Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Over the past 4 decades, chronic thromboembolic pulmonary hypertension has evolved from an autopsy curiosity to a potentially correctable form of pulmonary hypertension. Approximately 2500 thromboendarterectomy procedures have now been performed worldwide with mortality rates reported by established programs experiencing in the management of this disease process falling to a range of 4 to 8%. Following a successful pulmonary thromboendarterectomy, substantial improvement, and at times normalization, can be achieved in right ventricular function, gas exchange, exercise capacity, and quality of life. Reperfusion lung injury and residual postoperative pulmonary hypertension remain the major causes of mortality in patients undergoing the procedure.

KEYWORDS: Pulmonary hypertension, thromboembolism, pulmonary embolism, pulmonary thromboendarterectomy, chronic thromboembolic pulmonary hypertension

Objectives: Upon completion of this article the reader should understand the clinical presentation, evaluation, surgical management, and postoperative care of patients with chronic thromboembolic pulmonary hypertension.

Accreditation: The University of Michigan is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Credits: The University of Michigan designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award.

Once considered an unusual finding at autopsy, chronic thromboembolic obstruction of the major pulmonary arteries resulting in pulmonary hypertension is now recognized as a distinct clinical entity that is potentially correctable through pulmonary thromboendarterectomy. The advances that have occurred in the diagnostic and therapeutic approach to this disease state over the past 4 decades have been extraordinary and are worthy of mention. In a 1956 review, Ball and coworkers identified over 200 reported cases of massive thrombosis of the large pulmonary arteries, the first report attributed to Helie in 1837.1,2 The first successful pulmonary thromboendarterectomy using endarterectomy instruments was reported by Snyder et al in 1963.3 The following year, the first thromboendarterectomy procedure utilizing cardiopulmonary bypass and a sternotomy approach was reported by Castleman and colleagues.4 A review of the world literature in 1985 disclosed published reports on 85 patients undergoing thromboendarterectomy with an overall mortality of 22%.5 By the end of...
2001 at the University of California–San Diego (UCSD) Medical Center alone, over 1500 patients from national and international referral sources had undergone surgical thromboendarterectomy with a mortality rate that had fallen to 5.1% over the last 500 cases. Active, successful programs dedicated to the care of patients with thromboembolic pulmonary hypertension are now in place in the United States, Canada, Italy, France, Germany, Austria, The Netherlands, and Japan.

This dramatic increase in surgical experience does not appear to be related to an increased prevalence of disease. Instead, it would appear to arise from a number of identifiable factors, which include a better understanding of the often silent and recurrent nature of acute thromboembolic disease, improved cardiovascular diagnostic techniques, the introduction of effective therapeutic alternatives for a wide range of pulmonary hypertensive disorders, and increased physician recognition of chronic thromboembolic disease as a potentially curable form of pulmonary hypertension.

The reduction in perioperative mortality also appears to be related to a number of identifiable factors, including progressive refinements in operative technique and surgical expertise and experience, more selective surgical referral, an awareness of the anatomic limits of surgical accessibility of the thrombotic obstruction, and an awareness that the morbidity and mortality associated with thromboendarterectomy can be minimized through a cooperative, multidisciplinary approach.

**NATURAL HISTORY**

The natural history of chronic thromboembolic pulmonary hypertension is closely associated with the natural history of acute pulmonary embolism. Clinical experience would suggest that thromboembolic resolution with restoration of normal gas exchange and exercise tolerance occurs in the overwhelming majority of patients who experience an acute thromboembolic event. Inadequate thromboembolic resolution following one or more embolic events, regardless of whether those events are clinically symptomatic, appears to represent the predisposing condition in the overwhelming majority of patients who develop the disease.6–8 That acute embolism may not be diagnosed and therefore not appropriately treated is supported by evidence that indicates embolism can occur without symptoms and that symptomatic pulmonary embolism frequently is misdiagnosed.9,10 In patients in whom the diagnosis of acute venous thromboembolism is made and appropriate therapy instituted, recent data would also suggest that incomplete anatomic and hemodynamic recovery may be more common than previously suspected and that certain patients with incomplete resolution may be at subsequent risk for the development of thromboembolic pulmonary hypertension.11–13

