CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

INTERNAL MEDICINE GRAND ROUNDS
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

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Introduction

The first successful bilateral thromboendarterectomy was performed in 1961[1,2], and over the next 25 years, only 83 additional surgeries were performed. Perioperative mortality for these first 83 surgeries was 22%[3]. Subsequently it has been estimated that more than 3,000 thromboendarterectomy procedures have been performed worldwide, the majority at the University of California, San Diego Medical Center. Accompanying this increased experience, mortality rates reported by established programs have fallen to the 4 to 8 percent range[4,5,6]. In the absence of this experience, mortality rates are often several-fold higher[7,8,9] (Table, pg 18).

Chronic thromboembolic pulmonary hypertension occurs when pulmonary emboli fail to resolve *and* when there is a large enough area of compromised vasculature to elevate pulmonary pressures. This can occur after a single large pulmonary embolism or after multiple smaller pulmonary emboli. Chronic thromboembolic pulmonary hypertension occurs in 1-4% of survivors of a single episode of pulmonary embolism, and in up to 13% of those with recurrent venous thromboembolism[10]. Assuming 400,000 embolic survivors annually in the United States, these figures would suggest that the diagnosis is being overlooked in a substantial number of patients or that some patients are not receiving optimal medical care[11].

Natural History of Pulmonary Embolism:

Although pulmonary hypertension is not uncommon during the acute phase of a pulmonary embolism, pulmonary pressures usually eventually normalize with time[12,13]. In one study, pulmonary hypertension by echocardiogram usually resolved within two weeks[14]. Pulmonary hypertension that persisted at 4-6 weeks predicted continued pulmonary hypertension at one year and a high likelihood of the need for pulmonary thromboendarterectomy.

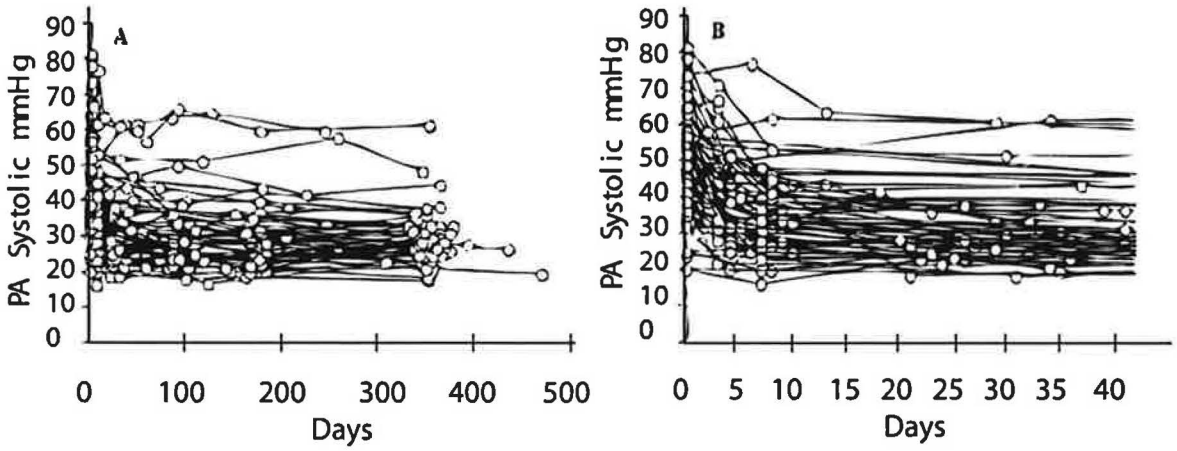


Figure: Echocardiograms After PE. Pulmonary artery systolic pressures by serial echocardiograms in 78 patients with acute PE over one year (left) and over the first 42 days (right). Three of four patients with elevated pressures at 42 days required pulmonary thromboendarterectomy for persistent pulmonary hypertension. Ribiero et al *Circulation*; 1999;99:1325.

Ventilation perfusion (VQ) scan changes are slightly slower to resolve, with improvement continuing for three to six months[15,16]. However, some of these later changes appear to be hemodynamically insignificant.

Incidence of Chronic Thromboembolic Pulmonary Hypertension after PE

Based on the relatively small number of patients referred annually for pulmonary thromboendarterectomy, experts previously suggested that as few as 0.01%-0.1% of pulmonary embolism survivors develop chronic thromboembolic pulmonary hypertension[17]. More recently, several long-term follow-up studies of pulmonary embolism survivors have shown that actually between 1.3% and 4% of patients will develop chronic thromboembolic pulmonary hypertension after a first pulmonary embolism[14,18,19,20].

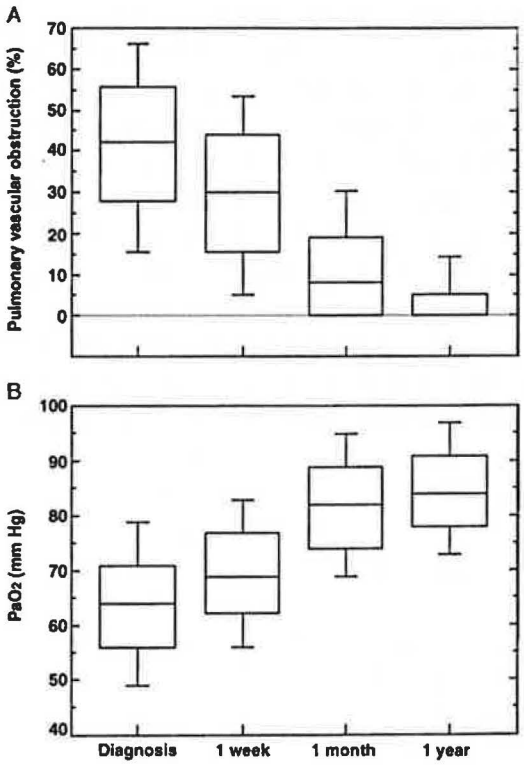


Figure: Improvement in VQ scans after PE. Improvement in VQ (top) continued beyond one month in some patients. PaO2 (bottom) improved between diagnosis and one month. Miniati et al. *Medicine* 2006;85:253.

This had been suggested by the 1999 echocardiography study above by Ribiero et al., where four of 78 patients had elevated pulmonary pressures on echocardiogram at 6 weeks and one year, and three of these four patients required pulmonary thromboendarterectomy. This much more common than expected frequency was then confirmed in three studies published between 2004 and 2006. In these studies, patients presenting with their first pulmonary embolism were asked at regular intervals whether they were having any shortness of breath. Those who had unexplained dyspnea underwent an echocardiogram, and then if the echocardiogram was abnormal they underwent additional evaluation. Chronic thromboembolic pulmonary hypertension was more likely with idiopathic pulmonary emboli and in younger patients One study also evaluated patients with a second pulmonary embolism, and approximately 13% of these patients developed chronic thromboembolic pulmonary hypertension. All cases of chronic thromboembolic pulmonary hypertension occurred during the first 2 years of follow-up, but this probably relates to earlier than usual detection due to increased surveillance.

Patients with anatomically massive pulmonary embolism, defined as greater than 50% obstruction of the pulmonary vascular bed, may be at even higher risk. In a 2003 study in China of patients with massive pulmonary embolism requiring thrombolytics, 46 of 227 patients (20.2%) were reported to have developed chronic thromboembolic pulmonary hypertension[21]. Adverse long-term outcome was more common when despite thrombolytics, pulmonary artery

systolic pressure was still greater than 50 mmHg, greater than 30% pulmonary vascular obstruction persisted, and evidence of right ventricular dysfunction was present. This higher than expected incidence is alarming on several counts. First, based on the small number of patients diagnosed annually with chronic thromboembolic pulmonary hypertension, this suggests that the diagnosis is being missed in many patients. Second, patients with a prior idiopathic pulmonary embolism should probably be routinely asked about dyspnea, and if present, should undergo additional evaluation with ventilation perfusion scanning and echocardiogram. Finally, given the even higher rates of pulmonary hypertension after a second pulmonary embolism, strategies to detect patients with greater than average risk of recurrent pulmonary embolism may be useful when making decisions about long-term anticoagulation.

