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The Effect of Time Delay between the Diagnosis of Chronic Thromboembolic Pulmonary Hypertension and Pulmonary Thrombo-Endarterectomy on the Postoperative Outcomes

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ABSTRACT

Background: pulmonary thrombo-endarterectomy (PTE) is the treatment of choice for chronic thromboembolic pulmonary hypertension in operable patients. Certain risk factors may be associated with bad outcomes after this surgery.

Objective: The aim of the current work was to investigate the effect of delay in having surgery on different outcomes after PTE.

Subjects and Methods: This interventional prospective`e and retrospective study included a total of 20 patients who underwent pulmonary thromboendarterectomy (PTE), attending at the Department of cardiothoracic surgery, Cairo University Hospitals. This study was conducted between June 2019 and April 2021.

Results: The more delayed the surgery, the higher the postoperative pulmonary vascular resistance (PVR), patients who had exceeded 13 months since the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) significantly developed poor postoperative functional class, patients who underwent surgery more than 16 months after the diagnosis of the disease significantly developed postoperative reperfusion lung injury.

Conclusion: It could be concluded that delayed PTE is associated with poor postoperative functional class, higher degree of pulmonary vascular resistance and more incidence of reperfusion lung injury.

Keywords: Chronic thromboembolic pulmonary hypertension, Pulmonary thromboendarterectomy, Reperfusion lung injury, Pulmonary vascular resistance.

INTRODUCTION

The clinical-based classification of pulmonary hypertension classified chronic thromboembolic pulmonary hypertension (CTEPH) as "group (4) pulmonary hypertension" (PH).

It results from an organized thromboembolic material obstructing the pulmonary arteries. Usually, this condition presents with unexplained dyspnea accompanied by increased pulmonary artery pressure (PAP) and high pulmonary vascular resistance in the presence of the occluding thrombus. If left untreated, it may be complicated with progressive impairment of the right heart function and irreversible pulmonary hypertension [(1-3)].

CTEPH may be a curable disease with early diagnosis and surgical removal of this offending thrombus in addition to performing pulmonary endarterectomy. This procedure is superior to both the medical treatment and lung transplantation [(4, 5)].

Although this surgery is considered the best option for operable patients, it may be associated with high mortality and a number of morbidities, including reperfusion lung injury, residual or persistent pulmonary hypertension, neurologic complications, and less-than-anticipated postoperative functional status. Therefore, careful case selection and risk assessment should be taken into account before surgery [(6)].

The aim of the present study was to investigate the effect of delay in having surgery on different outcomes after PTE.

SUBJECTS AND METHODS

This interventional prospective and retrospective study included a total of 20 patients who underwent pulmonary thromboendarterectomy (PTE), attending at the Department of cardiothoracic surgery, Cairo University Hospitals. This study was conducted between June 2019 and April 2021.

Inclusion criteria: The study included all patients with operable CTEPH having:

- Unexplained dyspnea (NYHA functional classes II, III, and IV) after recovery from acute pulmonary embolism for more than three months despite receiving effective anticoagulation.
- An echocardiogram revealed an estimated pulmonary artery pressure of 25 mmHg or more, regardless of RV dilatation or tricuspid regurgitation. However, heart or pulmonary conditions cannot explain PH.
- Planner ventilation/perfusion scan showed mismatched major perfusion abnormalities whether unilateral or bilateral.
- CT Pulmonary angiogram confirmed obstructed arteries with reduced pulmonary vasculature distal to the level of obstruction.
- Right sided heart catheter revealed mean pulmonary artery pressure of more than 30 mmHg and pulmonary vascular resistance ≥ 300 dyn. $s.cm^{-5}$.

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Exclusion criteria: The study excluded surgically inoperable patients and patients with surgically inaccessible disease distribution.

Pre-operative assessment:

A thorough clinical evaluation (including the time interval between the diagnosis CTEPH and the surgery) had been conducted for each patient enrolled in this study. Routine preoperative preparation including laboratory tests, chest X-ray were done along with confirming the echocardiography, ventilation/perfusion scan, MSCT pulmonary angiography, and the right heart catheter results.