A period of months to as long as a decade can ensue after the initial thromboembolic event before symptom onset or, in patients with a minor but unexplained degree of postembolic exercise intolerance, before symptoms progression. During this period of time, progressive pulmonary hypertension and limitation on maximal cardiac output develop. The extent of residual pulmonary vascular obstruction appears to be a major determinant of disease initiation, with involvement of > 30 to 40% of the pulmonary vascular bed present in the majority of patients. The pathophysiological events involved in disease progression have been far less clearly defined. In certain patients, hemodynamic progression may involve thromboembolic recurrence or in situ pulmonary artery thrombosis. However, pulmonary vascular remodeling and the development of a hypertensive pulmonary arteriopathy, similar to that encountered in other variants of secondary pulmonary hypertension, appear to be involved in the majority of patients.14,15 This supposition is supported by several lines of evidence: documented hemodynamic progression in the absence of recurrent embolic events or evidence of in situ pulmonary artery thrombosis; a poor correlation between the extent of central anatomic obstruction and the degree of pulmonary hypertension suggesting that a component of the increased pulmonary vascular resistance is arising from the distal vascular bed; and histopathology demonstrating arteriopathic changes in the resistance vessels of both the involved and the uninvolved pulmonary vascular bed.14

Although exact incidence figures are not available, approximately 200 to 300 patients undergo thromboendarterectomy annually in the United States. Based on the annual number of patients who experience embolism in the United States, it is probable that thromboembolic pulmonary hypertension of sufficient severity to require surgical intervention occurs in no more than 0.2 to 0.3% of patients who survive an acute embolic event.16

Survival without intervention is poor and, as in other forms of pulmonary hypertension, proportional to the degree of pulmonary hypertension and right ventricular dysfunction at the time of diagnosis. In one study, 5-year survival rate was 30% when the mean pulmonary artery pressure was > 40 mmHg and 10% when it was > 50 mmHg.17 In another study, a mean pulmonary artery pressure > 30 mmHg appeared to serve as a threshold value portending a poor prognosis.18

**CLINICAL PRESENTATION**

There is little in the clinical presentation to differentiate chronic thromboembolic pulmonary hypertension from other forms of pulmonary hypertension. As in other forms of pulmonary hypertension, progressive exertional dyspnea and exercise intolerance are characteristic. This re-
sults from a limitation in cardiac output with exertion along with increased minute ventilatory demands associated with an increased dead space ventilation. Later in the course, exertional chest pain, presyncope, or syncope may occur as the compromised right ventricle becomes incapable of meeting cardiac output demands.

Physical examination findings are dependent on the degree of pulmonary hypertension present when the patient is evaluated. With mild pulmonary hypertension, physical examination findings may be subtle, limited to an accentuation of the pulmonic component of the second heart sound. As the pulmonary hypertension and right ventricular hypertrophy progress, classic findings of pulmonary hypertension develop: a right ventricular lift, accentuation of the pulmonic component of the second heart sound, a right ventricular S4 gallop, and varying degrees of tricuspid regurgitation. Even at this stage of the disease, however, physical findings can be deceptive, particularly for physicians unfamiliar with the physical diagnostic manifestations of pulmonary hypertension. As right ventricular failure ensues, an elevated jugular venous pressure with a prominent v wave, a right-sided S4, hepatomegaly, ascites, and cyanosis develop. The intensity of the tricuspid regurgitant murmur may diminish as the tricuspid annulus dilates and the transvalvular pressure gradient decreases. Lower extremity edema may develop, the result of right heart failure combined with venous obstruction related to residual venous thrombosis.

