Chronic Thromboembolic Pulmonary Hypertension
An Update

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KEYWORDS

- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Chronic thromboembolic disease (CTED) • Pulmonary endarterectomy (PEA)
- Pulmonary thromboendarterectomy (PTE) • Balloon pulmonary angioplasty (BPA)
- Pulmonary hypertension (PH)

KEY POINTS

- Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disease with significant morbidity and mortality. It occurs in approximately 4% of pulmonary embolism (PE) survivors and is a sequela of nonresolving thromboemboli with persistent arterial obstruction.
- CTEPH develops within 2 years of an acute PE. Risk for CTEPH increases with recurrent thromboembolic disease, elevated pulmonary pressures at the time of acute PE, nonresolving PE, prothrombotic conditions, hypothyroidism, malignancy, and chronic inflammatory states.
- CTEPH requires an extensive evaluation for best outcomes. Diagnostic workup includes a thorough clinical assessment of cardiopulmonary status including pulmonary hemodynamics and diagnostic imaging.
- Surgical intervention remains the optimal management strategy for CTEPH. Select inoperable patients may be candidates for catheter-based intervention with balloon pulmonary angioplasty. Patients who are not candidates for intervention or those with postintervention pulmonary hypertension are treated with medical therapy.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, yet underdiagnosed pulmonary vascular disease, which is a sequela of prior pulmonary thromboemboli[1] and is classified by the World Health Organization (WHO) as group IV pulmonary hypertension (PH).[2] Although most of the pulmonary embolism (PE) survivors experience improvement over time with resolution of

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thromboembolic burden, there is a small group that develops CTEPH[3] due to an alternate natural history with limited resolution of vascular obstruction, thrombus organization, and recanalization.[1] This is associated with small pulmonary arterial vascular changes leading to increased pulmonary vascular resistance (PVR) and PH.[4] The pathophysiologic mechanisms of this condition have not been fully elucidated but seem to be a result of a complex interaction between the pulmonary arterial obstruction from prior PE and multifactorial molecular responses in the pulmonary microvasculature.[5]

EPIDEMIOLOGY AND RISK FACTORS

Conflicting data exist regarding the incidence and prevalence of CTEPH. In a recent detailed evaluation of published literature, population-based hospital databases, and surveys by Gall and colleagues,[3] it was estimated that CTEPH occurs in approximately 4% (0.1%–9.1%) of all PE survivors. These findings are similar to the results of The INFORM Study (3.8%)[6] and a prospective long-term follow-up study monitoring 223 patients after acute PE for up to 10 years (3.8%).[7] Based on this data, the annual incidence of CTEPH can be estimated at 3 to 5 cases per 100,000 in the United States and Europe with less than a third of cases (7%–29%) being diagnosed based on reviewed databases.[3] In the 2007 to 2009 International CTEPH Registry (679 newly diagnosed patients <6 months), men and women were affected equally, 75% had previous PE, and most were diagnosed in the 6th decade of life.[8] Most frequently, patients reported NYHA functional class III/IV symptoms at time of diagnosis[9] with the vast majority of CTEPH being detected within 2 years of an acute thromboembolic event.[7,10]

Several risk factors for the development of CTEPH have been identified. Pengo and colleagues[7] found in a prospective long-term follow-up study that recurrent PE, younger age, larger perfusion defects, and idiopathic presentation were all associated with increased risk of CTEPH. Several prothrombotic factors have also been associated with the development of CTEPH and include elevated factor VIII,[11] dysfibrinogenemia,[12] antiphospholipid antibodies, and lupus anticoagulant.[13] Additional factors that have been associated include splenectomy,[14,15] human leukocyte antigen (HLA) polymorphism HLA-DPB1,[16] elevated pulmonary pressures at the time of PE, lower-limb varicosities, residual obstruction on computed tomography (CT) imaging 3 months after acute PE,[10] hypothyroidism, malignancy, infected pacemaker wires, recurrent thromboembolic disease, non-O group blood type,[15] ventriculoatrial (VA) shunts, chronic inflammation due to osteomyelitis, and inflammatory bowel disease.[17] Compression of pelvic veins has also been shown to increase the risk of venous thromboembolism (VTE) and CTEPH. Compressing uterine fibroids are associated with CTEPH, and thus a history of fibroids or menorrhagia may raise clinical suspicion for this condition. May-Thurner syndrome, where the right common iliac artery compresses the left common iliac vein, can also lead to VTE and may be evident by recurrent unprovoked left lower extremity deep vein thrombosis (DVT)[18] (**Table 1**).

PATHOPHYSIOLOGY

The pathophysiologic mechanisms involved in the development of CTEPH are not fully understood but the inciting event is nonresolving large vessel thromboembolic disease.[1] Several potential triggers for lack of thrombus resolution have been postulated, including staphylococcal infection[19] and fibrinogen aberrations.[12] The role of staphylococcus is supported by a murine model of venous thrombosis with coexisting staphylococcal infection in which there was evidence of fibrotic

Table 1
Patient characteristics and risk factors associated with the development of CTEPH

PE History	Recurrent PE Large perfusion defect Idiopathic presentation Elevated pulmonary pressures with acute PE Residual obstruction on CT 3 mo after PE
Prothrombotic Factors	Elevated factor VIII Antiphospholipid antibodies Lupus anticoagulant Dysfibrinogenemia
Patient Characteristics	Splenectomy Malignancy Infected pacemaker wires Ventriculoatrial shunts Inflammatory bowel disease Lower extremity varicose veins Osteomyelitis Non-O blood group Hypothyroidism Uterine fibroids compressing pelvic veins May-Thurner syndrome