Title
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Journal
The Journal of Heart and Lung Transplantation, 42(8)

ISSN
1053-2498

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Publication Date
2023-08-01

DOI
10.1016/j.healun.2023.02.1500

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PII: S1053-2498(23)01568-1
DOI: https://doi.org/10.1016/j.healun.2023.02.1500
Reference: HEALUN 7873

To appear in: *Journal of Heart and Lung Transplantation*

Please cite this article as: Timothy M. Fernandes MD, MPH , Nick H. Kim MD , Kim M. Kerr MD , William R. Auger MD , Peter F. Fedullo MD , David S. Poch MD , Jenny Yang MD , Demosthenes G. Papamatheakis MD , Mona Alotaibi MD , M. Angela Bautista PA , Victor G. Pretorius MD , Michael M. Madani MD , Distal Vessel Pulmonary Thromboendarterectomy: Results from a Single Institution, *Journal of Heart and Lung Transplantation* (2023), doi: https://doi.org/10.1016/j.healun.2023.02.1500

Original Clinical Science

Distal Vessel Pulmonary Thromboendarterectomy: Results from a Single Institution

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Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is primarily managed by pulmonary thromboendarterectomy (PTE). As advanced surgical techniques permit resection at the segmental and subsegmental level, PTE can now be curative for CTEPH mostly involving the distal pulmonary arteries.

Methods: Between January 2017 and June 2021, consecutive patients undergoing PTE were categorized according to the most proximal level of chronic thrombus resection: Level I (main pulmonary artery), Level II (lobar), Level III (segmental) and Level IV (subsegmental). Proximal disease patients (any Level I or II) were compared to distal disease (Level III or IV bilaterally) patients. Demographics, medical history, preoperative pulmonary hemodynamics, and immediate postoperative outcomes were obtained for each group.

Results: During the study period, 794 patients underwent PTE, 563 with proximal disease and 231 with distal disease. Patients with distal disease more frequently had a history of an indwelling intravenous device, splenectomy, upper extremity thrombosis or use thyroid replacement and less often had prior lower extremity thrombosis or hypercoagulable state. Despite more use of PAH-targeted medications in the distal disease group (63.2% vs. 50.1%, $p<0.001$), pre-operative hemodynamics were similar. Both patient groups exhibited significant improvements in pulmonary hemodynamics postoperatively with comparable in-hospital mortality rates. Compared to proximal disease, a lower percentage of patients with distal disease showed residual pulmonary hypertension (3.1% vs. 6.9%, $p=0.039$) and airway hemorrhage (3.0% vs. 6.6%, $p=0.047$) post-operatively.

Conclusions: Thromboendarterectomy for distal (segmental and subsegmental) CTEPH is technically feasible and may result in favorable pulmonary hemodynamic outcomes, without increased mortality or morbidity

Keywords: *CTEPH, pulmonary thromboendarterectomy, surgical outcomes, distal disease*

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by intravascular thrombus organization that occurs in about 3% of survivors after acute pulmonary embolism.[1,2] Over the past several decades, pulmonary thromboendarterectomy (PTE) has been established as potentially curative for this form of pulmonary hypertension.[3,4] It is therefore imperative to not only establish the diagnosis of chronic thromboembolic disease in patients at risk, but also carefully assess operability to offer the most effective treatment option available to the greatest number of CTEPH patients.

With recent refinements of the thromboendarterectomy procedure, the definition of technically inoperable chronic thromboembolic disease requires re-examination. This concern is especially important given the rise in balloon pulmonary angioplasty (BPA) programs which can also offer interventions to patients with distal disease. Given the advances in surgical technique allowing more distal resections, the intra-operative surgical classification of chronic thromboembolic disease was revised to more exactly describe vessel localization of endarterectomized material and specifically address more segmental and subsegmental disease compared to a prior classification system.[5,6] Utilizing this intraoperative classification scheme, we identified risk factors for the distal phenotype of CTEPH (defined as bilateral level III or higher disease), as well as, examined the immediate post endarterectomy outcome differences in patients with distal versus proximal vessel resection during PTE surgery.

Methods

Patient Selection and Study Design

A retrospective cohort study was conducted to assess patient characteristics and clinical outcomes in consecutive patients undergoing PTE surgery at the University of California, San Diego (UCSD), between January 1, 2017 and June 30, 2021. All patient information was obtained from a de-identified quality improvement database for the UCSD Pulmonary Thromboendarterectomy Program. Informed consent was waived and data collected in accordance with the standards set by UCSD's Institutional Review Board.