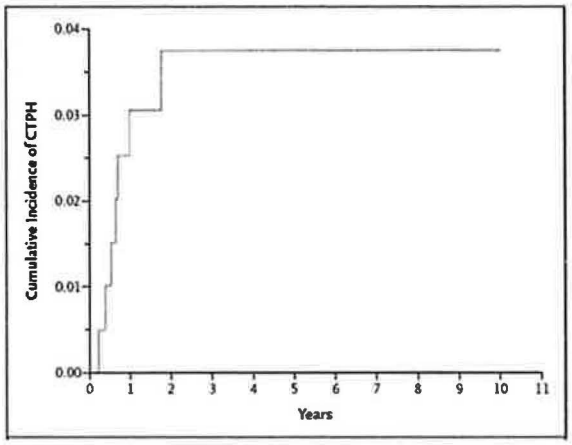


Figure: Incidence of chronic thromboembolic pulmonary hypertension after acute PE. Patients were asked routinely about unexplained dyspnea, and underwent echocardiogram and additional evaluation if indicated. All diagnoses of chronic thromboembolic pulmonary hypertension were made within the first two years of the initial pulmonary embolism. Pengo et al. *N Engl J Med* 2004; 350:2257.

Cause of Chronic Thromboembolic Pulmonary Hypertension After Pulmonary Embolism

The cause for the variable natural history after an acute pulmonary embolic event is not well understood. It is possible, albeit somewhat simplistic, that chronic thromboembolic pulmonary hypertension represents part of the normal spectrum of disease associated with pulmonary embolism: complete anatomic and hemodynamic resolution in a minority of patients, partial resolution associated with normal exercise capacity in most, and progression to pulmonary hypertension in the remaining few. Conversely, abnormalities in platelets, coagulation pathways, fibrinolytic pathways and the pulmonary vascular endothelium have all been considered as potential contributors.

While antiphospholipid antibodies do occur in 10%-20% of patients with chronic thromboembolic pulmonary hypertension, the majority of patients have not had identifiable coagulopathic tendencies. Rates of antithrombin III deficiency, protein C or S deficiency, and factor V Leiden have not been higher than the general population, and major deficiencies in the fibrinolytic system have not been identified[22,23,24,25]. One study did report increased levels of the clotting factor VIII in a large percentage of chronic thromboembolic pulmonary hypertension patients (41% of 122 patients compared with 5% of controls), while another small study reported increased rates of hyperhomocysteinemia[26,27]. If confirmed, these findings suggest that a larger percentage of patients may have an impairment of thrombotic or fibrinolytic mechanisms than previously appreciated.

Clinical Presentation

Patients with chronic thromboembolic pulmonary hypertension typically present with dyspnea on exertion that progresses over months or years. Patients accustomed to higher levels of activity on a daily basis may recognize the decline in exercise capacity earlier than those who lead a sedentary lifestyle. Later in the course of the disease, pre-syncopal symptoms and a chronic nonproductive cough may develop. Patients often complain of lightheadedness and increased dyspnea when bending from the waist, perhaps related to an altered venous return and cardiac output. Syncopal events may be precipitated by coughing or exertion, and exertional chest pain is often reported with advanced disease.

The majority (>60%) of patients can provide a history of a documented venous thromboembolic event or an incident consistent with that diagnosis such as a remote episode of pleurisy, lower extremity edema, or hemoptysis. In the absence of a history consistent with embolism, patients may describe a prolonged atypical pneumonia, a complicated hospitalization, or a surgical procedure following which they did not return to their baseline cardiopulmonary status. It is not uncommon for acute venous thromboembolism to be missed in the population at large, and thus it should not be surprising that some patients present with chronic thromboembolic pulmonary hypertension without a definite prior episode of venous thromboembolism[28,29]. It is also important to recognize that a considerable delay, extending from months to years , may exist between the documented or suspected embolic event and the onset of clinical symptoms. The degree to which this symptomatic and hemodynamic decline is related to recurrent embolic events, in situ thrombosis, changes in the pulmonary microvasculature, or loss of right ventricular adaptive mechanisms is uncertain[12]. There is evidence, based on lung biopsy findings obtained at the time of thromboendarterectomy, that changes in the microvasculature, similar to that encountered in other variants of pulmonary hypertension, may account for some of the progressive decline[30]. Supporting this possibility has been the finding of progressive symptomatic and hemodynamic decline in the presence of an abnormal but unchanged perfusion scan.

Diagnostic delay following symptom onset is common and in part due to the non-specific presentation and the subtlety of physical examination findings early in the course of disease. Diagnostic delays are most common in the absence of a prior history of acute thromboembolism. The progressive dyspnea and exercise intolerance associated with the chronic thromboembolic pulmonary hypertension are often erroneously attributed to asthma, physical deconditioning, advancing age, interstitial lung disease, coronary artery disease, or psychogenic dyspnea. Additionally, an increasing number of patients are diagnosed with idiopathic pulmonary arterial hypertension.

Physical Exam

Physical examination findings vary depending on pulmonary hypertension severity. Early in the course of the disease, physical exam may be near-normal, with perhaps a widening of the second heart sound or a subtle accentuation of its pulmonic component. As the disease progresses,

classic findings of pulmonary hypertension develop and include a right ventricular lift, fixed splitting of the second heart sound with an accentuated pulmonic component, a right ventricular S_4 gallop, and varying degrees of tricuspid regurgitation. Eventually right ventricular failure occurs and jugular venous distention, a right-sided S_3 gallop, lower extremity edema, hepatomegaly, ascites and cyanosis develop. Lower extremity edema may occur due to right heart failure or venous outflow obstruction related to residual venous thrombosis. Finally, approximately 30% of patients with chronic thromboembolic disease will have pulmonary flow murmurs[31]. Pulmonary flow murmurs are high pitched and blowing and are heard most loudly over the back during a breath hold; these bruits occur due to the turbulent flow across the partially obstructed pulmonary vascular segments. Flow murmurs have also been reported in other (rare) conditions associated with large pulmonary artery narrowing, but they have not been described in idiopathic pulmonary arterial hypertension, the most common competing diagnosis.

Laboratory Studies

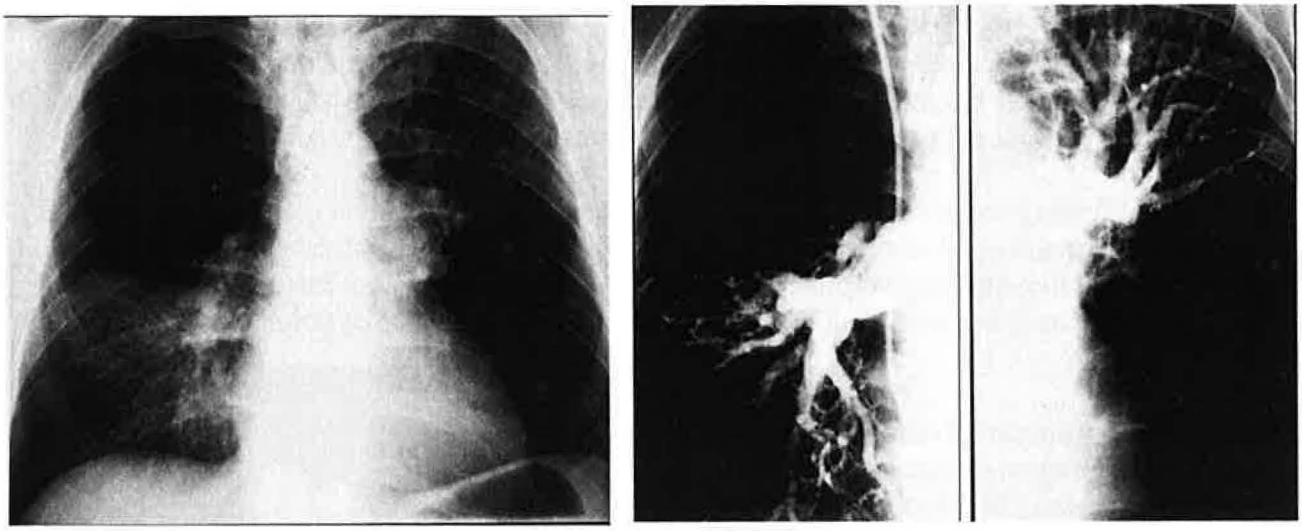
Routine laboratory studies are usually unremarkable. Mild liver function test abnormalities may suggest passive hepatic congestion. A prolonged activated partial thromboplastin time (aPTT) may suggest the possibility of a lupus anticoagulant or anticardiolipin antibody[24]. As in other variants of pulmonary hypertension, elevated uric acid levels and BNP levels appear to correlate with the level of mean right atrial pressure and inversely with the level of the cardiac output and are markers of cardiac dysfunction[32,33,34]. The alveolar-arterial oxygen gradient is typically widened, and most patients have a decrease in the arterial PO_2 with exercise. Dead space ventilation (Vd/Vt) is often increased at rest and worsens with exercise. Hypoxemia appears to be the consequence of moderate ventilation-perfusion mismatch along with a low cardiac output resulting in a depressed mixed venous PO_2[35]. Some patients, usually with other signs of right heart failure, may also have shunting across a patent foramen ovale.

Diagnostic Evaluation

The initial evaluation focuses on establishing the diagnosis of chronic thromboembolic pulmonary hypertension. This typically includes pulmonary function testing (PFT), chest x-ray, echocardiogram, and ventilation perfusion scanning. Subsequently, additional testing is required to determine severity, to confirm the presence of *surgically accessible* chronic thromboemboli, and to evaluate whether comorbidities are present that will affect surgical risk. Testing generally includes right heart catheterization and pulmonary angiography, and in patients over 40-50 years of age who are felt to be surgical candidates, left heart catheterization. In select cases at UCSD, pulmonary angioscopy and a technique to "partition" the pulmonary vascular resistance have been used to better determine surgical candidacy.

Chest Radiography

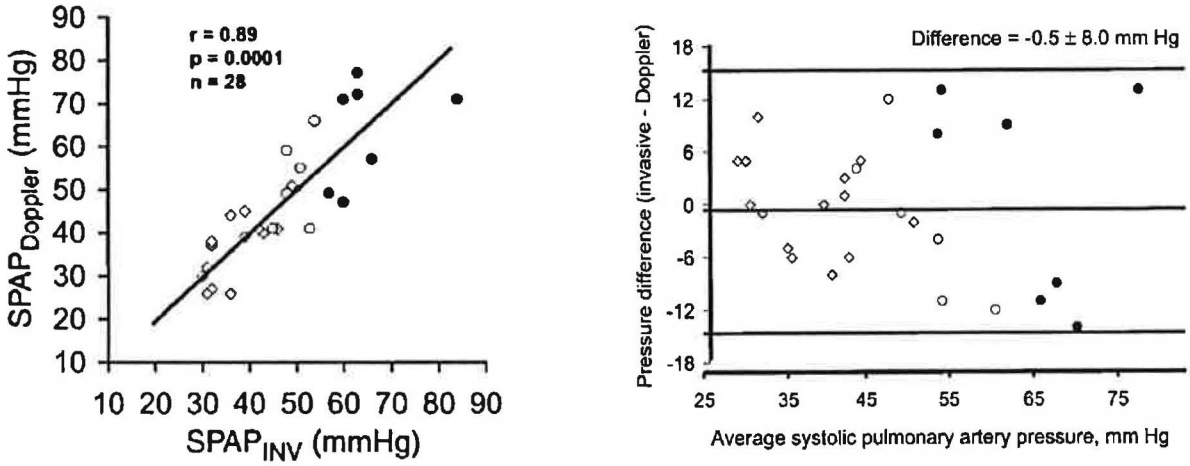
Chest radiography, while often normal, may demonstrate asymmetry or enlargement of the pulmonary arteries and areas of hypoperfusion and hyperperfusion. The areas of hyperperfusion may be so dramatic as to suggest a focal infiltrate or interstitial disease. There also may be pleural-based scars, consistent with prior infarcts[36,37]. The cardiac silhouette may show right ventricular enlargement. Lower extremity duplex ultrasonography findings will demonstrate evidence of prior venous thrombosis in approximately 45% of patients.



Chest X-ray: Westermark's Sign. Focal oligemia can occur with acute or chronic PE. In this case of chronic PE, the pulmonary angiogram (right) shows absence of perfusion in the right upper and left lower lung fields with hyperperfusion elsewhere, resulting in the appearance of an infiltrate on the chest x-ray (left).

Echocardiography

Echocardiography is useful early in the work-up of the suspected pulmonary hypertension patient. In experienced centers where simultaneous or sequential cardiac catheterization has been performed, directly measured PA systolic pressure and estimated PA systolic pressures using the tricuspid regurgitant jet velocity have correlated closely[38,39]. However, even in studies



Figures: Systolic pulmonary arterial pressure (SPAP). Pressures measured by Doppler echocardiography correlates closely with "invasive" (INV) right heart catheterization (left). The same data is shown in a Bland-Altman plot (right), where on average the measurements are very similar, but in individual patients significant variability is seen. This plot is generally a more appropriate way to compare two techniques that measure the same variable. Allemann Y. *Am J Physiol Heart Circ Physiol.* 2000; 279:

with excellent overall correlation, modest variaibility is seen such that in any individual patient, the catheterization derived pressure may be 5-10 mmHg higher or lower, and occasionally even further off. Another limitation of echocardiography is that not all patients have a measurable tricuspid regurgitant jet, particularly patients with mild pulmonary hypertension[40].

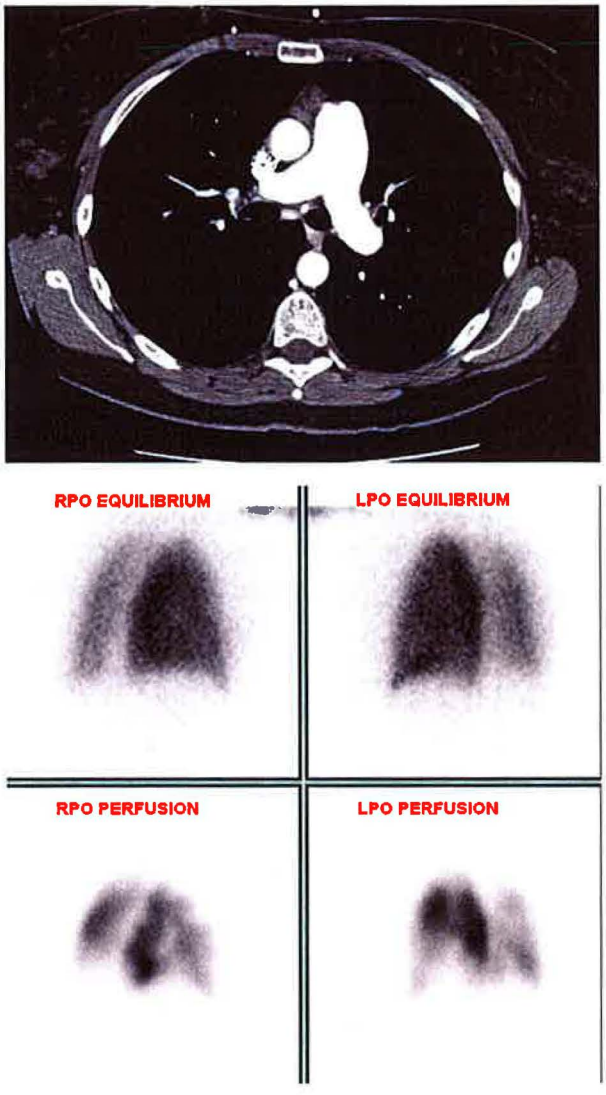
Additional findings on echocardiogram include enlargement of the right cardiac chambers and flattening or paradoxical motion of the interventricular septum[41]. Contrast echocardiography is useful in detecting interatrial or interventricular shunts such as a patent foramen ovale or septal defects, and should be considered when echocardiographic evidence of pulmonary hypertension is present.

Pulmonary Function Testing

Pulmonary function testing is useful mainly to exclude coexisting obstructive or restrictive lung disease. Mild to moderate restriction is seen in about 20% of patients with chronic thromboembolic pulmonary hypertension and has been demonstrated to be strongly associated with the degree of parenchymal scarring, possibly related to infarction accompanying acute pulmonary embolism[36]. As is the case in idiopathic pulmonary arterial hypertension, the most common pulmonary function test abnormality is a reduction in the diffusing capacity of carbon dioxide (DLCO)[42]. A normal DLCO does not exclude chronic thromboembolic pulmonary hypertension; severe reductions are uncommon and should lead to the consideration of possible alternative diagnoses. Interestingly, the reduction in DLCO does not appear to resolve following surgery despite the improvement in pulmonary artery pressure and cardiac output[43].

Ventilation Perfusion Scan and CT Angiography

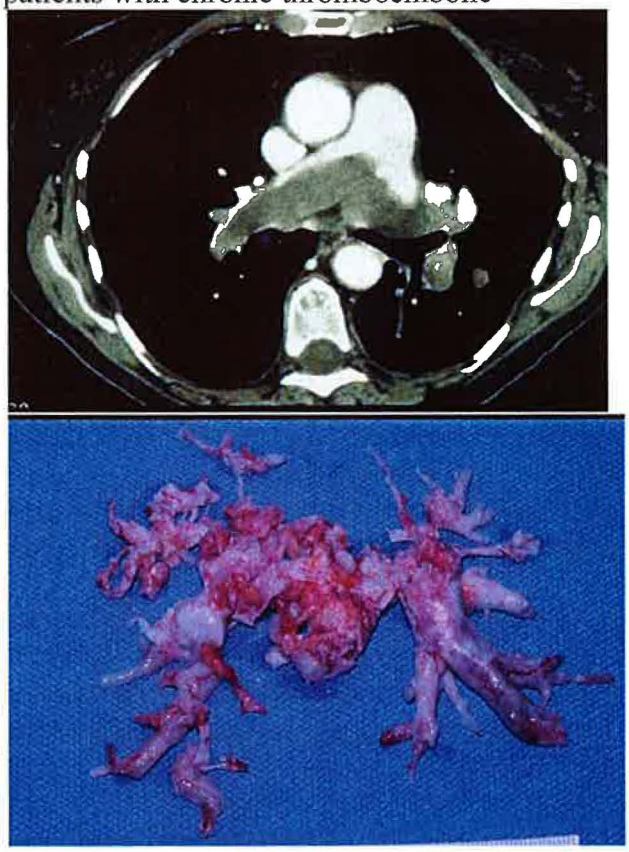
Patients with surgically accessible thromboembolic disease will usually demonstrate multiple segmental or larger sized perfusion defects on ventilation perfusion scanning[4445]. In contrast, in idiopathic pulmonary arterial hypertension, perfusion scans are either normal or exhibit a



Figures: CT Angiogram and VQ scan from the same patient. CT scan is read as negative for pulmonary embolism, while VQ scan is high probability. At surgery, extensive thrombus was removed.

"mottled" appearance characterized by small, subsegmental defects. Occasionally, the perfusion scan pattern in idiopathic PAH demonstrates a basilar redistribution of flow, suggesting obstruction of the upper and middle lobe arteries. This pattern of flow, however, is non-segmental and inconsistent with the usual lower lobe distribution of emboli and, at angiography, chronic thromboembolic disease is not present.

Ventilation-perfusion scanning is generally felt to be very sensitive but slightly less specific for chronic thromboembolic pulmonary hypertension. In one study of 75 patients undergoing evaluation for pulmonary hypertension, 24 of 25 patients with chronic thromboembolic pulmonary hypertension had a "high" probability scan while one patient had an intermediate probability scan. Including both intermediate and high probability scans as "suggestive of disease", the specificity of VQ was only 86%, requiring that patients with a suggestive V/Q scan undergo pulmonary angiography to confirm surgically accessible thromboembolic disease[46].

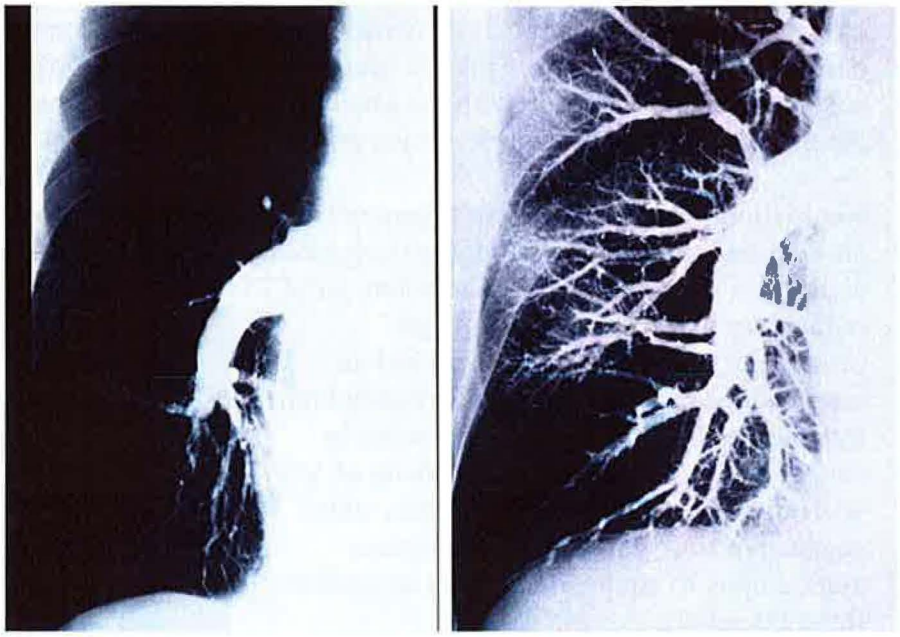


Images: CT scan and Pathology Specimen. Pulmonary artery sarcoma.

Causes of mismatched segmental defects in a patient with pulmonary hypertension other than thromboembolic obstruction include pulmonary artery sarcoma, large vessel pulmonary vasculitides, extrinsic vascular compression by mediastinal adenopathy or fibrosis, and, on occasion pulmonary veno-occlusive disease; CT angiogram may be useful if there is suspicion of these other entities.

Recently, computed tomography and magnetic resonance imaging have been advocated as screening techniques for the diagnosis of chronic thromboembolic disease[47,48,49]. Thrombus within the central pulmonary arteries can be demonstrated by helical tomography, and while the presence of central thrombus may help to establish surgical respectability, *the absence of proximal thrombus on CT scan does not exclude surgically accessible disease*. CT is less sensitive in detecting chronic thrombus that is mural rather than intraluminal, and may miss webs that impair flow but do not completely obstruct the vessel. In a head to head comparison study, VQ scan had a sensitivity of 97% and a specificity of 90% (again, considering intermediate and high probability scans as positive) while CT angiogram had a sensitivity of 51% and specificity of 99%.

A variety of computed tomographic abnormalities have been described in patients with chronic thromboembolic pulmonary hypertension: right ventricular enlargement, dilated central pulmonary arteries, chronic thromboembolic material within the central pulmonary arteries, bronchial artery collateral flow, parenchymal abnormalities consistent with prior infarcts, and mosaic attenuation of the pulmonary parenchyma. Computed tomography appears most useful in that small subset of patient with unilateral or predominantly unilateral vascular occlusion in whom the probability of other diagnostic possibilities (sarcoma, vasculitis, malignancy, and mediastinal fibrosis) is increased[50].



