Chronic Thromboembolic Pulmonary Hypertension

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KEYWORDS

• Chronic thromboembolic pulmonary hypertension • CTEPH • Pulmonary hypertension
• Pulmonary embolism • Chronic thromboembolism • Pulmonary endarterectomy
• Pulmonary artery balloon angioplasty

KEY POINTS

- Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct type of pulmonary hypertensive disease, characterized by incomplete or abnormal resolution of acute pulmonary embolism.
- CTEPH occurs in approximately 4% of patients with acute pulmonary embolism but nearly half of CTEPH cases are found in patients without a prior history of venous thromboembolism.
- Diagnosis is usually made by identifying persistent filling defects in the pulmonary circulation after 3 to 6 months of anticoagulation in patients with exertional dyspnea and signs of pulmonary hypertension or right heart failure.
- Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH and in properly selected patients usually provides significant improvements in pulmonary hemodynamics, functional capacity, and survival.
- Patients who are deemed inoperable by a center experienced in CTEPH and PEA may benefit from medical therapy with pulmonary vasodilator medications or pulmonary balloon angioplasty.

EPIDEMIOLOGY

Chronic thromboembolic pulmonary hypertension (CTEPH) refers to pulmonary hypertension (PH) that occurs as a result of persistent or recurrent pulmonary emboli and is classified as group 4 PH using terminology developed by the World Symposium on Pulmonary Hypertension (WSPH).[1] At the WSPH in 2013, CTEPH was defined as mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg and mean pulmonary artery wedge pressure (PAWP) less than or equal to 15 mm Hg measured by right heart catheterization (RHC) in the presence of chronic/organized flow-limiting thrombi/emboli in the elastic pulmonary arteries (PAs) after at least 3 months of effective anticoagulation therapy.[2] At the most recent WSPH in 2018, it was proposed that this definition be kept the same but that mPAP be changed to greater than or equal to 20 mm Hg. The rationale for distinguishing this type of PH from the other 4 groups is based on its unique cause, pathophysiology, clinical presentation, and treatment options.

The true incidence of CTEPH is difficult to determine because most patients with acute pulmonary

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embolism (PE) do not undergo routine follow-up assessment of PA pressure or repeat imaging to assess the degree of clot burden that remains. Furthermore, a surprisingly large number of patients with CTEPH, anywhere from 25% to 67%, cannot recall any past history of venous thromboembolism (VTE).[3,4] As a result, recent estimates suggest that CTEPH is significantly underdiagnosed.[5]

Initial studies reported CTEPH to be a rare complication of acute PE with an estimated incidence of less than 0.5%.[1] However, a recent review that analyzed data from 8 studies in Europe and the United States published between 2001 and 2009 found incident rates that ranged from 0.4% to as high as 9.1% with a weighted average of 4%.[6–13] This weighted average is remarkably similar to the rate of 3.8% over 2 years of follow-up in 223 consecutive patients with an acute episode of PE[14] and the estimated rate of 3.8% reported in a retrospective claims database analysis[15] and similar to the follow-up data from the PEITHO (Pulmonary Embolism Thrombolysis) study, which reported rates of 2.1% in 353 patients with acute PE assigned to thrombolytic therapy and 3.2% of 343 patients treated with heparin alone.[16] Using the weighted average rate of 4%, Gall and colleagues[5] calculated a crude annual incidence rate for CTEPH of 3 to 5 cases per 100,000 per year (**Fig. 1**), based on hospital databases and surveys that estimated an annual incidence of acute PE of 66 to 104 cases per 100,000 per year in the United Kingdom and United States, respectively, and a 92% rate of survival to discharge following acute PE.[17–20] The investigators also factored in an assumed 20% rate of under-reporting. However, this type of estimate is limited by the accuracy of the true rate of CTEPH after acute PE. A recent systemic review concluded that the overall rate of CTEPH following acute PE may be much lower, particularly in patients without any comorbidities.[21] More accurate reporting of the incidence of CTEPH will require prospectively collected data such as those from the Follow-Up after Acute Pulmonary Embolism (FOCUS) study, a prospective, multicenter, observational cohort study that will monitor patients with acute PE for 2 years to collect data on the incidence of CTEPH.[22]

Unlike idiopathic pulmonary arterial hypertension (IPAH), there does not seem to be a difference in disease prevalence between men and woman, with most registries reporting approximately equal numbers of both sexes.[3,6] CTEPH also occurs later in life than other types of PH, with most cases occurring in the sixth decade of life, likely reflecting the increase occurrence of deep-vein thrombosis (DVT) and PE with increasing age.[6]

PATHOPHYSIOLOGY

Although the symptoms of PE resolve rapidly in almost all patients treated with anticoagulants, many patients have evidence of residual thrombi months to years later. Early reports described partial or unresolved PE in 35% of patients after 1 to 7 years of treatment,[23] although most patients in that study were treated by vena caval interruption without long-term anticoagulation. However, more modern studies continue to show a high rate of

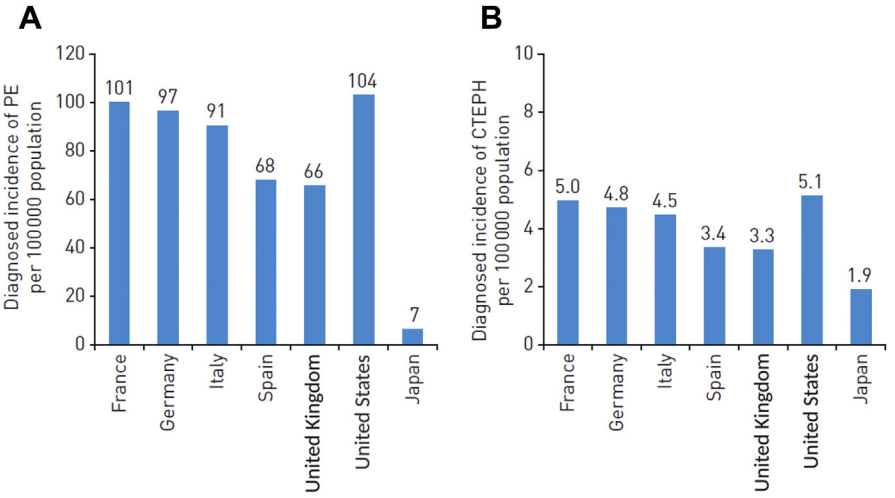

Fig. 1. Estimated annual incidence of acute PE (*A*) and calculated crude annual incidence rate for CTEPH (*B*). (*From* Gall H, Hoeper MM, Richter MJ, et al. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. Eur Respir Rev 2017;26(143):160121; with permission.)