Beginning in 2013, the earlier classification based on the type of surgical specimen, known as the Jamieson Classification[7], was abandoned to better describe the vascular level at which the disease started. The new UCSD Chronic Thromboembolic (CTE) Disease Classification describes the most proximal location of disease, without any reference to the quality or type of thrombus. Furthermore, it establishes a distinction between organized thrombus endarterectomized from the segmental and subsegmental vessels, with an expected correlation with surgical degree of difficulty.6 Naturally, endarterectomy of disease starting at more proximal main (Level I) or lobar arteries (level II) is less technically demanding than more distal disease (Table 1)[5] For the purposes of this study, specimen classification was based on the most proximal location of the resection. Distal disease was defined as Level III (segmental) or IV (subsegmental) bilaterally, while proximal disease was defined as presence of any Level I (main pulmonary artery) or II (lobar) disease regardless of the contralateral side. During the study period, patient characteristics and outcomes of patients with proximal disease were compared to distal disease. (Figure 1)

During the preoperative evaluation period, pulmonary hemodynamic values were acquired with right heart catheterization. Postoperative pulmonary hemodynamics were obtained within 3 days following surgery, off vasoactive medications and after extubation in the majority of patients. As balloon inflation of the pulmonary artery catheter is avoided post endarterectomy, pulmonary vascular resistance (PVR) calculations following surgery utilized an estimated pulmonary artery wedge pressure based on central venous filling pressures.

Days of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), hospital days following PTE, and postoperative complications were tabulated for each patient group. Airway hemorrhage was defined as the presence of frankly bloody secretions suctioned from the airways requiring standard postoperative anticoagulation to be interrupted, bronchoscopy to be performed to clear the airways of blood and clots, or placement of balloon bronchial blocker to control blood loss. Reperfusion lung injury was defined as the presence of hypoxemia (PaO_2/FiO_2 ratio < 300) with pulmonary infiltrates in an endarterectomized lung region developing within 72 hours of surgery in the absence of an alternative explanation for these findings.[8] Residual pulmonary hypertension was defined as PVR >400 $dyn.sec.cm^{-5}$ obtained post-operatively.

Operability Assessment and Surgical Technique

Patients were assessed as having operable chronic thromboembolic lesions based on findings from lung ventilation-perfusion (VQ) scans, biplane catheter-based pulmonary angiography with digital subtraction, and when necessary, CT angiography of the chest (i.e those with poor quality conventional pulmonary angiograms or in whom there was a disagreement between the VQ scan and angiogram). [8] Surgical candidacy was established after multidisciplinary consultation with cardiothoracic surgeons, pulmonary vascular medicine physicians, balloon pulmonary angioplasty practitioners, and chest radiologists. Records for patients turned down for surgery or diverted to balloon pulmonary angioplasty were not included in this dataset.

The technical aspects of pulmonary thromboendarterectomy surgery have been described in previous publications.[9]With newly designed resection instruments (Figure 2), as well as modifications of the surgical techniques, surgeons are now able to perform endarterectomy into the distal segmental and subsegmental vessels. All surgeries captured during the study period were performed by two surgeons who regularly perform PTE's at our institution (MMM, VGP). For patients whose evaluation suggested CTE disease at the segmental level and beyond, and confirmed intra-operatively, the endarterectomy plane was started proximally within the normal pulmonary artery at the level of the lobar and proximal segmental branches. The intima, and on occasion, the media was separated from the adventitia in a circumferential manner to allow a full grasp of this otherwise fragile tissue and moved distally to eventually engage and resect the more distal and firm chronic thrombotic material. Considerable care was exercised to prevent fragmentation of the resected material, and to avoid vessel perforation. With establishment of an appropriate dissection plane and with gentle traction, a degree of vessel eversion is established to access the distal CTE material. This facilitates the removal of the entire material to its distal "tail". Fragmentation of the specimen at this level prevents a complete endarterectomy from being achieved as access cannot be regained once traction is released. In some patients with favorable anatomy, visualization is adequate to be able to start the plane of endarterectomy at the segmental and/or subsegmental branches. In such patients, typically a web, wall thickening, or a pouch defect can be appreciated, and the plane of dissection can then be carefully started at this distal level. However, in these patients, each individual branch needs careful and thorough examination and the plane of dissection needs to be developed and established separately.

Statistical Analyses

All analyses were conducted using SPSS Version 28 (SPSS IBM, New York, U.S.A). A p-value of <0.05 was deemed significant in all analyses. Significant differences among the continuous variables were computed using a student T-test for normally distributed continuous variables. Normality was assessed by visualization of data. All categorical variables compared using chi-squared test. Distribution of Ventilator days, ICU LOS, and post-operative LOS were compared with Mann–Whitney U test.

