*Original*

# *Article* **Extracorporeal Mechanical Circulatory Support after Pulmonary Thromboendarterectomy: Experience of One Center**

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**Purpose: Pulmonary thromboendarterectomy (PTE) is the treatment for patients with chronic thromboembolic disease. In the immediate postoperative period, some patients may still experience life-threatening complications such as reperfusion lung injury, airway bleeding, and persistent pulmonary hypertension with consequent right ventricular dysfunction. These issues may require support with extracorporeal membrane oxygenation (ECMO) as a bridge to recovery or lung transplantation. This study aims to analyze our series of PTEs that require ECMO.**

**Methods: A descriptive and retrospective analysis of all PTE performed at the Favaloro Foundation University Hospital was conducted between March 2013 and December 2023. Results: A total of 42 patients underwent PTE with a median age of 47 years (interquartile range: 26–76). The incidence of patients with ECMO was 26.6%, of which 53.6% were veno-venous (VV) ECMO. Preoperatively, a low cardiac index (CI), high right and left filling pressures, and high total pulmonary vascular resistances (PVRs) were associated with ECMO with a statistically significant relationship. The hospital mortality was 11.9%, and the mortality in the ECMO group was 45.5%, with a statistically significant relationship. Veno-arterial ECMO has a worse prognosis than VV ECMO.**

**Conclusions: Preoperatively, a low CI, high right and left filling pressures, and high total PVRs were associated with ECMO after PTE.**

**Keywords:** chronic thromboembolic pulmonary hypertension, pulmonary thromboendarterectomy, extracorporeal membrane oxygenation, ECMO

# **Introduction**

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by the obstruction of the pulmonary arteries and their branches due to one or multiple episodes

of pulmonary embolisms and incomplete resolution of thrombi. The subsequent increase in pulmonary vascular resistance (PVR) is due to mechanical obstruction by thrombi in the proximal pulmonary arteries as well as the progressive development of arterial vasculopathy in the

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small pulmonary vessels. Pulmonary hypertension (PH) develops in 4% of patients with thromboembolic disease in the first 2 years after pulmonary embolism. $1,2$ )

Pulmonary thromboendarterectomy (PTE) is the treatment of choice for most of these patients. The procedure involves the removal of obstructive fibrotic tissue or fresh thrombi from the pulmonary arteries during total circulatory arrest and profound hypothermia. The decision to undergo a surgical procedure is based on the severity of symptoms, the quantity and accessibility of thromboembolic lesions (Jamieson classification), the degree of hemodynamic impairment, and the presence of comorbidities. $1,3,4$ )

The survival rate of patients with CTEPH has significantly improved since the introduction of surgical treatment in 1973. Currently, the 5-year survival rate is 75%–82%, whereas in the pre-PTE era, survival was  $20\% - 50\%$ . 4-8)

Perioperative mortality of PTE has improved markedly with advances in both technology and surgical technique. Early reports indicated a mortality rate close to 13%, whereas currently, it is estimated to be between 2.2% and  $4.7\%$ ,  $^{1,3,7,9}$  At our institution, the reported mortality in a 2011 analysis was  $17\%$ .<sup>10)</sup> The main risk factors for mortality are preoperative PVR exceeding 1000 dyn\*s/ cm5, postoperative PVR exceeding 500 dyn\*s*/*cm5, and distal thromboembolic disease type III/IV according to the Jamieson classification.<sup>2,11,12)</sup>

Despite improvements in outcomes, some patients may still experience life-threatening complications such as reperfusion lung injury, airway bleeding, and persistent PH with consequent right ventricular dysfunction. These complications may require mechanical circulatory support with extracorporeal membrane oxygenation (ECMO) as a bridge to recovery or lung transplantation. The reported incidence of ECMO in recent series is around 3%, with mortality ranging from 30% to 65%.4,12–18)

In patients with persistent postoperative PH, two subgroups are identified: the first may be due to local trauma from cardiopulmonary bypass (CPB) and reperfusion pulmonary edema with temporary residual PH that can cause transient right ventricular dysfunction. This form of respiratory failure has been reported in 5%–20% of PTE cases and 10%–20% of lung transplant cases. The second subgroup belongs to Jamieson classification type III or IV, meaning a more distal disease or difficult-toaccess distal vasculopathy that significantly contributes to persistently high PVR, leading to hemodynamic and/ or pulmonary deterioration. Both groups are candidates for ECMO.3,4,16,17)

This study aims to analyze and describe our series of PTE with ECMO performed in the last 10 years, as well as to evaluate potential risk factors, complications, and mortality.

