# Pulmonary Endarterectomy Surgery for Chronic Thromboembolic Pulmonary Hypertension: A Small-Volume National Referral Center Experience

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**ABSTRACT:** **Background:** Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, distinct pulmonary vascular disease, which is caused by chronic obstruction of major pulmonary arteries. CTEPH can be cured by pulmonary endarterectomy (PEA). PEA for CTEPH is a challenging procedure, and patient selection and the perioperative management are complex, requiring significant experience.

**Objectives:** To describe the establishment of a national CTEPH–PEA center in Israel and present results of surgery.

**Methods:** In this study, we reviewed the outcomes of PEA in a national referral, multi-disciplinary center for CTEPH–PEA. The center was established by collaborating with a high-volume center in Europe. A multidisciplinary team from our hospital (pulmonary hypertension specialist, cardiac surgeon, cardiac anesthesiologist and cardiac surgery intensivist) was trained under the guidance of an experienced team from the European center.

**Results:** A total of 38 PEA procedures were performed between 2008 and 2018. We included 28 cases in this analysis for which long-term follow-up data were available. There were two hospital deaths (7%). At follow-up, median New York Heart Association (NYHA) class improved from III to I ($P < 0.0001$), median systolic pulmonary pressure decreased from 64 mmHg to 26 mmHg ($P < 0.0001$), and significant improvements were seen in right ventricular function and exercise capacity.

**Conclusions:** A national center for performance of a rare and complex surgical procedure can be successfully established by collaboration with a high-volume center and by training a dedicated multidisciplinary team.

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**KEY WORDS:** chronic thromboembolic pulmonary hypertension (CTEPH), pulmonary endarterectomy (PEA), pulmonary vascular disease

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct pulmonary vascular disease caused by chronic obstruction of major pulmonary arteries, which can be cured by pulmonary endarterectomy (PEA) [1,2]. CTEPH is defined as pre-capillary pulmonary hypertension, as determined by right heart catheterization (mean pulmonary artery pressure ≥ 25 mmHg, mean pulmonary arterial wedge pressure ≤ 15 mmHg), in the presence of chronic/organized flow limiting thrombi/emboli in the elastic pulmonary arteries, following at least 3 months of effective anticoagulation [2].

Although the exact prevalence and annual incidence of CTEPH are unknown, recent data from the United Kingdom suggest that this condition occurs in approximately five people per million per year [3].

A survey of all major centers in Europe and the United States found that there are currently 1.7 PEAs per million of population performed in Europe annually compared with 0.9/million in the United States [1]. Based on these numbers, 8 to 14 PEAs would be expected to be performed per year in Israel. Notably, many experts agree that CTEPH is under-diagnosed and many patients therefore miss out on the potential benefit of PEA.

In small countries such as Israel, it is difficult to gain expertise in performing rare surgical procedures. PEA for CTEPH is a particularly challenging procedure. In addition to the complexity of the procedure, expertise is needed for patient selection and peri-operative management.

Since 2008, PEA has been performed in department of cardiac surgery at Sheba Medical Center. We have established a national center for CTEPH and PEA, predicated on two principles. The first is mentoring by an experienced PEA surgeon from a high-volume European PEA center (Homburg Saar, Germany) and the second is the assembly of a dedicated multidisciplinary CTEPH–PEA team. The core team includes a pulmonary hypertension specialist, cardiac surgeons, a cardiac anesthesiologist, and a cardiac surgery critical care specialist. In addition, the

core team collaborates with advisory services including interventional cardiology, echocardiography, clinical immunology, coagulopathy, laboratory medicine, and chest radiology.

Members of the core team trained in the German center and the mentor surgeon participated in the majority of the operations at Sheba Medical Center. All CTEPH patients have been evaluated by a pulmonary hypertension specialist, in collaboration with advisory services. Protocols for diagnostic pulmonary angiography and for peri-operative management were developed and implemented in collaboration with the mentor surgeon.

No other hospital in Israel has performed PEA since 2003, and the center has become the national quaternary referral center.

The purpose of this study is to report the outcome of PEA in Sheba Medical Center during the first 10 years of the program's activity.

## PATIENTS AND METHODS

### STUDY DESIGN

The study was approved by the Sheba institutional review board. The requirement for informed consent was waived due to the non-interventional and retrospective nature of the study.

