JSCAI
The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

Safety Window for Effective Lesion Crossing in Patients With Chronic Thromboembolic Pulmonary Hypertension

Sidney J. Perkins, MD, MSc [a], Miguel Funes, PhD [b], Daniel Cheah, MSE [c], Christian Argenti, MSE [b], Jorge Vinales, BS [d], David Gordon, MD [e], Jonathan W. Haft, MD [f], David M. Williams, MD [g], Vallerie V. Mclaughlin, MD [h], Prachi P. Agarwal, MBBS, MD, MS [i], Victor M. Moles, MD [h], Thomas Cascino, MD, MSc [h], Andrea Obi, MD [j], Aditya Pandey, MD [k], Albert Shih, PhD [b,†], Vikas Aggarwal, MBBS, MPH [l,†,*]

[a] *Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan;* [b] *Department of Mechanical Engineering, University of Michigan, Ann Arbor, Michigan;* [c] *Carle Illinois College of Medicine, University of Illinois Urbana Champaign, Urbana, Illinois;* [d] *University of Michigan Medical School, University of Michigan, Ann Arbor, Michigan;* [e] *University of Michigan Department of Pathology, University of Michigan, Ann Arbor, Michigan;* [f] *University of Michigan Frankel Cardiovascular Center Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan;* [g] *University of Michigan Vascular and Interventional Radiology, University of Michigan, Ann Arbor, Michigan;* [h] *University of Michigan Department of Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, Michigan;* [i] *University of Michigan Department of Diagnostic Radiology, University of Michigan, Ann Arbor, Michigan;* [j] *University of Michigan Section of Vascular Surgery, University of Michigan, Ann Arbor, Michigan;* [k] *University of Michigan Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan;* [l] *Department of Internal Medicine, Division of Cardiology, Henry Ford Hospital, Detroit, Michigan*

ABSTRACT

Background: Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (CTEPH) is limited by a lack of safe and effective tools for crossing these lesions. We aim to identify a safety window for an intraluminal crossing device in this vascular bed by studying the piercing properties of pulmonary arterial vessel walls and intraluminal CTEPH lesion specimens. As a secondary objective, we also describe the histopathologic features of CTEPH lesions.

Methods: Specimens were procured from 9 patients undergoing pulmonary endarterectomy. The specimens were subsampled and identified grossly as arterial wall or intraluminal CTEPH lesions. The force needed for tissue penetration was measured using a 0.38-mm (0.015-in) diameter probe in an ex vivo experimental model developed in our lab. Concurrent histology was also performed.

Results: The mean force needed to penetrate the arterial wall and intraluminal CTEPH lesions was 1.75 ± 0.10 N (n = 121) and 0.30 ± 0.04 N (n = 56), respectively ($P < .001$). Histology confirmed the presence of intimal hyperplasia with calcium and hemosiderin deposition in the arterial wall as well as an old, organized thrombus in the lumen.

Conclusions: The pulmonary arterial wall is friable and prone to perforation during instrumentation with workhorse coronary guide wires. However, the results of this study demonstrate that a much lower force is needed for the 0.38-mm (0.015-in) probe to penetrate an intraluminal CTEPH lesion compared to pulmonary arterial intima. This finding suggests the existence of a safety window for lesion-crossing devices, enabling effective balloon pulmonary angioplasty.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) results from pulmonary vascular obstruction due to unresolved organized thrombi within the pulmonary vasculature. Pulmonary endarterectomy (PEA) is the most effective therapy for CTEPH currently, although less than half of patients diagnosed with CTEPH undergo PEA due to frailty, insufficient access to specialty centers, and distal burden of disease.[1,2] Riociguat, a guanylate cyclase stimulator, is the only medication currently approved by the FDA for the treatment of inoperable CTEPH or persistent pulmonary hypertension after PEA and has only shown modest benefits in exercise capacity and clinical outcomes.[3–6]

Abbreviations: BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; PEA, pulmonary endarterectomy.

Keywords: balloon pulmonary angioplasty; chronic thromboembolic pulmonary hypertension; pulmonary embolism; pulmonary hypertension.

* Corresponding author: vaggarw2@hfhs.org (V. Aggarwal).
† Co-senior authors.

https://doi.org/10.1016/j.jscai.2024.102142
Received 28 January 2024; Received in revised form 14 April 2024; Accepted 15 April 2024
Available online 15 July 2024

Catheter-based balloon pulmonary angioplasty (BPA) has emerged as an effective option to address this unmet need. Unfortunately, BPA is limited by high incidence of complications. In reports of BPA, periprocedural mortality has been noted to be as high as 14%.[7–17] One explanation for the high rate of complications in BPA is that the unique mechanical properties of both intraluminal CTEPH lesions and pulmonary arterial wall predispose to vessel perforation. Intraluminal CTEPH lesions are rich in collagen and elastin compared to the more acute fibrin-rich thrombi in acute pulmonary embolism (PE). This organization of fibrin leading to abundant collagen deposition by fibroblasts changes the mechanical properties of the thrombus and makes it difficult to cross with conventional coronary angioplasty guide wires during BPA.[18] When operators push forcefully to cross these lesions, they risk buckling the guidewire and piercing the pulmonary arterial wall proximally, resulting in intraoperative complications, such as pulmonary artery perforation.

In addition, the mechanical properties of the pulmonary vasculature and systemic vasculature are significantly different, which further predisposes to vessel injury during BPA. In uniaxial loading studies, the ultimate tensile strength of the pulmonary artery is estimated to be 0.95 MPa, whereas it is roughly 1.44 MPa for the coronary artery. In the same studies, the pulmonary vasculature is noted to be 10-fold more distensible than the systemic vasculature.[19–21] This is consistent with the long-recognized relationship between blood pressure and mechanical properties of vascular beds—with lower arterial pressures in the pulmonary circulation, it is no surprise that the pulmonary vessels are more prone to perforation than systemic vessels.[22]

Unfortunately, despite the unique mechanical properties of CTEPH lesions and the pulmonary vasculature, there is currently a lack of dedicated percutaneous tools for pulmonary revascularization in CTEPH. The first step in developing dedicated tools for BPA is understanding the mechanical properties of the intraluminal CTEPH lesion compared to the diseased pulmonary arterial wall. Piercing is the key mechanical property investigated in this study. Our primary objective is to define the mechanical properties of intraluminal CTEPH lesions and pulmonary arterial walls in patients who have undergone PEA. We hypothesize that the force required to pierce intraluminal CTEPH lesions will be less than the force required to pierce the hyperplastic pulmonary arterial intima and that a clinically relevant safety window can be identified. As a secondary objective, we will characterize the histologic properties of the intraluminal and pulmonary arterial components of CTEPH lesions. We hypothesize that there will be hypertrophic intima present as well as heterogenous chronicity of intraluminal thrombus present in patients with CTEPH.

Methods

Patient selection

Nine patients with CTEPH who underwent PEA at University of Michigan Hospital over a period of 9 months were included in this study. For each patient, demographic information, past medical history, hemodynamic data from right heart catheterization, as well as operative and pathology reports were collected. Following PEA, tissue samples underwent mechanical characterization per study protocol. The research protocol was approved by the University of Michigan's Institutional Review Board (IRB HUM00157980). Informed consent was not required per our IRB, as the tissue obtained for this study was obtained as part of routine clinical care and would have been discarded otherwise.

Sample preparation

Samples were procured from the operating room and mechanically tested within 2 to 6 hours of procurement per our laboratory's protocol.[23–25] In total, 19 pulmonary arterial intima samples and 7 intraluminal CTEPH lesions were procured. As shown in Figure 1B, from these 26 samples, a total of 121 intima and 56 CTEPH lesion subsamples were obtained using an 8-mm biopsy punch.

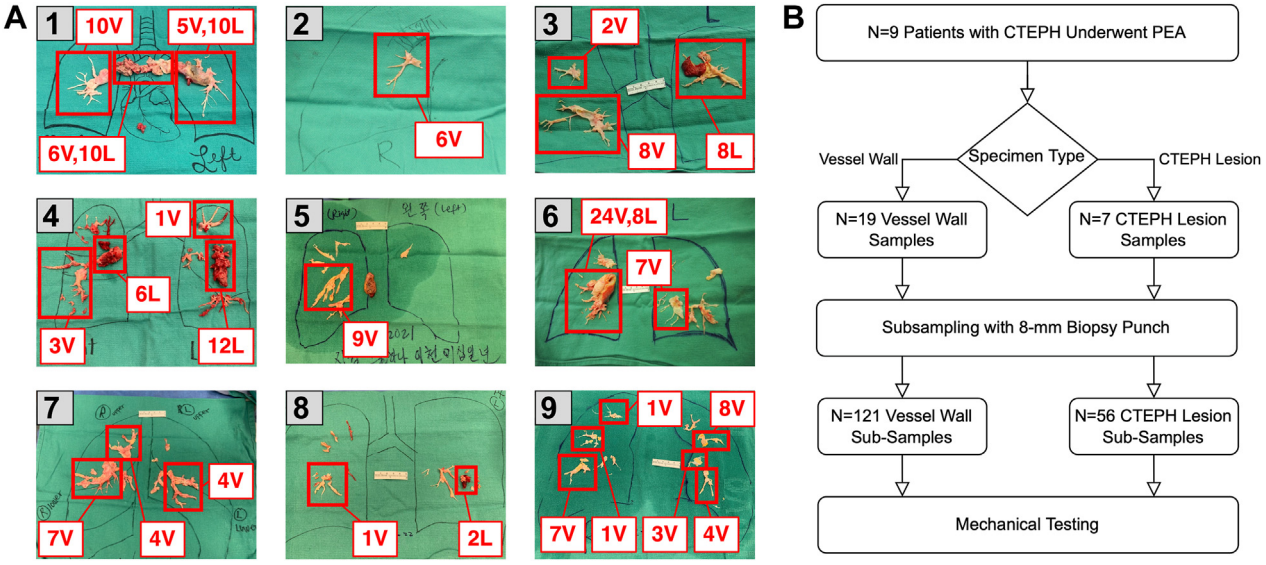


Figure 1.
Nineteen vessel wall (n = 112 subsamples) and 7 chronic thromboembolic pulmonary hypertension (CTEPH) lesion (n = 56 subsamples) samples were procured from the operating room. (**A**) Operative findings from patients 1-9. "V" denotes vessel wall subsamples, whereas "L" denotes CTEPH lesion subsamples. For patient 1, a total of 21 pulmonary vessel walls and 20 CTEPH lesion subsamples were obtained for mechanical testing. For patient 2, a total of 6 vessel wall subsamples were obtained from the right pulmonary vasculature. For patient 3, a total of 10 vessel walls and 8 CTEPH lesion subsamples were obtained. For patient 4, a total of 4 vessel walls and 18 CTEPH lesion subsamples were obtained for mechanical testing. For patient 5, a total of 9 vessel wall subsamples were obtained for mechanical testing. For patient 6, a total of 31 vessel wall and 8 CTEPH lesion subsamples were obtained for mechanical testing. For patient 7, a total of 15 vessel wall subsamples were obtained for mechanical testing. For patient 8, a total of 1 vessel wall and 2 CTEPH lesion subsamples were obtained for mechanical testing. For patient 9, a total of 24 vessel wall lesion subsamples were obtained for mechanical testing. (**B**) Flowchart showing an overview of patients, samples, and subsamples used for mechanical testing. PEA, pulmonary endarterectomy.

Mechanical testing

Experimental set-up. An ex vivo model of CTEPH was designed to measure the force associated with simulated lesion crossing during pulmonary angioplasty (Figure 2A). Components of the ex vivo testing fixture were printed using Formlabs Form3 3D printer and Formlabs Clear V4 photocurable resin (Formlabs). Three-dimensional printed tissue holders were equipped with 6 small holes into which steel pins (K&S Precision Metals) were introduced to ensure subsample fixation during mechanical testing. Lesion subsamples obtained from the surgical specimens were cut as described above and secured within the sample holder using a series of 6 steel pins (Figure 2C). Tissue holders with loaded subsamples were then placed in a second custom 3D-printed component, which was secured to a force transducer (Gamma Transducer, ATI Industrial Automation). For the duration of mechanical testing, the force transducer was mounted on an optics table. A steel 0.38-mm (0.015-in) diameter probe (K&S Precision Metals) was designed as a surrogate to mimic 0.36-mm (0.014-in) diameter workhorse coronary guide wires. Scanning electron microscopy was used to characterize the tip of the 0.38-mm (0.015-in) diameter probe (Figure 2B).

Tissue piercing and force measurement. The high-carbon steel probe was advanced at 2 mm/s into the specimen while the force was measured using the force transducer. A representative plot of the axial force measured with the force transducer over time during tissue piercing is shown in Figure 3A. The maximum force measured during piercing was recorded and was compared for pulmonary arterial intima and intraluminal CTEPH lesion subsamples. All data points between patients were compared in a pooled analysis. In addition, for patients with both intraluminal CTEPH lesion and arterial intima samples, a patient-specific comparison of CTEPH lesion and vessel wall piercing was performed.

Pathology

A surgical specimen involving both pulmonary artery intima and intraluminal CTEPH lesion was placed in 10% neutral buffered formalin and sent for routine processing and hematoxylin and eosin (H&E) staining in the clinical pathology laboratory for each patient. All slides were reviewed by our team's clinical pathologist (D.G.) and representative photomicrographs of the most common histological features were prepared. Standard pathologic criteria were used to describe the tissue samples.[26–29]

Statistical analysis

All statistics are reported as mean ± standard error of the mean (SEM) unless otherwise specified. Similarly, all error bars on graphs represent SEM, unless otherwise specified. For comparisons between groups, ANOVA was performed with follow-up 2-sample heteroscedastic *t* testing with Bonferroni correction for multiple comparisons.

Results

In total, 9 patients (3 female and 6 male) were included. All patients had a history of known PE or deep vein thrombosis. Two patients had a history of thrombophilia secondary to antiphospholipid syndrome, 4 patients had systemic inflammatory disease, and 1 patient had cancer-related PE. No patient had a history of splenectomy. Table 1 provides baseline summary characteristics for patients included in this study.

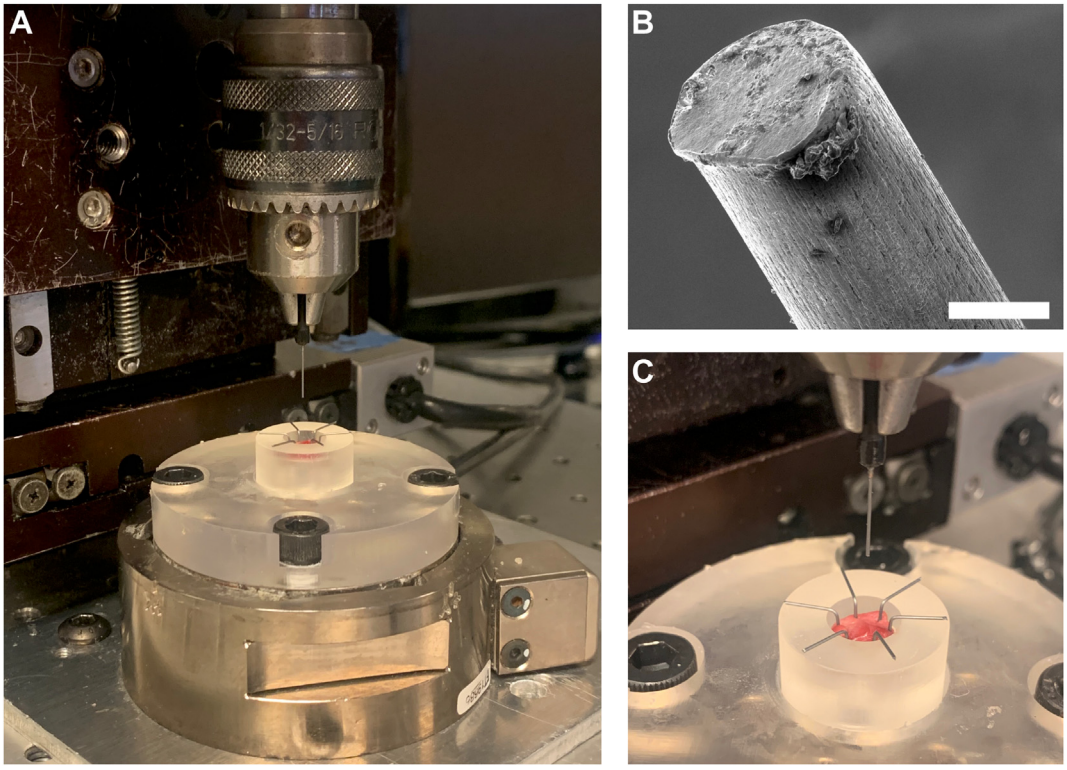


Figure 2.
Mechanical testing fixture. (**A**) Testing fixture showing the 0.015-in diameter probe held in place by a collet. The subsample is shown in a custom 3D-printed tissue holder with 6 fixation wires in place. The tissue holder is shown seated in a second custom 3D-printed component that is bolted to the force transducer. (**B**) Scanning electron microscopy of the probe tip used in mechanical testing. The scale bar is equal to 200 μm. (**C**) Close-up image of testing fixture showing a specimen fixed by 6 pins.

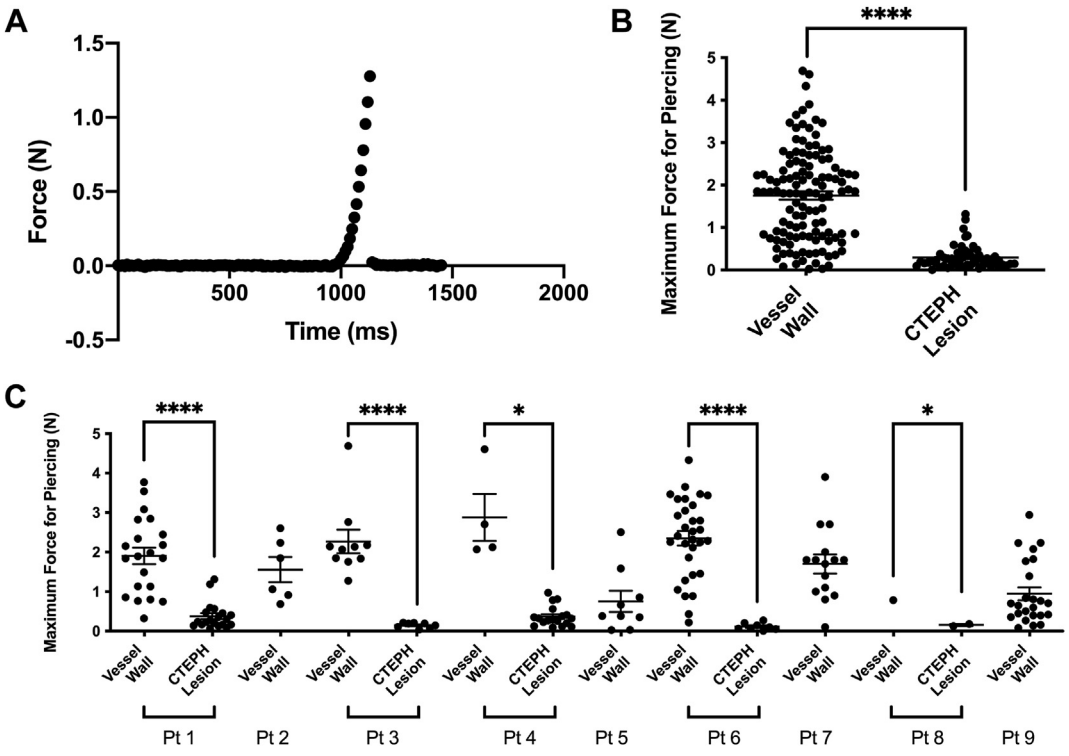


Figure 3.

Mechanical testing of patient lesions using the 0.015-in probe. (**A**) A representative plot of axial force versus time during uniaxial loading is shown. The peak force was measured for each replicate and compared between the vessel wall and intraluminal chronic thromboembolic pulmonary hypertension (CTEPH) lesion samples. (**B**) The peak force required to penetrate vessel wall samples was 1.75 ± 0.10 N (n = 121) whereas the peak force required to penetrate CTEPH lesion samples was 0.30 ± 0.04 N (n = 56, 5.83-fold difference, $P < .001$). (**C**) The peak force required to penetrate the vessel wall and CTEPH lesion samples is shown for each patient. Significance is noted *$P < .05$, ****$P < .001$.

Mechanical characterization

A summary of sample and subsample procurement for piercing testing of the vessel wall and intraluminal CTEPH samples in each patient is shown in Figure 1A. An ANOVA was performed to assess variation in piercing properties considering all patient-specific vessel walls and intraluminal CTEPH lesion subsamples ($P < .001$). The force needed to pierce the pulmonary arterial wall was consistently higher than the force needed to penetrate the intraluminal CTEPH lesions (Figure 3C). This finding was robust for all patients involved in the study who had both types of lesions available. The results of each patient's piercing study are included in Table 2.

Figure 3B summarizes the peak force required to pierce vessel wall and intraluminal CTEPH lesion samples in a pooled analysis for all patients. Among all patients, the peak force required to pierce vessel wall subsamples was 1.75 ± 0.10 N (n = 121; mean ± SEM), whereas the peak force required to penetrate intraluminal CTEPH lesion subsamples was 0.30 ± 0.04 N (n = 56; 5.83-fold difference, $P < .001$).

Histopathology

Intimal samples were available for all 9 patients in the study, each with evidence of diffuse intimal thickening (also known as intimal hyperplasia) consisting of collagen, smooth muscle, and focal proteoglycan matrix. Four intimal samples had evidence of hemosiderin deposition. One intimal sample had small foci of calcification (Figure 4A). CTEPH lesion samples were heterogeneous with varying stages of lesion age including acute (Figure 4B), organizing (Figure 4C), and chronic (Figure 4D). For the 5 patients with thrombus, 3 patients had evidence of focal fresh thrombus estimated to be less than 2 days old. Three patients had evidence of an old thrombus greater than 2 days old. Three patients had organizing thrombus estimated to be 1 to 2 weeks in age. Finally, 1 patient sample had evidence of multifocal urothelial adenocarcinoma that was intermixed with the thrombus. Supplemental Table S1 provides an overview of the surgical findings, gross pathology, and histopathologic findings for each lesion. Figure 1 summarizes the gross pathology findings from the operating room, and Figure 4 summarizes key representative histopathologic findings for the 9 patients.

Discussion

The results of this study confirm how commonly used workhorse coronary guide wires (with a force penetration of 0.008 N) are largely insufficient for crossing intraluminal CTEPH lesions. Consequently, CTEPH lesions may be penetrated in a poorly controlled manner, which predisposes the arterial wall to trauma during BPA procedures. It is not surprising that existing workhorse coronary wires designed for acute thrombi prove insufficient for lesion crossing in chronic intraluminal CTEPH lesions.

