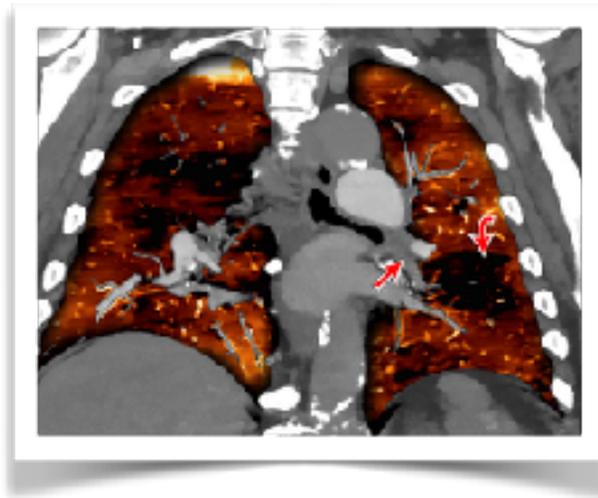


Chronic Thromboembolic Pulmonary Hypertension: An Update for 2018

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This is to acknowledge that Sonja Bartolome, M.D. has disclosed that she does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Specifically, she has done consulting and been on the speaker's bureaus for Actelion and Bayer pharmaceuticals. Dr. Bartolome will be discussing off-label drug uses in her presentation.

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Purpose and Overview:

The purpose of this session is to review the history of our understanding of CTEPH and its pathophysiology and natural history. The diagnostic evaluation of a patient with suspected CTEPH will be reviewed as will current concepts in the surgical, interventional and medical treatment of the disease.

Educational Objectives:

At the end of this lecture, participants will be able to:

- A. Define CTEPH and describe its natural history.
- B. Review the diagnostic evaluation of a patient with suspected CTEPH.
- C. Describe the approach to intervention or medical therapy for CTEPH.

Definition, Pathophysiology and Epidemiology

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a pre-capillary elevation in pulmonary vascular resistance (PVR) resulting from chronic, “scarred-in” thromboembolic material partially occluding the pulmonary arteries. This vascular obstruction, over time, results in failure of the right side of the heart and early mortality. CTEPH was first described in the early 1900s and was further characterized in an autopsy series from the Massachusetts General Hospital in 1931. On these postmortem examinations, it was noted that the affected patients had large pulmonary artery vascular obstruction, relatively normal pulmonary parenchyma distal to the vascular obstruction, and the presence of extensive bronchial collateral blood flow or “compensatory circulation.” [1] Still, it would take until the mid-20th century until imaging and cardiac catheterization techniques allowed the recognition of the diagnosis antemortem.

The pathobiology of the disease remains poorly understood, but clinical evidence suggests that the process most certainly begins with an acute pulmonary embolus. (Figure 1) Rather than resolving over time, the embolus develops into organized, fibrotic thromboembolic material which

adheres to and incorporates with the pulmonary artery wall. (Figure 2) These lesions tend to recanalize and may appear irregularly shaped, or like “bands” or “webs” inside the pulmonary artery. Histologic examination of the chronic thromboembolic material reveals intimal thickening composed of fibroblasts, collagen, lymphocytes and hemosiderin-laden macrophages. [2] Over time, this physical obstruction to the pulmonary vasculature raises the pulmonary vascular resistance and presents an increased workload to the right ventricle, which is geometrically,

Figure 1

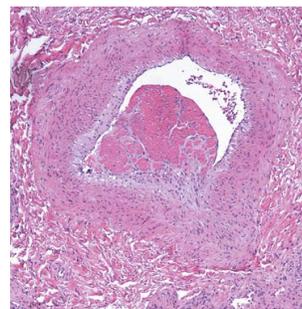
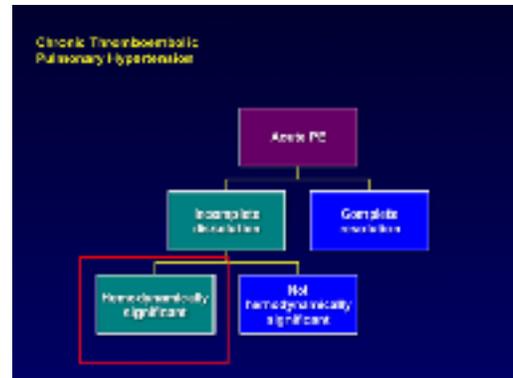