This retrospective cohort study included all patients who underwent PEA in Sheba Medical Center in the 10-year period between 2008 and 2017. Demographic, clinical, laboratory, echocardiographic, radiologic, and hemodynamic data prior to, and after surgery were retrieved from patient electronic medical records. Systolic pulmonary artery pressure (sPAP) was estimated by echocardiography using standard methodology [4]. In cases in which the tricuspid regurgitation signal on echocardiography was absent or trivial, an estimated sPAP value of 25 mmHg was imputed.

As quantitative measures of right ventricular (RV) function were available only in a small sample of echocardiographic studies, qualitative estimates of RV function (normal, mildly, moderately, or severely reduced) were used.

### STATISTICAL ANALYSES

Statistical analyses were performed using GraphPad Prism 4 software (GraphPad Software, Inc., California, USA). All reported *P* values were based on the non-parametric Wilcoxon repeated measures test or chi-square test as appropriate.

## RESULTS

Between 2008 and 2017, a total of 38 PEA procedures were performed at Sheba Medical Center. The number of procedures performed per year has slowly been increasing. During the first 5 years of the program (2008–2012) nine operations were performed (mean 1.8 per year), whereas in the second 5-year period (2013–2017) 19 PEAs were performed (mean 3.8 per year) and in 2018 alone, 10 operations were performed. Included in our analysis are the 28 patients referred from 12 centers throughout Israel who had surgery between 2008 and 2017 and for whom long-term follow-up data are available.

Baseline characteristics of the study patient population are shown in Table 1. The gender distribution was equal. Patient age ranged from 19 to 80 years. Of note is the high proportion (46%) of anti-phospholipid syndrome. Functional capacity was severely reduced, with 68% at NYHA class III or IV. The median six-minute walk test (6MWT) was 350 meters. Although hemodynamic values indicated a broad range of severity, patients mainly presented with severe disease. For example, median cardiac index (CI) was 2.2 L/min/m$^2$, while the median value of mean right atrial pressure was 12 mmHg.

### IN-HOSPITAL MORTALITY

Two patients (7%) out of a total of 28 died from complications of surgery. Both had anti-phospholipid syndrome as the underlying cause of CTEPH. Patient 9 was a 67-year-old man. His baseline hemodynamic levels were severe. CI was 1.4 L/min/m$^2$, mean PA pressure was 54 mmHg, mixed venous oxygen saturation 45%, mRAP 17, and PVRI 31 Woods units/m$^2$. He died on the 22nd postoperative day due to complications of reperfusion injury. We subsequently adopted a protocol of postoperative therapy with vasodilators and diuretics to aggressively reduce pulmonary pressures, and since then we have only had mild cases of reperfusion injury. Patient 25 was a 40-year old woman. Baseline hemodynamics were severe. CI was 3.5 L/min/m$^2$,

**Table 1.** Baseline (preoperative) characteristics of the patient population

| Characteristic | Median (range) |
|---|---|
| Age, years | 46 (19–80) |
| Gender, male: female | 14:14 |
| Risk factors for CTEPH, n | |
| Antiphospholipid syndrome | 13 |
| Heritable coagulopathy* | 2 |
| Oralcontraceptive | 1 |
| Post-splenectomy | 1 |
| None identified | 7 |
| Nodata | 4 |
| NYHA functional capacity I/II/III/IV/unknown | 0/8/14/5/1 |
| Six-minute walk test | 350 (180–570) |
| Mean pulmonary artery pressure, mmHg | 48 (22–66) |
| Mixed venous oxygen saturation, % | 66 (39–74) |
| Cardiac index, L/min/m$^2$ | 2.2 (1.0–4.5) |
| Mean right atrial pressure, mmHg | 12 (4–25) |
| Pulmonary vascular resistance index, Woods units/m$^2$ | 15.5 (2–47) |