Results

Between January 1, 2017 and June 30, 2021, 794 patients underwent PTE surgery with 563 patients (70.9%) having "*proximal*" disease involving any Level I or II disease resection, and 231 patients (29.1%) with "*distal"* disease of bilateral Level III (segmental vessel) or Level IV (subsegmental vessel) disease resection. In other words, level III and IV patients had no evidence of any disease more proximally in the main or lobar branches. Patient characteristics are presented in Table 2. Distal disease patients were slightly older than those in the proximal vessel resection group (54.8 vs 53.1 years, p=0.065). There was a greater percentage of females in the distal group relative to those patients with more proximal disease (52.4% vs 44.9%, respectively; p=0.056). A slightly lower body mass index

(BMI) was observed in the distal group compared to the proximal group (30.3 vs 31.5 kg/m2 respectively; p<0.001).

There were important differences in clinical history between the groups. A lower extremity deep vein thrombosis (DVT) history (42.0% vs 64.5%; p<0.001) and an identifiable coagulopathy (16.9% vs 27.4%; p=0.002) were less common among distal disease patients compared to proximal disease. Conversely, presence of an intravascular device (i.e. pacemaker leads, central venous catheters, venous catheters for chemotherapy, or shunts) (10.4% vs. 3.9%; p<0.001), splenectomy (6.9% vs. 3.0%, p=0.012), history of upper extremity thrombosis (6.5% vs. 3.2%; p=0.035) and venous malformation (3.5% vs. 1.1%, p=0.019) were more common in those with distal disease. Notably, the use of thyroid replacement, which has been identified as a risk factor for CTEPH development,[10,11] was more common among patients with distal disease (19.9% vs. 10.1%; p<0.001).

The use of pulmonary arterial hypertension (PAH)-targeted medical therapy in each patient group are presented in Table 3. A higher percentage of patients with distal disease were on PAH-targeted medical therapy relative to patients with proximal disease (63.2% vs. 50.1%; p<0.001) prior to surgery. Compared to the proximal resections, the use of multi-drug therapy (16.5% on 2 drugs, 9.1% on 3 drugs; p<0.001) and parenteral prostacyclins (9.1% vs. 4.1%; p=0.005) were more common in the distal disease group. Use of preoperative riociguat was similar between the groups. Balloon pulmonary angioplasty prior to PTE was rare in this cohort but more common in the distal disease group (2.2% vs. 0.5%; p=0.037).

Preoperative pulmonary hemodynamics were similar between patient groups. (Table 4) despite the aforementioned differences in PAH-targeted medical therapy. Both patient groups demonstrated a substantial change in PVR following surgery (pre/postoperative difference of PVR 292.9 vs. 313.8;

p=0.422). There were no significant differences in the post-operative hemodynamics between the distal and proximal groups nor differences between Level III and bilateral Level IV (Supplement Table 1).

The surgical and post-operative results are presented in Table 5 and Supplemental Table 2. The distal resections were technically more difficult and thus were associated with a significantly longer circulatory arrest time (56.3 vs. 40.3 minutes; $p<0.001$); the circulatory arrest times were 54.9 minutes with Level III and 63.1 minutes with Level IV ($p<0.001$) . Overall, the in-hospital mortality rate was very low at 2.0% with no difference in mortality between distal resections and proximal resections (2.6% vs. 1.8%; p=0.454). There were no deaths in patients with bilateral Level IV disease. The need for post-operative ECMO was low in distal resections and proximal resections (0.9% vs. 1.6%; p=0.421). The incidence of reperfusion lung injury was similar between the two groups. There were lower rates of airway hemorrhage (3.0% vs. 6.6%; p=0.047) and residual pulmonary hypertension (3.1% vs. 6.9%; p=0.039) among patients with distal disease. There was no difference in the median ventilator days, ICU length of stay or post-operative length of stay between the groups.

Discussion

This single center retrospective study demonstrates that immediate pulmonary hemodynamic benefit can be achieved with distal vessel endarterectomy in selected CTEPH patients. This hemodynamic improvement can be attained without an increase in post-surgical morbidity or mortality. Therefore, patients previously considered inoperable due to distal disease, may be considered potential endarterectomy candidates in the appropriate setting. Nevertheless, endarterectomy of the distal pulmonary vessels is technically more challenging.

It is important to highlight that even in experienced hands, distal endarterectomy is quite more challenging as evidenced by circulatory arrest times which were 16 minutes longer than the more proximal counterparts. This is mainly due to the difficulty establishing the correct endarterectomy plane either proximally in relatively normal intima, or individually and separately in each branch distally. We have designed specialized surgical instruments to facilitate these distal endarterectomies but distal endarterectomy remains technically challenging. For that reason, we would recommend emerging pulmonary thromboendarterectomy programs become facile in the proximal resections before attempting the technically more challenging distal cases.