The chronicity of CTEPH lesions allows for fibrosis and stiffening of the lesion compared to acute thrombi. Over a period of weeks to months, fibrin-rich acute pulmonary emboli remodel and become progressively more collagen-rich.[18] In this study, we observed a variety of stages of lesion chronicity within each patient. Previous clinical literature and animal models of CTEPH have similarly demonstrated various stages of thrombi fibrosis with fibrin, erythrocyte, and collagen predominance.[18,30] The microscopic changes seen in this study are consistent with the relatively high forces required to pierce intraluminal CTEPH lesions compared to those forces rated for workhorse coronary guide wires.

While we identify that the average force required to penetrate intraluminal CTEPH lesions is 40-fold higher than the maximum force rated by commonly available workhorse coronary guide wires, in this

Table 1. Baseline characteristics.

Patient information	N = 9
Age, y	53.8 (3.8)
Male sex	6 (66.7%)
Medical history	
History of acute pulmonary embolism	9 (100.0%)
Known thrombophilia	2 (22.2%)
Systemic inflammatory disease	4 (44.4%)
Ongoing malignancy	0 (0%)
Splenectomy	0 (0%)
Medication history	
Heparin product	1 (11.1%)
Vitamin K antagonist	4 (44.4%)
Anti-Xa agent	6 (66.7%)
Riociguat	1 (11.1%)
Bosentan	0 (0%)
Macitentan	0 (0%)
Percutaneous procedure history	
Catheter-directed thrombolysis	4 (44.4%)
Percutaneous mechanical thrombectomy	3 (33.3%)
Inferior vena cava filter placement	3 (33.3%)
Hemodynamics prior to thromboendarterectomy	
Pulmonary artery pressure systolic, mm Hg	82.0 (10.0)
Pulmonary artery pressure diastolic, mm Hg	33.4 (3.6)
Pulmonary artery pressure mean, mm Hg	50.4 (5.7)
Pulmonary vascular resistance, WU	8.1 (1.4)[a]
Cardiac index (thermodilution), L/min/m^2	2.23 (0.19)
Cardiac output (thermodilution), L/min	4.89 (0.54)

Continuous values are mean (standard error of the mean); categorical values are n (%).

[a] For 1 of the 9 patients, during diagnostic right heart catheterization, the operator attempted several times in both lungs to obtain a measurement of pulmonary capillary wedge pressure, but they were not able to obtain a reliable pressure tracing. However, for this same patient, a left heart catheterization was obtained 2 days prior to pulmonary thromboendarterectomy. The left ventricular end-diastolic pressure was noted during that catheterization and has been used as a stand-in for the pulmonary capillary wedge pressure for computation of pulmonary vascular resistance.

Table 2. Summary of piercing test results with 0.015-in probe.

Lesion	Piercing force ± SEM (N subsamples)	Fold difference	*P* value
Patient 1			
Thrombus	0.38 ± 0.08 N (20)	5.05	<.001
Intima	1.90 ± 0.21 N (21)		
Patient 2			
Thrombus	–	–	–
Intima	1.56 ± 0.32 N (6)		
Patient 3			
Thrombus	0.15 ± 0.02 N (8)	15.43	<.001
Intima	2.27 ± 0.29 N (10)		
Patient 4			
Thrombus	0.37 ± 0.06 N (18)	7.84	.023
Intima	2.88 ± 0.59 N (4)		
Patient 5			
Thrombus	–	–	–
Intima	0.75 ± 0.27 N (9)		
Patient 6			
Thrombus	0.11 ± 0.03 N (8)	20.45	<.001
Intima	2.35 ± 0.18 N (31)		
Patient 7			
Thrombus	–	–	–
Intima	1.70 ± 0.24 N (15)		
Patient 8			
Thrombus	0.15 ± 0.03 N (2)	5.09	–
Intima	0.78 (1)		
Patient 9			
Thrombus	–	–	–
Intima	0.95 ± 0.16 (24)		

SEM, standard error of the mean.

study, we additionally show that the force needed to pierce the hypertrophied pulmonary artery intima in patients with CTEPH is roughly 6-fold higher than the force needed to pierce the intraluminal CTEPH lesions. This effect was observed for data in aggregate, as well as for each individual patient. This finding suggests a safety window exists that can be used to design dedicated guide wires and microcatheters for performing more effective BPA (Central Illustration).

The safety window identified in this study is likely explained by hyperplastic remodeling of the pulmonary arterial intima in the setting of long-standing pulmonary hypertension. All 9 patients in this study exhibited diffuse intimal thickening (intimal hyperplasia) on H&E staining. This evidence of pulmonary artery remodeling and intimal thickening is consistent with what has previously been described in the clinical literature.[18,31] Conspicuous pulmonary artery remodeling and vessel intimal thickening have also been described in several animal models of CTEPH, including in rats, pigs, and dogs.[30–32] This is consistent with the overall clinical picture of long-standing pulmonary hypertension and the well-understood relationship between vessel wall properties and hemodynamics.[22] In the particular case of percutaneous management of CTEPH, the pathological intimal hyperplasia may advantageously contribute to the safety window noted above.

This study presents the use of a probe of comparable dimensions to the guide wires used clinically for BPA and specifically measures the peak force required to pierce different types of tissues. Previous studies have examined the mechanical properties of CTEPH lesions in humans and animal models using standard elastic and compressive moduli.[32] While these studies provide insights on differences between thrombus and vessel wall mechanical properties, this study is the first of its kind to use a probe of diameter 0.38 mm (0.015 in) and an ex vivo testing set-up that simulates lesion crossing. Our ex vivo model is also unique and may be used in tandem with the well-described porcine model of CTEPH for future research work.[33–35]

Finally, the approach identified in this study of carefully characterizing the piercing properties of a vessel and lesion with a clinically relevant testing methodology could be readily applied to additional vascular beds, such as the intracranial and splanchnic vascular beds.

Limitations

Because PEA is an invasive procedure thought to benefit only a small subset of patients with CTEPH, any study considering the piercing properties of CTEPH lesions will be limited to a small sample size. Nevertheless, because the variability in piercing properties between patients seen in this study was sufficiently small, the sample size was adequate. Second, this study considers only surgical patients following PEA, which is generally the subset of CTEPH patients in which BPA is not commonly performed. This is a subset of all patients with CTEPH; hence, selection bias may limit the generalizability of our results. Future work will correlate our results with cadaveric specimens of CTEPH to assess whether there is a clinically meaningful distinction between piercing properties of CTEPH lesions in patients thought to be appropriate and inappropriate surgical candidates. Last, whereas guide wires used in cardiac catheterization laboratories tend to have rounded tips and are very flexible, the probe used in this study was stiff with a flat tip. The 0.38-mm (0.015-in) diameter probe used in this study was chosen to ensure measurement accuracy and protect against probe buckling. Future studies will make use of a variety of probe shapes and stiffnesses to determine the optimal probe for piercing CTEPH lesions without piercing the vessel wall.

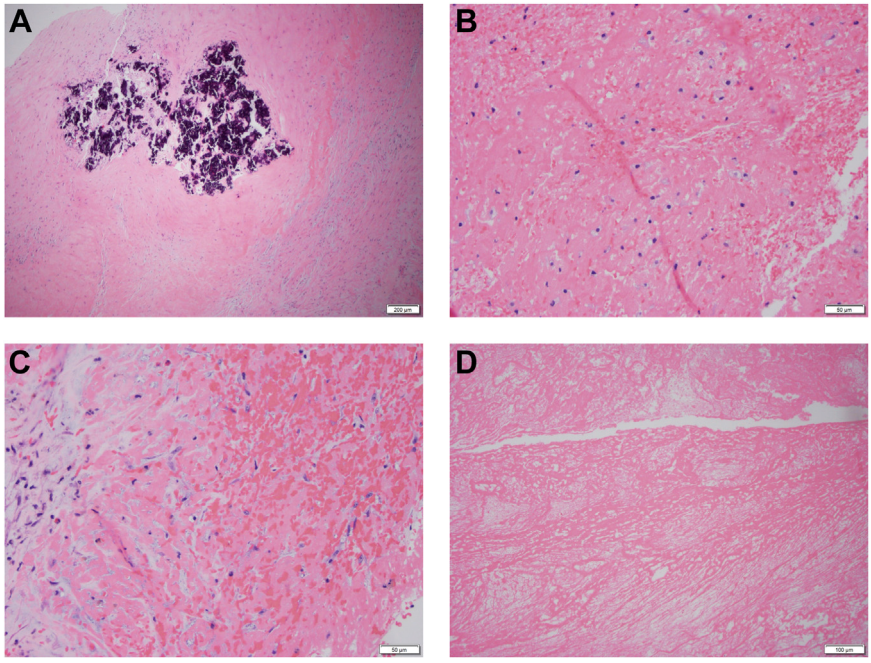
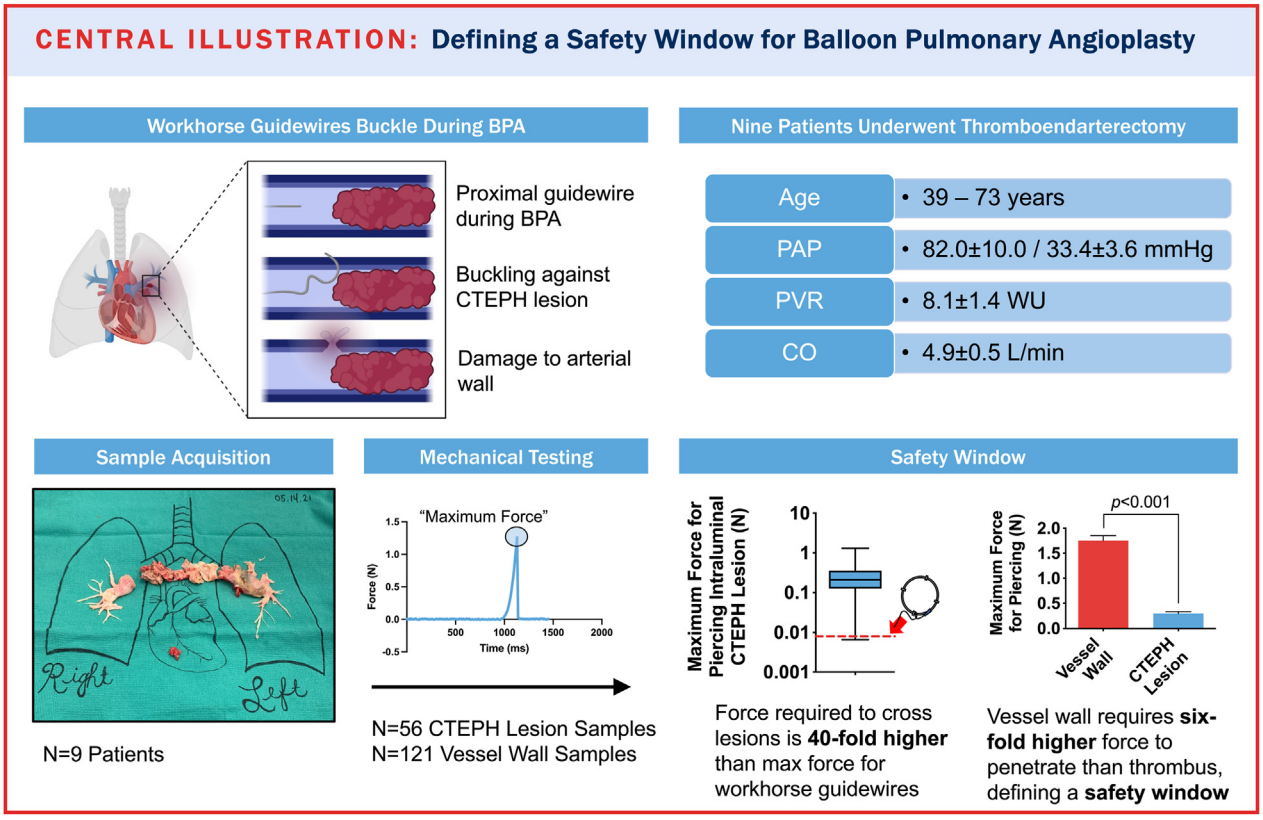