*One patient presented with MTHFR C677T homozygote and one with factor V Leiden heterozygote as well as prothrombin gene mutation heterozygote
NYHA = New York Heart Association

mean PA pressure was 64 mmHg, mixed venous oxygen saturation 65%, mean RAP 20 mmHg, and PVRI 13 Woods units/m$^2$. The patient was confined to her bed in the intensive care unit of another medical center for 8 weeks prior to surgery. She died on the 24th postoperative day due to complications of pleural hemorrhage on postoperative day one, necessitating withdrawal of anticoagulants and several additional surgical procedures. These conditions eventually led to multiple system organ failure. Patient 25 was the only patient for whom extracorporeal membrane oxygenation was used. Mortality reported in the literature from single centers ranges from 2.2% reported by a group in San Diego, CA, USA [6] to 12% reported from a group in Pavia, Italy [7]. A multicenter registry of 386 procedures performed in 17 centers in Europe and Canada reported 4.7% mortality [8]. The mortality in our center is not significantly higher ($P = 0.55$ compared to the multicenter registry, $P = 0.10$ compared to the San Diego series, chi-squared test).

### LATE OUTCOMES

*Functional capacity*

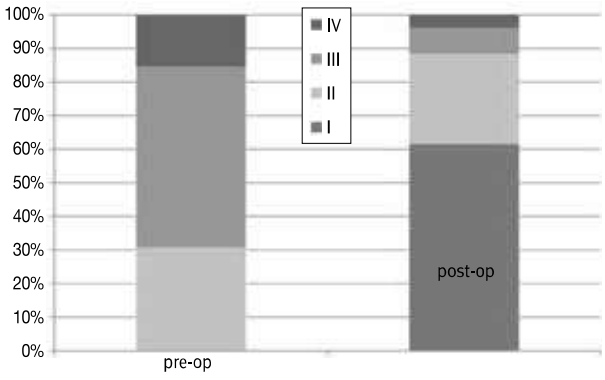
Preoperatively, close to 70% of patients were classified at NYHA III or IV, whereas postoperatively 90% were listed at NYHA I or II ($P < 0.0001$, Wilcoxon) [Figure 1].

*Hemodynamics*

The echocardiographically estimated systolic pulmonary artery pressure (sPAP) values decreased from a median value of 64 mmHg (range 27–88 mmHg) before surgery to 26 mmHg (range 17–52mm Hg) post-operatively ($P < 0.0001$, Wilcoxon) [Figure 2]. The RV function demonstrated by echocardiography in preoperative patients showed that 82% had moderate or severely reduced RV function, whereas postoperatively RV function was normal or mildly reduced in 86% ($P < 0.0001$, Wilcoxon) [Figure 3].

**Figure 1.** NYHA functional capacity before and after surgery

$P < 0.0001$ (Wilcoxon signed rank test)




PEA = pulmonary endarterectomy, NYHA = New York Heart Association, pre-op = before PEA, post-op = after PEA

*Exercise capacity*

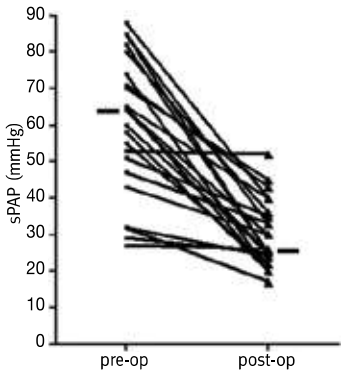
Preoperative and postoperative 6MWT results were available for 15 patients. Median 6MWT distance preoperatively was 338 meters. (Interquartile range [IQR] 300–377 m.), increasing to 437 meters (IQR 390–513 meters) postoperatively ($P < 0.0001$, Wilcoxon). Four other patients had preoperative and postoperative peak exercise oxygen consumption measurements (peak $V'O_2$). The mean preoperative peak $V'O_2$ was 50% predicted (range 31–60%), compared to 64% predicted (range 49–70%) postoperatively. Taken together, these 19 patients showed a 29% median improvement (IQR 17–59%) in exercise capacity (6MWT or peak $V'O_2$; $P < 0.0001$, Wilcoxon).