# **Materials and Methods**

A descriptive, observational, and retrospective analysis of all pulmonary thromboendarterectomies performed at the Favaloro Foundation University Hospital was conducted from March 2013 to December 2023. A subgroup analysis was performed on those patients with ECMO.

Demographic, intraoperative, and postoperative characteristics of all patients were analyzed. Functional class (FC) was assessed according to the New York Heart Association classification. The Jamieson classification was used for CTEPH classification.

The following echocardiographic variables were analyzed both pre- and postoperatively: left ventricular ejection fraction considered normal >55%, mild 55%–40%, moderate 40%–30%, and severe <30%. Right ventricular ejection fraction was categorized as mild (35%–30%), moderate  $(30\%-25\%)$ , or severe  $(\le 25\%)$  according to fractional area change. Tricuspid annular plane systolic excursion in millimeters, the basal diameter of the right ventricle in millimeters (mm), and the severity of tricuspid regurgitation as mild, moderate, or severe. Pulmonary artery systolic pressure in mmHg and the presence of mild  $(<10$  mm), moderate  $(10-20$  mm), or severe  $(>20$ mm) pericardial effusion were also evaluated.

Invasive measurements, including mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), cardiac output (CO), cardiac index (CI), PVR in dyn\*s/cm5, and total PVR (TPVR) calculated using the following formula: mPAP/CO. Preoperative right heart catheterization was performed and for postoperative assessment, the last measurement from the pulmonary artery catheter before removal was taken, with pulmonary diastolic pressure replacing PCWP on this occasion. Residual PH was considered in patients with mPAP >30 mmHg or those with less than a 50% decrease in both PVR and TPVR.

The surgical technique was described by Daily PO and extensively developed by SW Jamieson at the University of San Diego.3,18,19) All procedures were performed by a single surgeon. Thromboendarterectomies were performed via median sternotomy, always bilaterally, starting with the right pulmonary artery. The technique requires CPB, deep hypothermia (17°C), and intermittent circulatory arrest of up to 20 minutes with periods of reperfusion. Hemodilution was performed to decrease blood viscosity, maintaining the hematocrit between 18% and 25% during deep hypothermia and circulatory arrest. Cold antegrade cardioplegia was administered after aortic clamping for myocardial protection. Cerebral protection during circulatory arrest was achieved with sodium thiopental, phenytoin 15 mg/kg, and local cold. One gram of methylprednisolone was administered. During rewarming, 500 mg of methylprednisolone was added.<sup>18,20)</sup>

Intraoperative data included CPB time, aortic clamping time, circulatory arrest time in minutes, closure of patent foramen ovale, tricuspid valve repair, or concomitant coronary artery bypass grafting.

For patients with ECMO, analysis included whether it was veno-arterial ECMO (VA ECMO) or veno-venous ECMO (VV ECMO) and whether its placement was pre-, intra-, or postoperative. Causes for mechanical support with ECMO were classified as follows: severe hypoxemia (oxygen partial pressure/inspired oxygen fraction <100) associated with reperfusion injury, right ventricular dysfunction associated with severe hypoxemia/reperfusion injury, biventricular dysfunction associated with severe hypoxemia/reperfusion injury, and severe hypoxemia associated with airway bleeding.

Postoperative complications evaluated included length of stay, days on mechanical ventilation, stroke, renal replacement therapy (RRT), sepsis, life-threatening airway bleeding, low CO syndrome, atrial fibrillation (AF), and cardiac tamponade. Reperfusion injury was categorized according to the Berlin definition of acute respiratory distress syndrome.<sup>21)</sup> Finally, overall mortality and specific mortality in the ECMO group were analyzed.

