Concise Clinical Review

Chronic Thromboembolic Pulmonary Hypertension

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Over the past 4 decades, chronic thromboembolic pulmonary hypertension has evolved from an autopsy curiosity to a potentially correctable form of pulmonary hypertension. Advances in surgical techniques along with the introduction of pulmonary hypertension disease–modifying therapies provide a therapeutic option for the majority of patients afflicted with the disease. Approximately 5,000 thromboendarterectomy procedures have now been performed worldwide with mortality rates reported by established programs experienced in the management of this disease process falling to a range of 4 to 7%. A mortality rate of 1.3% has been reported in patients at low risk based on their preoperative hemodynamic profile. After a successful pulmonary thromboendarterectomy, substantial improvement and often normalization can be achieved in right ventricular function, gas exchange, exercise capacity, and quality of life. For patients not candidates for thromboendarterectomy, or for those with persistent post-thromboendarterectomy pulmonary hypertension, disease-modifying medical therapies have been demonstrated to stabilize and improve pulmonary hemodynamics, albeit not to the same extent as primary thromboendarterectomy. The current review focuses on the diagnostic approach to chronic thromboembolic pulmonary hypertension and the available surgical and medical therapeutic options. Additional research is necessary to more accurately predict postoperative hemodynamic outcome and to define the optimal therapeutic approach, especially in patients with involvement of the distal vasculature.

Keywords: pulmonary embolism; pulmonary hypertension; chronic thromboembolic pulmonary hypertension; pulmonary thromboendarterectomy

Chronic thromboembolic pulmonary hypertension (CTEPH) is the result of single or recurrent pulmonary emboli arising from sites of venous thrombosis. Although anatomic resolution of acute embolism is often incomplete, sufficient resolution occurs in the majority of patients to restore normal pulmonary hemodynamics associated with a return to a preembolism functional status. A recent metaanalysis evaluating the resolution of acute pulmonary embolism revealed that 52% of patients had evidence of residual emboli 11 months after the acute event (1). Miniati and colleagues found that the lung perfusion scan continued to demonstrated abnormalities in 35% of patients 1 year after the acute event, although the degree of pulmonary vascular obstruction was less than 15% in 90% of the patients (2).

For reasons still unclear, a divergent natural history occurs in certain patients, resulting in the development of CTEPH. Incomplete thromboembolic resolution results in endothelialized residua that obstruct or significantly narrow major pulmonary arteries. The development over time of a distal, small-vessel vasculopathy appears to contribute to the right ventricular afterload and progression of pulmonary hypertension (3, 4). The pathogenesis and time course of this vasculopathy remain unclear. Neither is it known whether the development of this vasculopathy is dependent on the extent, location, and/or susceptibility to lysis of the obstructing emboli or whether it requires a genetic predisposition. Pulmonary hypertension will develop once a threshold level of pulmonary vascular obstruction is reached. However, it has been observed that a relatively modest degree of central pulmonary vascular obstruction can result in progressive pulmonary hypertension in some patients. This latter population represents unique challenges in diagnosis, determination of operability, and short- and long-term management.

EPIDEMIOLOGY AND PATHOGENESIS

The role of acquired and hereditary risk factors in the development of CTEPH has not been fully defined. The antiphospholipid antibody syndrome is the most common hypercoagulable state associated with CTEPH, occurring in up to 20% of patients (5). Increased levels of factor VIII have been reported in patients with CTEPH when compared with patients with nonthrombotic pulmonary hypertension and to controls (6). The frequency of protein S or C deficiency, factor V Leiden mutation, and the prothrombin 20210G mutation have not consistently been found to be more common in CTEPH than in the general population. In terms of medical conditions, CTEPH has been associated with myeloproliferative syndromes as well as chronic inflammatory states, chronic ventriculoatrial shunts, splenectomy, recurrent episodes of venous thromboembolism, and chronic indwelling central venous catheters (7). Regarding details of the acute embolic event, systolic pulmonary artery pressure greater than 50 mm Hg at the time of diagnosis of acute embolism, systolic pulmonary artery pressure greater than 50 mm Hg at the time of hospital discharge after acute embolism, previous pulmonary embolism, and a larger degree of pulmonary vascular obstruction at the time of acute pulmonary embolism diagnosis have been identified as risk factors for CTEPH (8–13).

Initial estimates suggested that 0.1 to 0.5% of patients surviving an episode of acute pulmonary embolism would develop CTEPH (14). More recently, prospective observational studies suggest the cumulative incidence of CTEPH to be in the range of 0.57 to 3.8% (2, 8, 9, 15, 16). In the largest of these studies, a cohort screening study involving 866 survivors of acute pulmonary embolism, 4 patients were ultimately diagnosed with CTEPH. The cumulative incidence of CTEPH was 0.57% in the overall population and 1.5% in patients with unprovoked embolism (15). Because postembolism observational studies do not include patients referred for pulmonary thromboendarterectomy who present without a discrete history of acute pulmonary embolism, this incidence figure may understate the true incidence of the disease.

