

Key points

- Suspect CTEPH in patients with a history of PE and persistent dyspnea despite adequate anticoagulation.
- Obtain a V/Q scan as the initial screening test when CTEPH is suspected.
- An mPAP of 20 mm Hg or greater, mean PCWP of 15 mm Hg or less, and a PVR greater than 3 Wood units is diagnostic of pulmonary hypertension.
- Pulmonary angiography is the gold standard for establishing a CTEPH diagnosis.

months.⁶⁻⁸ CTEPH is a progressive pulmonary vascular disease that results from incompletely resolved PEs; the residual thrombotic material becomes organized and fibrotic in the pulmonary vasculature resulting in mechanical obstruction.^{2,7} This incomplete resolution results in a mechanical obstruction of the pulmonary arteries, which leads to an increase in pulmonary pressure and pulmonary vascular resistance, inducing right ventricular (RV) hypertrophy, subsequent right heart failure, and eventual death. Conversely, in about 25% of patients with CTEPH, a previous history of PE is not identified.^{1,2,6,9} The pathophysiology of CTEPH remains unclear and research is ongoing to better understand the contributing mechanisms, particularly the reason why certain patients have complete resolution of their PE and others progress to CTEPH. Patients with CTEPH may have abnormal fibrinolysis, which impairs clot lysis.⁸⁻¹⁰ However, a study by Halliday and colleagues does not support this theory, instead finding evidence of altered metabolism at the molecular level in endothelial and smooth muscle cells.¹⁰ Angiogenesis promotes thrombus resolution via the action of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which have been found to be deficient in patients with CTEPH.^{2,5} Inflammatory disorders also impair thrombus resolution.⁹ Several studies have revealed an accumulation of proteins involved in the complement cascade, immune defense, and inflammatory response in tissue specimens obtained from patients with CTEPH.^{5,10,11}

A substantial component of CTEPH development is pulmonary microvasculopathy (small-vessel disease), which contributes significantly to elevated PVR and disease progression.^{5,6} Following an obstruction of the proximal arteries by a PE, the pulmonary bloodflow is redistributed to more distal and smaller unobstructed vessels. This change in hemodynamics causes these smaller pulmonary vessels to become overperfused, subsequently increasing intravascular pressure.^{11,12} Over time, these small vessels start to show vascular wall remodeling, abnormal intimal thickening, and eccentric fibrosis, all of which alter the PVR. These pathologic changes are believed to occur in response to the high pressure and shear stress that the vessels are exposed to following the redistribution of pulmonary

bloodflow.^{6,7,11} The increase in PVR causes increased RV afterload, which is initially overcome by RV hypertrophy; however, unlike the left ventricle, the right ventricle is unable to sustain long-term pressure overload and becomes dilated, resulting in increased wall tension, subsequent increased myocardial oxygen demand, and reduced perfusion. RV contractility becomes compromised, which reduces the stroke volume, decreases pulmonary flow, and causes underfilling of the left ventricle. This leads to systemic hypotension, worsening RV coronary perfusion and further decompensating the right ventricle. This cascade of events causes RV failure and is ultimately the main cause of death in patients with CTEPH.^{7,11}

RISK FACTORS

Several risk factors are associated with an increased incidence of CTEPH, including recurrent venous thromboembolism, the presence of a large PE, an unprovoked PE, substantial perfusion defects on V/Q imaging, and a younger age.^{3,5,7,8} Certain hypercoagulable states are more evident in patients with CTEPH: antiphospholipid antibodies are found in about 20% of patients, lupus anticoagulant in about 10%, and elevated factor VIII levels in about 40%.^{8,9} Protein S deficiency, C deficiency, and factor V Leiden mutation have not been found to be more common in this population.^{5,6,8,9}

CLINICAL PRESENTATION

Suspect CTEPH in patients who present with a history of PE, persistent dyspnea despite adequate anticoagulation, and abnormal echocardiographic findings. Patients typically complain of progressive shortness of breath, fatigue, weakness, and exercise intolerance. In the later stages, symptoms of RV hypertrophy or failure often will be present. Some patients also may experience lightheadedness, presyncope, and/or syncope with activity.⁸