Over the past decade, options have emerged for the management of distal CTEPH including BPA and PAH-targeted medical therapy. Balloon pulmonary angioplasty is a percutaneous intervention using telescoping catheters placed in the pulmonary arteries, through which balloons over guidewires are used to mechanically disrupt chronic clot and relieve pulmonary vascular obstruction.[12] The initial efforts at employing BPA for CTEPH were fraught with high complication rates (especially vessel injury causing hemoptysis and reperfusion edema) and excessively high mortality.[13] Several innovations including serial sessions to gradually open the lumen to the full caliber, better imaging (optical coherence tomography or intravascular ultrasound), and improved lesion targeting (avoiding pouch defects or total occlusion) were made to the technique which brought these complication rates down to an acceptable range.[14]

While a head-to-head comparison between BPA and distal PTE is not possible with this data, surgical outcomes of distal PTE reported in this study can be put into context within the results from large BPA registries. Although representing a different CTEPH population with less access to PTE surgery, patients in the Japanese BPA registry[15] had more severe pre-procedure hemodynamics (mean PVR 853.4 dynes) compared to those seen in our study. The 30-day mortality after BPA in this registry was 2.6%, similar to that seen with distal PTE at our center (3.1% with Level 3 and 0 deaths seen in bilateral level 4 disease). Additionally, the rate of airway hemorrhage was 14.0% in the Japanese BPA registry compared to only 3.0% in distal endarterectomy. Reports from BPA centers in Europe where PTE is a more common option demonstrate lower rates of airway hemorrhage in the range of 9-12%.[16,17] In order to achieve the hemodynamic benefits with BPA, multiple sessions are required with a median of 4 sessions and range from 1 to 24 in the Japanese registry.[15] This opposed with our data in distal PTE where the benefits are seen in one hospitalization with a median length of stay of 10 days. Lastly, although current results of BPA are encouraging, the long-term effect of leaving the thickened and diseased material within the lumen of the pulmonary vasculature, and its hemodynamic effect during exercise remains unknown.

Aside from BPA, there has been increasing data supporting the use of PAH-targeted medical therapy in inoperable CTEPH over the past decade. Riociguat was FDA-approved for inoperable CTEPH based on the CHEST-1 trial demonstrating improvements in six minute walk at week 16.[18] In addition to riociguat, there is emerging evidence from randomized, controlled trials for the efficacy of both macitentan[19] and subcutaneous treprostinil[20] in selected patients with inoperable CTEPH. It is important to note that all these studies were extensively adjudicated to include only patients with inoperable CTEPH and there is no data to support use of PAH-targeted medications in those with operable disease. In our study, patients with distal disease were more likely to have been exposed to off-label use of PAH-targeted medical therapies prior to surgery. This difference in use of PAH-targeted medications may be related to the referring physicians believing the distal disease was inoperable. This highlights the need for second opinions regarding operability by experienced surgical centers, as the pre-operative use of PAH-targeted medication has been associated with delays in referral to CTEPH centers for consideration for PTE.[21] Whether PAH-targeted therapy affected outcomes is beyond the scope of this paper but is unlikely given there was no significant difference in morbidity and mortality between the distal and proximal groups.

Throughout in this study, our team conducted a weekly multi-specialty conference including radiologists, pulmonary vascular medicine specialists, and cardiothoracic surgeons who review all cases to determine the best course for management. The BPA program[22,23] and riociguat medical therapy[18] were both available alternatives since the inception of this study so there were management options for patients deemed not to be candidates for distal endarterectomy. Many factors go into the decision for a distal endarterectomy including the hemodynamics, extent of chronic clot burden and the patient's comorbidities.[1,24] Patients may be diverted from PTE to BPA if they either have disease that is surgically inaccessible or their operative risks are deemed to be too great despite having surgically accessible disease. In the experience of our multidisciplinary team in selecting patients for BPA, 59% of patients who underwent BPA at UCSD were referred for surgically inaccessible distal CTEPH while 7% were referred for BPA due to comorbidities precluding PTE surgery.[23] Therefore, we can comment that the patients deemed by the multi-specialty team to be of acceptable risk with operable disease do well with distal PTE.

Preoperative prediction of level of disease based on imaging by CTEPH providers has its limitations. At a high volume PTE center, there was only slight/fair agreement in specimen level predictions and actual surgical specimens.[25] However, this study has identified a number of clinical characteristics that are more prevalent in patients with distal CTEPH. Patients with distal disease were more likely to have upper extremity thrombosis, intravenous devices, venous malformations, use of thyroid replacement medications and splenectomy. Conversely, the history of DVT in the lower extremities or coagulopathy was more prevalent in proximal disease. These pieces of clinical history may be useful in determining whether proximal or distal disease will be encountered in cases with borderline or indeterminate pre-operative imaging.

