# EXPERT REVIEW

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## Recent Advances in Chronic Thromboembolic Pulmonary Hypertension

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**Surgical excellence in pulmonary thromboendarterectomy (PTE) for chronic thromboembolic pulmonary hypertension (CTEPH) has begun to spread around the world. The perioperative mortality for this procedure is typically under 10%. The maximal benefit from PTE is derived in those patients who have a high proximal clot burden that is surgically accessible, as outlined by the Jamieson classification. Residual pulmonary hypertension after successful PTE is common and increasingly is managed with maintenance oral pulmonary vasodilator therapy such as endothelin antagonists, phosphodiesterase inhibitors, and/or prostaglandins. The role of pulmonary vasodilator therapy in CTEPH before PTE is limited and should not delay definitive surgical therapy. Although plain deep hypothermic circulatory arrest (DHCA) is the classic technique for CTEPH, alternatives such as DHCA with antegrade cerebral perfusion are feasible as well. Prolonged mechanical ventilation after PTE remains common in part because of reperfusion pulmonary edema. Careful perioperative management can reduce the incidence of this syndrome. Because ventilator-associated pneumonia is also a common complication after PTE, it represents a major opportunity for outcome improvement, particularly because there are multiple modalities for its prevention and prompt diagnosis.**


***Key words: chronic thromboembolic pulmonary hypertension, pulmonary thromboendarterectomy, clinical outcomes, Jamieson classification, right ventricular dysfunction, pulmonary hypertension, endothelins, bosentan, phosphodiesterases, sildenafil, prostaglandins, epoprostenol, treprostinil, direct thrombin inhibitors, dabigatran, factor Xa inhibitors, apixaban, rivaroxaban, guanylate cyclase, riociguat, deep hypothermic circulatory arrest, moderate hypothermia, selective antegrade cerebral perfusion, reperfusion pulmonary edema, ventilator-associated pneumonia, procalcitonin***

CHRONIC THROMBOEMBOLIC pulmonary hypertension (CTEPH) is characterized by pulmonary arterial obstruction caused by recurrent pulmonary embolism.[1] The definition of CTEPH is a mean arterial pressure >25 mmHg that persists for longer than 6 months after the diagnosis of pulmonary embolism.[2] This syndrome develops in at least 4% of patients with acute pulmonary embolism but frequently is underdiagnosed because its development is asymptomatic in more than 50% of cases.[1,2] The definitive therapy for CTEPH is pulmonary thromboendarterectomy (PTE), which involves surgical removal of organized thrombus and related fibrous tissue from the pulmonary arterial tree under periods of deep hypothermic circulatory arrest (DHCA) on cardiopulmonary bypass.[3] The role of medical therapy in CTEPH beyond indefinite anticoagulation is likely to evolve yet further because of the advent of pulmonary vasodilator therapy such as endothelin blockers and phosphodiesterase inhibitors.[1,2]

There has been substantial progress in the diagnosis and management of pulmonary hypertension (PHTN), including CTEPH, which is classified as type-4 PHTN in the latest revised clinical classification.[4-6] These advances have prompted multiple recent guideline statements, most recently from the American Heart Association (AHA).[4-6] This expert review addresses the major innovations in CTEPH and PTE that are likely to significantly influence perioperative practice and therefore be relevant to the cardiovascular anesthesiologist.

### WHAT ARE THE CURRENT OUTCOMES AFTER PTE?

Dr Jamieson and his team at the University of California, San Diego have the largest PTE experience in the world, with more than 2,500 procedures since 1970.[7] Although the perioperative mortality rate for this entire series is 6.4%, it has fallen to 2.5% in the last 3 years because of yet further refinements in perioperative techniques.[3,4] The San Diego group also recently has published their pediatric PTE experience, which, although small (N = 17), showed safety with a 0% perioperative mortality rate and clinical efficacy with significant improvements in hemodynamics and functional status.[8] An important distinction in the pediatric group as compared with the adult group was the significantly increased risk of rethrombosis (38% *v* 4%), emphasizing the crucial role of aggressive anticoagulation in pediatric presentations of CTEPH.

The PTE gradually has spread worldwide. There are currently more than 40 recent reports from around the world (N > 20; range, 21-236: 2005-2010).[4] This surgical experience recently has been augmented by the formation of an international prospective CTEPH registry with participating centers in Europe and Canada.[9] In a recent publication from this registry

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(N = 679: 56.8% underwent PTE), the median age of surgical patients was 60 years.[9] The in-hospital mortality rate was 4.7%. Further perioperative complications included neurologic issues (11.2%), bleeding (10.2%), pericardial effusion (8.3%), residual pulmonary hypertension (16.7%), pulmonary reperfusion edema (9.6%), extracorporeal membrane oxygenation (3.1%), and infection (18.8%: 65.7% of this subgroup had ventilator-associated pneumonia). Neurologic complications were more common as DHCA time increased, 1.9% with DHCA <20 minutes versus 18.4% with DHCA time >60 minutes (odds ratio = 0.09; 95% confidence interval, 0.01-0.74). Furthermore, in this study, mortality at 1 year was 7.0%. The majority of patients evaluated at this time point had significant improvements in median pulmonary vascular resistance and functional status as measured by 6-minute walk distance and New York Heart Association functional class.

