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Predictors of Pulmonary Vascular Resistance after Pulmonary Thromboendarterectomy

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ABSTRACT
Background: pulmonary vascular resistance (PVR) is the most important postoperative parameter that drops dramatically after pulmonary thromboendarterectomy (PTE). It determines whether the endarterectomy procedure was successful and the presence of postoperative residual pulmonary hypertension.
Objectives: To measure predictors of postoperative PVR and residual pulmonary hypertension.
Patients and Methods: Through a prospective and retrospective study, 20 patients underwent PTE between June, 2019 and April, 2021.
Results: Postoperative PVR was affected by delay for surgery after diagnosis, preoperative PaO_2, preoperative PVR and cardiac index.
Conclusion: Better results can be obtained with early surgery, higher preoperative PaO_2 and cardiac index, and lower preoperative PVR.
Keywords: Chronic thromboembolic pulmonary hypertension, Mean pulmonary artery pressure, PVR, PTE.

INTRODUCTION
Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pre-capillary PH caused by obstruction of major pulmonary arteries [(1-3)]. The fibrosis of pulmonary artery thrombosis, which causes persistent blockage of the pulmonary arteries and is the pathologic characteristic of CTEPH, accounts for the elevated pulmonary vascular resistance in the afflicted individuals [(4-5)].

The five-year survival rate for untreated CTEPH is 30% and 10% in patients with mean pulmonary artery pressure (mPAP) more than 40 mmHg and 50 mmHg, respectively [(6)].

Pulmonary thromboendarterectomy is a potentially curative surgery for CTEPH. However, many patients may develop high postoperative PVR, which accounts for the postoperative residual pulmonary hypertension [(7-9)].
The study aimed to measure predictors of postoperative PVR and residual pulmonary hypertension.

PATIENTS AND METHODS
Study design
An interventional prospective and retrospective study was carried out in the Cardiothoracic Surgery Department at Kasr El-Aini Hospital in the period between June 2019 and April 2021. It involved 20 patients who underwent pulmonary thromboendarterectomy (PTE) by the same surgeon.

Inclusion criteria:
1. Previous pulmonary embolism caused by VTE with unexplained dyspnea (NYHA functional classifications II, III, and IV) after 3 months despite appropriate anticoagulation.
2. An echocardiogram showed a pulmonary artery pressure estimate of less than 25 mmHg, provided
3. that there were no chronic lung or cardiac conditions.
4. Mismatched substantial perfusion anomalies were discovered by a ventilation/perfusion scan.
5. Multislice CT Pulmonary angiography proved that the main pulmonary arteries or their lobar branches were blocked.
6. A right-sided heart catheter (RHC) demonstrated PVR of less than 300 dyn.s.cm-5 and a mPAP of more than 30 mmHg.

Exclusion criteria
1. A disease that is surgically inaccessible.
2. Other pulmonary conditions that are present simultaneously, such as severe parenchymal lung problems lesions that contribute to pulmonary hypertension or lung cancer.
3. Coexisting heart problems that could necessitate multiple cardiac procedures or render individuals inoperable.

Pre-operative assessment:
A thorough medical history and examination were taken in order to determine surgical candidacy. Investigations included laboratory testing, chest X-rays, echocardiograms, ventilation/perfusion scans, MSCT pulmonary angiography, and right heart catheterization. Four days before the procedure, warfarin was stopped and replaced with low molecular weight heparin. Surgery was allowed once the INR reached 1.3.

The operation:
1. Anesthetic management:
Under general endotracheal intubation, after connecting monitoring lines as in conventional cardiac surgery, a Swann-Ganz catheter was inserted along with TEE, and thermal probes.

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2. Operative technique:

In supine position, routine preparations were carried out likewise in standard cardiac surgery. Pericardiotomy and median sternotomy were performed. After thorough heparinization with intravenous unfractionated heparin (400 units/kg) and a goal activated clotting time > 400 seconds, CPB was formed using aorto-bicaval cannulation. The venae caval snares, LV, and pulmonary artery vents were all inserted. As low as 20°C was permitted for systemic hypothermia. Cardioplegia was administered using antegrade cold blood cardioplegia while an aortic cross clamp was in place. While giving cardioplegia, the ascending aorta was dissected from the SVC and RPA. Prior to performing the correct pulmonary arteriotomy, the ascending aorta and SVC were retracted from one another to gain access to the RPA.

