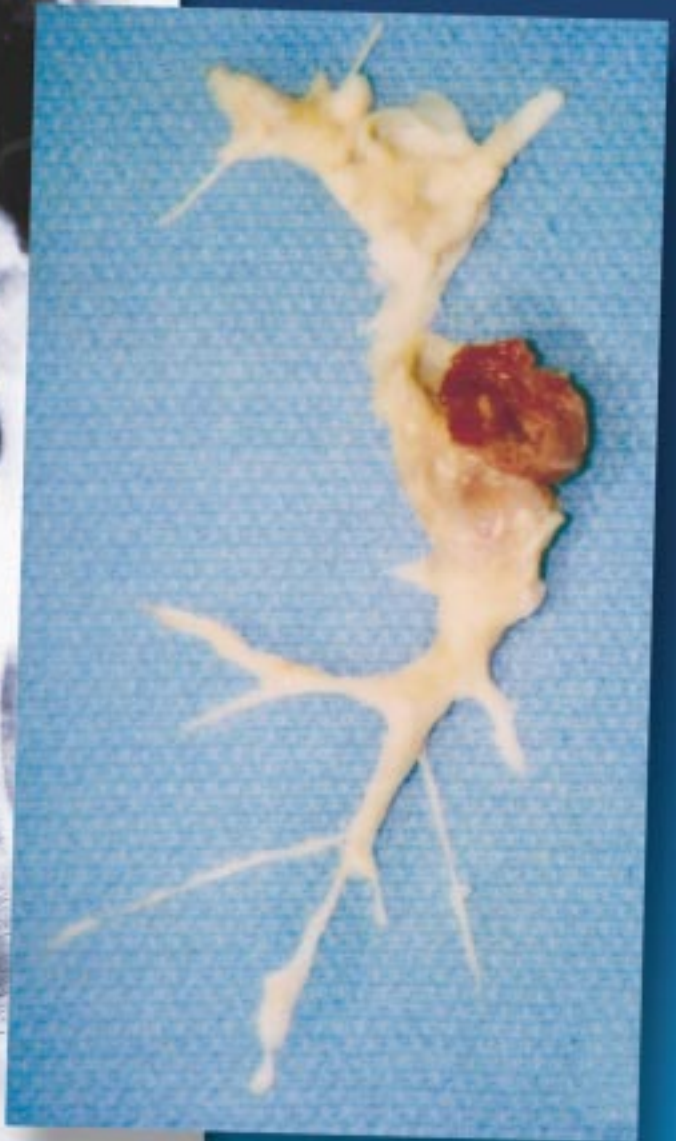
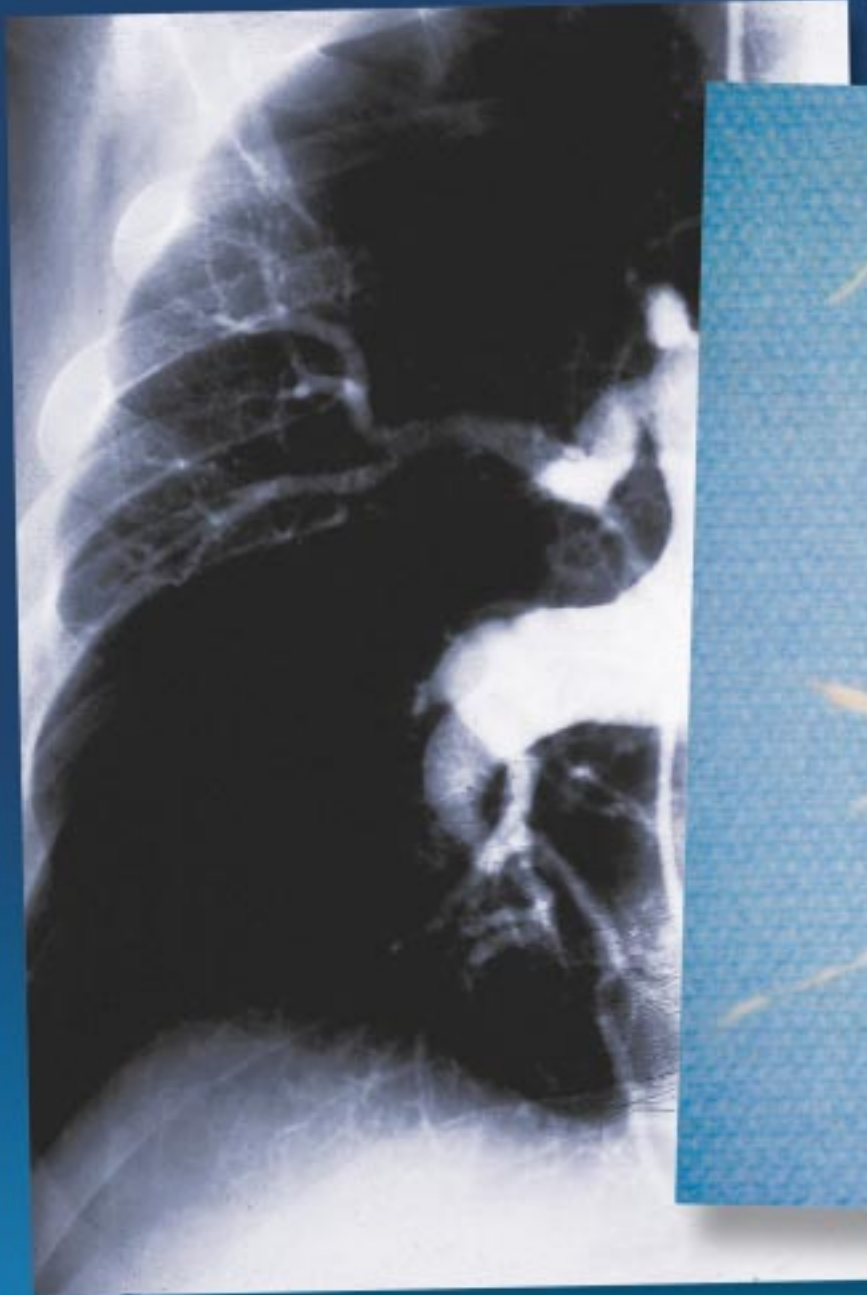


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*Advances in Pulmonary Hypertension* is committed to help physicians in their clinical decision making by informing them of important trends affecting their practice. Analyzing the impact of new findings and covering current information in the peer-reviewed literature, *Advances in Pulmonary Hypertension* is published four times a year. *Advances in Pulmonary Hypertension* is the official journal of the Pulmonary Hypertension Association.

