Current Concepts

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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THROMBOEMBOLIC obstruction of the major pulmonary arteries due to unresolved pulmonary embolism is a potentially correctable cause of pulmonary hypertension. Chronic thromboembolic pulmonary hypertension of sufficient severity to warrant surgical intervention is more common than previously suspected. Each year, there are 500 to 2500 patients with this condition in the United States, accounting for 0.1 to 0.5 percent of patients with pulmonary emboli who survive.[1,2] The diagnosis and management of chronic thromboembolic pulmonary hypertension require a multidisciplinary approach involving the specialties of surgery, pulmonary medicine, critical care, cardiology, anesthesiology, and radiology. With this approach, pulmonary thromboendarterectomy can be performed with an acceptably low risk of death.[2,3] After surgery, the majority of patients have a substantial improvement in hemodynamic variables, with improvements in functional status and long-term survival.[3-5]

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Most patients with chronic thromboembolic pulmonary hypertension present late in the course of the disease. For this reason, the early natural history of the condition is not completely known. Although its thromboembolic basis has been questioned, current evidence supports this cause, regardless of whether there is a documented history of acute venous thromboembolism.[6-8] This is not surprising, since recent studies indicate that embolism can occur without symptoms and that symptomatic pulmonary embolism is often overlooked or misdiagnosed.[9,10] Incomplete anatomical and hemodynamic recovery from an acute embolic event is also more common than previously thought.[11-13] No abnormality of the coagulation or fibrinolytic pathway or of the pulmonary endothelium has been identified that accounts for incomplete recovery, with the exception of an anticardiolipin antibody detected in approximately 10 percent of patients.[14-16]

Patients with thromboembolic disease may remain asymptomatic for months or years. The pathophysiological events in the progression of pulmonary hypertension during this period have not been well defined. The extent of vascular obstruction is a major determinant of pulmonary hypertension, and in the majority of patients, more than 40 percent of the pulmonary vascular bed is obstructed. Hemodynamic progression may involve recurrent thromboembolism or in situ pulmonary-artery thrombosis. In many patients, however, hemodynamic progression appears to involve pulmonary vascular remodeling and the development of a hypertensive pulmonary arteriopathy, similar to that encountered in patients with pulmonary hypertension due to other causes.[17,18] This supposition is supported by several lines of evidence: a low correlation between the extent of central anatomical obstruction and the degree of pulmonary hypertension, documented hemodynamic progression in the absence of recurrent embolic events or evidence of in situ pulmonary-artery thrombosis, and histopathological evidence of arteriopathic changes in the resistance vessels of both involved and uninvolved portions of the pulmonary vascular bed.[17,18]

Without intervention, the rate of survival is low and proportional to the degree of pulmonary hypertension at the time of diagnosis. In one study, the survival rate at five years was 30 percent among patients with a mean pulmonary-artery pressure that exceeded 40 mm Hg at the time of diagnosis and only 10 percent among those with a value that exceeded 50 mm Hg.[6] In another study, a mean pulmonary-artery pressure of 30 mm Hg appeared to be the threshold for a poor prognosis.[19]

CLINICAL MANIFESTATIONS

As with other forms of pulmonary hypertension, progressive exertional dyspnea and exercise intolerance are characteristic of thromboembolic pulmonary hypertension. In many cases, the only finding on physical examination is an accentuation of the pulmonic component of the second heart sound, which may be subtle and is easily overlooked. The symptoms are thus often attributed to other cardiopulmonary disorders, deconditioning, or even psychogenic dyspnea. Later in the course of the disorder, chest pain on exertion, presyncope, or syncope may occur as a result of severe pulmonary hypertension and the inability

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of a compromised right ventricle to meet the body's demands for cardiac output. As the disease progresses, the findings on physical examination become consistent with the presence of pulmonary hypertension or right ventricular failure. Approximately 30 percent of patients have bruits over the lung fields, which originate from turbulent flow through partially occluded or recanalized thrombi[20]; this finding is not characteristic of primary pulmonary hypertension.