Physical examination reveals a sinus tachycardia, hypoxemia (related to increased dead-space ventilation), lower extremity edema, auscultation of a bruit over the peripheral lung fields (caused by turbulent bloodflow in a partially occluded pulmonary artery and found in about 30% of patients), hepatomegaly, jugular venous distension (JVD) secondary to decreased RV function, fixed split S₂ (closure of the aortic and pulmonic valves, delayed pulmonary valve closure due to delayed emptying of the right ventricle), loud P2 (pulmonary valve closure; normally closure of the aortic valve is louder since the pressure in the aorta is higher), tricuspid regurgitation (holosystolic murmur), RV heave, and ascites.^{8,9}

DIAGNOSIS AND ASSESSMENT

The preferred initial screening test is a V/Q scan, which is extremely sensitive at detecting mismatched ventilation perfusion defects (Figure 1). Findings will show normal ventilation corresponding to a wedge-shaped perfusion

defect.⁸ A normal V/Q scan effectively rules out CTEPH.^{1,2,8,9} An echocardiogram provides an estimation of the RV systolic pressure and is capable of detecting right atrial enlargement and RV hypertrophy. In patients with more advanced disease, evidence strongly suggestive of pulmonary hypertension can be seen on chest radiograph, such as pruning of blood vessels, enlargement of the right atrium and ventricle, and enlargement of the pulmonary artery.^{8,9,13}

A chest CT can identify multiple features associated with CTEPH. In addition to a dilated pulmonary artery, RV hypertrophy, and RV/atrial enlargement, patients will have evidence of vascular remodeling, which is more indicative of CTEPH. These findings include endoluminal filling defects, vascular webs (crisscrossing of fibrotic disease) (Figure 2), bands (circumferential constriction), severely stenosed pulmonary arteries, eccentric clots, partially recanalized clots, hypertrophied collateral bronchial arteries, and parenchymal mosaic perfusion patterns (dark areas corresponding to relatively decreased perfusion) (Figure 3).^{6,8,13} Nevertheless, CT underestimates the chronic thrombotic burden at the segmental and subsegmental levels.

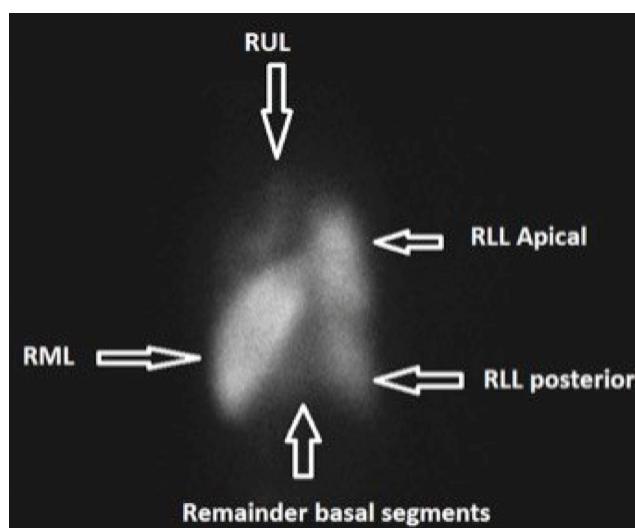
To confirm diagnosis, a more invasive modality is required. Pulmonary angiography is the gold standard for establishing a CTEPH diagnosis, assessing the location and extent of the disease, and determining surgical accessibility; this is especially important in cases of distal disease (Figure 4).^{2,8} Right heart catheterization should be used to assess patient hemodynamics and confirm pulmonary hypertension. Pulmonary arterial hypertension (PAH) is defined as an mPAP greater than 20 mm Hg at rest, a PCWP less than 15 mm Hg, and a PVR greater than 240 dynes/second/cm⁵ or greater than 3 Wood units.¹ PVR is an essential parameter used to determine prognosis.² Obtain a 6-minute walk test to assess the clinical severity of disease, which aids in the objective determination of patient exercise capacity and physical limitations.