Images: Pulmonary Angiography. Scans taken before and after pulmonary thromboendarterectomy.

Unlike scans in patients with acute pulmonary embolism, the size and number of defects on ventilation perfusion scans do not accurately predict hemodynamics in chronic thromboembolic pulmonary hypertension, and perfusion scans often understate the degree of obstruction[47,48]. This is thought to be due to partial recanalization of obstructed vessels allowing the radioisotopic agent to reach the periphery of the lung. Therefore, in a patient with pulmonary hypertension, even the presence of a single, mismatched, segmental ventilation-perfusion scan defect should raise concerns regarding a potential thromboembolic basis regardless of whether this defect appears disproportionate to the extent of the pulmonary hypertension.

Contrast-enhanced MR angiography has also proven useful in defining the extent of pulmonary vascular obstruction to the level of the subsegmental arteries. It did not appear capable, however, of accurately providing the hemodynamic data so essential to surgical referral, and the overall performance of MR angiography compared with CT angiography was reported as only "equally effective" at identifying the direct and indirect signs of chronic thromboembolic disease[51,52].

Right heart catheterization and pulmonary angiography

Right heart catheterization and pulmonary angiography are essential to define the degree of pulmonary hypertension, to establish the presence of chronic thromboembolic obstruction and to

define its surgical accessibility, and to exclude competing diagnostic possibilities. If hemodynamic measurements at rest demonstrate only modest degrees of pulmonary hypertension, measurements can be repeated after a short period of symptom-limited exercise[53]. The angiographic appearance of chronic thromboembolic disease bears little resemblance to that of acute pulmonary embolism[54]. Five distinct angiographic patterns have been described that correlate with the finding of chronic thromboembolic material at the time of surgery: (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. In most patients with extensive chronic thromboembolic disease, two or more of these angiographic findings are present.

Competing diagnoses exist with angiographic findings similar to those encountered in chronic thromboembolic disease. Band-like narrowing can be a feature of medium or large-vessel pulmonary arteritis or can be seen with congenital pulmonary artery stenosis. Total or partial obstruction of central pulmonary arteries can be the consequence of an intravascular process (primary pulmonary artery tumors) or an extravascular one (mediastinal or hilar lymphadenopathy, lung carcinoma, mediastinal fibrosis).

Pulmonary angiography can be performed safely despite concerns regarding the performance of pulmonary angiography in patients with severe pulmonary hypertension[55,56]. The widespread perception of risk of pulmonary angiography in patients with pulmonary hypertension cannot be supported by recent studies. Precautions taken to minimize the risk of the procedure include: (1) a single injection of nonionic contrast material into the right and left pulmonary arteries; (2) modification of the contrast volume and infusion rate based on the cardiac output; (3) careful patient monitoring and supplemental oxygen administration during the procedure; and (4) avoidance of repeated, selective injections. In terms of angiographic technique, cut-film biplane acquisition appears to be optimal. On occasion, areas of central recannalization have been obscured on digital subtraction studies. Routine utilization of the lateral projection has also proven invaluable in providing a much more detailed view of the lobar and segmental branches and avoiding the uncertainty resulting from dilated, overlapping vessels.

A major focus in the evaluation of patients with chronic thromboembolic pulmonary hypertension is differentiating the resistance conferred by the central, accessible component of the thromboembolic disease and that arising from the distal pulmonary vascular bed[57]. Persistent pulmonary hypertension after pulmonary thromboendarterectomy surgery remains a major cause of morbidity and mortality The majority of patients experiencing this complication appear to have undergone successful removal of the central thromboembolic obstruction with the residual vascular resistance arising from an arteriopathy affecting the distal pulmonary vascular bed Pre-operative identification of these patients can be difficult An elevated pulmonary vascular resistance that appears out of proportion to the angiographic findings may lead to clinical suspicion, but diagnostic uncertainty often remains.

Surgical selection

The decision to proceed to pulmonary thromboendarterectomy can be a complex one. The

central goals of the evaluative process are to establish the need for surgical intervention, to determine the surgical accessibility of the chronic thromboemboli, and to estimate both the risk of thromboendarterectomy as well as the anticipated hemodynamic outcome in the individual patient.

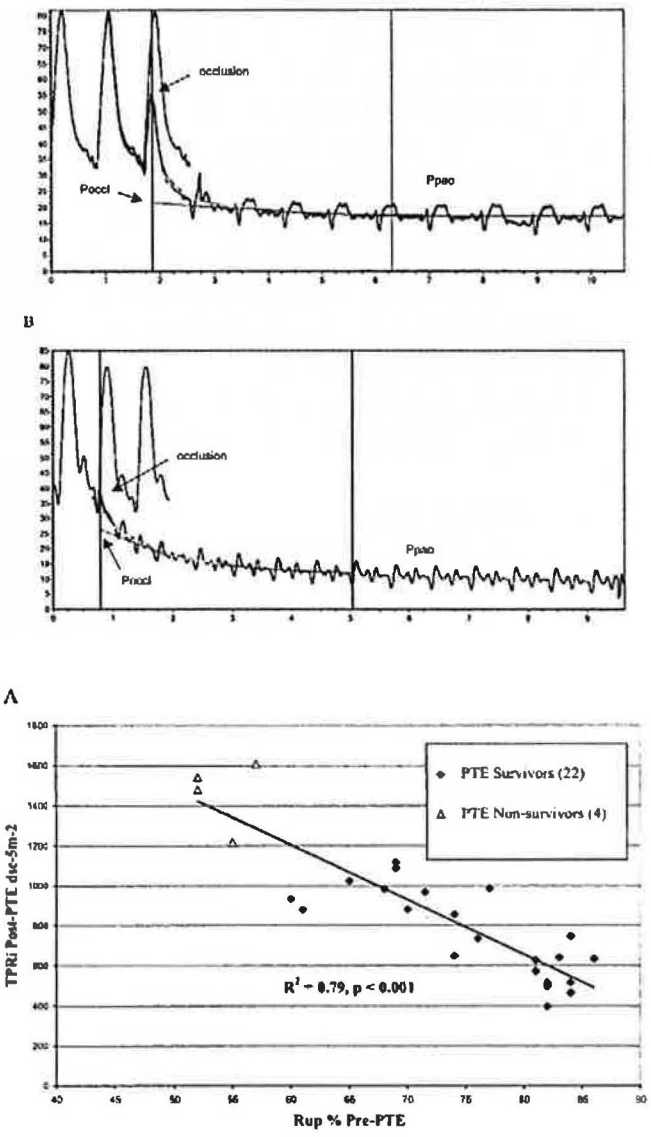
The majority of patients who undergo thromboendarterectomy exhibit a pulmonary vascular resistance greater than 300 dyne-sec-cm-5. At centers reporting their experience with thromboendarterectomy surgery, preoperative pulmonary vascular resistance is typically in the range of 700 to 1100 dyne-sec-cm-5[58,59,60,61,62,63,64]. At this level of pulmonary hypertension, patient impairment at rest and with exercise can be considerable.

Occasional patients without substantially altered pulmonary hemodynamics, such as those with involvement of one main pulmonary artery, those with unusually vigorous lifestyle expectations, and those who live at altitude, may also be considered for surgery to alleviate the exercise impairment associated with their high dead space and minute ventilatory demands. Surgery is also offered to patients with normal pulmonary hemodynamics or only mild levels of pulmonary hypertension at rest who develop significant levels of pulmonary hypertension with exercise.