An abnormality of the pulmonary vascular bed should be considered whenever a definitive cause of dyspnea cannot be identified. Once the possibility of pulmonary vascular disease has been considered, the diagnostic approach has three goals: to establish the presence and extent of pulmonary hypertension, to determine its cause, and if thromboembolic disease of major vessels is present, to determine whether it is amenable to surgical correction.

Findings on standard laboratory tests are nonspecific and similar to those in other cases of unexplained pulmonary hypertension. However, duplex scanning of the legs reveals evidence of prior venous thrombosis in 35 to 45 percent of patients with thromboembolic pulmonary hypertension.[7,21-26]

Transthoracic echocardiography is usually the first study to suggest that an abnormality of the pulmonary vasculature is present. Depending on the stage of the disease when echocardiography is performed, it 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.[27] Contrast echocardiography may demonstrate a patent foramen ovale.

Radioisotopic ventilation–perfusion scanning has a pivotal role in determining whether pulmonary hypertension has a thromboembolic basis. In patients with chronic thromboembolic pulmonary hypertension, the ventilation–perfusion scan invariably demonstrates one or more mismatched, segmental or larger defects (Fig. 1).[28] In contrast, perfusion is normal or characterized by the presence of subsegmental defects in patients with primary pulmonary hypertension or other small-vessel forms of pulmonary hypertension.[29] The magnitude of the perfusion defects in patients with chronic thromboembolic disease, however, often understates to a considerable extent the actual degree of pulmonary vascular obstruction, determined angiographically or at surgery.[30] Therefore, the presence of even a single mismatched, segmental perfusion defect in a patient with pulmonary hypertension should raise the question of a thromboembolic basis. Mismatched, segmental defects may arise from other processes that result in obstruction of the central pulmonary arteries or veins, such as pulmonary-artery sarcoma, large-vessel pulmonary vasculitis, extrinsic vascular compression due to mediastinal adenopathy or fibrosis, or pulmonary veno-occlusive disease.[31]

The role of computed tomographic (CT) scanning in the evaluation of patients with chronic thromboembolic disease remains incompletely defined. CT studies have shown a variety of abnormalities: chronic thromboembolic material located in an eccentric position within the central pulmonary arteries, right ventricular enlargement, dilated central pulmonary arteries, bronchial-artery collateral flow, parenchymal abnormalities consistent with prior infarcts, and mosaic attenuation of the pulmonary parenchyma (Fig. 2).[32] The absence of these findings, however, does not rule out surgically accessible chronic thromboembolic disease. Furthermore, central thrombus has been reported in patients with primary pulmonary hypertension or other chronic pulmonary disorders.[33,34] CT studies do not provide essential hemodynamic data, but they are particularly useful in the evaluation of the main pulmonary arteries and of unilateral or predominantly unilateral pulmonary vascular obstruction, as determined by ventilation–perfusion scanning.[35] Under these circumstances, the probability of another disorder, such as pulmonary-artery sarcoma, vasculitis, cancer, or mediastinal fibrosis, is increased. CT also has a role, along with physiological testing, in determining the status of the pulmonary parenchyma in
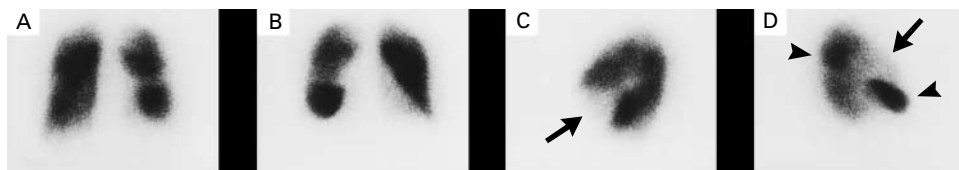
Figure 1. Representative Perfusion Lung Scan in a Patient with Chronic Thromboembolic Pulmonary Hypertension.
The ventilation study (not pictured) showed no abnormalities. The perfusion scan shows multiple, segmental, mismatched defects. Panels A and B show the posterior and anterior views, respectively. In Panel C, which shows the left lateral view, there is a segmental defect involving the lingula (arrow). In Panel D, which shows the right lateral view, areas of hyperperfusion involving the posterior aspect of the right upper lobe as well as the right middle lobe (arrowheads) are interspersed with areas of relative hypoperfusion involving the anterior aspect of the right upper lobe (arrow) and the majority of the lower lobe.
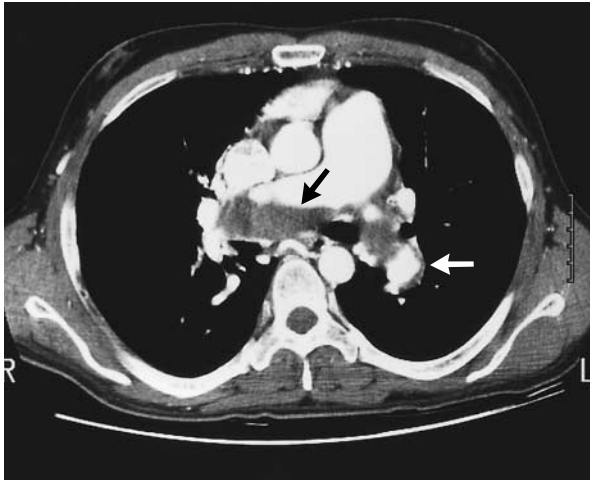
Figure 2. Computed Tomographic Angiogram in a Patient with Chronic Thromboembolic Pulmonary Hypertension.