An important physical diagnostic finding in many patients with chronic thromboembolic disease is the presence of pulmonary flow bruits.19 These bruits, present in approximately 30% of patients with chronic thromboembolic pulmonary hypertension, appear to result from turbulent flow across partially obstructed pulmonary vascular segments. In terms of their quality, they are high pitched and blowing, audible over the anterior and posterior lung fields rather than the precordium, and most apparent during an end-inspiratory breath-holding maneuver. These bruits are not unique to chronic thromboembolic disease. They have been described in other disease states associated with focal narrowing of large pulmonary arteries such as congenital branch stenosis and pulmonary arteritis. They have not, however, been described in primary pulmonary hypertension, the most common competing diagnosis.

**DIAGNOSTIC EVALUATION**

The diagnostic pathway is straightforward once the possibility of pulmonary vascular disease has been considered. Diagnostic delay, unfortunately, occurs commonly. This is in part attributable to the often nonspecific presentation of the disease process and, early in its natural history, the subtlety of its physical examination findings. Disorders of the pulmonary vascular bed may be overlooked in the evaluation of chronic dyspnea. In patients with chronic thromboembolic pulmonary hypertension this is especially true in the absence of a prior history of acute venous thromboembolism or in the presence of other confounding historical details (e.g., childhood asthma, smoking history, obesity). The progressive dyspnea associated with chronic thromboembolic pulmonary hypertension is often erroneously attributed to asthma, physical deconditioning, advancing age, interstitial lung disease, coronary artery disease, or psychogenic dyspnea. Due in part to this delay in diagnosis, the majority of patients have advanced disease at the time of presentation with a pulmonary vascular resistance exceeding 600 dynes-sec-cm⁻².

Once the presence of pulmonary vascular disease has been considered, the diagnostic pathway has three central goals: to quantify the degree of pulmonary hypertension at rest or with exercise, to define its etiology, and, if major vessel thromboembolic disease is present, to determine whether it is accessible to surgical correction.

Routine hematologic and blood chemistry studies are usually unremarkable. A prolonged activate partial thromboplastin time in the absence of heparin therapy or a decreased platelet count may suggest the possibility of a lupus anticoagulant or anticardiolipin antibody, which has been identified in 10 to 50% of patients with chronic thromboembolic pulmonary hypertension.20–22 Other thrombophilic tendencies such as protein C, protein S, and antithrombin III deficiency, factor V Leiden mutation, and the prothrombin G20210A gene mutation do not appear to be more common among patients with chronic thromboembolic disease.21 Pulmonary function testing, often performed as part of the evaluation of the patient’s dyspnea, is usually within normal limits but may demonstrate a mild to moderate restrictive impairment, to a large extent caused by parenchymal scarring related to prior infarcts.24 Although a mild to moderate reduction in single-breath diffusing capacity for carbon monoxide (DLCO) can be observed, a normal value does not exclude the diagnosis.25,26 A severe reduction in DLCO due to chronic thromboembolic disease alone is rare and should alert the clinician to other diagnoses affecting the pulmonary vascular bed or pulmonary interstitium such as systemic sclerosis or pulmonary veno-occlusive disease.27,28 Chest radiography, although often normal, may demonstrate one or more findings that suggest the diagnosis of pulmonary hypertension such as right ventricular prominence, asymmetry in the size of the central pulmonary arteries, or enlargement of both pulmonary arteries.29,30 Areas of mosaic oligemia also may be present.30