Operative steps:

Anesthetic management:

In the operating room, proper monitoring lines were applied as standard cardiac surgery. An endotracheal intubation following induction of anesthesia then subsequently Swann-Ganz catheter was inserted to measure right sided pressures, PAPs as well as to calculate cardiac index. Final preparations for the surgery were the insertion of intraoperative TEE and thermal probes.

The operative technique:

In supine position, routine prepping and draping as standard open cardiac procedures was done. Median sternotomy and Pericardiotomy were done. Full heparinization was accomplished using intravenous unfractionated heparin (400 units/kg) with target activated clotting time >400 seconds, then full CPB was instituted with aorto-bicaval cannulation. LV vent, pulmonary artery vent, and venae caval snares were all inserted.

Systemic hypothermia was allowed down to 20°C and the head was placed inside a head cooling jacket. Aortic cross clamp was applied and cardioplegia was given with antegrade cold blood cardioplegia to arrest the heart and achieve good myocardial protection. During cooling the patient and giving cardioplegia, dissection between the ascending aorta, superior vena cava, and right pulmonary artery could be done. Before making the right pulmonary arteriotomy, the surgeon stood on the left side of the patient and retracted the ascending aorta and SVC away from each other to work on the RPA.

The arteriotomy extended under the SVC and as far as the take-off of the middle lobe artery. Any loose thrombus detected now was removed. Circulatory arrest commenced once core temperature reached the deep hypothermic levels and arteriotomy had been made to create a bloodless field suitable for complete and effective endarterectomy **(figure 1)**.

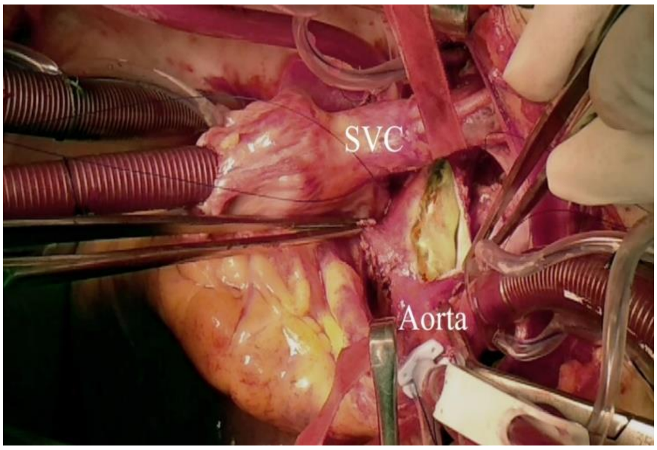

Figure (1): The organized thrombus inside right pulmonary artery with a pearly white dissection plane (From our work in Kar El-Aini Hospitals).

This procedure usually continued for at most 20 minutes before the circulation was re-allowed for 10 minutes. Next, the surgeon stands on the right side of the patient to start another 20 minute DHCA period to work on the left PA in the same manner as used in the right pulmonary endarterectomy.

During stitching of the left pulmonary arteriotomy, rewarming was allowed gradually to the euthermic levels. Cross-clamp was removed after deairing the heart, then weaning from CPB was allowed gradually, followed by the removal of CPB lines. Subsequently, adequate hemostasis was done, followed by inserting two mediastinal chest drains, and finally, sternotomy and wound closure could be done.

Post-operative care:

Patients were transferred to the ICU on mechanical ventilation and, if needed, on proper inotropic support or IV milrinone. The intensivist continues monitoring of the invasive blood pressure, oxygen saturation, central venous pressure, Swann-Ganz readings, and urine output that reflect the systemic perfusion status.

***Ethical Consideration*:**

An approval of the study was obtained from Cairo University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data was collected, coded, clustered in groups when needed, and analyzed using Medcalc 18.9.1, IBM SPSS 21 and Microsoft Excel 2016. Categorical data are described as percentages. Parametric data are described as mean and standard deviation. Non-parametric data are defined as median and interquartile ranges. Chi-squared test was used to analyze categorical variables.

Correlation coefficients were used to identify the degree of correlation between the length of time before surgery and the degree of postoperative PVR Logistic regression analysis was used to identify the impact of delayed surgery v on the different outcomes with their odds ratios.

ROC curves were used to determine the most sensitive and specific cut-offs predicting outcomes. For all the statistical tests, the level of significance was set at 5% level. A p value > 0.05 indicated that there was no significant value. A p value ≤ 0.05 indicated presence of a significant value.

RESULTS

Baseline characteristics:

There were 11 males (55%) and 9 females (45%). The age ranged from 20 to 62 years, with a mean age of 41.7 ± 10.14 years. The mean body mass index was 22.5 ± 5.3 (kg/m^2). There were 18 patients (90%) with a previous history of venous thromboembolism (VTE). The average duration between the last episode of VTE and the diagnosis of CTEPH was 14.9 ± 4.8 months. The median time between CTEPH diagnosis and having surgery was 11.5 (10-14.5) months.

Concerning the preoperative hemodynamic and respiratory status, eleven patients (55%) had FC-III, seven patients (35%) had FC-IV, and two patients (10%) had FC-II. The mean resting respiratory rate was 17.3 ± 1.9 breaths/min. The respiratory rate after exercise was measured in all patients except in the seven cases with FC-IV, the respiratory rate reached a mean of 31.6 ±3.4 breaths/minute. The mean arterial oxygen tension (PaO_2) was 71.7 ± 9.4 mmHg.

Before surgery, echocardiography identified 4 patients (20%) with normal RV dimensions, 5 cases (25%) with mild RV dilatation, 7 cases (35%) with moderate RV dilatation, and 4 cases (20%) with significantly dilated RV. The mean tricuspid annulus plane systolic excursion (TAPSE) was 2.36 ± 0.39. Four cases (20%) presented to surgery with no tricuspid regurg. Another four cases (20%) had mild degree of tricuspid valve regurg. Moderate tricuspid regurgitation was present in 4 cases (20%). Eight patients had a severe degree of tricuspid regurg before they underwent PTE.

The Right heart catheter (RHC) revealed a median mean pulmonary artery pressure (mPAP) of 57.7 (53.1-62.9) mmHg. The mean pulmonary vascular resistance was 758.7 ± 177.3 dyn.sec.cm-5. The cardiac index was 2.4 ± 0.5 L/min/m^2 on average. The mean mixed venous oxygen saturation (SVO2) was 53.9 ± 10.6%. Three patients (15%) had an IVC filter inserted prior to surgery.

Table (1): Patients demographics before surgery

Total number		N=20
Clinical review	Age (years)	41.7 ±12.6
	Sex	
	• Male	11 (55%)
	• Female	9 (45%)
	BMI (kg/m^2)	22.5 ± 5.3
	Previous VTE	18 (90%)
	Time between VTE & CTEPH symptoms (ms)	14.9 ± 4.8
	Time between CTEPH diagnosis & PTE (ms)	11.5 (10-14.5)
Hemodynamic status	NYHA functional class	
	• Class II	2 (10%)
	• Class III	11 (55%)
	• Class IV	7 (35%)
Respiratory status	Resting respiratory rate (BPM)	17.3 ± 1.9
	Respiratory rate after exercise*	31.6 ± 3.4
	P_aO_2 (mmHg)	71.1 ± 9.4
Echocardi-ography	Right ventricle size	
	• Normal sized	4 (20%)
	• Mildly dilated	5 (25%)
	• Moderately dilated	7 (35%)
	• Severely dilated	4 (20%)
	Degree of tricuspid regurge	
	• Normal valve	4 (20%)
	• Mild regurgitation	4 (20%)
	• Moderate regurgitation	4 (20%)
	• Severe regurgitation	8 (40%)
	Tricuspid annulus plane systolic excurtion	2.36 ± 0.39
Right heart catheter	mPAP (mmHg)	57.7 (53.1 - 62.9)
	PVR (dyn.sec.cm^{-5})	758.7 ± 177.3
	CI (L/min/m^2)	2.1 ± 0.5
	SVO_2 (%)	53.9 ± 10.6
IVC filter		3 (15%)

* Tests were done only in 13 cases as the remaining cases had dyspnea at rest.

BMI: body mass index, VTE: venous thromboembolism, BMP, breaths/min CTEPH: chronic thromboembolic pulmonary hypertension PTE: pulmonary thromboendarterectomy, ms: months, N: total number, n: number of cases, mPAP: mean pulmonary artery pressure, CI: cardiac index, SVO_2: mixed venous oxygen saturation, PaO_2 partial arterial oxygen pressure.

Intra-operative data:

The mean **cardiopulmonary bypass time** was 114.2 ± 47.81 minutes. It took about 30–60 minutes to cool the patients down to (20°C) and rewarm them to normal body temperature. In 10 cases (50%), the CPB time was ≤ 100 minutes in 10 cases (50%), while in 2 cases (10%), the CPB time of ≥ 180 minutes.

The mean **deep hypothermic circulatory arrest time** for both pulmonary arteries together was 36 ± 4.7 minutes. In 15 cases (75%), the DHCA time was less than or equal to 40 minutes, while in 5 patients (15%), the DHCA time was longer than 40 minutes **(Table 2)**.

During surgery, one patient died from a catastrophic pulmonary haemorrhage. This patient was orthopneic with massive pericardial effusion and hypoxia (PaO_2 of 62.6 mmHg), which necessitated urgent intervention.

Table (2): Intraoperative variables

Parameters	**Results (n=20)**
CPB time (mins)	**114.2 ± 47.8**
• **≤ 100 min**	10 (50%)
• **101 – 140 mins**	4 (20%)
• **141 – 180 mins**	4 (20%)
• **> 180 mins**	2 (10%)
DHCA time (mins)	**36 ± 4.7**
• **DHCA ≤ 40 mins**	15 (75%)
• **DHCA > 40 mins**	5 (25%)
Intraoperative mortality	1(5%)

CPB: cardiopulmonary bypass, DHCA: deep hypothermic circulatory arrest, PTE: pulmonary thromboendarterectomy, mins: minutes.

Early postoperative outcomes:

The median **length of stay in the ICU** after surgery was 3 (3-4) days. The median **duration of MV** was 15 (10.25 – 25.5) hours. 13 cases (68.4%) had been extubated within one day, while the remaining 6 cases (31.6%) had prolonged mechanical ventilation. The mean **hospital stay** was 10.9 ± 2.12 days.

Concerning ICU and in-hospital mortality, there were two cases (10.5%) of postoperative mortality. One of them died as a result of severe RLI. The other case had protein C and protein S deficiency and died as a consequence of recurrent pulmonary embolism.

In terms of **hemodynamic outcomes**, six cases (35.3%) had NYHA-I, nine cases (52.9%) had NYHA-II, and two cases (11.8%) had NYHA-III. The mPAP was 24.3 ± 5.8 mmHg. The mean cardiac index was 3.4 ± 0.5 L/min/m2. The mean PVR was 201.9 ± 55.7 dyn.sec.cm-[5].

Table (3): Post-operative (ICU and in-hospital) outcomes

Parameter		**Results (n=19)**
Duration of MV (hours)		15 (10.25 – 25.5)
	≤24 hours	13 (68.4%)
	>24 hours (prolonged)	6 (31.6%)
ICU stay (days)		3 (3 – 4)
Hospital stay (days)		10.9 ± 2.12
ICU mortality		2 (10.5%)
Reperfusion lung injury		4 (21%)
Hemodynamic outcomes		
• NYHA on discharge (n=17)	• Class I	6 (35.3%)
	• Class II	9 (52.9%)
	• Class III	2 (11.8%)
• mPAP (mmHg)		24.3 ± 5.8
• CI before discharge		3.4 ± 0.5
• PVR before discharge ($dyn.s.cm^{-5}$)		201.9 ± 55.7

MV: mechanical ventilation, ICU: intensive care unit, NYHA: New York heart association, mPAP: mean pulmonary artery pressure, CI: cardiac index, PVR: pulmonary vascular resistance.

The impact of time between diagnosis and surgery on the postoperative outcomes:

The length of time between diagnosis and surgery in our patients was used in a logistic regression analysis as an independent factor for the various early postoperative outcomes that were reported above. It was found that this time has a significant correlation with the incidence of reperfusion lung injury, postoperative functional class, and the postoperative pulmonary vascular resistance.

