RPH with the risk of periprocedural complications.

Conclusion

Preoperative CTPA parameters can be used to assess hemodynamic improvement after PEA. The aortopulmonary index has significant predictive value for RPH and for a reduction in PASP after PEA. Lower values of an aortopulmonary index ($\leq$0.88 for the Ao and $\leq$0.64 for the DAo) appear to predict a better outcome after PEA.

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Declaration of conflicting interest

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Chylous pericardial effusion as a rare complication after pulmonary endarterectomy

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Abstract

Chylous pericardial effusion is a rare complication of cardiac surgery. We report a case of a patient who underwent pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension and was diagnosed with chylopericardium after the procedure. We present the surgical management of this condition, which included bilateral pedal lymphangiography followed by ligation of injured lymph vessel.

Keywords: Pulmonary endarterectomy • Chylopericardium • Lymphangiography • Chronic thromboembolic pulmonary hypertension

INTRODUCTION

Pulmonary endarterectomy is a treatment of choice for patients with chronic thromboembolic pulmonary hypertension (CTEPH) [1]. Chylopericardium is a rare complication of cardiac surgery, first reported by Thomas and McGoon in 1971 [2]. We have found no reports of this complication after pulmonary endarterectomy. The methods of treatment can be conservative or surgical. Surgical treatment commonly requires thoracic duct ligation and is considered to be curative [3]. However, thoracic duct ligation can be associated with the risk of malnutrition, immunological deficits and metabolic complications. We report thoracic duct-saving surgical treatment, which included bilateral pedal lymphangiography followed by ligation of the injured lymph vessel.

CASE REPORT

We report a case of a 48-year old female patient with progressive dyspnoea (NYHA III) after two episodes of pulmonary embolism. She was diagnosed with severe CTEPH (PAMP 57 mmHg, PVR 14 Wood units, Cardiac index 1.7 l/min/m^2, multiple occlusions bilaterally on pulmonary angiography and multiple perfusion defects in both lungs on V/P scan) and was indicated for pulmonary endarterectomy.

After median sternotomy, we established cardiopulmonary bypass and the patient was cooled down to 16.9°C. We cross-clamped aorta and achieved cardiac arrest using crystalloid cardioplegia. We performed bilateral pulmonary endarterectomy from the right and left pulmonary incisions during three circulatory arrests (22 + 15 + 21 min) with ∼10 min reperfusion periods between individual circulatory arrests. The perioperative findings were in accordance with Jamieson class III (Fig. 1A). Weaning from the bypass was uneventful.

The patient was extubated on Day 1 and was haemodynamically stable with sufficient cardiac output. On Day 3, milky pericardial effusion in mediastinal drain (50 ml/h) appeared. The fluid analysis demonstrated triglycerides of 420 mg/dl, white blood cell count of 880/ul (95.6% lymphocytes), and total proteins of 4.5 g/dl.

On Day 5, we started conservative treatment. We inserted peripherally inserted central catheter line and began total parenteral nutrition to reduce fat input. The milky effusion turned to serous effusion; however, the amount of fluid production remained high (500–1000 ml/day). The chest X-ray was in accordance with normal postoperative image. On Day 15, the drain got obstructed and the patient started to show signs of cardiac tamponade. We inserted a pigtail catheter which immediately drained 40 ml of serous liquid and the patient's vital functions improved rapidly. Within 2 weeks after operation, the patient lost almost 12 kg of weight.

We indicated surgical treatment. We first performed pedal lymphangiography which showed normal thoracic duct, no aberrant lymph vessels and collection of contrast liquid in the superior mediastinum (Fig. 2). However, we did not identify the exact leakage point. On Day 20, we performed operation to treat the leaking lymph vessels. Three hours before the procedure, we applied lipids containing vitamin A via jejunal tube to increase the effusion. After median sternotomy, we found collection of cloudy fluid in the pericardium. We inspected surrounding tissues and in the left lobe of thymus we found the injured lymph vessel (2 mm in diameter), with the lymph leaking (Fig. 1B). We ligated the

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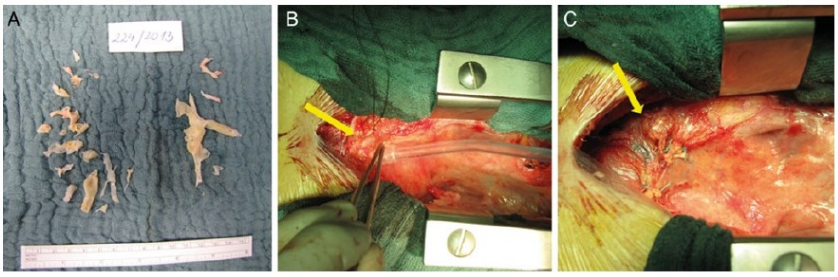

Figure 1: (**A**) Specimens collected from the pulmonary endarterectomy. (**B**) Arrow points to the leaking lymph vessel. (**C**) Ligated lymph vessel and the left lobe of the thymus.

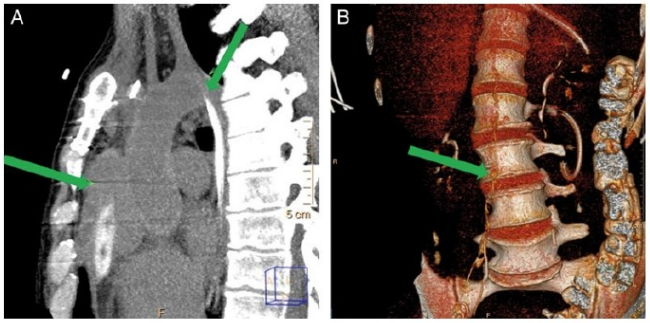

Figure 2: (**A**) Arrows point to the thoracic duct and collection of contrast fluid in the mediastinum. (**B**) Computed tomography lymphangiography (3D reconstruction), arrow points to the thoracic duct.

vessel and we also sutured and ligated the whole left lobe of thymus and sealed it with tissue glue (Fig. 1C). There were no signs of lymphatic effusion. The patient was transported in a haemodynamically stable condition to the ICU.

After the procedure, there was minimal pericardial effusion. The drain was extracted on the first postoperative day and we started enteral nutrition. The patient was stable and was discharged from hospital 12 days after the lymph vessel ligation, 32 days after the pulmonary endarterectomy.

CONCLUSION

Chylous pericardial effusion can occur as a primary condition; however, most often it is secondary to heart surgery, radiation therapy, trauma, malignancy, infection or pancreatitis [4]. Chylopericardium after cardiac surgery is rare, because the thoracic duct and its main tributaries are not typically in the operative field during median sternotomy procedures [3].

In order to avoid effusion from lymph vessels in the anterior mediastinum, we recommend ligation or suture of thymic tissue, if preparation is being done in this area. Coagulation may not be sufficient to avoid postoperative lymphatic effusion. Tissue glue may be applied in case small lymph vessel damage is suspected.

Patients with chylopericardium are at risk of cardiac tamponade if the fluid is not drained properly—either by drainage tubes or by pericardial window. If the fluid is drained properly, there is yet another complication, especially if the effusion is prolonged. The loss of substances normally transported in chyle results in malnutrition, immunological deficits and metabolic complications.

Conservative treatment, based on fat input reduction and total parenteral nutrition, is meant to decrease the chyle production, reduce chyle flow via the thoracic duct and therefore decrease the chylous effusion.

When it fails, surgical treatment is indicated. The most common technique is thoracic duct ligation. We, however, were aware of possible complications after this procedure. In case, there is no lymph vessel substituting the function of thoracic duct, its ligation may lead to malnutrition, immunological deficits or metabolic complications.

We performed lymphangiography before the operation. Lymphangiography is not a standard procedure to treat chylopericardium [4] because it rarely helps to identify the leaking vessel, and the resolution is not high enough. However, it can show the anatomy of thoracic duct and its tributaries and reveal an atypical position of the duct or presence of any aberrant vessels.

Because chylopericardium truly is not common in cardiac surgery, there are not many described cases and therefore not enough evidence for individual treatment methods. Our strategy was curative, it did not require thoracic duct ligation and led to successful treatment of our patient's condition.

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Conflict of interest: none declared.

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