Techniques and Outcomes of Pulmonary Endarterectomy for Chronic Thromboembolic Pulmonary Hypertension

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Cardiopulmonary function in patients with chronic thromboembolic pulmonary hypertension can almost be normalized by pulmonary endarterectomy. The procedure involves the removal of organized and incorporated fibrous obstructive tissue from the pulmonary arteries during circulatory arrest under deep hypothermia. Mortality rates reported for patients who have undergone pulmonary endarterectomy range from 4 to 24%. The operation is not an embolectomy but a true endarterectomy. After proximal intrapericardial pulmonary artery incision, the correct endarterectomy plane is established and circumferentially followed down to the lobar, segmental, and sometimes subsegmental pulmonary artery branches in each lobe. Completion of the endarterectomy procedure in one lung is usually possible within a 15-min period of circulatory arrest. This is followed by reperfusion and another period of circulatory arrest for the endarterectomy on the contralateral side. Additional cardiac procedures can be performed after arteriotomy closure, during the rewarming period, if necessary. The outcomes with regard to functional status, quality of life, hemodynamics, right-ventricular function, and gas exchange are very favorable. After surgery, significant and persistent decreases of pulmonary artery pressures and pulmonary vascular resistance are observed in a large majority of patients. Cardiac output is increased and right-heart function is persistently improved. Postoperative management of patients undergoing pulmonary endarterectomy can be challenging. Important complications are persistent pulmonary arterial hypertension due to inadequate endarterectomy or significant secondary vasculopathy, and reperfusion edema in the endarterectomized parts of the lung. Adequate postoperative care is therefore essential. Preoperative hemodynamic severity and the site of anatomic obstruction are believed to be key predictors of postoperative outcome.

Keywords: endarterectomy; hypertension, pulmonary; thromboembolic

Chronic thromboembolic pulmonary hypertension is a severe disease that is caused by obstruction of the pulmonary arteries by single or recurrent pulmonary thromboemboli that do not undergo complete resolution (1). These lesions lead to endothelialized residua that obliterate or significantly narrow major pulmonary arteries, resulting in functional impairment and poor prognosis (2). Since 1957, pulmonary endarterectomy has evolved to become the treatment of choice in most patients with chronic thomboembolic pulmonary hypertension (3). To date, this pioneering surgical procedure has been performed on approximately 3000 patients with the disease, at a limited number of centers around the world. Initially, operative mortality rates were high, but with growing experience and refinement of the technique, these rates have decreased substantially. This is illustrated by data from the University of California at San Diego, where an operative mortality rate of 17% was reported for the 200 patients who underwent pulmonary endarterectomy between 1970 and 1990. A much lower rate of 4.4% was achieved for the 500 patients who underwent surgery between 1998 and 2002 (3).

Pulmonary endarterectomy is a bilateral procedure, because chronic thromboembolic pulmonary hypertension is mostly a bilateral disease (4). Removal of all thrombotic material is crucial to surgical outcome. The surgical approach includes median sternotomy, cardiopulmonary bypass, deep hypothermia, and circulatory arrest. What is considered accessible is, to a large degree, dependent on the surgical team's expertise. The purpose of this article is to give a state-of-the-art description of the pulmonary endarterectomy procedure, together with a discussion of surgical outcome and associated risk factors.

INDICATIONS AND PATIENT SELECTION FOR PULMONARY ENDARTERECTOMY

The selection criteria for surgical intervention have evolved over the years. Recent clinical guidelines from the American College of Chest Physicians recommend that the following four basic criteria should be met: (*1*) New York Heart Association (NYHA) functional class III or IV symptoms, (*2*) a preoperative pulmonary vascular resistance (PVR) of greater than 300 dyn · s · cm^{-5}, (*3*) surgically accessible thrombus in the main lobar or segmental pulmonary arteries, and (*4*) no severe comorbidities (5). Severe underlying chronic lung disease, either obstructive or restrictive, is a contraindication to pulmonary endarterectomy, regardless of severity of chronic thromboembolic pulmonary hypertension. In an accompanying article, Rubin and colleagues (6) list a mean pulmonary artery pressure of 40 mm Hg or greater, level of surgical expertise, and the presence or absence of advanced secondary arteriopathy as further major factors that should influence the overall decision of whether to proceed to pulmonary endarterectomy. The most common reasons for rejection of patients referred for pulmonary endarterectomy are severe comorbidity and significant distal disease in combination with excessive pulmonary hypertension. Although precise cut-off values denoting levels of preoperative pulmonary resistance that are acceptable in patients proceeding to surgery need to be established, Dartevelle and coworkers (7) proposed that patients should be selected for pulmonary endarterectomy only if a reduction of pulmonary resistance of more than 50% can be expected.

