Chronic thromboembolic pulmonary hypertension (CTEPH) is increasingly recognized as a possible sequela of acute pulmonary emboli (PE). Histological findings in the pulmonary arteries of patients with CTEPH are different from those with acute PE: while acute clot may be present, classically, the vessels are filled with a white, fibrous material (Figure 1). Without treatment, CTEPH can lead to progressive pulmonary vascular obstruction, right heart failure, and death. CTEPH is a cause of pre-capillary pulmonary hypertension (PH), Group 4 in the most recent classification of PH, and distinguishing CTEPH from other causes of PH is important as it is potentially curable with surgical treatment. In CTEPH patients in whom surgery is not an option, medical therapies and interventional procedures may offer some benefit.

CTEPH develops in 0.6 – 3.8% of patients following acute PE. While most patients with CTEPH have a prior history of acute PE, 25% of patients with CTEPH have no history of thromboembolic disease. Risk factors for CTEPH include hypercoagulable states, indwelling catheters and leads, ventriculoatrial shunts, splenectomy, history of malignancy, inflammatory bowel disease, and thyroid replacement therapy.

Patients with CTEPH present with signs and symptoms of PH, and as disease progresses, of right heart failure: progressive dyspnea, exercise intolerance, lower extremity edema, fatigue, palpitations, lightheadedness, and exertional syncope. Findings on physical examination frequently include an accentuated P2, right ventricular heave, murmur of tricuspid regurgitation, and occasionally a bruit over the lungs indicative of focal pulmonary artery stenosis. Initial evaluation of the patient with CTEPH is similar to evaluation of other causes of PH and includes a chest X-ray, pulmonary function tests, EKG (may be unremarkable but often shows right ventricular hypertrophy, right atrial enlargement, and/or right axis deviation), and echocardiogram. Because prior history of thromboembolic disease is not universal, a ventilation/perfusion lung scan should be performed to assess for CTEPH in any patient with significant PH.

The pivotal goals of invasive testing to confirm CTEPH are to: 1) establish the extent and location of vascular obstruction, 2) determine the severity of hemodynamic impairment and, 3) determine surgical suitability based on anatomic and physiologic features. CTEPH is defined as a mean pulmonary artery pressure $\geq 25$mmHg and pulmonary artery wedge pressure $< 15$mmHg in the presence of chronic PE. Ventilation/perfusion (VQ) scanning remains the test of the choice for screening and initial assessment of CTEPH due to high sensitivity (> 95%). VQ scans in CTEPH show multiple segmental or lobar perfusion defects (Figure 2). CT angiogram is an excellent test to diagnose acute PE and can frequently be a
useful test to suggest the diagnosis of CTEPH; however, findings of CTEPH may be overlooked on CT angiography. Pulmonary angiography (digital subtraction angiography) is the gold standard test for diagnosing chronic PE and evaluating operability, that is, the burden of disease and the extent of proximal versus distal disease.\(^7\) Findings on angiography in CTEPH are different from those found in acute PE and include arterial stenosis, post-stenotic dilatation, intimal irregularities or “scalloping,” webs, and bands (Figure 3).

Surgical treatment of CTEPH remains the best treatment option for symptomatic patients with surgically accessible disease. Distal disease — disease in the sub-segmental or smaller arteries — is often not accessible surgically, and is treated medically or with pulmonary angioplasty (discussed below). Successful pulmonary endarterectomy (PEA), also sometimes referred to as a pulmonary thromboendarterectomy (PTE), was first described over 50 years ago, and is often a life-saving operation that markedly improves pulmonary hemodynamics in the majority of patients, even normalizing them in some cases.\(^8\) The operation is a true endarterectomy, distinct from an embolectomy which is performed for removal of large, proximal acute PE. Determination of surgical candidacy is a complex decision weighing the risks of operative intervention, anatomic location of chronic emboli (“accessibility”), and patient factors (age, conditioning, degree of hemodynamic impairment, preoperative PVR). All patients diagnosed with CTEPH should be evaluated for surgery, and “inoperability” determined only after methodical evaluation at an experienced center.

PEA is a relatively safe procedure in experienced hands with an in-hospital operative mortality as low as 2.2% in a large single center series\(^8\) and <5% in a registry of European CTEPH centers.\(^9\) PEA is performed under profound hypothermic circulatory arrest to provide the best possible visualization of the pulmonary arteries without collateral blood flow obscuring the field. The surgeon dissects in a plane, endarterectomizing and freeing the chronic clot material from each segmental branch until there is no further obstruction distally.\(^10\) Reperfusion pulmonary edema related to increased vessel permeability and lack of vasoactive regulation in areas endarterectomized and reperfused is seen in up to 40% of patients, with greater risk in patients with more severe pre-operative PH and those with significant residual post-operative PH.\(^10\) Treatment is supportive, including lung protective ventilation and diuresis, although use of extracorporeal membrane oxygenation in severe cases of reperfusion edema can be helpful. Persistent PH after PEA is seen in up to 35% of cases, though many cases are mild and require only oral therapy. Occasionally persistent PH is an important cause of perioperative mortality.\(^10\)

Several medications have been evaluated in the treatment of CTEPH when the disease is inoperable due to surgically inaccessible disease or additional factors felt to make the risk of PEA excessive, and in CTEPH patients (Continued on page 10)
with persistent PH following PEA. The endothelin receptor antagonist bosentan showed improvement in PVR but failed to demonstrate improvement in 6 minute walk distance. Recently, the guanylate cyclase stimulator riociguat demonstrated significant improvement in exercise capacity, and this agent is FDA-approved for the treatment of inoperable CTEPH or persistent PH following PEA. Balloon pulmonary angioplasty has also been evaluated in the treatment of inoperable CTEPH, mainly with distal disease. Several case series have been published with sustained hemodynamic improvement reported for up to 2 years.

Evaluation and treatment of CTEPH at Vanderbilt is a collaborative effort between the divisions of Cardiovascular Medicine, Pulmonary and Critical Care, Interventional Radiology, Cardiac Anesthesiology, and Cardiac Surgery.

References: