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# Chronic pulmonary thromboembolic disease

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## ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH), defined as precapillary pulmonary hypertension (PH) with right heart catheterization and imaging consistent with chronic thromboembolism, is a long-term complication of pulmonary embolism (PE). CTEPH defines symptomatic patients with maladaptive perfusion disorders after at least 3 months of therapeutic anticoagulation. In this setting, pulmonary hypertension results from extensive pulmonary artery (PA) obstruction by only organized fibrotic clots and may also be present as micro vasculopathy. Echocardiographic (ECHO) examination to determine a pulmonary surgical operation if the patient complains of anticipation and/or the risk for CTEPH is widely demonstrated (prior PE episodes, existing imaging size as index event suggestive of CTEPH, key features such as hypothyroidism and cancer), It is the preferred recognition method because of its availability and the high data value and amount of data. Patients diagnosed with CTEPH or with a strong suspicion of CTEPH should be referred to a specialist pulmonary cardiovascular clinic for further multidisciplinary diagnosis and treatment, such as pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), and/or targeted pulmonary medical therapy. In recent years, significant progress has been made in evaluating patients with sequelae after a pulmonary embolism, confirming clinical, biochemical, and hemodynamic criteria. Further work is needed to elucidate and develop appropriate standing protocols to support limited purposes and ongoing archives to ensure physical care capacity and life security.

**Keywords**: Pulmonary embolism, chronic thromboembolism, pulmonary hypertension

## INTRODUCTION

According to the International Thrombosis Society and International Hemostasis Society (ISTH) common data results, the term "post-pulmonary embolism (post-PE) syndrome" includes the presence of any of the following after 3 months of adequate therapeutic anticoagulation: 1. Post-PE functional limitation 2. Post-PE heart failure 3. Chronic without pulmonary hypertension thromboembolic lung disease and 4. Chronic thromboembolic pulmonary hypertension (CTEPH).[1,2]

Chronic thromboembolic pulmonary respiration involves patients with a progressive pulmonary vein with chronic obstruction by organized thrombi that limits the main pulmonary arteries. Furthermore, It has classified in Group 4 at the World Symposium on Pulmonary Hypertension (WSPH), and at rest, in right heart catheterization, hemodynamically mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary vascular resistance (PVR) ≥3 Wood's units (WU), and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg.[3]

## EPIDEMIOLOGY

Chronic thromboembolic pulmonary hypertension is a rare disease and therefore likely to be underdiagnosed. The annual incidence rates of confirmed CTEPH have been found 0.9, 4.0, and 5 per million adults in the western world.[4] In the follow-up after acute pulmonary embolism (FOCUS) study, 16 (1.6%) patients were diagnosed with CTEPH; the estimated two-year cumulative incidence was 2.3% (1.2-4.4%).[5] Multicenter US and International CTEPH registries in Canada and Europe reported a high proportion of CTEPH patients with a prior history of acute PE (87.9% and 75%, respectively). The median age at presentation was 59-63 years, and both sexes were affected in equal numbers.[6]

## PATHOPHYSIOLOGY

Chronic thromboembolic pulmonary hypertension/ Chronic thromboembolic disease (CTEH) is the hallmark of fibrotic transformation of the pulmonary artery thrombus, leading to mechanical occlusion of the pulmonary arteries. Unlike acute PE, there is no linear relationship between the degree of mechanical obstruction and hemodynamics, probably due to concomitant small vessel pulmonary arteriopathy in approximately 40% of cases. Moreover, there is no relationship between perfusion defects and oxygen consumption at peak exercise (VO2max).[7] Pulmonary arterial hypertension (PAH)-specific mutations have not been identified in CTEPH, and a relationship with ADAMTS13 has been found.[8] Lupus anticoagulant, antiphospholipid antibodies, high plasma concentrations of factor VIII,

increased von Willebrand factor, abnormal fibrinolysis and dysfibrinogenemia are associated with CTEPH. Previous splenectomy, history of infected ventriculoatrial shunts and indwelling catheters and leads to the treatment of hydrocephalus, thyroid replacement therapy, cancer and chronic inflammatory disorders such as osteomyelitis and inflammatory bowel disease have a negative impact on CTEPH and survival. Endothelial dysfunction, unbalanced fibrinolysis, dysfunctional angiogenesis, and immunological mechanisms have been associated with disease mechanisms underlying CTEPH.[9]