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**Cover Photo:** Preoperative angiogram from patient with thromboembolic pulmonary hypertension and surgical specimen showing removal of thromboembolic material. (Images courtesy of Richard Channick, MD, and Kim Kerr, MD.)

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## Inside the Surgical Suite: Meeting the Challenges of CTEPH



It is so rare to find a curable cause of pulmonary arterial hypertension (PAH). In preparing the topics to be covered for this issue we decided that surgically curable PAH is one of the most challenging situations we face, particularly in terms of appropriate selection of patients and in our preoperative preparation. One of the major challenges confronting us is bringing the right patient into the operating room suite and addressing all of the issues impinging on our decision to perform surgery as we determine whether the chronic thromboembolic pulmonary hypertension (CTEPH) is surgically accessible and to what extent we can make a correlation between angiographic and hemodynamic findings. This is one of the critical issues we addressed in our Roundtable Discussion as we touched on a broad range of topics related to thromboendarterectomy to bring you the latest thinking from preeminent experts in the United States and abroad.

As we consulted these experts, we turned to the University of California, San Diego, because this center is so widely recognized as the world's leading referral center for pulmonary thromboendarterectomy surgery. Beginning with the pioneering work of Ken Moser, MD, UCSD has contributed enormously to developing guidelines for the evaluation of patients to determine their surgical candidacy and for performance of the procedure itself. Continuing the theme of this issue, two articles written by UCSD investigators provide an in-depth analysis of preoperative and operative considerations. The first begins with the subtle and nonspecific symptoms that may provide the first clues of CTEPH and offers important insights on confirmatory catheterization studies. The second article is an insider's view of thromboendarterectomy, information that anyone would want to retain as an essential reference for one's files.

The wealth of information presented here highlights how far we have come in the evolution of our thinking about thromboembolic disease in the setting of PAH. We have made dramatic strides, moving away from the earlier and simplistic view of its being merely a mechanical obstruction of the major pulmonary arteries. The experience at major centers has redefined our approach and given us important new tools with which to achieve that rare cure in many patients with this disease.

Vic Tapson, MD  
Editor-in-Chief

### Profiles in Pulmonary Hypertension

## The Legacy of Ken Moser Lives on at UCSD

Peter Fedullo, MD, and William Auger, MD



Kenneth M. Moser, MD

Behind every great medical program is an invisible presence, a pioneering spirit who established its course and mapped a road to excellence now well traveled by colleagues and new trainees. The physicians in the Division of Pulmonary and Critical Care Medicine at the University of California, San Diego, School of Medicine are following in the footsteps of Kenneth M. Moser, MD, the "gentle giant" who still serves as that invisible yet powerful presence guiding the division as a model of care for the larger pulmonary hypertension community. The contributions to this issue by members of the UCSD team serve as reminders of Dr Moser's continuing influence among those who trained under him and benefited from his mentorship.

Although Dr. Moser died in 1997 after more than 30 years at the pulmonary division, his work as one of the original faculty

members and his role as the founder and leader of the division continue to inspire the staff today. Widely recognized for his work in pulmonary vascular diseases, he was a world-renowned authority on acute and chronic thromboembolic disease. He was instrumental in establishing UCSD as the world's leading referral center for pulmonary thromboendarterectomy surgery and one of the country's models for the management of chronic thromboembolic pulmonary hypertension.

After earning his medical degree from the Johns Hopkins School of Medicine in 1954, Dr Moser completed his residency at Georgetown University and was later recruited by Eugene Braunwald, MD, to direct the pulmonary division at UCSD. Widely consulted for his medical opinion, he was a consummate teacher and an exponent for new and future developments in pulmonary disease care. Presenting a case to him—in private or at his famed "Professor Rounds"—was a memorable experience because of the way he challenged trainees and older physicians alike.

Those who knew him best remember him primarily as a staunch defender of academic medicine and the special role that medical schools like UCSD play in nurturing and developing tomorrow's leaders. In his biography in *Who's Who in America* he summed up his views this way: "Participating in academic medicine and research is like being a member of a relay team engaged in a race of infinite length. Two forces keep one running through the often difficult terrain: the goal of improving health, and the privilege of passing the baton to many others who will seek the same goal." As the legacy of Dr Moser continues to thrive and the achievements of UCSD as a premier center for pulmonary care are more widely appreciated, it is clear that he succeeded in passing the baton to his colleagues.

# Chronic Thromboembolic Pulmonary Hypertension: When to Suspect It, When to Refer for Surgery



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*Chronic thromboembolic obstruction of the major pulmonary arteries is an underrecognized sequela of acute pulmonary embolism. Depending on the burden and location of thrombus, as well as on the duration of vessel obstruction, chronic thromboembolic disease may lead to pulmonary hypertension and cor pulmonale. Chronic thromboembolic disease affects an estimated 500 to 2500 patients each year in the United States, roughly 0.1 to 0.5 percent of patients who survive acute pulmonary embolism. Consequently, while this disease is uncommon, chronic thromboembolic pulmonary hypertension (CTEPH) is not rare, and should be considered in patients with unexplained dyspnea, as it is potentially correctible with pulmonary thromboendarterectomy.<sup>1</sup>*

## Epidemiology and Pathophysiology

Since most patients with CTEPH present late in their disease course, the early natural history of this disease process is poorly understood. However, current evidence suggests that an acute thromboembolism is likely the precipitating event even when the patient has no documented history of acute venous thromboembolism. Studies have documented not only that symptomatic pulmonary embolism is often overlooked or misdiagnosed, but that pulmonary embolism may be asymptomatic.<sup>2</sup> Complete anatomic and hemodynamic resolution is also probably less common than previously appreciated. Although serial angiographic studies are limited to small numbers of patients, only partial resolution is visible in many patients as long as 21 days after an acute pulmonary embolic event.<sup>3</sup> When serial lung perfusion scans have been performed several months after the primary embolic event, up to 66% of patients show persistently abnormal perfusion patterns, reflecting incomplete resolution.<sup>4</sup> These figures may actually underestimate the degree of residual thromboembolic disease since perfusion scanning often understates the extent of angiographic obstruction in chronic thromboembolic disease.<sup>5</sup>

It is still unclear why acute emboli fail to resolve in a sub-

set of patients who subsequently develop pulmonary hypertension. An identifiable hypercoagulable state is found in only a minority of patients. A lupus anticoagulant is present in 10% to 20% of patients with CTEPH.<sup>6,7</sup> Inherited deficiencies of protein C, protein S, and antithrombin III, as a group, can be identified in up to 5% of this population.<sup>8</sup> Efforts to identify abnormalities in the fibrinolytic pathway or within the pulmonary endothelium that would account for incomplete thrombus dissolution have been unrevealing.<sup>9-11</sup>