Partially organized thrombus (black arrow) lines both pulmonary arteries, with narrowing of the right main pulmonary artery at the origin of the upper lobe. Asymmetric wall thickening is also evident along the lateral aspect of the left descending pulmonary artery (white arrow).

patients with coexisting obstructive or restrictive lung disease.

Right-heart catheterization should be considered in any patient with unexplained dyspnea and segmental or larger defects on ventilation–perfusion scanning, especially if there is echocardiographic evidence of right atrial or right ventricular dysfunction. Catheterization is not necessary in patients with residual, postembolic perfusion defects in the absence of symptomatic limitation or echocardiographic abnormalities, unless the perfusion defect is substantial, accounting for 40 percent or more of total pulmonary perfusion. In patients who do undergo catheterization, pulmonary angiography must be performed carefully to establish whether chronic thromboembolic obstruction is present, to determine its extent and proximal extension (and therefore its accessibility to surgery), and to rule out other causes. With modification of standard angiographic approaches and careful monitoring of the patient, pulmonary angiography can be performed safely regardless of the degree of pulmonary hypertension.[36] Biplane imaging provides optimal anatomical detail. When dilated and overlapping vessels are present, the lateral view provides more detailed images of lobar and segmental anatomy than those obtained with an anterior–posterior view alone (Fig. 3).

The angiographic appearance of chronic thromboembolic disease differs from that of acute pulmonary embolism, which is characterized by well-defined, in-traluminal filling defects. In chronic thromboembolic disease, the angiographic findings reflect the complex patterns of organization and recanalization caused by the process of partial embolic resolution.[37]

The pulmonary angioscope, a diagnostic fiberoptic device, was developed specifically for preoperative evaluation.[38,39] The angioscopic features of organized, chronic emboli consist of roughening or pitting of the intimal surface, bands and webs traversing the vascular lumen, pitted masses of chronic embolic material within the lumen, and partial recanalization. Intimal plaques are a nonspecific finding in pulmonary hypertension of any cause. Angioscopy is performed in approximately 30 percent of patients undergoing evaluation for thromboendarterectomy, 60 percent of whom subsequently undergo surgery. The procedure appears to be most useful for two purposes: to predict a beneficial hemodynamic outcome in patients who have relatively low levels of pulmonary hypertension and in whom the angiographic findings do not precisely indicate the proximal extent of the thromboembolic disease, and to confirm operability in patients with severe pulmonary hypertension who would not be considered candidates for surgery on the basis of the angiographic findings alone.[39]

TREATMENT AND PROGNOSIS

Pulmonary thromboendarterectomy is considered in symptomatic patients who have hemodynamic or ventilatory impairment at rest or with exercise. The mean pulmonary vascular resistance in patients undergoing surgery is 800 to 1000 dyn·sec·cm^{-5} (range, 300 to 2000).[40] Patients with values at the lower end of the range include those with involvement limited to one main pulmonary artery; those accustomed to vigorous activity, in whom high dead space and minute ventilatory demands are disabling; and those who live at high altitudes. Thromboendarterectomy is also considered in patients who have normal or nearly normal pulmonary hemodynamics at rest but in whom marked pulmonary hypertension develops during exercise. If surgery is deferred in such patients, careful monitoring for progression of the pulmonary hypertension is recommended.

The location and extent of the proximal thromboembolic obstruction are the most critical determinants of operability. Occluding thrombi must involve the main, lobar, or proximal segmental arteries. Those that originate more distally are not amenable to thromboendarterectomy with current techniques. In terms of the extent of obstruction, the anatomical and hemodynamic findings must be interpreted in concert. An acceptable hemodynamic outcome requires that the preoperative hemodynamic impairment be consistent with the amount of surgically accessible thromboembolic material. This determination is crucial. If the hemodynamic impairment derives mainly from surgically inaccessible disease or from the resistance
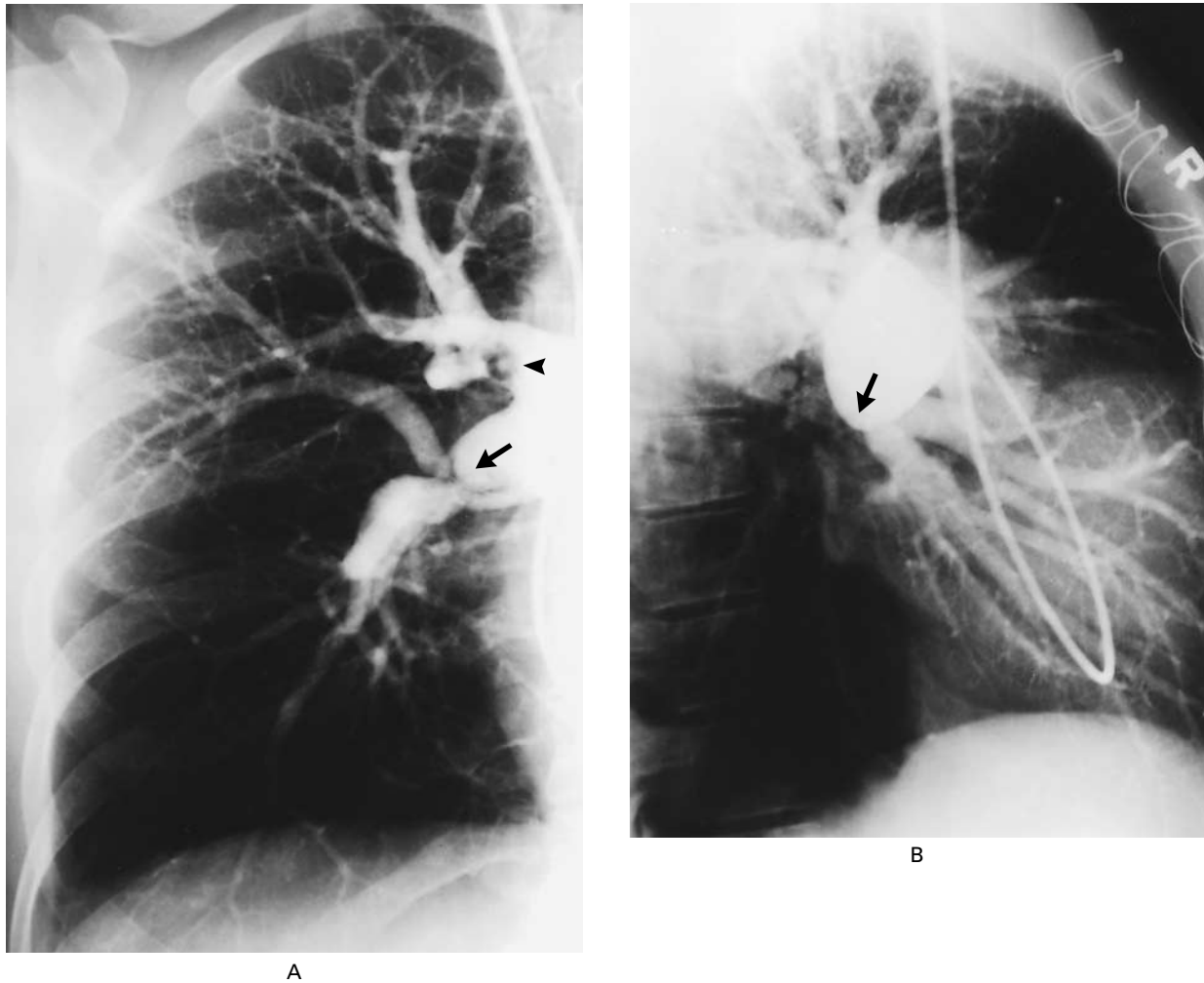
Figure 3. Right Pulmonary Angiogram Showing Features of Chronic Thromboembolic Disease.