Complicating estimates of the overall scope of the problem are widely disparate, extrapolated estimates of the annual

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incidence of pulmonary embolism in the United States. Data derived from the National Center for Health Statistics Multiple-Cause Mortality Files listed pulmonary thromboembolism as the cause of death or contributing cause of death in 24,979 decedents in 1998 (17). It has been well documented, however, that the antemortem diagnosis of pulmonary embolism substantially understates the true incidence (18). Based on a case fatality rate of 8 to 10%, there may be as many as 200,000 survivors of embolism annually in the United States (19). The number of thromboendarterectomy procedures performed annually in the United States is unknown. However, based on an estimated incidence of CTEPH of 1%, as many as 2,000 patients would be potentially eligible for the procedure.

Although acute pulmonary embolism represents the initiating event for CTEPH, several lines of evidence suggest that subsequent progression of the disease involves secondary events in the pulmonary microvascular circulation. Lung biopsy findings obtained at the time of PTE surgery demonstrate histopathologic changes in the microvasculature similar to those seen in other forms of small-vessel pulmonary hypertension, distal to both obstructed and nonobstructed central arteries (3). Studies have also demonstrated a poor correlation between the scintigraphic and angiographic extent of central thromboembolic obstruction and the severity of hemodynamic compromise, suggesting that a component of the elevated pulmonary vascular resistance is arising from a compartment other than the central pulmonary vasculature (20, 21). Supporting this dual compartment model of vascular resistance are reports of varying levels of postoperative pulmonary hypertension in as many as 35% of patients with CTEPH despite a satisfactory surgical endarterectomy of major vessel chronic thromboemboli (22). Finally, patients with inoperable chronic thromboembolic disease and those with persistent postoperative pulmonary hypertension have been demonstrated to derive benefit from disease-modifying pulmonary hypertension therapy (23–25). These agents should have no effect on the central, fixed vascular obstruction associated with residual embolic obstruction and can be assumed to be exerting their effects on the pulmonary microvasculature.

CLINICAL PRESENTATION

The clinical presentation of CTEPH is similar to other variants of pulmonary hypertension. The complaint common to patients with CTEPH is exertional dyspnea, the result of increased dead space ventilation as well as a limitation in cardiac output response to increased physiologic demand (26, 27). With disease progression and further limitation of cardiac output, exertion-related presyncope, frank syncope, and exertional chest pain may develop. The latter may be due to decreased right ventricular systolic flow related to increased right ventricular systolic pressure and mass (28). Physical examination findings early in the course of the disease may be entirely unremarkable, thereby contributing to diagnostic delay. As disease progression occurs, findings consistent with pulmonary hypertension develop: prominence of the right ventricular impulse, a closely split second heart sound with accentuation of its pulmonic component, a right ventricular S4 gallop, and varying degrees of tricuspid regurgitation. With the onset of right ventricular failure, jugular venous distension, peripheral edema, hepatomegaly, ascites, a right-sided S_3, and a widened split of the second heart sound may be present. Pulmonary flow bruits encountered in approximately 30% of patients with CTEPH are best appreciated during an inspiratory, breath-holding maneuver and appear to result from turbulent flow across partially obstructed central pulmonary vascular segments (29). Although not unique to chronic thromboembolic disease, having been described in other disease states associated with focal narrowing of large pulmonary arteries (e.g., congenital branch stenosis or large vessel pulmonary arteritis), they have not been described in pulmonary hypertensive disorders arising from the microvasculature.

The nonspecific and often subtle clinical presentation of CTEPH, especially early in the course of the disease, demands that a high level of suspicion be maintained in patients presenting with unexplained dyspnea. Diagnostic delay remains common, especially in patients without a prior documented history of venous thromboembolism. Careful consideration should be given to prior medical conditions and the circumstances surrounding the onset of dyspnea and/or exercise intolerance. In retrospect, patients without a documented history of venous thromboembolism often provide a history consistent with that diagnosis, such as an episode of pneumonia or a surgical procedure from which they never fully recovered.

Underscoring the importance of correct, early diagnosis is the issue of long-term survivorship in the absence of appropriate treatment. Survival without intervention is poor, and, similar to other forms of pulmonary hypertension, is proportional to the degree of pulmonary hypertension and 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 was greater than 40 mm Hg and 10% when it was greater than 50 mm Hg (30). In another study, a mean pulmonary artery pressure greater than 30 mm Hg appeared to serve as a threshold value portending a poor prognosis (31). Furthermore, early diagnosis and intervention may reduce the likelihood of developing a secondary vasculopathy, thereby potentially reducing perioperative mortality risk, enhancing the likelihood of restoring normal postoperative pulmonary hemodynamics, and optimizing long-term hemodynamic and functional outcome. Elevation of the preoperative pulmonary vascular resistance beyond 1,000 dyne s/cm^5, which is often substantially contributed to by the secondary vasculopathy, has been associated with an increased perioperative mortality and a less than optimal postoperative hemodynamic outcome (32–37).

DIAGNOSTIC EVALUATION

The primary evaluation goals in patients with suspected CTEPH are to confirm the presence of organized thromboembolic pulmonary vascular obstruction and to quantify the degree of hemodynamic impairment. Beyond these central goals, however, are a number of auxiliary goals that directly affect subsequent management decisions. These include the surgical accessibility of the disease and an estimation of the anticipated postoperative hemodynamic result. This interpretation of the hemodynamic-anatomic abnormalities remains largely subjective and requires a substantial amount of clinical experience.

