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CTEPH

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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PUBLISHER
Pulmonary Hypertension Association
Matt Granato, LL.M., MBA, President and CEO

PHA OFFICE
Pulmonary Hypertension Association
8401 Colesville Road, Suite 200
Silver Spring, MD 20910
301-565-3004; 301-565-3994 (fax)
Advances@PHAssociation.org

PUBLISHING OPERATIONS
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Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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Chronic thromboembolic pulmonary hypertension (CTEPH) is unique among the many etiologies of pulmonary hypertension (PH), in that it can be treated very effectively, even cured, with the surgical extraction of occlusive thrombo-fibrotic lesions via pulmonary thromboendarterectomy (PTE) surgery. More recently, balloon pulmonary angioplasty (BPA) has emerged as a viable option for patients who cannot or should not be operated upon, and for those with residual disease after PTE. Arguably, BPA is one of the major advancements in pulmonary vascular disease over the past 2 decades, although surgical therapy with PTE remains the treatment of choice whenever feasible. Effective PH-targeted medical therapy is also available, and increasingly multimodality approaches including a combination of these treatment options are being utilized in expert centers to achieve the best outcomes. And yet, CTEPH remains a vastly under-recognized disease, with considerable delays and confusion in its diagnosis. As a result, many patients are still not being effectively treated. This issue of *Advances in Pulmonary Hypertension* represents an effort to update our readers on the key current diagnostic and therapeutic approaches for CTEPH.

In "Post-Pulmonary Embolism Follow-Up and Epidemiology of Chronic Thromboembolic Pulmonary Hypertension", Jasuja and colleagues provide a comprehensive framework of the many issues that need to be addressed in follow-up after an acute pulmonary embolism (PE). In addition, the authors review the available evidence and challenges on the epidemiology and risk factors for CTEPH, as well as the evolving understanding of the post-PE syndrome.

In the article "Diagnostic Evaluation of CTEPH", Vaidya and Forfia describe the multiple steps and testing needed to arrive at the correct diagnosis of CTEPH, including several chest imaging studies that can accurately identify and quantify chronic thrombo-fibrotic occlusive disease of pulmonary arteries, as well as detailed imaging and hemodynamic studies that measure the impact of occlusive disease on right ventricular afterload.

The article "Pulmonary Thromboendarterectomy: Patient Selection, Techniques, Outcomes, and Recent Advances" by Madani and Higgins provides a discussion on the current role of surgical therapy for CTEPH, which remains the treatment of choice for a majority of patients.

In "Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension" Serfas and Krasuski share an expert insight into patient selection, procedural technique and complications of this relatively novel interventional treatment modality for CTEPH, which is gaining an increasingly important role in management of CTEPH in expert centers.

In "Medical Management of Chronic Thromboembolic Pulmonary Hypertension" Goyanes and Heresi review the medical management of CTEPH, including lifelong anticoagulation to prevent recurrent PE and PH-targeted therapy (pulmonary vasodilators) directed at the concomitant microscopic vasculopathy. The authors detail the available literature and current knowledge gaps regarding choice of anticoagulant, patient selection for pulmonary vasodilator therapy, and the place of PH therapy in the context of PTE and BPA.

Finally, in the round table discussion, Co-editors Drs. Heresi and Krasuski gather Drs. Auger, Tapson and Lang for a lively conversation on the practical aspects and current challenges in the diagnosis of CTEPH, including recognition of CTEPH after acute PE, and the use of detailed and precise imaging and hemodynamic techniques to phenotype CTEPH.

We are confident our readers will find this issue informative and we sincerely thank all the contributors for their efforts and time devoted to this issue.

Gustavo A. Heresi, MD, MS
Section Head, Pulmonary Vascular Disease
Respiratory Institute, Cleveland Clinic
Cleveland, OH 44195

Richard A. Krasuski, MD
Professor of Medicine, Duke University
School of Medicine
Durham, NC 27710

REGULAR ARTICLE

Postpulmonary Embolism Follow-Up and Epidemiology of Chronic Thromboembolic Pulmonary Hypertension

Sonia Jasuja, MD
Division of Pulmonary and Critical Care
University of California Los Angeles
David Geffen School of Medicine
Los Angeles, CA

Alexander E. Sherman, MD
Division of Pulmonary and Critical Care
University of California Los Angeles
David Geffen School of Medicine
Los Angeles, CA

Rajan Saggar, MD
Division of Pulmonary and Critical Care
University of California Los Angeles
David Geffen School of Medicine
Los Angeles, CA

Richard N. Channick, MD
Division of Pulmonary and Critical Care
University of California Los Angeles
David Geffen School of Medicine
Los Angeles, CA

The follow-up of patients with acute pulmonary embolism is an essential component of their comprehensive care. This manuscript will discuss the critical components involved in the outpatient follow-up of pulmonary embolism, including the development of post hospitalization follow-up clinics, assessment of functional capacity and residual right ventricular function, anticoagulation, recurrence risk of venous thromboembolism, and retrieval of inferior vena cava filters. In addition to these listed topics, the epidemiology of chronic thromboembolic pulmonary hypertension will be discussed, including the spectrum of postpulmonary embolism syndrome (PPES), risk factors for the development of chronic thromboembolic pulmonary hypertension, and the incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism.

INTRODUCTION

The follow-up of patients with acute pulmonary embolism (PE) is an essential component of their comprehensive care. This manuscript will discuss post-PE follow-up recommendations as well as the epidemiology of chronic thromboembolic pulmonary hypertension (CTEPH). While there is a good collection of data to call upon for the epidemiology of CTEPH, there is little primary data on the outpatient follow-up of acute PE, and more research is needed in this area. PE is a disease process that leads to significant morbidity and mortality, with the 30-day mortality rate for massive PE ranging from 12% to 34%.[1,2] While the treatment of acute PE is an important and necessary consideration, it is crucial to concomitantly address the outpatient follow-up of patients after their acute PE, especially given that the recurrence rate for venous thromboembolism (VTE) events is up to 30%, with the highest recurrence rate occurring immediately after the initial event.[3] In patients with submassive PE, the mortality risk persists after the index hospitalization to the posthospitalization time period.[1] Furthermore, the outpatient follow-up of acute PE should include monitoring for the development of post-PE syndrome (PPES), which is a spectrum of disease that includes chronic thromboembolic disease (CTED) and CTEPH. Between 0.1% and 9.1% of patients go on to develop CTEPH after an episode of acute PE.[4-11] The European Society of Cardiology and the PERT (PE response team) Consortium have published consensus guidelines on the follow-up of patients with PE, which will be expanded upon in this manuscript (Figure 1).[12-14]

OUTPATIENT FOLLOW-UP OF PE

Timing and Logistics of Post-PE Follow-Up

The outpatient follow-up of patients diagnosed with acute PE begins during the index hospitalization, when transitions of care are set up for outpatient follow-up. Recently, several medical centers have developed dedicated outpatient post-PE clinics, as an extension of the inpatient PERT that evaluates acute PE patients during inpatient hospitalization. The primary aim of an outpatient, post-PE follow-up clinic is to monitor for recurrent, persistent, or progressive symptoms after PE and determine an appropriate plan for anticoagulation (Figure 2). Furthermore, these clinics

Key Words——pulmonary embolism, chronic thromboembolic pulmonary hypertension (CTEPH), postpulmonary embolism syndrome, chronic thromboembolic disease (CTED), venous thromboembolism (VTE) recurrence risk
Correspondence: rchannick@mednet.ucla.edu
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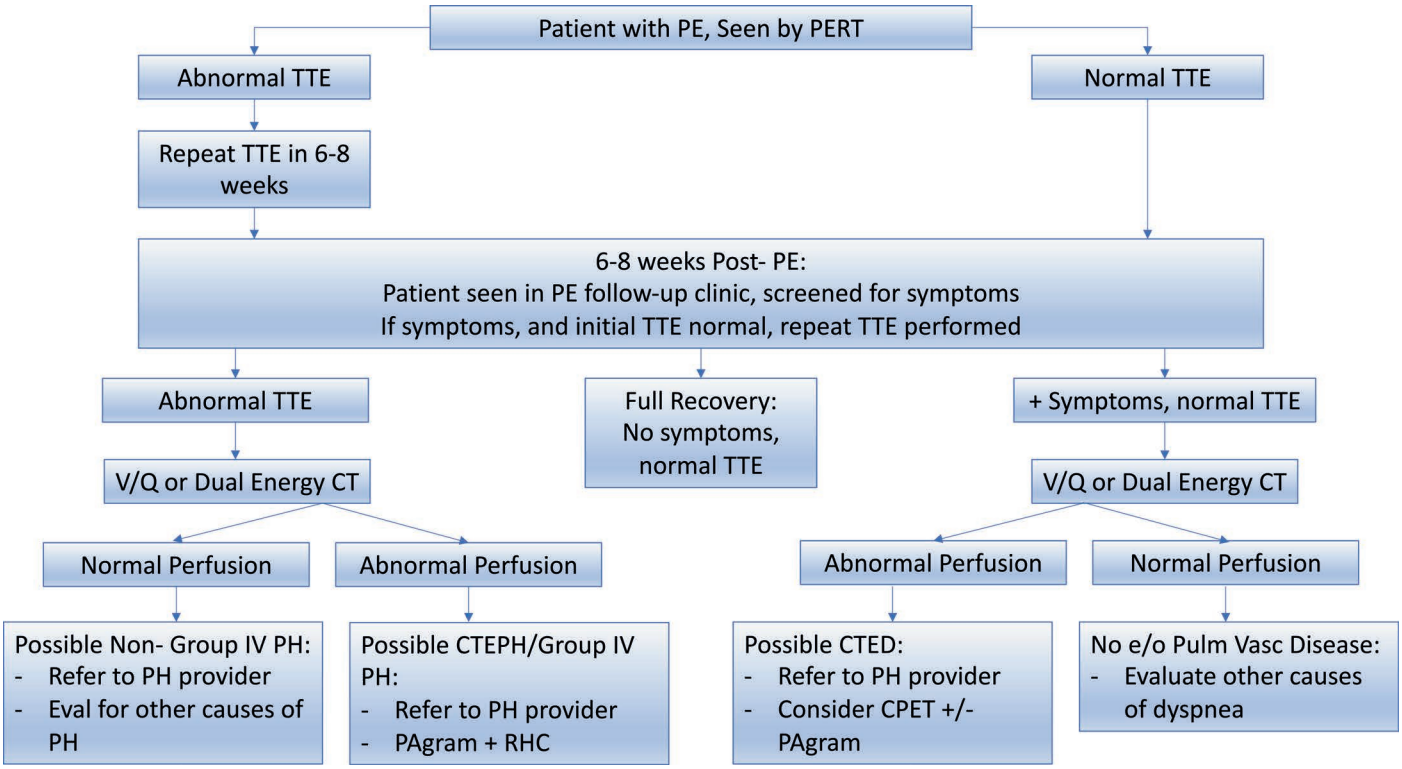

Figure 1: Post-PE follow-up algorithm. PE indicates pulmonary embolism; PERT, PE Response Team; TTE, transthoracic echo; V/Q, ventilation perfusion scan; CT, computed tomography; PH, pulmonary hypertension; Pulm Vasc, pulmonary vascular disease; PAgram, pulmonary angiogram; RHC, right heart catheterization; CPET, cardiopulmonary exercise test.

address possible underlying factors contributing to the development of the PE, including workup of acquired thrombophilia in appropriate situations and age-appropriate cancer screening. Lastly, these clinics facilitate the appropriate removal of temporary inferior vena cava (IVC) filters, and perhaps most importantly, monitor for and identify PPES, including CTED and CTEPH.[15] These post-PE clinics are run by a variety of specialties, including pulmonary, pulmonary vascular disease, cardiology, hematology, or interventional radiology. Oftentimes, the inpatient PERT will refer patients to the post-PE clinic upon discharge.

The initial follow-up visit in the post-PE clinic occurs 2 to 12 weeks after hospital discharge, depending on the patient's clinical course while in the hospital.[12,14] Patients with more severe PE, such as massive PE requiring embolectomy, extracorporeal membrane oxygenation support, systemic thrombolysis, or patients with a high bleeding risk are seen in follow-up sooner than patients with an uncomplicated low or intermediate-risk PE. Patients who

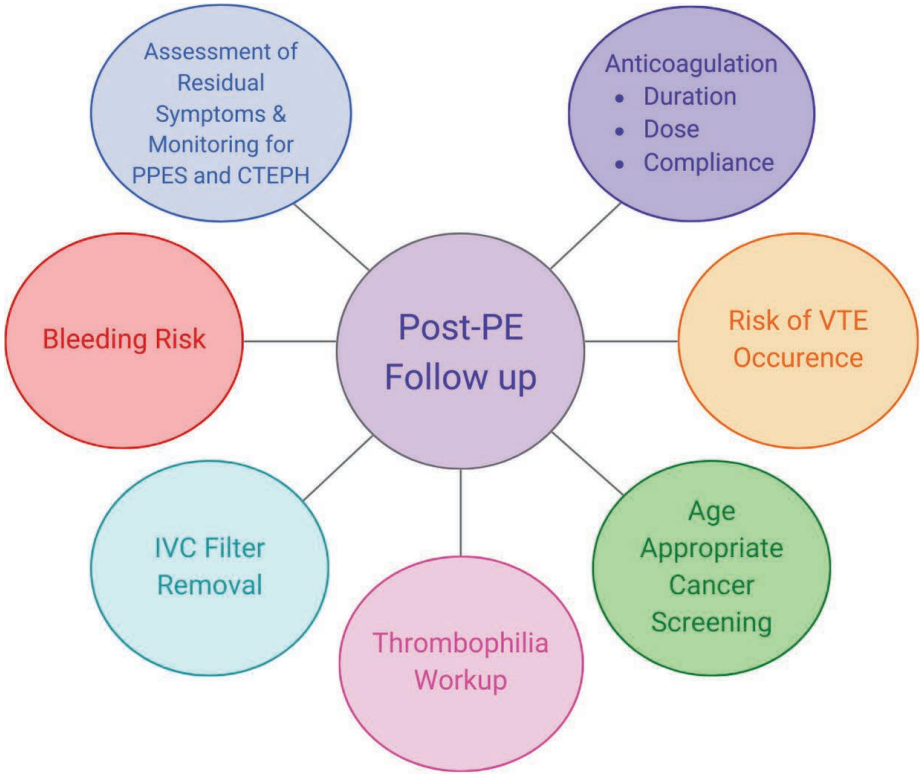

Figure 2: Post-PE follow-up: Components of post-PE care. PE indicates pulmonary embolism; PPES, post-PE syndrome; CTEPH, chronic thromboembolic pulmonary hypertension; VTE, venous thromboembolism; IVC, inferior vena cava.

had evidence of right ventricular (RV) dysfunction at the time of PE diagnosis, either on transthoracic echocardiogram or computed tomography angiogram of the chest, undergo a follow-up transthoracic echocardiogram to evaluate for resolution of RV dysfunction 6 to 8 weeks after their acute PE event. Guidelines do not recommend the universal screening of all post-PE patients with echocardiography, however the first post-PE clinic visit provider should review initial computed tomography imaging from hospitalization to determine if the initial presentation was due to a diagnosis of CTEPH, rather than acute PE. This determination is based on the findings of elevated pulmonary artery systolic pressure on transthoracic echocardiogram and the presence of computed tomography findings consistent with CTEPH, such as the presence of eccentric clot, arterial bands or webs, bronchial artery collaterals, distal tapering of pulmonary vessels, stenotic lesions or poststenotic dilation of pulmonary artery, complete occlusion or pouch defects, and a pattern of mosaicism indicating differential perfusion to the lungs.[5,16-18] Persistent RV dysfunction 6 to 8 weeks after acute PE in conjunction with persistent or worsening functional deficits prompts further workup of PPES.

The initial visit with the post-PE clinic mainly addresses plans for anticoagulation, including specific agent and supply, planned duration of therapy, and appropriate monitoring of anticoagulation. In certain populations of patients, the post-PE clinic provider will address any recommended age-appropriate cancer screening and will consider a limited thrombophilia workup in the appropriate clinical setting.[13]

A second visit to the post-PE clinic occurs at the 3-mont or 6-month mark after acute PE, depending on the planned duration of therapeutic anticoagulation. In patients with strongly provoking factors who can stop anticoagulation after 3 months, the second post-PE clinic visit occurs at 3 months after PE diagnosis. For patients who require either 6 months of therapeutic anticoagulation or indefinite anticoagulation, the second visit to the post-PE clinic occurs at the 6-month mark, when any indicated changes in dose of anticoagulation can be prescribed.

The second visit to the post-PE clinic also assesses for any residual respiratory symptoms or functional limitations, as a first step in monitoring for the PPES. Patients who present to post-PE clinic with persistent or progressive pulmonary symptoms, including dyspnea at rest or exertion, presyncope or syncope, chest pain, or exercise intolerance should be evaluated for PPES, which can range from a mild chronic condition to the most severe form, CTEPH.[19] The ELOPE cohort study demonstrated that 46.5% of PE patients had residual exercise limitation, defined as a persistent percent-predicted peak Vo_2 of <80%, 1 year after PE event. This functional limitation did not correlate with the presence of residual clot on either chest computed tomography angiogram or ventilation perfusion scan.[20]

The results of this study demonstrated that residual limitation in functional capacity after acute PE is frequently because of underlying patient comorbidities, such as obesity or heart failure with preserved ejection fraction, rather than because of an underlying diagnosis of CTED or CTEPH.

The PPES is described as a spectrum of disease, with the mildest form presenting as residual symptoms of dyspnea or exercise intolerance after 3 to 6 months from the acute PE event. It is important to further characterize exercise limitation in this group of patients, which can be done with formal cardiopulmonary exercise testing.[19,21] Patients with persistent pulmonary symptoms and residual unmatched lobar or segmental perfusion deficits on ventilation perfusion imaging after 3 months of therapeutic anticoagulation who do not have evidence of pulmonary hypertension are characterized as CTED. Finally, patients with residual pulmonary symptoms and residual unmatched lobar or segmental perfusion deficits on ventilation perfusion imaging after 3 months of therapeutic anticoagulation who have evidence of pulmonary hypertension on right heart catheterization are diagnosed with CTEPH.[19,22] Pulmonary hypertension is defined as a mean pulmonary artery pressure >20 mm Hg, a pulmonary capillary wedge pressure of ≤ 15 mm Hg, and a pulmonary vascular resistance of ≥ 3 Wood units on right heart catheterization.[22,23]

Duration of Anticoagulation

Duration of anticoagulation is a major topic addressed at every visit to the post-PE clinic and is a crucial portion of post-PE follow-up, as it has major implications for recurrence risk, which is highest in the months after acute PE and after anticoagulation is stopped.[24] At least 3 to 6 months of anticoagulation should be prescribed to every patient with acute PE.[25]

Recurrence Risk of VTE

Once this initial period of therapeutic anticoagulation is complete, an assessment of VTE recurrence risk should be the determining factor of whether it is appropriate to stop anticoagulation.[26] The case-fatality rate for death from recurrent PE is between 4% and 9%, and data from the International Cooperative Pulmonary Embolism Registry suggests that 7.9% of patients experience recurrent PE within 3 months of their index event, with the mortality rate of recurrent PE reaching 33.7% at 14 days after recurrence and as high as 46.8% at 30 days after recurrence.[26,27] In determining recurrence risk, the provider must assess the presence or absence of provoking factors, which may be transient or persistent, that contributed to the development of the acute PE. VTE in the setting of nonsurgical predisposing factors, such as minor surgery, hormone replacement therapy/oral contraceptive pill use, or short hospital admission have a lower risk of VTE recurrence, between 3% and 8% per year. Patients with active cancer, a history of prior VTE without provoking factors, or antiphospholipid antibody syndrome have the highest rate of VTE recurrence.[3,12] Postoperative VTE has a very low risk of recurrence, whereas malignancy-associated VTE has the highest risk of recurrence.[28] Patients with major transient or reversible provoking factors, such as the postoperative state or recent trauma, can stop anticoagulation after 3 to 6 months of therapy.[12] Practitioners should consider continuation of anticoagulation, either at therapeutic or prophylactic dosing,

in patients with persistent provoking factors, weak provoking factors, or for patients without any identifiable provoking factors.[12,29-32] More in-depth guidelines for duration of anticoagulation after PE are reviewed elsewhere and are outside the scope of this manuscript.

Prediction Tools for VTE Recurrence

Several models have been developed to aid in the prediction of VTE recurrence. The Vienna prediction model can be used in patients with a first episode of unprovoked PE to calculate the 1-year and 5-year recurrence risk of VTE event. These tools can be especially helpful when used in shared decision making discussions to help decide the best duration of anticoagulation for each patient.[33,34] The DASH prediction score is another prediction tool and can also be used to assess VTE recurrence risk in patients with unprovoked VTE.[35]

Presence of Residual Deep Vein Thrombus

Another consideration during the second post-PE clinic visit at 3 to 6 months after the VTE event is the presence of residual or chronic deep vein thrombosis (DVT). Repeat lower extremity venous duplex ultrasound is obtained in patients who presented with DVT and PE at diagnosis. If these patients have evidence of residual or chronic DVT, anticoagulation should be continued given increased risk of PE recurrence with residual DVT.[36]

Bleeding Risk

The strategy for anticoagulation addressed in the post-PE follow-up assessment should include an assessment of bleeding risk. There are several bleeding risk calculators that can be used when assessing bleeding risk among this patient population. HAS-BLED, ATRIA, and HEMORR2HAGES-score are all studied in patients with atrial fibrillation, but they can also be applied in the setting of VTE.[37-39] Additionally, the RIETE score was developed as a bleeding risk assessment specifically for VTE patients.[40]

IVC Filter Retrieval

The timely retrieval of temporary IVC filters is an important consideration in the follow-up of post-PE patients. These filters should be removed as soon as the patient is tolerating therapeutic anticoagulation, generally within 2 to 4 weeks after implantation.[12,41] IVC filter removal should be addressed systematically at regular intervals in cases where expeditious removal is not feasible. The long-term presence of IVC filters places patients at risk for further venous stasis and development of DVT, with the most extreme example being phlegmasia cerulea dolens. Thus, the use of these filters has fallen out of favor given increased long-term risk for clot formation.

EPIDEMIOLOGY OF CTEPH

The Post-PE Syndrome

As discussed above, CTEPH is the most severe diagnosis on a spectrum of long-term complications that can arise after the diagnosis of acute PE.[19,21,42,43] It is unknown whether this spectrum of disease exists as a progressive continuum versus a group of related disease processes after acute PE. While the incidence of CTEPH after acute PE episode is between 0.1% and 9.1%, multiple studies have reported that up to 50% of patients experience residual pulmonary symptoms or exercise/functional limitations after acute PE, thus bringing about the entity of the PPES, which includes CTEPH, CTED, post-PE cardiac impairment and post-PE functional impairment.[4-11,43] Boon et al recently published a thorough review of the prevalence of PPES and broke down the spectrum of disease into these 4 categories. The PPES is reported in as many as 40% to 60% of PE survivors.[43,44] The epidemiology of CTEPH, specifically, will be discussed in this manuscript.

Chronic Thromboembolic Pulmonary Hypertension

It is well known that acute PE is a predisposing factor for the development of CTEPH.[4,5,45,46] Approximately 75% of patients diagnosed with CTEPH have a known prior history of PE, and approximately 50% of patients diagnosed with CTEPH have a history of DVT.[45] The timely diagnosis of CTEPH is of crucial importance to the well-being of these patients because CTEPH is a severe, progressive, and life-threatening disease that can be successfully treated and potentially cured if identified appropriately.[10,47] Multiple studies have been conducted to assess the incidence of CTEPH after acute PE, with considerable variability in study design, including screening protocols and inclusion criteria. Overall, the cumulative incidence of CTEPH after acute PE is between 0.1% and 9.1%.[4-11,43] More clinically relevant is the systematic review and meta-analysis by Ende-Verhaar et al that determined that the overall incidence of CTEPH was 0.56%, and increased to 3.2% in survivors of PE and 2.8% in survivors without major comorbidities.[18] This meta-analysis included low bias studies that used right heart catheterization to establish the diagnosis of CTEPH, thus providing the current best estimate of CTEPH incidence.