Organized thromboembolic occlusion in the large pulmonary arteries and secondary small vessel arteriopathy in non-occluded areas are the two main mechanisms of increased pulmonary vascular resistance (PVR) in CTEPH, progression of PH, and development of right heart failure. Distal flow obstruction from fibrotic clots increases endothelial heart stress by promoting redistribution of blood to unaffected vessels, alters vascular remodeling, and eventually causes secondary micro vasculopathy similar to pulmonary arterial hypertension (PAH). Histologically, plexiform lesions and arterial eccentric intimal fibrosis can be seen. Small vessel disease can lead to a discrepancy between PVR and the degree of mechanical occlusion on imaging. It may be responsible for residual PH following endarterectomy.[10]

In addition, microvascular remodeling and hypertrophy of the bronchial arteries are observed below the pulmonary artery occlusion.

The bronchopulmonary shunt contributes to the pathobiology by causing systemic circulation to flow into the low-pressure pulmonary system, increasing micro vasculopathy similar to hemangiomatosis-like lesions and pulmonary veno-occlusive-like lesions.[9]

## CLINICAL APPROACHES

The symptoms and signs of CTEPH are non-specific and may resemble acute PE. In Europe, there is an average of 14 months between symptom onset and diagnosis in specialized pulmonary hypertension centers. Symptoms; exertional dyspnea (91%), edema (38%), chest discomfort (29%), dizziness (26%), fatigue (25.9%), cough (22.1%), shortness of breath at rest (19%).5), palpitations (14.8%), pre-syncope (10.7%), syncope (7.6%), anxiety (5.7%), and hemoptysis (4.5%) (6). Physical findings include pulmonary flow murmurs and a prominent pulmonary component of the second heart sound, tricuspid regurgitant murmur, and S4 murmur. A combination of peripheral edema, precordial right ventricular (RV) elevation, and high jugular venous pressure is suggestive of severe PH. Right ventricular S3, hepatomegaly, ascites, and cyanosis are late manifestations of advanced right heart failure.[11]

## DIAGNOSIS

Patients diagnosed with chronic thromboembolic pulmonary hypertension or with a strong suspicion of CTEPH should be referred to a specialized pulmonary hypertension centers for further multidisciplinary diagnosis and treatment such as PEA, BPA, and/or targeted pulmonary hypertension medical therapy. Although CT pulmonary angiography (CTPA) is the investigation of choice for the diagnosis of acute PE, planar ventilation/perfusion (V/Q) scintigraphy is an appropriate first-line screening method for diagnosis of CTEPH, as it has a sensitivity of 96-97% and a specificity of 90-95%. In the absence of ECG findings of right ventricular hypertrophy, NT-proBNP can exclude with a sensitivity of 94% and a specificity of 65%. Both V/Q data and modern CT pulmonary angiography are used in expert hands to detect CTEPH with excellent diagnostic efficiency (100%, 93.7% and 96.5% sensitivity, accuracy and accuracy for V/Q and 96.1%).

Multi-detector (MD) CTPA has become a remote monitoring method for guiding CTEPH; However, this study alone cannot exclude the disease. CTPA helps to identify proactive behaviors such as pulmonary artery (PA) dilatation, which causes compression of the left main visual artery, and hypertrophic bronchial artery collaterals, which can lead to hemoptysis.[12]

Ultimate diagnosis and operability assessment is provided by right heart catheterization and selective pulmonary angiography in anteroposterior and lateral projections showing bronchial collaterals as well as ring-like stenosis, webs ("clefts"), sacs, wall irregularities, and complete vascular occlusions. The final diagnostic and operability assessment supports the assessment of technical operability or suitability for BPA.[13]

## TREATMENT

Initial treatment includes diuretics, appropriate vaccination, pulmonary rehabilitation, and supplemental oxygen at rest, activity, or sleep as needed. Vitamin K antagonists (KVAs) targeting the International Normalized Ratio (INR) 2-3 are commonly used for lifelong anticoagulation. There is inadequate data on the efficacy and safety of direct oral anticoagulants (DOACs) for CTEPH.