Due to the fact that an arteriotomy had been done and the core temperature had reached profound hypothermic levels, circulatory arrest began to provide a bloodless field sufficient for a thorough and successful endarterectomy. It can take up to 20 minutes before circulation is restored for 10 minutes. To work on the left PA in the same way as the right pulmonary endarterectomy, another 20-minute DHCA session is required. The specimen was prepared on either side, then placed on a table to be evaluated for the inner branch shape and pulmonary artery segment configuration till its distal tail terminates (figure 1).

Figure (1): Pulmonary thromboendarterectomy specimen taking the shape of both pulmonary arteries it was extracted from a patient in our series.

Rewarming was permitted gradually to euthermic levels in 15 to 20 minutes while the left pulmonary arteriotomy was being closed. After deairing the heart, the cross-clamp may be taken off, and subsequently the CPB lines could be withdrawn. Two mediastinal chest drains were inserted after obtaining enough hemostasis, and after that, the sternotomy and wound closure could be finished.

3. Post-operative care:

On a mechanical ventilator, with or without inotropes or IV milrinone, patients were sent to the intensive care unit. Every patient had monitoring of their invasive blood pressure, oxygen saturation, central venous pressure, Swann-Ganz readings, and urine output.

Ethical approval: The Ethics Committee of Cairo University's Faculty of Medicine granted the study approval. All participants signed informed consents after a thorough explanation of the goals of the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Using SPSS version 21, percentages were used to describe categorical data. The mean and standard deviation are two terms used to represent parametric data. The median and interquartile range were used to describe non-parametric data. Categorical variables were analysed using the chi-square test. A linear regression analysis was utilized to determine the degree of the predictors' contributions to postoperative PVR. Using the ROC curve, the highest sensitive and specific postoperative PVR at which there was no residual pulmonary hypertension was identified [10, 11, 12]. P values ≤ 0.05 were regarded as significant.

RESULTS

Baseline characteristics:

The study was carried out on 11 men (55%) and 9 women (45%). The participants were aged from 20 to 62 years, with a mean age of 41.7 ± 10.14 years. BMI was 22.5 ± 5.3 on average. 18 (90%) of the patients had VTE in the past. The average time between the last VTE event and the CTEPH diagnosis was 14.9 ± 4.8 months. Between the diagnosis of CTEPH and having surgery, it took an average of 11.5 (10–14.5) months. Eleven patients (55%) had FC-III, seven patients (35%) had FC-IV, and the two remaining patients (10%) had FC-II in terms of preoperative hemodynamic and respiratory condition. At rest, the average breathing rate was 17.3±1.9 breaths per minute. All patients had their post-exercise respiratory rates measured, with the exception of the seven patients who had FC-IV, where the rate averaged 31.6 ± 3.4 breaths per minute. The mean arterial oxygen pressure (PaO_2) was 71.7 ± 9.4 mmHg.

Prior to surgery, echocardiography revealed that four patients (20%) had normal RV dimensions. Five patients (25%) had mild RV dilatation, seven (35%) had moderate RV dilatation, and four other patients (20%) had a severely enlarged RV. The TAPSE (tricuspid annulus plane systolic excursion) was 2.36 ± 0.39 on average. Surgery was performed on four patients (20%) with no tricuspid regurgitation. Four other patients (20%) had mild tricuspid valve regurgitation. Four more patients (20%) had a moderate tricuspid regurgitation. Before having PTE, eight patients had a severe degree of tricuspid regurgitation. The median of mPAP was 57.7 (53.1 - 62.9) mmHg using the right heart catheter (RHC). The mean PVR was 758.7 ± 177.3 dyn.sec.cm-5. The average cardiac index was 2.4 ± 0.5 L/min/m^2. The demographics of the patients were outlined in as shown in table (1).