The initial objective evidence for the presence of pulmonary hypertension is commonly provided with transthoracic echocardiography. Routine cardiopulmonary screening after an episode of pulmonary embolism has a low yield in the detection of CTEPH and does not appear to increase detection beyond that provided by routine clinical practice (16). As in other forms of pulmonary hypertension, standard echocardiography can provide only an estimate of pulmonary hemodynamics. Preliminary data suggest that the echocardiographically derived right ventricular Tei index, an indicator of right ventricular myocardial performance, correlates well with pulmonary vascular resistance (38). Although not specifically studied in CTEPH, exercise echocardiography may demonstrate an increase in pulmonary artery pressure or right ventricular dilatation in symptomatic

patients with normal or only modestly elevated pulmonary artery pressures at rest.

The finding of pleural abnormalities or regions of avascularity on a chest radiograph can suggest a chronic thromboembolic basis for the pulmonary hypertension (39). Approximately 20% of patients will demonstrate a mild restrictive ventilatory defect, which appears to be related to parenchymal scarring associated with acute embolism (40). Some degree of hypoxemia is common and is related to a moderate ventilation/perfusion (V/Q) inequality and a depressed mixed venous saturation resulting from limitation in cardiac output (26). A reduced diffusion capacity for carbon monoxide is common and appears to be predominantly related to a reduction in pulmonary membrane diffusion capacity (41).

Despite being supplanted by computed tomographic (CT) angiography in the diagnostic pathway for acute pulmonary embolism, V/Q scintigraphy continues to have a pivotal role in the evaluation of patients with pulmonary hypertension. A single-center retrospective survey comparing V/Q scanning with CT angiography in 227 patients with pulmonary hypertension revealed a sensitivity of 97.4% for V/Q scanning but only 51% for CT angiography in the detection of chronic thromboembolic disease (42). Reliance on CT angiography as a screening tool to differentiate CTEPH from other variants of pulmonary hypertension, therefore, may overlook a substantial number of patients with potentially operable chronic thromboembolic disease.

With the exception of pulmonary venoocclusive disease in which segmental defects have been described, the perfusion scan in disorders of the distal pulmonary vascular bed is normal or exhibits a mottled appearance characterized by nonsegmental defects (43). Alternatively, the V/Q scan in chronic thromboembolic disease is characterized by at least one, and more commonly several, segmental or larger mismatched perfusion defects. The degree of perfusion scan abnormality can substantially understate the degree of obstruction determined angiographically or at surgery (20). Therefore, the presence of even a single, mismatched segmental perfusion defect in a patient with pulmonary hypertension should raise concerns regarding a thromboembolic basis. Segmental perfusion defects in patients with pulmonary hypertension may result from nonembolic disorders, such as extrinsic vascular compression, pulmonary vasculitides, mediastinal fibrosis, or pulmonary artery sarcoma.

CT angiography, although not recommended as a routine screening tool, may demonstrate a variety of parenchymal, vascular, or mediastinal abnormalities in patients with CTEPH. These include a mosaic parenchymal perfusion pattern, parenchymal scars, enlargement of the right ventricle and/or central pulmonary arteries, asymmetry in the size and distribution of lobar and segmental vessels, intraluminal thrombus, organized thrombus lining the pulmonary vascular walls, arterial webs or bands, and mediastinal collateral vessels (44). Accuracy of CT scanning has improved with technological advances. In a preliminary study involving 27 patients with suspected CTEPH, sensitivity of 64-detector row CT was 98.3% at the main and lobar level and 94% at the segmental level when compared with digital subtraction angiography (45). When indicated, CT scanning also may be useful in excluding potential differential possibilities, such as mediastinal fibrosis, extrinsic vascular compression, or pulmonary artery sarcoma (Figure 1).

Magnetic resonance (MR) imaging has the potential to provide both anatomic and hemodynamic information (46). However, as is the case with CT angiography, studies comparing MR techniques to conventional angiography as a basis for surgical referral remain limited.

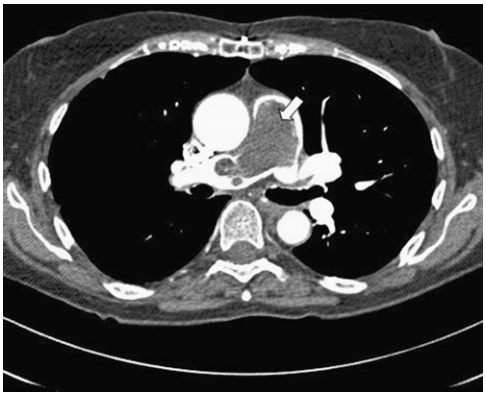

Figure 1. Computed tomography angiogram demonstrating large mass nearly occluding the main pulmonary artery (*arrow*) and extending into the right and left pulmonary arteries representing a pulmonary artery sarcoma.

A positive CT or MR angiogram can be used as a basis for surgical intervention in selected patients. Technologic advances in both MR and CT scanning, their three-dimensional capabilities, and the lack of radiation exposure and ability to provide hemodynamic information in the case of MR imaging suggest they may play an expanded role in the future. However, until further comparative and outcome studies have been performed, their wholesale substitution for conventional angiography does not yet appear warranted.