Figure 4.
Representative hematoxylin and eosin staining of chronic thromboembolic pulmonary hypertension (CTEPH) lesions. (**A**) Diffuse vessel wall thickening with focal calcification shown at ×4 magnification. (**B**) Fresh CTEPH lesion estimated to be less than 2 days in age shown at ×4 magnification. (**C**) Organizing CTEPH lesion estimated to be 1 to 2 weeks old shown at ×20 magnification. (**D**) Old CTEPH lesion estimated to be greater than 2 days in age shown at ×4 magnification (note the lack of viable appearing cells in this old thrombus).



Central Illustration.
Workhorse guide wires are poorly equipped to cross intraluminal chronic thromboembolic pulmonary hypertension (CTEPH) lesions, resulting in guide wire buckling and trauma to the proximal intima. In this study, 9 patients (aged 39-73 years) underwent thromboendarterectomy. Prior to surgery, right heart catheterization was performed. The patients in this study had systolic pulmonary pressures of 82.0 ± 10.0 mm Hg, diastolic pulmonary pressures of 33.4 ± 3.6 mm Hg, pulmonary vascular resistances of 8.1 ± 1.4 Woods Units, and cardiac output of 4.9 ± 0.5 L/min. A representative image of the CTEPH lesion samples is shown. The maximum force measured while piercing the samples with a 0.015-in probe was measured for intraluminal CTEPH lesions and vessel wall samples. The average force required to cross CTEPH lesions was 0.30 ± 0.04 N (n = 56), which exceeds the maximum tip force of workhorse guide wires by 40-fold (box and whisker plot with whiskers showing the minimum and maximum data points). Finally, the average force required to pierce the vessel wall was 1.75 ± 0.10 N (n = 121), nearly 6-fold higher than the force needed to pierce intraluminal CTEPH lesions ($P < .001$). This suggests the existence of a safety window that may be used to design more appropriate tools for performing balloon pulmonary angioplasty (BPA).

Conclusions

This study demonstrates that the force required to penetrate intraluminal CTEPH lesions exceeds the maximum force that can be provided by the tip of workhorse coronary guide wires by more than 40-fold. This highlights the inadequacy of existing percutaneous tools for the minimally invasive management of CTEPH and offers a mechanistic explanation for the high rate of periprocedural complication. Importantly, this study also demonstrates that there is a clinically relevant roughly 6-fold difference between the piercing properties of the pulmonary arterial intima and intraluminal CTEPH lesions. To our knowledge, this is the first study identifying a safety window for the force associated with CTEPH lesion crossing during BPA. The results of this study will be useful in the design and evaluation of the next generation of guide wires, balloons, microcatheters, and other percutaneous tools for the BPA treatment of CTEPH.

Acknowledgments

The cartoon illustration of guide wire buckling included in the Central Illustration was created with BioRender.com.

Declaration of competing interest

David M. Williams is on the Medical Advisory Board of Boston Scientific. The other authors declare no conflicts of interest.

Funding sources

Sidney J. Perkins received funding from the National Institutes of Health's T35 Short-Term National Service Award and the Sarnoff Cardiovascular Research Foundation.

Ethics statement and patient consent

The research protocol was approved by the University of Michigan's Institutional Review Board (IRB HUM00157980). Informed consent was not required per our IRB, as the tissue obtained for this study was obtained as part of routine clinical care and would have been discarded otherwise.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2024.102142.