While UCSD is the largest referral center for CTEPH in the United States, most of our patients are not local, which hinders our ability for return visits and post-operative hemodynamic assessment. For long-term follow-up data, we rely on our colleagues from centers in countries with nationalized medical systems that allow for single-center long-term follow-up. A previous publication from D'Armini and colleagues addressing endarterectomy of distal CTEPH was similar to the current study in describing favorable immediate outcomes as well as favorable long-term (median time of 31 months) postoperative pulmonary hemodynamic outcomes.[26] Consistent with the current report was the profile of patients exhibiting distal disease demonstrated fewer with a DVT history and a greater prevalence of indwelling intravascular devices though no difference in the history of splenectomy. This group also reported airway bleeding as the cause of in-hospital mortality in 30% of patients who died post-operatively, while the rate of airway hemorrhage was much lower in our series than was reported by D'Armini. The Canadian CTEPH Working group noted an increase in the number of distal PTE cases involving the segmental arteries in the most recent 5 years, compared to earlier cohorts.[27] They also demonstrated excellent long-term results with distal PTE but patients with segmental resections were more likely to require additional post-operative therapy with PAH-targeted medical therapy and/or balloon pulmonary angioplasty. However, the use of the Jamieson surgical classification[7] in this previous study does not provide a distinction between segmental and subsegmental resection. The UCSD level classification is more reflective of the surgical difficulty (as evidenced by successively longer circulation arrest times with more distal resections) than the prior Jamieson classification which focused on the type of material encountered.

This study is limited by the generalizability of this single center study, as the results are specific to an active and experienced center and therefore cannot easily be applied to other emerging PTE centers. The experience of the team in selecting the appropriate patients for distal endarterectomy and the surgeons in performing the surgery at a busy CTEPH center surely influence the excellent outcomes seen in this study. Whether less experienced centers would see similar results for distal endarterectomy remains to be seen. It is our opinion that emerging centers should focus endarterectomy efforts on proximal disease that may be technically less challenging. Furthermore, prior to proceeding with balloon angioplasty in patients with distal disease, the opinions on operability for distal pulmonary thromboendarterectomy should be obtained from a center with experience with this more challenging procedure.

In conclusion, PTE for distal (segmental and subsegmental pulmonary artery disease) CTEPH is feasible and can be effective in the appropriate setting. Mortality in these cases is similar to more proximal disease and morbidity may actually be lower. We suspect that surgical technique, post-operative care, overall center experience, and proper patient selection are the major reasons for achieving such low mortality rates in patients with more distal disease. Additionally, the revised surgical classification presented here becomes relevant as a greater number of PTE centers are established worldwide. With a clearer description of disease resection, future comparison of outcomes between centers of excellence becomes feasible and lays the groundwork for potential future comparison of outcomes between distal surgical resections and balloon pulmonary angioplasty.

Acknowledgements:

There was no external funding or other source of funding for this study and the submitted manuscript. Furthermore, none of the authors have relevant disclosures related to the conduct of the study and/or preparation of the manuscript.

References

1. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(1). doi:10.1183/13993003.01915-2018

2. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2):1601792. doi:10.1183/13993003.01792-2016

3. Jenkins DP, Madani M, Mayer E, et al. Surgical treatment of chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2013;41(3):735-742. doi:10.1183/09031936.00058112

4. Madani MM, Auger WR, Pretorius V, et al. Pulmonary Endarterectomy: Recent Changes in a Single Institution's Experience of More Than 2,700 Patients. *Ann Thorac Surg*. 2012;94(1):97-103. doi:10.1016/j.athoracsur.2012.04.004

5. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*. 2017;26(143). doi:10.1183/16000617.0111-2016

6. Madani M, Mayer E, Fadel E, Jenkins DP. Pulmonary Endarterectomy. Patient Selection, Technical Challenges, and Outcomes. *Ann Am Thorac Soc*. 2016;13 Suppl 3:S240-247. doi:10.1513/AnnalsATS.201601-014AS

7. Thistlethwaite PA, Mo M, Madani MM, et al. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg*. 2002;124(6):1203-1211. doi:10.1067/mtc.2002.127313

8. Levinson RM, Shure D, Moser KM. Reperfusion pulmonary edema after pulmonary artery thromboendarterectomy. *Am Rev Respir Dis*. 1986;134(6):1241-1245. doi:10.1164/arrd.1986.134.6.1241

9. Mahmud E, Madani MM, Kim NH, et al. Chronic Thromboembolic Pulmonary Hypertension: Evolving Therapeutic Approaches for Operable and Inoperable Disease. *J Am Coll Cardiol*. 2018;71(21):2468-2486. doi:10.1016/j.jacc.2018.04.009

10. Fernandes T, Auger W, Fedullo P. Epidemiology and risk factors for chronic thromboembolic pulmonary hypertension. *Thromb Res*. 2018;164:145-149. doi:10.1016/j.thromres.2018.01.012

11. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost*. 2016;14(1):121-128. doi:10.1111/jth.13175