The reference standard for the diagnosis and determination of surgical accessibility remains combined right heart catheterization (to quantify the hemodynamic impairment) and conventional pulmonary angiography (to determine the extent and proximal location of the chronic thromboembolic obstruction). Vasodilator testing does not appear to be useful or necessary in determining operability, although preliminary data in a small cohort of patients suggest that preoperative vasodilator responsiveness (>10.4% reduction in mean pulmonary artery pressure) is associated with an improved long-term hemodynamic outcome in patients who subsequently undergo thromboendarterectomy (47).

Even in the presence of severe pulmonary hypertension, pulmonary angiography can be performed safely in patients with CTEPH (48). In terms of angiographic technique, multiple selective injections are not required. A single injection of nonionic contrast into both proximal pulmonary arteries, with the volume and injection rate adjusted based on cardiac output, can provide sufficient anatomic detail. Biplane acquisition provides optimal anatomic detail, the lateral projection providing more detailed definition of lobar and segmental anatomy than can be achieved with an anteroposterior view alone (Figure 2). Under essentially all circumstances, a properly performed biplane angiogram will provide sufficient information on which to base a decision regarding surgical accessibility.

Five discrete angiographic abnormalities have been described in chronic thromboembolic disease: (*1*) pouch defects; (*2*) pulmonary artery webs or bands; (*3*) intimal irregularities; (*4*) abrupt, often angular narrowing of the major pulmonary arteries; and (*5*) complete obstruction of main, lobar, or segmental vessels at their point of origin (49). In most patients with chronic thromboembolic disease, two or more of these angiographic findings are present, typically involving both lungs.

Pulmonary angioscopy was developed as an adjunct to pulmonary angiography at the University of California, San Diego (50). The angioscope is a flexible fiberoptic device capable

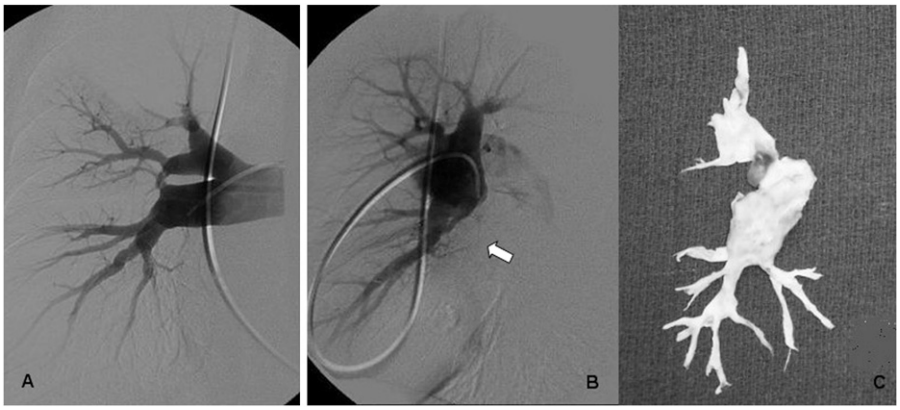

Figure 2. (*A*) Right anteroposterior and (*B*) lateral digital subtraction angiogram in a patient with chronic thromboembolic pulmonary hypertension. Note enhanced detail provided by the lateral projection demonstrating absent flow to superior and posterior basal segment arteries (*arrow*). (*C*) Specimen obtained at the time of thromboendarterectomy.

of being passed through the right atrium and right ventricle into the pulmonary arteries by way of an internal jugular or femoral percutaneous approach. Distal balloon inflation with carbon dioxide transiently obstructs proximal blood flow and provides visualization of the vascular bed. Although useful in predicting hemodynamic outcome in patients with mild pulmonary hypertension and confirming operability in patients with severe pulmonary hypertension, its use has been supplanted by improved and less invasive imaging techniques and interpretation.

SURGICAL SELECTION

Pulmonary thromboendarterectomy (PTE) remains the procedure of choice in symptomatic patients with surgically accessible CTEPH. Confounding any discussion of operability, however, is a lack of consensus regarding the desired hemodynamic goal of surgery. That is, whether PTE should be limited to those in whom normalization of pulmonary hemodynamics is expected and, if not, whether there is a threshold level of absolute reduction in pulmonary vascular resistance (PVR), relative PVR reduction, or anticipated postoperative PVR for which surgery would provide a justifiable benefit. Contributing to this lack of consensus is the subjective nature of the preoperative evaluation during which partitioning the operable, thromboembolic component from the inoperable distal component and concurrent microvascular disease is attempted. With experience in anatomic–hemodynamic correlation, this determination can be made with reasonable accuracy. This determination is an essential one in that failure to lower pulmonary vascular resistance, especially in patients with severe pulmonary hypertension and right ventricular dysfunction, may be associated with hemodynamic instability and death in the early postoperative period. In a series by Thistlethwaite and colleagues involving 1,100 consecutive operated patients, the overall mortality was 4.7% (34). The overwhelming majority of deaths occurred in those with a postoperative PVR greater than 500 dyne·s/cm^5. Patients with disease proximal to the segmental arteries, a group encompassing 80% of operated patients, had a lower mortality and more favorable hemodynamic outcome in terms of both absolute and relative reduction in PVR.

An attempt to objectively partition the different elements of the vascular resistance has been investigated. Kim and colleagues, using pulmonary artery occlusion waveform analysis, demonstrated excellent inverse correlation between the percent upstream resistance and postoperative mean pulmonary artery pressure and pulmonary vascular resistance (33). All four deaths in this series occurred in patients in whom the upstream resistance was less than 60%. This technique requires specialized equipment, and obtaining adequate occlusion waveforms has proven to be problematic in patients with chronic thromboembolic disease.

Reesink and colleagues evaluated the correlation between endothelin-1 (ET-1) levels and the hemodynamic severity in patients with thromboembolic pulmonary hypertension (52). As is the case with nonthromboembolic variants of pulmonary hypertension, ET-1 levels correlated strongly with preoperative hemodynamic values. Preoperative ET-1 levels also proved to be predictive of an adverse postoperative outcome defined as either death or the presence of persistent pulmonary hypertension. An ET-1 level greater than 1.77 pg/ml had a sensitivity of 79% and a specificity of 85% for these outcomes.

At centers reporting their experience with PTE surgery, mean preoperative pulmonary vascular resistance typically falls within the range of 600 to 1,200 dyne s/cm^5. Certain patients may present with significant dyspnea and minimally abnormal resting pulmonary hemodynamics. Such patients include those with proximal unilateral disease, those with vigorous lifestyle expectations, and those who live at altitude. PTE is effective in these patients by alleviating the exercise impairment associated with their high dead space and minute ventilatory demands (27). Surgery should also be considered in patients with mild levels of pulmonary hypertension at rest who develop significant levels of pulmonary hypertension with exercise. There is a natural tendency to avoid this invasive, high-risk intervention in patients with only modest levels of pulmonary hypertension. However, given what is currently known about the natural history of the disease and the potential for progressive pulmonary hypertension associated with the development of a distal vasculopathy, early surgical intervention may be warranted. If the decision is made to defer surgery, then careful follow-up is required to assure that progressive pulmonary hypertension does not occur.

Placement of an inferior vena cava filter should be considered before surgery given the risk of embolic recurrence both over the long term and especially during the high-risk perioperative period when bleeding complications may contraindicate the administration of even prophylactic doses of anticoagulation. Coronary angiography should also be considered preoperatively for those at risk of coronary artery disease. Coronary artery bypass surgery, if necessary, can be done without additional operative risk at the time of the PTE (53).

SURGICAL MANAGEMENT AND OUTCOME

Early attempts at PTE used a thoracotomy or transverse sternotomy approach without cardiopulmonary bypass (54). The current approach, established and subsequently modified at the University of California, San Diego (UCSD), involves

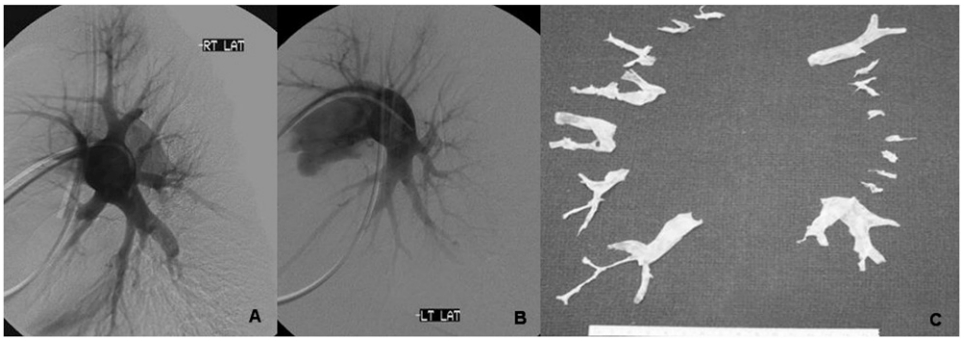

Figure 3. (*A*) Right and (*B*) left lateral pulmonary angiogram demonstrating chronic thromboembolic obstruction of multiple segmental arteries. (*C*) Specimen obtained at the time of thromboendarterectomy confirming segmental-level disease. Preoperative pulmonary artery pressure = 84/32, pulmonary vascular resistance (PVR) = 820 dyne·s/cm^5. Postoperative pulmonary artery pressure = 42/14, PVR = 162 dyne·s/cm^5.

median sternotomy, cardiopulmonary bypass, and periods of hypothermic circulatory arrest (55). A median sternotomy provides access to the central pulmonary vessels of both lungs and avoids the potential for disruption of the extensive bronchial collateral circulation and pulmonary adhesions that may develop after longstanding pulmonary artery obstruction. The use of cardiopulmonary bypass with periods of hypothermic circulatory arrest avoids back-bleeding from retrograde bronchial artery-to–pulmonary artery anastomoses and provides the necessary bloodless field to perform the meticulous dissection required for an optimal procedure. Modifications of this approach intended to avoid the neurologic complications of deep hypothermia and/or circulatory arrest have been described and include the use of moderate hypothermia (28–32°C), aortic bronchial artery occlusion with a balloon catheter, antegrade cerebral artery perfusion with and without total circulatory arrest, and application of negative pressure in the left ventricle (56–58). It has not yet been demonstrated that any of these modifications provides substantive benefit when compared with the traditional technique.

In the majority of patients undergoing PTE, both the short-term and long-term hemodynamic outcomes are favorable. A dramatic and immediate post-PTE reduction, and at times normalization, of the mean pulmonary artery pressure and pulmonary vascular resistance occurs. The mean reduction in pulmonary vascular resistance has approximated 70 percent and a PVR in the range of 200 to 350 dyne·s/cm^5 can be achieved (59).

Overall perioperative (30-d) mortality rates at centers experienced in the management of this disease process have dropped to the range of 4 to 7%. A mortality rate of 1.3% has been reported in patients at low risk based on their preoperative hemodynamic profile (35). Potentially contributing to the improved outcome is a better understanding of the natural history of the disease, earlier and more selective surgical referral, improved diagnostic techniques, and advances in postoperative care. Surgical expertise and experience are essential and endarterectomy of disease limited to the segmental level can result in a satisfactory outcome (Figure 3). As longer-term data have accrued, it appears the hemodynamic and functional improvements are sustained (22, 60, 61). Most patients initially in New York Heart Association (NYHA) functional class III or IV preoperatively return postoperatively to NYHA class I or II and are able to resume normal activities.

Attributable reported causes of death after PTE surgery are consistent with those associated with other high-risk, open-heart procedures. Cardiac arrest, multiorgan failure, uncontrollable mediastinal bleeding, sepsis syndrome, and massive pulmonary hemorrhage are among the causes of death cited. In recent series, the major causes of postoperative morality are right ventricular failure related to persistent pulmonary hypertension and acute lung injury.

Depending on the definition, estimates of the number of patients with persistent pulmonary hypertension after PTE have varied between 5 and 35% (22, 37, 51, 62). Whether this is related to surgically inaccessible chronic thromboembolic disease or to a distal vasculopathy is uncertain.

The early intensive care management goals for the patient with persistent pulmonary hypertension after attempted PTE should be directed toward minimizing systemic oxygen consumption, optimizing right ventricular preload, and providing inotropic support. Attempts to pharmacologically reduce right ventricular afterload in the early postoperative period may result in adverse consequences. Pulmonary vascular resistance is commonly fixed and attempts at pharmacologic manipulation of right ventricular afterload may result in systemic hypotension and decreased right coronary artery perfusion pressure. Limited

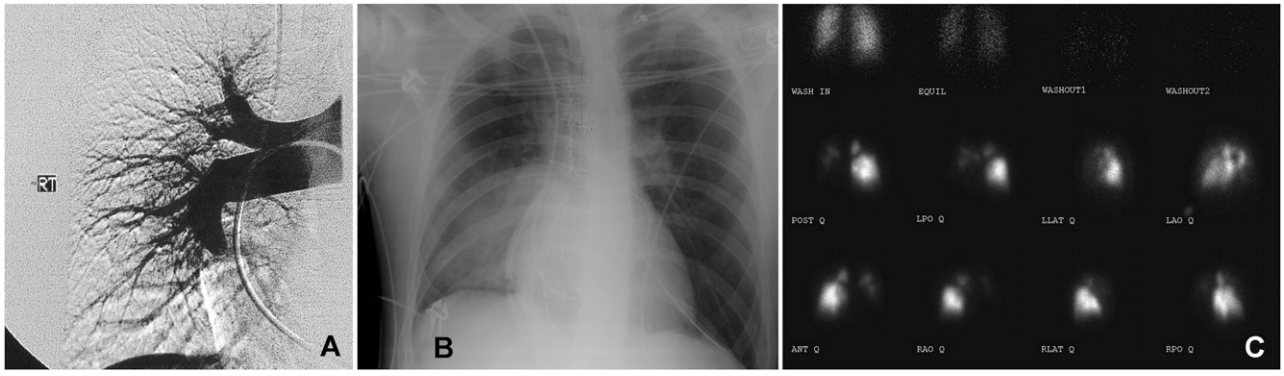

Figure 4. (*A*) Right-sided pulmonary angiogram demonstrating "pouch" defect in the right lower lobe pulmonary artery. (*B*) Immediate postoperative chest radiograph demonstrating right lower lobe air space opacity consistent with reperfusion lung injury. (*C*) Postoperative perfusion scan demonstrating marked redistribution of pulmonary blood flow (pulmonary artery "steal") into endarterectomized region of lung.

data suggest that the postoperative administration of inhaled iloprost or nitric oxide may have positive effects on both pulmonary hemodynamics and gas exchange (63, 64).

Although persistent pulmonary hypertension is associated with a higher perioperative mortality risk, Freed and colleagues in a recent series involving 306 patients demonstrated that significant functional improvement and an equivalent 5-year survival can be achieved in those with persistent postoperative pulmonary hypertension (defined as a mean pulmonary artery pressure $\geq$ 30 mm Hg) compared with those who normalize their pulmonary hemodynamics (62). A threshold value of anticipated postoperative PVR has not been defined. It is possible that the absolute or relative reduction in vascular resistance correlates more closely with perioperative mortality risk rather than any fixed value of postoperative PVR.

Acute lung injury after PTE may appear immediately after termination of cardiopulmonary bypass to as long as 72 hours after surgery. It is highly variable in severity, ranging from a mild form resulting in postoperative hypoxemia to an acute, hemorrhagic, and fatal form of lung injury. When accompanied by pulmonary artery steal, a temporary postoperative redistribution of pulmonary blood flow into the endarterectomized segments, it can result in profound postoperative hypoxemia (Figure 4). As with other forms of acute lung injury, management is supportive until resolution occurs. In a series of 47 patients undergoing PTE, the postoperative avoidance of inotropic and vasodilator support, along with a strategy of low-volume ($<$ 8 ml/kg) ventilation, resulted in a lower incidence of lung injury (65).