Transthoracic echocardiography plays a valuable role in the diagnostic sequence. It usually is the first study to suggest or confirm the presence of pulmonary hypertension and is capable of excluding primary disease of the left ventricle, valvular disease, or intracardiac shunt as the basis for the pulmonary hypertension.
Diagnosis may demonstrate variable degrees of right atrial and right ventricular enlargement, abnormal right ventricular systolic function, tricuspid regurgitation, a leftward displacement of the interventricular septum, decreased left ventricular size, and abnormal left ventricular systolic and diastolic function. Contrast echocardiography may demonstrate evidence of a patent foramen ovale. Echocardiographic estimation of a mild degree of pulmonary hypertension at rest should not be overlooked because estimates of pulmonary artery pressure at rest are incapable of delineating the pulmonary hemodynamic response to exercise. With thromboembolic obstruction of sufficient extent, the normal vasodilatory capacity of the pulmonary vascular bed is abolished and augmentation of cardiac output is associated with a linear increase in pulmonary artery pressure.

Radioisotopic ventilation–perfusion (V/Q) scanning plays a pivotal role in differentiating pulmonary vascular obstruction arising from central vessels from that arising from the distal vasculature. The V/Q scan in chronic thromboembolic pulmonary hypertension invariably demonstrates one or more mismatched, segmental, or larger defects (Fig. 1). This is in contrast to the perfusion scan findings in primary pulmonary hypertension and other small vessel forms of pulmonary hypertension in which perfusion typically is normal or characterized by the presence of subsegmental defects. In certain instances, the perfusion scan in small vessel pulmonary arterial hypertension may demonstrate a lower lobe redistribution of flow that may be so prominent as to suggest isolated embolic disease of the upper lobes (Fig. 2). Such a distribution of embolization would be uncommon and, at angiography, patent upper lobe vessels are present.

The magnitude of the perfusion defects in chronic thromboembolic disease often understates to a considerable extent the actual degree of pulmonary vascular obstruction determined angiographically or at surgery. Therefore, the presence of even a single, mismatched, segmental V/Q scan defect in a patient with pulmonary hypertension should raise concerns regarding a potential thromboembolic basis. Mismatched segmental defects in patients with pulmonary hypertension may also arise from other processes that result in obstruction of the central pulmonary arteries or veins such as pulmonary artery sarcoma, large vessel pulmonary vasculitides, extrinsic vascular compression by mediastinal adenopathy or fibrosis, and pulmonary veno-occlusive disease.

The persistence of mismatched defects following embolism in an asymptomatic patient with normal echo-

![Figure 1](image1.png) Ventilation–perfusion scan in a patient with chronic thromboembolic pulmonary hypertension. Note multiple, bilateral segmental perfusion defects and normal ventilation.
cardiographic findings does not necessarily require further evaluation. In patients with persistent and extensive perfusion defects, surveillance echocardiography should be considered on an annual basis. Furthermore, consideration should be given to prolonged or indefinite anticoagulation in such patients given the risk of recurrent thromboembolism in the setting of an already compromised pulmonary vascular bed.

Once the presence of pulmonary hypertension has been established by echocardiography and its potential thromboembolic basis by V/Q scanning, right heart catheterization and pulmonary angiography should be undertaken. The role of computed tomographic (CT) scanning in the evaluation of patients with chronic thromboembolic disease remains incompletely defined.40,41 Although a variety of CT abnormalities have been described in patients with chronic thromboembolic disease, including the presence of thrombus within the central pulmonary arteries, the absence of these findings does not preclude the possibility of surgically accessible chronic thromboembolic disease. Furthermore, the presence of central thrombus has been described in primary pulmonary hypertension and other chronic pulmonary disorders (Fig. 3).42,43 Of greatest importance, CT scanning is incapable of providing essential hemodynamic data and in helping to discriminate between the resistance arising from the central vascular bed and that arising from the distal vessels. Given the potential consequences of diagnostic error, it is our impression that under all but the most unusual circumstances, CT alone should not be used as a primary basis for surgical referral or the denial

Figure 2  Ventilation–perfusion scan in a patient with primary pulmonary hypertension. Although no segmental defects are present, upper lobes appear relatively hypoperfused. Patent proximal vessels were present at the time of angiography.