Reperfusion lung injury:

Logistic regression analysis revealed that the longer the period between diagnosis and surgery, the higher the likelihood that a postoperative reperfusion acute lung injury will occur. Odds ratio and 95% CI were **1.92 (1.04 - 3.57), p value <0.01*.** The ROC curve displayed that the most significant criterion was (>16 months) of delay, after which RLI occurred in 3 cases out of the 4 cases with RLI in this study. In other words, 75% of RLI cases occurred in patients delayed for PTE by more than 16 months (p = 0.004). Error! Reference source not found.**2** and **Table** 4 displayed these values in details.

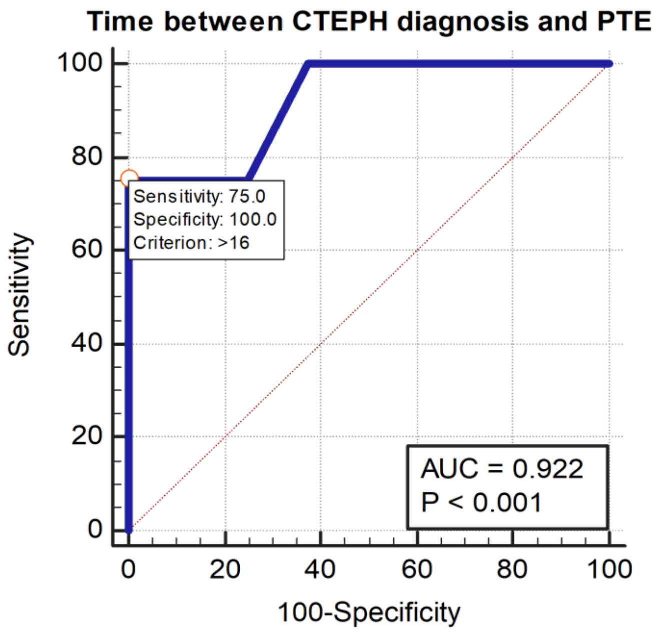

Figure (2): ROC curve correlating time delay for surgery in months and development of RLI. Note that cases presented to surgery within less than 16 months had lower rates of developing RLI.
RLI: reperfusion lung injury, CTEPH: chronic thromboembolic pulmonary hypertension, PTE: pulmonary thromboendarterectomy, AUC: area under the curve.

Table (4): Delay in having surgery and development of RLI.

RLI	Time between diagnosis and PTE ≤16 months	Time between diagnosis and PTE >16 months	Total
Not occurred	**15** (93.8%)	**0** (0.0%)	15 (78.9%)
occurred	**1** (6.3%)	**3** (100%)	4 (21%)
Total	16 (84.2%)	3 (15.8%)	19

RLI: reperfusion lung injury, PTE: pulmonary thromboendarterectomy.

NYHA Functional class:

Both HYHA III and NYHA IV were considered unfavorable FC after PTE, whereas NYHA I and II were considered favorable outcomes after surgery.

There were 15 cases (88.2%) achieved favorable FC, while only 2 cases (11.8%) had unfavorable FC following surgery. It was found that earlier presentation to surgery was significantly associated with more probability for having good postoperative functional class.

Odds ratio and 95% CI were 0.64 (0.39 - 1.02) and p value 0.02. The ROC curve revealed that postoperative functional class was significantly improved when patients underwent surgery within 13 months. Sensitivity and specificity were 93.3% and 100%, respectively **(Figure 3)**.