Table (1): Patients demographics before surgery

Total number		**N=20**
Clinical review	Age (years)	41.7 ±12.6
	Sex	
	1. Male	11 (55%)
	2. Female	9 (45%)
	BMI	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	
	3. Class II	2 (10%)
	4. Class III	11 (55%)
	5. 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
Echocardiography	Right ventricle size	
	6. Normal sized	4 (20%)
	7. Mildly dilated	5 (25%)
	8. Moderately dilated	7 (35%)
	9. Severely dilated	4 (20%)
	Degree of tricuspid regurge	
	10. Normal valve	4 (20%)
	11. Mild regurge	4 (20%)
	12. Moderate regurge	4 (20%)
	13. Severe regurge	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 average time required for cardiopulmonary bypass was 114.2 ± 47.81 minutes. The patients had to be cooled to 20°C and then warmed back up to their normal body temperatures, which took around 30 to 60 minutes. The CPB time was ≤ 100 minutes in 10 instances (or 50%), and ≥180 minutes in 2 cases (10%).

The mean DHCA time was 36 ± 4.7 minutes. In 15 cases (75%), the DHCA time was under or equal to 40 minutes, it was longer than 40 minutes in 5 patients (15%). One patient passed away during surgery due to a serious lung haemorrhage. This patient needed immediate PTE since they were orthopneic, had a significant pericardial effusion, and had hypoxia (PaO_2 of 62.6 mmHg) (Table 2).

Table (2): Intraoperative variables

Parameters		**Results (n=20)**
Cardiopulmonary bypass time (mins)		**114.2 ± 47.8**
1.	**≤ 100 min**	10 (50%)
2.	**101 – 140 mins**	4 (20%)
3.	**141 – 180 mins**	4 (20%)
4.	**> 180 mins**	2 (10%)
DHCA time (mins)		**36 ± 4.7**
5.	**DHCA ≤ 40 mins**	15 (75%)
6.	**DHCA > 40 mins**	5 (25%)
Video-assisted angioscope		
7.	**Used**	6 (30%)
8.	**Not used**	14 (70%)
Intraoperative mortality		1 (5%)

Predictors for postoperative pulmonary vascular resistance:

According to the outcomes of a linear regression study, the interval between the diagnosis of CTEPH and surgery had a strong positive link with postoperative PVR, as well as with preoperative PVR and cardiac index. On the other hand, the correlation between postoperative PVR and preoperative PaO_2 changes was negative. The extent of these correlations was shown in table (3).

Table (3): Linear regression analysis for postop. PVR with its significant predictors

Predictor	**Correlation coefficient (r)**	**95% CI**	**p value**
Time since diagnosis	0.8324	0.62 – 0.93	<0.01
Preop. PaO_2	-0.5042	-0.77 – -0.08	0.02
Preop. PVR	0.7632	0.48 – 0.90	<0.01
Preop. CI	-0.6741	-0.86 – -0.33	<0.01

It was found that achieving a postoperative PVR ≤ 222 dyn.sec.cm^{-5} was associated with postoperative mPAP ≤ 25 mmHg (i.e., no residual PH). Using this cut-off value, there were 13 cases out of 17 (76.4%) had postoperative PVR ≤ 222 dyn.sec.cm^{-5} and only 4 cases (23.5%) had PVR higher than 222 dyn.sec.cm^{-5}.

Further analysis revealed that a preoperative mPAP values less than or equal to 61 mmHg was the most significant independent variable associated with a good PVR after surgery (i.e.: ≤ 222 dyn.sec.cm^{-5}) In our study, there were 13 cases with preoperative mPAP ≤ 61 mmHg, 10 cases of them (76.9%) developed good postoperative PVR and associated with no residual PH (Figures 2, 3 & 4).

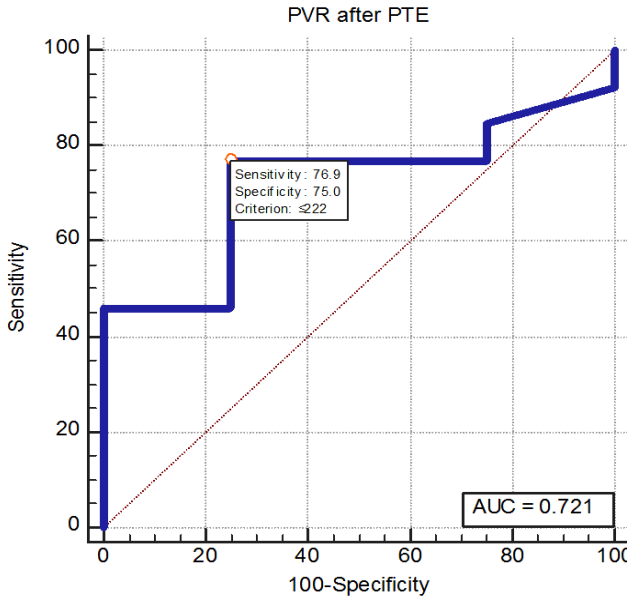

Figure (2): ROC curve showing that postoperative PVR ≤ 222 dyn.sec.cm^{-5} was strongly associated with postoperative PH ≤ 25 mmHg.