It is posited that studies that used echocardiography without right heart catheterization to diagnose pulmonary hypertension resulted in a higher incidence than studies that assessed hemodynamics invasively. Another study that required a stepwise approach to the diagnosis of CTEPH, estimated a 2-year cumulative incidence of 0.79%.[48] When discussing incidence of CTEPH, it is also important to note that the initial presentation of CTEPH is often misclassified as acute PE during index hospitalization. Guerin et al evaluated signs of CTEPH at initial presentation, which occurred at a rate of 4.8% and encompassed all 7 of 108 patients who were diagnosed with CTEPH in the study.[5]

Factors in Delayed Diagnosis of CTEPH

The diagnosis of CTEPH after PE is often delayed due to the nonspecific nature of clinical presentation and diagnostic misclassification, with a median delay of more than 1 year.[42] Furthermore, the clinical symptoms of CTEPH after acute PE often lags due to a well-described honeymoon period before the onset of symptoms from pulmonary hypertension.[49] In the study by Hsu et al, 4% of patients with acute PE were eventually diagnosed with CTEPH, with a median time from PE event to CTEPH diagnosis of 36 months.[4] This highlights the importance of a high index of suspicion for CTEPH

in patients with either a history of VTE or in patients who present with dyspnea on exertion of unclear origin.

Risk Factors for the Development of CTEPH

It is important to be aware of the risk factors that are associated with the development of CTEPH after acute PE. Several studies have evaluated possible risk factors for the development of CTEPH. Klok et al followed patients after acute PE and identified 6 factors that were independently associated with the diagnosis of CTEPH: unprovoked PE, known hypothyroidism, symptom onset >14 days prior to the diagnosis of PE, the presence of RV dysfunction on computed tomography or echocardiogram, a known history of diabetes mellitus, and thrombolytic therapy or embolectomy.[50] Of these factors, unprovoked PE had an odds ratio of 20 and onset of symptoms >14 days before diagnosis had an odds ratio of 7.9. Using these factors, Klok et al developed a CTEPH prediction score, which categorizes patients into a risk category for the development of CTEPH.[50]

Another study showed that older age, multiple previous VTE events, proximal PE, higher levels of BNP and higher pulmonary artery systolic pressures were risk factors for the diagnosis of CTEPH after acute PE.[5]

Additionally, Bonderman et al discuss that specific medical diagnoses, including splenectomy, ventriculoatrial shunt, inflammatory bowel disease, and osteomyelitis are risk factors for the development of CTEPH in comparison to the development of pulmonary arterial hypertension.

CONCLUSION

The follow-up of patients after acute PE is of critical importance in their comprehensive care. Purposeful follow-up after PE allows for assessment of RV function, determination of an appropriate anticoagulation dose and duration and monitoring for PPES, including CTEPH. Given the high incidence of PPES in the absence of CTEPH, it is imperative to monitor for this spectrum of disease. Finally, in reviewing the epidemiology of CTEPH, a high index of suspicion should be maintained for CTEPH both at initial hospitalization and in the follow-up of acute PE given frequent delays in the diagnosis and treatment of CTEPH.

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REGULAR ARTICLE

Diagnostic Evaluation of Chronic Thromboembolic Pulmonary Hypertension

Anjali Vaidya, MD
Pulmonary Hypertension, Right Heart Failure, CTEPH Program, Temple Heart & Vascular Institute, Temple University Hospital & Lewis Katz School of Medicine, Philadelphia, PA

Paul R. Forfia, MD
Pulmonary Hypertension, Right Heart Failure, CTEPH Program, Temple Heart & Vascular Institute, Temple University Hospital & Lewis Katz School of Medicine, Philadelphia, PA

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct form of pulmonary hypertension, uniquely characterized by pulmonary artery narrowing and occlusion from clot material. With advances in medical education and therapeutic options, awareness of CTEPH has grown significantly in recent years. The diagnostic evaluation remains complex, warranting an integrated assessment of history, physical exam, echocardiogram, chest imaging including computerized tomography with angiography, ventilation–perfusion scanning, right heart catheterization, catheter-based pulmonary angiography, and assessment for medical and mechanical CTEPH risk factors. The diagnostic evaluation of CTEPH is reviewed here.

INTRODUCTION

While the field of pulmonary hypertension (PH) has evolved dramatically in recent years regarding available medical therapy, much of PH remains a chronic, progressive, and often fatal disease. In the evaluation of the patient with PH, particularly with hemodynamics consistent with precapillary PH (elevated pulmonary vascular resistance [PVR] with normal left heart filling pressures), it is critical to make an accurate diagnosis of chronic thromboembolic PH (CTEPH) as the treatment options are vastly different.[1] CTEPH remains the sole PH diagnosis with the potential for cure, which is achieved on the basis of pulmonary thromboendarterectomy (PTE); alternatively, management may include balloon pulmonary angioplasty (BPA) or medical therapy with riociguat.[2–4]

HISTORY AND PHYSICAL EXAM

The history in CTEPH can range from elusive to quite informative. Up to 50% of patients ultimately diagnosed with CTEPH are not known to have had a prior pulmonary embolism (PE). In patients with an established diagnosis of acute PE followed prospectively, the risk of developing CTEPH is estimated to be approximately 3%–4%.[5] Risk factors for CTEPH are vast and should be elicited in the history. Hematologic abnormalities that portend a hypercoagulable state such as antiphospholipid antibody syndrome, history of splenectomy, red blood cell dyscrasias, history of prior PE, or young age at the time of first PE increase the risk of developing CTEPH. A diagnosis of cancer is a risk factor for CTEPH, both by the associated hypercoagulable state that often coexists with it and from indwelling central venous catheters used for chemotherapy that serve as a nidus for thrombus formation, which can then embolize into the lungs. Similarly, indwelling pacemakers have been associated with small thrombi embolizing and leading to a distal type of CTEPH.[6,7] More recently, pelvic vein obstructions have been described as a risk for developing CTEPH, including uterine fibroids and May-Thurner syndrome. Thus, in women, a history of fibroids, iron deficiency anemia, or menorrhagia can be a clue. May-Thurner syndrome, in which the right common iliac artery overlies and compresses the left common iliac vein, can also lead to stasis and venous thromboembolism (VTE); as such, a history of PE associated with recurrent left lower extremity deep vein thrombosis that by traditional risk factor evaluation is unprovoked can also be a helpful historic clue in the workup of CTEPH.[8,9]

The physical exam in CTEPH typically represents PH and right heart failure, including elevated jugular venous pressure (JVP) with abdominojugular reflux, tricuspid regurgitation markers such as a prominent V wave in the JVP or a holosystolic murmur increasing with inspiration, a loud pulmonic component of the second heart sound (P2), and peripheral edema. Pulmonary bruits may be present from turbulent flow caused by proximal disease, suggesting potentially operable disease. Indwelling venous catheters, ports, or pacemaker devices may reveal the etiology of CTEPH, while also revealing a necessary target for removal to prevent recurrence. Postthrombotic syndrome may be noted in CTEPH, including hyperpigmentation, skin thickening, lower extremity swelling, and varicose veins. If noted in the left lower extremity, May-Thurner syndrome should be considered.[7]

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Correspondence: anjali.vaidya@tuhs.temple.edu
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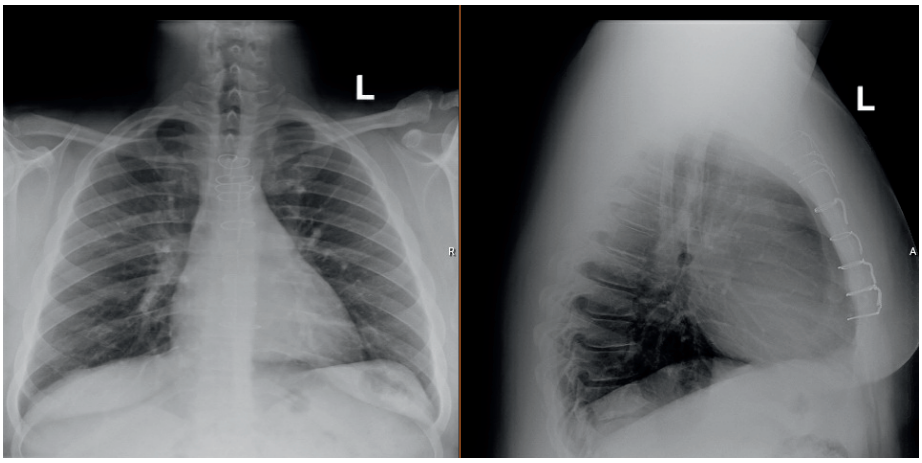

Figure 1: Chest radiograph demonstrating prominent descending right pulmonary artery, right ventricular enlargement with loss of retrosternal space.

CHEST X-RAY

Chest x-ray findings (Figure 1) include a prominent main pulmonary artery (PA) and Palla's sign (enlarged PA along the right atrial border), and often pruning of the distal pulmonary circulation. An enlarged right atrium extends the cardiac silhouette laterally, and a loss of retrosternal space on the lateral film suggests right ventricular (RV) enlargement.[10] Evidence of pulmonary infarct may also be seen as a subpleural wedge or round opacification. This is often referred to as Hampton's hump, described by Hampton and Castleman in 1940.[11]

ELECTROCARDIOGRAM

In chronic thromboembolic disease (CTED) without the presence of PH, the electrocardiogram (ECG) may be normal. When PH is present (CTEPH), there may be significant abnormalities (Figure 2) of the right side of the heart, including right axis deviation, right atrial enlargement, RV hypertrophy (RVH) as indicated by large R waves in V1-V2, and right heart strain evidenced by T-wave inversions in the right-sided precordial (V1-V3) and inferior leads (II, III, avF).[12]

Importantly, the presence or absence of normal sinus rhythm can have very significant implications in patients with CTEPH and right heart failure. Sinus rhythm and the maintenance of atrial-ventricular synchrony is critical to overall right heart function, and loss of this due to atrial tachyarrhythmias such as atrial fibrillation can lead to a loss of up to half of right heart function.[13] Amid the diagnostic workup of CTEPH, if a patient is noted to have significant PH with RV dysfunction, recognition of an atrial tachyarrhythmia should be considered a target for urgent intervention to maintain hemodynamic stability and minimize the clinical syndrome of right heart failure.

ECHOCARDIOGRAM

Like the ECG, the abnormalities seen on transthoracic echocardiography will depend on the degree of elevated PVR impact on the right heart (Figure 3). While acute and chronic PE can cause RV dysfunction and chamber dilatation, the presence of RVH, defined as RV free-wall thickness greater than 5.0 mm, is more indicative of CTEPH.[14]

Multiple findings on echocardiography are well known to predict an elevated PVR, including systolic interventricular septal flattening, a flying W on M mode of the pulmonic valve, and notching with reduced acceleration time (AT) in the pulse wave Doppler profile in the RV outflow tract (RVOT).[15,16] While ventilatory inefficiency contributes significantly to dyspnea in CTEPH, the other major contributor is the degree of RV dysfunction and right heart failure. Tricuspid annular plane systolic excursion, S′ velocity, RV fractional area change (RV FAC), or RV index of myocardial performance are all

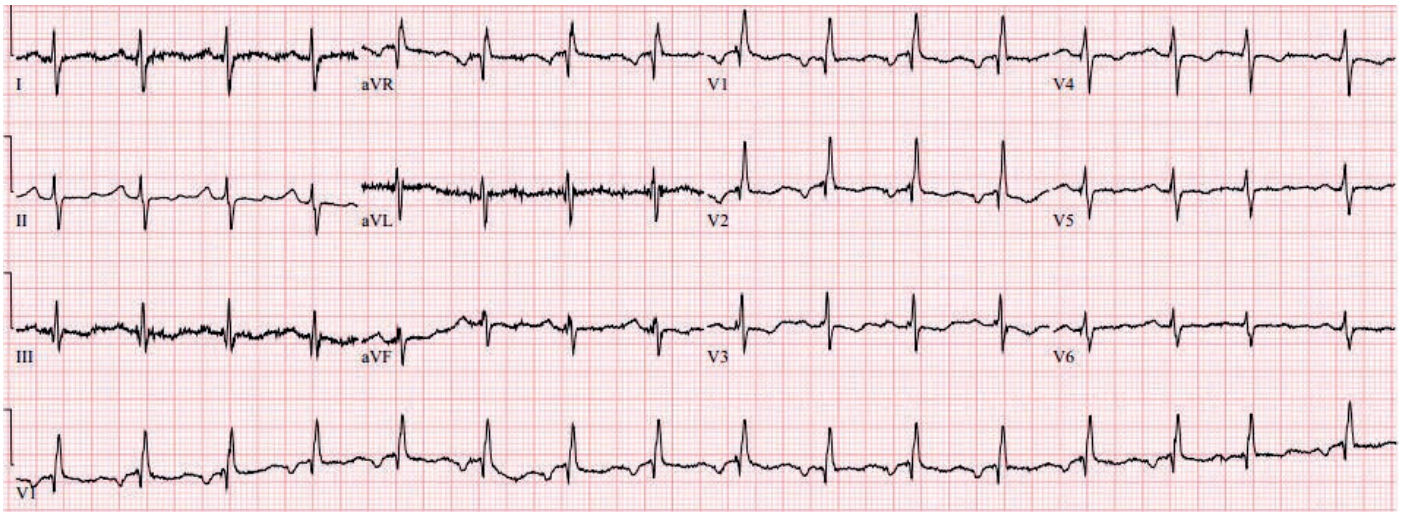

Figure 2: Electrocardiogram demonstrating right ventricular hypertrophy, incomplete right bundle branch block, and right heart strain.

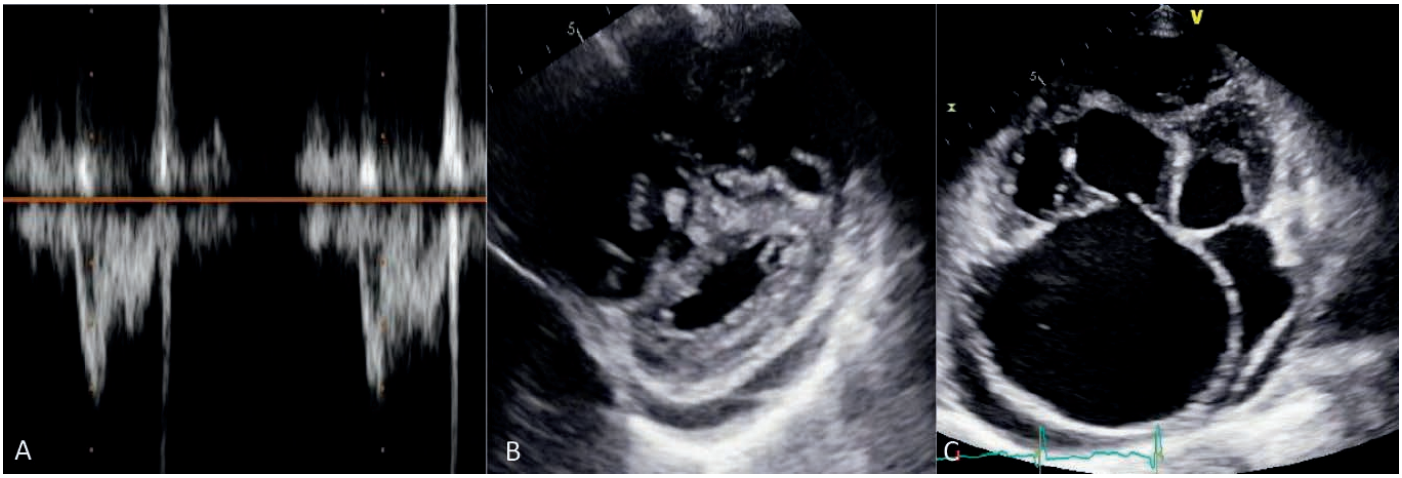

Figure 3: Echocardiography imaging: (**A**) Right ventricular (RV) outflow tract Doppler notch with reduced acceleration time. (**B**) Severe systolic septal flattening. (**C**) Severe right atrial and RV enlargement with RV hypertrophy and pericardial effusion.

methods used on echocardiography to quantify RV function.[17]

After PTE, the abnormal findings on echocardiogram associated with elevated PVR, RV enlargement, and RV dysfunction have been shown to improve. The AT falls; the ratio of RV:LV decreases; RVOT velocity time integral, a representative of stroke volume, increases; and RV FAC increases.[18] Importantly, ongoing RV structure and function abnormalities post-PTE are highly suggestive of residual or recurrent PH and should be monitored carefully after PTE.[19]

VENTILATION-PERFUSION SCAN

The combination of normal ventilation with unmatched perfusion defects, which can occupy an entire lung, lobe, segment, or subsegmental region is very suspicious for CTEPH. In CTEPH, the prevalence of thromboembolic burden tends to favor the lower lobes more so than upper lobes. The sensitivity is >96% for a radioisotopic ventilation–perfusion (VQ) scan in detecting CTEPH.[20] Importantly, a perfusion defect does not distinguish between acute versus chronic disease, nor is it specific to thromboembolic versus other forms of PA obstruction, such as vasculitis, fibrosing mediastinitis, tumor, or sarcoidosis.[7]

Camera positioning may underestimate perfusion defects in planar imaging if there is normal perfusion in overlying lung tissue. Single photon emission computed tomography (SPECT) increases the sensitivity by generating 3-dimensional images (Figure 4).[21] Additionally, partial recanalization of clot can allow for tracer to pass distally, thus underestimating the degree of thromboembolic disease. As such, this may pose a limitation in the accuracy of the VQ scan in delineating the proximal nature of disease, correlating with operability for PTE.[22] This limitation underscores the importance of the use of direct forms of pulmonary vascular imaging such as computed tomography (CT) angiography or magnetic resonance angiography, which are well suited to detect proximal web stenoses that may have been underappreciated by perfusion lung scan.

CT ANGIOGRAPHY

CT of the chest with angiography can provide extensive anatomic information in the evaluation of CTEPH (Figure 5).Like pulmonary arterial hypertension, the cardiac structures are revealing, typically with right atrial and RV enlargement, tricuspid valve annular dilatation, and RVH. In fact, the presence of RVH can be a very telling clue that thromboembolic disease is chronic, rather than acute, which can often be difficult to distinguish, particularly in very proximal disease.[23]

The vascular findings are the hallmark clues in CTEPH, including dilatation of the main pulmonary arteries. Where there is thromboembolic disease, there may be arterial wall thickening with lining thrombus, vessel caliber attenuation with poststenotic dilatation, occlusions, and linear webs representing partially recanalized vessels. This differs from the appearance of acute thromboembolic disease, where clot material is more frequently central in the vessel lumen with bright contrast seen surrounding it, and distal vessel contraction is distinctly absent.[7] Arterial collaterals from systemic to pulmonary circulation can be seen when thromboembolic disease is proximal and occlusive. These collaterals may stem from the aorta, intercostal, internal mammary, or coronary arteries and coexist with enlarged bronchial arteries; rupture may lead to hemoptysis.[24]

Normal perfusion to lung parenchyma, in contrast to hypoperfused dark areas, imparts a mosaic perfusion pattern typical for CTEPH.[10] Also seen on parenchymal lung assessment is evidence of pulmonary infarction, appearing as subpleural or peripheral wedge-shaped hypovascular opacifications with curvilinear, fibrous scarring, loss of lung volume, or at times, thick-walled cavitary type lesions that are conspicuously present distal to an occluded arterial segment. These findings may often lead to misdiagnosis of pneumonia or other chronic processes.[7]

More recent advances in CT have increased diagnostic accuracy in the use of CT for CTEPH. Dual-energy CT scanning acquires information for tissue characterization including parenchymal abnormalities, normal lung tissue, and perfused blood volumes. This can help

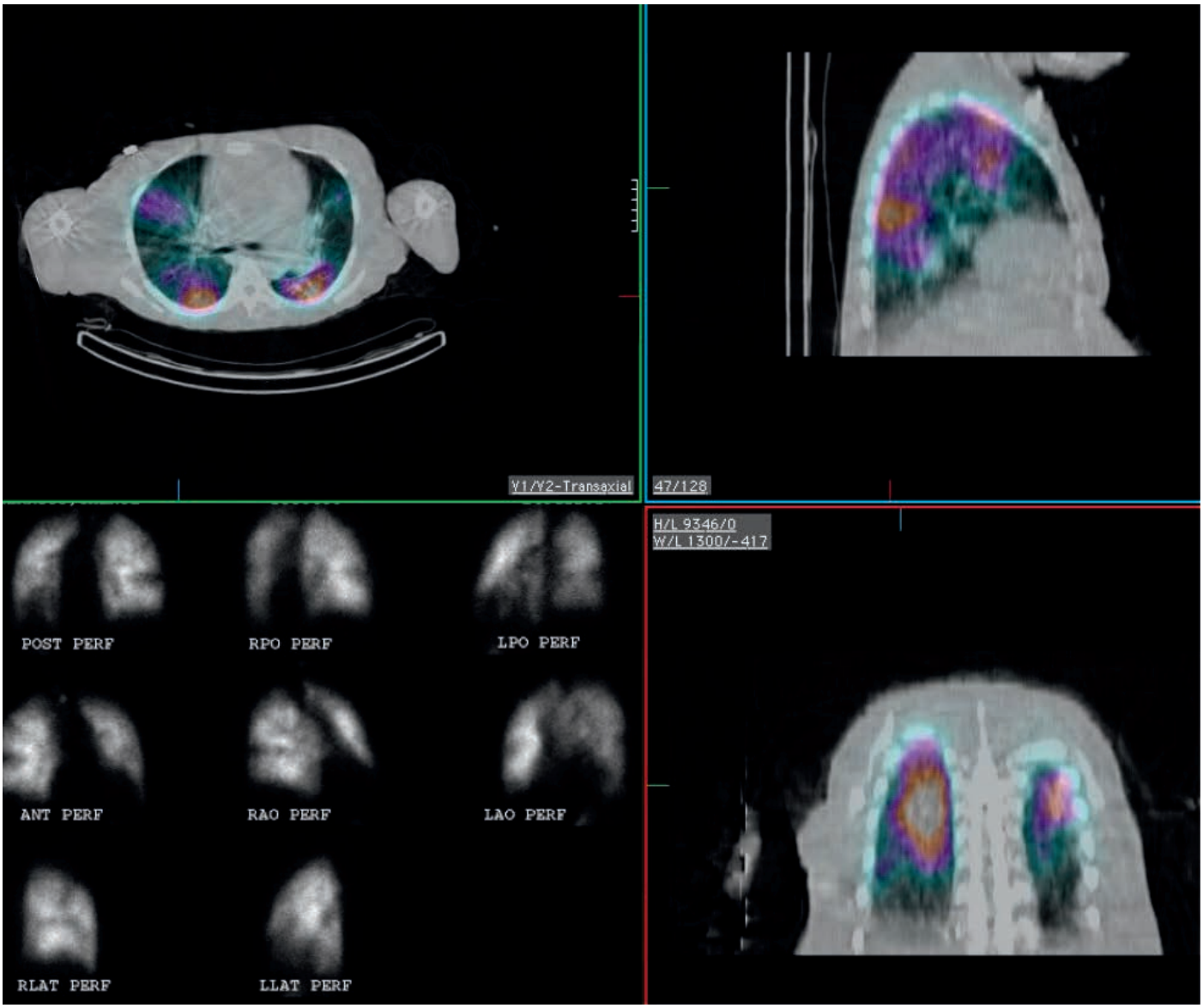

Figure 4: Single photon emission computed tomography (SPECT) and Q scan demonstrating heterogeneous perfusion in chronic thromboembolic pulmonary hypertension.