Data were analyzed using Stata 13 software. Categorical variables were expressed as absolute value and percentage, continuous variables were expressed as mean and standard deviation, or as median and interquartile range (IQR) as appropriate. The 75th percentile of hospitalization duration was used to define prolonged hospitalization, which was greater than 15 days. Categorical variables were analyzed using chi-squared, or Fisher's exact test as appropriate, and continuous variables were compared using the T-test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. A p-value less than 0.05 was considered significant.

## **Results**

A total of 42 patients underwent PTE between March 2013 and December 2023, with a median age of 47 years (IQR: 26–76), and 59.5% were female. The main etiologies of thromboembolic disease were deep venous thrombosis/recurrent pulmonary embolism in 42.9% of cases, thrombophilia in 38.1%, and 2.4% associated with embolisms secondary to intracardiac devices. Demographic variables are shown in **Table 1**, with no significant differences between groups.

The incidence of patients with ECMO was 26.6% (11/42) of which 53.6% (7/11) were VV ECMO and the rest (4/11) were VA ECMO. There was only one patient with VA ECMO who required extending the support to veno-arterio-venous ECMO. Only two mechanical assist devices were placed postoperatively, the remaining nine were intraoperative (81.8%).

**Tables 2** and **3** describe the preoperative right heart catheterization and echocardiography of the ECMO and non-ECMO groups, demonstrating the association of severe right ventricular dilatation (>57.4 mm) with the ECMO group  $(p \le 0.02)$ . Furthermore, CO lower than 3.3 L/min, CI lower than 1.8 L/min/m<sup>2</sup> (p <0.004) and p <0.005, respectively), as well as right and left filling pressures higher than 15 mmHg ( $p < 0.0004$  and p <0.003, respectively), and TPVRs higher than 1457  $dyn*s/cm<sup>5</sup>$  (p <0.0002) were significantly associated with the ECMO group.

Moreover, a mPAP greater than 53 mmHg also showed a statistical trend toward mechanical support with ECMO. The variables associated with ECMO are summarized in **Fig. 1**.

There were no significant differences between both groups in intraoperative variables such as CBP time (median 218 minutes vs. 260 minutes,  $p \le 0.09$ ), crossclamp time (median 128 minutes vs 130 minutes, p <0.57), or circulatory arrest time (median 49 minutes vs. 56 minutes, p <0.18) for the group without ECMO and with ECMO, respectively. Closure of the patent foramen ovale was performed in 4/11 (36.4%) of patients in the ECMO group and 6/31 (19.3%) of patients without ECMO. Only two patients underwent tricuspid valve repair, one in each group. Also, four patients underwent coronary artery bypass grafting; two of them were in the ECMO group.

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a: median and interquartile range 25%–75%; b: mean; c: diffusing capacity for carbon monoxide.

DVT/PE: deep venous thrombosis/pulmonary embolism; Acute PE: acute pulmonary embolism; NYHA: New York Heart Association; FEV<sub>1</sub>: forced expiratory volume in 1 second; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; CTEPH: chronic thromboembolic pulmonary hypertension, Jamieson classification; ECMO: extracorporeal membrane oxygenation

The causes for using ECMO are detailed in **Fig. 2**. The median length with ECMO was 7 days (IQR: 1–9), and weaning was achieved in 63.6% of patients. Only one patient died post-weaning due to septic shock with multiorgan failure. Length of stay was 14 days (IQR:

11–22) for the non-ECMO group and 37.5 days (IQR: 30–61) for the ECMO group, with a statistically significant difference (p <0.0008).

Postoperative complications are shown in **Table 4**. Among them, significant differences were found in



#### **Table 2 Preoperative echocardiogram**

a: mean and standard deviation.

ECMO: extracorporeal membrane oxygenation





a: mean and standard deviation; b: median and interquartile range 25%–75%.