Figure 3  Computed tomographic scan in a patient with primary pulmonary hypertension. Pulmonary arteries are massively enlarged. Lining thrombus is apparent along the anterior and lateral wall of right pulmonary artery.
of surgical referral in patients with suspected chronic thromboembolic pulmonary hypertension.

CT does have a role in the diagnostic pathway in selected patients. It is useful in those patients with unilateral, predominantly unilateral, or atypical vascular involvement in whom other diagnostic possibilities such as sarcoma, vasculitis, malignancy, and mediastinal fibrosis should be considered. It is also useful, along with physiologic testing, in helping to define the status of the pulmonary parenchyma in patients with coexisting obstructive or restrictive lung disease.

Five distinct angiographic patterns have been described that correlate with the finding of chronic thromboembolic material at the time of surgery. These findings include (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 and the findings are present bilaterally (Figs. 4, 5).

Even in the presence of severe pulmonary hypertension, pulmonary angiography can be performed safely if simple precautions are taken. The procedure appears to be associated with less risk in patients with chronic thromboembolic disease and well-compensated right ventricular function than in those with right ventricular dysfunction in the setting of acute pulmonary embolism. In terms of 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, appears to be sufficient. The patient is also carefully monitored and supplemental oxygen provided during the procedure. 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.

The pulmonary angioscope, a diagnostic fiberoptic device, was developed specifically to assist in preoperative evaluation. The angioscope, a fiberoptic device 120 cm in length and 3.0 mm in external diameter with distal 180 degree flexion and extension capability, is introduced through a vascular sheath, preferably using a right internal jugular approach, and passed into the pulmonary arteries using fluoroscopic guidance. Inflation of the distal balloon with carbon dioxide obstructs pulmonary artery blood flow and allows visualization of the arterial lumen. At UCSD Medical Center, angioscopy is performed in approximately 25% of patients undergoing evaluation to determine their candidacy for thromboendarterectomy. The procedure appears to be most useful under two circumstances: (1) predicting a beneficial hemodynamic outcome in patients with relatively modest levels of pulmonary hypertension in whom the angiographic findings do not precisely define the proximal extent of the thromboembolic disease, and (2) confirming operability in patients with severe pulmonary hypertension who would not have been referred to surgery based on the angiographic findings alone.

**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 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 > 300 dynes/sec/cm⁻⁵. At centers reporting their experience with thromboendarterectomy surgery, preoperative pulmonary vascular resistance is typically in the range of 700 to 1100 dynes/sec/cm⁻⁵. At this level of pulmonary hypertension, patient impairment at rest and with exercise can be considerable. Intervention at this level of
pulmonary hypertension is to a large part a consequence of the time of referral which, in many patients, can be months to years after symptom onset.

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 or angioscopy. 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 relation 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 partition the proximal component of the elevated vascular resistance from the distal 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. Several techniques intended to improve the partitioning of the upstream from the downstream components of the elevated pulmonary vascular resistance are currently under evaluation.41,51,52

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. Coexisting coronary artery disease, parenchymal lung disease, renal insufficiency, or hepatic

Figure 5  Left-sided pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension, anteroposterior and lateral views. The descending pulmonary artery narrows abruptly at the level of the lingula and a prominent web is visible traversing the vessel. Lateral view demonstrates absence of flow to the lingula and lower lobe flow confined to the anterior and medial segments.
Surgery and Outcome
Details of the surgical approach to chronic thromboembolic pulmonary hypertension have been described extensively elsewhere. However, there are several features of the procedure that 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. A sternotomy approach also provides adequate exposure for additional procedures that need to be performed. In a recent review of 1190 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 thromboendarterectomy procedures). Of these 90 patients, 83 underwent coronary bypass graft surgery, three underwent tricuspid valve repair, two underwent mitral valve repair, and two underwent aortic valve replacement. 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.