References

1. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation*. 2011;124(18):1973–1981. https://doi.org/10.1161/CIRCULATIONAHA.110.015008
2. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost*. 2001;86(1):452–463.
3. 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. https://doi.org/10.1056/NEJMoa1209657
4. 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. https://doi.org/10.1016/S2213-2600(17)30305-3
5. Escribano-Subias P, Bendjenana H, Curtis PS, Lang I, Vonk Noordegraaf A. Ambrisentan for treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH). *Pulm Circ*. 2019;9(2):2045894019846433. https://doi.org/10.1177/2045894019846433
6. Suntharalingam J, Treacy CM, Doughty NJ, et al. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest*. 2008;134(2):229–236. https://doi.org/10.1378/chest.07-2681
7. Tanabe N, Kawakami T, Satoh T, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: a systematic review. *Respir Investig*. 2018;56(4):332–341. https://doi.org/10.1016/j.resinv.2018.03.004
8. 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. https://doi.org/10.1161/01.cir.103.1.10
9. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv*. 2012;5(6):748–755. https://doi.org/10.1161/CIRCINTERVENTIONS.112.971077
10. 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. https://doi.org/10.1161/CIRCINTERVENTIONS.112.971390
11. Andreassen AK, Ragnarsson A, Gude E, Geiran O, Andersen R. Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Heart*. 2013;99(19):1415–1420. https://doi.org/10.1136/heartjnl-2012-303549
12. Inami T, Kataoka M, Shimura N, et al. Pressure-wire-guided percutaneous transluminal pulmonary angioplasty. *JACC Cardiovasc Interv*. 2014;7(11):1297–1306. https://doi.org/10.1016/j.jcin.2014.06.010
13. Akizuki M, Serizawa N, Ueno A, Adachi T, Hagiwara N. Effect of balloon pulmonary angioplasty on respiratory function in patients with chronic thromboembolic pulmonary hypertension. *Chest*. 2017;151(3):643–649. https://doi.org/10.1016/j.chest.2016.10.002
14. 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):1602409. https://doi.org/10.1183/13993003.02409-2016
15. Yanaka K, Nakayama K, Shinke T, et al. Sequential hybrid therapy with pulmonary endarterectomy and additional balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *J Am Heart Assoc*. 2018;7(13):e008838. https://doi.org/10.1161/JAHA.118.008838
16. 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. https://doi.org/10.1161/CIRCOUTCOMES.117.004029
17. 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):1802095. https://doi.org/10.1183/13993003.02095-2018
18. Bochenek ML, Rosinus NS, Lankeit M, et al. From thrombosis to fibrosis in chronic thromboembolic pulmonary hypertension. *Thromb Haemost*. 2017;117(4):769–783. https://doi.org/10.1160/TH16-10-0790
19. Saouti N, Westerhof N, Postmus PE, Vonk-Noordegraaf A. The arterial load in pulmonary hypertension. *Eur Respir Rev*. 2010;19(117):197–203. https://doi.org/10.1183/09059180.00002210
20. Karimi A, Navidbakhsh M, Shojaei A, Faghihi S. Measurement of the uniaxial mechanical properties of healthy and atherosclerotic human coronary arteries. *Mater Sci Eng C Mater Biol Appl*. 2013;33(5):2550–2554. https://doi.org/10.1016/j.msec.2013.02.016
21. Hoerstrup SP, Kadner A, Breymann C, et al. Living, autologous pulmonary artery conduits tissue engineered from human umbilical cord cells. *Ann Thorac Surg*. 2002;74(1):46–52. https://doi.org/10.1016/S0003-4975(02)03649-4
22. Cox R. Pressure dependence of the mechanical properties of arteries in vivo. *Am J Physiol*. 1975;229(5):1371–1375. https://doi.org/10.1152/ajplegacy.1975.229.5.1371
23. Liu Y, Zheng Y, Reddy AS, et al. Analysis of human emboli and thrombectomy forces in large-vessel occlusion stroke. *J Neurosurg*. 2020;134(3):893–901. https://doi.org/10.3171/2019.12.JNS192187
24. Liu Y, Reddy AS, Cockrum J, et al. Standardized fabrication method of human-derived emboli with histologic and mechanical quantification for stroke research. *J Stroke Cerebrovasc Dis*. 2020;29(11):105205. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105205
25. Reddy AS, Liu Y, Cockrum J, et al. Construction of a comprehensive endovascular test bed for research and device development in mechanical thrombectomy in stroke. *J Neurosurg*. 2020;134(4):1190–1197. https://doi.org/10.3171/2020.1.JNS192732
26. Fineschi V, Turillazzi E, Neri M, Pomara C, Riezzo I. Histological age determination of venous thrombosis: a neglected forensic task in fatal pulmonary thromboembolism. *Forensic Sci Int*. 2009;186(1-3):22–28. https://doi.org/10.1016/j.forsciint.2009.01.006
27. Carol A, Bernet M, Curós A, et al. Thrombus age, clinical presentation, and reperfusion grade in myocardial infarction. *Cardiovasc Pathol*. 2014;23(3):126–130. https://doi.org/10.1016/j.carpath.2014.01.007
28. Leu HJ, Leu AJ. Phlebosclerosis, phlebothrombosis, and thrombophlebitis: a current perspective. *Cardiovasc Pathol*. 1996;5(4):183–192. https://doi.org/10.1016/1054-8807(96)00026-9
29. Stone JR. Diseases of small and medium-sized blood vessels. In: Buja LM, Butany J, eds. *Cardiovascular Pathology*. 4th edition. Academic Press; 2016:125–168. https://doi.org/10.1016/B978-0-12-420219-1.00004-5
30. Arias-Loza PA, Jung P, Abeßer M, et al. Development and characterization of an inducible rat model of chronic thromboembolic pulmonary hypertension. *Hypertension*. 2016;67(5):1000–1005. https://doi.org/10.1161/HYPERTENSIONAHA.116.07247
31. Dorfmüller P, Günther S, Ghigna MR, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and

systemic vasculature. *Eur Respir J*. 2014;44(5):1275–1288. https://doi.org/10.1183/09031936.00169113
32. Golob MJ, Tabima DM, Wolf GD, et al. Pulmonary arterial strain- and remodeling-induced stiffening are differentiated in a chronic model of pulmonary hypertension. *J Biomech*. 2017;55:92–98. https://doi.org/10.1016/j.jbiomech.2017.02.003
33. Schwein A, Magnus L, Chakfé N, Bismuth J. Critical Review of Large Animal Models for Central Deep Venous Thrombosis. *Eur J Vasc Endovasc Surg*. 2020;60(2):243–252. https://doi.org/10.1016/j.ejvs.2020.03.051
34. Sondeen JL, de Guzman R, Amy Polykratis I, et al. Comparison between human and porcine thromboelastograph parameters in response to ex-vivo changes to platelets, plasma, and red blood cells. *Blood Coagul Fibrinolysis*. 2013;24(8):818–829. https://doi.org/10.1097/MBC.0b013e3283646600
35. Fufa D, Shealy B, Jacobson M, Kevy S, Murray MM. Activation of platelet-rich plasma using soluble type I collagen. *J Oral Maxillofac Surg*. 2008;66(4):684–690. https://doi.org/10.1016/j.joms.2007.06.635