The anterior–posterior view (Panel A) shows abrupt narrowing in a rounded fashion ("pouch defect") of the right interlobar artery (arrow), followed by opacification of vessels to the right lower lung field. An intraluminal thrombus (arrowhead) is present in the proximal upper-lobe artery. The lateral view in the same patient (Panel B) shows the extent of thromboembolic obstruction. The vessels in the right middle lobe are dilated, with complete obstruction of flow to the right lower lobe (arrow).

conferred by a secondary, small-vessel arteriopathy, then pulmonary hypertension will persist postoperatively and may have adverse short-term and long-term consequences.

The only absolute contraindication to thromboendarterectomy is the presence of severe underlying lung disease, either obstructive or restrictive. Advanced age, severe right ventricular failure, and the presence of collateral disease influence the risk assessment but are not absolute contraindications. Patients as young as 16 and as old as 84 years, as well as those with complex coexisting conditions, have successfully undergone the procedure.[2]

Coronary angiography is performed before surgery in patients with risk factors for coronary athero-sclerotic disease. If necessary, coronary-artery bypass grafting can be performed at the time of thromboendarterectomy. Placement of a filter in the inferior vena cava is recommended before surgery in all patients except those with a clearly defined source of emboli other than the deep veins in the legs.
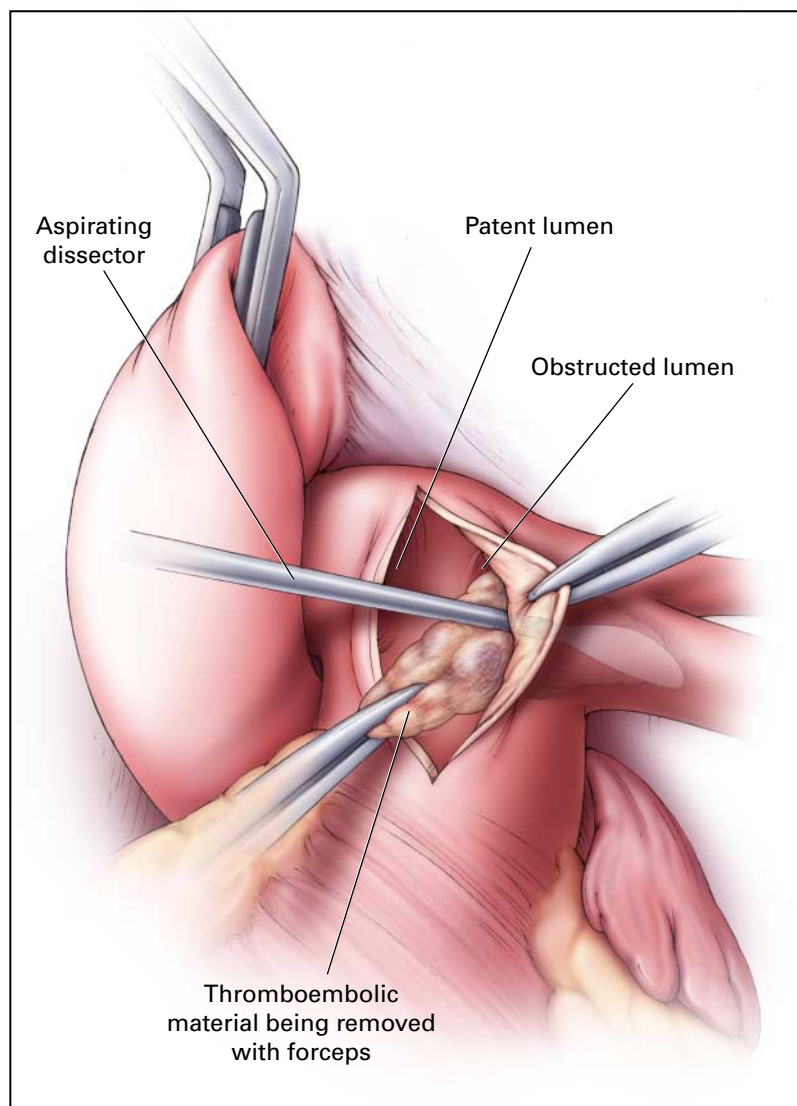
Pulmonary thromboendarterectomy is a true endarterectomy and bears little resemblance to pulmonary embolectomy. The organized thromboembolic material is fibrotic and adheres to the vessel wall. The procedure, reviewed in recent reports, involves median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest to ensure adequate visualization in the presence of retrograde bronchial arterial flow during the

bilateral procedures.[2,40] The right and left thromboendarterectomies are performed sequentially.