Beyond initial work-up, diagnosis of chronic thromboembolic pulmonary hypertension is based on echocardiography, lung perfusion–ventilation scintigraphy, right-heart catheterization, and bilateral pulmonary angiography. More recently, computed tomography and magnetic resonance imaging are superseding perfusion–ventilation scans at some centers. These aspects are covered in detail elsewhere in this issue (8, 9).

(*Received in original form May 15, 2006; accepted in final form July 5, 2006*)

Supported by an unrestricted educational grant from Actelion Pharmaceuticals.

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Proc Am Thorac Soc Vol 3. pp 589–593, 2006
DOI: 10.1513/pats.200605-120LR
Internet address: www.atsjournals.org

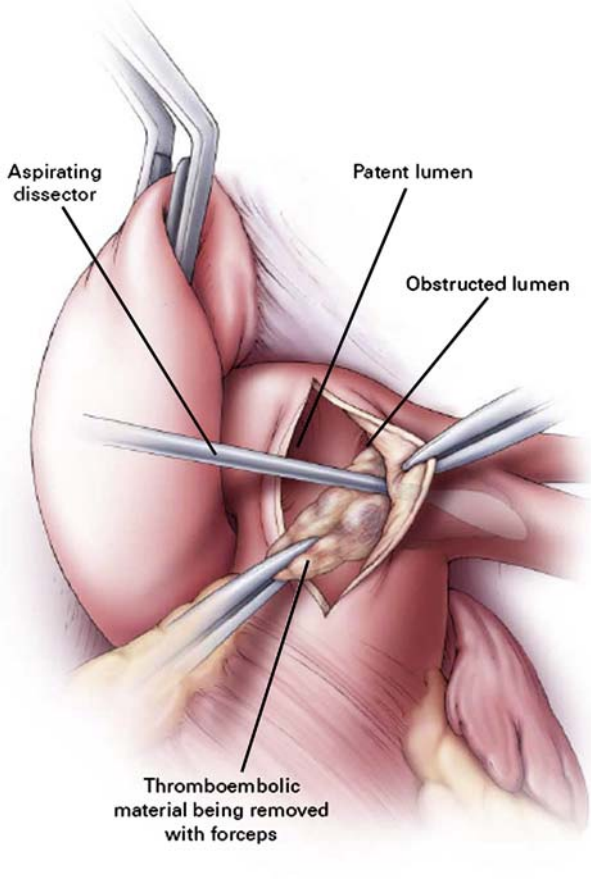

Figure 1. Intraluminal view of the pulmonary artery during pulmonary endarterectomy. Reprinted by permission from Reference 16.

SURGICAL PATHOLOGY OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Over the initial weeks after acute pulmonary embolism, the embolic material evolves to acquire a thrombotic phenotype, with subsequent transformation over a period of months to years into fibrous tissue that is incorporated into the intima and media of the arterial wall (10). This thromboembolic material may extend to the segmental and subsegmental branches of each pulmonary artery. Partial recanalization often occurs at the level of the large trunks, although occlusion persists at the ostia of segmental branches. Surgical removal requires a true endarterectomy as opposed to a thrombectomy or embolectomy, because the intraluminal material is inseparable from the intima. Balloon pulmonary angioplasty has been performed successfully in some patients who are not candidates for pulmonary endarterectomy (11, 12), but this technique is only an option for a very limited number of patients treated in specialized centers.

SURGICAL PROCEDURE

Operative Strategy

The pulmonary endarterectomy procedure is performed during total circulatory arrest under conditions of profound hypothermia (18–20°C). This is required to enable visibility in the distal pulmonary arterial branches, which would otherwise be subject to back-bleeding during the endarterectomy due to the development of a systemic-to-pulmonary artery circulation at the precapillary level (13). Cumulative periods of circulatory arrest are usually less than 40 min and should not exceed 50 to 60 min in individual cases. Pulmonary endarterectomy is performed using intrapericardial pulmonary artery incisions without opening the pleura.