The inability to adequately lyse a pulmonary embolus in the proximal pulmonary arteries can result in a reduction in the cross sectional area of the pulmonary vascular bed. If significant, patients may be left with residual dyspnea after the acute embolism. However, many patients may remain asymptomatic for months or years following their initial embolic event. While hemodynamic decline may be due to recurrent thromboembolic events or in situ thrombosis with extension of organized thrombus, clinical experience and analysis of sequential perfusion scans in a large number of CTEPH patients suggest that an alternative process may contribute to the hemodynamic deterioration in this population. The development of a pulmonary hypertensive arteriopathy, similar to that seen in patients with other forms of pulmonary hypertension, has been documented in unobstructed lung regions as well as in vessels distal to partially or completely occluded proximal pulmonary arteries.<sup>12</sup> These small-vessel changes therefore appear to be a significant contributor to the hemodynamic progression seen in many of these patients.

Without surgical intervention, survival of CTEPH patients is poor and is inversely related to the degree of pulmonary hypertension at the time of diagnosis. Riedel et al found a 5-year survival rate of 30% among patients with a mean pulmonary artery pressure greater than 40 mmHg at the time of diagnosis and 10% in those whose pressure exceeded 50 mmHg.<sup>13</sup> In another study, a mean pulmonary artery pressure as low as 30 mmHg was identified as a threshold for poor prognosis.<sup>14</sup>

## Clinical Manifestations

Similar to patients with other forms of pulmonary hypertension, patients may present with subtle or nonspecific symptoms. The most common symptoms in patients with CTEPH are progressive exertional dyspnea and exercise intolerance. These symptoms are secondary to elevated dead space ventilation and a limitation in cardiac output from obstruction of the pulmonary vascular bed. As the disease progresses, additional symptoms, such as edema, chest pain, light-headedness and syncope may develop. Early in the course of thromboembolic disease, physical findings may be limited to an accentuated P<sub>2</sub>, which may be easily overlooked during the physical exam. With progression of the disease, physical findings compatible with the presence of pulmonary hypertension and right ventricular failure develop. Meticulous auscultation of the lungs may provide a clue to the etiology of the pulmonary hypertension. Short systolic bruits may be audible over the lung fields in 30% of patients with CTEPH. They are high pitched and blowing in quality and are auscultated over the lung fields rather than the precordium. More audible during an end-inspiratory breath-holding maneuver, these bruits are caused by turbulent flow through larger pulmonary arteries partially occluded by thrombus. They may also be present in other disease states that cause narrowing of the pulmonary arteries such as large-vessel arteritis, tumors of the pulmonary artery and congenital branch stenosis. However, they have not been described in primary pulmonary hypertension, a common competing diagnosis.<sup>15</sup>

A delay of two to three years from the onset of symptoms to confirmation of the correct diagnosis is common.<sup>16</sup> A delay is most common when there is no history of acute thromboembolism. The nonspecific symptoms of this disease as well as the subtle physical findings early in its natural history contribute to the delay in correct diagnosis. Symptoms are frequently erroneously attributed to deconditioning, advancing age, psychogenic dyspnea, or more commonly occurring cardiopulmonary diseases such as obstructive lung disease or coronary artery disease. A lack of awareness of the disease entity by physicians also plays a role in the difficulty of achieving the correct diagnosis.

## Diagnostic Evaluation

Pulmonary vascular disease must always be considered in the differential diagnosis of unexplained dyspnea. The diagnostic evaluation serves three purposes: to establish the presence and severity of pulmonary hypertension, to determine its etiology, and, if thromboembolic disease is present, to determine whether it is surgically correctible. Routine laboratory tests may be normal early in the disease. The development of right ventricular dysfunction may result in abnormal liver function studies from hepatic congestion and elevation of blood urea nitrogen, creatinine, and uric acid from a reduction in renal blood flow. Long standing hypoxemia may lead to secondary polycythemia. The presence of a lupus anticoagulant may be suggested by an elevated activated partial thromboplastin time and may be accompanied by a low platelet count.

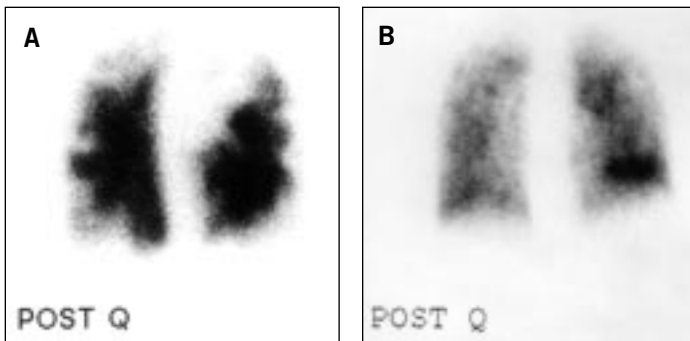
Chest radiography may be unrevealing in the early stages of CTEPH. However, several radiographic abnormalities may be seen with progression of pulmonary hypertension and cor pulmonale. The lung fields are typically clear in the absence of

coexisting lung disease or may demonstrate peripheral opacities suggestive of scarring from previous infarction. Careful inspection may reveal areas of hypoperfusion or hyperperfusion with a prominent interstitial pattern. Cardiomegaly with dilation and hypertrophy of the right-sided chambers and dilation of the central pulmonary arteries are radiographic signs of long standing pulmonary hypertension. Asymmetric enlargement of the central pulmonary arteries is suggestive of chronic thromboembolic occlusion of major vessels. This radiographic finding may be mistaken for adenopathy, which is important to exclude.

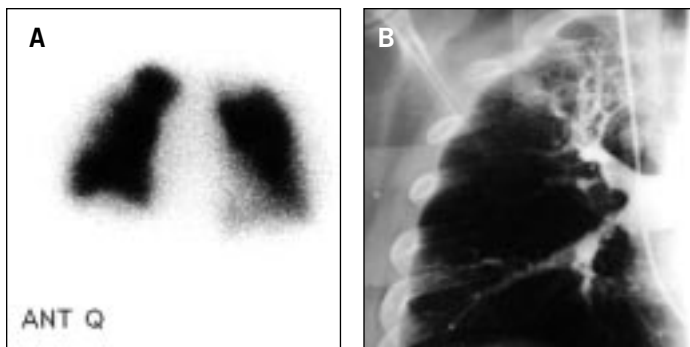
Pulmonary function tests are often obtained in the evaluation of dyspnea and serve to exclude the presence of obstructive airways or parenchymal lung disease. There are no characteristic spirometric changes diagnostic of CTEPH. Approximately 20% of patients will have a mild to moderate restrictive defect that is caused by parenchymal scarring.<sup>17</sup> The single breath diffusing capacity for carbon monoxide (DCO) may be normal, mildly or moderately reduced; a severe reduction in DCO should alert the physician to other diseases that severely compromise the small pulmonary vascular bed. Arterial blood oxygen levels can be normal even in the setting of significant pulmonary hypertension. With exertion, many will experience a decline in pO<sub>2</sub>. When present, hypoxemia in the setting of CTEPH is due to ventilation-perfusion inequalities, a reduction in cardiac output causing a decline in mixed venous oxygen saturation, and right-to-left shunting of blood through a patent foramen ovale.<sup>18</sup>

Transthoracic echocardiography is commonly the first study to provide objective evidence of the presence of pulmonary hypertension. An estimate of the pulmonary artery systolic pressure can be provided by Doppler evaluation of the tricuspid regurgitant envelope. Additional echocardiographic findings vary depending upon the stage of the disease and include enlargement of the right-sided chambers, leftward displacement of the interventricular septum, and encroachment of the enlarged right ventricle on the left ventricular cavity with abnormal systolic and diastolic function of the left ventricle.<sup>19</sup> Contrast echocardiography may demonstrate a patent foramen ovale or septal defects.

Once the diagnosis of pulmonary hypertension has been established, distinguishing between major-vessel obstruction and small-vessel pulmonary vascular disease is the next critical step. Radioisotope ventilation-perfusion (V/Q) lung scanning plays a central role in determining whether pulmonary hypertension has a thromboembolic origin. The V/Q scan typically shows one or more mismatched, segmental or larger defects in CTEPH. This is in contrast to the normal or "mottled" perfusion scan seen in patients with primary pulmonary hypertension or other small-vessel forms of pulmonary hypertension<sup>20</sup> (**Figure 1**). It is important to note that during the process of reorganization, thromboemboli may recanalize or narrow the vessel lumen so that macroaggregated albumen may pass beyond the point of partial vessel obstruction. This results in relative areas of hypoperfusion which appear as "gray zones," a finding frequently observed on the V/Q scans of patients with CTEPH. One consequence of this partial recanalization is that the magnitude of the perfusion defects with CTEPH frequently underestimates the actual degree of pulmonary vascular obstruction as determined by angiography or surgery<sup>5</sup> (**Figure 2**). Even a single mis-



**Fig. 1**—A. A perfusion scan in a patient with CTEPH demonstrating multiple, bilateral, segmental perfusion defects. B. A patient with PPH with a "mottled" perfusion scan without any segmental perfusion defects.



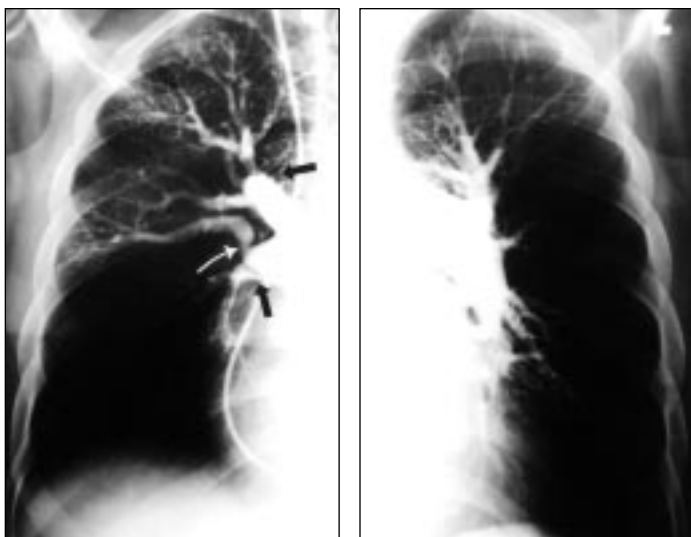
**Fig. 2**—Due to recanalization of chronic thrombus, the defects seen on the perfusion scan (2A) grossly understate the degree of obstruction seen on the pulmonary angiogram (2B) and the findings at the time of surgery (2C).

matched segmental defect in a patient with pulmonary hypertension should raise the suspicion of chronic thromboembolic disease. Furthermore, mismatched segmental perfusion defects are not specific for thromboembolic disease and may be seen with other processes that result in obstruction of the central pulmonary arteries, such as mediastinal adenopathy or fibrosis, large-vessel arteritis, pulmonary vascular or bronchogenic tumors, and pulmonary veno-occlusive disease. Therefore, additional imaging studies may be required to establish the correct diagnosis.

Cardiac catheterization provides essential information in the evaluation of patients with suspected pulmonary hypertension. Right heart catheterization provides data that allow for quantification of the severity of pulmonary hypertension and an assessment of cardiac function. Hemodynamics during symptom-limited exercise should be obtained when there is evidence of only modest pulmonary hypertension at rest, especially when the patient's symptoms seem out of proportion to the degree of resting pulmonary hypertension or the extent of thromboembolic obstruction. Measurement of oxygen saturations in the vena cava, right heart chambers and the pulmonary artery may document previously undetected left-to-right shunting. Coronary angiography and left heart catheterization provide additional information in those at risk for coronary artery disease and in patients in whom left ventricular dysfunction or valvular heart disease is suggested by echocardiography. This information is crucial in the preoperative risk assessment of patients deemed candidates for pulmonary thromboendarterectomy.