It also should be underscored that the procedure is a true thromboendarterectomy and not an embolectomy (Fig. 6). The chronic thromboembolic material is fibrotic and incorporated into the native vascular lumen. The neo-intima must be meticulously dissected away from the native intima and considerable surgical experience with this procedure is required to identify the correct operative plane. The removal of nonadherent, 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; and selective antegrade cerebral perfusion to decrease the risk of neurologic sequelae.

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. In addition to complications common to other forms of cardiac surgery (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 nonoperated pulmonary segments, and that the distribution of pulmonary blood flow improves over time in the majority of patients.

Biochemically and clinically, the acute lung injury that may occur following thromboendarterectomy...
appears to represent a localized form of high-permeability lung injury. 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 some other combination of causes. Whatever the cause, 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 arterial 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 has been used to modulate the inflammatory component of the process, though its effectiveness is unpredictable and frequently minimal. In a recent trial of 51 randomized patients, the intraoperative and early postoperative administration of a novel, selectin-mediated neutrophil adhesion blocking agent reduced the relative risk of reperfusion injury by 50% but had no impact on mortality, ventilator days, or days in the intensive care unit. In another study, 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 reperfusion pulmonary edema in 47 patients undergoing thromboendarterectomy. As in other forms of acute lung injury, the use of inverse ratio ventilation, a low-volume ventilatory strategy to minimize the risk of ongoing alveolar damage, and incremental levels of positive end expiratory pressure have proved useful in improving V/Q relationships and gas exchange. 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. 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, a group that encompasses approximately 5% of those undergoing the procedure. Depending on the level of residual pulmonary hypertension, postoperative hemodynamic instability may result from the adverse physiological consequences of cardiopulmonary bypass, deep hypothermia, acidosis, and hypoxemia. Management goals include minimizing systemic oxygen consumption, maximizing right ventricular preload, and providing aggressive inotropic support. Pulmonary vascular resistance in these patients is generally fixed, and pharmacological attempts to reduce pulmonary vascular resistance simply decrease systemic vascular resistance, systemic blood pressure, and right coronary artery perfusion pressure. Inhaled nitric oxide is theoretically ideal for this circumstance because it has negligible systemic effects. Experience with this intervention in the setting of persistent postoperative pulmonary hypertension, however, has been disappointing. Notwithstanding attempts at aggressive management, persistent pulmonary hypertension in the postoperative
period remains a major cause of mortality in patients undergoing pulmonary thromboendarterectomy.

Although exact figures are not available, approximately 2500 thromboendarterectomy procedures have been performed worldwide with more than 1500 of these at UCSD. In reported series of patients undergoing thromboendarterectomy since 1996 (Table 1), inhospital mortality rates have ranged between 5 and 24%.53,54,65–75 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 > 70 years, 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.54,74,76 Other series have not demonstrated that the preoperative severity of pulmonary hypertension or the degree of cardiac failure correlated with early postoperative death.73 Given what is known about the natural history of the disease and the progressive nature of the pulmonary hypertension associated with it, however, 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 6 to 8 weeks of conventional therapy is recommended to allow optimum thrombus resolution. Beyond this period of time, further improvement in the level of pulmonary hypertension cannot be achieved with medical therapy alone.11

In the 32-year history of thromboendarterectomy operations at UCSD, a trend of declining mortality rates has been noted (Fig. 7). In the initial 249 patients undergoing surgery between 1970 and 1990, the perioperative mortality rate was 14.5%, whereas in the 251 patients undergoing surgery during the years 2000 and 2001 the mortality rate had decreased to 4.5%; the majority of these deaths related to residual postoperative pulmonary hypertension and/or acute lung injury. It is possible that increased physician recognition of the disease resulting in referral prior to the development of a secondary arteriopathy or the onset of right ventricular failure has contributed to this decline in mortality. It is also reasonable to suggest that there may exist a strong relationship between volume of procedures performed and the outcome as has been demonstrated with other high-risk surgical procedures.77 In the case of thromboendarterectomy, 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. Should this prove to be the case, strong consideration could be given to performing the procedure at a limited number of referral centers. With only 250 thromboendarterectomy procedures estimated to be performed annually in the United States, the overall public health impact of such an approach would be limited. However, given that the procedure is usually performed on an elective basis, it might provide substantial benefit to the individual patient in terms of both mortality and extent of hemodynamic improvement.