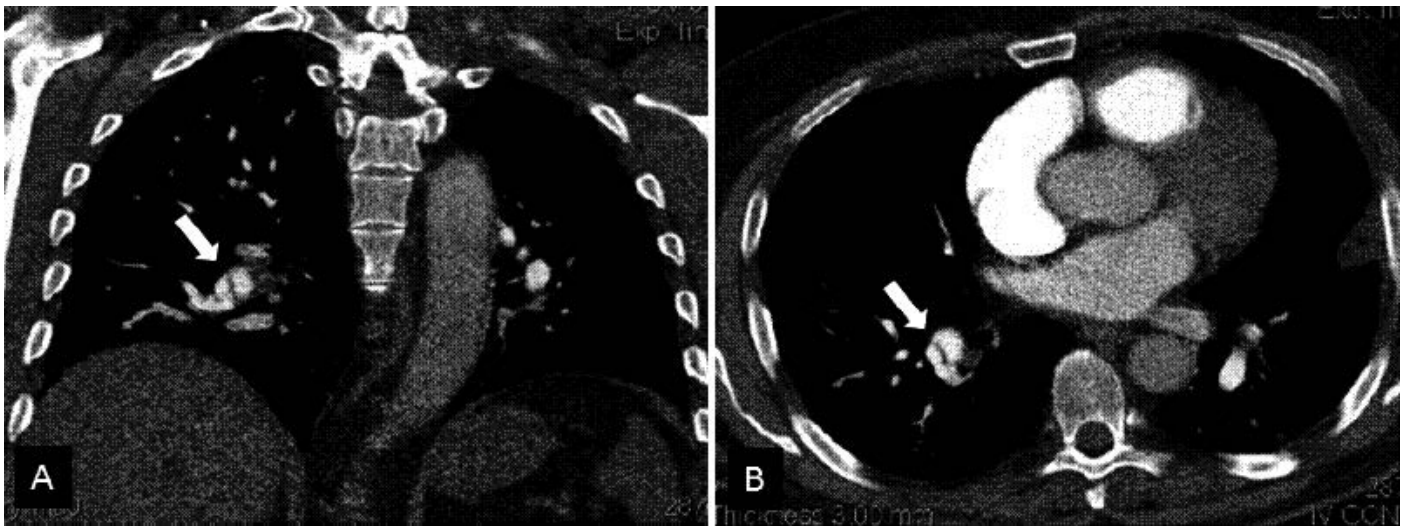

Figure 5: Computed tomography angiography chest with intravascular linear webs characteristic of chronic thromboembolic pulmonary hypertension (arrow). (**A**) Coronal plane. (**B**) Axial plane.

identify wedge-shaped and pleural defects in CTEPH that have been shown to correlate with pulmonary angiography.[25] Lung subtraction iodine mapping with SPECT imaging has been shown to correlate well with VQ scan in identifying regions of vascular malperfusion to the lungs.[26] For further imaging clarity on distal segmental PA branches, 3-dimensional SPECT–CT fusion imaging may have additional value, particularly in the guidance of BPA.[27]

Finally, CT angiography of the chest identifies diagnoses that may have unmatched perfusion defects on VQ scan and similar clinical presentations as CTEPH but for which the treatment is very different. Pulmonary arterial hypertension, when longstanding and associated with systemic-to-pulmonary shunting such as atrial and ventricular septal defects, can lead to markedly enlarged pulmonary arteries with in situ thrombosis that is not flow limiting.[28] Metastatic solid tumors have been known to metastasize to and mimic thromboembolic disease in the pulmonary arteries.[29] Similarly, PA sarcoma can pose significant occlusion, and perfusion defects of proximal pulmonary arteries, often with the conspicuous absence of more distal involvement, are often unilateral and may even involve the pulmonic valve.[30] In the case of PA sarcoma, comparison with a previous CT angiography may reveal an interval increase in size of the intravascular material, providing a clue to tumor growth. Vascular aneurysms with a narrowed main PA, particularly when accompanied by systemic arterial involvement, should raise suspicion for large vessel vasculitis (such as Takayasu or Bechet syndromes).[31] Sarcoidosis or fibrosing mediastinitis may cause significant PA abnormality and occlusion, often associated with marked hilar lymphadenopathy or pulmonary infiltrate in the case of sarcoid, and pulmonary venous stenosis or occlusion in the case of fibrosing mediastinitis.[32]

CARDIOPULMONARY EXERCISE TESTING

Although not warranted in all patients with suspected CTEPH, cardiopulmonary exercise testing (CPET) can be quite informative to further delineate the physiologic contributors to a patient's subjective dyspnea and functional limitation. In an era where our patients are advancing to older ages with many comorbidities, the exact or predominant cause of dyspnea may not be clear. This is particularly the case in the context of other cardiac or pulmonary disease, obesity, deconditioning, and even anemia in patients receiving chronic anticoagulation therapy.

Findings on a CPET that suggest CTEPH are those of cardiac limitation and ventilatory inefficiency. These include a reduced O_2 pulse (representing stroke volume) and systolic blood pressure response to exercise, ventilatory inefficiency with elevated VE/VCO_2, and reduced end-tidal CO_2 ($ETCO_2$). Furthermore, the degree of dead space ventilation in distal CTEPH has been shown to correlate with functional capacity and survival. Particularly in patients with CTED who do not have resting evidence of PH on echocardiography or right heart catheterization but who have significant dyspnea and thrombus burden on chest imaging, CPET findings of elevated VE/VCO_2 and reduced $ETCO_2$ can help secure the link between a patient's dyspnea and CTED.[33–36]

Finally, combined CPET with invasive right heart catheterization can further demonstrate abnormalities in hemodynamics during exertion, such as a fixed or rising PVR, reduced augmentation of stroke volume or cardiac output, and elevated right atrial pressure : pulmonary capillary wedge ratio. This combined assessment can be very helpful in making the decision to proceed with PTE or BPA in a patient who does not have overt PH or right heart failure.[37]

RIGHT HEART CATHETERIZATION AND CATHETER-BASED PULMONARY ANGIOGRAPHY

Right heart catheterization is paramount for hemodynamic assessment and is commonly done in the initial evaluation of a patient with PH, before the diagnosis or recognition of CTEPH. Careful assessment of hemodynamics should be performed, with accurate leveling, calibration, and measurement of pressures at end expiration.[37]

Invasive pulmonary angiography (Figure 6) can characterize the thromboembolic location and burden before consideration for PTE or BPA. Occlusions or pouch defects, narrowed vessels, intravascular webs or bands, poststenotic dilatation, and hypovascularity are all findings of CTEPH.[38]

To optimize diagnostic yield, biplane imaging or sequential imaging with anterior-posterior followed by lateral oblique projections can help reveal filling defects that may have been obscured by overlying vessels. Rather than injecting into the main PA, selective angiography of each lung allows clearer angiographic assessment of distal segmental and subsegmental branches. Finally, digital subtraction angiography limits nonangiographic structures from obscuring the image and allows for less intravenous contrast use.[39]

VENOGRAPHY

As previously discussed, risk factors for CTEPH have historically been well described to include hypercoagulable states related to hematologic abnormalities or other medical comorbidities. Additionally, mechanical pelvic vein obstructions have been recognized as an important association with CTEPH, including large uterine fibroids, May-Thurner syndrome, or other levels of pelvic vein obstruction. As such, as part of the diagnostic evaluation for CTEPH, invasive or noninvasive venography may guide further interventions such as hysterectomy, myomectomy, or iliac vein stenting to reduce the risk of recurrent thromboembolic disease.[8,9,18]

CONCLUSIONS

The diagnostic evaluation for CTEPH remains a multifaceted clinical assessment. History of functional limitation, driven by PH and RV dysfunction and ventilatory inefficiency, accompanies a vast array of potential abnormalities on cardiopulmonary testing. ECG and echocardiogram demonstrate evidence of right heart strain, elevated PVR,

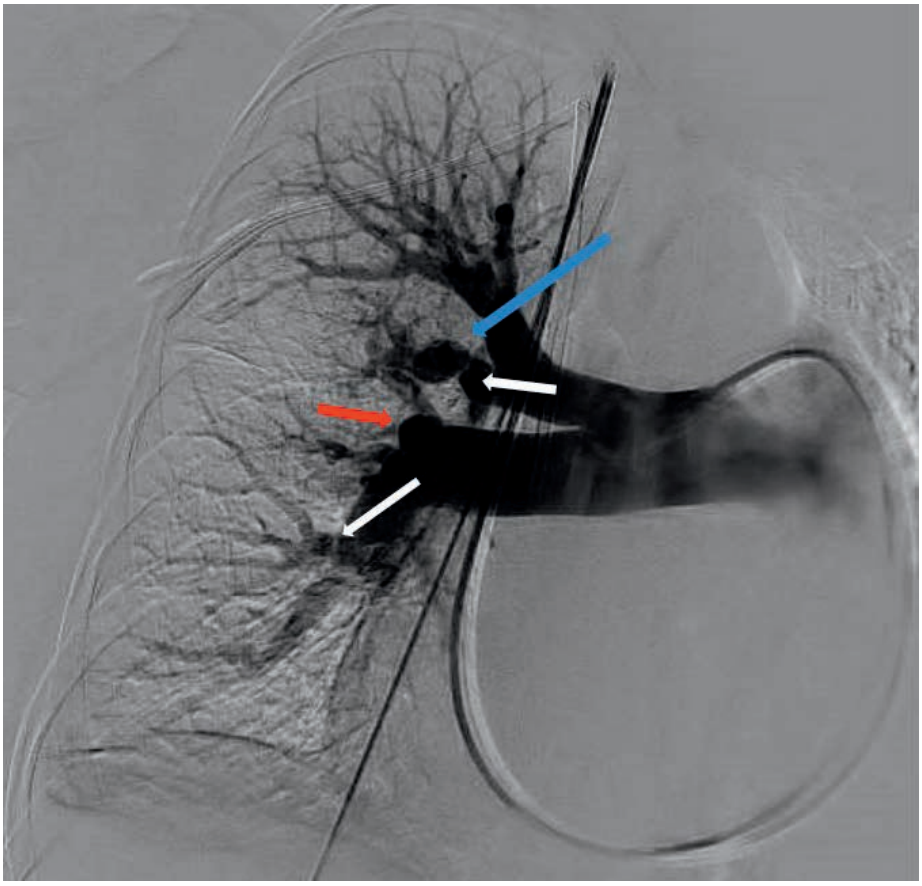

Figure 6: Pulmonary angiography of right lung demonstrating pouch occlusion (red arrow), poststenotic dilatation (blue arrows), and intravascular bands (white arrows).

and RV dysfunction. VQ scan with unmatched perfusion defects has a very high sensitivity for CTEPH. Chest radiography by x-ray and CT angiography reveal enlarged right heart and PA structures. CT may also demonstrate a mosaic perfusion pattern, lung infarct, systemic-to-pulmonary collaterals, and intravascular abnormalities of the PA branches, while providing clues for alternative diagnoses that mimic and often are mistaken for CTEPH. CPET can be performed to characterize findings of ventilatory inefficiency, noninvasively or in conjunction with right heart catheterization at the time of catheter-based pulmonary angiography. Hematologic, medical, and mechanical risk factors for developing CTEPH should be identified for possible intervention to mitigate future recurrent VTE. The clinical assessment remains complex and should ideally be performed by specialized CTEPH centers for accuracy and to guide treatment options.

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REGULAR ARTICLE

Pulmonary Thromboendarterectomy: Patient Selection, Techniques, Outcomes, and Recent Advances

Michael M. Madani, MD, FACS
University of California San Diego Cardiovascular Institute
Cardiovascular and Thoracic Surgery
University of California San Diego
La Jolla, CA

Jill R. Higgins, ACNP
University of California San Diego Cardiovascular Institute
Cardiovascular and Thoracic Surgery
University of California San Diego
La Jolla, CA

Chronic ThromboEmbolic Pulmonary Hypertension (CTEPH) is a potentially curative form of pulmonary hypertension, which continues to be underdiagnosed. Pulmonary ThromboEndarterectomy (PTE, also referred to as PEA for Pulmonary Endarterectomy) is a technically challenging procedure that requires careful patient selection, meticulous surgical techniques, and expertise in postoperative care. Over the last decade, there have been significant advances not only in the techniques of the operation, but also in the postoperative management of major complications. Furthermore, advances have been made not only in medical therapy, but also in percutaneous interventions, in the form of balloon pulmonary angioplasty (BPA). BPA and medical therapy are considered to be palliative; they are reserved for patients who are inoperable, or for those who continue to have symptomatic PH postoperatively. PTE remains the gold standard treatment for CTEPH, as long as the patient has evidence of surgically accessible disease, and the patient has acceptable surgical risk. All CTEPH patients should be evaluated and considered for surgery, and no patient should be turned down without consultation with a multidisciplinary team at an expert center. Furthermore, no amount of PH or degree of right heart failure is a contraindication to surgery, as long as there is corresponding level of disease. Excellent short- and long-term results can be achieved with current data suggesting significant advantage with 10-yr survival of 85-90%.

INTRODUCTION

Pulmonary thromboendarterectomy (PTE) is the treatment of choice for patients with operable chronic thromboembolic pulmonary hypertension (CTEPH), as it is potentially curative. In expert centers that conduct > 50 PTE procedures per year, peri- and postsurgical mortality rates are very low and long-term outcomes are excellent, with 3-year postoperative survival of > 80%.[1] Therapeutic decisions in CTEPH are based largely on the location of the arterial obstruction, with PTE for obstructions in main, lobar, and segmental vessels, and even for some subsegmental disease at expert centers, and balloon pulmonary angioplasty (BPA) and medical therapy for more distal or microvascular disease, respectively. Medical therapy and BPA are also options for patients with persistent or recurrent pulmonary hypertension (PH) after PTE. With increasing surgical experience and improvements in instruments and procedures, an increasing number of patients are now considered operable who would previously have been inoperable, including some patients with subsegmental disease. At the University of California, San Diego (UCSD), around 200 PTE procedures are performed every year and several advances have been developed, including resection of more distal disease, availability of PTE to patients previously considered to be too high risk for surgery, improved management of post-PTE complications, and minimally invasive PTE.[2,3]

While PTE can be combined with other treatment modalities, such as combination PTE and BPA, medical therapy for persistent or recurrent PH after PTE, and bridging therapy with medical therapy or BPA before surgery, data are generally limited. Combination treatment should therefore be considered on an individual patient basis. Though the majority of patients will have significant benefit from surgery and may not need additional treatment, some patients may require multimodal therapy with PTE, BPA, and/or medical therapy.

It is imperative to emphasize that for patients with surgically accessible disease, PTE is preferred and the standard of care, as it is potentially curative. For patients with inoperable CTEPH, as determined by an expert multidisciplinary team, percutaneous treatment with BPA is an emerging option, and the soluble guanylate cyclase stimulator, riociguat, is licensed for the treatment of patients with inoperable CTEPH and those with persistent or recurrent CTEPH after PTE.[4] In addition, other pulmonary arterial hypertension–specific medical therapies (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and proteinoids) are widely used off label to treat CTEPH. Regardless of operability status and choice of therapy, all patients with CTEPH should receive lifelong anticoagulation.

Key Words—CTEPH, PEA, PTE, surgical outcomes
Correspondence: mmadani@ucsd.edu

It is estimated that 1 to 1.36 PTE operations per million population are performed annually in the United States and around 1.7 per million population in Europe, representing a steady increase over the past decade as surgical expertise has improved and the number of expert centers has increased worldwide.[5-7] What follows is a discussion around the role of PTE in the management of CTEPH, with a focus on our experience at UCSD.

OPERABILTY ASSESSMENT

PTE is the treatment of choice for CTEPH, and surgical mortality rates are low, particularly in large volume PTE centers.[5] The proportion of patients with CTEPH considered inoperable has varied from 10% to 50%.[1,5] Reasons for inoperability include the presence of distal pulmonary artery obstructions not accessible to surgery, imbalance between increased pulmonary vascular resistance (PVR) and the number of accessible occlusions (which suggests the presence of microvascular disease), and old age or comorbid conditions that make the patient unsuitable for surgery. Elevated PVR (> 1500 $dyn \cdot s \cdot cm^{-5}$) alone is not a contraindication to surgery; in fact there is no higher limit of PVR that may make a patient inoperable, as long as there is a corresponding degree of obstructive disease. In some patients, severely elevated PVR in combination with other risk factors may render a patient inoperable. Furthermore, some patients with operable disease choose not to undergo surgery. Experience suggests that the number of patients considered inoperable may be overestimated due to some patients being incorrectly diagnosed as having CTEPH. Treatment guidelines recommend that patients with suspected CTEPH be referred to expert centers for confirmation of diagnosis and treatment, including PTE.[5-10]

An expert center is defined as one with a high annual volume of PTE procedures (> 50/y), surgical mortality < 5%, and the ability to perform segmental endarterectomy.[9] In addition, expert centers should be capable of evaluating the need for other established treatment modalities and offering any that are deemed necessary.[1] All expert centers must be able to call on a multidisciplinary team for evaluation and management of CTEPH, including a surgeon experienced with PTE, a PH specialist, a BPA interventionist, and a CTEPH-trained radiologist.[1] It should be noted that some patients initially considered inoperable go on to have surgery after a second opinion at an expert center.[5,9,10]

Ultimately, therapeutic decisions in CTEPH are made according to the

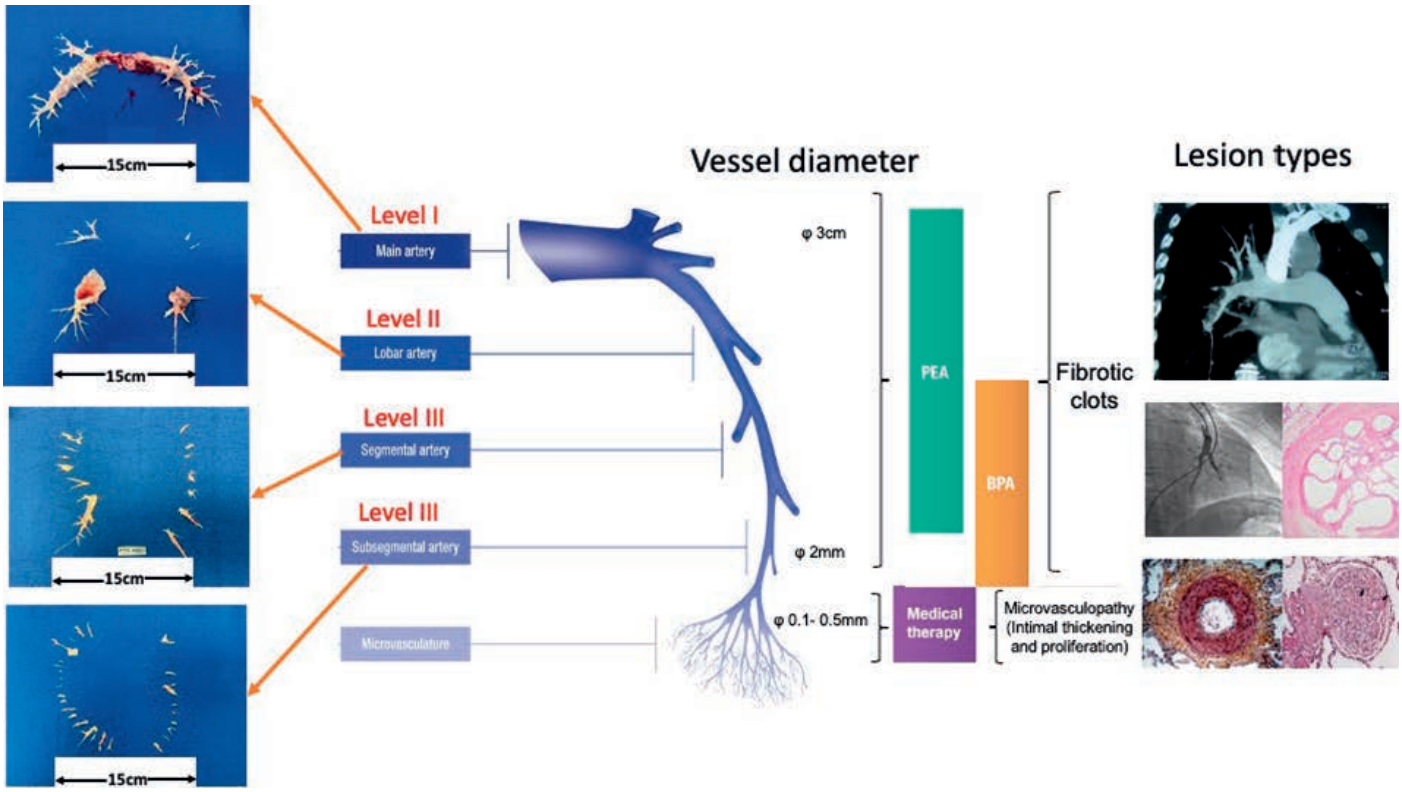

Figure 1: Treatment options for chronic thromboembolic pulmonary hypertension. A schematic representation of a pulmonary artery is shown (note that vessel diameter is not to scale). Pulmonary thromboendarterectomy (PTE) is used to remove thromboembolic lesions primarily in the proximal main artery (diameter of 1-3 cm), and lobar and segmental arteries; in expert surgical centers, lesions in distally located midsegmental and subsegmental branches can be targeted by PTE, down to vessels of 2 to 3 mm in diameter. Balloon pulmonary angioplasty mainly targets distal lesions in the segmental and subsegmental vasculature, down to small pulmonary arteries of 1 to 5 mm in diameter. Medical therapy targets microvasculopathy, including intimal thickening and fibromuscular proliferation, in vessels of 0.1 to 0.5 mm in diameter. Typical surgical specimens based on the most proximal level of obstruction are shown. The scale is in centimeters.

location of the arterial obstruction, with PTE for obstructions in larger vessels, BPA when the obstruction is in smaller vessels inaccessible to PTE, and medical therapy for obstructions not amenable to either intervention (Figure 1). As surgeons gain more experience with PTE and instruments and procedures improve, the distal limits of operability are becoming redefined, leading to a greater percentage of patients being considered operable.[11-13]

For example, data from > 300 PTE operations at an Italian expert center showed similar in-hospital mortality in patients with distal disease as in those with more proximal disease, with significant, sustained improvements in hemodynamic, echocardiographic, and functional parameters.[13] PTE also plays a role in the management of chronic thromboembolic disease (CTED), a condition in which pulmonary thromboembolic occlusions are present without PH at rest, but with similar symptoms to CTEPH. Data on PTE in patients with CTED are limited, although small-scale studies (n = 23-42) have shown hemodynamic and clinical improvements, with 1-year survival of 95% and improvements in quality of life.[14-16]

Around 200 PTE operations are conducted at UCSD annually, where multidisciplinary teams for management of CTEPH consist of a PTE surgeons, pulmonary vascular medicine specialists, interventional cardiologists, and imaging specialists. Diagnosis of CTEPH is confirmed using ventilation-perfusion scanning, and anatomical correlation is further investigated by computed tomography pulmonary angiography, as well as conventional pulmonary angiography. Patient selection for PTE is based on severity of CTEPH symptoms, degree of PH, right heart dysfunction, extent and level of obstruction, correlation of severity of PH and degree of obstruction, comorbidities, degree of difficulty, risk-benefit ratio, and the patients expectation of surgery and associated risks.[17]

As recommended by various guidelines, once the diagnosis of CTEPH is made, patients should be considered for surgery. No patient should be turned down without consultation from a multidisciplinary team at an expert center. As with any procedure, the success of PTE owes as much to appropriate patient selection as it does to surgical technique and postoperative management. In addition to determination of surgical accessibility, 2 other key components contribute to the determination of operability. Perhaps the most important determination is the correlation between the degree of hemodynamic impairment with the degree of disease burden as evidenced by imaging studies. This becomes a crucial determination, as there is no degree of hemodynamic impairment and no degree of PH to make a patient inoperable, as long as there is corresponding obstructive disease. These patients will tolerate the procedure well and enjoy excellent short- and long-term outcomes, as long as there is corresponding clot burden, and a full, thorough endarterectomy has been performed. The last component of the operability assessment relates to the patient's underlying condition and comorbidities. Like any other major surgical procedure, PTE is individually based and heavily dependent on the surgeon's and the center's experience.

Correlating clot burden with hemodynamic impairment can be difficult. This is particularly true for patients with segmental and subsegmental level disease and advanced right heart failure. When considering operability, the goal is to identify adequate surgically accessible disease so that a relatively normal postoperative PVR can be predicted.

SURGICAL TECHNIQUE

There are several guiding principles that are specific to PTE. These include an approach that provides excellent exposure of the pulmonary vasculature, cardiopulmonary bypass with profound hypothermia and periods of circulatory arrest to achieve a bloodless field, and a complete bilateral endarterectomy in the correct plane.[18,19] The operation is typically performed via median sternotomy. Some experienced centers have performed this procedure utilizing minimally invasive techniques[2,3]; however, the median sternotomy approach will be described here.