An absolute criterion for surgery is the presence of accessible chronic thrombi as assessed by pulmonary angiography. Current surgical techniques allow removal of organized thrombi whose proximal extent is in the main and lobar arteries and, depending on surgical skill and experience, those involving the proximal segmental arteries. Not only is the proximal location of the occluding thromboemboli of importance, but also the extent of accessible thromboembolic disease in relationship to the degree of hemodynamic impairment. As experience with this disease process has grown, it has become apparent that the increased pulmonary vascular resistance associated with chronic thromboembolic disease arises not only from the central, surgically-accessible chronic thromboembolic obstruction but also from the distal, surgically-inaccessible obstruction and the resistance arising from a secondary, small vessel arteriopathy. Thromboendarterectomy will relieve only that portion of the pulmonary hypertension that arises from the accessible component of the chronic thromboembolic disease. A major focus of the preoperative evaluation, therefore, is attempting to determine the proximal component of the elevated vascular resistance and, by extension, estimating the anticipated hemodynamic outcome. With experience in hemodynamic-anatomic correlation, this determination can be made with reasonable accuracy. This determination is an important one. Failure to lower pulmonary vascular resistance, especially in patients with severe pulmonary hypertension and right ventricular dysfunction, may be associated with severe hemodynamic instability and death in the early postoperative period.

A formal technique to partition the pulmonary vascular resistance into "proximal" (surgically accessible) and "distal" (surgically inaccessible) pulmonary vascular abnormalities using a modified Swan-Ganz catheter has been developed and is occasionally used as an adjunctive test in the evaluation of surgical candidacy. This technique was developed with the intention of measuring pulmonary capillary pressures, but experimental evidence suggested that the small pulmonary arteriole pressure contributed[65]. This technique is performed during a right heart

catheterization, and involves the calculation of a computer generated "upstream resistance percentage", from the decay curve between pulmonary artery pressure and pulmonary capillary wedge pressure. Using this approach, investigators have shown that the average "upstream resistance percentage" is higher in chronic thromboembolic pulmonary hypertension than in pulmonary arterial hypertension, while patients with pulmonary veno-occlusive disease have the lowest upstream resistance percentages. Significant overlap exists between these three forms of pulmonary hypertension, and as a single test it can not differentiate between chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension[66]. A recent study of 26 patients undergoing pulmonary thromboendarterectomy suggests that it may be useful in identifying patients who are unlikely to improve with surgery. Post-operative hemodynamics correlated closely with pre-operative up-stream resistance measurements. In this study, all four deaths occurred in patients who had very low upstream resistance percentages and significant postoperative residual pulmonary hypertension[67].



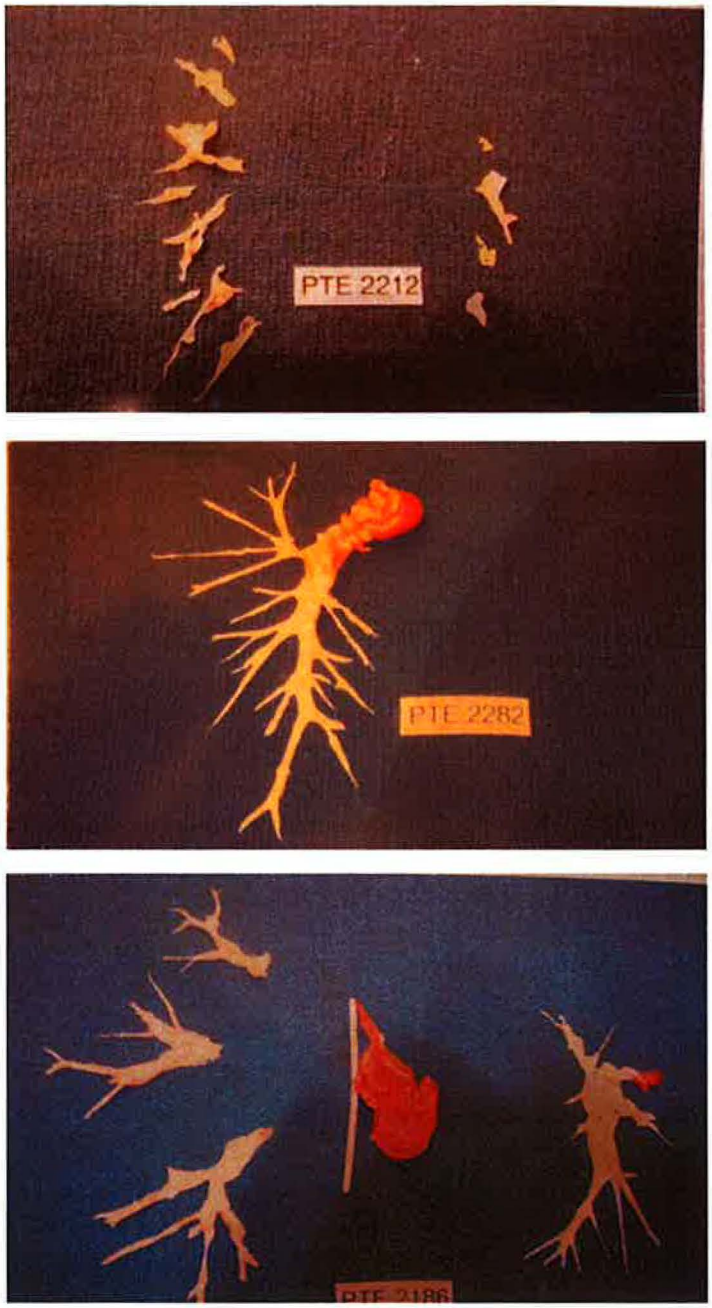
Figures: Pulmonary artery occlusion pressures (wedge pressures). The wedge pressure in patients with greater "upstream" resistance (figure A) takes a shorter time to reach a plateau. In contrast, when the small pulmonary arteries are more diseased (as in PAH), pressure remains slightly elevated for a few seconds even after balloon inflation. Kim NH et al. *Circulation* 2004;104:19.

The presence of comorbid conditions that may adversely affect perioperative mortality or morbidity as well as long-term survival must also be considered prior to surgical referral. This requires a careful assessment of hemodynamics as well as age and medical comorbidities, and is separate from the determination of operability. Coexisting coronary artery disease, parenchymal lung disease, renal insufficiency, or hepatic dysfunction may substantially complicate patient management in the postoperative period. Advanced age or the presence of collateral disease do not represent absolute contraindications to pulmonary thromboendarterectomy, but they do influence risk assessment. The prognosis from advanced chronic thromboembolic pulmonary hypertension is generally so

poor that surgery may be considered even in high risk patients. The one exception to this guideline is the presence of severe underlying obstructive or restrictive parenchymal lung disease. The postoperative course in these patients frequently is complicated by the need for prolonged ventilatory support. Furthermore, the hemodynamic benefits of thromboendarterectomy often results in minimal symptomatic improvement.

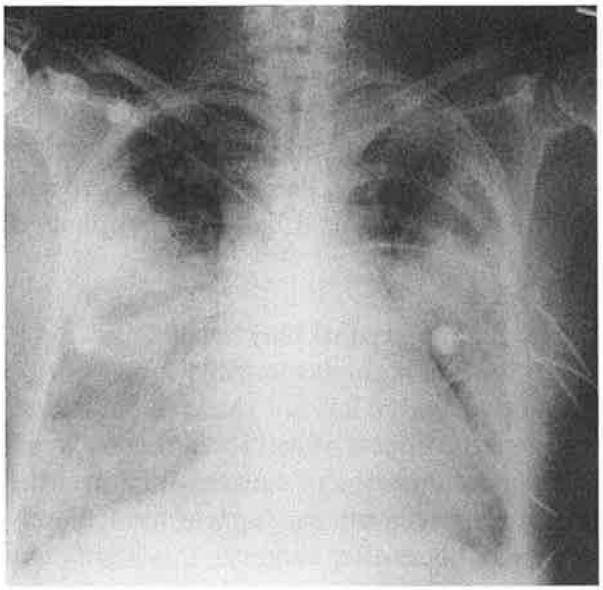
Surgical approach

Details of the surgical approach to chronic thromboembolic pulmonary hypertension have been described extensively and are beyond the scope of this review[4,68]. However, there are several features of the procedure which should be emphasized. Although a thoracotomy approach has been utilized in the past, the standard approach now involves median sternotomy and cardiopulmonary bypass. Given that the disease is rarely unilateral, a sternotomy approach provides access to the central pulmonary vessels of both lungs. A sternotomy approach also avoids the potential for disruption of the extensive bronchial collateral circulation and pulmonary adhesions that may develop following pulmonary artery obstruction. This also provides adequate exposure for additional procedures that need to be performed. In a recent review of 1,190 patients undergoing thromboendarterectomy at UCSD Medical Center, 90 patients (7.6%) required such a combined procedure exclusive of solitary closure of a patent foramen ovale (which is performed in approximately 30% of



