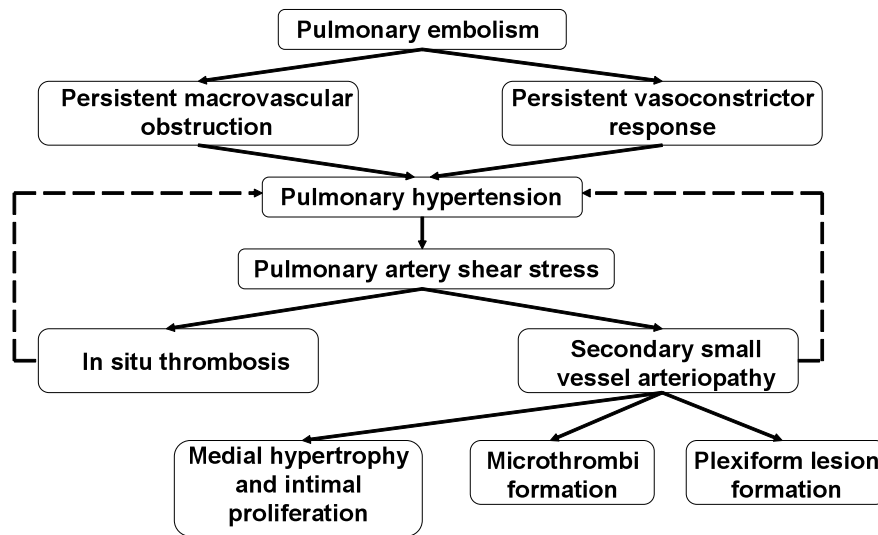


Chronic Thromboembolic Pulmonary Hypertension

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The Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008) distinguishes chronic thromboembolic pulmonary hypertension (CTEPH) from other forms of pulmonary hypertension [1]. CTEPH is defined as pulmonary artery systolic pressure greater than 30 mm Hg that persists 6 months after pulmonary embolism (PE). CTEPH used to be considered a rare complication but is now recognized to occur in 2-4% of patients after PE [2,3]. CTEPH is often overlooked because many patients lack a history of clinically overt PE [4]. Patients with CTEPH typically experience a “honeymoon” period following acute PE during which symptoms are absent despite the onset of pulmonary hypertension. CTEPH is usually detected when pulmonary hypertension worsens and causes dyspnea, hypoxemia, and right ventricular (RV) dysfunction. Death frequently results from progressive pulmonary hypertension culminating in RV failure. The risk of developing CTEPH is increased by PE-specific factors, certain chronic medical conditions, thrombophilia, and genetic predisposition [2,3,5-9].

In 1971, Drs. Nina Braunwald and Kenneth Moser discovered a paradox when they examined the histopathology of pulmonary thromboendarterectomy specimens from patients with CTEPH. They found marked small vessel abnormalities that appeared similar to idiopathic pulmonary arterial hypertension distal to patent pulmonary arterial segments, whereas tissue distal to occluded segments appeared to be normal. The small vessel arteriopathy is characterized by medial hypertrophy and intimal proliferation, microvascular thrombosis, and plexiform lesion formation. CTEPH results in persistent macrovascular obstruction and vasoconstriction. Chronic staphylococcal infection, abnormal sialylation of fibrinogen γ -chains, and abnormal fragmentation of fibrinogen have been proposed as mechanisms for ineffective fibrinolysis [10-12]. Neurohumoral factors, including endothelin-1, play a central role in CTEPH as potent vasoconstrictors as well as triggers of microvascular changes [13]. Reductions in cross-sectional area of the pulmonary arteries due to thrombosis and vasoconstriction cause further abnormal vascular remodeling. In situ thrombosis may also accompany the secondary small vessel arteriopathy. A combination of persistent macrovascular obstruction, small vessel arteriopathy, and vasoconstriction results in pulmonary hypertension and RV pressure overload that exceeds what is expected based on the degree of pulmonary artery macrovascular obstruction.