FIGURE 2 — An organized thrombus inside a small pulmonary artery. Endothelial cells line the surface of the thrombus and there is early ingrowth of the vascular wall into the thrombus. *N Engl J Med* 2011;364:351-60.

histologically and physiologically adapted for a low-pressure high volume circulation. When approximately half of the effective pulmonary vascular bed at rest is affected, the pulmonary circulation becomes a high resistance, lower flow system and right ventricular failure results in early death. It should also be noted that in some cases, especially with longstanding disease, small vessel pulmonary arteriopathy may develop in addition to the large vessel obstructive disease. This is postulated to possibly develop in response to shear stress in better perfused areas of lung or in response to activated inflammatory pathways which precipitate small vessel endothelial cell dysfunction. Regardless of the underlying cause, in these clinical cases, removal of the large vessel disease may not improve hemodynamics and outcomes are particularly poor. [3]

CTEPH is a rare complication of acute pulmonary embolism and can be a difficult diagnosis to make, therefore data on the true incidence and prevalence is lacking. Interrogation of insurance databases in the recent INFORM study indicated that the guideline recommended screening tests for CTEPH are underutilized even in symptomatic, at-risk patients, with a known history of previous acute pulmonary embolus.[4] Therefore, CTEPH is likely under-diagnosed. Still, pulmonary hypertension registry data indicates that CTEPH represents 19% of patients referred to pulmonary hypertension centers with an estimated incidence of 5 patients per million per year. [5] Recent registry data from Canada and Europe indicates that the median age at CTEPH diagnosis is 63 years and patients are 50.1% male, in contrast to idiopathic pulmonary arterial hypertension which is a predominantly (80%) female disease. 21% of the CTEPH population in this registry had significant cardiopulmonary comorbidities.

Without intervention, the natural history of CTEPH is progressive and outcomes are poor. Historical, untreated cohorts have reported 3-year survival of only 30%, and risk of death does appear to correlate with the degree of pulmonary hypertension. [6, 7]

Clinical Presentation and Evaluation

A history of venous thromboembolism in a patient with persistent dyspnea should spur a screening evaluation for CTEPH. 75% of patients with CTEPH have a history of prior known acute pulmonary embolus (note that 25% do not), and 56% of patients report a prior diagnosis of deep venous thrombosis. [5, 8] Only a few thrombophilias (elevated Factor VIII level, elevated circulating von-Willebrand factor, anticardiolipin antibody and antiphospholipid antibody) have been associated with CTEPH, whereas disorders such as Factor V leidin, Protein C or S deficiency and antithrombin III deficiency have not been associated. Other clinical factors such as the presence of hypothyroidism, malignancy, ventriculoatrial shunt for hydrocephaly, infected pacemaker or other vascular device, a history of splenectomy and the presence of a non-O blood group also are associated with a higher odds ratio of developing CTEPH in case-control studies. [8-11]

When evaluating a patient with a possible acute pulmonary embolus, if the clot is massive and/or recurrent, or if the echocardiogram shows an estimated pulmonary artery pressure >60 mm Hg or significant right ventricular dysfunction the patient is at higher risk for developing CTEPH. [5] Still, following the patient's symptoms over time is probably the best tool to help screen for CTEPH. (Table 1) Acute clot is primarily composed of erythrocytes and fibrin, which is degraded by plasmin into fibrin degradation products such as D-dimer. D-dimer levels persist for a week after an acute PE in 80% of patients, for 1 month in 40%, and for three months in only in 13%. [12] In general, an acute pulmonary embolus will fibrinolyse early in therapy, with the vast majority but not all, of the vascular obstruction resolving by the 3rd month. [13] (Figure 3). For these reasons, screening for possible CTEPH after pulmonary

embolus should be timed at least 3 months after the acute event. Because of the rarity of CTEPH after an acute PE, routine screening is not recommended.