Images: Three patients underwent pulmonary thromboendarterectomy. 2212: Modest improvement hemodynamically, remained on PAH medications, but with improved exercise capacity. 2282: normal pre-operative pulmonary pressures; dyspnea improved. 2186: atrial clot and extensive thrombus removed; doing well.

thromboendarterectomy procedures). Of these 90 patients, 83 underwent coronary bypass graft surgery, 3 underwent tricuspid valve repair, 2 underwent mitral valve repair, and 2 underwent aortic valve replacement[69]. The thromboendarterectomy procedure also involves periods of complete hypothermic circulatory arrest to assure a bloodless operative field and optimal exposure of the pulmonary vascular intima. Circulatory arrest periods are limited to 20 minutes, with resumption of blood flow and restoration of mixed venous O2 saturation between each interruption



Chest x-ray: Severe post-operative "reperfusion" pulmonary edema.

The procedure is a true thromboendarterectomy, not an embolectomy. The chronic thromboembolic material is fibrotic and incorporated into the native vascular lumen. The neo-intima must be dissected away from the native intima, and considerable surgical experience with this procedure is required to identify the correct operative plane. The removal of non-adherent, partially-organized thrombus within the lumen of the central pulmonary arteries is ineffective in reducing right ventricular afterload; creation of too deep a plane poses the risk of pulmonary artery perforation and massive pulmonary hemorrhage at the time of discontinuation of cardiopulmonary bypass.

Modifications of the surgical approach, intended to decrease risk or improve hemodynamic outcome continue to be explored. These include the use of intraoperative video-assisted angioscopy to increase visibility in the distal pulmonary arteries, thereby allowing surgical intervention in patients with previously inaccessible disease; division rather than retraction of the superior vena cava; selective antegrade cerebral perfusion to decrease the risk of neurologic sequelae; and bronchial artery occlusion to minimize retrograde bronchial artery flow[73,80,707172].

Post-Operative Care

Careful postoperative management is essential for a successful outcome following thromboendarterectomy. Although most patients have an immediate improvement in pulmonary hemodynamics, their postoperative course can be complex[4,73,74]. The contractile state and preload and afterload of the *right* ventricle rather than the left ventricle often dominate the postoperative course in terms of cardiovascular function.

In addition to complications common to other forms of cardiac surgery (bleeding, arrhythmias, atelectasis, wound infection, pericardial effusions, delirium, nosocomial pneumonia), patients undergoing pulmonary thromboendarterectomy often experience two unique complications that may adversely affect gas exchange in the postoperative period: pulmonary artery 'steal' and

reperfusion pulmonary edema. Pulmonary artery 'steal' represents a postoperative redistribution of pulmonary arterial blood flow away from previously well perfused segments and into the newly endarterectomized segments. Although the basis for this phenomenon is uncertain, clinically relevant observations regarding steal are that it occurs commonly following pulmonary thromboendarterectomy, that it does not involve thrombosis of the non-operated pulmonary segments, and that the distribution of pulmonary blood flow improves over time in the majority of patients[75,76].

The acute lung injury that may occur following thromboendarterectomy appears to represent a localized form of high-permeability lung injury[77]. Although often referred to as 'reperfusion pulmonary edema', it has not yet been defined whether the phenomenon is related to ischemia-reperfusion, the effects of cardiopulmonary bypass, details of the surgical procedure itself or to some other combination of causes. Whatever the basis, acute lung injury following thromboendarterectomy 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. The unique aspect of this form of lung injury is that it is limited to those areas of lung from which proximal thromboembolic obstructions have been removed.

The development of reperfusion injury can represent a significant postoperative challenge in terms of ventilator management. This is especially true in the setting of coincident pulmonary artery 'steal'. Under this circumstance, the majority of pulmonary blood flow is shunted into areas of lung that have a low compliance and are poorly-ventilated thereby resulting in transpulmonary shunting and hypoxemia. Management of reperfusion edema, as with other forms of acute lung injury, is supportive until resolution occurs. High-dose corticosteroid therapy and occasionally trials of novel agents[78] have been used to attempt to modulate the inflammatory component of the process, though their effectiveness has is often minimal.

Post-operative ventilator and inotropic strategies appear to be fairly institution specific, and no formal guidelines exist. Aggressive use of low tidal volume ventilation can worsen oxygenation more than expected. However, some have advocated its use: in an uncontrolled study, low tidal volume ventilation (<8 ml / kg) and avoidance of inotropic support resulted in lower mortality than another centers higher tidal volume ventilation (10-15 ml / kg) and routine inotropic support[79]. Inhaled nitric oxide has been reported to improve gas exchange, although in our experience this effect is transient and does not affect the progression of the disease[80,81,82,83]. In extreme situations, extracorporeal support (ECCO2R) has been used successfully in patients when aggressive conventional measures have been inadequate to maintain oxygenation.

Patients posing the most difficult management problem following thromboendarterectomy are those with persistent pulmonary hypertension. Even patients with well-compensated right ventricular function before the procedure may experience postoperative hemodynamic instability as a result of the depressant effects of cardiopulmonary bypass, deep hypothermia, acidosis and hypoxemia. Management goals include minimizing systemic oxygen consumption, optimizing right ventricular preload, and providing aggressive inotropic support. The use of afterload

reduction in this patient population may have adverse consequences. Cardiac output and pulmonary vascular resistance are commonly fixed and attempts at pharmacologic manipulation of right ventricular afterload may simply decrease systemic vascular resistance, systemic blood pressure and right coronary artery perfusion pressure. Inhaled nitric oxide is theoretically ideal for this circumstance since it has negligible systemic effects. Experience with this intervention in the setting of persistent postoperative pulmonary hypertension, however, has been disappointing.

Persistent pulmonary hypertension in the postoperative period remains a major cause of mortality in patients undergoing thromboendarterectomy notwithstanding attempts at aggressive management. Mortality from this cause will not be diminished by advances in the operating suite or intensive care unit but by improved methods of preoperative evaluation and surgical referral.

Outcome

In reported series of patients undergoing thromboendarterectomy since 1996, in-hospital mortality rates have ranged between 4.4% and 23.5% (Table). The specific factors affecting perioperative mortality have not been completely defined. Several studies have suggested that New York Heart Association functional class IV status, age greater than 70 years, the presence of comorbid conditions, the severity of preoperative pulmonary vascular resistance, the presence of right ventricular failure as manifested by high right atrial pressures, and perhaps the duration of pulmonary hypertension may adversely influence outcome[4,63,84]. Of these, the severity of the pre-operative and post-operative pulmonary vascular resistance appears to have the greatest prognostic power, and it is post-operative pulmonary vascular resistance that is the stronger predictor of outcome. Given what is known about the natural history of the disease and the progressive nature of the pulmonary hypertension associated with it, these findings suggest that early referral is preferable to late unless the possibility of a recent embolic event exists. Under this circumstance, a period of 3 months of conventional therapy is recommended to allow optimum thrombus resolution.

Center experience also appears to affect outcome, as has been demonstrated with other high-risk surgical procedures[85,86]. This may be related to consistency of patient evaluation, surgical experience, uniform delivery of postoperative care, and the presence of dedicated resources for dealing with postoperative complications.

