# Chronic Thromboembolic Pulmonary Hypertension

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**KEYWORDS**

- Chronic thromboemboli • Pulmonary hypertension
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Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the few forms of pulmonary hypertension (PH) that can be cured surgically. It is critical that every patient presenting with PH have CTEPH excluded in order to avoid missing the chance to cure this otherwise fatal condition. This article discusses the epidemiology and predisposing factors of CTEPH, as well as the natural history of this disorder with and without treatment. Although an exact understanding of the mechanisms resulting in fibrosed thromboembolic residua is lacking, current research suggesting abnormalities in fibrin side chains rendering them resistant to lysis are reviewed. The proper preoperative assessment to diagnose CTEPH and to define surgical candidacy for pulmonary thromboendarterectomy (PTE) are discussed as well as technical aspects of the operation itself. Although PTE is the treatment approach of choice, some patients who are not surgical candidates for a variety of reasons have been treated with pulmonary arterial hypertension (PAH)–specific medical therapies. This article also reviews the current evidence from the literature for medical therapies in CTEPH.

## CTEPH: EPIDEMIOLOGY AND PREDISPOSING FACTORS

The incidence of CTEPH following an acute pulmonary embolic event (or events) has not been adequately defined. Early characterization of patients with CTEPH resulted in the speculation that 0.1% to 0.5% of acute embolic survivors might develop this disease.[1] However, more recent data suggest that this estimate may be a significant understatement of how common CTEPH might be worldwide.[2] A recent prospective longitudinal study by Pengo and colleagues[3] reported a 2-year, cumulative incidence of 3.8% following a single episode of pulmonary embolism (median follow-up of 94.3 months in 223 patients) and 13.4% following recurrent venous thromboembolism. Another prospective series from Becattini and colleagues[4] suggested a lower incidence. Following 259 patients for an average period of 46 months, 2 patients were diagnosed with CTEPH (0.8%). For those patients in whom the pulmonary embolic event was considered to be idiopathic (n = 135), the incidence was 1.5%. In a larger group of patients, Miniati and colleagues[5] reported a CTEPH incidence of 1.3% in 320 pulmonary embolic survivors followed for a minimum of 1 year. If an incidence of 1% proves to be correct, and there is an estimated 200,000 pulmonary embolic survivors annually in the United States who are believed to have long-term survival potential,[6] up to 2000 patients would be expected to develop CTEPH. Available information suggests that this exceeds the number of patients with

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CTEPH diagnosed annually in the United States, suggesting that this disease remains underdiagnosed. Furthermore, because it is reported that 42% to 63% of patients with the established diagnosis of CTEPH have no previously documented acute venous thromboembolism,[2,7,8] it is likely that the number of CTEPH cases is even greater than is projected to follow known thromboembolic events.

In the absence of appropriate treatment, long-term survivorship of patients with chronic thromboembolic disease is poor. As in other forms of PH, early reports found survivorship for patients with chronic thromboembolic disease to be proportional to the degree of right ventricular dysfunction at the time of diagnosis. In one study, the 5-year survival rate in patients with CTEPH was 30% when the mean pulmonary artery pressure (mPAP) was greater than 40 mm Hg and 10% when it was greater than 50 mm Hg.[9] More recently, in a study of 49 patients with CTEPH receiving standard anticoagulation therapy alone, Lewczuk and colleagues[10] showed that an exercise capacity of less than 2 metabolic equivalents, an mPAP greater than 30 mm Hg, or the presence of significant chronic obstructive pulmonary disease appeared to predict a poor prognosis. Condliffe and colleagues,[8] in a multivariate analysis of 148 patients with distal, inoperable CTEPH, showed that walk distance and cardiac index (CI) were predictors of survivorship. Univariate analysis in this same group showed that patients in World Health Organization (WHO) functional class III or IV had greater than 3 times the mortality relative to those patients in functional class I or II. However, a recent study demonstrated that disease-modifying medical therapy provided to patients with CTEPH with inoperable disease resulted in improved survivorship and better prognosis.[11]

There seem to be several predisposing factors that place patients at risk for developing chronic thromboembolic disease. For those patients having survived 1 or more pulmonary embolic events, several clinical observations have been reported. The overall extent of pulmonary vascular obstruction at presentation may be important in the development of CTEPH. Pengo and colleagues[3] suggested that having larger perfusion defects at the time of the initial pulmonary embolus diagnosis was a risk factor for developing CTEPH. They also showed that a history of multiple pulmonary embolic events, a younger age at presentation, and an idiopathic pulmonary embolic event placed patients at greater risk. In a report in which massive pulmonary embolism was defined as greater than 50% obstruction of the pulmonary vascular bed, the incidence of CTEPH was 20.2% despite the use of thrombolytic therapy.[12] The presence of PH when an acute pulmonary embolism is diagnosed might be an important risk factor and should alert the clinician to the possibility that CTEPH may be a potential problem. In patients presenting with an acute pulmonary embolus, Ribeiro and colleagues[13] reported that those with pulmonary artery systolic pressures greater than 50 mm Hg were apt to experience persistent PH after 1 year.

There is also an association between certain medical conditions and the development of chronic thromboembolic disease. The presence of a thrombophilic state has been examined in patients with chronic thromboembolic disease. In the largest study investigating this issue, the prevalence of a hereditary thrombophilia (deficiencies of antithrombin III, protein C or protein S, or mutations of the genes that code for factor II and factor V) was not increased in samples analyzed in 46 patients with CTEPH or 64 patients with idiopathic pulmonary hypertension (IPAH) relative to 100 control subjects.[14] However along with a recent evaluation of 687 consecutive patients with CTEPH (N = 433) and nonthromboembolic PH (N = 254), this study found antiphospholipid antibodies to be more commonly associated with chronic thromboembolic disease.[15] Antiphospholipid antibodies were present in 20% of patients with CTEPH as reported by Wolf and colleagues[14]; Bonderman and colleagues[15] showed antiphospholipid antibodies or a lupus anticoagulant in 10% of their patients with CTEPH. In an earlier report, Bonderman and colleagues[16] also showed increased levels of factor VIII in 41% of 122 patients with CTEPH, levels that were substantially higher than those in control subjects and patients with nonthromboembolic PAH. The factor VIII levels remained increased following successful PTE surgery.

Several other medical conditions have been associated with an increased risk of developing CTEPH. In a report from 2005, Bonderman and colleagues[7] compared 109 consecutive patients with CTEPH with 187 patients who did not develop chronic thromboembolic disease after experiencing an acute pulmonary embolism. Multivariate analysis revealed that prior splenectomy, the presence of a ventriculoatrial shunt to treat hydrocephalus, and certain chronic inflammatory disorders, such as osteomyelitis and inflammatory bowel disease, were risk factors for CTEPH. A follow-up study gathering data in 687 patients with pulmonary hypertension from 4 European pulmonary vascular centers between 1996 and 2007 found the presence of ventriculoatrial shunts and infected pacemakers, prior splenectomy, previous and recurrent venous thromboembolism, thyroid