The surgical techniques for PTE have matured and subsequently have generalized to multiple centers of excellence throughout the world. It is likely that this dissemination will continue throughout Asia in the coming years.[10] This success story has been assisted significantly by the advances in perioperative management of the right ventricular dysfunction and pulmonary hypertension, which have been highlighted recently both in this *Journal* and elsewhere.[1,11]

## ARE THERE PREDICTORS FOR ADVERSE CLINICAL OUTCOME AFTER PTE?

The major predictor of outcome after PTE is based on the Jamieson classification of CTEPH, namely the pattern of pulmonary arterial occlusion based on the anatomic location of the obstruction.[12] Type-1 disease is defined as fresh thrombus in the main and/or lobar arteries (about 25% of cases). Type-2 disease is defined as chronic intimal thickening proximal to the segmental arteries (about 40% of cases). Type-2 disease may have organized thrombus. Type-3 disease is defined as intimal disease limited to the segmental arteries; this disease pattern is technically the most difficult and may represent CTEPH with resorption of the proximal clot burden (about 30% of cases). Type-4 disease is defined as distal arteriolar vasculopathy with no visible thromboembolic disease (<5% of cases). In the San Diego series (N = 202: 1998-2000), patients with distal disease (type 3 and type 4) had significantly increased tricuspid regurgitation and pulmonary vascular resistance ($p < 0.0001$) versus the patients with surgically accessible thromboembolic burden (type 1 and type 2).[12] Patients with distal CTEPH types had increased inotropic requirements, hospital stays, and perioperative mortality.[4,12] Patients with type-4 disease frequently account for most of the perioperative mortality after PTE. This patient subgroup in CTEPH does not benefit from PTE. The major focus in the current era is to enhance preoperative identification of type-4 disease so as to preclude these patients from PTE.[13]

The degrees of PHTN and/or right ventricular dysfunction are not regarded as contraindications to PTE.[4] Patients with operable disease may derive immense clinical benefit with significant reduction of PHTN coupled with recovery of the right heart and resolution of severe tricuspid regurgitation.[14,15]

It remains an imperative that patients with type-4 CTEPH are diagnosed preoperatively because they qualify primarily for medical therapy and not PTE.[16] Careful pulmonary angiography can reliably determine the thromboembolic pattern by formal criteria that correlate with clinical outcomes after PTE.[17] A recent series from the United Kingdom (N = 314: 1997-2007) focused on the outcome importance of residual PHTN after PTE in patients with CTEPH (types 1, 2, and 3).[18] Although all patients experienced a significant reduction in mean arterial pulmonary artery pressure (48 ± 12 to 26 ± 10 mmHg, $p < 0.001$), 31% of the cohort had residual PHTN, which was defined as mean pulmonary artery pressure ≥30 mmHg. Although residual PHTN after PTE did not affect 5-year survival, it significantly worsened functional status. Furthermore, the study highlighted the clinical necessity for further investigation of targeted medical therapy in this patient cohort who persisted with PHTN despite appropriate PTE.

Residual PHTN is common after PTE. This finding is explained by the 2-compartment model proposed by Moser and Braunwald in 1973.[2,19] This model recognizes that patients with CTEPH who have proximal mechanical obstruction also can have distal small vessel vasospasm as a microvascular phenomenon in the pulmonary vasculature.[2,19,20] This distal vasculopathy provides a therapeutic target for selective pulmonary vasodilator therapy, which will be examined in detail in the following 2 sections.

## WHAT IS THE ROLE OF MEDICAL THERAPY BEFORE PTE?

Standard medical therapy for CTEPH includes chronic anticoagulation with warfarin for a goal international normalized ratio of 2 to 3.[2] Although pulmonary vasodilator therapies have been tested in CTEPH before PTE, the evidence is very limited.[21,22] A large retrospective study (n = 111 pulmonary vasodilator exposure and n = 244 control group: 2005 to 2007) examined the effects of monotherapy with bosentan (endothelin antagonist), sildenafil (phosphodiesterase inhibitor), or epoprostenol (prostaglandin) and combinations thereof.[22] The investigators observed a significant increase in exposure to these medications in the study period despite their lack of perioperative benefit. They also documented that exposure to these medications often resulted in delayed referral for PTE, the proven therapy for this disease. Consequently, the recent AHA guideline strongly suggests that pulmonary vasodilator therapy should never delay evaluation for PTE (AHA class III recommendation, level of evidence B).[4] Furthermore, the role of medical therapy in the management of CTEPH before PTE requires further study before any conclusive recommendations are possible.[23]

## WHAT IS THE ROLE OF MEDICAL THERAPY AFTER PTE?

Patients with proven CTEPH require indefinite therapeutic anticoagulation in the absence of contraindications (AHA class I recommendation, level of evidence C).[4] Until recently, this goal has been achieved with chronic warfarin titrated to a therapeutic international normalized ratio. Given the advent of novel oral anticoagulants, such as the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban and rivaroxaban, it is likely that warfarin therapy may be challenged by these newer anticoagulants.[24] The advantages of these novel