MANAGEMENT

Clinicians must rapidly recognize patients at risk of developing CTEPH. The mnemonic SCAR (Suspect, based on echocardiogram and V/Q results; Confirm, via right heart catheterization and pulmonary angiogram; and Assess Risk, via patient hemodynamics, comorbidities, and surgeon/CTEPH team experience) has been proposed for the diagnosis and management of patients with CTEPH.¹⁴ These patients should be referred to a specialist for further management and coordination of care. CTEPH is a complex and challenging disease that is best managed by a dedicated multidisciplinary team.⁸ The goal of treatment is to restore bloodflow distribution in the pulmonary vasculature, reduce PVR, offload the right ventricle, and treat the small-vessel disease.^{7,9}

Pulmonary endarterectomy (Figure 5) is considered the treatment of choice; however, determining surgical candidacy is a multifaceted decision. Patients must have surgically accessible disease (proximal disease: main, lobar, and

FIGURE 1. V/Q scan of the right lung with corresponding pulmonary angiogram demonstrating the areas of decreased perfusion



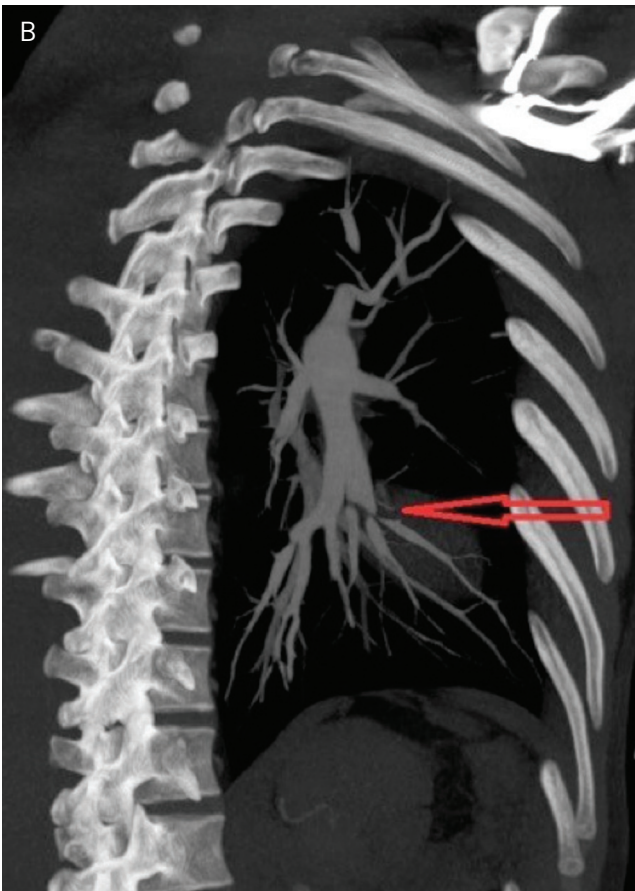


FIGURE 2. CTs showing web-like defects (thin, central filling defects, see arrows) in the right (A) and left (B) lungs