A relatively recent technical advance is the introduction of video-assisted pulmonary endarterectomy, which uses a video camera connected to a rigid angioscope (7). Video technology is beneficial because it provides a source of light, allows visualization of the distal pulmonary vascular tree, and facilitates a close view of the surgery by the assistant surgeons. Consistent with these

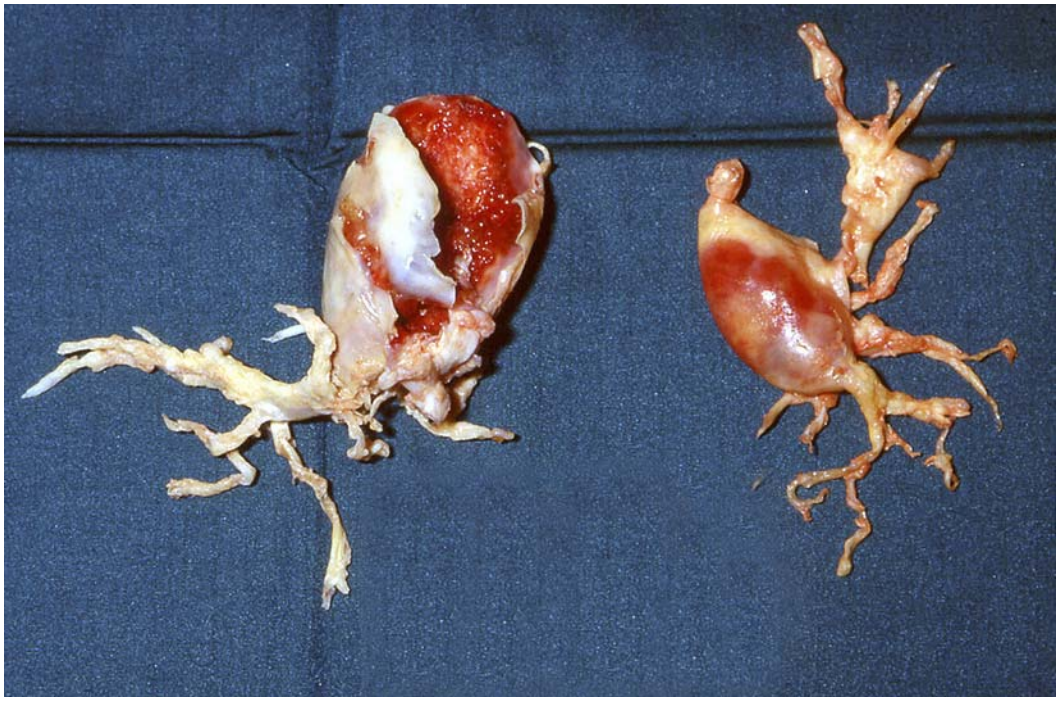

Figure 2. Thromboembolic material removed from the right and left pulmonary arteries during pulmonary endarterectomy. Patient details: 57-yr-old male patient with a 5-yr history of increasing breathlessness. At-angiography evidence for chronic thromboembolic pulmonary hypertension (CTEPH) type 1–2. Preoperative pulmonary arterial pressure (PAP; systolic/mean/diastolic), 97/58/32 mm Hg; cardic index (CI), 1.9 L · min · m^{-2}; pulmonary vascular resistance (PVR), 978 dyn · s · cm^{-5}. Postoperative PAP (systolic/mean/diastolic), 42/31/25 mm Hg; CI, 2.7 L · min · m^{-2}; PVR, 327 dyn · s · cm^{-5}.

advantages, and based on the experience of a single center, Dartevelle and colleagues have concluded that video assistance during pulmonary endarterectomy allows improved quality and degree of endarterectomy, with associated benefits on functional outcome (7).