In the majority of patients undergoing thromboendarterectomy, both the short-term and long-term hemodynamic outcomes are favorable. Dramatic reduction, and at times normalization, of the pulmonary artery pressure and pulmonary vascular resistance can be achieved. In published series, the mean reduction in pulmonary vascular resistance has approximated 70 percent and a pulmonary vascular resistance in the range of 200 to 350 dyne-sec-cm-5 can be achieved (Table). A corresponding improvement in right ventricular function determined by

Table: Published results for pulmonary thromboendarterectomy since 1996:

Year	Author	Location	Patients (n)	Preoperative PVR *	Postoperative PVR *	Mortality (%)
1997	Nakajima[87]	Japan	30	937 ± 45	299 ± 16	13.3
1997	Mayer[88]	Germany	32	967 ± 238	301 ± 151	9.3
1998	Gilbert[89]	Baltimore	17	~ 700 ± 200[a]	~ 170 ± 180[a]	23.5
1998	Miller[61]	Philadelphia	25	?	?	24
1999	Dartevelle[90]	France	68	1174 ± 416	519 ± 250	13.2
1999	Ando[8]	Japan	24	1066 ± 250	268 ± 141	20.8
2000	Jamieson[4]	San Diego	457	877 ± 452	267 ± 192	7
2000	Mares[79]	Austria	33	1478 ± 107[b]	975 ± 93[b]	9.1
2000	Mares[79]	Austria	14	1334 ±135[b]	759 ± 99[b]	21.4
2000	Rubens[5]	Canada	21	765 ± 372	208 ± 92	4.8
2000	D'Armini[6]	Italy	33	1056 ± 344	196 ± 39[c]	9.1
2001	Tschol[91]	Germany	69	988 ± 554	324 ± 188	10.1
2001	Masuda[9]	Japan	50	869 ± 299[d]	344 ± 174[d]	18
2003	Hagl[92]	Germany	30	873 ± 248	290 ± 117	10
2004	Jamieson[4]	San Diego	500	893 ± 444	285 ± 214	4.4
2005	Puis[93]	Belgium	40	1236±482	515±294	
2005	Iverson[94]	Germany	250			14.4
2008	Freed[95]**	United Kingdom	229	800±494	244±253	Not reported
2008	Corsico[96]	Italy	157	1140±517	327±238	11.5

* PVR = Pulmonary vascular resistance in dynes-sec-cm^{-5}

a Estimate derived from graph

b Results expressed as pulmonary vascular resistance *index*

c Data in 23 patients at 3-month follow-up

d 34 patients by sternotomy, 16 patients by thoracotomy

** Freed et al reported on long-term outcome of those who survived to hospital discharge

echocardiography, gas exchange, exercise capacity and quality of life has also been reported[97,98,99,100,101,102,103,104]. Most patients initially in New York Heart Association functional Class III or IV preoperatively return postoperatively to New York Heart Association Class I or II and are able to resume normal activities.

Lifelong anticoagulation is strongly recommended following thromboendarterectomy. A second thromboendarterectomy has been necessary in several patients in whom anticoagulation was discontinued or maintained at a sub-therapeutic level. Repeat thromboendarterectomy has also been performed successfully in a number of patients who initially underwent an inadequate procedure, either by way of thoracotomy or sternotomy approach. A second procedure can be performed with comparable morbidity and mortality as the primary procedure, but the consequent improvements in hemodynamics has been less impressive[105].

Medical Therapy

Survival of patients with chronic thromboembolic disease treated medically with anticoagulation has traditionally been very poor. In one study, the 5-year survival rate was 30 percent when the mean pulmonary artery pressure exceeded 40 mmHg and 10 percent when it exceeded 50 mmHg[106]. In another study, patients with a mean pulmonary artery pressure above 30 mmHg had a survival of less than 20 percent at three years[107]. More recently medications investigated for use in idiopathic pulmonary arterial hypertension have been attempted in a number of clinical settings. Potential indications include long-term use for inoperable or distal chronic thromboembolic pulmonary hypertension, perioperative use for patients with a pulmonary vascular resistance > 1000 dyne-sec-cm-5, and post-operative use (long-term) for patients with residual pulmonary hypertension (usually PVR >500 dyne-sec-cm-5) after pulmonary thromboendarterectomy.

Patients with chronic thromboembolic pulmonary hypertension have been included in occasional clinical trials of pulmonary arterial hypertension medical therapy. One study included patients with primary pulmonary hypertension (N=102), pulmonary arterial hypertension associated with other conditions (N=44) and patients with inoperable chronic thromboembolic pulmonary hypertension (N=57), randomized to inhaled iloprost or placebo for a 12 week period[108]. Treated patients showed improvement in hemodynamics, New York Heart Association Class, and quality-of-life compared with placebo patients, and were less likely to drop out of the study early. Sub-group data reported that 'nonprimary' pulmonary hypertension patients as a group (101 patients) had less improvement than in those with primary pulmonary hypertension.

Patients with chronic thromboembolic pulmonary hypertension have also been included in a number of non-randomized studies, including studies of intravenous prostacyclin[109,110,111], beraprost[112,113] and sildenafil[114]. These studies reported statistically significant improvement in clinical status, hemodynamics and exercise capacity compared with baseline. Two studies reported a possible survival benefit, but the lack of a randomized control group makes interpretation of this type of information difficult.

The limited amount of information from clinical trials is reflected in the ACCP practice guidelines on chronic thromboembolic pulmonary hypertension. The guideline states that medical therapy for inoperable chronic thromboembolic pulmonary hypertension 'may be considered', with the level of evidence reported as low, the benefit small / weak, and the grade of recommendation a "C"[115].

Hemodynamics in patients who do not undergo pulmonary thromboendarterectomy do usually worsen over time despite stability or even improvement in ventilation-perfusion scans[116], suggesting perhaps some role for a secondary small vessel vasculopathy. Additionally, lung biopsy specimens from patients with chronic thromboembolic pulmonary hypertension do show the full range of pulmonary hypertensive lesions, including in some patients well-formed plexogenic lesions that are indistinguishable from those of patients with idiopathic pulmonary arterial hypertension [17,117]. Finally, patients with chronic thromboembolic pulmonary hypertension, like those with pulmonary arterial hypertension, have abnormally increased levels of both endothelin-1 and angiopoietin-1, two mediators of smooth muscle cell growth[118119120].

Most patients with inoperable chronic thromboembolic pulmonary hypertension or with residual pulmonary hypertension after surgery should be offered a trial of medical therapy in light of the lack of alternatives. Post-operatively, medical therapy is usually considered when the post-operative pulmonary vascular resistance is greater than 500 dyne-sec-cm-5. Patients with modest elevations in their pulmonary vascular resistance (between 300 and 500 dyne-sec-cm-5) should be followed with annual echocardiography and clinical evaluation, and may be considered for treatment if progressive symptoms and hemodynamic decline are seen.

Conclusion

Substantial progress has occurred in the diagnostic and therapeutic approach to patients with chronic thromboembolic pulmonary hypertension. However, the development of chronic thromboembolic pulmonary hypertension represents a failure, at least in some patients, in the prevention or initial diagnosis of venous thromboembolism and, in the long term, in the management and follow-up surveillance of those with documented disease. Given current estimates of the incidence of the disease following acute embolism, it is also probable that the disease continues to escape diagnosis in a substantial number of patients and contributes to their premature death.

The early detection of those with persistent pulmonary hypertension following an acute thromboembolic event would serve to identify patients at risk of further hemodynamic impairment and shed light on the pathophysiologic mechanisms involved in the progression of their pulmonary hypertension. Once detected, improved diagnostic and hemodynamic partitioning techniques are necessary to identify patients at risk for persistent postoperative pulmonary hypertension.

However, the introduction of potentially effective, pharmacologic interventions might mandate a change in that approach. Investigation into the efficacy of pulmonary vascular dilating or antiproliferative agents, alone or combined with surgical intervention, needs to be conducted. Finally, a principle challenge in this patient population lies in the prevention and/or management of reperfusion lung injury. This patient population offers a unique opportunity to enhance our understanding of the pathophysiologic mechanisms involved in acute lung injury and to evaluate the effect of preventive or therapeutic interventions.

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