After a median sternotomy is performed, the pericardium is incised longitudinally and attached to the wound edges. Typically, the right heart is enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation. There is usually severe right ventricular hypertrophy. These patients are typically sensitive to manipulation of the heart and can become quite unstable.

After full heparinization (activated clotting time > 400 seconds), full cardiopulmonary bypass is instituted with high ascending aortic cannulation and bicaval cannulation. Once the heart is emptied on bypass, a vent is placed in the midline of the main pulmonary artery 1 cm distal to the pulmonary valve and directed into the right pulmonary artery. In addition to blood cooling via the heater-cooler, surface cooling with both a head ice-jacket and a cooling blanket is initiated at this time. Cooling typically takes about 45 minutes to an hour. Once ventricular fibrillation occurs, an additional vent is placed in the left ventricle via the right superior pulmonary vein (Figure 2).

The primary surgeon starts the operation on the patient's left side. The superior vena cava is fully mobilized, and right pulmonary artery dissected (Figure 3). An incision is then made in the right pulmonary artery from beneath the ascending aorta out under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the take-off of the middle lobe artery.

When the patient's temperature reaches 20°C, the aorta is cross-clamped and cold cardioplegic solution (1 L) is administered. Additional myocardial protection is obtained with the use of a cooling jacket. The entire procedure is now performed with a single aortic cross-clamp period with no further administration of cardioplegic solution.

A modified cerebellar retractor or Madani PTE retractor is placed between the aorta and superior vena cava. Upon opening the pulmonary artery, loose thromboembolic material is removed, and plane of dissection is identified. Recognizing the plane is the most crucial and technically challenging part of the operation. It is important to recognize that (1) an embolectomy without

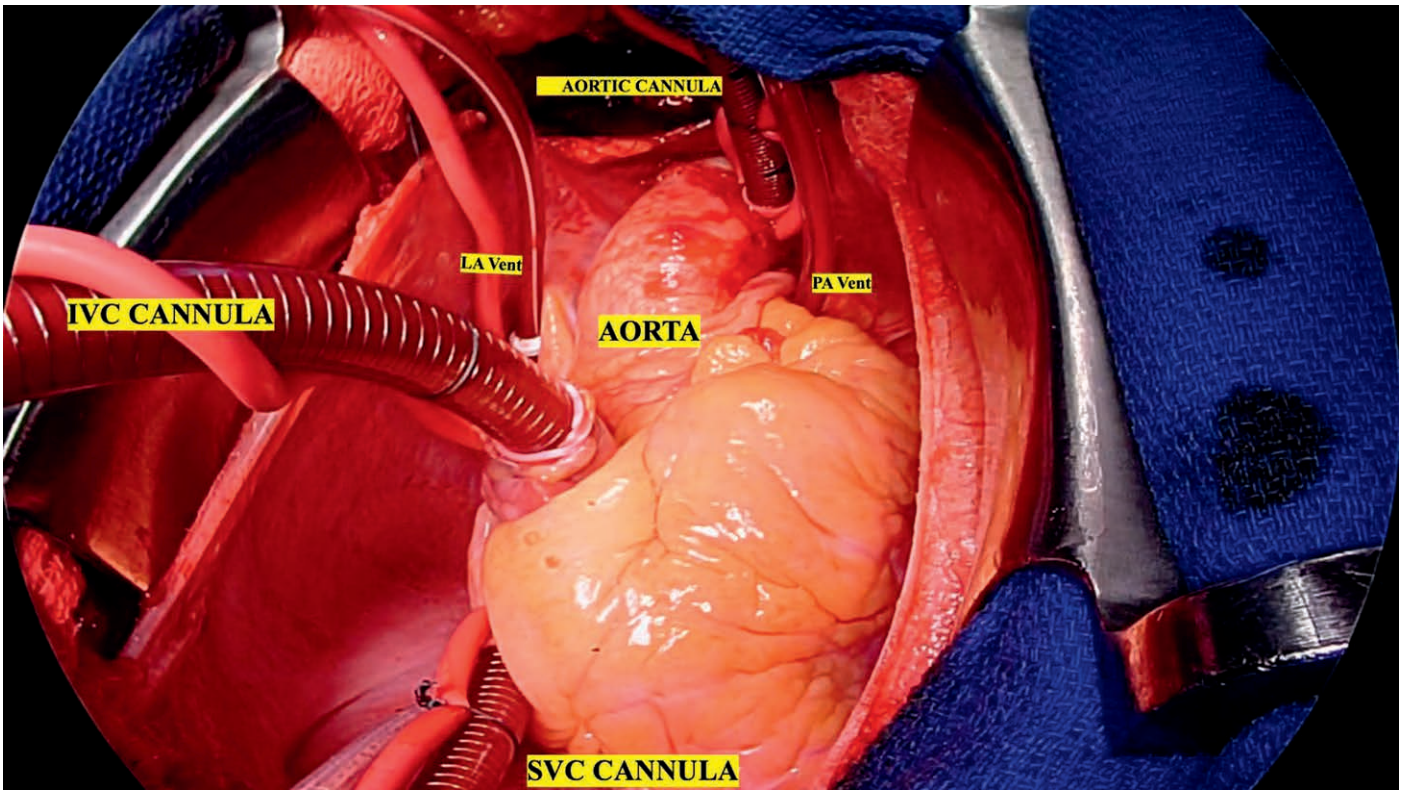

Figure 2: Surgical field view. Please note the high ascending proximal arch aortic cannulation. Typically, the SVC and IVC cannulae are crossed for easier initiation of bypass, without manipulating the right heart. SVC indicates superior vena cava; IVC, inferior vena cava; PA, pulmonary artery; and LA, left atrium.

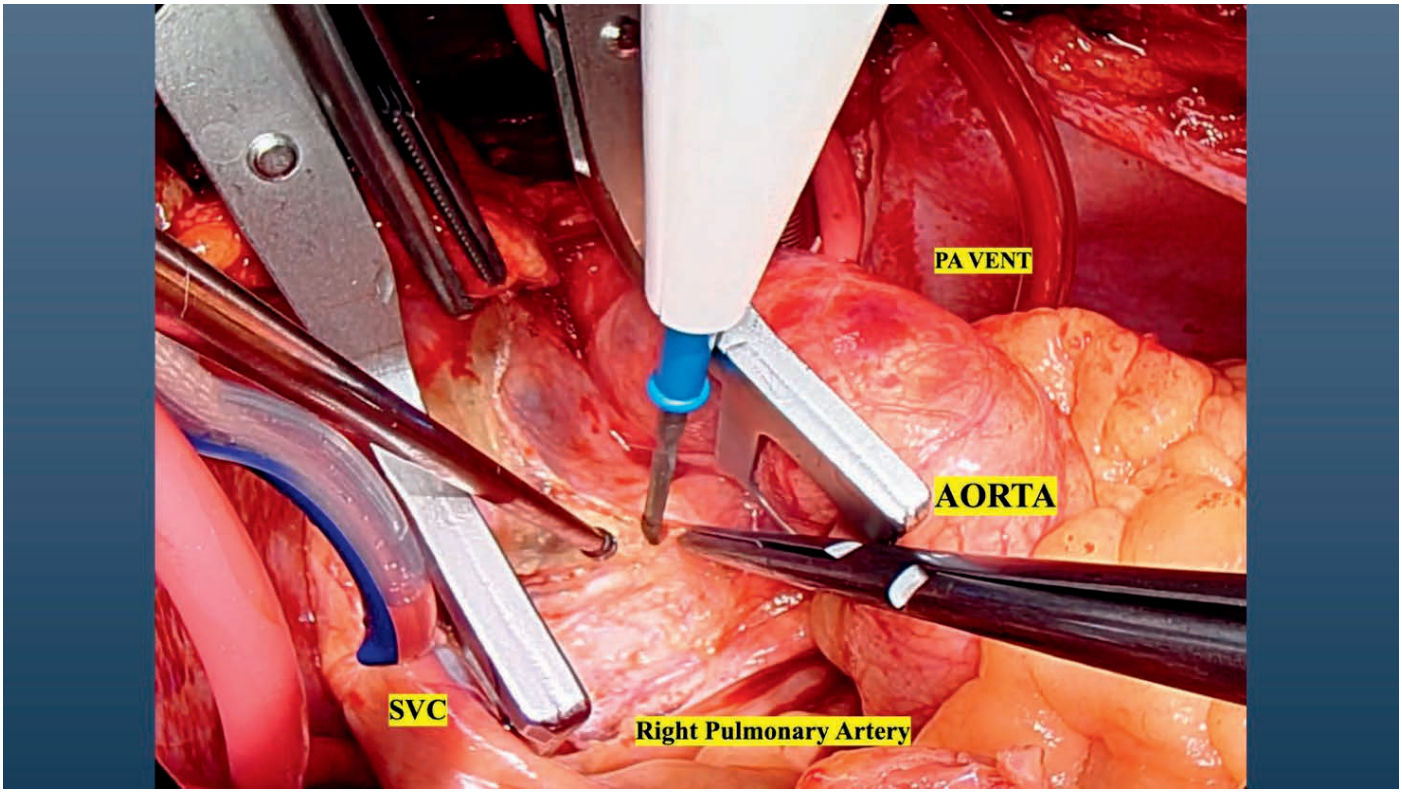

Figure 3: Right pulmonary artery exposure and dissection. Please note the approach is between the aorta and the SVC. SVC indicates superior vena cava; and PA, pulmonary artery.

endarterectomy is ineffective, and (2) in most patients with CTEPH, the initial glance at the pulmonary vascular bed may appear normal, even with severe disease.

When blood obscures direct vision of the pulmonary vascular bed, circulatory arrest is initiated and the patient is exsanguinated. All monitoring lines to the patient are turned off to prevent the aspiration of air. Snares are tightened around the cannulae in the superior and inferior vena cavae.

An experienced surgeon will notice some subtle and some obvious signs of CTEPH. Figure 4 is a picture of intraoperative findings during right pulmonary endarterectomy, showing some obvious signs of obstructive disease.

One must be very careful when starting the dissection plane, because if it is not deep enough, inadequate amounts of the chronic thromboembolic material will be removed, leaving the patient with residual PH. Too deep of a plane may result in pulmonary vessel perforation, with catastrophic and possibly fatal complications. Identification of the correct plane can be the most challenging part of this operation, in particular when segmental and subsegmental endarterectomies are being performed. The endarterectomy is then performed with an eversion technique and carried out to subsegmental branches. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction.

Once the right-sided endarterectomy is completed, circulation is restarted, and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. After completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, a heart net is used to retract the heart up, and an arteriotomy is made in the middle of the left pulmonary artery lateral to the pericardial reflection, avoiding entry into the left pleural space. Additional lateral dissection does not enhance intraluminal visibility, may endanger the left phrenic nerve, and makes subsequent repair of the left pulmonary artery more difficult. The left-sided dissection is virtually analogous in all respects to that accomplished on the right.

After completion of the endarterectomy, cardiopulmonary bypass is reinstituted and warming is commenced. The rewarming period generally takes approximately 90 minutes, but varies according to the body mass of the patient.

The pulmonary artery is then closed, and the pulmonary arterial vent is replaced. If there is any evidence of patent foramen ovale, atrial septal defect, or right atrial clot formation, the right atrium is then opened. Any interatrial communication is closed, and clot removed. Although tricuspid valve regurgitation is variable in these patients and can be severe, tricuspid valve repair is not performed unless the tricuspid annulus is > 4 cm and there is severe regurgitation. If other cardiac procedures are required, these are performed conveniently during the systemic rewarming period. Figure 5 shows a typical specimen removed form

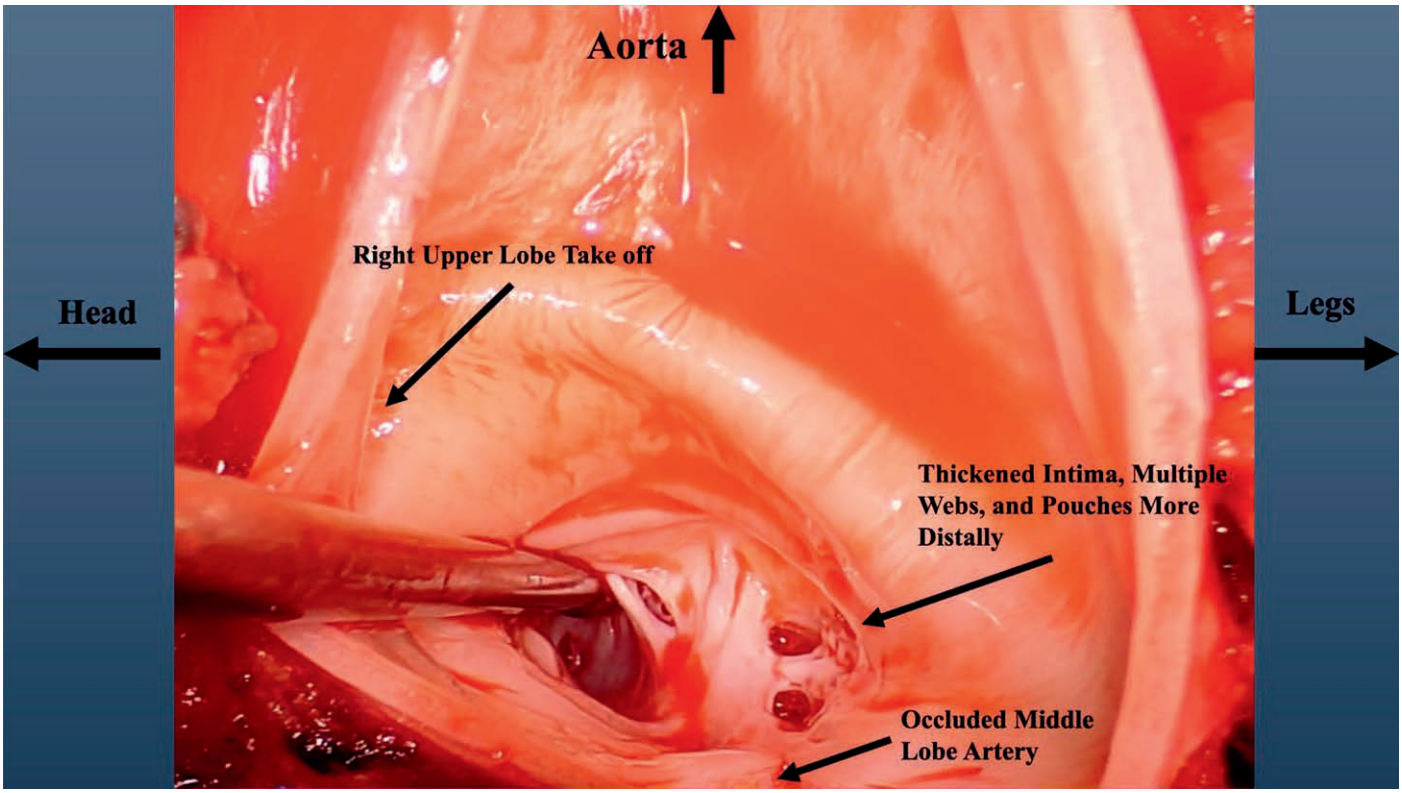

Figure 4: Typical chronic thromboembolic pulmonary hypertension findings within the pulmonary artery. Please note this picture is taken with the camera coming on the right side of the patient with the aorta retracted to the left side, and at the top of the picture.

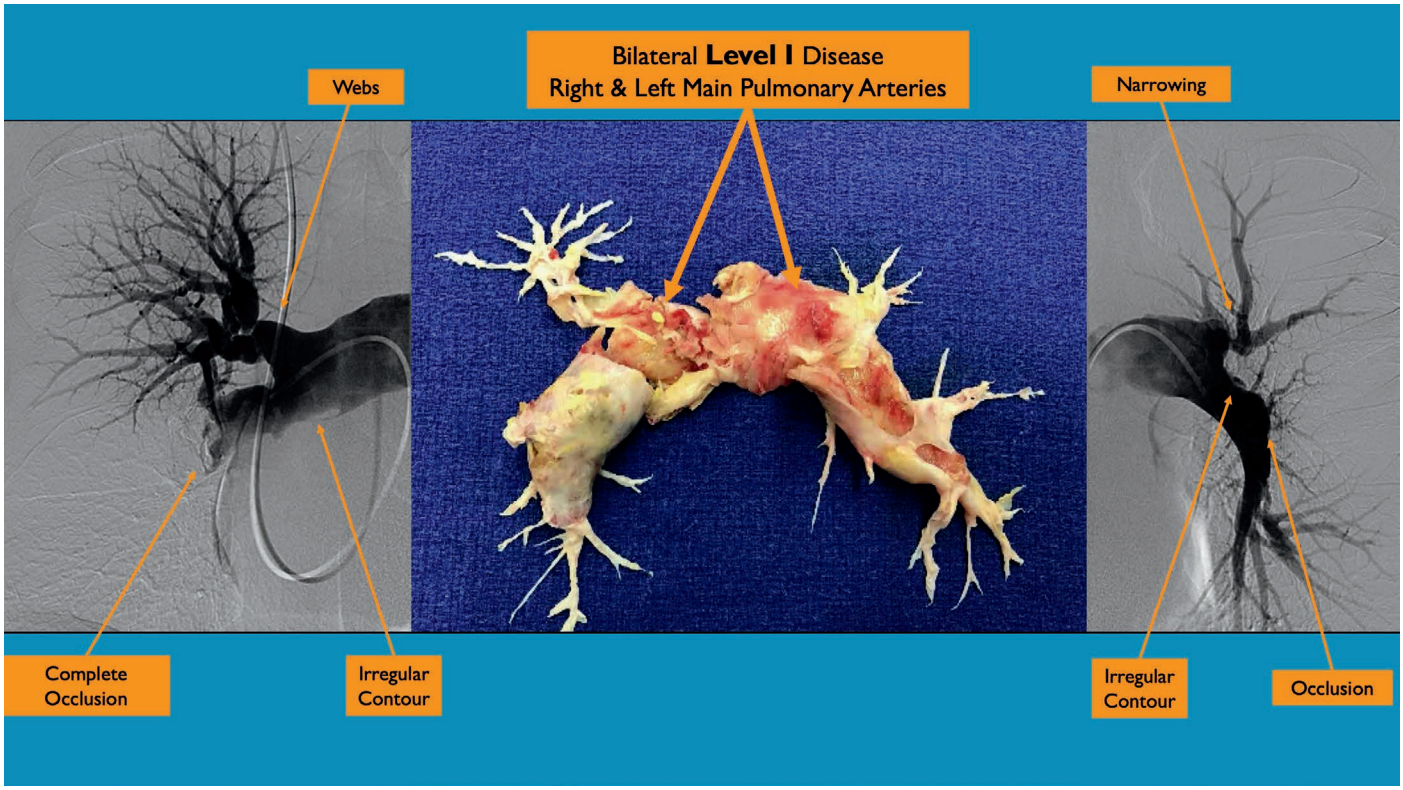

Figure 5: Specimen removed from a patient with bilateral main pulmonary artery disease (right and left level I disease). Please note the corresponding intraoperative findings with preoperative pulmonary angiographic findings.

a patient with bilateral main pulmonary artery disease, along with the preoperative findings on the patient's pulmonary angiogram.

Patients are weaned from cardiopulmonary bypass in the usual manner, with the use of dopamine and other vasoactive agents. Wound closure is routine. The cardiac output tends to be high with low systemic vascular resistance, and despite the long time on cardiopulmonary bypass, blood products are generally unnecessary. Patients tend to have vigorous auto-diuresis immediately postop.

POSTOPERATIVE MANAGEMENT

The postoperative management of PTE patients is similar to that of other postoperative heart and lung surgery patients, centered on hemodynamic support and optimizing oxygenation and fluid management. Patients are hemodynamically supported on dopamine and atrially paced, with a goal cardiac index of 2 to 3 L/min/m^2, as a cardiac index > 3 L/min/m^2 can be associated with the development of reperfusion pulmonary edema. Patients remain intubated overnight to allow for careful monitoring of oxygenation, fluid balance, and bleeding. They are kept on the dry side with intravenous furosemide, though frequently they auto-diurese on their own for the first several hours. Anticoagulation with a heparin drip is started within a few hours, as long as bleeding is at a minimum. The anticoagulation therapy and target levels are dictated by the presence of an underlying hypercoagulable condition, as well as the risk for rethrombosis. The temporary pacing wires are typically removed on the first postoperative day, unless the patient requires pacing. Once the pacing wires are removed, coumadin is started, with a heparin drip used for bridging. The goal partial thromboplastin time (PTT) is typically 60 to 80 seconds, alternatively anti-Xa levels are monitored with a goal of 0.35 to 0.7 U/mL, and a goal international normalized ratio (INR) of 2.5 to 3.5. In patients with antiphospholipid antibodies or unilateral disease, who are at a higher risk of rethrombosis, the goal INR is 3 to 4.

COMPLICATIONS

In addition to the complications seen in other forms of open heart and major lung surgery, patients who undergo PTE may develop complications specific to this operation, such as airway bleeding, reperfusion pulmonary edema, and residual PH.

Airway Hemorrhage

Frank blood from the endotracheal tube signifies a mechanical violation of the blood-airway barrier that has occurred at the time of operation. This complication can stem from a technical error, or inadvertent opening of a communicating channel with an enlarged bronchial collateral during endarterectomy. Airway bleeding should be managed, if possible, by identification of the affected area by bronchoscopy and balloon occlusion of the affected lobe until coagulation can be normalized. Utilization of extracorporeal membrane oxygenation (ECMO) can be very helpful in managing significant airway hemorrhage, and choices of both veno-arterial (VA) and veno-venous (VV) ECMO can be considered, although in patients with severe airway

hemorrhage related to vascular injury, VA ECMO may be more appropriate. In some patients, hemoptysis from a bronchial collateral can be encountered, as airway bleeding starts with bright red blood while the patient is still on full cardiopulmonary bypass, with no pulmonary artery flow. This may subside and fully resolve with termination of bypass and full forward flow through the pulmonary circulation. It is rare to require bronchial artery embolization following successful endarterectomy, but this can be a consideration, particularly in patients with severely dilated bronchial collaterals. In contrast, the amount of airway bleeding secondary to vessel wall injury directly correlates with the amount of pulmonary artery flow, and will be at its worst upon termination of bypass. There have been reports of successful management of severe airway hemorrhage by temporary institution of VA ECMO in the operating room and complete reversal of anticoagulation, with subsequent separation from ECMO over the next few hours.[20–21]

Regardless, the principles of management involve adequate protection of the unaffected lung, adequate ventilation and oxygenation to allow safe separation from cardiopulmonary bypass, and reversal of anticoagulation. Many patients can tolerate single-lung ventilation with endobronchial blockage of the affected lung, with subsequent deflation and removal of the endobronchial blocker once there is no evidence of further hemoptysis despite systemic anticoagulation. In those who cannot tolerate single-lung ventilation, ECMO should be instituted.

Reperfusion Pulmonary Edema

Reperfusion pulmonary edema is a syndrome that develops because of restoration of blood flow to an area of the lung that has been endarterectomized. Reperfusion pulmonary edema is defined as a Pao_2/Fio_2 ratio < 300, and an opacity on the chest x-ray in a region of a reperfused lung, with no alternative explanation for the opacity. True reperfusion injury that has a direct adverse impact on the clinical course of the patient occurs in approximately 10% to 15% of patients. In its most dramatic form, it occurs soon after operation (within a few hours) and is associated with profound desaturation. Edema-like fluid, sometimes with a bloody tinge, is suctioned from the endotracheal tube. Management of reperfusion pulmonary edema centers around supportive care with oxygen and positive end-expiratory pressure and the use of diuretics. Steroid administration is discouraged, as it has not been shown to be effective and may increase the risk of infection.[21] Infrequently, inhaled nitric oxide at 20 to 40 parts/million can improve gas exchange. In severe cases, the authors have used VV and VA ECMO. VV ECMO is used in most patients, VA ECMO is reserved for patients who have persistent PH and/or right heart failure. ECMO support is continued until ventilation can be resumed satisfactorily, which could take several days, and rarely as long as 2 to 3 weeks. In general, VV ECMO is preferred to VA ECMO, whenever possible. If VA ECMO is used, it is important to ensure that there is adequate forward flow through the newly endarterectomized pulmonary arteries. Otherwise, resultant pulmonary thrombosis can occur, which can be catastrophic. Historically, patients who require VA ECMO have a worse prognosis than patients requiring VV ECMO.