Procedure

A median sternotomy is performed, followed by a vertical pericardiotomy. After institution of extracorporeal circulation, cooling of the patient is then started, accompanied by complete dissection of the superior vena cava to access the right pulmonary artery. Once cooling to 20°C has been achieved, the ascending aorta is clamped and crystalloid cardioplegia is injected into the aortic root. After a proximal intrapericardial incision along the anterior aspect of the right pulmonary artery, the correct endarterectomy plane is established in the media of the posterior surface. During a first period of circulatory arrest, the plane is circumferentially followed down to the segmental and sometimes subsegmental branches of each lobe using special suction dissectors (Figure 1), until a complete endartectomy is achieved. Establishment of the correct plane is crucial to the success of the procedure because an excessively deep plane is associated with a risk of artery perforation, whereas a plane that is too superficial is likely to result in residual pulmonary hypertension and poor clinical outcome.

The patient is reperfused for approximately 15 min with cardiopulmonary bypass, while the arteriotomy is closed with a back-and-forth running suture. An arteriotomy is performed on the left pulmonary artery and the endarterectomy is repeated in the left lung within another period of circulatory arrest. The final stage comprises reperfusion during closure of the left pulmonary artery, de-airing of the cardiac chambers, unclamping of the aorta, and slow rewarming of the patient to 37°C. Figure 2 shows a typical example of the thromboembolic material that is removed during a representative bilateral pulmonary endarterectomy procedure.

After closure of the pulmonary artery incision on the left side, additional cardiac procedures can be performed during the rewarming period, if required. For example, in a recent review of 1,190 patients undergoing pulmonary endarterectomy, 90 patients required a combined procedure, including coronary artery bypass (CAB) surgery in 83 patients (14). These concomitant procedures were performed without adversely affecting the postoperative outcome.

Operative Classification of Chronic Thromboembolic Pulmonary Hypertension

Patients with chronic thromboembolic pulmonary hypertension may be classified into four types, according to the classification of surgical specimens proposed by Thistlethwaite and colleagues (15). The four types are characterized as follows: type 1, fresh thrombus in main-lobar pulmonary arteries; type 2, intimal thickening and fibrosis proximal to the segmental arteries; type 3, disease within distal segmental arteries only; and type 4, distal arteriolar vasculopathy without visible thromboembolic disease. However, this is an intraoperative classification scheme, which does not assist in the selection of patients who are good surgical candidates. Therefore, there is a need for a preoperative classification system (9).

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

The postoperative management of patients undergoing pulmonary endarterectomy can be challenging. One of the most important complications is persistent pulmonary hypertension (mean pulmonary arterial pressure > 25 mm Hg), which may be seen in approximately 10% of patients. This is due to inadequate endarterectomy of inaccessible distal thrombotic pathology, or to significant secondary vasculopathy (small-vessel arteriopathy), and is likely to lead to right-ventricular failure (16). Pulmonary hypertension also persists after surgery in patients with morphologic type IV chronic thromboembolic pulmonary hypertension, who exhibit pronounced preoperative pulmonary hypertension in the absence of significant proximal thromboembolism; infrequent cases have been wrongly selected for pulmonary endarterectomy, but are actually considered to have primary pulmonary arterial hypertension with secondary thrombotic lesions.

Another potential concern is reperfusion edema in the endarterectomized parts of the lung (estimated incidence, 10–15%). Adequate postoperative mechanical ventilation and fluid restriction are therefore of particular importance. Positive inotropic catecholamines and vasodilators have been used for termination of cardiopulmonary bypass; however, Mares and colleagues (17) have reported that nonaggressive mechanical ventilation (tidal volumes < 8 ml/kg, duration of inspiration:duration of expiration $= 3{:}1$; peak inspiratory pressures < 18 cm H_2O) and avoidance of positive inotropic agents are associated with a lower incidence of reperfusion pulmonary edema and right-heart failure. Immediate postoperative extracorporeal membrane oxygenation support is an appropriate option if weaning from cardiopulmonary bypass proves to be difficult, and has been used for the management of patients with no improvement in PVR after surgery. Prostanoid inhalation can be helpful for control of persistent pulmonary hypertension (18). Nitric oxide has anecdotally been reported to improve gas exchange in patients with persistent pulmonary hypertension and in those with reperfusion edema; however, this does not appear to produce benefits in terms of need for ventilatory support or prolongation of survival (19). Currently, there are limited data on the influence of different postoperative treatment strategies on mortality and complications.

Other adverse outcomes after pulmonary endarterectomy include arteriotomy rupture, which is due to spiking of pulmonary artery blood pressure, nosocomial pneumonia, and hemoptysis. Intrapulmonary bleeding occurs in an estimated 0.5 to 1% of patients. Rethrombosis of the endarterectomized area is rare.