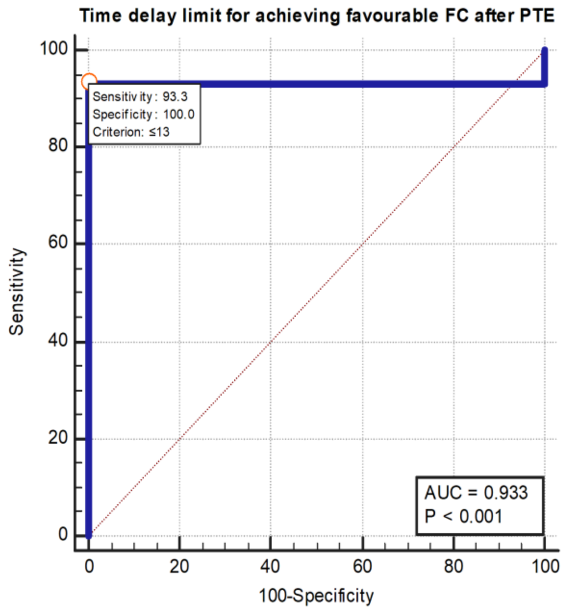

Figure (3): ROC curve showing that performing surgery within 13 months after diagnosis of CTEPH is the most sensitive and specific cut-off for predicting postoperative FC.
FC: functional class, PTE: pulmonary thromboendarterectomy, AUC: area under the curve.

Postoperative pulmonary vascular resistance:

Linear regression analysis showed that postoperative PVR was positively correlated to the time between CTEPH diagnosis and surgery. **r** = 0.8324 (0.62 – 0.93) and **p** value (<0.01). Therefore, the more the surgery was delayed, the higher the predicted postoperative PVR.

DISCUSSION

Chronic thromboembolic occlusion of the pulmonary arterial tree results in a form of pre-capillary pulmonary hypertension known as chronic thromboembolic pulmonary hypertension (CTEPH) [(1)]. This orphan disease is the only form of pulmonary hypertension that can be treated by surgical removal of the offending thromboembolic material [(7)].

Pulmonary thrombo-endarterectomy (PTE) is the treatment of choice in operable patients with surgically accessible lesions that account for the high PAP and PVR. However, its results differ between patients depending on different factors that may be beneficial or harmful [(8, 9)]. A number of changes in the operation technique have been evolved and most of the current experience comes from the University of California – San Diego medical center. This center now has more than 4000 cases with the best worldwide success rate and mortality of less than 1% [(10, 11)].

In this study, 20 patients underwent PTE by the same surgeon in Kasr El-Aini Hospitals between January 2014, and April, 2021. The aim of the study was to determine how the time intervening between the diagnosis of CTEPH and the surgery could affect the early postoperative outcomes.

It was found that this time interval was a strong predictor for postoperative functional class, pulmonary vascular resistance, and the incidence of postoperative reperfusion pulmonary edema.

The incidence postoperative reperfusion lung injury was significantly higher among patients delayed for surgery by more than 16 months.

Patients who underwent surgery after more than 13 months following their diagnosis were more likely to develop unsatisfactory postoperative functional classes (NYHA FC-III and IV).

There was a strong positive correlation between the time interval before surgery and the resulting postoperative PVR.

The former results are comparable to those of **Chen *et al.*** [10]**, Madani *et al.*** [11] **and Delcroix *et al.*** [12] who highlighted the importance of the time passed before surgery in determining the early results of PTE.

Furthermore, **Moser *et al.*** [13] initially described that CTEPH has dual mechanism that account for the resultant high PAP and PVR. **Dorfmüller *et al.*** [14] explained that both the proximal occluding thrombus and exposing the non-occluded vessels to high degree of pulmonary artery pressure cause irreversible distal pulmonary vascular changes (pulmonary micro-angiopathy) in both occluded and un-occluded pulmonary artery segments. This vascular remodeling involves the wall of distal muscular pulmonary arteries of 0.1-0.5 mm in diameter, and may reach arterioles and venules of less than 0.1 mm in diameter.

CONCLUSION AND RECOMMENDATIONS

It could be concluded that time is an important factor that accelerates the disease's progression. It gives a chance to develop distal pulmonary microvascular remodeling which in turn affects the post-PTE outcomes, resulting in residual pulmonary hypertension, high pulmonary vascular resistance, unacceptable postoperative functional class, and a higher incidence of reperfusion lung injury after pulmonary thromboendarterectomy.

Therefore, to get the best benefit from PTE, we strongly recommend early surgery once CTEPH is diagnosed in operable patients with good surgical targets.

LIMITATIONS

The main limitation of this study was the small sample size which may impact the reliability of our results. So, further studies are recommended to get more precise results in the future for this rare condition with relatively low rate of proper diagnosis.

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Author contribution: Authors contributed equally in the study.

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