ECMO: extracorporeal membrane oxygenation

favor of the ECMO group for RRT, hemorrhagic stroke, mechanical ventilation time, airway bleeding, sepsis, AF, cardiac tamponade, and blood transfusion.

The total hospital mortality was 11.9% (5/42), and the mortality in the ECMO group was 45.5% (5/11), with a statistically significant relationship (p <0.0001). Within the ECMO settings, mortality for the VA ECMO group was 100% (4/4), while for the VV ECMO was 14.2%  $(1/7)$  (p <0.0001), showing that isolated lung support has a better prognosis.

A total of five patients died in the ECMO group; the causes of these deaths were as follows: three due to bleeding and refractory coagulopathy, one due to septic shock, and one from hemorrhagic stroke.

Among the ECMO group, patients who died had higher postoperative TPVR than those who did not  $(1848 \pm 656 \text{ mmHg vs } 1131 \pm 446 \text{ mmHg, respectively})$ with a statistical trend ( $p < 0.06$ ). On the other hand, of the patients who died in the ECMO group, 80% (4/5) of them had an advanced preoperative FC. Poor prognostic factors for ECMO assistance are summarized in **Fig. 3**.

Regarding residual PH defined as mPAP >30 mmHg, an incidence of 72% was found for the ECMO group vs 12.9% for the non-ECMO group, which was statistically significant ( $p \le 0.0002$ ). In addition, there was a statistical significance in the mortality of this subgroup, as 80% (4/5) of patients with ECMO who died had residual



**Fig. 1** Preoperative variables associated with ECMO after pulmonary endarterectomy. RV: right ventricle; TPVR: total pulmonary vascular resistance; CI: cardiac index; RAP: right atrial pressure; PCWP: pulmonary capillary wedge pressure; ECMO: extracorporeal membrane oxygenation

PH with mPAP  $>30$  mmHg ( $p < 0.006$ ). However, when we used the definition of residual PH as a less than 50% reduction of both PVRs and TPVRs, this relationship could not be confirmed.

## **Discussion**

Despite significant advances in the management of CTEPH, PTE remains the only curative therapeutic option for many patients. However, it is a highly complex surgical procedure that involves substantial respiratory and cardiovascular risks in the immediate postoperative period. In this context, ECMO emerges as a crucial tool for hemodynamic and respiratory support.

Regarding preoperative hemodynamic variables, most of the authors identify high PVR as a factor associated with ECMO circulatory support, while we also include both high ventricular filling pressure and low CI as potential factors associated with ECMO after thromboendarterectomy.11–14,16,17) The Jamieson classification did not show statistical significance regarding mortality or ECMO assistance in our analysis. However, among patients who died in the ECMO group, 80% had an advanced preoperative FC, indicating it may be a risk factor for mechanical assistance, although our statistical power was not sufficient.

Kelava et al., in their study of 150 patients undergoing PTE, revealed that patients who died within the ECMO group had a higher incidence of right ventricular dysfunction. This partially aligns with our analysis, showing that severe right ventricular dilatation, regardless of dysfunction, is an associated risk for ECMO assistance after PTE.15)

The incidence of ECMO reported by the abovementioned author was 9.3%. The duration of ECMO assistance was comparable to our analysis, of 7.3 days, with a mortality rate of 57%. The mortality rate with VA ECMO was also  $100\%$ , consistent with our report.<sup>15)</sup>

Similarly, Thistlethwaite et al., in their analysis of 1790 patients undergoing PTE between 1990 and 2006, found that only 1.12% received VV ECMO. Successful weaning occurred in 40% of cases, with two deaths occurring after decannulation. The hospital mortality rate for the mechanically assisted group was 70%, with all these patients classified as Jamieson III/IV. Pneumonia was the main complication, while RRT occurred in 45% of patients, and sepsis accounted for  $21\%$ .<sup>17)</sup>

Other authors reported an RRT incidence of 25%, as well as longer clamping and circulatory arrest times, more days of hospitalization, and longer durations of mechanical respiratory assistance in the ECMO group with respect to the non-ECMO group, similar to our study.<sup>16,22)</sup>