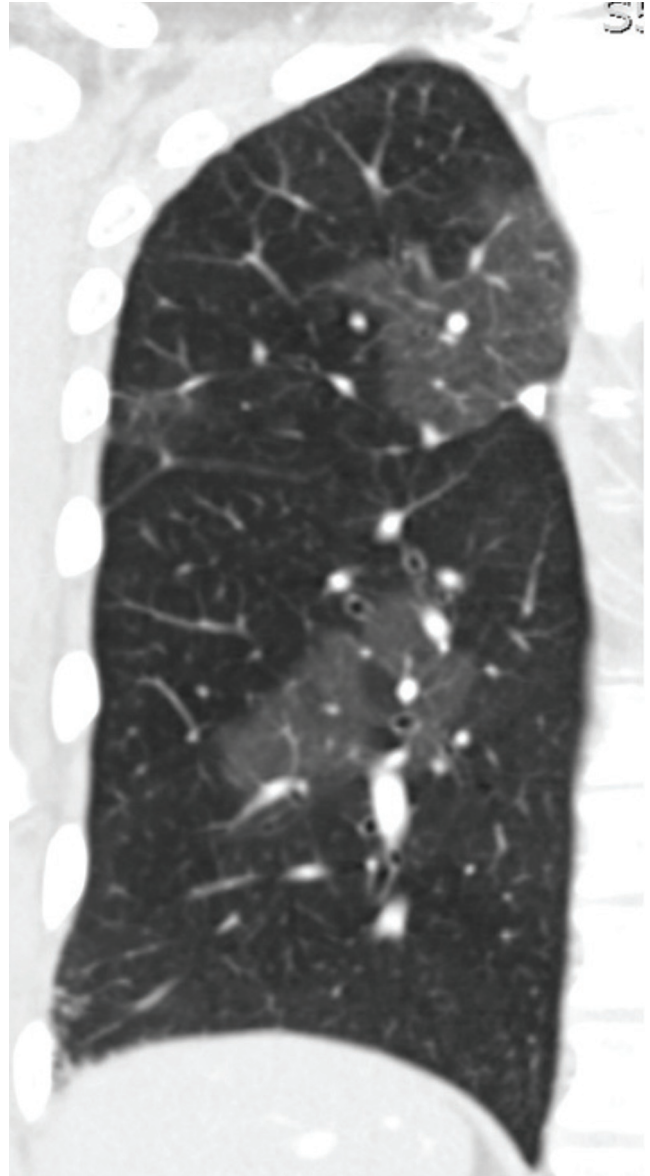


FIGURE 3. CT of the right lung showing a mosaic pattern, depicting areas of hypoperfusion and hyperperfusion

segmental arteries). The presence of comorbidities and the degree of hemodynamic impairment may render the patient a high-risk surgical candidate.^{8,9} About 63% of CTEPH patients are surgical candidates.¹⁵ Pulmonary endarterectomy immediately corrects the right ventricular function and hemodynamics, potentially curing CTEPH.^{2,8} Surgical complications can include dysrhythmias, pericardial or pleural effusion, atelectasis, wound infection, reperfusion lung injury, and death.^{8,10} Residual or recurrent pulmonary hypertension postpulmonary endarterectomy is estimated to affect 5% to 35% of patients.^{4,16} Recurrence may be caused by residual or recurrent thrombosis and pulmonary

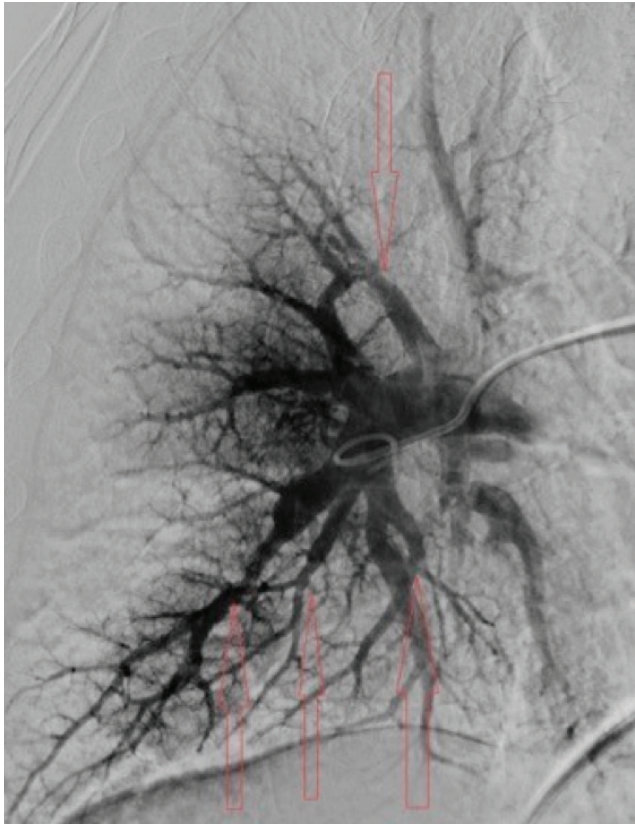


FIGURE 4. Pulmonary angiogram depicting abrupt vascular narrowing and occlusion in the basal branches (arrows)



FIGURE 5. Surgical specimens obtained from right and left pulmonary artery endarterectomy in a patient with CTEPH

Photo courtesy of Michael Zhen-Yu Tong, MD, Cleveland Clinic cardiothoracic surgery

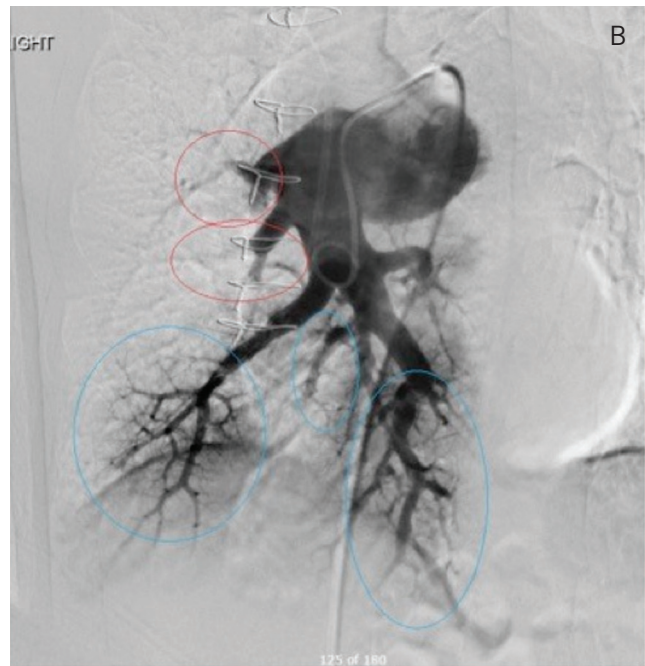
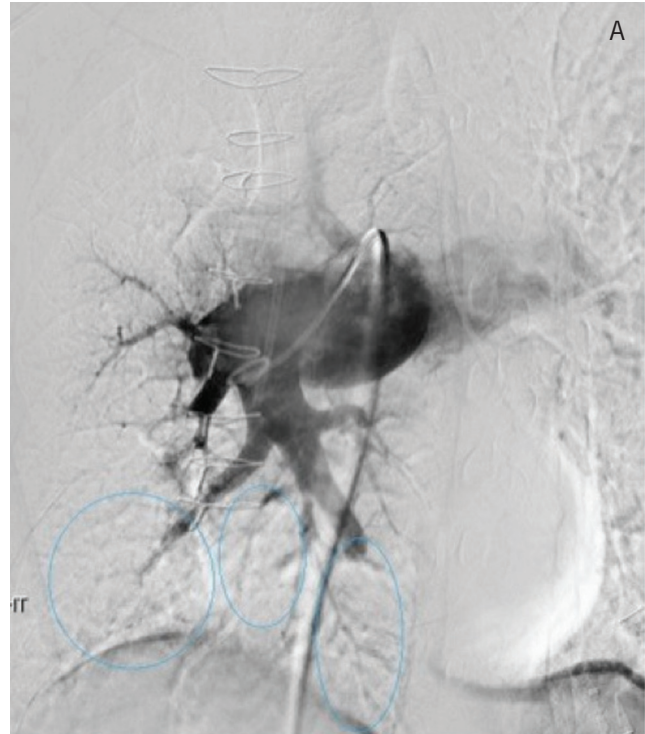


FIGURE 6. Pulmonary angiograms before balloon pulmonary angioplasty (A) and after (B), showing recanalization of the anterior/lateral and posterior basal branches in blue. Treatment planning for medial/lateral branches of the right middle lobe during subsequent sessions is shown in red.

microvasculopathy.¹¹ Reports on long-term outcomes are limited; however, survival rates are 75% to 90% at 5 years and 72% at 10 years.^{1,9,10}

Patients with CTEPH need lifelong anticoagulation even after pulmonary endarterectomy and resolution of pulmo-

nary hypertension, unless contraindicated, to prevent subsequent pulmonary arterial thrombosis and/or venous thromboembolism.⁹ Supportive medical therapy with diuretics and supplemental oxygen should be used when appropriate.²

Riociguat, a soluble guanylate cyclase, is the only medical therapy approved by the FDA for inoperable CTEPH or patients with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy. This drug causes vasorelaxation and dilation and has antiproliferative and antifibrotic effects.^{9,15} Riociguat is taken orally three times a day and titrated to a dose of 2.5 mg. Adverse reactions include hypotension, hemoptysis, and syncope.^{9,15} The drug has shown efficacy in improving hemodynamics and exercise capacity and can reduce PVR by up to 25%.^{4,15,16} It also improves N-terminal pro-B type natriuretic peptide (NT proBNP) levels and WHO functional class.^{9,14,15}