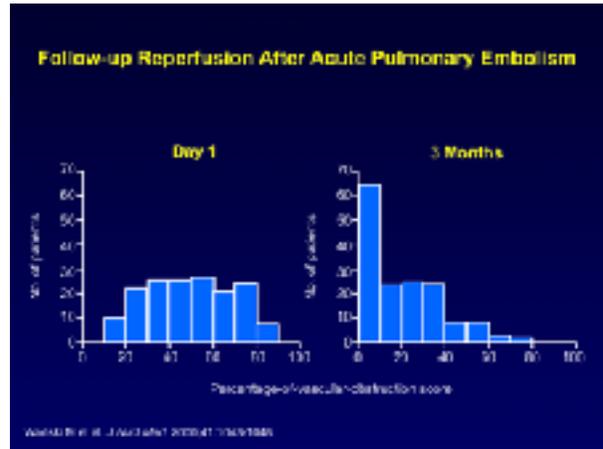
Rather, if the patient continues to report a significant exercise limitation after three

Table 1

Symptoms Indicative of CTEPH		
Exertional Dyspnea	Chest Pain	Edema
Fatigue	Hemoptysis	Hoarseness
Nonproductive Cough	Fatigue	Presyncope/ Syncope

months of appropriate anticoagulation or has physical exam signs of increased pulmonary artery pressure (increased pulmonic component of the second heart sound, tricuspid regurgitant murmur, etc) or signs of right ventricular dysfunction (such as jugular venous distention or lower extremity edema) the recommendation is to pursue a clinical evaluation.[14] The initial evaluation for CTEPH begins with a transthoracic echocardiogram (TTE) and Ventilation/Perfusion (V/Q) Scintigraphy. On TTE, an elevated estimated pulmonary artery systolic pressure and/or right ventricular hypertrophy, dilation or dysfunction should prompt further evaluation. Although CT angiography is now the diagnostic test of choice for acute pulmonary embolus, Ventilation/Perfusion scanning remains the preferred screening test for CTEPH. A retrospective study comparing V/Q scan and multi-detector CT revealed that V/Q scanning had a sensitivity and specificity of 97% and 95% for CTEPH, while CTPA had good specificity at 99% but only 51% sensitivity. [15] Recanalation through the chronic embolus probably limits detection in CT angiography, especially for an inexperienced reader. More recent work has suggested that in expert hands, and with modern CT technology, the sensitivity and specificity for CTEPH diagnosis is improved, and likely in the future it may be included in the screening recommendations. If the patient has a V/Q scan with continued mismatched perfusion abnormalities without concomitant ventilation abnormalities, and/or an abnormal echocardiogram then additional testing is recommended. (Figure 4)

Figure 3



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Figure 4— V/Q Scan and CT Angiogram from a patient with CTEPH

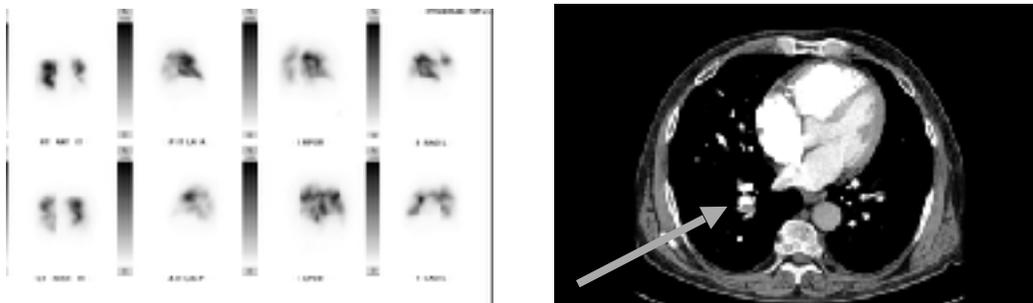


Figure 4 — The perfusion images from the V/Q scan to the left show multiple bilateral perfusion abnormalities consistent with CTEPH. The CT angiogram on the right shows a chronic eccentric clot adhering to the vessel wall (arrow). Additional CT findings supporting CTEPH are the large, hypertrophied right ventricle, flattened septum and enlarged right atrium.