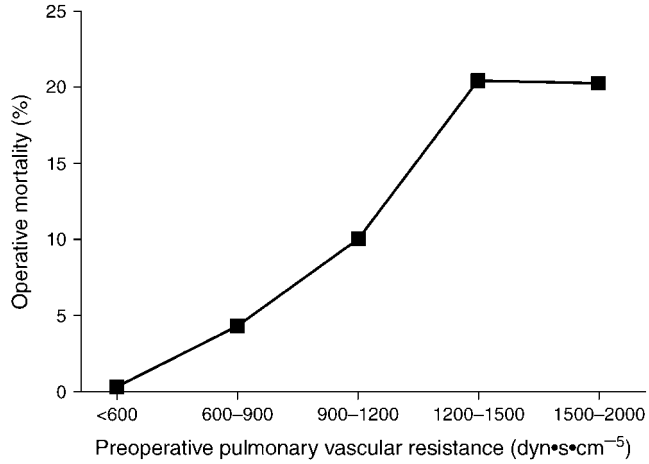

Figure 3. Operative mortality according to preoperative PVR in patients with CTEPH undergoing pulmonary endarterectomy. Reprinted by permission from Reference 13.

TABLE 1. PRE- AND POSTOPERATIVE HEMODYNAMIC VALUES ACCORDING TO LOCATION OF THROMBOEMBOLIC MATERIAL IN PATIENTS WITH CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION UNDERGOING PULMONARY ENDARTERECTOMY

	All Patients (*n = 500*)	Type 1 (*n = 187*)	Type 2 (*n = 245*)	Type 3 (*n = 60*)	Type 4 (*n = 8*)
PVR, dyn · s · cm^{-5}	893 ± 443.5	973 ± 444.3	809 ± 419.2	973 ± 487.6	1163 ± 490.5
	285 ± 214.7	275 ± 201.2	273 ± 219.2	344 ± 193.9	868 ± 421.6
Cardiac output, L/min	3.8 ± 1.3	3.6 ± 1.4	4.1 ± 1.2	3.8 ± 1.5	3.4 ± 1.2
	5.5 ± 1.5	5.6 ± 1.5	5.6 ± 1.5	5.3 ± 1.6	4.2 ± 1.6
Systolic PAP, mm Hg	77 ± 18.1	78 ± 16.2	76 ± 19.6	77 ± 18.1	86.5 ± 11.4
	47 ± 17.6	46 ± 15.1	45 ± 16.7	53 ± 17.2	101 ± 38.9
Diastolic PAP, mm Hg	30 ± 9.8	30.3 ± 8.9	28.8 ± 10.2	30.1 ± 10.3	36.9 ± 11.1
	19 ± 7.6	18.1 ± 6.9	18.1 ± 7.4	20.5 ± 9.1	37.8 ± 11.7
Mean PAP, mm Hg	46 ± 11.0	47 ± 9.7	46 ± 11.7	47 ± 11.7	55 ± 9.8
	28 ± 10.1	28 ± 8.9	28 ± 10.3	32 ± 10.9	55 ± 13.2
Mortality, %	22 (4.4%)	4 (2.1%)	13 (5.3%)	3 (5.0%)	2 (25%)

Definition of abbreviations: PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

Data are means ± SD. For each hemodynamic parameter, top values are preoperative and bottom values are postoperative values. Postoperative changes in all values were statistically significant at $p \leq 0.001$, except in type 4 disease, where they were not significant. Reproduced by permission from Reference 3.

POSTOPERATIVE OUTCOME

Assessment of operability and establishment of a differential diagnosis are critical for the outcome of pulmonary endarterectomy. Mortality rates reported for patients who have undergone pulmonary endarterectomy range from approximately 4 to 24% (3, 16). In a series of 275 patients with chronic thromboembolic pulmonary hypertension who underwent pulmonary endarterectomy between 1996 and early 2003, the principal cause of operative mortality was persistent pulmonary hypertension (17 patients, or 60.7% of all operative deaths), followed by pulmonary edema (3 patients) and pneumopathy (3 patients) (13). The operative mortality rate from pulmonary endarterectomy appears to be closely related to hemodynamic severity, with a mortality rate of 4% observed in patients with a preoperative PVR of less than 900 dyn · s · cm^{-5}, 10% in those with a PVR of between 900 and 1,200 dyn · s · cm^{-5}, and 20% in patients with higher preoperative PVR values (Figure 3) (13). Consistent with this, Jamieson and coworkers (3) reported a 30.6% mortality rate in pulmonary endarterectomy patients with a postoperative PVR of greater than 500 dyn · s · cm^{-5}, compared with a rate of 0.9% in those with lower postoperative values. Whether patients with PVR values of greater than 1,200 dyn · s · cm^{-5} should be regarded as suitable candidates for pulmonary endarterectomy continues to be a matter of controversy.