Lifelong anticoagulation is strongly recommended after PTE. Thromboembolic recurrence can occur when anticoagulation is discontinued or maintained at a subtherapeutic level. Reoperative PTE is feasible with a perioperative risk comparable with primary PTE (66).

ALTERNATE THERAPY

Lung transplantation remains a therapeutic alternative for patients not deemed candidates for PTE based on the location and/or extent of their thromboembolic disease and for patients who have undergone PTE with an inadequate hemodynamic outcome not responsive to medical therapy. Candidates have usually failed medical therapy as well and satisfy the other standard guidelines for transplantation. There are currently no data on how patients with CTEPH fare after lung transplantation compared with other categories of patients.

Disease-modifying therapies developed for use in idiopathic pulmonary arterial hypertension, including prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, have been studied in patients with CTEPH (67). Potential indications for medical therapy in CTEPH include (*1*) surgically accessible CTEPH in patients who elect not to undergo surgery for personal choice or where comorbidities are so substantial as to exclude the patient from consideration of PTE, (*2*) distal chronic thromboembolic disease or limited central disease that is so disproportionate to the severity of the pulmonary hypertension that the surgical mortality risk of PTE is prohibitive, (*3*) use as a preoperative therapeutic bridge to surgery in patients with severe right ventricular dysfunction, and (*4*) management of persistent pulmonary hypertension after PTE.

In terms of the role of pulmonary hypertension–specific medical therapies, it is worth reiterating that PTE remains the definitive intervention for CTEPH. The hemodynamic and symptomatic benefits accrued from medical therapy, although often positive, are modest in comparison to those resulting from PTE. A decision to forego PTE and to use medical therapy should be made only after a comprehensive evaluation has been performed, only for defined indications, and only after consultation with a center experienced in the management of this disease process. In a retrospective review of patients undergoing PTE at UCSD in 2007, 37% of patients had been prescribed pulmonary hypertension–specific medical therapy at the time of referral, a substantial increase compared with approximately 20% of patients so managed in 2005. Analysis revealed no discernible pulmonary hemodynamic benefit or postoperative mortality benefit in the patients receiving medical therapy before surgery (68). Condliffe and colleagues reported a similar increase in the use of pulmonary hypertension–specific medical therapy before PTE, with 65% of patients receiving such therapy since 2002 (22). Not only do these findings raise concerns regarding unnecessary delays in referral before surgical intervention but they also raise the possibility that another cohort of patients with potentially operable disease may exist who are being primarily and inappropriately managed with medical therapy.

The majority of data with medical therapy for inoperable CTEPH come from trials with the dual endothelin receptor antagonist, bosentan. In a recent metaanalysis involving 11 studies comprising 269 patients, treatment with bosentan was associated with an improvement in functional status as measured by a 6-minute-walk test as well as a weighted improvement in cardiac index (0.23 L/min/m^2) and weighted reductions in mean pulmonary artery pressure (2.62 mm Hg) and PVR (159.7 dyne s/cm^5) (69). In the largest and only randomized controlled trial, which involved 157 patients (bosentan = 77, placebo = 80), approximately 30% of whom had undergone previous PTE, treatment with bosentan resulted in a 24.1% decrease in PVR compared with baseline without observed improvement in exercise capacity (23).

Although data associated with the use of phosphodiesterase inhibitors and prostacyclin analogs are less robust than with bosentan, they have also been used in patients with inoperable CTEPH. In a double-blind, placebo-controlled pilot study comparing sildenafil to placebo for 12 weeks in 19 patients with inoperable CTEPH, Suntharalingam and colleagues found no significant difference between groups in terms of exercise capacity (25). However, there was a significant difference in World Health Organization class and in pulmonary vascular resistance. Control patients were then transferred to open-label sildenafil use and follow-up obtained at 12 months. At that time, significant differences were noted in 6-min walk distance (6MWD), symptom score, and pulmonary vascular resistance. In a larger patient group, Reichenberger and colleagues conducted an open-label study of sildenafil (50 mg three times a day) in 104 patients with inoperable CTEPH. They were able to demonstrate a decrease in pulmonary vascular resistance from 863 $\pm$ 38 dyne s/cm^5 to 759 $\pm$ 62 dyne s/cm^5 after 3 months. After 12 months of treatment, 6MWD increased from 310 $\pm$ 11 m to 366 $\pm$ 18 m (70). Olchewski and colleagues compared aerosolized iloprost to placebo in a randomized controlled trial involving 203 patients with pulmonary hypertension (57 with chronic thromboembolic disease) (71). Administration of iloprost improved a clinically important combined end point consisting of exercise capacity, NYHA class, and clinical deterioration. The treatment effect, however, was less than the comparative group of patients with idiopathic pulmonary arterial hypertension. In a single-center uncontrolled observational study, 28 patients with severe inoperable CTEPH were treated with subcutaneous treprostinil (72). Follow-up catheterization was performed in 19 patients after 19 $\pm$ 6.3 months. Treprostinil therapy was associated with a significant improvement in pulmonary vascular resistance. Five-year sur-

vival rate was 53% compared with 16% in an untreated historical control group. Cabrol and colleagues retrospectively reviewed 27 patients with inoperable CTEPH treated with epoprostenol. After 3 months of therapy, a decrease in mean pulmonary artery pressure (56 ± 9 mm Hg to 51 ± 8 mm Hg), total pulmonary resistance (29.3 ± 7.0 U/m^2 to 23.0 ± 5.0 U/m^2), and an increase in 6MWD of 66 m were noted. Eleven of 23 patients experienced an improvement in NYHA functional status by one class (73).