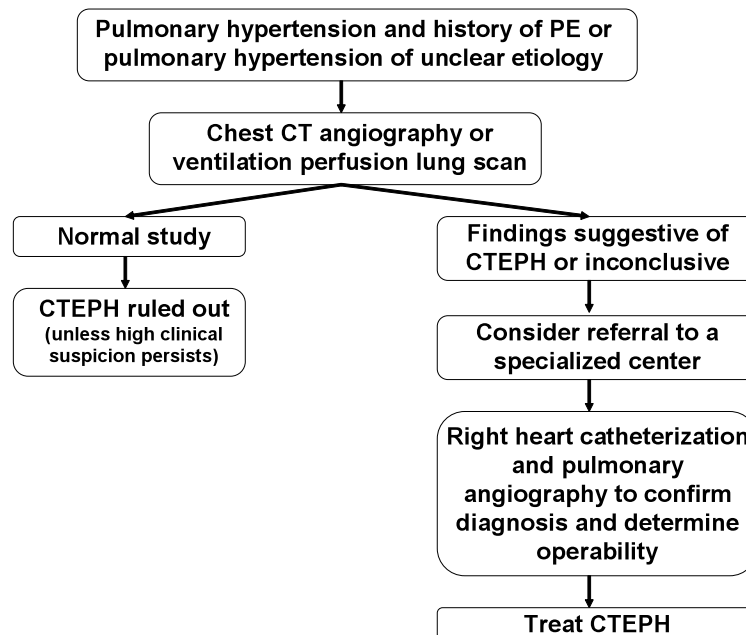


Exercise intolerance, fatigue, and dyspnea comprise the most commonly reported symptoms. Subsequently, patients may report chest discomfort, syncope, hemoptysis, lightheadedness, or peripheral leg edema. Diagnostic delays are common because many patients do not provide a history of PE. Therefore, symptoms are often attributed to coronary artery disease, cardiomyopathy, pulmonary disease, or physical deconditioning. Initial physical examination findings may include a reduction in the splitting of the second heart sound (S2), accentuation of the sound of pulmonic closure (P2), and a palpable RV heave. Subsequent findings correspond to declining RV function and include jugular venous distension, fixed splitting of S2, a right-sided 3rd heart sound (S3), tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema. Subtle bruits may be auscultated over the peripheral lung fields and arise from turbulent flow through partially obstructed pulmonary arteries. Six-minute walk distance may be a useful component of the evaluation because it reflects the clinical and hemodynamic severity of disease [14].

Patients with symptoms and signs of pulmonary hypertension and a clinical history compatible with PE or pulmonary hypertension of unexplained etiology should be evaluated for CTEPH with imaging tests. Echocardiography is sensitive for the detection of pulmonary hypertension and RV dysfunction but is not specific for the diagnosis of CTEPH. Routine echocardiographic evaluation 6 weeks after acute PE has been proposed to identify patients at risk for CTEPH [15]. Ventilation perfusion lung scanning is often useful to differentiate CTEPH from other causes of pulmonary hypertension. Ventilation perfusion lung scanning does not anatomically localize the extent of disease and cannot determine surgical accessibility [16]. Chest computed tomography (CT) angiography may complement the information obtained from ventilation-perfusion lung scanning by providing additional data regarding

anatomical localization and surgical accessibility [17]. Magnetic resonance (MR) angiography is an alternative imaging modality that remains unproven for the diagnosis of CTEPH, but has been a major disappointment for diagnosis of acute PE [18].

We prefer CT angiography as the initial test of choice because expertise in the interpretation of ventilation-perfusion lung scanning is waning. If either CT angiography or ventilation-perfusion lung scanning is inconclusive for CTEPH or if surgery is being considered, right heart catheterization and invasive pulmonary angiography are typically performed to confirm the diagnosis and further define the anatomy. Centers of excellence in the care of patients with CTEPH continue to utilize right heart catheterization and invasive pulmonary angiography as the gold standard for establishing the diagnosis and assessing operability. Right heart catheterization performed in conjunction with invasive pulmonary angiography quantifies the degree of pulmonary hypertension and can be used to assess responsiveness to vasodilator therapy. A reduction in pulmonary artery pressure after administration of the vasodilator, inhaled nitric oxide, may help to predict improved long-term survival in patients with CTEPH who undergo pulmonary thromboendarterectomy [19]. Patients with pulmonary hypertension and findings of PE on CT or ventilation-perfusion lung scanning or those with unexplained elevations in pulmonary artery systolic pressure should be referred to specialized centers. Additional testing such as right heart catheterization with vasodilator challenge and pulmonary angiography to establish the diagnosis of CTEPH and to determine suitability for pulmonary thromboendarterectomy is best performed at centers experienced in such procedures.



Pulmonary thromboendarterectomy is the most effective therapy for CTEPH [20]. Successful surgery removes obstructive chronic thromboembolic material and markedly improves the hemodynamic parameters of pulmonary artery pressure, pulmonary vascular resistance, and cardiac output. Improved hemodynamics reverse RV remodeling with return of RV function toward normal [21,22]. Measures of functional capacity, such as New York Heart Association class, markedly improve [22,23].

Pulmonary thromboendarterectomy is performed under cardiopulmonary bypass with intermittent circulatory arrest to permit dissection from the main pulmonary arteries to the subsegmental branches. Patients with symptomatic CTEPH, surgically accessible disease, and an acceptable peri-operative risk should be referred for pulmonary thromboendarterectomy. Preoperative predictors of favorable outcomes include a pulmonary vascular resistance of less than 1,200 dynes second/cm⁵ and absence of major comorbid conditions [24]. A postoperative pulmonary vascular resistance that declines at least 50% to a value of less than 500 dynes second/cm⁵ is also correlated with a favorable response to surgery [20]. Patients with symptomatic CTEPH in whom pulmonary thromboendarterectomy is being considered should be referred to specialized centers with experience in both the assessment of potential surgical candidates and performance of the surgery. Contraindications to pulmonary thromboendarterectomy include small vessel disease as suggested by a pulmonary vascular resistance out of proportion to the degree of obstruction, expected postoperative reduction in pulmonary vascular resistance of less than 50%, and prohibitive peri-operative risk. Thirty-day mortality ranges from less than 5% in the most experienced centers to 10% elsewhere [22]. The two most common postoperative complications are pulmonary artery steal syndrome, which occurs when blood flow is redistributed from previously well-perfused segments to newly opened ones, and reperfusion pulmonary edema. Residual pulmonary hypertension, which may result from incomplete endarterectomy, inaccessible chronic thromboemboli, or small vessel arteriopathy is an important predictor of late postoperative adverse events [22].