An incision is made in the right pulmonary artery where it passes the aorta to the division of the lower-lobe branches. On the left, the incision extends from the main pulmonary artery to the origin of the left upper-lobe branch. An endarterectomy plane is established between the intima and the fibrotic embolic material. The obstructing material is then grasped with a forceps, and distal, circumferential dissection is performed with an aspirating dissector to permit complete removal (Fig. 4). Considerable experience is required to identify and establish the correct plane. Too deep a plane will result in perforation of the vessel, whereas too superficial a plane will result in inadequate endarterectomy. The arteriotomy sites are closed with a continuous, double running suture to ensure hemostasis. In some cases, after prolonged retraction of the artery, placement of a bovine pericardial patch is required to restore the normal circumference of the vessel.

In 1984, there were published reports on 85 pa-

Figure 4. Intraluminal View of the Pulmonary Artery during Thromboendarterectomy.

The fibrotic, thromboembolic material is grasped with a forceps and circumferentially dissected from the vessel wall with an aspirating dissector. The material is then grasped at a more distal point, and the process is repeated until all the material has been removed and the patency of the vessel restored.

tients who had undergone thromboendarterectomy, with an overall mortality of 22 percent.[41] Approximately 2000 thromboendarterectomy procedures have now been performed worldwide, about 1400 of them at a single center. Since 1996, mortality rates in series that have included more than 10 patients undergoing the operation have ranged from 5 to 24 percent[2,3,42-51] (Table 1). Because of the high risk associated with this intervention, it should be provided as part of a multidisciplinary approach by a team of physicians with experience in the complex details of the diagnosis and management of chronic thromboembolic pulmonary hypertension.