Residual Pulmonary Hypertension

In cases of persistent severe PH, right heart dysfunction or failure following PTE, and/or hemodynamic impairment refractory to inotropic and pressor support, VA ECMO can be used. This can provide a window for possible remodeling and improvement of function, or provide a bridge while other forms of treatment are used. In extreme cases, this can also provide a bridge to possible lung transplantation.

For patients whose residual PH and accompanying right heart dysfunction is persistent despite being able to wean off ECMO, there are now approved forms of medical therapy which can be used. Riociguat is a soluble guanylate cyclase simulator that has been shown to be beneficial in patients who have residual PH following PTE. This is particularly effective for patients in whom microvascular disease exists.[4] Of course, if there are concerns for residual thromboembolic disease that was beyond surgical accessibility (distal subsegmental branches), BPA should be considered. If a significant amount of residual obstructive disease is encountered in the pulmonary vasculature as a direct result of incomplete endarterectomy or possible recurrent disease, a second surgical opinion and evaluation at an expert center should be obtained. In such cases, the patient may benefit from repeat operation. In recent years, we are seeing more referrals to our center due to incomplete endarterectomy. Regardless of etiology, appropriate treatment modality and management of this postoperative complication can be challenging. In many patients this can be a multimodality approach, including medical therapy, BPA, ECMO, possible reoperation, and consideration of transplantation. Based on such experiences, guidelines from the World Symposium on Pulmonary Hypertension recommend that centers performing PTE have the capability of advanced therapy, including ECMO.

OUTCOME

The ages of the patients in our series have ranged from 6 to 89 years. A typical patient will have a severely elevated PVR level at rest, the absence of significant comorbid disease unrelated to right heart failure, and the appearances of chronic thrombi on angiography that appear to be in balance with the measured degree of PVR. Exceptions to this general rule, of course, occur.

Although most patients have a PVR level in the range of 600 to 700 $dyn \cdot s \cdot cm^{-5}$ and pulmonary artery pressures less than systemic, the hypertrophy of the right ventricle that occurs over time makes suprasystemic PH possible. Therefore, many patients possess PVRs > 1000 $dyn \cdot s \cdot cm^{-5}$ and suprasystemic pulmonary artery pressures. There is no upper limit of PVR, pulmonary artery pressure, or degree of right ventricular dysfunction that excludes patients from the operation, as long as there is a corresponding amount of disease present.

Our last large series from UCSD demonstrated a mortality of 4.1% for patients with preoperative PVR >1000 $dyn \cdot s \cdot cm^{-5}$ compared with 1.6% for

PVR < 1000 dyn · s · cm^{-5}.[22] Persistent PH following PTE has a much more dramatic influence on operative and 1-year mortality than elevated preoperative PVR. In 500 consecutive cases performed at UCSD, mortality was 10.3% for patients with a postoperative PVR > dyn · s · cm^{-5} compared with 0.9% for patients with a postoperative PVR < 500 dyn · s · cm^{-5}.[22] All efforts should be made to perform complete endarterectomy to avoid persistent PH. Distal location of thrombotic material and thus surgical accessibility plays a significant role in determining operability. Based on data from the European CTEPH registry, coronary artery disease increases in the hospital and 1-year mortality associated with the surgery from 2.1% to 10% and 5.1% to 15% respectively.[5] Other factors that make the surgery technically more difficult but have not been shown to increase mortality include elevated body mass index, taller patient height, and the presence of prior sternotomy.[11]

Cannon et al[23] looked at long-term survival and outcomes following pulmonary endarterectomy. Long-term survival of patients post PTE surgery at 5 and 10 years were 79% and 72% respectively. However, when in-depth analysis of survival was performed following the initial experience with 500 cases, survival at 5 years for the remaining 442 patients was 90%, clearly highlighting the importance of surgeon and center experience. Furthermore, 85% of patients had a significant improvement to functional class I or II, from a baseline of 91% in class III or IV. Although 51% of patients had residual PH (mean pulmonary artery pressure > 25 mm Hg), long-term follow-up suggested that the majority of patients maintained good functional status. Only a mean pulmonary artery pressure > 38 mm Hg or PVR > 425 dyn · s · cm^{-5} was associated with worse long-term survival.[23]

As mentioned above, surgeons have become increasingly aware of the changes that can occur in the remaining patent (unaffected by clot) pulmonary vascular bed subjected to the higher pressures and flow that result from obstruction in other areas. Therefore, with the increasing experience and safety of the operation, the authors tend to offer surgery to symptomatic patients whenever the angiogram demonstrates thromboembolic disease. CTED refers to a subgroup of patients who have evidence of chronic thromboembolic obstruction and have normal pulmonary artery pressures and right ventricular function at rest, but can have elevated pulmonary pressures with exercise. This is typically a young patient with unilateral pulmonary artery occlusion and unacceptable exertional dyspnea because of an elevation in dead space ventilation. Surgery, in this circumstance, is performed to reperfuse lung tissue, reestablish more normal ventilation-perfusion relationships (thereby reducing minute ventilatory requirements during rest and exercise), and preserve the integrity of the contralateral pulmonic circulation.

RECENT ADVANCES

Over the last decade, several innovations have enhanced surgical techniques and approach. Perhaps the most important surgical advancement has been redefining the limits of distal endarterectomy. In expert centers, PTE surgery can be successfully performed in patients with distal disease. This is attributed to advances in technology, instruments, and surgical experience. With the advent of newly designed surgical instruments and retractor, we are now able to visualize distal pulmonary vasculature better and are able to remove disease that may be limited to only segmental and/

Table 1. University of California San Diego Chronic Thromboembolic Disease Surgical Classification for Right and/or Left Lungs

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

[a]Classification based on the most proximal disease identified in each pulmonary artery, and designated R (right) and L (left).

or subsegmental vessels. By utilizing the techniques described above, we are now able to offer surgery to patients with distal disease, whom we may have turned down in the past.

Over the last several years a new surgical classification (UCSD Level Classification) has been developed to reflect the level versus type of disease (ie, lobar, segmental, subsegmental); see Table 1.[1,9-11,24]

This classification allows accurate intraoperative designation of the location of disease, while indicating the degree of difficulty of the operation; thus, the higher the level of disease, the more challenging the operation. Depending on the experience of a center, operability determination may vary. A new definition of an expert center has been proposed, and includes the following: surgical mortality < 5%, surgical volume > 50 cases/y, and the ability to perform segmental endarterectomy at a center that offers all treatment modalities (PTE, BPA, medical therapy).[9]

Also, more recently, the team at UCSD sought to determine if a minimally invasive approach to PTE surgery was possible.[2,3] Initial laboratory experiments were performed on multiple cadavers, which proved feasibility of performing a full endarterectomy into distal, segmental, and subsegmental arteries via miniature anterior thoracotomy incisions, while providing adequate exposure. Using a preoperative computed tomography scan for surgical planning, the procedure is performed utilizing the second, or the third intercostal space through bilateral or unilateral miniature anterior thoracotomies approximately 4 to 5 cm in length. The ideal location of the incisions is both high enough for central aortic cannulation, yet low enough for access to the pulmonary arteries. The arterial cannula is placed centrally in the ascending aorta, and venous cannulae in the femoral vein, right atrium, and/or right internal jugular vein. For all patients, cross-clamp and cardioplegia were not used for purposes of simplification and to maximize space. An aortic root vent is intermittently utilized just prior to going back on cardiopulmonary bypass with each circulatory arrest. Pulmonary artery and left atrial vents are used. The usual protocol for circulatory arrest and exposure of the pulmonary arteries was used. The minimally invasive approach to PTE surgery is not recommended for the novice PTE or minimally invasive cardiac surgeon.

In addition to the advances in surgical techniques, as well as less invasive procedures, there have also been significant improvements in management of postoperative complications. As we have gained quite a bit of experience using ECMO for a variety of cardiopulmonary diseases, we are able to utilize ECMO more successfully for certain postoperative complications in the PTE patient population. ECMO is quite helpful in management of severe reperfusion pulmonary edema, as well as significant airway hemorrhage, thereby improving overall prognosis and outcome in these devastating complications. Furthermore, in select patients with severe right heart dysfunction and persistent PH, ECMO can also be used as a bridge to recovery or further therapy. Expertise in initiation and management of VV, as well as VA, ECMO has afforded us a very important tool in the armamentarium of management of post-PTE complications. Although its use remains at a low number, over the last decade we have witnessed a steady improvement in outcomes of patients who would have been otherwise severely ill because of these complications, with questionable survival.

CONCLUSION

It is increasingly apparent that PH caused by chronic pulmonary embolism is a condition that is underrecognized and carries a poor prognosis. Medical therapy is ineffective in prolonging life and only available for patients who are not surgical candidates or have residual PH following surgery. PTE is the guideline-recommended treatment of choice for CTEPH as it has excellent long-term outcomes, and advances in surgical techniques are leading to refinement of operability definitions and improved outcomes. As a result, many previously inoperable patients with more distal disease or higher surgical risk can now be considered operable at expert centers. Although PTE is technically demanding for the surgeon and requires careful dissection of the pulmonary artery planes and the use of circulatory arrest, excellent short- and long-term results can be achieved, as long it is performed at expert centers. The mortality for thromboendarterectomy at our institution is currently in the range of 1% to 1.8% with sustained clinical benefit. In the future, multimodal therapy with PTE, BPA, and/or medical therapy is likely to be an important treatment strategy for many patients. These treatment options should be looked as complimentary to each other, as opposed to being in competition.

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REGULAR ARTICLE

Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

J.D. Serfas, MD
Duke University Medical Center

Richard A. Krasuski, MD
Duke University Medical Center

Balloon pulmonary angioplasty (BPA) is a rapidly emerging and developing therapy for inoperable chronic thromboembolic pulmonary hypertension (CTEPH). BPA is associated with improvements in functional and hemodynamic status, imaging indices of right ventricular performance, and survival. However, BPA should only be undertaken at a CTEPH referral center with pulmonary thromboendarterectomy capability, and only after multidisciplinary discussion determines the patient is a poor candidate for pulmonary endarterectomy. Meticulous attention to procedural technique is critical to ensure procedural success and to limit the risk of complications. Randomized controlled trials are also needed to further refine BPA's role in comprehensive CTEPH care. Nonetheless, BPA is an increasingly effective and safe therapy for CTEPH that is associated with clinical improvements and is rapidly becoming a cornerstone of referral center CTEPH care.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is unique in that it is potentially reversible with pulmonary thromboendarterectomy (PTE), which should be considered first-line therapy in eligible patients.[1] For patients who are poor candidates for PTE or have residual or recurrent pulmonary hypertension after PTE, balloon pulmonary angioplasty (BPA) has developed into a useful therapy that is associated with hemodynamic, imaging, and clinical improvements and is occupying an ever-enlarging niche in the care of CTEPH patients. In this review we will summarize the history, technical details, and recent data on BPA.

HISTORY OF BALLOON PULMONARY ANGIOPLASTY

BPA was first reported for CTEPH in 1988,[2] after having been used for applications in congenital heart disease for several years,[3] but it wasn't until 2001 that a larger series of 18 CTEPH patients who underwent BPA was reported.[4] The procedure was associated with improvements in World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), and mean pulmonary artery pressure (mPAP), but the majority of patients developed pulmonary edema with 3 requiring mechanical ventilation and 1 dying within a week of the procedure. Because of the high rate of serious complications, physicians in the United States and Europe abandoned the procedure for many years. However, Japanese physicians continued to perform the procedure, which underwent iterative refinements and improvement in their hands, ultimately reducing complication rates and improving efficacy.[5-10] Owing to this success, it has been readopted by European and American centers[11-18] and is becoming a cornerstone of referral center CTEPH care throughout the world.

PATIENT SELECTION

BPA should be considered for patients who are deemed inoperable candidates for PTE, whether due to surgically inaccessible distal disease or other patient factors.[19] It may also be used for patients with residual post-PTE obstructive disease and pulmonary hypertension and occasionally as a stabilizing procedure in critically ill patients, ideally as a bridge to PTE.[20] BPA is best suited to treatment of segmental or subsegmental vessels, and should not be attempted on large, central clots or occlusions. The ultimate treatment strategy should be determined at an expert center after multidisciplinary discussion and only after careful consideration of PTE.

OUTCOMES

The evidence base for BPA began with several small and single-center studies[11-13,15,16,21-31] that demonstrated improved hemodynamics, WHO functional class, 6MWD (typically by 50 to 100 meters), brain natriuretic peptide levels, and imaging parameters.[21,22,24,26] These findings have since been largely confirmed in larger multicenter studies and meta-analyses,[14,32-38] including a 7-center registry that included 308 patients who underwent 1408 BPA procedures in Japan. In the latter study, mean pulmonary artery pressure was reduced from 43 mmHg to 23 mm Hg, pulmonary vascular resistance from 10.7 Wood units (WU) to 3.6 WU, brain natriuretic peptide level from 240 pg/mL to 39 pg/mL, and 6MWD increased by 111 meters.[39] In the absence of a well-powered randomized trial, little is known regarding the effect of BPA on survival, though multiple observational datasets have suggested a survival

Key Words——chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, pulmonary thromboendarterectomy, interventional cardiology
Correspondence: richard.krasuski@duke.edu

benefit.[29,40] The publication of the results of the Riociguat versus BPA in Nonoperable CTEPH (RACE) trial is eagerly awaited; preliminary data from its presentation at the European Respiratory Society meeting in 2019 are very encouraging.[41]

PREPROCEDURAL EVALUATION AND LESION SELECTION

Patients typically have undergone an extensive evaluation prior to determination of candidacy for both PTE and BPA, including echocardiography, computed tomography pulmonary angiography with or without dual-energy perfusion imaging, ventilation-perfusion scanning, and invasive nonselective pulmonary angiography. Once BPA is determined in multidisciplinary discussion to be the optimal treatment strategy, target lung zones for intervention should be identified. This is accomplished by assessing for perfusion defects, which can be seen on ventilation-perfusion scanning, dual-energy computed tomography perfusion imaging, or assessment of distal perfusion on invasive pulmonary angiography. Improvement of perfusion defects in the lower lung zones is likely to yield greater benefit than upper lung zones given their greater perfusion under physiologic conditions. Lower lung zones are also technically easier to approach, and as such should be prioritized.

Once a target lung zone has been identified, selective segmental or subsegmental injections are performed at the time of BPA to completely characterize specific vessels feeding the target zone. Lesions are categorized as ring-like stenoses, web lesions, subtotal occlusions, total occlusions, or tortuous lesions; success rates are highest and complications lowest with ring-like and web lesions, while total occlusions and tortuous lesions are riskier and less likely to be successfully treated,[31] although as experience has grown with BPA, more complex lesions have been successfully and safely treated, often with greater hemodynamic improvements.[42] Figure 1 reviews the approach to assessing and preparing a patient for BPA.

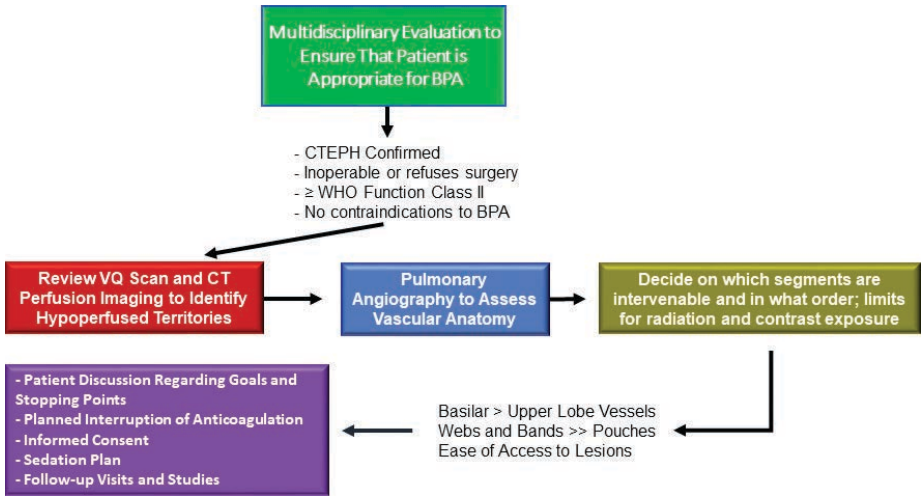

Figure 1: Clinical approach to potential candidates for balloon pulmonary angioplasty. There is significant evaluation and planning that is necessary before taking the patient for a BPA procedure. Imaging studies and clinical data must be thoroughly vetted to ensure that surgery is not the preferred treatment modality. Patients must have appropriate vascular access, adequate renal function, and ability to consent for the procedure. Lesions in territories that correspond to perfusion defects are preferred, as are regions normally with high perfusion (lower lobes) and those most easily accessed. In general webs, bands, and ring-lesions respond best to BPA. Anticoagulation must be appropriately interrupted to minimize the risk for recurrent thromboembolism. BPA indicates balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; V/Q, ventilation/perfusion; WHO, World Health Organization.

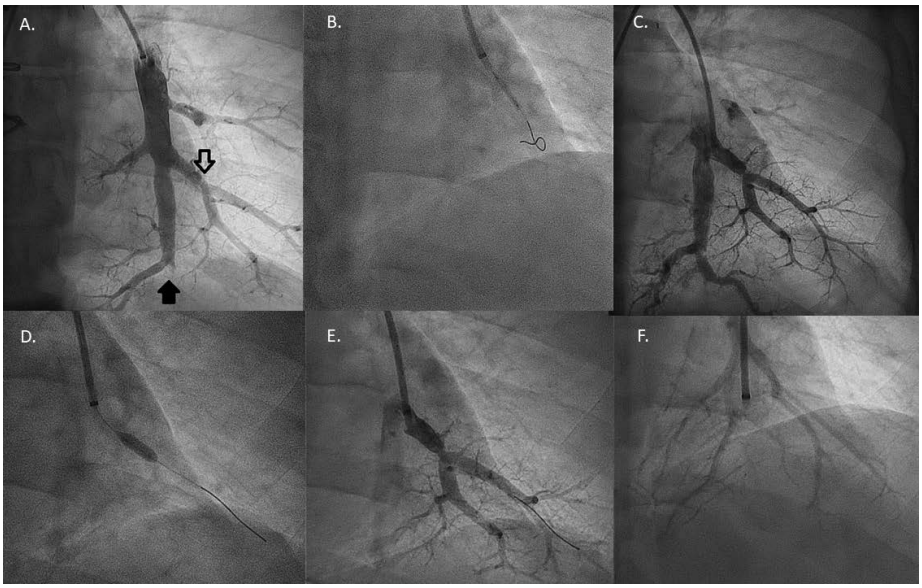

Figure 2: BPA of a web lesion in a 51-year-old male with prohibitive comorbidities and CTEPH complicated by severe pulmonary hypertension. His mean pulmonary artery pressure was 52 mm Hg and pulmonary vascular resistance was 9 Wood units before the first BPA. Panel **A** shows a selective angiogram of the left lower lobe. There are multiple lesions seen in several branches. The hollow arrow shows a complex web at the subsegment branch, the intervention for which is illustrated in this Figure. The lesion was first crossed with a *workhorse* wire and then ballooned several times with a 2 mm noncompliant balloon (**B**). Angiography afterwards (**C**) showed improved perfusion, but limited venous return (not shown). Two months later the lesion was dilated with a 4 mm noncompliant balloon (**D**) with some improvement in angiographic appearance (**E**), but dramatically improved venous return (**F**). CTEPH indicates chronic thromboembolic pulmonary hypertension.

TECHNICAL DETAILS

BPA is performed under conscious sedation over the course of several (typically 4 to 6) sessions to limit radiation and contrast exposure. Heparin is given to maintain an activated clotting time of 200 to 250 seconds. Femoral venous access is most commonly used, and a long (~90 cm) 6, 7, or 8 French sheath is advanced into the target pulmonary artery; a 6 or 7 French preshaped guide catheter is advanced through the sheath and positioned in the target segment. An atraumatic 0.014 in or 0.018 in guidewire is advanced across the target lesion, often under an inspiratory breath hold. The use of microcatheters, guide extensions, and balloon catheters can provide additional support. Polymer-jacketed guidewires have been associated with a higher risk for vascular injury and should ideally be avoided.[17] When the location of a web lesion is not readily apparent based on angiography alone, pressure wires can be used to identify areas of significant flow restriction, and have also been used to reduce the incidence of complications by titrating balloon dilation to keep pulmonary pressure distal to the lesion under 35 mm Hg.[36] Initial balloons are undersized to minimize the risk of vascular injury and reperfusion edema, although larger balloons can then be used, either in the same session or in later sessions if the risk of reperfusion edema is felt to be high. Sculpting or cutting balloons are not associated with improved performance compared with conventional balloons,[43] and should be used sparingly and only in experienced hands.[17] Intravascular ultrasound, optical coherence tomography, and cone beam computed tomography have also been used sparingly[44,45] but are often impractical.[46] Figures 2 and 3 present examples of an intervention to web lesion and a chronic total occlusion, respectively. This patient experienced significant improvements in 6-minute walk and function class; the effect of his procedure on his heart chambers is shown in Figure 4.

PREVENTING AND MANAGING COMPLICATIONS

Despite improvements in technique and improving safety over the years, BPA complications are still common.[27,28]

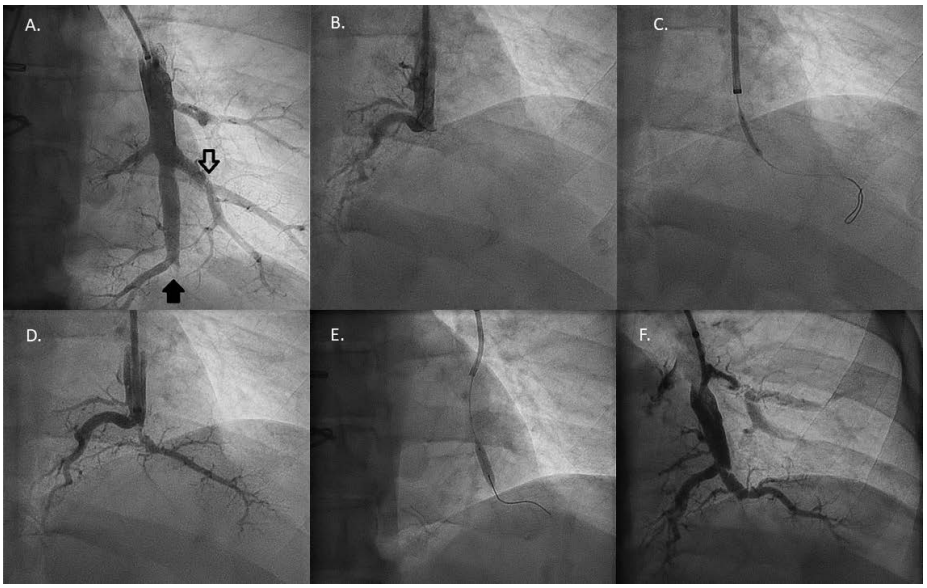

Figure 3: BPA of a distal occlusion in a 51-year-old male with prohibitive comorbidities and CTEPH complicated by severe pulmonary hypertension. His mean pulmonary artery pressure was 52 mm Hg and pulmonary vascular resistance was 9 Wood units before the first BPA. Panel **A** shows a selective angiogram of the left lower lobe. There are multiple lesions seen in several branches. The blackened arrow shows an occlusion at a distal branch, the intervention for which is illustrated in this Figure. Selective distal angiography (**B**) confirmed that the distal branch was occluded. This lesion was considerably more challenging to cross, but the *workhorse* wire was again successful (**C**), and the vessel was ballooned in several segments with a 2 mm noncompliant balloon. Angiography afterwards (**D**) showed dramatically improved perfusion and a sizable new vessel is evident. Two months later the lesion was redilated with a 4 mm balloon (**E**) with dramatic improvement in angiographic appearance (**F**) and pulmonary venous return (not shown). BPA indicates balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension.