Balloon pulmonary angioplasty offers an alternative therapy for selected patients who have inoperable disease due to distal surgically inaccessible disease or persistent or recurrent pulmonary hypertension after thromboendarterectomy [25]. However, experience is very limited, and the procedure is rarely performed.

Anticoagulation is prescribed in most patients with CTEPH, although randomized clinical trial data to support this widespread practice are lacking. The rationale is to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism. In patients who had unprovoked or idiopathic PE, indefinite duration anticoagulation reduces the risk of recurrent venous thromboembolism [26,27].

Up to 50% of patients with CTEPH are inoperable and 10% of post-thromboendarterectomy patients suffer persistent or recurrent pulmonary hypertension [28]. Consequently, pulmonary vasodilators are being prescribed

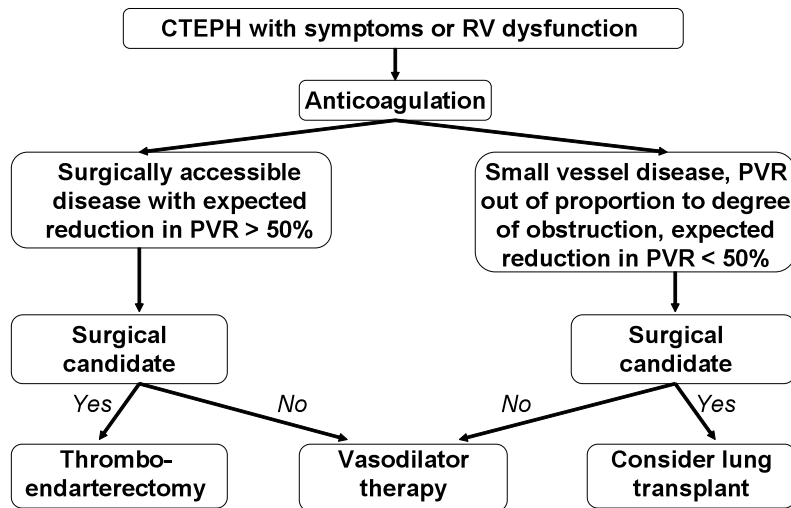
with increasing frequency among patients with CTEPH. Advanced medical therapies include the endothelin receptor antagonist, bosentan, the phosphodiesterase inhibitor, sildenafil, and prostacyclin analogues, such as epoprostenol or treprostinil. The underlying principle for this practice is that CTEPH vessel morphology closely resembles that of idiopathic pulmonary arterial hypertension. Patients with CTEPH show acute vasoreactivity to inhaled pulmonary vasodilators, suggesting at least some degree of shared pathophysiology [29].

The Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension (BENEFiT) Trial randomized 157 patients to 16 weeks of therapy with the endothelin receptor antagonist bosentan versus placebo [30]. Significant improvements in hemodynamic parameters of PVR and cardiac index as well as levels of NT-proBNP were noted. Sustained improvements in 6-minute walk distance have been observed in earlier non-randomized studies [31,32].

In an open-label trial, 104 patients with inoperable CTEPH were treated with sildenafil 50 mg 3x/day [33]. In follow-up, significant improvements in PVR, cardiac index, 6-minute walk distance, and WHO functional class were observed. A small randomized controlled trial subsequently demonstrated similar improvements in hemodynamic and functional parameters [34].

An open-label trial investigated the use of treprostinil in 25 patients with inoperable CTEPH [35]. Patients were required to have WHO functional class \geq 3, 6-minute walk distance \leq 360 m, and at least 1 admission for RV failure in the previous 6 months. Significant improvements in 6-minute walk distance, WHO functional class, cardiac output, and PVR were noted. Survival at 1, 2, 3, and 5 years was significantly increased in patients receiving treprostinil compared with disease severity-matched controls.

Newer agents that have shown promise in the treatment of pulmonary arterial hypertension include endothelin receptor antagonists, sitaxsentan and ambrisentan, and the phosphodiesterase inhibitor tadalafil. Inhaled treprostinil and oral prostacyclin analogues have also been evaluated in patients with severe pulmonary hypertension, including those with CTEPH. A novel soluble guanylate cyclase stimulator, riociguat, has been evaluated in CTEPH and has shown promise.



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