Pulmonary angiography continues to be the gold standard for defining the pulmonary vascular anatomy and is performed to identify whether chronic thromboembolic obstruction is present, to determine its location and surgical accessibility, and to rule out other diagnostic possibilities. Despite concerns regarding the safety of performing pulmonary angiography in patients with pulmonary hypertension, with careful monitoring and modification of standard angiographic procedures, pulmonary angiography can be performed safely even in patients with severe pulmonary hypertension.<sup>21</sup> Biplane imaging is preferred, offering the advantage of lateral views that provide greater anatomic detail compared with the overlapped and obscured vessel images often seen in the anterior-posterior view. Interpretation of these angiograms can be difficult in large measure because the appearance of chronic thromboemboli bears little resemblance to the well-defined, intraluminal filling defects of acute pulmonary embolism. Maturation and organization of clot results in vessel retraction and partial recanalization resulting in several angiographic patterns suggestive of chronic thromboembolic disease: (1) pouch defects; (2) pulmonary artery webs or bands; (3) intimal irregularities; (4) abrupt narrowing of major pulmonary vessels; and (5) obstruction of main, lobar, or segmental pulmonary arteries, frequently at their point of origin<sup>22</sup> (Figure 3). However, competing diagnoses exhibit angiographic findings similar to those encountered with chronic thromboembolic disease. For instance, areas of focal vessel narrowing, or "bands," can be seen as a feature of congenital stenosis of the pulmonary arteries as well as of medium- or large-vessel arteritis. Total obstruction or abrupt narrowing of the central pulmonary arteries can be a feature of an intravascular process such as pulmonary vascular tumors or extravascular compression from lung carcinoma, hilar or mediastinal adenopathy, or mediastinal fibrosis. Since chronic thromboembolic disease is usually bilateral, the presence of unilateral central pulmonary artery obstruction should always prompt consideration of one of these rival diagnoses.

In approximately 25% of patients evaluated at the University of California, San Diego, pulmonary angioscopy is used to supplement the information obtained from pulmonary angiography. The pulmonary angioscope is a diagnostic fiberoptic device that was developed to visualize the intima of central



**Fig. 3—Angiographic findings of chronic thromboembolic disease: pouches in the right upper lobe and interlobar artery (black arrows), a band with post-stenotic dilatation (white arrow), and rapid tapering of the left descending pulmonary artery.**

pulmonary arteries. It is inserted through a vascular sheath inserted in a central vein and passed through the right heart into the pulmonary artery under fluoroscopic guidance. Inflation of a latex balloon affixed to the tip of the angioscope results in obstruction of blood flow in the artery and permits visualization of the arterial intima. The most useful role for pulmonary angiography is in identifying operative candidates whose angiographic findings suggest limited disease.

Helical CT scanning has been used increasingly in the screening of patients with suspected thromboembolic disease, but its role in the evaluation of patients with chronic thromboembolic disease is not completely defined. CT features suggestive of CTEPH include evidence of organized thrombus lining the pulmonary vessels in an eccentric or concentric fashion, enlargement of the right ventricle and central pulmonary arteries, variation in size of segmental arteries (relatively smaller in the affected segments compared with uninvolved segments), bronchial artery collaterals, a mosaic perfusion pattern of the lung parenchyma, and parenchymal changes compatible with infarcts.<sup>23</sup> The absence of these findings does not rule out surgically accessible disease and further evaluation is warranted if CTEPH is suspected. CT imaging has significant value in evaluating those patients who may have alternative causes of pulmonary artery obstruction, including carcinoma, lymphadenopathy, fibrosing mediastinitis, and primary pulmonary vascular tumors. In addition, CT imaging along with physiologic testing plays an important role in evaluating patients with coexistent parenchymal lung disease, such as emphysema or restrictive lung disease.

A critical, but sometimes difficult, distinction to make is between patients with CTEPH and patients with other forms of pulmonary hypertension who also have thrombus lining the central pulmonary arteries. The presence of centrally located thrombus on spiral CT scanning does not uniformly confirm the diagnosis of CTEPH since this radiologic finding has been documented in patients with primary pulmonary hypertension and other chronic pulmonary diseases.<sup>24,25</sup> Presumably, these lesions are due to *in situ* thrombosis rather than pulmonary

embolism. Endarterectomy in these patients carries a substantial mortality risk and is unlikely to provide hemodynamic benefit. Historical information is typically helpful in establishing the correct diagnosis and the perfusion scan is either normal or demonstrates minimal abnormalities in this setting.

### Surgical Selection

Pulmonary endarterectomy is considered in patients who are symptomatic and have evidence of hemodynamic or ventilatory impairment at rest or with exercise. Patients undergoing surgery usually exhibit a preoperative pulmonary vascular resistance greater than 300 dynes/sec/cm<sup>-5</sup>, typically in the range of 800-1000 dynes/sec/cm<sup>-5</sup>.<sup>26</sup> For those with milder pulmonary hypertension, the decision to operate is based on individual circumstances. Some with mild elevation in pulmonary pressures at rest may develop a significant rise in pressure with exertion. While not yet substantiated, it is suspected these elevated pressures over a prolonged period of time contribute to the development of small-vessel arteriopathy in the patent vascular bed. Some patients may elect to undergo surgery at this early stage of disease because of dissatisfaction with their exercise limitation or concerns about clinical deterioration in the future. Those who choose not to pursue surgical intervention at this stage of their disease require close monitoring for progression of pulmonary hypertension. Thromboendarterectomy is also considered in patients with normal or nearly normal hemodynamics with significant involvement of one pulmonary artery, those with lifestyles that involve vigorous activity (eg athletes), and those who live at higher altitude. Dyspnea in these patients is a function of elevated dead space and minute ventilation requirements and suboptimal cardiac output with higher level exercise.

Operability is determined by the location and extent of proximal thromboemboli. The experience of the surgical team will determine what is considered surgically accessible. Thrombi must involve the main, lobar, or proximal segmental arteries; disease originating more distally is not accessible with current endarterectomy techniques. Crucial to determining surgical candidacy and predicting operative outcome is determining whether the amount of surgically accessible thrombus is compatible with the degree of hemodynamic impairment. This is particularly true in patients with severe preoperative pulmonary hypertension and right ventricular dysfunction. Failure to significantly reduce the pulmonary vascular resistance with endarterectomy, usually a result of secondary small-vessel arteriopathy, is associated with a greater perioperative mortality rate and a worse long-term outcome.<sup>27</sup>

The assessment of comorbid conditions is the next step in preoperative surgical evaluation. Severe left ventricular dysfunction is the only absolute contraindication to pulmonary thromboendarterectomy. Advanced age, severe right ventricular dysfunction, and other significant comorbid illnesses increase the perioperative morbidity and mortality, but these do not preclude surgical consideration. Pediatric patients and octogenarians, as well as those with complex coexistent disease have successfully undergone the surgical procedure.<sup>28</sup> Patients at risk for coronary atherosclerotic disease should undergo coronary angiography preoperatively and coronary artery bypass grafting or valve replacement can be performed at the time of endarterectomy.