Hospital mortality rates for the ECMO group reported by other authors were also similar to ours, 51.6% for Boulate et al. and 40% with a significant increase in the first month, according to Nierlich et al. Regarding mortality according to ECMO configuration, Kelava et al. reported that all patients with VV ECMO survived. In our analysis, we also found that patients with VV ECMO had a better prognosis with a survival rate of 85.8%, while patients with VA ECMO had a mortality rate of  $100\%$ , 15, 16, 22)

Taking into account residual PH, there is still no consensus on its definition. In their prospective multicenter analysis, Mayer et al. define residual PH as a mean pulmonary arterial pressure >25 mmHg or systolic pulmonary artery pressure >40 mmHg on echocardiogram. The reported incidence of residual PH by this group of authors was 16% with a hospital mortality rate of 4.7%. However, this mortality rises to 10% when postoperative PVR exceeds 1200 dyn\*s/cm<sup>5</sup>, regardless of mPAP, indicating that persistently high PVR after PTE is an independent risk factor for mortality. On the other hand,



**Fig. 2** Causes of ECMO assistance after pulmonary endarterectomy. ECMO: extracorporeal membrane oxygenation





a: median and interquartile range; b: ratio of arterial oxygen pressure to inspired oxygen fraction. PAFI: PaO2/FiO2.

contrary to the aforementioned author, we did not find statistical significance when defining residual PH with respect to PVR and TPVR.1)

Likewise, Freed et al. used a mPAP >30 mmHg to define residual PH as Riedel et al. indicated that this is the cutoff value that affects survival. The incidence of residual PH according to this analysis was  $31\%$ .<sup>5,6)</sup>

In our study, residual PH defined as mPAP >30 mmHg occurred in 72.7% of the ECMO group vs 12.9% in the non-ECMO group (p <0.0002). Furthermore, mortality was higher and statistically significant for those patients with ECMO who remained with residual PH ( $p < 0.006$ ).

Other authors have shown that higher postoperative PVR correlates with increased mortality. When postoperative PVR is less than 900 dyns/cm<sup>5</sup>, between 900 and 1200 dyns/cm5, or greater than 1200 dyn\*s/cm5, mortality rates increase by 4%, 10%, and 20%, respectively.13) However, we observed that within the ECMO group, *Bertazzo B, et al.*



**Fig. 3** Poor prognostic factors in the ECMO group. TPVR: total pulmonary vascular resistance; PH: pulmonary hypertension; mPAP: mean pulmonary artery pressure; ECMO: extracorporeal membrane oxygenation

patients who died had a higher TPVR than those who survived, showing a statistical trend in this relationship.

The main limitation of our study is the retrospective design and the limited number of patients. This did not allow us to draw significant conclusions comparing the results between patients with ECMO who died versus those who did not.

# **Conclusions**

Among preoperative variables, severe right ventricular dilatation, low CI, high filling pressures, and high TPVRs were significantly associated with the ECMO group after PTE.

Residual PH and postoperative TPVR had a significant association with the ECMO group.

As we have observed, ECMO emerges as a tool for pulmonary and hemodynamic support following PTE. While the associated mortality remains high compared to patients who did not receive ECMO, it constitutes an effective tool for supporting the patient until the underlying cause that led to mechanical assistance is resolved. Within the configurations, VA ECMO implies a worse prognosis than VV ECMO.

It is imperative to conduct randomized clinical trials to highlight these potential risk factors mentioned as well as their prognostic value.

#### **Declarations**

**Ethics approval and consent to participate** Not applicable.

#### **Consent for publication**

Not applicable.

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# **Data availability statement**

Not applicable.

#### **Author contributions**

Brunella Bertazzo: main author, biographical research, data collection, and manuscript writing.

Alejandro Cicolini: biographical research and data collection.

Martin Fanilla: statistical analysis.

Liliana Favaloro: revision of the manuscript.

Jorge Caneva: revision of the manuscript.

Roberto R. Favaloro: final revision of the manuscript.

#### **Disclosure statement**

The authors declare no conflict of interest.

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