If the V/Q scan and echocardiogram are suggestive of CTEPH, further required testing should include right heart catheterization and invasive bi-plane pulmonary angiography. This testing confirms the diagnosis, grades severity, and allows an evaluation for surgically accessible versus distal disease. On right heart catheterization, a mean pulmonary artery pressure ≥ 25 mmHg, with a normal left heart pressure (pulmonary artery occlusion pressure or left ventricular end diastolic pressure) confirms the hemodynamic diagnosis. Evidence of chronic thromboembolism on invasive pulmonary angiography includes “pouch-like” defects, intraluminal webs or bands, abrupt narrowing of pulmonary vessels, intraluminal irregularities and obstruction of pulmonary vessels. (Figure 5) In contrast, pulmonary arterial hypertension of other causes will appear like peripheral pruning and enlarged vasculature. Some conditions which “mimic” CTEPH on imaging include pulmonary artery sarcoma, pulmonary vasculitis, external vascular compression, fibrosing mediastinitis, pulmonary capillary hemangiomatosis and pulmonary veno-occlusive disease. [15] Because of this diagnostic challenge, review at an expert center experienced in CTEPH is recommended. Some CTEPH centers utilize additional imaging techniques such as magnetic resonance angiography, angiography, optical resonance imaging, spectral CT scanning with iodine perfusion images and intravascular ultrasound. [14] These modalities and their place in the diagnostic algorithm are under investigation.

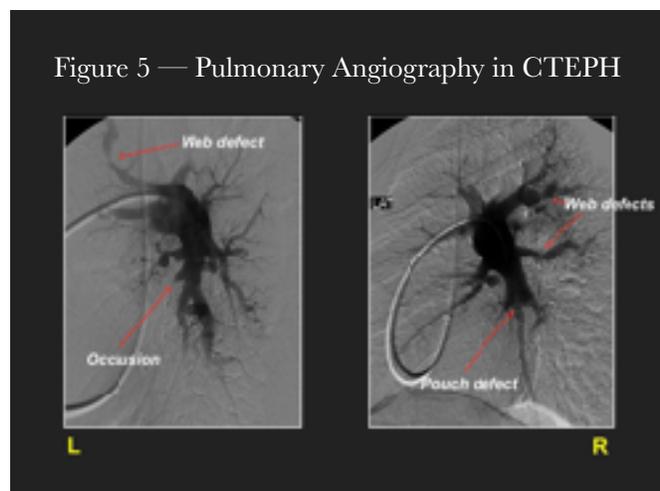
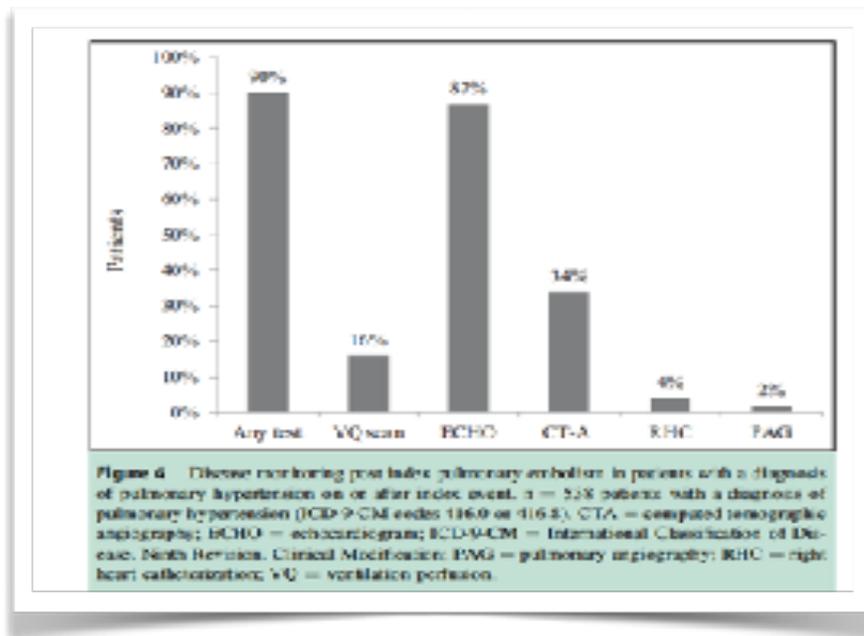


Figure 6 — Diagnostic Tests Performed by Physicians in a Cohort of Patients with a history of PE and and ICD 9 code for pulmonary hypertension.



Am J Med. 2016. 129: 978-985.

Despite academic societal diagnostic recommendations, the recent INFORM study reported that of over 7,000 people with a claim for acute pulmonary embolus between 2010 and 2011 who had long term follow up, 87% had a persistent symptom that was possibly related to pulmonary hypertension but only 61% of the symptomatic group underwent some kind of follow up testing. Further, 7.6% of patients had an ICD-9 code for pulmonary hypertension at 2 year follow-up. But, despite the diagnosis very few had completed any part of the recommended evaluation outside of an echocardiogram. [4] (Figure 6)

Surgical Treatment for CTEPH

The early autopsy work describing CTEPH as chronic thromboembolic material incorporated into the vessel wall, but with distal healthy lung that had been perfused by collateralization and the bronchial circulation allowed Dr. Ken Moser to postulate the procedure whereby the material might be surgically removed and allow normal pulmonary blood flow. Using his ideas, the first pulmonary thromboendarterectomy was performed at the University of California San Diego in 1970. UCSD would then pioneer the procedure, developing techniques and tools

that were adopted and contributed to by other centers across the world. Surgical mortality rates were high in the initial experience. In 1984, a report of 85 world-wide cases published an average mortality rate of 22%, but as high as 40% in some centers. [16] Still, pioneering efforts to improve the procedure continued given the dismal prognosis of untreated disease and the potential of an effective “cure” with successful surgery. Over the ensuing years with improvements in surgical technique, the utilization of deep hypothermia and cardiac arrest during the procedure, the development of a specialized myocardial “cooling jacket”, improvements in surgical instruments, and better understanding of appropriate diagnostics, patient selection and postoperative care outcomes have steadily improved with recent reports of surgical mortality of 2-4% in more experienced centers. [17]

The operation is done through a median sternotomy. Cardiopulmonary bypass is used and the patient is cooled to 18-20 ° Celsius. The main pulmonary artery on one side is then opened and the intima is isolated. Then, using specialized surgical instruments, the intimal layer and its adherent chronic clot are carefully dissected, and removed as far down the pulmonary circulation as possible, allowing the vessel to evert. After the initial part of the dissection, to achieve a bloodless field and allow good visualization, hypothermic cardiac arrest is utilized. This is done in 20 minute increments, with at least 10 minute recovery cardiopulmonary bypass and rewarming in between arrest periods, until dissection in both lungs is complete. The most crucial aspect of the procedure is to utilize the arrests periods to perform a complete endarterectomy, which will preclude the possibility of residual distal disease and pulmonary hypertension. (Figure 7) The Pulmonary Endarterectomy Cognitive (PEACOG) trial demonstrated that the cooling and arrest periods were both necessary for complete disease clearance and well-tolerated by the patients without resultant cognitive impairments. [18]

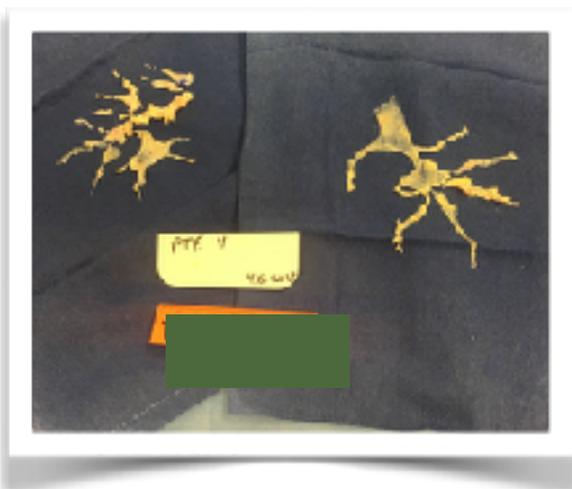


Figure 7 — Pulmonary Thromboendarterectomy Specimen from Recent Surgery at Clements University Hospital.

Postoperatively, approximately 25% of patients undergoing PTE surgery will develop reperfusion lung injury in the newly revascularized areas of lung. The likelihood of reperfusion lung injury increases with worsened preoperative hemodynamics including right atrial pressure >12 (1.99 OR) or a pulmonary vascular resistance >12.5 Wood Units (2.0 OR). Reperfusion lung injury increases morbidity, ICU time, ventilator days and length-of-stay postoperatively, but not mortality. [19] In the most severe cases with significant reperfusion lung injury and resultant hypoxia, veno-arterial ECMO has been utilized to support the patient while the inflammatory response heals.

Persistent pulmonary hypertension after pulmonary thromboendarterectomy carries the most significant risk of postoperative morbidity and mortality. In the international CTEPH registry, this occurred in 16.7% of patients and was associated with higher in-hospital and 1-year mortality. [5] Persistent pulmonary hypertension after PTE may be related to incomplete removal of distal disease by a less experienced surgical team or by concurrent small vessel pulmonary arteriopathy (the so-called 2-compartment pathological theory).