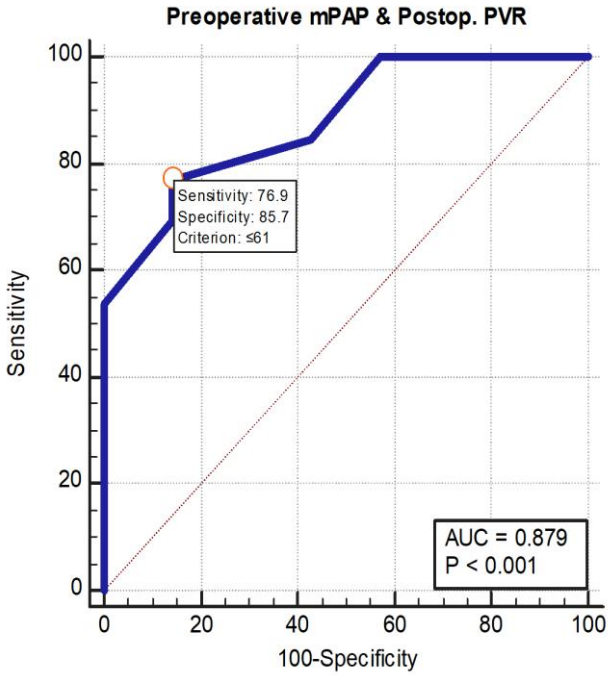

Figure (3): ROC curve showing that preoperative mPAP ≤ 61 mmHg was significantly associated with PVR ≤222 dyn.sec.cm^{-5}.

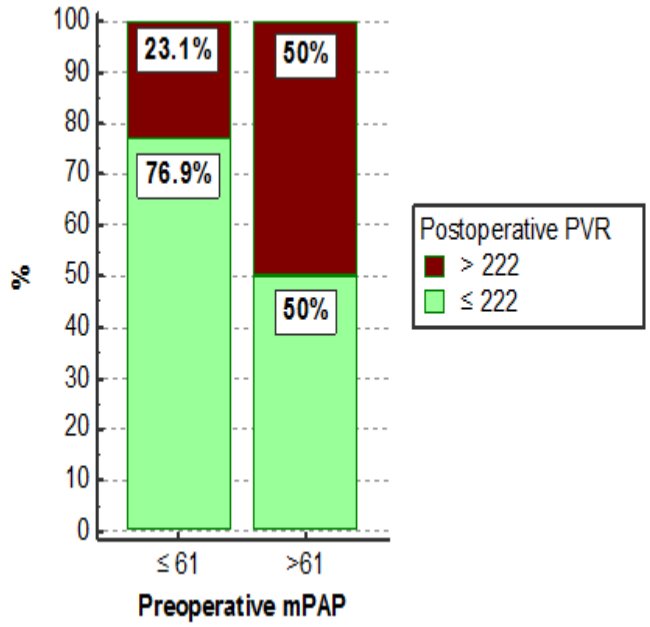

Figure (4): Preoperative mPAP and postoperative PVR

DISCUSSION

CTEPH represents a distinctive subset of pre-capillary pulmonary hypertension characterized by the occlusion of the pulmonary arterial tree due to the presence of organized thromboembolic material [(1)]. This occlusive phenomenon arises from the incomplete resolution of acute pulmonary embolism, whereby thrombi persist within the pulmonary vasculature, leading to the formation of fibrous tissue that adheres to the vessel walls and induces persistent obstruction [(10-11)].