The factors associated with death after pulmonary thromboendarterectomy, aside from those that are common with high-risk, open-heart procedures, are reperfusion lung injury and right ventricular failure related to residual pulmonary hypertension.[52] Reperfusion lung injury develops in most patients undergoing the procedure and appears, biochemically and clinically, to represent a localized form of high-permeability, neutrophil-mediated lung injury.[53] Most commonly manifested in the first 24 hours after surgery, the condition is characterized by arterial hypoxemia, with radiographic evidence of infiltrates involving the endarterectomized pulmonary segments. The severity of reperfusion injury is highly variable, ranging from a mild form resulting in postoperative hypoxemia, present in most patients, to profound alveolar flooding that may be fatal. Therapy, as with other forms of acute lung injury, is primarily supportive. The administration of nitric oxide may improve gas exchange, although in our experience it does not reduce the need for ventilatory support or increase survival.[54] Extracorporeal support has been used successfully in selected patients with overwhelming reperfusion injury.

Persistent pulmonary hypertension with right ventricular failure occurs when a substantial component of the hemodynamic impairment arises from thromboembolic obstruction that is beyond the limits of surgical accessibility or from the resistance due to secondary, small-vessel arteriopathy. The early management of these problems after attempted thromboendarterectomy involves minimizing systemic oxygen consumption, maximizing right ventricular preload, and providing aggressive inotropic support. The administration of nitric oxide may improve gas exchange in patients with severe reperfusion injury, but again, in our experience, it does not reduce the need for ventilatory support or prolong survival.

Even though there has not been a controlled investigation of the short-term and long-term hemodynamic outcomes of thromboendarterectomy, for most patients the outcomes are favorable.[2,3,42-51,55] Dramatic reduction, and at times normalization, of the pulmonary-artery pressure and pulmonary vascular resistance can be achieved (Table 1); the mean reduction in pulmonary vascular resistance is approximately 65 percent.[2,3,42-51] Corresponding improvements in gas

TABLE 1. RESULTS OF PULMONARY THROMBOENDARTERECTOMY, 1997 TO 2000.*

YEAR	STUDY	LOCATION	NO. OF PATIENTS	PULMONARY VASCULAR RESISTANCE		MORTALITY
				PREOPERATIVE	POSTOPERATIVE	
				dyn·sec·cm^{-5}		%
1997	Nakajima et al.[43]	Japan	30	937±45	299±16	13
1997	Mayer et al.[44]	Germany	32	967±238	301±151	9
1998	Gilbert et al.[45]	Baltimore	17	700±200†	170±80†	24
1998	Miller et al.[46]	Philadelphia	25	NA	NA	24
1999	Dartevelle et al.[47]	France	68	1174±416	519±250	13
1999	Ando et al.[48]	Japan	24	1066±250	268±141	21
2000	Jamieson and Kapelanski[2]	San Diego, Calif.	457	877±452	267±192‡	7
2000	Mares et al.[49]	Austria	33	1478±107‡	975±93‡	9
2000	Mares et al.[49]	Austria	14	1334±135‡	759±99‡	21
2000	Rubens et al.[50]	Canada	21	765±372	208±92	5
2000	D'Armini et al.[51]	Italy	33	1056±344	196±39§	9

*Plus−minus values are means ±SD. NA denotes not available.

†The value, derived from a graph, is approximate.

‡The value is the pulmonary-vascular-resistance index (pulmonary vascular resistance divided by body-surface area).

§The value is for 23 patients at three months of follow-up.

exchange and exercise capacity have also been reported. Most patients are in New York Heart Association functional class III or IV before surgery; after surgery, they are in class I or II and are able to resume normal activities.[3-5]

Lifelong anticoagulant therapy is strongly recommended after thromboendarterectomy. Recurrent thromboembolism necessitating a second thromboendarterectomy has occurred in several patients in whom anticoagulant therapy was discontinued or maintained at a subtherapeutic level.[56] Patients who are not considered candidates for thromboendarterectomy and those in whom the results of thromboendarterectomy are inadequate may be considered candidates for lung transplantation. Preliminary data suggest that selected patients may benefit from long-term treatment with epoprostenol.[57]

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