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 pres-

### Table 1 Published Results for Pulmonary Thromboendarterectomy since 1996

| Year | Author | Location | Patients (n) | Preoperative PVR* | Postoperative PVR* | Mortality (%) |
|------|--------|----------|-------------|-------------------|--------------------|---------------|
| 1997 | Nakajima⁵⁵ | Japan | 30 | 937 ± 45 | 299 ± 16 | 13.3 |
| 1997 | Mayer⁶⁶ | Germany | 32 | 967 ± 238 | 301 ± 151 | 9.3 |
| 1998 | Gilbert⁶⁷ | Baltimore | 17 | -700 ± 200⁷ | -170 ± 80⁷ | 23.5 |
| 1998 | Miller⁶⁸ | Philadelphia | 25 | 1174 ± 416 | 519 ± 250 | 24.0 |
| 1999 | Dartevelle⁶⁹ | France | 68 | 1066 ± 250 | 268 ± 141 | 20.8 |
| 1999 | Ando⁷⁰ | Japan | 24 | 250 ± 192 | 13.2 |
| 2000 | Jamieson⁵³ | San Diego | 457 | 877 ± 452 | 267 ± 192 | 7.0 |
| 2000 | Mares⁷¹ | Austria | 33 | 1478 ± 10⁷ | 975 ± 93⁷ | 9.1 |
| 2000 | Mares⁷¹ | Austria | 14 | 1334 ± 135⁷ | 759 ± 99⁷ | 21.4 |
| 2000 | Rubens⁷² | Canada | 21 | 765 ± 372 | 208 ± 92 | 4.8 |
| 2000 | D’Armini⁷³ | Italy | 33 | 1056 ± 344 | 196 ± 39³ | 9.1 |
| 2001 | Tscho⁷⁴ | Germany | 69 | 988 ± 554 | 324 ± 188 | 10.1 |
| 2001 | Masuda⁷⁵ | Japan | 50 | 869 ± 299⁴ | 344 ± 174⁴ | 18.0 |

*PVR, pulmonary vascular resistance in dynes-sec cm⁻⁵
*Estimate derived from graph
*Results expressed as pulmonary vascular resistance index
*Data in 23 patients at 3-month follow-up
*34 patients by sternotomy, 16 patients by thoracotomy
sure and pulmonary vascular resistance can be achieved. In published series, the mean reduction in pulmonary vascular resistance (PVR) has approximated 70% and a PVR in the range of 200 to 350 dynes-sec-cm⁻⁵ can be achieved (see Table 1). A corresponding improvement in right ventricular function determined by echocardiography, gas exchange, exercise capacity, and quality of life has also been reported. Most patients initially in NYHA (New York Heart Association) functional Class III or IV preoperatively return postoperatively to NYHA Class I or II and are able to resume normal activities.

Figure 7
Number of procedures performed at University of California–San Diego Medical Center and deaths in 4-year sequences, 1986 to 2001. A threefold reduction in case-fatality (15.7–5.2%) has been achieved over that 16-year period of time.

The only therapeutic alternative for patients not deemed candidates for thromboendarterectomy and for those who have undergone thromboendarterectomy with an inadequate hemodynamic outcome is lung transplantation. Preliminary results suggest that selected patients may benefit from chronic epoprostenol therapy. The use of agents such as epoprostenol or bosentan to support cardiac function in the preoperative period or to ameliorate residual pulmonary hypertension in the postoperative period represents an exciting area of clinical investigation.

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