The pathogenesis of CTEPH involves a complex interplay of molecular, cellular, and hemodynamic factors. The process usually begins with the initial event of acute pulmonary embolism, wherein a thrombus obstructs one or more pulmonary arteries. However, in CTEPH, the unresolved thrombus undergoes a series of intricate changes, including organization and fibrosis, ultimately resulting in the characteristic diffuse obstruction observed throughout the pulmonary arterial system [(12)]. Alongside the mechanical obstruction caused by the organized thromboembolic material, a cascade of pathological alterations ensues within the affected vessels. These changes encompass intimal fibrosis, medial hypertrophy, recanalization, and angiogenesis collectively contributing to the remodeling process. Consequently, these vascular remodeling processes not only perpetuate the persistent obstruction but also lead to increased pulmonary vascular resistance, elevated pulmonary arterial pressure, and subsequent right ventricular dysfunction [(1,2, 13)]. However, several independent studies, such as those conducted by **Dorfmüller *et al.* [(14)], Ghigna and Dorfmüller** [(15)] and **Moser and Bloor** [(16)] highlighted that the initial pre-capillary thromboembolic lesions alone do not account for the entirety of the pathological processes involved in the evolution of the disease and its associated symptoms. Rather, there is evidence of the presence of pulmonary microvasculopathy (small vessel disease) in varying degrees, which develops gradually over time and contributes to the observed elevation in mPAP and PVR.

Pulmonary thromboendarterectomy is the only curative option for CTEPH in operable patients when the lesions were surgically accessible. If PTE is performed before the development of pulmonary microangiopathy, it is typically followed by a dramatic decrease in PVR [(1, 3, 8, 17)].

In our study, according to the outcomes of a linear regression study, the interval between the diagnosis of CTEPH and surgery had a strong positive link with postoperative PVR, as well as with preoperative PVR and cardiac index. On the other hand, the correlation between postoperative PVR and preoperative PaO_2 changes was negative. It was found that achieving a postoperative PVR ≤ 222 dyn.sec.cm^{-5} was associated with postoperative mPAP ≤ 25 mmHg (i.e. no residual PH). Using this cut-off value, there were 13 cases out of 17 (76.4%) had postoperative PVR ≤222 dyn.sec.cm^{-5} and only 4 cases (23.5%) had PVR higher than 222 dyn.sec.cm^{-5}.

In a linear regression analysis, postoperative PVR was found to be positively correlated with both the time delay for surgery after CTEPH diagnosis and the preoperative PVR while it was negatively correlated with changes in preoperative PaO_2 and cardiac index. The study defined a good PVR as the post-operative value associated with no residual pulmonary hypertension. The mPAP value was set at levels lower than or equal to 25 mmHg following the WHO definition for PH [(18)]. This cut-off yielded a PVR lower than or equal to 222 dyn.sec.cm^{-5}. In accordance with this threshold, further analysis revealed that preoperative mPAP served as a significant independent predictor of good postoperative PVR. Moreover, A preoperative mPAP lower than 61 mmHg was strongly associated with a good PVR.

In our study, analysis revealed that a preoperative mPAP values less than or equal to 61 mmHg was the most significant independent variable associated with a good PVR after surgery (i.e.: ≤ 222 dyn.sec.cm^{-5}). In our study, there were 13 cases with preoperative mPAP ≤ 61 mmHg, 10 cases of them (76.9%) developed good postoperative PVR and associated with no residual PH.

The study of **Kunihara and colleagues** [(19)] utilized PVR as the primary measure to assess the haemodynamic outcome. Their findings revealed that both male gender and lower preoperative mPAP were correlated with favorable postoperative PVR.

The significance of timely diagnosis and treatment of CTEPH with early pulmonary thromboendarterectomy was underscored by both **Gerges and Yacoub** [(20)] and **Humbert *et al.*** [(21)]**.** Their research emphasized the potential ramifications of delayed diagnosis, including the emergence of postoperative residual pulmonary hypertension and elevated pulmonary vascular resistance. This, in turn,

increased the probability of patients requiring pulmonary vasodilator medications after surgery. As a result, it was imperative to detect and address CTEPH at an early stage to halt this preventable progression of the disease.

LIMITATIONS

The study had some limitations that may affect the results. The small sample size was due to the low incidence of the disease and diagnosis rate. Even though other studies suggest the use of ECMO, it couldn't be utilized here due to financial limitations. As a result, in certain instances, it was challenging to provide proper postoperative care. An additional factor that contributed to an overall dismal survival rate was the delay in surgery following diagnosis.

CONCLUSION

Lower PVR levels can be obtained with early PTE, higher preoperative PaO_2 and cardiac index, and lower preoperative PVR.

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Competing interests: Nil.

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