*(continued on page 10)*

(continued from page 7)

### Referring for Pulmonary Endarterectomy

Since surgery has the potential to substantially improve symptoms and pulmonary hemodynamics and the long-term outcome is poor in medically treated patients, pulmonary thromboendarterectomy should be considered in any patient once the diagnosis of CTEPH is made. Prior to surgery, most patients are in New York Heart Association functional class III or IV but postoperatively are in class I or II and able to resume normal activities.<sup>29</sup> Approximately 2000 endarterectomy procedures have been performed worldwide, with roughly 1500 of them done at one center. In a review of surgical series published since 1996, perioperative mortality rates ranged from 5% to 24%, with significant variation in hemodynamic improvement reported.<sup>1</sup> Given the high risk of pulmonary endarterectomy, patients should be referred to centers that are able to provide a multidisciplinary team with experience in the details of the evaluation and treatment of chronic thromboembolic disease. Since perioperative morbidity and mortality are significantly influenced by the degree of right ventricular dysfunction and the presence of secondary small-vessel vasculopathy, surgical intervention is best pursued sooner in the disease process rather than waiting until the patient suffers from significant clinical and hemodynamic impairment.

Patients who are not candidates for thromboendarterectomy, and those who suffer from significant residual pulmonary hypertension following surgery, should be considered for lung transplantation. Long-term treatment with epoprostenol may also be of benefit in selected patients.<sup>30</sup> The long-term efficacy of prostacyclin analogs, endothelin-receptor antagonists, and sildenafil has yet to be determined.

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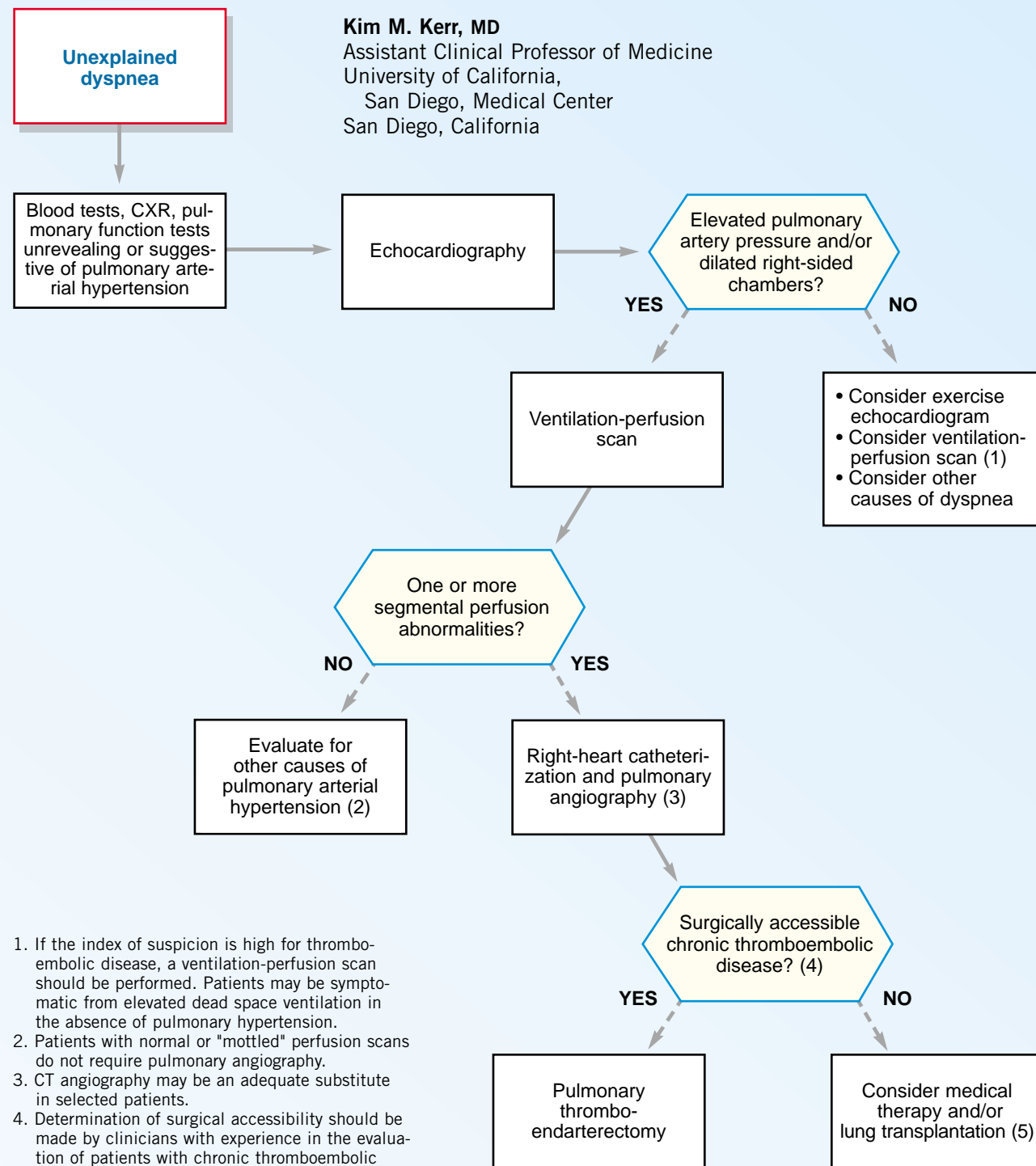
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Pull-Out Algorithm 

## Clinical Algorithm

# Evaluation of Chronic Thromboembolic Pulmonary Hypertension

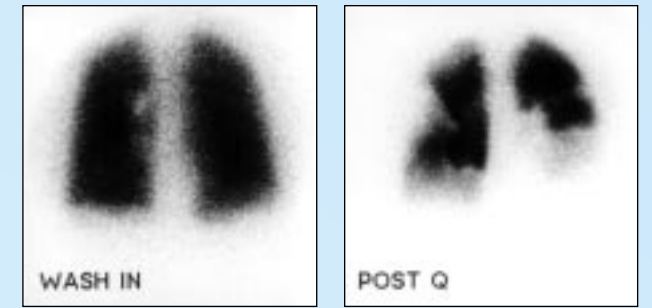
**Kim M. Kerr, MD**  
 Assistant Clinical Professor of Medicine  
 University of California,  
 San Diego, Medical Center  
 San Diego, California