Surgical selection for PTE surgery requires a multidisciplinary and experienced team of radiologists, pulmonologists, cardiologists, anesthesiologists and thoracic surgeons to 1) evaluate the severity of the pulmonary hypertension, 2) use radiologic studies to clarify the location (distal versus proximal) of the disease and therefore surgical accessibility, 3) compare the hemodynamics to the degree of vascular obstruction to determine if they correlate, 4) analyze any comorbid conditions or complicating factors which could portend a poorer outcome and 5) weigh the risks versus benefits of the surgery for the individual patient. Long-term outcomes of successful PTE surgery remain good at 90% 3-year survival versus 70% for those that do not undergo surgery and are medically treated. Also, importantly, 90% of postoperative patients report functional class I or II symptoms at 1 year. [20]

Balloon Pulmonary Angioplasty

Despite the advances in PTE surgery, some patients are not operative candidates either due to very distal and surgically inaccessible disease, or because of comorbidities. In 2001, Feinstein et al, described a series of 18 CTEPH cases treated with balloon pulmonary angioplasty (BPA). [21] Promising hemodynamics effects were reported with the PVR decreasing from 43.0 ± 12.1 to 33.7 ± 10.2 mm Hg ($P=0.007$) and the patients' walk distance and functional class improved. However, the procedure had an unacceptable

complication rate with 11 patients developing reperfusion lung injury, 3 patients requiring mechanical ventilation, and one death. In the ensuing years, Japanese and Norwegian groups have independently developed improved techniques for BPA. Through these improved techniques they have reported acceptable safety with hemodynamic and symptomatic improvement.

(Figure 8) BPA is done in a series of sessions (average 4-6), 1-4 weeks apart, where small (2-3 mm) balloons are directed toward distal, diseased pulmonary vessels. Only a single area of lung is intervened upon at a time and the site is chosen carefully by an experienced team to avoid complications, while maximizing reperfusion to well ventilated areas of lung. Common complications include reperfusion injury, vessel injury, hemoptysis and more rarely, respiratory failure. Still, early experience suggests this procedure decreases pulmonary vascular resistance by 33-65% over time, improves right ventricular function, and improves patients' symptoms. [22, 23]. The most severe complication is pulmonary artery

Figure 8

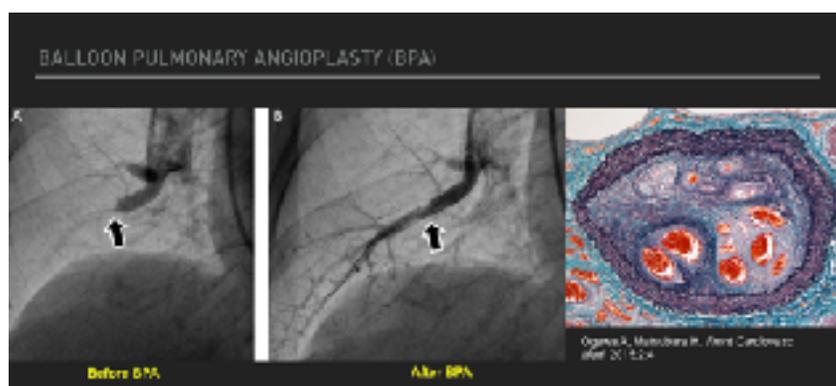


Table 1. Recent studies of balloon pulmonary angioplasty

	Sugimura et al. [15]	Katsuda et al. [11]	Mizoguchi et al. [13]	Andersen et al. [15]	Fukui et al. [14*]	Iwami et al. [13*]	Toniguchi et al. [16]
Pulmonary year	2012	2012	2012	2013	2014	2014	2014
n	12	22	68	30	20	48	26
Follow-up, years	1	0.5	2.2	4	4	2	1
Severe reperfusion necrosis, %	0	2	9	0	0	7	3.5
Pulmonary artery perforation, %	0	3.4	7	0	0	0.9	Not stated
Per-procedural mortality, %	0	3.4	1.5	10	0	1.5	3.4

perforation, which may lead to pulmonary hemorrhage and death. Death has been reported in one case in the Japanese series, was thought to be due to wire perforation and the technique has been altered since that time. The experience with this procedure is limited, but growing in the United States, with only a handful of centers currently performing BPAs and collecting data. Long-term data outside of Japan is lacking. Still, this is a promising and emerging option for those in whom the definitive operation is not possible.