Operability should be evaluated by a multidisciplinary team and should meet the criteria. An experienced PH center team should consist of a PEA surgeon, BPA intervention specialist, PH specialist, and thoracic radiologist trained in high-volume PEA and BPA centers.[2] The appropriateness of patients for PEA, BPA, medical therapy, or any combination of these therapies is determined by many factors that have not yet been standardized; these relate to patient factors, the expertise of surgical and percutaneous multidisciplinary teams, and available resources. General criteria include preoperative New York Heart Association (NYHA) functional classes and surgical accessibility of thrombi in the main, lobar, or segmental pulmonary arteries. Old age is not a contraindication for surgery. Although PEA is officially the gold standard of CTEPH treatments, available records indicate that at least 40% of patients are poor surgical candidates and do not undergo surgery. PEA is generally curative and life-saving and should be offered to all eligible patients. It alleviates PH and symptoms by up to 75% and improves survival.[14] The early death rate in experienced centers is <5%, and overall survival rates at 1, 3, 5, and 10 years are 86%, 84%, 79%, and 72%, respectively. Significant residual PH is rare and associated with in-hospital mortality. Milder residual PH is probably due to distal vasculopathy, in 50% at 3-6 months after PTE. Symptomatic patients with persistent or/recurrent post-operative PH should receive PH-targeted medical therapy and be evaluated for BPA or re-PTE if mPAP >30 mmHg.[9]

Although BPA is not widely used, it is rapidly gaining worldwide attention. One of the largest Japanese registries reported results similar to those from PEA in both short-term and long-term clinical follow-up. BPA is a proven minimally invasive procedure that safely treats inoperable CTEPH or symptomatic persistent/recurrent PH after PTE. BPA requires multiple sessions to expand occlusive fibrotic meshes/bands with an inflated balloon.[15] BPA can be combined with medical treatment in a hybrid or stepwise approach. Clinical trials comparing the efficacy and safety of BPA versus riociguat for inoperable CTEPH are currently underway in the USA (NCT02634203) and Japan. Complications of BPA include wire perforation during wire or balloon manipulation, balloon overexpansion, contrast extravasation, vascular injury such as pulmonary hemorrhage, hemoptysis or hypoxemia, and less commonly reperfusion injury. Overall complication rates are approximately 10% per procedure and are associated with severe PH during BPA.[16]

Patients with persistent or recurrent PH after PEA may be candidates for targeted medical therapy. The use of targeted therapy as a bridge to PEA in operable patients with severe hemodynamic impairment has not yet been supported by scientific evidence. Riociguat, an enteral soluble guanylate cyclase stimulant, resulted in a mean increase in 6-minute walking distance of 39 m in patients with inoperable CTEPH or persistent/recurrent PH 16 weeks after PEA, with the least squares mean difference 246 is. dyn cm·s 5 in PVR (p<.001, secondary endpoint); the time to clinical worsening did not change.[17] Recently, the dual endothelin receptor blocker macitentan has been shown to significantly improve PVR in patients with inoperable CTEPH and is well tolerated. In addition, a recent multicenter randomized controlled trial has shown that treatment with subcutaneous treprostinil is safe and improves exercise capacity in patients with severe CTEPH.[18]

## CONCLUSION

Many patients are diagnosed late, and concerns remain that a large proportion of patients remain undiagnosed and/or are never referred for effective medical, interventional, and surgical treatments. A history of severe PE and acute pulmonary embolism should suggest CTEPH. ECO should be performed in symptomatic patients 3-6 months after acute PE. It should be ensured that patients have been using anticoagulation for 3 months before coming to the tests for the diagnosis of CTEPH. Careful screening and follow-up of patients after acute PE and widespread use of V/Q scans in unexplained dyspnea and all PH patients may lead to better clinical outcomes and survival. Patients should be treated in a CTEPH center. Future research is needed to identify better screening tools, explore new pathobiological pathways, and discover new treatments to reverse the disease process.

## ETHICAL DECLARATIONS

**Referee Evaluation Process:** Externally peer-reviewed.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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