## DISCUSSION

PEA is the treatment of choice for CTEPH [1,2,5]. CTEPH is a rare disease, and PEA is a demanding procedure that requires skill and experience. In small countries such as Israel, it is dif-

**Figure 2.** Systolic pulmonary artery pressure before and after surgery, as estimated by echocardiography

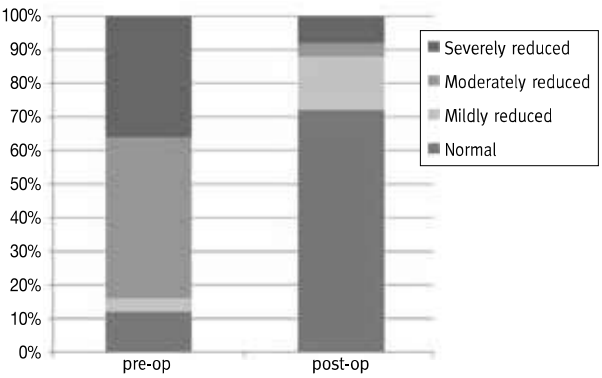
$P < 0.0001$
(Wilcoxon signed rank test)




PEA = pulmonary endarterectomy, pre-op = before PEA, post-op = after PEA, sPAP = systolic pulmonary artery pressure; Horizontal bars denote median values

**Figure 3.** Right ventricular function before and after surgery, as estimated by echocardiography

$P < 0.0001$ (Wilcoxon signed rank test)




PEA = pulmonary endarterectomy, pre-op = before PEA, post-op = after PEA

ficult to gain expertise in rare surgical procedures. Whereas some small countries can transfer difficult cases to quaternary referral centers in neighboring countries, this is not an option in Israel due to geopolitical isolation. Until recently, Israeli CTEPH patients had to undergo PEA abroad. However, this is obviously not an ideal situation, particularly since some patients may be too ill to travel. We therefore established a PEA program at Sheba Medical Center. To this end, we established a close collaboration with an experienced PEA surgeon from a high-volume center in Germany. We assembled a dedicated multidisciplinary team within our institution, including a pulmonary hypertension specialist, a cardiac surgeon, a cardiac surgery intensivist, and a cardiac surgery anesthesiologist. In addition to the core team, other key services such as interventional cardiology, echocardiography, chest radiology, clinical immunology, and coagulopathy consulted with the core team.

During the first 10 years of the program, we performed 28 PEAs with good results. In this report we showed clinically meaningful and statistically significant improvements in pulmonary artery pressure, RV function, functional capacity, and exercise capacity.

Two patients (7%) died peri-operatively. These patients had severe disease and no good alternative to PEA. The mortality in our center was not significantly higher than that reported in other centers.

This study has some limitations. The number of procedures is small, which reflects the reality of a rare disease in a small country. As noted, an increase in the number of procedures is being shown over time. Another limitation is that we do not have late postoperative hemodynamics or detailed echocardiographic indices of RV size and function. However, we were able to show a significant postoperative improvement in NYHA functional capacity, echocardiographically estimated systolic pulmonary artery pressure, global RV function, and exercise capacity. Perhaps most significant is the NYHA data, a key patient reported outcome. We found 90% of patents were classified as NYHA I or II postoperatively, compared to only 30% before surgery.

## CONCLUSIONS

Our PEA experience at Sheba Medical Center shows that national centers for performance of rare surgery, requiring experience that is difficult to attain in Israel, can be successfully established by collaboration between surgeons from abroad and dedicated multidisciplinary teams within the national center. We call on our colleagues from other centers in Israel to refer all CTEPH patients for evaluation by our team so that the best available care can be offered to these patients, and to further improve results as our national center gains more and more experience.

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## Capsule

### Interferon-λ modulates dendritic cells to facilitate T cell immunity during infection with influenza A virus

Type III interferon (IFN-λ) is important for innate immune protection at mucosal surfaces and has therapeutic benefit against influenza A virus (IAV) infection. However, the mechanisms by which IFN-λ programs adaptive immune protection against IAV are undefined. **Hemann** et al. found that IFN-λ signaling in dendritic cell (DC) populations was critical for the development of protective IAV-specific CD8+ T cell responses. Mice lacking the IFN-λ receptor (*Ifnlr1*$^{-/-}$) had blunted CD8+ T cell responses relative to wild type and exhibited reduced survival after heterosubtypic IAV re-challenge. Analysis of DCs revealed IFN-λ signaling directed the migration and function of CD103+ DCs for development of optimal antiviral CD8+ T cell responses, and bioinformatic analyses identified IFN-λ regulation of a DC IL-10 immunoregulatory network. Thus, IFN-λ serves a critical role in bridging innate and adaptive immunity from lung mucosa to lymph nodes to program DCs to direct effective T cell immunity against IAV.

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