Medical Therapy For CTEPH

Lifelong anticoagulation, oxygen if hypoxemic, and diuretics for right heart failure are recommended for patients with CTEPH. As discussed previously, the pathobiology of CTEPH is different from that of small vessel pulmonary hypertension. Still, because of limited treatment options, medications proven effective for PAH including prostacyclin therapy, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors have been used off-label by clinicians and reported in favorable case-reports and series. Still, until recently, none of these treatments have proven effective for CTEPH in larger phase III trials. The first successful large phase III medication study for CTEPH was the CHEST-1 trial published in 2013. This was a multicenter, randomized, placebo-controlled trial of the soluble guanylate cyclase stimulator riociguat. [24] Riociguat directly stimulates soluble guanylate cyclase to increase cyclic GMP production in the lung. The study enrolled 261 patients with inoperable CTEPH (inoperability was adjudicated by an expert committee) or persistent pulmonary hypertension after CTEPH surgery. Riociguat was titrated from 1 mg po tid to 2.5 mg po tid on a weekly basis, as tolerated. The primary end point was 6 minute walk distance at 12 weeks. The treatment group showed a 46 m improvement ($p < 0.001$). Secondary end points of pulmonary vascular resistance, NT-proBNP level and functional class also improved. Common side effects include headache, dizziness, dyspepsia and gastritis. Hemoptysis was reported in 2% of patients in the trial and hypotension in 9%. This pivotal trial led to the FDA approval of riociguat for inoperable or persistent postoperative CTEPH.

MERIT-1, a phase II, randomized placebo-controlled double trial of macitentan, (an oral endothelin receptor antagonist) was recently completed. It enrolled 80 patients with inoperable CTEPH. The primary endpoint was pulmonary vascular resistance at week 16, expressed as a percentage of baseline. At week 16 the patients in the treatment arm had a PVR 73% of baseline versus 87.2% in the treatment group. The most common adverse events were peripheral edema and anemia. This medication is not FDA approved for the treatment of inoperable CTEPH. [25]

Pulmonary Hypertension medication has been postulated as a possible way to “pre-treat” patients before pulmonary thromboendarterectomy surgery, perhaps lowering preoperative pulmonary vascular resistance and surgical risk. However, there is currently no convincing data to support this practice and medical treatment has been associated with delay in surgical treatment, possibly making it counterproductive. Clinical trials regarding this “induction” therapy before PTE surgery are ongoing.

Chronic Thromboembolic Disease (CTED)

Chronic Thromboembolic Disease (CTED) is a recently coined term addressing patients who have chronic thromboembolism on imaging but have normal resting hemodynamics. Whether CTED represents simply unresolved clot that will never progress to CTEPH or is an early point on the continuum of disease, is not well-defined and a controversial topic among experts. At many centers, patients with CTED and symptoms may then undergo exercise testing to look for exercised induced pulmonary hypertension or an increase in dead space ventilation as a cause of their symptoms. If this can be physiologically proven, some experts recommend intervention but data is lacking. A retrospective series of carefully chosen CTED patients who underwent PTE surgery reported improvements in symptoms and overall quality of life, without increased complications. [26] However, further work into the epidemiology and prognosis of CTED to understand the natural history of the disease and prospective clinical study is required before operative intervention can be recommended.

Conclusion

Chronic Thromboembolic Pulmonary Hypertension results from unresolved organized thrombotic material after an acute pulmonary embolus. Over time, the large vessel obstruction presents an increased workload to the right ventricle and patients die of right ventricular failure. Patients with persistent dyspnea or signs of right heart failure 3 months or more after their acute pulmonary embolus should be screened with ventilation/perfusion scintigraphy and transthoracic echocardiography. The definitive treatment for this disease is surgical pulmonary thromboendarterectomy, but to achieve the best outcomes this procedure needs to be performed at expert centers with multidisciplinary team experience. Patients who are poor operative candidates or with surgically inaccessible disease may be considered for balloon pulmonary angioplasty. For patients without more curative options, medication has been shown to improve exercise capacity. The field of CTEPH has been rapidly expanding over the last decade, leading to better patient outcomes and more treatment options.

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