12. Lang I, Meyer BC, Ogo T, et al. Balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*. 2017;26(143). doi:10.1183/16000617.0119-2016

13. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation*. 2001;103(1):10-13. doi:10.1161/01.cir.103.1.10

14. Kataoka M, Inami T, Hayashida K, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv*. 2012;5(6):756-762. doi:10.1161/CIRCINTERVENTIONS.112.971390

15. Ogawa A, Satoh T, Fukuda T, et al. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension: Results of a Multicenter Registry. *Circ Cardiovasc Qual Outcomes*. 2017;10(11):e004029. doi:10.1161/CIRCOUTCOMES.117.004029

16. Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(5). doi:10.1183/13993003.02095-2018

17. Olsson KM, Wiedenroth CB, Kamp JC, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. *Eur Respir J*. 2017;49(6). doi:10.1183/13993003.02409-2016

18. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319-329. doi:10.1056/NEJMoa1209657

19. Ghofrani HA, Simonneau G, D'Armini AM, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med*. 2017;5(10):785-794. doi:10.1016/S2213-2600(17)30305-3

20. Sadushi-Kolici R, Jansa P, Kopec G, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. *Lancet Respir Med*. 2019;7(3):239-248. doi:10.1016/S2213-2600(18)30367-9

21. Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. *Circulation*. 2009;120(13):1248-1254. doi:10.1161/CIRCULATIONAHA.109.865881

22. Mahmud E, Patel M, Ang L, Poch D. Advances in balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *Pulm Circ*. 2021;11(2):20458940211007384. doi:10.1177/20458940211007385

23. Poch DS, Mahmud E, Patel M, et al. Patient selection for balloon pulmonary angioplasty: Six-year results from a high volume PTE surgical center. *Pulm Circ*. 2022;12(4):e12148. doi:10.1002/pul2.12148

24. Madani MM. Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension: Pulmonary Thromboendarterectomy. *Methodist DeBakey Cardiovasc J*. 2016;12(4):213-218. doi:10.14797/mdcj-12-4-213

25. Pirompanich P, Fernandes T, Kerr K, et al. Accuracy of pre-operative specimen level prediction in chronic thromboembolic pulmonary hypertension (CTEPH) patients undergoing pulmonary thromboendarterectomy (PTE). *Eur Respir J*. 2020;56(suppl 64). doi:10.1183/13993003.congress-2020.1538

26. D'Armini AM, Morsolini M, Mattiucci G, et al. Pulmonary endarterectomy for distal chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg*. 2014;148(3):1005-1011; 1012.e1-2; discussion 1011-1012. doi:10.1016/j.jtcvs.2014.06.052

27. de Perrot M, Donahoe L, McRae K, et al. Outcome after pulmonary endarterectomy for segmental chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg*. Published online March 1, 2022. doi:10.1016/j.jtcvs.2021.10.078

Table 1: UCSD Chronic Thromboembolic Disease Surgical Classification*

UC San Diego Surgical Classification
Level 0
No evidence of chronic thromboembolic disease
Level I:
Chronic thromboembolic disease encountered in the main pulmonary artery
Level IC:
Complete occlusion of one main pulmonary artery with chronic thromboembolic disease
Level II:
Chronic thromboembolic disease starting at the level of lobar arteries, or in the main descending pulmonary arteries
Level III:
Chronic thromboembolic disease starting at the level of the segmental arteries
Level IV:
Chronic thromboembolic disease starting at the level of the subsegmental arteries

*Classification based on the most proximal disease identified

Table 2: Patient Demographics

	Distal Disease	**Any Proximal Disease**	**P value**
	N = 231	**N = 563**	
Age, years (SD)	54.9 (16.8)	53.9 (15.7)	0.443[a]
Gender (% Female)	52.4% (N=121)	44.9% (N=253)	0.056
BMI kg/m^2 (SD)	28.7 (6.5)	31.2 (7.7)	**<0.001[a]**
WHO Functional Class			0.629
I or II	22.0% (N=51)	19.6% (N=110)	
III	70.6% (N=163)	72.6% (N=409)	
IV	7.4% (N=17)	7.8% (N=44)	
Deep Vein Thrombosis	42.0% (N=97)	64.5% (N=363)	**<0.001**
Pre-operative PVR >1000 dynes	9.1% (N=19)	10.8% (N=54)	0.673
History of UE Thrombus	6.5% (N=15)	3.2% (N=18)	**0.035**

