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Chronic Thromboembolic Pulmonary Hypertension

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The description of organized thrombus in major pulmonary arteries can be found in autopsy reports dating back to the late nineteenth and early twentieth centuries, typically in association with other diseases, such as tuberculosis, lung cancer, and congenital heart disease, and rarely in the absence of another pathologic condition [1]. Not until the 1950s was the antemortem diagnosis and clinical syndrome of chronic thrombotic obstruction of the major pulmonary arteries better characterized [1–4]. Carroll [4] was the first to use cardiac catheterization and pulmonary angiography in detailing features of this unusual disease. In 1958, Hurwitt and colleagues [5] reported the first surgical attempt to remove the adherent thrombus from the vessel wall. Although the patient died, this operation provided the conceptual foundation for the distinction between acute and chronic thromboembolic disease of the pulmonary vascular bed, and established that an endarterectomy, and not an embolectomy, would be necessary if a surgical remedy for this disease was to be successful.

The first bilateral pulmonary thromboendarterectomy (PTE) performed through a transverse sternotomy using cardiopulmonary bypass is credited to Houk and colleagues [6] in 1963. Over the following 2 decades, reports describing the natural history and clinical characteristics of chronic thromboembolic disease, and small, anecdotal series of surgical successes in the treatment of this disorder appeared with increasing frequency [7–14]. A review of the world's experience with PTE up to 1985 showed an overall perioperative mortality rate of 22% in 85 patients who underwent the procedure [15]. With improvements in diagnostic capabilities, surgical techniques, endarterectomy instrumentation, and postoperative management, Moser and colleagues [16] at the University of California, San Diego (UCSD) published results of a study of 42 patients who had chronic thromboembolic pulmonary hypertension (CTEPH) and underwent surgery at a single medical center, showing in-hospital mortality of 16.6%. This publication further documented the considerable postoperative improvements in pulmonary hemodynamics and functional capabilities experienced by these patients, which were sustained a year or more beyond surgery.

Over the past 2 decades, the number of programs worldwide dedicated to the diagnosis and management of patients who have chronic thromboembolic pulmonary vascular disease has increased steadily. At UCSD, nearly 2000 patients from national and international referral sources underwent PTE between 1989 and 2006 [17]. During this same period, programs in North America, Europe, Japan, and Australia were developed to manage an increasing medical need [18–25]. Worldwide interest has been fueled by the rise in physician recognition of this treatable form of pulmonary hypertension, the appreciation that medical management of CTEPH is minimally effective in altering prognosis, declining perioperative mortality rates, and the knowledge that thromboendarterectomy can dramatically improve pulmonary hemodynamic status, functional outcome, and long-term survival.

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Epidemiology and risk factors

Available evidence suggests that CTEPH is an extension of the natural history of acute pulmonary embolic disease, although it occurs in a minority of individuals who survive a pulmonary embolism. The actual incidence of CTEPH, however, has been difficult to define. Based on patients diagnosed with CTEPH and the rate of patients known to survive pulmonary embolic events each year in the United States, an estimated 0.1% to 0.5% of survivors later develop symptomatic CTEPH [26,27]. This estimate would equate to an annual incidence between 500 to 2500 cases in the United States alone. Because limited information has been available from centers in the United States specializing in the treatment of patients who have pulmonary hypertension, these projections markedly exceed the number of patients diagnosed with symptomatic CTEPH each year. Consequently, these estimates are either overstated or CTEPH is significantly underdiagnosed, the latter of which seems most likely given the results of recent publications.

In a prospective study of 78 patients surviving an acute pulmonary embolus, Ribeiro and colleagues [28] examined echocardiographic findings for a year, and performed clinical follow-up for 5 years. Four patients (5.1%) developed clinically significant CTEPH, three of which underwent PTE for progressive right ventricular failure. In a more recent prospective longitudinal study, Pengo and colleagues [29] evaluated the incidence of symptomatic CTEPH in consecutive patients after an acute pulmonary embolic event. Median follow-up was 94.3 months in 223 patients who had no history of prior venous thromboembolism. Seven patients developed CTEPH within the first 2 years, for a cumulative incidence of 3.8%. No additional patients developed CTEPH beyond this 2-year period. CTEPH occurred more frequently in patients who experienced a prior venous thromboembolism: 11 of 82 patients (13.4%) compared with 3 of 58 (5.2%) patients who experienced a prior deep vein thrombosis and 8 of 24 (33.0%) patients who had a previous pulmonary embolus. Another prospective study reported a CTEPH incidence of 1.3%, in a group of 320 patients who had an acute pulmonary embolism who were followed up for a minimum of 1 year [30].

Currently, limited information is available regarding what factors might predispose patients to developing CTEPH. Links between observed associations and the pathophysiologic mechanisms leading to chronic thromboembolic disease are similarly unknown. However, growing experience with this disease entity has provided several insights about potential risk factors. In the Pengo study, not only did a history of multiple pulmonary embolic events place patients at a greater risk for developing CTEPH, but a younger age at presentation, larger perfusion defects at diagnosis, and idiopathic pulmonary embolic disease were found to be significant risk factors [29]. In patients who have an acute pulmonary embolism, Ribeiro and colleagues [28] reported that pulmonary artery systolic pressures higher than 50 mm Hg at presentation were associated with persistent pulmonary hypertension after 1 year. However, in contrast to the Pengo study, Rebeiro and colleagues [28] found that age older than 70 years at presentation was statistically linked to a higher risk for developing CTEPH. The size of the initial thrombus burden may also be important. In a study where 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 [31].

Although hereditary thrombophilic states (deficiencies of antithrombin III, protein C or protein S, or factor II and factor V Leiden mutations) represent risk factors for venous thromboembolism, their prevalence in patients who have established CTEPH was shown to be no different than in patients who have primary pulmonary hypertension or control subjects [32,33]. The presence of antiphospholipid antibodies (with or without an accompanying lupus anticoagulant) has been found to be one of the most common hypercoagulable states associated with the development of CTEPH. The antiphospholipid antibodies can be found in up to 21% of patients who have CTEPH [32]. Bonderman and colleagues [34] also showed increased levels of factor VIII in 41% of 122 patients who had CTEPH, levels that were substantially higher compared with patients who had nonthromboembolic pulmonary arterial hypertension. Additionally, the factor VIII levels remained elevated after successful PTE surgery, which would suggest a genetic basis for this finding. In one series of only 24 patients, hyperhomocysteinemia was shown in 7 of 14 patients who had CTEPH, whereas 12 of 24 patients were reported to have antiphospholipid antibodies [33].

An association between several medical conditions and CTEPH has been reported. In

a case-control study, Bonderman and colleagues [35] compared 109 consecutive patients who had CTEPH with 187 patients who did not develop chronic thromboembolic disease after experiencing an acute pulmonary embolism. Multivariate analysis showed that prior splenectomy, the presence of a ventriculoatrial shunt to treat hydrocephalus, and chronic inflammatory disorders (such as osteomyelitis and inflammatory bowel disease) were associated with an increased risk for CTEPH. A link between CTEPH and splenectomy was also reported in a retrospective study by Jais and colleagues [36]. Over a 10-year period, 257 patients who had CTEPH were compared with patients who had idiopathic pulmonary hypertension ($n = 276$) and with patients who had other chronic pulmonary conditions evaluated for lung transplantation ($n = 180$). The prevalence of prior splenectomy in patients who had CTEPH was found to be 8.6%, compared with 2.5% in the idiopathic pulmonary arterial hypertension group and 0.56% in patients who had other pulmonary disorders. Additionally, in the CTEPH group, the chronic thromboembolic disease was generally more distal, and therefore these patients were less likely to be surgical candidates (8 of 22 patients). The pathophysiologic basis for this association is not entirely clear; a prothrombotic state related to the loss of filtering abnormal erythrocytes by the spleen has been postulated [37].

Pathogenesis of chronic thromboembolic pulmonary hypertension

Clinical observation and what is known about the natural history of acute pulmonary embolism would suggest that incomplete resolution of pulmonary emboli rather than in situ thrombosis of the pulmonary arteries is the inciting event in chronic thromboembolic disease [38–40]. However, the aberrant mechanisms through which thromboembolic material undergoes incomplete thrombolysis and is then incorporated into the pulmonary arterial wall remain elusive. In normal subjects, Rosenhek and associates [41] showed that, under physiologic conditions, the pulmonary artery has increased fibrinolytic capabilities compared with the aorta. This finding seems to be based on higher levels of tissue plasminogen activator (TPA) expression versus plasminogen activator-inhibitor (PAI-1). However, in patients who had CTEPH, Olman and colleagues [42] and Lang and colleagues [43] were unable to show a reversal in the TPA–PAI-1 relationship that would favor incomplete thrombus dissolution. Although this same group was able to show a greater expression of PAI-1 and factor VIII on the surface of neovessels within organized thromboemboli, the exact role this played in sustaining thrombus within the pulmonary vascular bed is unclear [44]. More recently, in a small group of patients who had this disease, fibrin itself was shown to be resistant to plasmin-mediated lysis [45], seemingly because of an alteration in fibrin(ogen) structure. Additional investigation in a larger group of patients who have CTEPH is required to validate this aberration as a common pathway in the organization of acute pulmonary thromboemboli.

Even more incomplete is the understanding of the hemodynamic evolution to pulmonary hypertension after an acute pulmonary embolic event. In otherwise healthy individuals, the degree of hemodynamic impairment after an acute pulmonary embolus tends to correlate with the degree of pulmonary vascular obstruction. More than 3 decades ago, McIntyre and Sasahara [46] studied 20 healthy patients who had newly diagnosed pulmonary embolism. Obstruction of at least 25% to 30% of the pulmonary vascular bed was required to significantly raise pulmonary vascular pressures, although a mean pulmonary artery pressure higher than 40 mm Hg was not observed despite angiographically massive obstruction. As the degree of pulmonary arterial obstruction increased to 40% to 50%, cardiac index declined, reflecting a normal right ventricular response to an abrupt and significant rise in pulmonary vascular resistance. The frequency at which hemodynamic impairment was witnessed was notable in this study. Of these 20 patients, 70% exhibited a mean pulmonary artery pressure higher than 25 mm Hg. Similar observations regarding the hemodynamic impact of acute pulmonary emboli have been more recently reported. Although no correlation with thrombus burden was seen, Grifoni and colleagues [47] showed echocardiographic evidence of right ventricular dysfunction in 53% of 209 patients presenting with acute symptomatic pulmonary embolism. Of the patients with right ventricular compromise, 58% were normotensive and clinically stable (31% of 209). In the setting of existing cardiopulmonary disease, the degree of obstruction necessary to cause pulmonary hypertension is likely to be considerably less [40,46].

However, for most patients undergoing antithrombotic therapy, pulmonary perfusion scan

abnormalities and echocardiographic abnormalities steadily improve and typically stabilize over 4 to 6 weeks [48,49]. However, incomplete resolution of perfusion scan defects can be seen and is more common than is generally appreciated. In a review of four clinical studies, normalization of perfusion scan defects occurred in less than 50% of patients when evaluated 6 months after the acute event [50]. In 244 patients who survived a year after an acute pulmonary embolism, Miniati and colleagues [30] showed an improving but incomplete restoration of pulmonary blood flow during this period. At diagnosis, median pulmonary vascular obstruction as assessed by perfusion scans was 42.3% (range, 8.2%–72.9%). After 1 month of antithrombotic therapy, 90% of patients had a residual vascular obstruction of 30% or less; after 1 year, residual pulmonary vascular obstruction was 15% or less in 75% of patients and 5% or less in 75%. Only in 153 of 235 patients (65.1%) was the lung scan assessed as normal. However, because the incidence of CTEPH in this same study was 1.3% (four patients), the fact that chronic thrombotic residual may be common after acute pulmonary emboli strengthens prior observations that they are typically of little hemodynamic consequence [27].

For patients who develop CTEPH, the pathophysiologic mechanisms to explain the progression to pulmonary hypertension remain unclear, although an apparent deviation exists from the normal events described earlier. A large percentage of patients who have established CTEPH—up to 40% to 50% in some series [19,51]—have not been previously diagnosed with acute venous thromboembolic disease, and therefore have not benefited from antithrombotic therapy. One can argue that recurrent, asymptomatic pulmonary emboli [52], or asymptomatic pulmonary emboli whose initial hemodynamic impact failed to resolve [28], may be operative in the development of clinically significant CTEPH in this group of patients. However, another plausible explanation is based on clinical observations in patients diagnosed with acute pulmonary embolic disease who undergo anticoagulant therapy and ultimately develop CTEPH. Two distinct processes seem to occur: (1) nonresolution and organization of the acute thrombus burden in the proximal pulmonary vascular bed, and (2) the gradual development of a peripheral vasculopathy, indistinguishable from that seen in idiopathic pulmonary arterial hypertension, in the vascular bed unencumbered by thrombus. Several observations support this theory: (1) pulmonary hypertension is seen to progress in the absence of recurrent thromboembolic events or in situ thrombosis, as judged by stable perfusion scan defects over time [30]; (2) a poor correlation exists between the extent of proximal vessel involvement and the degree of pulmonary hypertension, suggesting a component of pulmonary vascular resistance (PVR) in the distal, unobstructed vascular bed; (3) histopathology showing hypertensive arteriopathic changes in the resistive vessels of patients who have CTEPH [53] in the obstructed and unobstructed lung regions; (4) persistent post–PTE pulmonary hypertension despite chronic proximal thrombus removal and reestablishment of perfusion to the previously obstructed lung regions.

The reasons for the development of this vasculopathy are being investigated. It has been hypothesized to be secondary to high pressures and sheer stress, although these vessel changes would be expected to occur only in the unobstructed vascular bed [53]. Other possibilities, including genetic factors, have been examined. Bone morphogenetic protein receptor type 2 (BMPR-2) down-regulation has been associated with the development of idiopathic and familial pulmonary arterial hypertension, but has not been observed in patients who have CTEPH [54,55]. Angiopoetin-1, a protein molecule involved in the recruitment of smooth muscle cells around blood vessels, is upregulated in CTEPH and has been associated with other forms of pulmonary hypertension [55]. As is the case in idiopathic pulmonary hypertension, the endothelin system may also be upregulated in patients who have CTEPH [56,57].

Clinical presentation

Patients who have CTEPH typically complain of exertional dyspnea and a gradual decrease in exercise tolerance over months to years. Numerous factors are likely to affect the progression of these symptoms and, therefore, the timing of patient presentation. For example, patient age, previous physical health, state of conditioning, residence at altitude, and comorbid medical conditions (eg, parenchymal lung disease) seem to influence the clinical impact of chronic thromboembolic disease on patients. Although individual tolerances vary, the physiologic basis for these complaints relates to limitations in cardiac performance caused by an elevated PVR, and increased minute ventilatory needs from an elevated alveolar dead space.

Other symptoms are reported with varying frequencies, such as a nonproductive cough (especially with exertion), hemoptysis, and palpitations. A change in voice quality or hoarseness may result from vocal cord dysfunction caused by compression of the left recurrent laryngeal nerve between the aorta and an enlarged left main pulmonary artery. Chest discomfort is often pleuritic in nature, presumptively because of peripherally infarcted lung. However, exertion-related chest pain can also occur, often prompting evaluation for coronary artery disease. This complaint typically occurs late in CTEPH, as does exertion-related presyncope, syncope, and resting dyspnea, with resting dyspnea indicating that right ventricular function is unable to accommodate normal resting metabolic needs.

The nonspecific nature of these complaints undoubtedly contributes to the diagnostic delay experienced by most patients who have chronic thromboembolic disease. Another confounder is that fact that patients who have CTEPH may not provide a history of prior acute symptomatic pulmonary embolism or deep vein thrombosis. Reports indicate that the average delay from the onset of cardiopulmonary symptoms to establishment of the correct diagnosis can range from 2 to 3 years [19,27]. Consequently, many patients are improperly labeled with alternative diagnoses during the course of their illness, such as physical deconditioning, mild chronic obstructive pulmonary disease, congestive heart failure, or, occasionally, psychogenic dyspnea.

Physical examination findings similarly reflect the stage of pulmonary vascular disease at which a patient presents for evaluation. In the absence of right-sided cardiac dysfunction, physical signs attributable to CTEPH may be subtle or absent. Even in the setting of severe pulmonary hypertension, patients can appear relatively well. The examination findings of pulmonary hypertension, such as a right ventricular lift, fixed splitting of the second heart sound with an accentuated pulmonic component, a right ventricular S_4 gallop, and a tricuspid regurgitation murmur, must be carefully discerned. In the absence of coexisting parenchymal lung disease or airflow obstruction, pulmonary auscultation is typically unremarkable. In approximately 30% of patients who have CTEPH, pulmonary flow murmurs can be appreciated [58]. Jugular venous distention, a right ventricular S_3 gallop, severe tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema suggest more advanced right-heart dysfunction. The presence of cyanosis may suggest right-to-left shunting through a patent foramen ovale in patients who have pulmonary hypertension. Lower-extremity examination may also disclose superficial varicosities and venous stasis skin discoloration in patients who have experienced prior venous thrombosis.

Diagnostic evaluation

Patients who have unexplained exertional dyspnea should be carefully evaluated, and pulmonary vascular disease considered. Even some of the more standard diagnostic tests, such as chest radiography and pulmonary function tests, may provide clues to the presence of pulmonary hypertension and chronic thromboembolic disease.

In CTEPH, chest radiography is often unremarkable in the early stages, but several radiographic abnormalities may be apparent as the disease progresses. With significant pulmonary hypertension, dilatation of the central pulmonary arteries often occurs, and patients who have CTEPH frequently exhibit irregularly shaped and asymmetrically enlarged proximal vessels [59]. This finding may be mistaken for hilar adenopathy. With the increasing afterload placed on the right ventricle, radiographic signs of chamber enlargement, such as obliteration of the retrosternal space and prominence of the right heart border, may become apparent. In the absence of coexisting parenchymal lung disease, the lung fields are free of alveolar–interstitial markings, although hypo- and hyperperfused lung regions may be present. In poorly perfused lung regions, peripheral alveolar opacities, linear scar-like lesions, and localized pleural thickening can be observed and often represent sequelae of prior infarctions.

Electrocardiographic findings are similarly dependent on the hemodynamic severity of the disease. Right axis deviation, right ventricular hypertrophy, right atrial enlargement, right bundle-branch block, ST segment displacement, and T-wave inversions in anterior precordial and inferior limb leads can be seen in CTEPH, although they are not specific to this condition.

Pulmonary function testing, commonly performed during an evaluation for dyspnea, is most useful for excluding coexisting parenchymal lung disease or airflow obstruction. For patients who have CTEPH alone, spirometry is generally unremarkable, although in some patients lung

volume measurements may disclose a mild to moderate restrictive defect believed to be related to parenchymal scarring from prior lung infarction [60]. Similarly, a mild to moderate reduction in single-breath diffusing capacity for carbon monoxide (DL_{CO}) can be present in CTEPH, but a normal value does not exclude the diagnosis [61]. A severe reduction in DL_{CO}, however, should prompt consideration of an alternative pulmonary process significantly affecting the distal pulmonary vascular bed.

Even in the setting of significant pulmonary hypertension caused by chronic thromboembolic disease, resting arterial blood gas analysis may show a normal oxygen level (Pao_2), although when measured, dead-space ventilation will frequently be elevated. When exercising, patients who have CTEPH will often exhibit a decline in Pao_2 levels and an inappropriate increase in dead-space ventilation. These findings reflect ventilation–perfusion (V/Q) inequalities and an inappropriate cardiac output response to exercise resulting in a low mixed venous oxygen saturation [62]. Hypoxemia at rest implies very severe right ventricular dysfunction or the presence of a right-to-left shunt, as through a patent foramen ovale.

Transthoracic echocardiography has become a valuable noninvasive tool for evaluating the presence of pulmonary hypertension in patients who have unexplained exertional dyspnea. Currently available technologies allow for an estimate of pulmonary artery systolic pressures using Doppler analysis of the tricuspid regurgitant envelope, and an estimate of cardiac output. Right heart chamber enlargement, abnormal right ventricular systolic function, paradoxical interventricular septal motion, and the impact of an enlarged right ventricle on left ventricular filling are additional echocardiographic findings in the setting of significant pulmonary hypertension [63]. The echocardiogram is also useful for the excluding left ventricular dysfunction, valvular disease, or complex cardiac malformations as possible causes for pulmonary hypertension. Contrast echocardiography after the venous injection of agitated saline is useful in detecting a patent foramen ovale or a previously unsuspected septal defect. In symptomatic patients with echocardiographic evidence of only minimally elevated pulmonary artery pressures or right ventricular compromise at rest, obtaining a study during exercise may document a substantial rise in pulmonary artery pressures along with an increase in right heart size.

With the diagnosis of pulmonary hypertension, radioisotopic V/Q scanning plays a pivotal role in distinguishing between large-vessel occlusive disease and small-vessel pulmonary vascular disease. Patients who have CTEPH will invariably show one or more segmental or larger perfusion defects in lung regions with normal ventilation. This finding contrasts with the normal or subsegmental mottled perfusion pattern observed in idiopathic pulmonary arterial hypertension or other forms of small-vessel pulmonary vascular disease [64,65]. Experts have also observed that the magnitude of perfusion defects in chronic thromboembolic disease often understates the actual degree of vascular obstruction determined with angiography or at surgery [66]. During organization, proximal vessel thromboemboli may recanalize or narrow the vessel in such a manner that radiolabeled macroaggregated albumin may pass beyond the region of partial obstruction to a limited degree, thereby creating *gray zones*, or areas of relative hypoperfusion on the perfusion scan. Furthermore, mismatched segmental or larger defects in patients who have pulmonary hypertension are not specific for chronic thromboembolic disease. Extrinsic vascular compression from mediastinal adenopathy or fibrosis; primary pulmonary vascular tumors such as angiosarcoma; pulmonary venoocclusive disease; and large-vessel pulmonary arteritis may result in a V/Q appearance indistinguishable from CTEPH [67–69]. Consequently, additional imaging studies are needed to define the vascular abnormality and establish the diagnosis.

Largely because of recent improvements in the speed, quality, and resolution of thoracic imaging afforded by the ongoing refinements in multidetector CT, this modality has assumed an increasingly important role in diagnosing and managing thromboembolic disease. CT findings in chronic thromboembolic disease include mosaic perfusion of the lung parenchyma; central pulmonary artery enlargement; right atrial and right ventricular enlargement; variations in the size of lobar and segmental-level vessels (often diminutive in lung regions most involved with chronic thrombi); peripheral, scar-like densities in hypoattenuated lung regions; and the presence of mediastinal collateral vessels arising from the systemic arterial circulation [70–72]. CT imaging is also valuable in providing information on the status of the lung parenchyma in patients who have coexisting emphysematous or restrictive lung disease and in detecting mediastinal

pathology that might account for occlusion of the central pulmonary arteries [73]. This last capability is particularly important in patients who have unilateral occlusion of a main pulmonary artery [74,75].

With well-timed contrast enhancement of the pulmonary vasculature during CT imaging, organized thrombus will often seem to line the larger pulmonary vessels in either a concentric or eccentric manner. Abrupt narrowing and tapering of pulmonary arteries, web-like strictures, pouch defects, and other irregularities of the intimal surface may also be appreciated. These findings should be distinguished from the intraluminal filling defects and abrupt vessel cutoff seen in acute thromboembolic disease. Although the equivalence, if not superiority, of CT to pulmonary angiography for detecting chronic central vascular lesions has been established [72], the ability of the newer multislice scanners to evaluate segmental and subsegmental vessels now seems to be approaching that of pulmonary angiography [76]. Clinicians must recognize, however, that thromboemboli may organize and become endothelialized along the vessel wall in such a manner that their presence on CT angiography may not be apparent. Consequently, the absence of lining thrombus visualized within the central pulmonary vessels on CT scan does not exclude the diagnosis of chronic thromboembolic disease or the possibility of surgical intervention. Conversely, the demonstration of central thrombus has been described in primary pulmonary hypertension and other end-stage lung disorders [77,78]. Surgical endarterectomy in these cases not only involves a substantial perioperative mortality risk but also is unlikely to mitigate the existing pulmonary hypertension.

For patients who have suspected CTEPH, pulmonary angiography represents the gold standard and, when properly performed, remains a safe and reliable way to define the extent and proximal location of organized thromboemboli [79]. Several angiographic patterns have been found to correlate with the presence of chronic thromboembolic material at surgery [80], including vascular webs or band-like narrowings, intimal irregularities, pouch defects, abrupt and often angular narrowing of major pulmonary arteries, and proximal obstruction of pulmonary vessels (Fig. 1). As with CT findings, the angiographic appearance of chronic thromboembolic disease is distinct from the intraluminal filling defects observed after acute pulmonary embolism. In most patients who have CTEPH, two or more of these angiographic findings are present and distributed bilaterally. From a technical standpoint, the diagnostic usefulness of the pulmonary angiogram depends on an appropriately sized and time-contrast bolus and minimization of any chest movement. At UCSD, simultaneous frontal and lateral views are routinely obtained, because the extent of disease may be significantly underappreciated from a single projection.

Cardiac catheterization may be performed at pulmonary angiography, providing valuable information for assessing perioperative risk in patients who have CTEPH. Right heart catheterization defines the severity of the pulmonary hypertension and degree of cardiac dysfunction. Measurements of oxygen saturation in the vena cava, right-sided cardiac chambers, and pulmonary artery can occasionally document left-to-right shunts undetected by echocardiography. Left heart catheterization and coronary arteriography supply essential supplemental information in patients at risk for coronary artery disease or believed to have left heart dysfunction or valvular disease.

Management of chronic thromboembolic pulmonary hypertension: surgical therapy

The evaluation of patients who are believed to have CTEPH is intended to establish whether a PTE (ie, the surgical removal of organized thrombus from the pulmonary vascular bed) is possible and appropriate. An absolute criterion for surgery is the presence of accessible chronic thromboembolic disease. Current surgical techniques allow organized thrombi to be removed from the main, lobar, and proximal segmental vessels. With an accurate determination of surgical accessibility, the clinical prediction that the removal of these lesions will reduce right ventricular afterload and pulmonary pressures is essential to the decision to perform surgery. In this assessment, the clinician must consider the extent of surgically accessible disease in relation to the degree of pulmonary hypertension. The increase in PVR associated with chronic thromboembolic disease seems to arise not only from the central, surgically accessible lesions but also from a distal, small vessel arteriopathy. PTE relieves only the portion of the overall PVR arising from the surgically accessible component of the chronic thromboembolic disease.

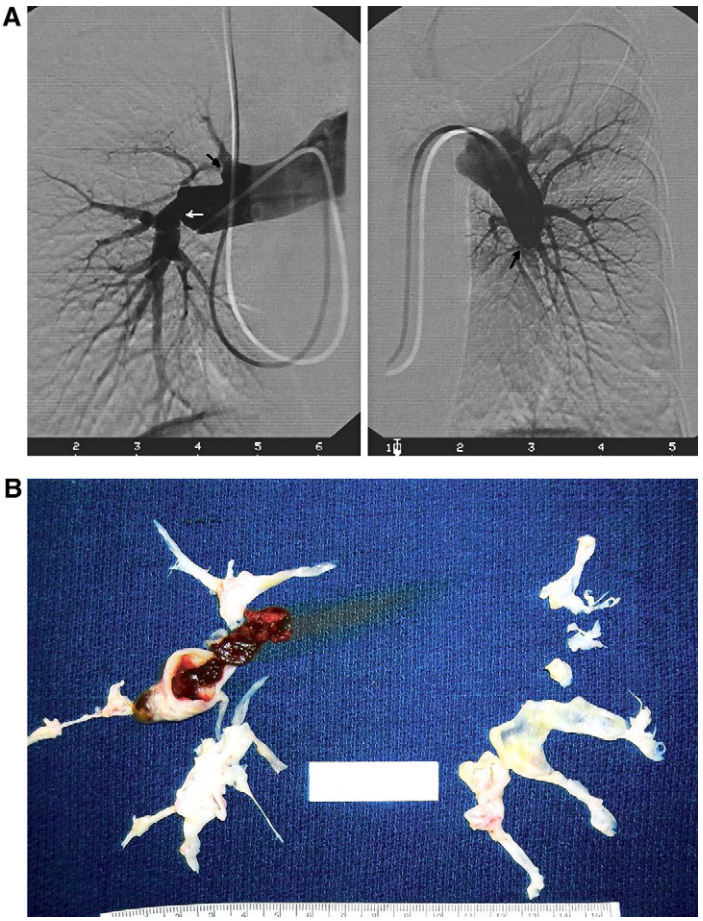

Fig. 1. (*A*) Right and left pulmonary arteriogram in patient who has CTEPH. Dark arrows depict near occlusive "pouch" defects; white arrow indicates vascular narrowing from chronic thrombus in the right interlobar vessel. (*B*) Thromboendarterectomy specimen from patient whose angiogram in shown in Fig. 1A.

When patients have a significant amount of coexisting distal vascular disease, an endarterectomy of the proximal lesions may not substantially reduce the PVR, placing them at risk for hemodynamic instability and death in the early postoperative period. Therefore, a key focus of the preoperative workup is to partition vascular resistance into proximal and distal components. Currently, this determination remains part of the art of the PTE evaluation. When the PVR seems elevated disproportionately to the degree of proximal disease as visualized by CT scan, angiography, or angioscopy [81,82], this information should be considered in discussions of perioperative risks with the patient. Several more quantitative techniques are being investigated with the goal of partitioning "upstream and downstream" components of PVR in patients who have CTEPH [83,84]. Using a pulmonary artery occlusion technique, Kim and colleagues [84] showed a strong negative correlation between the preoperative upstream (or proximal) resistance and postoperative measures of PVR, with all postoperative deaths occurring in patients whose preoperative upstream resistance was less than 60%.

When determining whether PTE surgery is appropriate, the individual patient's symptoms and the personal impact of the disease on functional capabilities and survivorship must be considered. Patients presenting for evaluation typically exhibit significant limitations from the hemodynamic or ventilatory compromise caused by the pulmonary vascular obstruction. Most patients who ultimately undergo surgery have preoperative PVRs greater than 300 dynes/s/cm^{-5}, generally in the range of 700 to 1100 dynes/s/cm^{-5} [17,19–25]. With this

degree of vascular resistance, patient impairment at rest and with exercise can be debilitating and, in the absence of surgical intervention, prognosis is poor [85,86]. For patients who have less severe pulmonary hypertension, surgery is considered based on individual circumstances. Included in this category are patients who have chronic thromboemboli involving one main pulmonary artery, those who have particularly vigorous lifestyle expectations (eg, professional athletes), and those who live at altitude. In such cases, surgery would be performed to alleviate the exercise impairment associated with high dead space and minute ventilatory demands. Surgery is also occasionally offered to patients who have normal pulmonary hemodynamics or mild pulmonary hypertension at rest who have documented pulmonary pressure elevation with exertion. This group of patients has received greater attention because of growing concerns that their pulmonary hypertension will likely progress without surgical intervention.

An assessment of the comorbid conditions that could adversely affect perioperative mortality or morbidity should also be considered when discussing PTE candidacy with patients and their families. Coexisting coronary artery disease, parenchymal lung disease, renal insufficiency, hepatic dysfunction, or the presence of a hypercoagulable state may complicate patient management during the postoperative period. Correction of pulmonary hypertension and right ventricular dysfunction with PTE surgery will often improve hepatic and renal function postoperatively. For patients who have coronary artery or valvular heart disease, coronary artery bypass grafting or valve replacement can be performed at thromboendarterectomy without increased surgical risk [87]. Similarly, advanced age and morbid obesity are not absolute contraindications to PTE, although they impact risk assessment and postoperative management strategies. One exception seems to be the presence of severe parenchymal or obstructive lung disease. The postoperative course in these patients is frequently complicated by prolonged ventilatory support, and once successfully weaned, patients may experience only minimal symptomatic improvement given their underlying pulmonary disease.

A detailed description of the PTE procedure is beyond the scope of this article, although several articles can be referenced [17,88,89]. However, several features of the procedure can be highlighted. Surgical success is founded on the concept that a true endarterectomy to remove the organized thrombi is to be accomplished, not an embolectomy. The chronic thromboembolic material is fibrotic and incorporated into the native vascular wall. An endarterectomy involves identification of the ''pseudo-intima'' and creation of a dissection plane to adequately free the thrombotic residua from the central pulmonary vascular bed. Removal of nonadherent, partially organized thrombus within the lumen of the central pulmonary arteries without the full endarterectomy is ineffective in reestablishing blood flow and reducing right ventricular afterload. Cardiopulmonary bypass with periods of circulatory arrest is essential to ensure optimal exposure of the pulmonary vascular intima in a bloodless field. The significant back-bleeding created by bronchial arterial blood flow is mitigated through interrupting cardiopulmonary bypass (circulatory arrest periods). This exposure allows the circumferential dissection of thromboembolic residua from the involved lobar, segmental, and subsegmental vessels.

Safeguards to ensure tissue integrity therefore become an integral component of this surgical procedure, allowing circulatory arrests to be accomplished without adverse consequences. Although standard flow for cardiopulmonary bypass is used, the patient is systemically cooled to 20°C. Hemodilution to a hematocrit in the range of 18% to 25% is performed to decrease blood viscosity during hypothermia and to optimize capillary blood flow. Additional cerebral protection is provided by surrounding the head with ice and a cooling blanket, and phenytoin is administered intravenously during the cooling period to reduce the risk for perioperative seizure activity. When the patient's temperature reaches 20°C, the aorta is cross-clamped and a single dose of cold cardioplegic solution is administered. Further myocardial protection is achieved with the use of a cooling jacket wrapped around the heart. After the aorta is cross-clamped, thiopental is administered until the electroencephalogram becomes isoelectric. When the patient is cooled to the optimal level of hypothermia, periods of circulatory arrest can be initiated. The endarterectomy can proceed at this point, usually first on the right side, then on the left. After the endarterectomy is completed, cardiopulmonary bypass is resumed and rewarming commenced. Given the high incidence of sinus arrest within the first 24 hours postendarterectomy, atrial and ventricular epicardial wires are placed. Mediastinal chest tubes also are left in place to evacuate any accumulated blood during the first two to three postoperative

days. After rewarming and successful defibrillation of the heart, cardiopulmonary bypass is discontinued and mechanical ventilation resumed.

The short-term and long-term hemodynamic outcomes have been favorable in most patients who have CTEPH who undergo thromboendarterectomy surgery. With restoration of blood flow to previously occluded lung segments, an immediate reduction in right ventricular afterload occurs, resulting in a decline in pulmonary artery pressures and an augmentation in cardiac output. Since 1997, several groups have reported this improvement in pulmonary hemodynamics after surgery [17,22–25,90–92]. Furthermore, studies have reported this hemodynamic improvement to be sustained months to years postendarterectomy, accompanied by substantial gains in functional status, gas exchange, and quality of life [20,93–97]. However, not all patients who have CTEPH experience normalization or near-normalization of their pulmonary hemodynamics after undergoing endarterectomy surgery; approximately 10% to 15% of patients are left with a residual PVR more than 500 dynes/s/cm^{-5}. Although the postoperative hemodynamic improvement is significant in two thirds of these patients, approximately 3% to 5% of patients experience minimal to no hemodynamic benefit from surgery. This finding is based the presence of a distal vasculopathy, with PVR, pulmonary arterial pressures, and cardiac function unaffected by whatever amount of proximal vessel chronic thromboembolic material was removed. If the patient survives the immediate postoperative period, long-term pulmonary vasodilator therapy, such as the use of intravenous epoprostenol or an endothelin antagonist, should be considered.

In patient series reported since 1996, operative mortality rates range from 4.4% to 24% [17,21–25,90–92,98]. Factors contributing to perioperative mortality risks have not been completely elucidated, although New York Heart Association (NYHA) class IV functional status, age older than 70 years, the presence of right ventricular failure (correlated with high right atrial pressures), morbid obesity, and the duration of pulmonary hypertension have been to reported to impact postoperative survivorship [17,21,90,99,100]. Several studies have also suggested that more severe preoperative pulmonary hypertension correlates with higher postoperative mortality rates. In a report by Hartz and associates [21], a preoperative PVR more than 1100 dynes/s/cm^{-5} and a mean pulmonary artery pressure more than 50 mm Hg predicted a significantly higher operative mortality. Similarly, Tscholl and colleagues [90] showed that a preoperative PVR more than 1136 dynes/s/cm^{-5} adversely influenced postoperative survivorship. Furthermore, in a report of 500 patients who had PTE, Jamieson and colleagues [17] showed that a preoperative PVR of more than 1000 dynes/s/cm^{-5} was associated with an significantly higher operative mortality rate of 10.1% compared with only 1.3% in those who had a lower preoperative PVR. Causes of death after PTE surgery are variable, and include cardiac arrest, multiorgan failure, uncontrollable mediastinal bleeding, sepsis syndrome, and massive pulmonary hemorrhage [21,23–25,90]. However, a series involving 1500 patients showed that severe reperfusion lung injury and residual pulmonary hypertension and right ventricular dysfunction were the leading contributors to perioperative mortality [17]. Results from this same group have also shown that long-term survivorship after hospital discharge is dramatically improved relative to the expected longevity if these patients had forgone surgical intervention. In a cohort of 532 patients followed up postoperatively for up to 19 years, Archibald and colleagues [96] showed a 75% probability of survivorship beyond 6 years.

Management of chronic thromboembolic pulmonary hypertension: medical therapy

Pharmacotherapy for treating pulmonary hypertension may be beneficial in select patients who have chronic thromboembolic disease. Four distinct patient groups to consider include (1) patients who have surgically accessible CTEPH who elect not to undergo PTE surgery because of personal choice or in whom comorbidities are so significant that surgery is contraindicated; (2) patients who have severe pulmonary hypertension and right ventricular dysfunction who exhibit distal chronic thromboembolic disease or a limited amount of resectable chronic thrombus, and therefore are unlikely to benefit from attempted PTE surgery; (3) patients who have not yet undergone PTE who have severe pulmonary hypertension and right heart failure, in whom pharmacotherapy would be a ''stabilizing bridge'' to surgery to reduce the postoperative mortality risk; and (4) patients who have undergone PTE and have residual pulmonary hypertension. Data examining the use of pulmonary vasodilator therapy in each one of these groups are limited.

However, based on the pathophysiologic mechanisms explaining the evolution of pulmonary hypertension in chronic thromboembolic disease, the use of vasodilator therapy in select patients warrants careful evaluation.

For inoperable CTEPH, Ono and colleagues [101] evaluated the use of beraprost (an oral prostacyclin analog) and conventional therapy in a small group of patients (N = 20) compared with a matched group (N = 23) undergoing conventional therapy alone. Fifty (50%) percent of patients in the beraprost group experienced an improvement in functional class during a follow-up period of 2 ± 1 month, and no functional class improvement was seen in patients only undergoing conventional therapy. During this same period, hemodynamic measurements were performed in a small number of patients (n = 10). Overall, the decline in mean PA pressure and total peripheral resistance was modest, although statistically significant, an no significant rise in cardiac output occurred. Throughout the extended follow-up period, improved survivorship was also seen in the patients treated with beraprost.

More recently, the use of bosentan, an endothelin receptor antagonist, has been studied in patients who have inoperable CTEPH. Bonderman and colleagues [102] evaluated 16 patients treated with bosentan for 6 months, showing an improvement in NYHA functional status in 11 patients, a reduction in pro-brain natriuretic peptide levels (pro-BNP), and an improvement in 6-minute walk distance. In a retrospective study, Hughes and colleagues [103] reported on 47 patients who had CTEPH treated with bosentan for a year (39 patients who had distal chronic thromboembolic disease and 8 patients who had post-PTE pulmonary hypertension), and obtained hemodynamic data on 28 patients at 1 year. Overall, an improvement was seen in 6-minute walk distance, functional classification, cardiac index, and total pulmonary resistance. The greatest improvement was observed in patients who had pulmonary hypertension after undergoing endarterectomy surgery. In an open-label pilot trial evaluating 3 months of bosentan therapy in 19 patients who had inoperable CTEPH, Hoeper and colleagues [104] showed that a significant reduction in pulmonary vascular resistance, an increase in 6-minute walk distance, and an improvement in pro-BNP levels occurred.

Sildenafil, a PDE-5 inhibitor, has also been studied to a limited extent in patients who have inoperable CTEPH. Ghofrani and colleagues [105] treated 12 patients who had CTEPH with sildenafil for 6 months. Baseline hemodynamics showed severe pulmonary hypertension (PVR index, 1935 ± 228 dyn/s/cm^{-5}; cardiac index, 2.0 L/min^{-1}/m^{-2}), with acute pulmonary vasoreactivity documented at initial right heart catheterization (inhaled nitric oxide and sildenafil). After 6 months, 6-minute walk distance substantially increased, PVR index was markedly improved, and cardiac index significantly increased. Sheth and coworkers [106] examined the effects of sildenafil in six patients who had severe inoperable CTEPH and left ventricular dysfunction. At 6 weeks, an improvement was seen in mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, dyspnea scores, and NYHA functional class.

Given the greater perioperative mortality rates seen in patients who have operable chronic thromboembolic disease with severe pulmonary hypertension [17,21,90], experts hypothesize that using pulmonary vasodilator therapy preoperatively may have beneficial effects on early postoperative survival. Using intravenous prostacyclin for a period of 46 ± 12 days before surgery, Nagaya and colleagues [107] showed a preoperative decrease in PVR of 28% (1510 + 53 dynes/s/cm^{-5} to 1088 + 58 dynes/s/cm^{-5}) and a reduction in BNP levels in 12 patients who ultimately underwent pulmonary thromboendarterectomy. Postoperative mortality in this group was 8.3% compared with no deaths in the 21 patients who had CTEPH with a preoperative PVR of 1200 dynes/s/cm^{-5} or less. Postoperative hemodynamic improvement was comparable between the groups. Although this study was able to show a hemodynamic benefit of prostacyclin in a small number of patients who had severe pulmonary hypertensive CTEPH, the effect of pulmonary vasodilator pretreatment as a bridge to PTE and its effects on postoperative outcome remain unknown. As a result, the use of pulmonary vasodilator therapy in patients who have CTEPH who are likely to have operable chronic thromboembolic disease should not inappropriately delay surgical intervention.

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