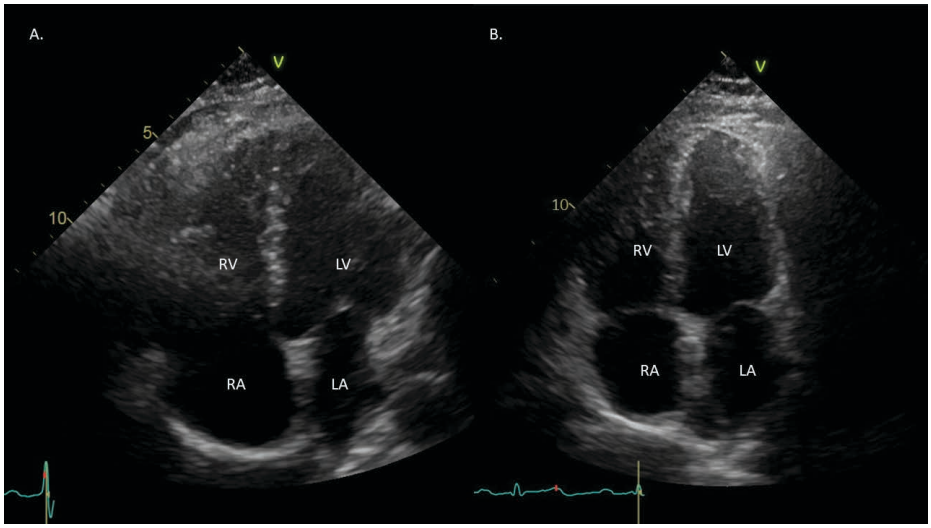

Figure 4: Cardiovascular remodeling after successful BPA. Apical 4-chamber views of transthoracic echocardiograms performed 2 weeks before BPA sessions began (**A**) and 1 year after sessions completed (**B**) for the male patient presented in Figures 2 and 3. This patient had 4 total sessions with 9 different lesions treated. Note the decrease in size of the RV and RA afterwards, with concomitant increase in size of the LA. There was also notable improvement in right ventricular systolic function seen. BPA indicates balloon pulmonary angioplasty; LA, left atrium; LV, left ventricle; RA, right atrium; LV, left ventricle.

Vascular injury due to wire or balloon trauma is the most common type of complication, and most often results in minor clinical manifestations such as asymptomatic infiltrate on chest X-ray or mild, self-limited hemoptysis,[39] which are not associated with worse long-term outcomes.[47] More serious complications can arise, however, and great care should be taken to prevent them.

This process should ideally begin well before the procedure; based on the observation that elevated pulmonary artery pressures are associated with higher risk for complications,[4,5] optimizing medical therapy for pulmonary hypertension prior to first BPA is likely wise,[48] and has been associated with reduced complication rates in the extension study of the RACE trial.[49]

Several intraprocedural techniques to reduce risk of complications have already been mentioned, such as prioritizing lower-risk web and ring-like lesions and the use of atraumatic wires and undersized balloons, which is especially important in the setting of severely elevated pulmonary pressures.

Complications must be swiftly recognized and treated, whether with heparin reversal, balloon sealing, covered stent placement, or vessel occlusion with coils or resorbable gel.[50] Traditional life support measures including intubation and mechanical ventilation, bronchoscopy, and surgical intervention are rarely necessary but should be readily available.

CONCLUSION

BPA is rapidly becoming a cornerstone therapy for referral center CTEPH care and continues to improve with rapid refinements in technique. Randomized trial data assessing the efficacy and safety of BPA is eagerly awaited.

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REGULAR ARTICLE

Medical Management of Chronic Thromboembolic Pulmonary Hypertension

Alice M. Goyanes, MD
Pulmonary Vascular Disease Section
Department of Pulmonary Medicine
Cleveland Clinic Respiratory Institute
Cleveland, OH

Gustavo A. Heresi, MD, MS
Pulmonary Vascular Disease Section
Department of Pulmonary Medicine
Cleveland Clinic Respiratory Institute
Cleveland, OH

Medical therapy in chronic thromboembolic pulmonary hypertension (CTEPH) has two primary goals- to prevent recurrent thromboembolic events and to reduce right ventricular afterload with targeted medications (vasodilators) for pulmonary hypertension. These medical strategies are used in conjunction with mechanical treatments for CTEPH (pulmonary thromboendarterectomy (PTE) or balloon angioplasty). In the context of this review, we discuss anticoagulation strategies, patient selection for vasodilator therapy with particular focus on hemodynamic and clinically meaningful definitions of residual pulmonary hypertension after PTE and inoperable disease and then summarize the current randomized clinical trials (RCT) which have studied effectiveness of vasodilators in patients with CTEPH.

INTRODUCTION

Medical therapies in chronic thromboembolic pulmonary hypertension (CTEPH) have 2 primary focuses: prevention of recurrent thromboembolic events with lifelong anticoagulation, and reduction in right ventricular afterload with targeted medicines (vasodilators) for pulmonary hypertension (PH). These cornerstones of medical therapy are used in conjunction with mechanical treatments for the disease: pulmonary thromboendarterectomy (PTE) and balloon pulmonary angioplasty. Vasodilators are used in the case of inoperable CTEPH as well as for patients with residual PH after PTE surgery. In this review we will address recommendations and considerations for anticoagulation, patient candidacy for vasodilator therapy, and the timing of initiating therapy after PTE, and review the randomized controlled trials (RCT) of vasodilator therapies for inoperable CTEPH and residual PH after PTE surgery.

ANTICOAGULATION

Duration and Choice of Anticoagulation

Even though a known thrombophilia is identified in a minority of CTEPH patients (32% in the international CTEPH registry[1]), this population is considered a high risk for recurrent venous thromboembolic events and thus, lifelong anticoagulation is recommended. Traditionally, vitamin K antagonists (VKAs) have been used.[2] With the increasing use of direct-acting oral anticoagulants (DOACs) as safe and effective treatments for acute venous thromboembolism (VTE), more patients have been using this class of medications for long-term anticoagulation in the setting of CTEPH. There are no direct head-to-head trials comparing these 2 anticoagulation strategies; only observational registry data are available.

VKAs have been used most frequently, given a longer period of bioavailability, and are generally reported to be safe and efficacious at preventing recurrent VTE in CTEPH patients. Jujo-Sanada et al[3] observed major bleeding in 8.1%/person-year and recurrent VTE in 1.2%/person-year in their retrospective cohort of CTEPH patients on VKAs, while Henkens et al[4] reported major bleeding events at 2.4%/person-year in CTEPH patients.

As DOAC therapy has gained traction for treatment of acute VTE with several studies demonstrating similar efficacy for prevention of recurrent VTE and fewer bleeding events,[5] more patients with CTEPH have remained on DOAC therapy as their anticoagulant of choice. Registry data have provided some perspective on using DOAC therapy in the CTEPH patient population, although several controversies regarding safety and efficacy of this class of drugs remain.[6]

Bunclark et al[7] published a large retrospective analysis specifically dedicated to evaluating VKA compared with DOAC therapy. In this cohort, 794 patients on VKAs and 204 patients on DOAC therapy had PTE surgery at the United Kingdom national PTE center from 2007 to 2018. Both groups of patients had similar hemodynamic and functional status improvement after PTE and major bleeding events were equivalent (0.67%/person-year versus 0.68%/person-year). Patients on DOAC therapy had higher rates of recurrent VTE after stabilization on oral anticoagulation therapy (4.62%/person-year) compared with those on VKAs (0.76%/person-year), although survival was similar between the 2 groups.[7] A retrospective analysis of surgical specimens presented solely in abstract form suggested a higher rate of acute or subacute thrombi in the CTEPH tissue in patients on DOAC therapy (13.3%) compared to those on VKAs (6.7%).[8] Finally, a recent

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Correspondence: heresig@ccf.org
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study using the EXPERT registry (an international, multicenter prospective registry of 841 patients treated with riociguat for pulmonary arterial hypertension or CTEPH) collected data regarding hemorrhagic events and recurrent thromboembolic events in patients with CTEPH on VKA and DOAC therapy. The authors reported no difference in absolute rates of hemorrhagic events or any difference in rates of exposure-adjusted hemorrhagic events between VKA and DOAC therapy (9.5% and 12.1% respectively). However, while recurrent thromboembolic events had low absolute numbers overall, the exposure-adjusted event rate was lower in patients treated with VKAs compared those treated with DOACs (1.7% and 4.6% respectively). While data are limited and these are retrospective studies, it does call into question the efficacy of DOACs for anticoagulation in CTEPH.[9]

Conversely, Sena et al[10] examined rates of bleeding events, death, and recurrent VTE in 501 patients with CTEPH-412 patients on VKAs and 134 on DOACs. There was no difference in survival or recurrent VTE, but in patients treated with VKAs there were higher rates of major bleeding events (odds ratio: 1.94; 95% confidence interval: 1.05-3.62).[10] Overall, more studies need to be done to help settle the question of efficacy of DOAC therapy in CTEPH patient populations.

Anticoagulation in Special Patient Populations

VKAs are the preferred method of anticoagulation in patients with anti-phospholipid antibody syndrome (APS), particularly high-risk triple-positive APS. This recommendation comes from several observational cohort studies as well as a randomized open-label non-inferiority study in which patients with triple-positive APS had higher rates of recurrent thromboembolic events and shorter event-free survival on DOAC therapy compared to VKA.[11,12]

Another special situation is bariatric surgery. Absorption of any DOAC could be potentially reduced by Roux-en-Y gastric bypass, because all the drugs in this class require some degree of absorption in the proximal small bowel.[13] Regarding gastric banding or sleeve gastrectomy, given that the surface area of the stomach is dramatically reduced, medications that primarily rely on the stomach for absorption can be impacted (dabigatran, edoxaban, and rivaroxaban).[13] Low-molecular-weight heparin or VKA may be more appropriate in this patient population.

SELECTION OF PATIENTS FOR ADVANCED MEDICAL (VASODILATOR) THERAPY

PH in CTEPH is due to the combination of large-vessel thrombo-fibrotic obstruction and concomitant microscopic vasculopathy. The latter is similar to what is observed in group 1 PH[14] and provides the rationale for use of advanced medical therapy (pulmonary vasodilators) for pulmonary hypertension.

Two patient populations may be candidates for vasodilator therapy in the context of CTEPH: patients with inoperable disease or patients who have residual PH after PTE. The assessment of operability must be performed by a multidisciplinary team of PTE surgeons, radiologists, and PH specialists with experience and expertise in CTEPH.[15] More in-depth discussion regarding diagnosis and determining operability is outside the context of this review.

Inoperable Disease

For patients who are not able to be offered PTE surgery, because their vascular occlusions are inaccessible or because their degree of PH is elevated out of proportion to thrombotic burden or they have prohibitive medical comorbidities, vasodilator therapy can be considered. In the small number of clinical trials that have been conducted in this patient population, the hemodynamic thresholds at which to consider vasodilator therapy were variable—typically patients were included with a mean pulmonary artery pressure (mPAP) ≥25 mm Hg and a pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg—the hemodynamic definition of CTEPH provided in the 2015 European Respiratory Society (ERS) guidelines.[16] However, pulmonary vascular resistance (PVR) thresholds varied from trial to trial. In practice, vasodilatory therapy is typically considered with mPAP ≥25 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg and PVR ≥240 dynes/s/cm^5 (PVR of 3 Wood units [WU]). In 2019 the 6th World Symposium on PH proposed a new hemodynamic definition, lowering the threshold from mPAP ≥25 mm Hg to an mPAP of >20 mm Hg.[17] It is not yet clear if this new definition is applicable to patients with CTEPH. The ongoing MACiTEPH trial (NCT04271475; macitentan 75 mg daily versus placebo) is the first RCT to enroll CTEPH patients with this new hemodynamic definition of PH.[18]

Vasodilators Prior to PTE

There are not robust data from RCTs to currently suggest that there is a benefit from using pulmonary vasodilators prior to PTE surgery in operable patients. In spite of this, registry data reveal that a substantial proportion of operable patients are on vasodilators prior to surgery.[1] Although preoperative treatment has been reported to improve preoperative hemodynamics, it has no effects on post-PTE outcomes and may induce unnecessary delay to a potentially curative surgical intervention.[19] Data from the international CTEPH registry showed that preoperative bridging therapy was not only associated with no improvement in PTE outcomes, but also with worsened long-term survival, although in this case patients who were bridged with medical therapy to PTE likely represented a population with more severe baseline disease.[20] A prospective clinical trial was being conducted studying the safety and efficacy of riociguat as a bridging therapy to PTE surgery (NCT03273257), but unfortunately it was stopped due to slower than expected recruitment brought on by the COVID-19 pandemic.[21] At this time, it is not recommended to routinely provide bridging therapy with vasodilators if a patient is a PTE candidate, as operability assessment is a crucial early step after diagnosis that should not be delayed.

Residual PH after PTE

The exact hemodynamic definition of residual PH after PTE is not established, nor is a standard time for mea-

surement in the postoperative course. The 2015 ERS guidelines recommend performing a right heart catheterization 3 to 6 months after PTE. In the immediate postoperative period residual PH has been associated with increased operative (30-day) mortality. A PVR > 500 dynes/s/cm^5 (PVR of 6.25 WU) was associated with higher mortality (10.3% versus 0.9% respectively) in a cohort of 1500 patients who received PTE at the University of San Diego between 1999 and 2010.[22]

Regarding outcomes in patients who survive the immediate postoperative period, clinically meaningful definitions of residual PH have varied. In a retrospective national cohort study in the United Kingdom, which defined residual PH as mPAP ≥25 mm Hg and PVR > 240 dynes/s/cm^5 (PVR of 3 WU), 162 patients had hemodynamic assessment 3 months after PTE surgery. The authors reported no difference in 1- and 3-year survival when comparing those with residual PH to those without.[23] Until 2019, mPAP ≥25 mm Hg and PVR > 240 dynes/s/cm^5 (PVR of 3 WU) was the hemodynamic definition of CTEPH at the time of diagnosis, as well as the hemodynamic definition of precapillary PH.[16] It is interesting to note that these thresholds may be too sensitive to differentiate poor outcomes in postoperative patients with residual PH.

Raising the hemodynamic threshold for defining residual PH after PTE may better differentiate patients who can benefit from vasodilator therapy. A retrospective study from the United Kingdom national CTEPH registry of 881 patients who underwent PTE surgery demonstrated that an mPAP ≥38 mm Hg and PVR > 425 dynes/s/cm^5 (PVR of 5.3 WU) measured 3 to 6 months after surgery was associated with worse long-term survival. In this cohort, mPAP ≥30 mm Hg and PVR ≥318 dynes/s/cm^5 (PVR of 3.9 WU) was associated with initiation of vasodilator therapy.[24] An observational cohort study of 441 patients who underwent PTE in Sweden and Denmark between 1994 and 2020 demonstrated that using a threshold of mPAP ≥30 mm Hg measured 48 hours after PTE was associated with worse long-term survival, and this relationship strengthened after excluding patients who experienced operative mortality.[25]

Further studies will hopefully inform exact definitions of clinically meaningful residual PH after PTE and assist in standardization of the timing of initiation of vasodilator therapy or referral for post-PTE balloon angioplasty.

VASODILATOR THERAPIES

To date, there have been a number of completed randomized placebo-controlled clinical trials investigating the safety and efficacy of pulmonary vasodilators for the treatment of both inoperable CTEPH and residual PH after PTE (Table). As with the treatment of PAH, CTEPH clinical trials have evolved from monotherapy versus placebo to including patients on background therapy (possibly suggesting some benefit from sequential combination therapy in CTEPH).

Nitric Oxide Pathway

Riociguat, a soluble guanylate cyclase stimulator, is currently the only US Food and Drug Administration (FDA)-approved pulmonary vasodilator for treatment of inoperable or residual CTEPH. In CHEST-1, a RCT comprised of 261 patients with inoperable CTEPH or residual PH after PTE, riociguat significantly increased exercise capacity and reduced PVR after 16 weeks compared to placebo.[26] There was also an improvement in biomarkers of right ventricular function (N-terminal pro-brain natriuretic peptide [NT-proBNP]) as well as World Health Organization functional class and there was no significant difference in serious safety events. Importantly, in this study, operability was determined by a central adjudication committee of international CTEPH experts.

Sildenafil, a phosphodiesterase type 5 inhibitor (PDE5i) was studied in a very small population of patients with inoperable CTEPH and demonstrated an improvement in PVR compared with placebo, without an improvement in 6-minute walk distance at 12 weeks.[27]

Endothelin Receptor Antagonists

Two endothelin receptor antagonists have been studied in CTEPH: bosentan and macitentan. In the BENEFiT RCT comparing bosentan to placebo in 157 patients with inoperable CTEPH or residual PH after PTE, bosentan did not impact 6-minute walk distance, which was the primary endpoint; however, a significant reduction in PVR was seen.[28] Because the trial did not meet its primary endpoint for improvement in exercise capacity, bosentan did not gain regulatory approval.

The safety and efficacy of macitentan was studied in the MERIT-1 study, a phase 2 placebo-controlled RCT. Eighty patients with inoperable CTEPH were randomized to macitentan or placebo and the study found an improvement in PVR, exercise capacity, and NT-proBNP.[29] Patients were permitted to be on background PDE5i or oral prostacylins and there was still a treatment effect, suggesting some benefit from combination therapy in CTEPH. The FDA requested further study after an initial request for approval for macitentan for CTEPH, and there is a clinical trial currently enrolling to further define efficacy and safety of macitentan for inoperable CTEPH as well as residual PH after PTE (NCT04271475).[18]

Prostacylins

A single RCT examined long-term use of subcutaneous treprostinil (a prostacyclin analogue) in 105 patients with inoperable CTEPH.[30] High-dose (~30 ng/kg/min) subcutaneous treprostinil compared to low-dose (~3 ng/kg/min) resulted in improvement in PVR, exercise capacity, functional class, and NT-proBNP; approximately one third of these patients were on background vasodilator therapies.[30] Although not FDA approved, it is used off label in clinical practice for severe disease, and has been approved in Europe.

The oral prostacyclin agonist selexipag is approved in Japan based on an RCT that showed improvements in PVR at 20 weeks, but no effect on 6-minute walk distance.[31] An international multicenter RCT of selexipag (a prostacyclin receptor agonist) for CTEPH was recently stopped due to futility (NCT03689244)[32]; more detailed results of this study are currently awaited.

Table. Randomized Placebo-Controlled Clinical Trials for Treatment of CTEPH

Year	Drug	Study	Patient population	n	Background therapy?	Intervention	Primary endpoint	Main finding	Approval
2008	Sildenafil[27]		Inoperable	19	No	Sildenafil (40 mg 3 times a day) versus placebo	6WMD	• Did not meet primary endpoint to significantly change 6WMD • Increased WHO FC and cardiac index, reduced PVR and Nt-PRONP	No
2008	Bosentan[28]	BENEFiT	Inoperable or Residual PH after PTE	157	No	Bosentan (62.5-125 mg twice daily) versus placebo	6WMD, Change in PVR	• Met one primary endpoint: reduced PVR by 24% • Did not significantly change in 6MWD	No
2013	Riociguat[26]	CHEST-1	Inoperable or Residual PH after PTE	261	No	Riociguat (0.5-2.5mg 3 times a day) versus placebo	6WMD	• Met primary endpoint:increased 6WMD • Increased WHO FC, reduced PVR and NT-proBNP	USA, Europe, Japan
2017	Macitentan[29]	MERIT-1	Inoperable	80	Yes	Macitentan (10 mg daily) versus placebo	Change in PVR	• Met primary endpoint: reduced PVR by 26% • Increased 6WMD, reduced NT-proBNP	No
2018	Treprostinil[30]	CTREPH	Inoperable or Residual PH after PTE	105	Yes	Treprostinil 30 ng/kg/min versus treprostinil 3ng/kg/min	6WMD	• Met primary endpoint: increased 6WMD • Increased WHO FC, reduced PVR and NT-proBNP	Europe
2022	Selexipag[31]		Inoperable or Residual PH after PTE	78	Yes	Selexipag (200-1600 µg twice daily) versus placebo	Change in PVR	• Met primary endpoint: decreased PVR • Did not significantly improve 6WMD	Japan

Abbreviations: CTREPH, chronic thromboembolic pulmonary hypertension; 6MWD, 6-minute walk distance; WHO FC, World Health Organization functional class; PH, pulmonary hypertension; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance; Nt-proBNP, N-terminal pro-brain natriuretic peptide.

CONCLUSIONS

The mainstays of medical therapy for CTEPH are comprised of lifelong anticoagulation for all, and in patients who have inoperable disease or residual PH after PTE, consideration for advance medical (vasodilator) therapy for PH. Future studies will hopefully improve areas of uncertainty, including a standardized hemodynamic definition of residual PH after PTE to better define which patients benefit from treatment, more rigorous examination of the efficacy of DOACs in CTEPH populations, and also the role of combination PH therapy in CTEPH.

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Tailoring CTEPH Imaging for Evaluation and Postintervention Assessment—What Works and What's New?

This summer, Dr Richard Krasuski of Duke University; Dr Gustavo Heresi of Cleveland Clinic; Dr Victor Tapson of Cedars-Sinai; Dr Irene Lang of the Medical University of Vienna, Austria; and Dr William R. Auger, Emeritus Professor at University of California, San Diego, gathered to discuss imaging in the assessment of chronic thromboembolic pulmonary hypertension (CTEPH).

Richard Krasuski: As you know, CTEPH is a common problem that we all see in our pulmonary hypertension (PH) clinics. Somewhere between 3% and 4% of all pulmonary embolism patients develop CTEPH afterwards. We're challenged to identify these patients early so we can get them the appropriate treatments they need including surgery, balloon pulmonary angioplasty, and advanced medical therapies. Despite many efforts, it still takes up to 2 years from the time of symptom onset to confirmed diagnosis.

We have collected an amazing group of panelists and friends for today's session. Pretty much a "Who's Who in CTEPH." This includes Dr Bill Auger, guru of CTEPH and Professor Emeritus at UCSD and Temple and now my fabulous colleague at Duke; Dr Vic Tapson, a sage in pulmonary thromboembolism and pulmonary hypertension who I learned so much about pulmonary hypertension from when I was a fellow at Duke; as well as Dr Irene Lang, Professor of Medicine at the University of Vienna and an expert hemodynamicist and pulmonary vascular interventionalist. It's a real pleasure to be able to comoderate this panel today with my esteemed colleague Dr Gustavo Heresi, who is the head of the Pulmonary Vascular Clinic at the Cleveland Clinic and was my colleague for about 10 years when I was at the Cleveland Clinic. He is going to ask most of the questions, and I'll try to interject when necessary. He was a fellow when I joined Cleveland Clinic and collaborated with the PH program, and he is now the head of the whole thing. It's very impressive, Gustavo, please continue.

Gustavo Heresi: Thank you, Rich. Yes, that brings me back to good times. It was really nice to have you here, and it was a loss for us, but I know you're doing great in North Carolina. Anyway, really excited to have you guys here, and I think, without further ado, we'll just start talking. Rich and I went over a template of some of the questions that we wanted to bounce off of you. The first one, as Rich was saying, the challenge of diagnosing this disease even in this day and age: One of the things that we wanted to start hearing from you guys is what kind of studies you think are needed for every patient with suspected CTEPH.

I guess we can start by talking a little bit about the ventilation/perfusion scan, which, of course, we still consider the best screening method, but we wanted to hear some thoughts from you as to how do you view the ventilation perfusion scan (V/Q) scan in 2022? Do you still consider it the best screening method? Should it be different based on a patient history of prior pulmonary embolism (PE) or not? During the COVID-19 pandemic, has SPECT/CT V/Q scanning changed the way you think about this test?

Vic Tapson: I'll just mention the fact that I still believe the V/Q scan is useful. I think it's underestimated and underutilized by many of our colleagues out there. One of the key values of the V/Q scan, as you well know, is when it's normal, we're done. If it's not normal, you need to move on and be certain there is expertise reading the compute tomography angiography. Reading a CT for CTEPH takes tremendous expertise. Acute PE is easy. The ability to accurately read a CT for CTEPH like Bill Auger does, for example, is a rarity. A true rarity. Most pulmonologists, cardiologists, and surgeons can't read CTEPH CT scans like the people on this call.

Irene Lang: I think V/Q scan is a great tool just for the screen. However, COVID has brought in diagnostic uncertainties to the old technique because COVID infection of the lung changes the V and the Q, probably independent of concurrent acute PE. I think we have to sort out the COVID changes before we use the V/Q as a screening tool for PE during or after COVID-19 infection. I think it's not so trivial. A relationship between COVID infection and CTEPH is still unconfirmed. I do think there's a lot of research ongoing currently, at least in Europe. I know of some studies where people are screened with V/Q after COVID and that isn't trivial.

William Auger: I completely agree. If you speak with experts around the world about screening patients for suspected CTEPH, the V/Q scan still plays an essential role, and the test of time clearly shows that, if the perfusion scan is deemed to be normal, CTEPH has been ruled out.

It's also important to appreciate what you're looking at with the V/Q scan. You're simply evaluating for perfusion abnormalities. It's a nondiagnostic study,

so when folks tell me that CTEPH has been diagnosed with a V/Q scan. . . this is overstated. If there is a known history of pulmonary embolism, the VQ scan might be suggestive of CTEPH, but given the wide range of diagnoses that can result in unmatched perfusion abnormalities, a more diagnostic study such as CT, MR, or catheter-based pulmonary angiography [needs] to be performed to accurately diagnose CTEPH.

Vic Tapson: The great thing is, Bill, a normal perfusion scan, like you said, rules out CTEPH. A normal CT scan does not rule out CTEPH unless a true expert reads it. We've seen major medical centers completely miss CTEPH by CT.

William Auger: I think we still rely on a number of studies that look at the sensitivity of CT and CT angiography for CTEPH which were performed at expert CTEPH centers. . . people who knew what they were looking for and knew how to interpret these studies. However, when you look at "real-world data," another story is told and seems more in line with our day-to-day experience. By way of example, there was a recent small study out of Sweden that examined the original preoperative CT reports of patients with known CTEPH. . . patients who ultimately underwent pulmonary thromboendarterectomy surgery. The diagnostic sensitivity for CTEPH in these reports was found to be only 26% (Rogberg et al. *Acta Radiol*. 2019;60(11):1576–1583). This underscores what you just said Vic that the CT scan can be very difficult to read, particularly at the segmental and subsegmental level.

Gustavo Heresi: Vic, you've done some work in the post-PE population, and I think you showed us that the post-PE population is certainly not well studied. Do you want to comment on what's your approach in somebody with persistent dyspnea and also a little bit about whether or not you see a role for exercise testing, cardiopulmonary exercise testing, even invasive cardiopulmonary exercise testing? How do you view the post-PE population in terms of picking up CTEPH or chronic thromboembolic disease (CTED)?

Vic Tapson: We published 1 study not long ago, Gustavo, the INFORM study, and it was a big claims database. You have to be a little cautious with claims database data, but what it told us is, in a cohort of incident PE patients, that clinicians very often do not look for CTEPH. When patients are dyspneic and have pulmonary hypertension, they're not getting V/Q scans ordered. They may work the patient up for pulmonary hypertension, but VQ scans are often not done or are done very late, again, not a randomized trial, not a registry, but a claims database study. Still, I think the evidence and our experience tell us that people are not looking for it.

I wish we did a better job upfront following patients with acute PE long term. I think patients with acute venous thromboembolism (VTE) should be followed by an expert forever. New studies are published. Patients' risk factors change. Our European colleagues have done a great job with long-term follow-up data. Look at the studies that have been done by Meneveau, Bonnefoy, Nijkeuter, and others. All these studies looked for residual pulmonary vascular obstruction (RPVO) and studied its implications. We don't generally do this. We know RPVO with or without PH is common. The percentage of patients that have more than 10% RPVO with or without PH is 20% to 50%. If you have RPVO, your risk of recurrent VTE is higher, and your mortality is higher.

In many situations, post-PE patients go to their PCP, or they go to an internist. They may go to a pulmonologist, cardiologist, or hematologist. Whoever it is, they ideally need to be followed by an expert. If you have cystic fibrosis, you go back to the CF doctor when you're discharged, and you're followed up. If you have PE, you don't. You end up in a PH clinic years down the line seeing one of you guys, seeing an expert when someone could have been following all along. I think the whole PE world needs to be less fragmented and more organized. Re-imaging and considering CPET in symptomatic patients is not done in a systematic manner.

Richard Krasuski: Let's discuss timing when seeing these patients back after PE. I've seen 3 months or 6 months used in the literature. At what point do you think it's important to assess whether these patients still have dyspnea? Should we be doing studies like cardiopulmonary exercise testing (CPET) routinely to try to establish whether they are functionally limited and need further evaluation?

Irene Lang: I just wanted to remind you, there was a very recent study now published in the *European Heart Journal*, the FOCUS study, where 1000 PE patients were followed up prospectively. Actually, if you go through the list of centers in Germany, a majority of those were PH centers. They had both knowledge on PE and on CTEPH, and they found in 2 years 2.3%, with all the care that was part of the FOCUS study, which is a lot. They had several follow ups, very structured follow ups, since the acute event assessing numerous parameters, including exercise testing.

I think it's still rare, and I wonder if you don't find more CTEPH cases if you look in the ED acute PE presentations and rather than in the post-PE because I think, in the post-PE, you get a mixture of everything. When you look in the emergency room for CTEPH, you may find more. Maybe that is not so clear to you, but I do think, if you do CPET later on, you will find more coronary disease and aortic stenosis than CTEPH.

William Auger: Irene, you are making some important points, emphasizing some of the ongoing difficulties that we're having trying to establish a true prevalence of the disease, either being CTED or CTEPH. In the majority of the studies, patients are followed (on average) for about 2 to 3 years after an acute event in an effort to establish the incident rate of CTEPH.

Two comments that can be made about that: One is that the time period following acute PE patients in these studies may be too short to get an accurate sense of CTEPH incidence. Many of the CTEPH patients that I have seen in clinic relate the story of

having experienced their PE 6 or 10 or 15 years ago. I don't have the exact percentage of patients with established CTEPH who share this history, but the timeline between acute PE transitioning to CTEPH remains an unknown. So, the available studies may be limited, as the follow-up may not be long enough to get a true incident rate, and in support of Irene's comment, many of these incident studies may have been combined patients with established disease. If you look at the condition of PE patients at presentation, the presence of significant pulmonary hypertension, right ventricle (RV) strain, and/or RVH may reflect that their initial presentation may actually be decompensated CTEPH and not acute PE.

Vic Tapson: There's a movement now by the PE Response Team Consortium for VTE Centers of Excellence, which I really think we need. Patients need to be followed from the onset of their acute PE; they need to be seen by a PE expert. This is not just to look for CTEPH or to look for RPVO but to look for postthrombotic syndrome, determine how long to anticoagulate, decide when to look for cancer, whether to look for thrombophilia, etc. I follow my PE patients forever because, who knows, in 5 years, we may know their point mutation. We may be able to give them gene therapy, and they may get CTED or CTEPH.

Irene Lang: It's part of the guidelines in Europe to look at persistent dyspnea at 3 or 6 months; it's open. I don't know, to be honest, how many patients will be seen, what the percentage is, but I think quite a few because people have embraced not only CTEPH but also the post-PE impairment syndrome, which is probably even worse than CTEPH and more common, definitely. It was found in 16% in FOCUS.

Richard Krasuski: It's estimated that up to half of patients post-PE will have persistent dyspnea after 3 to 6 months. As you correctly identified, Irene, it's only a small number of those that'll eventually be diagnosed with CTEPH, but there are other etiologies that may need to be assessed, as Vic mentioned.

Irene Lang: Many.

Richard Krasuski: These can be worked up and potentially treated. A lot of these people have numerous comorbidities, including morbid obesity, deconditioning, and other disease processes that can contribute to their functional limitation.

William Auger: Agreed.

Richard Krasuski: Lifestyle modification can be very important for them.

Vic Tapson: Erik Klok, Irene, and others wrote a very nice paper a couple of months ago in the *European Heart Journal*, and it was on optimal follow up after acute PE, a beautiful paper with a nice table that goes through things: bleeding risk, thrombophilia testing, oral contraceptives, when can a patient fly after PE, when can they exercise, and when and how to look for CTEPH. I think that needs to get distributed more. Again, I think our European colleagues are way ahead of us in this disease state in terms of [at] least following the acute patient up.

Gustavo Heresi: Before we move on, I wanted to circle back to a quick point about how, during the pandemic, many centers dropped the V part of the ventilation/perfusion scan and started using more widespread SPECT CT-Q. Is that, in your experience, something that your centers did? Do you think it added any value? Do you think that's the way to move forward, or just the planar V/Q scan is enough as the screening test of choice? Irene, what are you guys doing in Europe?

Irene Lang: We dropped V scans for a while, but also Q, and then started both again. I think we had a period of low referrals as well. I do believe that those went in parallel, so we didn't miss anything. As we speak, patients are coming back, and they get the whole array of diagnostics. As I mentioned in the beginning, the perfusion part of the test is, of course, also altered by COVID infection, so that, I think, has still to be learned. As was pointed out correctly, any V/Q is an unspecific perfusion test.

I think we tend to look more at CT scans and refine those and use the dual source and the iodine map [to] replace the V/Q. I still like to look at the Q, to be honest, if it's about CTEPH diagnosis.

Vic Tapson: I feel the same. We're still getting our feet wet with dual-energy CT and reading it and looking at perfusion. I still think us old-fashioned people are going to probably stick with a V/Q scan for a while, but CT technology is getting better.

William Auger: To address your question, Gustavo, at the onset of the COVID pandemic, ventilation studies were not performed. . . reasonably so, and yes, a SPECT study is helpful in providing more anatomical information that might cause an abnormal ventilation scan. . . as you might expect if a pleural effusion was present. Whether SPECT imaging adds value relative to planar perfusion imaging when evaluating patients for CTEPH is a separate issue. There's no argument that perfusion imaging with SPECT is more sensitive than planar VQ in the detection of perfusion abnormalities, but whether you see 11 perfusion abnormalities versus 8, it doesn't really matter. In many instances, the perfusion abnormalities on SPECT seem exaggerated without adequate definition on CT to account for those findings. Bottom line, as is the case with planar V/Q, further investigation with diagnostic studies is still required to define the cause of the perfusion defects.

Gustavo Heresi: That's a beautiful segue actually into the next point, which is: If the V/Q is done, and it's abnormal, what comes next? Is it a CT for everybody, and if yes, how do you see it? How does it help you make the diagnosis? Perhaps exclude some mimickers? Then also, are you guys using dual energy? What do you see the role for dual-energy CT scan is in this condition at the moment and perhaps in the future?

Irene Lang: I think CT is the next step there. Nobody doubts that, right? I think dual energy—I'm not so sure about

dual energy as yet. It's more radiation. I personally rely on CT scan, 3D reconstructions, as good as they are possible. I think they are very useful. In case of CTEPH diagnostics, I move quickly to a nice digital subtraction because I can do this very well in 2 planes. I know exactly what's going on. This is my little toolbox. I go from V/Q to CT scan, conventional 3D reconstruction to pulmonary angiograms (PAGs).

Gustavo Heresi: In everybody, Irene?

Irene Lang: Everybody with the suspicion of CTEPH or CTED.

Gustavo Heresi: Even if the CT shows you, for example, nice main or lobar disease, even in those cases, you'd still proceed to a PA gram?

Irene Lang: Yes, because you need hemodynamics anyways, even if you do surgery. The PAG is very fast, and it gives you all the details on all mechanical intervention. Balloon pulmonary angioplasty (BPA) may become necessary unexpectedly. We have had a bailout BPA during COVID because there was no surgical theater available.

Gustavo Heresi: Vic, what's your practice after an abnormal V/Q scan?

Vic Tapson: I think what Irene says makes great sense. After an abnormal V/Q, our next move is a CT. If CT is very obvious, this patient is going to get referred for endarterectomy if they're a candidate. We're not doing endarterectomies at Cedars right now. A right-heart cath would be the next move, but since we still refer to San Diego and they will do the cath/PA gram anyway, so we don't, and they will get the usual very thorough work up and therapy.

To have San Diego in your backyard or have Bill Auger on a phone call is worth its weight in gold. Even though we don't have an actual CTEPH center, we see plenty of it and refer it.

William Auger: The CT is just a marvelous tool, and I just think it provides a tremendous amount of information, not only about the pathology involving the pulmonary vascular bed but also the status of the lung parenchyma, mediastinal issues, and large pulmonary vein abnormalities, all of which can result in an abnormal V/Q scan. When done properly and when read properly, it can provide all the information necessary to diagnosis pulmonary vascular obstruction due to chronic thromboembolic disease and to establish whether or not the patient has technically operable disease. At many CTEPH centers of excellence, an abnormal V/Q and a diagnostic CT angiogram precludes the need for catheter-based pulmonary angiography.

However, as we discussed, interpretation of CT angiography becomes more difficult at the level of segmental and subsegmental vessels, and this becomes increasingly relevant from a patient care perspective with the availability of balloon pulmonary angioplasty, an intervention that can be effective in treatment of distal vessel CTEPH. It's in this setting where there may be questions as to the diagnosis, and particularly in the assessment of operability, that proceeding to catheter-based pulmonary angiography is necessary.

The other point to make is just how valuable perfusion imaging can be in the interpretation of CT angiography and even conventional pulmonary angiography. . . essentially asserting that the perfusion scan can be used as a guiding tool in your diagnostic evaluation. I've recently just had this experience with a case where a patient exhibited a large apical right upper lobe perfusion defect, and the initial CT scan reading failed to account for this abnormality. The perfusion scan provoked another look at the CT, with a more care review showing an obstructed pulmonary artery that originated from the main PA at an unusual spot.

Perfusion imaging can also be useful as a guide for conventional angiography. . . focusing the evaluation of vessel anatomy in regions where there are perfusion defects, even if the CT findings have been assessed as "unremarkable," and it's worth re-emphasizing that this effort in defining the segmental and subsegmental anatomy is worth it. Though the patient with chronic thromboembolic disease may ultimately be assessed as inoperable, their lesions may be amenable to BPA. . . an increasingly available intervention that can really help treat patients like this.

Irene Lang: I think it's a great quality control for the surgeon as well because, if the patient comes out of surgery with mean PA pressure of 32 and wants to go and exercise vigorously, you may want to go back and see the segments that have been missed.

Vic Tapson: How do most experienced surgeons feel about hemodynamics before endarterectomy?

William Auger: With my advocacy of CT, I hope I haven't left folks with the impression that a catheter-based PA gram has lost value in the evaluation process. In fact, I prefer having all 3 studies—perfusion imaging, CT, and pulmonary angiography—available, as they each provide different and potentially important information about your CTEPH patients.

I agree with the points made by Irene and Richard. As well, the pulmonary angiogram is often used for "mapping" in planning the surgical approach, especially to more distal disease. Especially with distal segmental level disease and subsegmental disease, surgeons are not necessarily seeing the chronic thrombotic lesions intraoperatively. However, using the available diagnostic studies as guides, such as a perfusion scan or pulmonary arteriogram, they'll start an endarterectomy plane in a normal appearing vessel to access the distal vessel lesions exhibited on these studies.

Vic Tapson: They have to be able to say, "Perhaps I can find a dissection plane here or something because this vessel was abnormal."

Richard Krasuski: Yes, that's a great point, Vic. Getting to that distal plug operatively can potentially improve the clinical outcomes and reduce the need for further intervention afterwards.

Gustavo Heresi: But for that, isn't the perfusion scan just as good or even

perhaps better than the digital subtraction angiogram?

William Auger: Yes, it may well be, Gustavo, but as you know, the remarkable surgeons that we all work with appreciate that perfusion imaging may not correlate well with the pulmonary vascular anatomy, and as such, the findings on pulmonary angiography can be preferred for surgical planning, particularly with distal vessel endarterectomies.

Irene Lang: Just one more comment: If there is uncertainty about the diagnosis of chronic thromboembolic pulmonary disease, we put an OCT (optical coherence tomography) down there, and that really shows you whether there are webs in veins, and I completely agree that PAGs have to be read in conjunction with the CT scan. It's very clear. Chronic lung disease can mimic CTEPH on PAG.

William Auger: You remember the old days in San Diego, right? Now you're using OCT. What did we use? We use angioscopy. Remember? It's the same thing.

Vic Tapson: A bronchoscope with a balloon on it.

William Auger: Pulmonary angioscopy, Irene. It was essentially a very long (120 cm) pediatric bronchoscopy with an inflatable balloon tied onto the tip. That's what we used.

Vic Tapson: Yes, you guys, I remember from 20 years ago going to San Diego, Peter Fedullo was doing a procedure on—did the PA gram on an 18-year-old kid with one lung disease, single-lung disease. I think this could be sarcoma. He went down with the angioscope. As soon as he saw that lesion, he said, "This is thromboembolic disease."

I'm so glad to see that. It was a fascinating study. I don't know now what CT would have shown on that, but that was an exciting moment for me, was a revelation about how good angioscopy was with someone that really knew what they were doing.

William Auger: Yes. It's a passé instrument simply because of the superiority of CT, and with other imaging modalities like OCT, we have the diagnostic capabilities comparable to what was provided with angioscopy. What originally motivated the San Diego group to pursue this approach was to address the problem of the occasional discrepancy between a markedly abnormal perfusion scan and a not-so-remarkable PA gram.

Irene Lang: I'd like to engage Rich in this conversation because, as soon as you become interventionally active, you want to see an angiogram. It's the same in coronary. We have very nice coronary CTs, maybe even further along in development and imaging power than the pulmonary artery CT scan. Best is angiogram for the precision of ballooning or stenting or any other intervention.

Richard Krasuski: The old expression is "dye don't lie," and it still holds today.

Gustavo Heresi: What do you guys think about this? One way we think about it in our group is, if we have a pretty abnormal VQ and a pretty striking CT and we know that patient is going to go to the operating room, we frequently don't do a digital subtraction angiogram, but I can totally see the value of doing that. However, we would never say that a patient is inoperable based on CT alone because I think the case that you were describing illustrates some of the challenges even for experienced people.

Sometimes even on CT scan, the absence of findings is what's important, if you don't see a vessel coming out where it is supposed to, but some of those findings are difficult to identify. In our hands, we will never stop at a CT for operability assessment. Then we definitely move on to a digital subtraction angiogram. Frequently, especially if the VQ scan is abnormal, the angiogram actually shows you particularly segmental disease in a way that the CT sometimes is less striking. Is that fair, or do you guys have a problem with that approach in general?

William Auger: As more experience is gained in CTEPH centers around the United States, your approach is the more common approach than just doing all 3 studies regardless of the situation.

Irene Lang: You all agree that there needs to be a right heart cath, right?

Gustavo Heresi: Of course.

William Auger: I think that the pulmonary hemodynamic information that you obtain with right heart catheterization is so important, not only for prognostic purposes, but if the hemodynamic profile is really bad, there is the opportunity to get patients to a "better clinical space" prior to surgery, and if you're going to do BPA, the hemodynamic results ensure that appropriate patients are on PH-targeted medical therapy before you do angioplasty.

Vic Tapson: You think there's a role for any other novel imaging? We diagnosed acute PE with intravascular ultrasound in the mid-'90s, but we usually don't need it. It hasn't caught on. We have great CT scans. In terms of chronic disease, we use intravascular ultrasound for chronic deep vein thrombosis cases to better assess them. Do you think there's a role for intravascular ultrasound or OCT or other imaging, or do you think we can do a good enough job without those in most cases?

Irene Lang: You mean in acute PE or in CTEPH?

Vic Tapson: In the CTEPH pre-op evaluation, with a VQ scan and CT angiogram, we do a pretty good job, but as you mentioned, Irene, some clinicians may use OCT. Are there particular cases where you're thinking OCT is beneficial?

Irene Lang: That's exceptional. It's really for those where you cannot make a decision like you described this 18-year-old. I think it remains a very rare thing.

William Auger: There may be a role at some point. There's nothing more uncomfortable when a surgeon comes out of the operating room and says they saw more disease than we did with

on our diagnostic studies. Thankfully, I don't think this happens a lot, but I think more aggressive imaging may be necessary for those questionable cases, such as patients with really abnormal perfusion scans, and a CT that's really not all that impressive. I also hear from our interventional colleagues that perform balloon angioplasties that some of the minor vessel irregularities on catheter-based pulmonary angiogram are sites where there's considerable and hemodynamically significant disease. These are sites where it was difficult to pass a wire, or there was a pressure gradient across the lesion. Is that not true, Rich?

Richard Krasuski: Even with angiography, we can still be fooled. Biplane angiography can help at times, but there still may be an area that doesn't necessarily look that diseased. You realize after poking at it for about 10 minutes with a wire that there is a pretty severe web lesion present. As you get more selective into the distal branches, your pictures get better and better. We find that the more proximal in the vessels you are when you do an angiogram, the more the contrast goes everywhere, and the harder it is to see something distal.

The more selective you get, the easier it is to define the anatomy. Before any transcatheter intervention, you really have to perform selective angiography.

William Auger: Is that the equivalent of the surgeon saying they're seeing more organized clot than we're seeing as diagnosticians?

Richard Krasuski: I totally agree with you, Bill. I think we always end up seeing more when we go in and take selective pictures. As you said, the V/Q starts the process, mainly for the purpose of exclusion of CTEPH. You do the V/Q, and if it's abnormal, you move on to the CT. Certainly, for any patient in whom I'm planning a transcatheter intervention, I'm always going to get selective angiograms. With selective angiography, I generally see more disease than I saw on the PA gram. It's not because I'm necessarily better at taking pictures; it's just that the contrast injection is focused into that one spot. There's a lot of overlap in blood vessels on PA grams, and lesions can be missed.

Vic Tapson: I think that gets back to the point Gustavo was making earlier about being careful about ruling out operability with the CT.

Richard Krasuski: True. As always, I'm learning so much from all of you during this session. One of my take-home pearls is how important each of these studies are and that probably we're cutting corners when we don't do a PA gram for a patient going to the operating room. Circling back and thinking about what Bill mentioned earlier, you hate to have that feeling that you've missed more distal disease. The surgeon needs to know this for their gameplan. Like you said, they're planning their attack based on how distally they're going to go for their resections based on the imaging. If there's a better way to provide that for them before the procedure, we should probably be doing this routinely.

William Auger: It's such a different world now. With effective BPA and other treatment approaches for patients with distal vessel CTEPH, a careful and complete evaluation is necessary. This has been an exciting decade for both diagnostic and therapeutic advances for our CTEPH patients. We can help more people now than we've ever been able to help in the past.

Irene Lang: I think we also help the surgeons. My surgeons benefited most from BPA, I think, because they saw pictures they'd never seen. Although they had seen the lesions, their intravascular look is not really capturing the lesions. They only see the vascular explant and not all lesions.

William Auger: Exactly, Irene. That's the thing that Stuart Jameson taught me early on: When they look in the pulmonary vascular bed, the appearance of organized thrombus is quite variable. It could be a straightforward web. It could be some dimpling along the wall. It could be what some people interpreted as a "plaque" or vascular roughening. It could be complete obstruction of a vessel. There's a number of findings consistent with organized clot from a surgical perspective.

Vic Tapson: I know I said it already, but we have to get these patients to experts. We have to get the fragmented acute PE care coordinated and organized. It's a huge problem. Then these patients can, when they have dyspnea at 3 months, 6 months, 1 year, get seen instead of waiting years to get to someone, get seen, and get help instead of being told they are overweight or deconditioned, or it's their asthma. I think it's critical to make sure we move ahead with better coordinated acute PE care.

William Auger: I couldn't agree with you more, Vic.

Vic Tapson: You have a heart attack; you go to a cardiologist. You have a stroke; you go to a neurologist. You have a PE; you go to a hematologist, maybe a pulmonologist, maybe a cardiologist, maybe a vascular medicine person, maybe a hospitalist, maybe a PCP or an internist. It is okay to be any of these, but it has to be an expert.

Gustavo Heresi: Yes, 100%.

Richard Krasuski: One thing I wanted to add and we've not discussed at all today is the role of echocardiography. It's readily available and so easy to get. It's noninvasive, and no radiation or contrast is necessary, which makes it so different from some of the other studies that we've been discussing today.

I think, for any patient that has had dyspnea for a while and has an abnormal echocardiogram, particularly a big right ventricle that's dysfunctional or an abnormal TAPSE or whatever estimate of RV function you routinely look at, in the context of a normal left heart, it certainly makes me focus on the pulmonary vasculature.

I also feel that follow-up echocardiography is incredibly important, particularly after any intervention.

I find that it's probably the most helpful in terms of knowing how patients

have responded because a lot of patients that are persistently dyspneic and have residual disease will continue to have abnormal echocardiograms. I'd love to hear how you utilize echo in these patients.