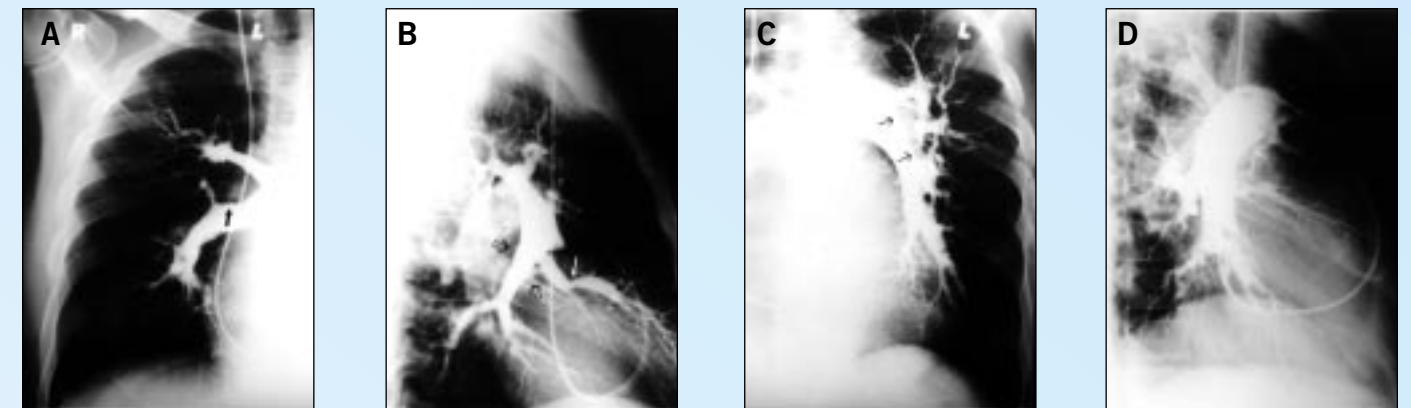
1. If the index of suspicion is high for thromboembolic disease, a ventilation-perfusion scan should be performed. Patients may be symptomatic from elevated dead space ventilation in the absence of pulmonary hypertension.
2. Patients with normal or "mottled" perfusion scans do not require pulmonary angiography.
3. CT angiography may be an adequate substitute in selected patients.
4. Determination of surgical accessibility should be made by clinicians with experience in the evaluation of patients with chronic thromboembolic disease.
5. Anticoagulation is indicated in all patients. Epoprostenol has been beneficial in some patients. The role of bosentan, treprostinil, and investigational agents has yet to be determined.

## Evaluation of Patient With CTEPH

**Fifty-six-year-old man** with a history of recurrent DVT/pulmonary embolism starting 18 years prior to admission. The preoperative ventilation-perfusion scan demonstrated multiple unmatched perfusion defects. Right heart catheterization revealed pulmonary artery pressure of 82/35 (mean 54) mmHg with a cardiac output 4.5 L/min. Pulmonary angiography was consistent with surgically accessible chronic thromboembolic disease. Pulmonary thromboendarterectomy resulted in significant symptomatic and hemodynamic improvement; postoperative pulmonary artery pressure was 48/18 (mean 20) mmHg with a cardiac output of 6.8 L/minute.



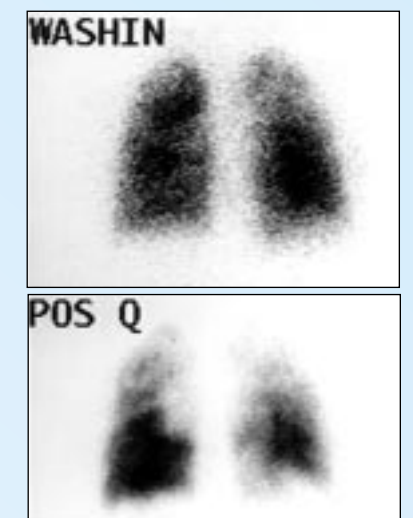
Preoperative ventilation-perfusion scan: the ventilation scan (left) is normal. The perfusion scan (right) demonstrates absence of perfusion to the right lower lobe and segmental defects in the right middle lobe, lingula, and left lower lobe.



Preoperative pulmonary angiogram: Note the intimal irregularities of the interlobar (solid black arrow) and descending pulmonary arteries on the right anterior-posterior view (A). Occlusion of several segments of the right lower lobe at their origin (open black arrows) as well as a web in the right middle lobe (white arrow) are seen on the lateral view of the right lung (B). A large filling defect (black arrows) is present in the left descending pulmonary artery (C). Note how the anatomy is better defined on the right (B) and left (D) lateral views compared with the anterior posterior views (A, C).



Surgical specimen: A large amount of chronic thromboembolic material was removed from both the right and left lungs at the time of pulmonary thromboendarterectomy. The ruler is 15 cm in length.



Ventilation-perfusion scan obtained one week following surgery demonstrates significant improvement in perfusion to both lower lobes. Lung perfusion will continue to redistribute and become more homogenous during the year following surgery.

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# An Insider's Guide to Pulmonary Thromboendarterectomy: Proven Techniques to Achieve Optimal Results



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Pulmonary thromboendarterectomy is the definitive treatment for chronic pulmonary hypertension as the result of thromboembolic disease. Although pulmonary embolism (PE) is one of the more common cardiovascular diseases affecting Americans, pulmonary thromboendarterectomy remains an uncommon procedure, mainly because this form of chronic pulmonary hypertension remains an underdiagnosed condition. These patients may present with a variety of debilitating cardiopulmonary symptoms. However, once diagnosed there is no curative role for medical management, and surgery remains the only option.

The exact incidence of PE remains unknown, but there are some valid estimates. Acute PE is the third most common cause of death (after heart disease and cancer). Approximately 75% of autopsy-proven PE is not detected clinically.<sup>1</sup> Dalen and Alpert<sup>2</sup> calculated that PE results in 630,000 symptomatic episodes in the United States yearly, making it about half as common as acute myocardial infarction, and three times as common as cerebral vascular accidents. This is, however, a low estimate, since in 70% to 80% of the patients where the primary cause of death was PE, premortem diagnosis was unsuspected.<sup>3,4</sup> The disease is particularly common in hospitalized elderly patients. Of hospitalized patients who develop PE, 12% to 21% die in the hospital, and another 24% to 39% die within 12 months.<sup>5-7</sup> Thus approximately 36% to 60% of patients who survive the initial episode live beyond 12 months, and may present later in life with a wide variety of symptoms. More than 90% of clinically detected pulmonary emboli are associated with lower extremity deep vein thrombosis (DVT), but in two-thirds of patients with DVT and PE, the DVT is asymptomatic.<sup>8,9</sup> Greenfield<sup>10</sup> estimates that approximately 2.5 million Americans develop DVT each year.