Medical therapy has also been used as a therapeutic bridge before PTE. Nagaya and colleagues administered intravenous prostacyclin at a mean dose of 6 ± 1 ng/kg/min for a period of 46 ± 12 days before PTE in 12 patients with severe CTEPH (PVR > 1,200 dyne s/cm^5). This intervention resulted in substantial preoperative decreases in PVR (1,510 ± 53 to 1,088 ± 58 dyne s/cm^5) as well as in brain natriuretic protein levels (74). Postoperative mortality was 8.3% in the treated group compared with no deaths in the 21 patients with CTEPH who had a preoperative PVR of 1,200 dyne s/cm^5 or less. Postoperative hemodynamic improvement was comparable between the groups.

Only limited data are available regarding the medical management of persistent pulmonary hypertension after PTE and what is available is derived from studies involving patients with inoperable disease. Condliffe and colleagues performed a retrospective, observational study involving patients with inoperable disease as well as those with persistent post-PTE pulmonary hypertension (22). Seventy patients, representing 35% of the patients undergoing PTE, had persistent pulmonary hypertension defined by an mPAP 25 mm Hg or greater and PVR 240 dyne s/cm^5 or greater. Using treatment criteria of mPAP 30 mm Hg or greater, 18% of patients were receiving disease-modifying therapy at 2 years. One- and 3-year survival for those with post-PTE persistent pulmonary hypertension was 99 and 94%, equivalent to those without persistent pulmonary hypertension. In the BENEFiT study, bosentan had a significantly positive effect on hemodynamics but not on 6MWD, both in patients with inoperable CTEPH and those with persistent/recurrent PH after PTE (23).

In summary, disease-modifying pulmonary hypertensive therapies appear to have a valuable role in stabilizing and improving pulmonary hemodynamics in patients with inoperable CTEPH. Hemodynamic improvement with all agents, however, is relatively modest, approximating a 100 to 200 dyne s/cm^5 or 20% reduction in pulmonary vascular resistance, an amount three- to fourfold less than achieved with PTE. Appropriate patient selection is paramount for this select subgroup of patients with CTEPH. Disease-modifying therapy also appears beneficial in those with persistent pulmonary hypertension after PTE, although the threshold level of postoperative pulmonary hypertension requiring therapy remains to be defined. Alternatively, existing data do not appear to support the routine use of disease-modifying therapy in patients with operable disease before PTE, with the possible exception of those with severe pulmonary hypertension and/or evidence of profound right ventricular failure. In this latter group, aggressive preoperative standard medical care (supplemental oxygen, diuresis, digoxin, inotropic support) may be of equivalent value.

CONCLUSIONS

Substantial advances have occurred over the past quarter century in the diagnostic and therapeutic approach to CTEPH. As is so often the case with medical progress, these advances have been accompanied by a number of new, unanswered questions. Among the issues meriting future investigation are the following. First, it remains uncertain why certain patients experiencing pulmonary embolism incompletely resolve their emboli. Perhaps, as certain researchers have suggested, differences in fibrinogen structure making them more resistant to thrombolysis may be implicated (75). Furthermore, the biological mechanisms in the subset of patients with unresolved embolism who subsequently experience pulmonary vascular remodeling and progression of their pulmonary hypertension remains undefined. Although it is possible that this vasculopathy may be a flow-related phenomenon, it does not explain why pathologic evidence of remodeling has been found in both the occluded and patent pulmonary vascular beds (3). If a genetic predisposition is involved, it does not appear to be related to bone morphogenetic protein receptor mutations, as is the case with familial and idiopathic pulmonary hypertension (76).

In terms of management, it would be beneficial to have a more objective definition of what is considered to be operable and inoperable disease based on anatomic and hemodynamic variables. At the present time, this is a purely subjective determination made at centers with varying levels of experience, surgical expertise, and postoperative hemodynamic expectations. Recent data would suggest that the risk of some element of persistent postoperative pulmonary hypertension should not serve as a contraindication to PTE (22, 62). However, criteria have not been defined beyond which the risk of PTE outweighs the potential benefit. This determination requires the development of diagnostic techniques or algorithms capable of more objectively partitioning the central, surgically correctable component of the pulmonary vascular resistance from the peripheral component. Finally, the risks, benefits, and long-term outcome of primary medical therapy versus combined surgical-medical therapy needs to be determined in patients with hemodynamically mild CTEPH, distal CTEPH, or CTEPH associated with pulmonary hypertension disproportionate to the degree of central vascular obstruction. Such studies should involve more than short-term hemodynamic or mortality outcomes, instead addressing long-term mortality, hemodynamic, quality-of-life, and functional endpoints.

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