Vic Tapson: Quick point, Rich, would just be that you guys probably read Akhi Sista and Jeff Klein's meta-analysis on post PE syndrome, and they found that close to 20% of post-PE patients had abnormal RVs on echo. Echo is such a simple test to do. If it's abnormal, figure out why the RV is abnormal.

William Auger: That's correct, and as others have pointed out, the other important trigger point for clinicians to push forward with an evaluation is ongoing cardiovascular symptoms experienced by PE patients having undergone a reasonable course of antithrombotic treatment. Even if an echocardiogram in this setting is normal, that's where I think more advanced exercise assessments are warranted. An invasive or noninvasive CPET can provide an assessment of ventilatory efficiency and other abnormalities that might direct you toward pulmonary vascular disease or other conditions that might be causing ongoing cardiopulmonary symptoms.

Vic Tapson: I think that goes back to the RPVO issue. The fact that you can have RPVO without pulmonary hypertension and still have increased mortality, increased VTE recurrence rates, and increased dyspnea, that's something we need to explore more, I think.

Gustavo Heresi: In the last few minutes, I wanted to ask something that I think a lot of people struggle with. I think you mentioned earlier that the arrival of BPA has changed the field. There's a lot of patients now that we can help, but I also think that presents us diagnosticians with a more difficult task in terms of calling CTEPH. For example, now we can detect tiny little clots. We're getting really good at imaging, sometimes OCT. We use cone-beam CT, and then you have a clot here and there, and the patient has severe PH.

Is that CTEPH, or is that pulmonary arterial hypertension (PAH)? When do you use BPA? I think, before, those patients, you knew they were not surgical candidates. It didn't really matter that much. You will give medical therapy, but now with BPA, do you struggle with that? Is that something that you guys see in your practices? If you do, how do you make decisions as to when to go after lesions that you think you can balloon? The question is: Is this CTEPH really? Are we going to make patients better? I wonder if you guys have any thoughts on that and would love to hear what our interventionalists think, Irene and Richard as well.

Irene Lang: It's a good question. I stick to the rule that I do not diagnose CTEPH BPA able condition unless there have been 3 months of anticoagulation. That's the first rule that I've always tried to stick to. Sometimes, it's hard, but because there's people who find that there's no doubt this is CTEPH for other reasons, but there are some patients where I insist. Then there's, of course, patients with a disconnect between hemodynamic severity and the amount of vascular obstruction.

For those patients, I think it's very good to have an excellent hemodynamic evaluation to assess wedge correctly do an left ventricular end-diastolic pressure because some of those patients have severe left heart disease as well. Then go ahead and do a good PAG with maybe selective injection, and then take the time and put them on dual upfront medical treatment, or we use a lot of prostacyclin still for the very severe, for 1200 dynes, and a few defects.

Then the next step is take the angiograms, send it to Japan, and get Professor Matsubara's opinion. Usually what comes back is, "Please try." Then I have the patient after hemodynamics, angiogram, pretreated, and then I go in, and I do as many lesions as I can reach. Sometimes, it's an eye opener, and you find many lesions that you have missed before because, when you do a distal injection, you see so many things.

Other cases, not so many lesions, I stop. I say there is nothing more to do, but those are very few patients where really there is few lesions, and then you may think there's another reason for pulmonary hypertension. It's possible. Whenever there's a comorbidity of PAH like M Recklinghausen or some of these scary things, then I'm very cautious.

Richard Krasuski: That's so well said, Gustavo. I don't think I have much to add to what Irene already mentioned. That's just a cornucopia of everything you need to know about performing catheterization in patients with pulmonary hypertension. Diagnostically, it's so important to get that wedge pressure measured accurately. You have to start at step one because so many of these patients have left heart disease. Especially on my end, I see a lot of congenital heart patients. There's a big differential diagnosis that comes with PH in these patients.

You probably remember a patient with congenital heart disease and Eisenmenger physiology with calcified vessels that was initially sent to us at the Cleveland Clinic as a CTEPH case. Sometimes stepping back and making sure that you've made the diagnosis properly before you decide on interventional management is so important. I think Irene's point about an adequate period of anticoagulation before you approach any lesion you think could be CTEPH is so important, as well as initiating medical therapy for those patients that are pretty ill before bringing them to the lab for intervention.

From diagnosis all the way to intervention, there are so many steps there. Catheterization can be helpful at any of those. I think we all agree that CTEPH is still a catheterization hemodynamic diagnosis. Every CTEPH patient, just like every PH patient, needs a right heart catheterization, case closed. My takeaways: V/Q scanning for screening, CT for assessment of anatomy, PA gram to know how distal the disease extends out to, then right heart cath. Every single patient undergoing this evaluation should get one. Probably all 4 of these studies are necessary, even though the patient may end up with surgery, transcatheter intervention, or get treated medically (or some combination of each). I think, as interventionalists, sometimes we have to step back and realize that we're all diagnosticians

first, and we shouldn't be ballooning what [we] haven't first fully assessed and understood.

Richard Krasuski: There are a lot of important mimickers of CTEPH, as you mentioned. I think that CT is obviously an important way to exclude those. I want to go around one time last. Any closing statements from each of the panelists?

Vic Tapson: Let me say mine, Rich. I've said it twice already. I want to say this is a closing statement. We need to organize acute PE. We have great CTEPH experts out there, but we need to get the patients to them. Patients need to be seen for acute PE by experts in the hospital, get referred to experts when they go home. This is not a slam dunk internal medicine thing to take care of. You need to know the new studies. You need to know EINSTEIN CHOICE and AMPLIFY-Extension.

How do we extend anticoagulation? When can we drop the dose? When can we stop it? We've got data that shows chronic care with a half-dose rivaroxaban is better than aspirin alone. It's as safe and better. There's a lot of information. Acute PE needs to become unfragmented and focused so we can do a better job getting these CTEPH patients to experts.

William Auger: My final comment would be very similar. The fields of acute and chronic thromboembolic disease and the transition between these clinical spaces continue to evolve. If questions arise, reach out to your local experts in this field. As Irene and my colleagues on this call have pointed out, there's a lot of expertise out there that can help us interpret a diagnostic study or to make the right decision for our patients. It's just a phone call or a Zoom meeting away.

PH GRAND ROUNDS

COVID-19 Infection Causing Delayed Pulmonary Arterial Hypertension

Abhijit Raval, MD
Department of Pulmonary and Critical Care
AnMed Health
Anderson, SC

Nancy Edwards, MSIV
Medical University of South Carolina
Anderson, SC

Ravi Kant, MD
Department of Endocrinology, Diabetes and Metabolism
AnMed Health
Anderson, SC

Vipin Verma, MD
Department of Medicine
AnMed Health
Anderson, SC

McAnto Antony, MD
Department of Endocrinology, Diabetes and Metabolism
AnMed Health
Anderson, SC

Dhruv Raval, MD
SMIMER Medical College
Surat, India

INTRODUCTION

A42-year-old woman was readmitted to the hospital 6 weeks after being treated for COVID-19 infection. She presented in the emergency department with shortness of breath (SOB). Her SOB was progressively getting worse after being almost normal to baseline from the original infection.

Her clinical course during the previous 20 days of hospital admission during initial infection in April of 2020 was complicated by respiratory failure requiring noninvasive ventilatory support and treatment with azithromycin, hydroxychloroquine, dexamethasone, tocilizumab, and convalescent plasma therapy for COVID-19 infection. She had an echocardiogram which showed normal ejection fraction (EF) with no sign of pulmonary hypertension (PH) with normal right ventricular size (Figure 1). Her chest x-ray showed bilateral patchy infiltrates. Her chest computed tomography (CT), as shown in Figure 2, showed no pulmonary embolism with diffuse bilateral infiltrates. Pertinent laboratory values on admission included elevated d-dimer of 388 ng/mL (≤230 ng/mL) and elevated C-reactive protein of 32.25 mg/dL (0.0–0.9 mg/dL). Her beta natriuretic peptide (BNP) on initial admission was 324 pg/mL. Her CT chest angiogram was neg-

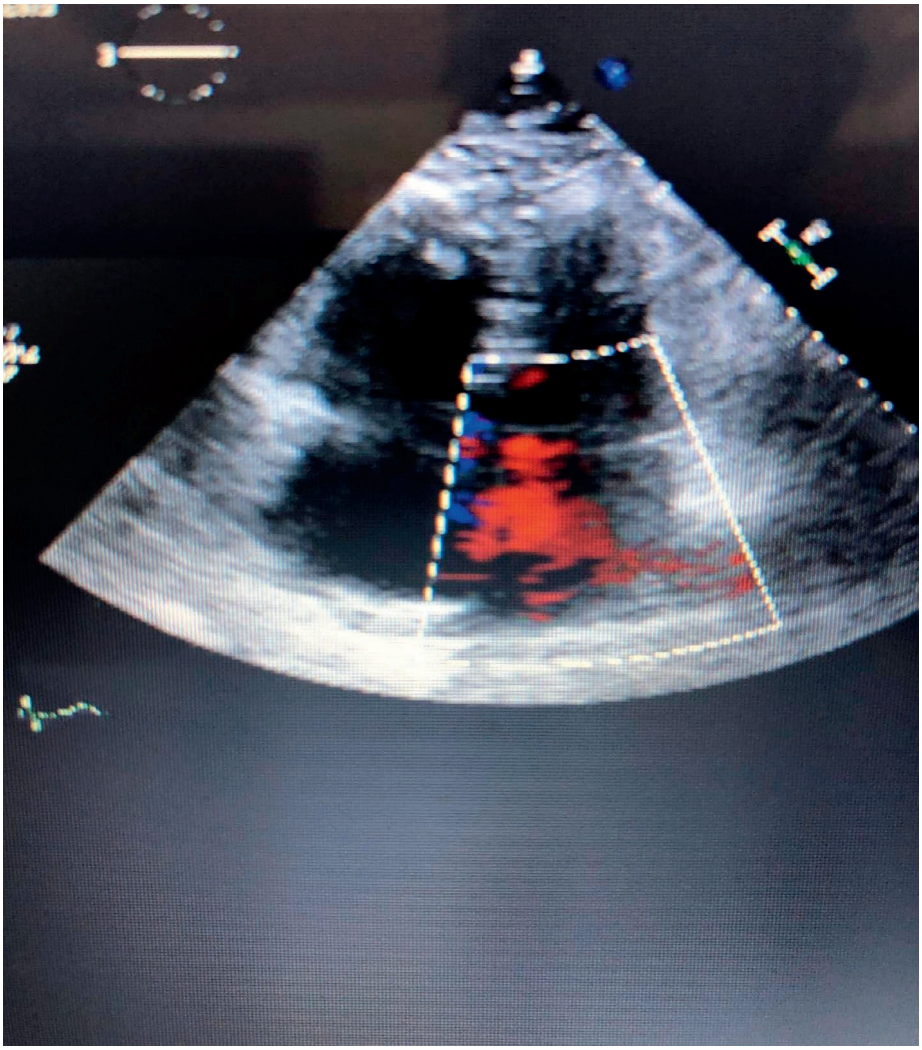

Figure 1: Echocardiogram.

Key Words—COVID-19 infection, pulmonary hypertension, cardiac complications
Correspondence: drravallung@gmail.com
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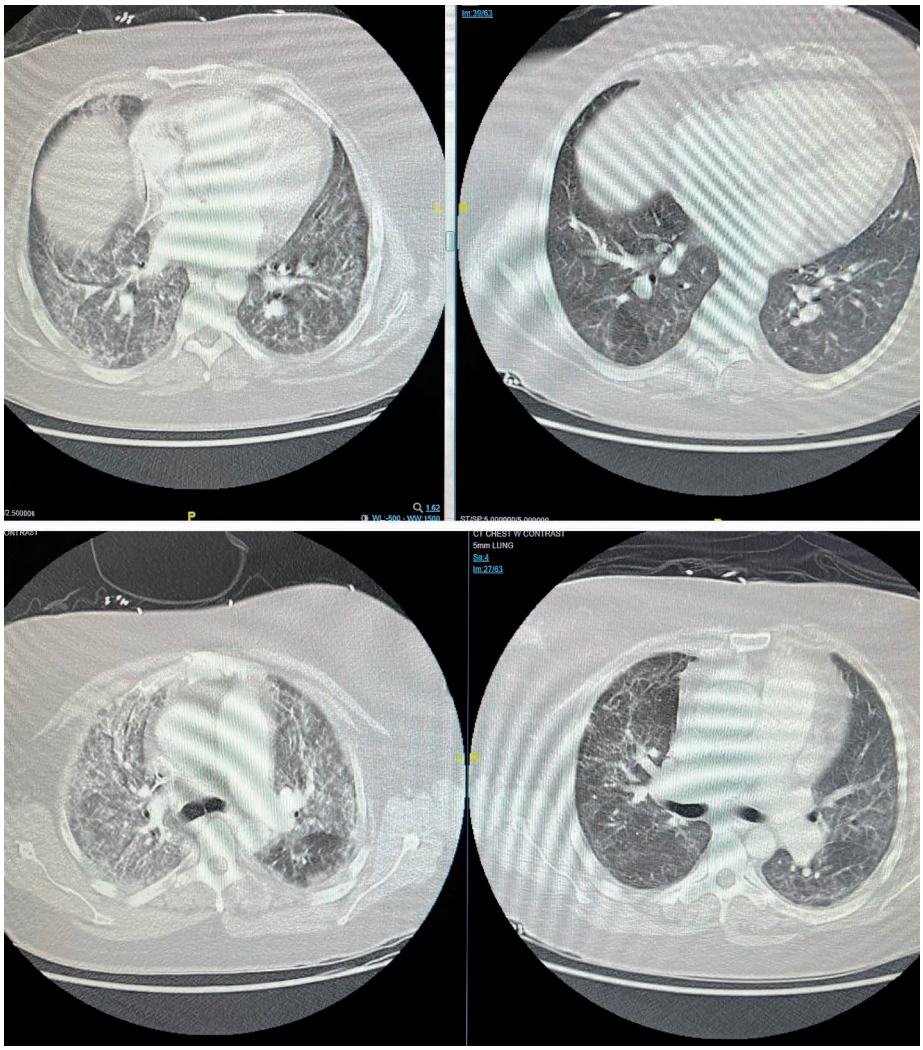

Figure 2: Computed tomography chest comparison, April 2020 to June 2020 (lower lobes).

Table 1. Patient Workup During 6 Week Span of COVID-19 Related Hospitalization

Test	Results
Computed tomography (CT) chest scan (June 2020)	Negative for pulmonary embolism and negative pulmonary venogram. Second CT scan showed improving infiltrates (Figure 2)
Echocardiogram (echo), 2 separate echos	First baseline echo April 3, 2020: Normal ejection fraction (EF), mild left ventricular hypertrophy, and normal right ventricular systolic function (RVSP).
	Second echo on June 17, 2020, in second admission: Normal EF, worsening right ventricular (RV) function with RVSP of 65. Noted mild RV enlargement and tricuspid annular plane systolic excursion of 1.9.
Pro-BNP (June 17, 2020)	1824 pg/mL (0–125 pg/mL)
Ventilation–perfusion scan (June 19, 2020)	Low probability scan with no sign of subsegmental emboli.
Venous duplex (June 18, 2020)	Negative for venous thromboembolism.
Cultures	All blood cultures, urine culture, and urine streptococcal antigen were negative.
Trend in pro-BNP (April 30, 2021)	324 pg/mL

ative for pulmonary embolism, showed bilateral diffuse infiltrates.

She was discharged home without any requirement for home oxygen therapy with a 10-day course of Decadron, and she had a negative COVID-19 reverse transcription polymerase chain reaction test 10 days after discharge and was able to resume her work.

Due to worsening SOB almost 6 weeks after her discharge from the original infection, given her recent diagnosis of COVID-19, cardiopulmonary and thromboembolic events were high on differential, causing rebound SOB. Bacterial pneumonia, recurrent COVID-19, and other pulmonary pathologies including PH were also considered in differential diagnosis. Further workup during the current hospitalization is described in Table 1.

Due to new onset of PH with significant change in her echocardiogram without any obvious etiology like thromboembolic disease and improving lung parenchymal changes, primary COVID-19-associated PH was considered as a primary differential diagnosis. She underwent right heart catheterization (RHC) which revealed moderate PH with high pulmonary vascular resistance (PVR) of 5 Wood units, right atrial pressure of 8 mmHg, pulmonary capillary wedge pressure (PCWP) of 9 mmHg, mean pulmonary arterial pressure of 34 mmHg, and cardiac output of 5 L/min (Figure 3). The patient was diagnosed with COVID-19-associated pulmonary artery hypertension (PAH), with high PVR and normal PCWP. She was started on single-agent phosphodiesterase-5 therapy, tadalafil. Follow-up chest x-ray showed improvement in infiltrates, and the pro-BNP levels also decreased significantly to 160 ng/mL with judicious diuresis. Oxygen support was completely weaned off, and the patient was discharged home after 6 days of hospitalization with a plan to have a follow-up echocardiogram in 3 months, which showed normal EF, no major tricuspid regurgitation, right ventricular systolic function of 42, and tricuspid annular plane systolic excursion of 21. Currently, the patient is off diuretic therapy and continuing with tadalafil

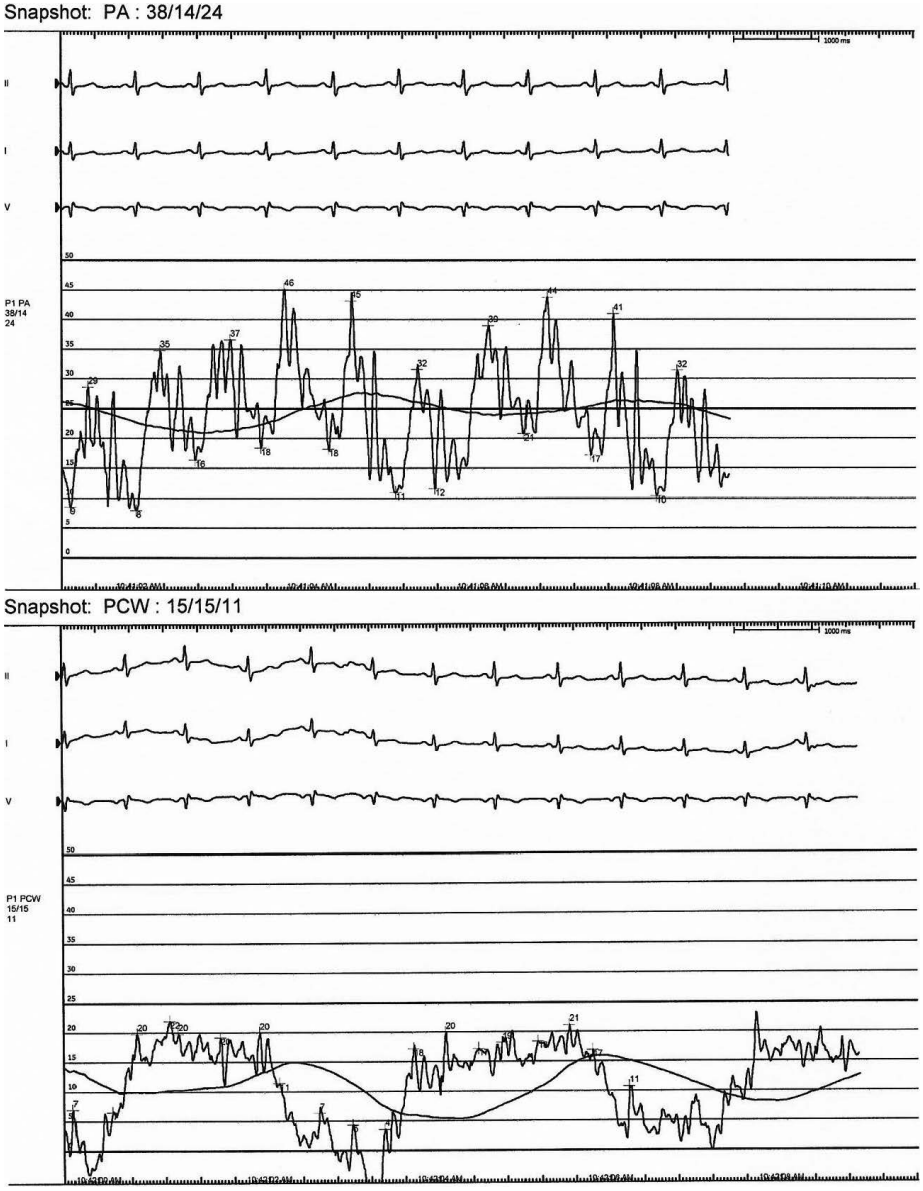

Figure 3: Right heart catheterization wave form.

with improvement in symptoms, and recent 6-minute walk test was 520 m.

DISCUSSION

Symptomatology of COVID-19 has been variable, with most patients predominantly presenting with pulmonary symptoms,[1] which include cough, SOB, and fatigue. Gastrointestinal symptoms have also been reported in COVID-19 patients.[2,3] COVID-19 is known to cause several cardiovascular sequelae, as outlined in Table 2. There have also been several reports about SARS-CoV-2 causing hypercoagulable conditions and contributing to several thrombotic complications.[4,5] The new onset of PH, diagnosed on RHC, associated with a history of COVID-19 infection in the absence of thromboembolic disease is unique as reported in our case. One of the mechanisms which explains the pathophysiology of SARS-CoV-2 is binding of the virus to the enzymatic domain of angiotensin converting enzyme 2 receptors located on various cell surfaces which include type 2 pneumocytes, perivascular pericytes, and cardiomyocytes, leading to entry of the virus into these cells and causing subsequent pulmonary and cardiovascular manifestations of the disease.[6] Another mechanism is the suppression of endothelial nitric oxide (NO) synthase with concomitant NO deficiency which hastens endothelial dysfunction, resulting in thrombotic and vascular disease.[7] In one case report, inhaled NO resulted in improved functional status and symptomatic relief in a patient with PAH and COVID-19.[8]

Table 2. Cardiovascular Complications of COVID-19 Infection

Complications
• Arrythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation)
• Cardiac injury
• Fulminant myocarditis
• Heart failure
• Pulmonary embolism
• Disseminated intravascular coagulation
• Acute coronary syndrome or myocardial infarction
• Transient diastolic dysfunction
• Transient cardiomegaly
• Subendocardial infarction
• Valvular vegetations

The World Health Organization (WHO) classifies PAH as Group I PH, and known disease states that are associated with PAH include connective tissue disease, human immunodeficiency virus, portal hypertension, congenital heart disease, schistosomiasis, and the use of methaphetamines.[9] Our case sheds light into the possibility that COVID-19 viral illness represents a disease state that can cause new onset PH with a precapillary component. There is always a possibility of developing PH in COVID-19-infected patients due to development of pulmonary parenchymal injury and significant hypoxia, which causes secondary pulmonary vasoconstriction, leading to PH. This classifies as WHO Group 3 PH associated mainly with hypoxic drive from primary lung pathology. Generally, in this situation, primary treatment of the underlying pulmonary condition and oxygen supplementation is the main course of action until recently, when inhaled prostacyclin has become available as a treatment alternative.

In a COVID-19 patient, it would be reasonable to link hypoxia-induced lung injury or hypercoagulability-induced embolic phenomenon to the development of PH. Interestingly, in our patient, neither hypoxia nor thromboembolic disease were identified during the workup, indicating COVID-19 infection

as a primary trigger for pulmonary vascular disease. Post-COVID-19 delayed vascular complications are becoming increasingly recognized.[10] Similarly, postacute COVID-19 syndrome or long-hauler syndrome, which comprises various symptoms that persist for many weeks to months after the initial infection, is also being increasingly recognized with SOB as the most common persistent symptom.[11] PH should be considered in the differential diagnosis in a post-COVID-19 patient presenting with a new onset of SOB.

TEACHING POINTS

1. Post-COVID-19 infection-related complications are an emerging problem.
2. PH should be considered in the differential diagnosis of SOB occurring in a patient with a history of COVID-19 infection.
3. PH should also be considered among a specific group of patients known as long haulers who have persistent post-COVID-19 symptoms which impact their quality of life.
4. Considering some mechanisms of development of PH, the role of NO modification-dependent pathways should be entertained as a treatment choice in COVID-19-induced PH.

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Silver Spring, MD 20910-4496