In a cohort of 308 patients who underwent pulmonary endarterectomy between 1970 and 1994, 6-yr survival after pulmonary endarterectomy was approximately 75%, with essentially the same level of survival out to 15 yr (19). Therefore, the survival rate after pulmonary endarterectomy appears to be superior to that after lung transplantation for chronic thromboembolic pulmonary hypertension.

In suitable patients (those with NYHA functional class III or IV symptoms, a preoperative PVR of > 300 dyn · s · cm^{-5}, surgically accessible lesions in the main lobar or segmental pulmonary arteries, a correlation between hemodynamic compromise and degree of vascular obliteration, and no severe comorbidity or left-ventricular dysfunction), the outcomes of the operation with regard to functional status, quality of life, hemodynamics, right-ventricular function, and gas exchange are usually favorable. Hemodynamic parameters can be expected to improve beyond the immediate postoperative period, with sustained benefits demonstrated at medium-term follow-up (13–48 mo) (20). This observation is suggestive of postsurgery vascular remodeling, facilitated by reduced pulmonary vessel pressures, although solid evidence for this is lacking. As discussed in detail by Bresser and colleagues in this issue (21), this raises the possibility that postoperative outcome might be favorably affected by preoperative use of medical therapy (e.g., prostacyclin analogs, endothelin-receptor antagonists, or phosphodiesterase-5 inhibitors) to improve hemodynamic parameters before surgery. However, this has not yet been rigorously assessed in randomized, controlled trials.

An important clinical consideration in the evaluation of whether to proceed to pulmonary endarterectomy is the site of anatomic obstruction, with patients with a high PVR and a low (distal) anatomic obstruction being at higher risk than those with a comparable PVR but with proximal anatomic obstruction. Location of disease, as categorized by the traditional operative classification system (22), also has effects on hemodynamic parameters after pulmonary endarterectomy (Table 1) (3). Clinical factors that are known to influence postoperative outcome are summarized in Table 2 (13).

TABLE 2. PREDICTORS OF SUCCESSFUL OUTCOME AND INCREASED RISK IN PULMONARY ENDARTERECTOMY

Predictors of Surgical Success	Predictors of High Operative Risk
• Prior history of pulmonary embolism and/or deep vein thrombosis	• No history of acute thromboembolic event
• "Honeymoon period" (period of months to years between acute embolic event and clinical symptoms of chronic thromboembolic pulmonary hypertension)	• Hemodynamic:angiographic imbalance
• Angiographic lesions located proximally in pulmonary arteries or lobar branches	• Distal location of thrombotic material
• Correlation between pulmonary vascular resistance and anatomic obstruction	• Presence of indwelling catheter
	• Normal bronchial arteries
	• Myeloproliferative syndrome

CONCLUSIONS

Pulmonary endarterectomy is a complex surgical procedure that can be considered curative, with significant and sustained functional and hemodynamic improvement in the vast majority of patients with chronic thromboembolic pulmonary hypertension. Mortality rates after pulmonary endarterectomy continue to decrease and are dependent on a high level of surgical expertise and the selection of appropriate patients. The site of pulmonary artery obstruction is an important determinant of surgical outcome. Preoperative hemodynamics, particularly PVR, are believed to be important predictors of the postoperative outcome. Preoperative medical therapy (e.g., treatment with prostacyclin analogs, endothelin-receptor antagonists, or phosphodiesterase-5 inhibitors) may represent an opportunity to reduce postoperative mortality in patients undergoing pulmonary endarterectomy, although this possibility requires further investigation.

Conflict of Interest Statement: E.M. received $4,500 in 2004 and 2005 for speaking at conferences sponsored by Actelion and Schering. W.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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