History of Intravenous Device	10.4% (N=24)	3.9% (N=22)	**<0.001**
Venous Malformation	3.5% (N=8)	1.1% (N=6)	**0.019**
Coagulopathy[#]	16.9% (N=39)	27.4% (N=154)	**0.002**
Hemoglobinopathy	4.3% (N=10)	3.4% (N=19)	0.515
Post Splenectomy	6.9% (N=16)	3.0% (N=17)	**0.012**
History of Malignancy[***]	13.0% (N=30)	11.4% (N=64)	0.521
Diabetes Mellitus	12.1% (N=28)	14.6% (N=82)	0.365
Thyroid Replacement Rx	19.9% (N=46)	10.1% (N=57)	**<0.001**
PAH Risk Factors[****]	7.8% (N=18)	7.1% (N=28)	0.753
OSA	13.4% (N=143)	10.5% (N=59)	0.235

[***]All categorical variables compared using chi-squared test excluding non- melanoma skin cancers

[#]Factor V Leiden, antithrombin III, Protein S or Protein C deficiency, lupus anticoagulant or anticardiolipin antibodies

[****]PAH risk factors includes history of anorexigen use, methamphetamine abuse, scleroderma, congenital heart disease, HIV, cirrhosis, systematic lupus erythematous or mixed connective tissue disease.

Table 3: Pulmonary Hypertension Targeted Medical Therapy

	Distal Disease	**Any Proximal Disease**	**p-value**
	N = 231	**N = 563**	
Any PAH-targeted Therapy	63.2% (N=146)	50.1% (N=282)	<0.001
2 drug therapy	16.5% (N=38)	9.8% (N=55)	<0.001
3 drug therapy	9.1% (N=21)	2.8% (N=16)	
Riociguat	42.4% (N=98)	36.8% (N=207)	0.137
PDE-5i	18.6% (N=43)	11.2% (N=63)	0.004
ERA	21.2% (N=49)	9.9% (N=56)	<0.001
Selexipag	2.2% (N=5)	1.8% (N=10)	0.715
Parenteral Prostacyclin	9.1% (N=21)	4.1% (N=23)	0.005
Inhaled Treprostinil	3.9% (N=9)	1.1% (N=6)	0.008
BPA prior to PTE	2.2% (N=5)	0.5% (N=3)	0.037

Table 4: Perioperative Pulmonary Hemodynamics

		Distal Disease	**Any Proximal Disease**	**P value**
		N = 230	**N = 536**	
Pre-operative	RA mean (mmHg)	9.0 ± 6.1	9.8 ± 5.4	0.066
	PA mean (mmHg)	37.9 ± 12.8	39.0 ± 13.5	0.305

	Cardiac Output (L/min)	4.80 ± 1.28	4.88 ± 1.43	0.434
	Cardiac Index (L/min/m2)	2.43 ± 0.54	2.37 ± 0.62	0.184
	PVR (d.s.cm-5)	509.3 ± 325.7	530.9 ± 331.0	0.426
	TPR (d.s.cm-5)	713.3 ± 364.0	744.0 ± 376.0	0.318
Post-operative	RA mean (mmHg)	7.8 ± 3.1	8.2 ± 3.6	0.381
	PA mean (mmHg)	22.0 ± 6.0	22.8 ± 7.3	0.079
	Cardiac Output (L/min)	5.72 ± 1.22	5.65 ± 1.33	0.476
	Cardiac Index (L/min/m2)	2.81 ± 0.52	2.77 ± 0.53	0.355
	PVR (d.s.cm-5)	209.7 ± 97.3	222.1 ± 121.7	0.178
	TPR (d.s.cm-5)	324.8 ± 116.9	343.9 ± 151.0	0.063

T-test used for continuous variables. Note: Post-operative PVR calculated with estimated pulmonary capillary wedge pressure.

Table 5: Surgical and Postoperative Results

	Distal Disease	**Any Proximal Disease**	
	N = 231	**N = 563**	**P value**
Total CPB time, min (mean ± SD)	248.3 ± 38.0	250.5 ± 32.4	0.453
Circulatory Arrest, min (mean ± **SD)**	56.3 ± 21.3	40.3 ± 14.5	<0.001
Mortality	2.6% (N=6)	1.8% (N=10)	0.454
Ventilator Days			
Median (IQ range)	1 (1-2)	1 (1-2)	0.074
ICU Length of Stay, days			
Median (IQ range)	4 (3-6)	4 (2-5)	0.21
Postoperative Length of Stay, days			
Median (IQ range)	10 (8-13)	10 (8-14)	0.483
Need for ECMO	0.9% (N=2)	1.6% (N=9)	0.421
Need for PAH Medication at Discharge	0.9% (N=2)	0.9% (N=5)	0.978
Need for Oxygen at Discharge	62.9% (N=144)	62.1% (N=346)	0.841
Airway hemorrhage	3.0% (N=7)	6.6% (N=37)	0.047
Reperfusion Lung Injury	9.1% (N=21)	10.9% (N=61)	0.459
Residual PH (PVR >400)	3.1% (N=7)	6.9% (N=35)	0.039

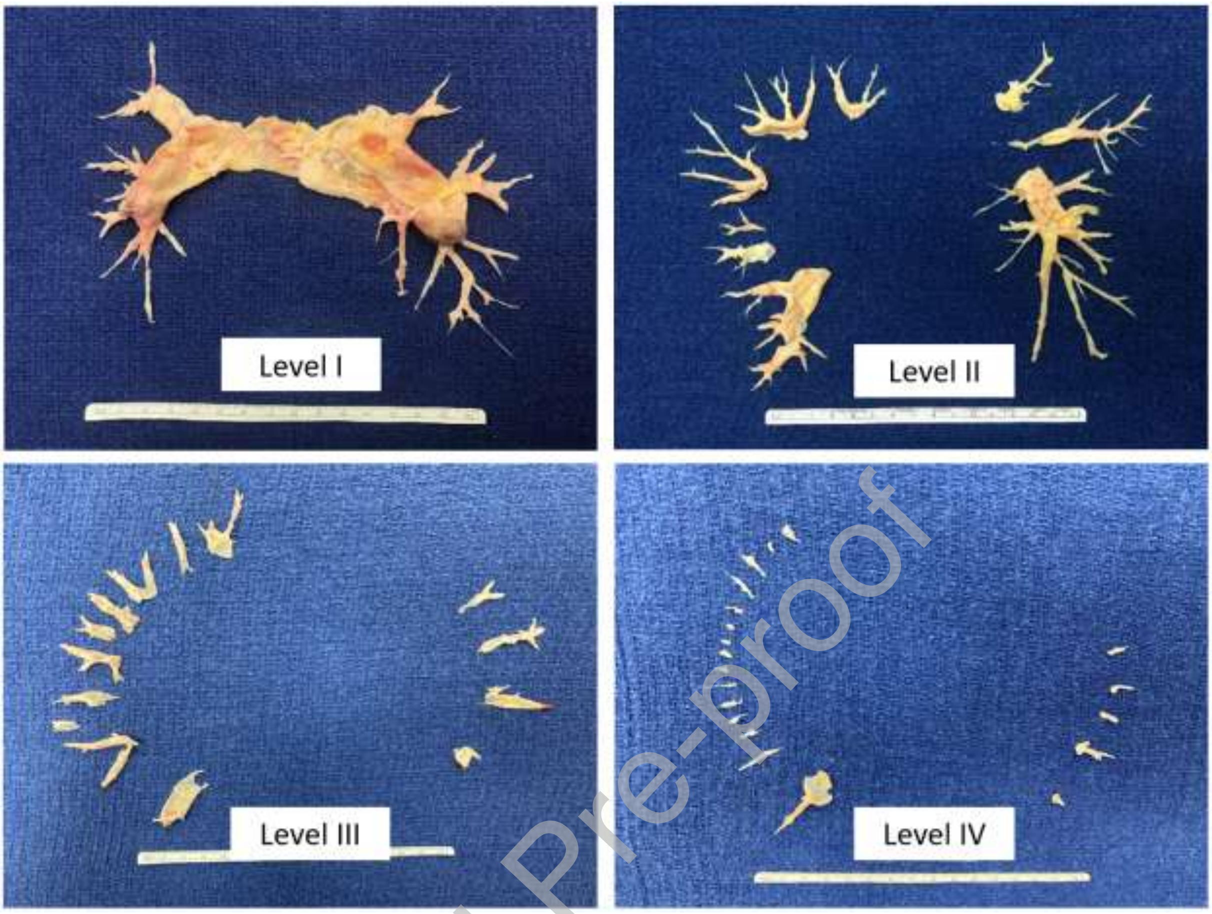

Figure 1: UCSD CTE Classification. The 15 cm ruler is provided for gauging the size of each of the example specimens. Level I resections begin at the main pulmonary artery. In Level II resections, the majority of the resection begins at the lobar pulmonary artery. Level III resection begins at segmental arteries while Level IV resection begins in the subsegmental arteries.

Figure 2: Redesigned Endarterectomy Instruments. Madani PTE Instrument Set : A) 16" Double Action Madani *PTE* Forceps with 1mm tip, B) 16" Double Action *Madani PTE* Forceps with 2.5 mm tip, C) 12" Double Action *Madani PTE* Forceps with 1mm tip, D) 12" Double Action *Madani PTE* Forceps with 2.5mm tip, E) Modified Jamieson PTE Suction/Dissector, F) Modified Curved Jamieson PTE Suction/Dissector, G) Madani PTE Retractor, H) Micro-Penfield 4 Dissector, I) Fine Beaver Blade, J)

"Mini-Nut" Dissector – Small 7mmx3mmx1mm PTFE Buttress Pledget in a 10" Tonsil Clamp. Inset: The Forceps are available with either 1 mm or 2.5 mm tips.