ANGIOPLASTY

Balloon pulmonary angioplasty is an option that can be offered to the subset of patients who are technically inoperable, carry a high surgical risk, or suffer from recurrent or persistent pulmonary hypertension following surgery.^{8,11,16} This catheter-based intervention uses different-sized balloons to dilate narrowed pulmonary vessels under fluoroscopic guidance.¹¹ Candidates have distal disease confined to the subsegmental pulmonary arteries. Angioplasty can offer improvements in symptoms and hemodynamics following revascularization of multiple diseased segments and regions, specifically, improved mPAP, PVR, and cardiac index.^{8,12} The results of angioplasty are promising; nevertheless, it should not replace pulmonary endarterectomy as the treatment of choice. All patients who are surgical candidates should undergo pulmonary endarterectomy because it is considered curative and provides the best long-term outcome.²

BALLOON PULMONARY ANGIOPLASTY

Balloon pulmonary angioplasty was first used to treat CTEPH in 1988, but was performed sporadically because of lethal complications and high mortality.¹¹ Over the past decade, improvements in technique and method have substantially improved the efficacy and safety of balloon pulmonary angioplasty.^{1,9} Sustained hemodynamic improvement has been demonstrated for up to 2 years after the procedure.

The approach to balloon pulmonary angioplasty may differ slightly depending on the medical facility. Patients are titrated to the recommended optimal dose of riociguat (2.5 mg three times a day) to allow for a reduction in pulmonary artery pressure, minimizing the risk of reperfusion injury before the first angioplasty session.^{15,16}

To reduce complications, angioplasty is performed using a staged method. The treatment course typically involves four to eight separate sessions spaced about 1 month apart. Vascular access is obtained percutaneously through the femoral vein and/or internal jugular vein. A microcatheter is directed to the area of occlusion, narrowing, or webbing and a balloon is used to dilate the vessel and break apart the webs or chronic clot, increasing perfusion to that area

of the lung and improving venous return (**Figure 6**). The areas with the largest perfusion defects are targeted for revascularization first. Right heart catheterization and hemodynamic measurements are performed before the first angioplasty procedure and then regularly to monitor the effect of treatment on cardiopulmonary hemodynamics.¹⁶ Postprocedure, patients are admitted and observed for at least 24 hours. They then are discharged from the hospital on an anticoagulation regimen, as long as no complications were encountered.

COMPLICATIONS

Complications of balloon pulmonary angioplasty include access site injury, wire- or balloon-induced pulmonary arterial injury (such as perforation, rupture, or dissection), hemoptysis, reperfusion pulmonary edema (incidents increase with the severity of pulmonary hypertension and BNP levels), renal injury secondary to contrast load, radiation exposure, and death.^{2,8,16}

CONCLUSION

CTEPH is much more prevalent than once thought. The pathophysiology is multifactorial, complex, and requires further research to fully understand the cause. When CTEPH is suspected, patients should be referred to an expert center for management. The persistent pulmonary pressure overload seen in CTEPH patients induces progressive RV remodeling, myocardial hypertrophy, and ventricular dilation.¹² Without treatment, the prognosis is poor. Patients with an mPAP greater than 40 mm Hg have a 5-year survival rate of 30%, but for those with an mPAP greater than 50 mm Hg, the 5-year survival rate decreases to 10%.¹¹ Although pulmonary endarterectomy is the treatment of choice, balloon pulmonary angioplasty is an option for patients with inoperable CTEPH, residual CTEPH post-pulmonary endarterectomy, or those with comorbidities that carry a high surgical risk. The disadvantage of balloon pulmonary angioplasty is that it requires multiple procedures to achieve beneficial results.¹⁴ The goal of treatment is to decrease the mean pulmonary arterial pressure and PVR and increase the cardiac index, thereby improving functional status and exercise capacity and decreasing home oxygen requirements. Studies have shown that pulmonary endarterectomy and balloon pulmonary angioplasty can improve right-sided heart failure symptoms, in addition to reversing RV remodeling.^{11,12} Long-term outcomes remain unknown and balloon pulmonary angioplasty continues to be an ongoing investigation.⁹ **JAAPA**

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