The prognosis for patients with pulmonary hypertension is poor, and it is worse for those who do not have intracardiac shunts. Thus, patients with primary pulmonary hypertension and those with pulmonary hypertension due to pulmonary emboli fall into a higher risk category than those with Eisenmenger's syndrome and encounter a higher mortality rate. In fact, once the mean pulmonary pressure in patients with thromboembolic disease reaches 50 mmHg or more, the 3-year mortality approaches 90%.<sup>11</sup> Surgical options are dependent on

both the primary disease process and the reversibility of the pulmonary hypertension. With the exception of thromboembolic pulmonary hypertension, lung transplantation is the only effective therapy for patients with pulmonary hypertension, when the disease reaches end stage. Pulmonary transplantation is also still used in some centers as the treatment of choice for those with thromboembolic disease. However, a true assessment of the effectiveness of any therapy should take into account the total mortality once the patient has been accepted and put on the waiting list. Thus, the mortality for transplantation (and especially double-lung or heart-lung transplantation) as a therapeutic strategy is much higher than is generally appreciated because of the significant loss of patients awaiting donors. Considering the long-term use of antirejection medications with their associated side effects, the higher operative morbidity and mortality, the long waiting time, and inferior prognosis even after transplantation, transplantation is clearly an inferior option to pulmonary thromboendarterectomy. We consider it to be inappropriate therapy for this disease.

## **Pulmonary Thromboendarterectomy: Indications**

Although there were previous attempts, Allison et al<sup>12</sup> did the first successful pulmonary "thromboendarterectomy" through a sternotomy using surface hypothermia, but only fresh clots were removed. The operation was done 12 days after a thigh injury that led to PE, and there was no endarterectomy. Since then, there have been many occasional surgical reports of the surgical treatment of chronic pulmonary thromboembolism,<sup>13, 14</sup> but most of the surgical experience in pulmonary endarterectomy has been reported from the UCSD Medical Center. Braunwald commenced the UCSD experience with this operation in 1970, which now totals more than 1500 cases. The operation described below<sup>15</sup>, using deep hypothermia and circulatory arrest, is now the standard procedure.

When the diagnosis of thromboembolic pulmonary hypertension has been firmly established, the decision for operation is made based on the severity of symptoms and the general condition of the patient. Early in the pulmonary endarterectomy experience, Moser and colleagues<sup>16</sup> pointed out that there were three major reasons for considering thromboendarterectomy: hemodynamic, alveolo-respiratory, and prophylactic. The hemo-

dynamic goal is to prevent or ameliorate right ventricular compromise caused by pulmonary hypertension. The respiratory objective is to improve respiratory function by the removal of a large ventilated but unperfused physiologic dead space. The prophylactic goal is to prevent progressive right ventricular dysfunction or retrograde extension of the obstruction, which might result in further cardiorespiratory deterioration or death.<sup>16</sup> Our subsequent experience has added another prophylactic goal: the prevention of secondary arteriopathic changes in the remaining patent vessels. Most patients who undergo operation are within New York Heart Association (NYHA) class III or class IV. The ages of the patients in our series have ranged from 8 to 85 years. A typical patient will have a severely elevated pulmonary vascular resistance (PVR) level at rest, the absence of significant comorbid disease unrelated to right heart failure, and the appearance of chronic thrombi on angiography that appear to be in balance with the measured PVR level. Exceptions to this general rule, of course, occur.

Although most patients have a PVR level in the range of 800 dynes/sec/cm<sup>-5</sup> and pulmonary artery pressures less than systemic, the hypertrophy of the right ventricle that occurs over time makes pulmonary hypertension to suprasystemic levels possible. Therefore, many patients (perhaps 20% in our practice) have a level of PVR in excess of 1000 dynes/sec/cm<sup>-5</sup> and suprasystemic pulmonary artery pressures. There is no upper limit of PVR level, pulmonary artery pressure, or degree of right ventricular dysfunction that excludes patients from operation. We have become increasingly aware of the changes that can occur in the remaining patent (unaffected by clot) pulmonary vascular bed subjected to the higher pressures and flow that result from obstruction in other areas. Therefore, with the increasing experience and safety of the operation, we are tending to offer surgery to symptomatic patients whenever the angiogram demonstrates thromboembolic disease. A rare patient might have a PVR level that is normal at rest, although elevated with minimal exercise. This is usually a young patient with total unilateral pulmonary artery occlusion and unacceptable exertional dyspnea because of an elevation in dead space ventilation. Operation in this circumstance is performed to reperfuse lung tissue, to reestablish a more normal ventilation, perfusion relationship (thereby reducing minute ventilatory requirements during rest and exercise), and to preserve the integrity of the contralateral circulation. If not previously implanted, an inferior vena caval filter is routinely placed several days in advance of the operation.

### **Guiding Principles of the Operation**

There are several guiding principles for the operation. It must be bilateral because, for pulmonary hypertension to be a major factor, both pulmonary arteries must be substantially involved. The only reasonable approach to both pulmonary arteries is through a median sternotomy incision. Historically, there were many reports of unilateral operation, and occasionally this is still performed, in inexperienced centers, through a thoracotomy. However, the unilateral approach ignores the disease on the contralateral side, subjects the patient to hemodynamic jeopardy during the clamping of the pulmonary artery, and does not allow good visibility because of the continued presence of bronchial blood flow. In addition, collateral channels develop in

chronic thrombotic hypertension not only through the bronchial arteries but also from diaphragmatic, intercostal, and pleural vessels. The dissection of the lung in the pleural space via a thoracotomy incision can therefore be extremely bloody. The median sternotomy incision, apart from providing bilateral access, avoids entry into the pleural cavities and allows the ready institution of cardiopulmonary bypass.

Cardiopulmonary bypass is essential to ensure cardiovascular stability when the operation is performed and to cool the patient to allow circulatory arrest. Very good visibility is required, in a bloodless field, to define an adequate endarterectomy plane and to then follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually present in these cases, periods of circulatory arrest are necessary to ensure perfect visibility. Again, there have been sporadic reports of the performance of this operation without circulatory arrest. However, it should be emphasized that although endarterectomy is possible without circulatory arrest, a complete endarterectomy is not. We always initiate the procedure without circulatory arrest, and a variable amount of dissection is possible before the circulation is stopped, but never complete dissection. The circulatory arrest periods are limited to 20 minutes, with restoration of flow between each arrest. With experience, the endarterectomy usually can be performed with a single period of circulatory arrest on each side.

A true endarterectomy in the plane of the media must be accomplished. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. Indeed, in most patients, no free thrombus is present; and on initial direct examination, the pulmonary vascular bed may appear normal. The early literature on this procedure indicates that thrombectomy was often performed without endarterectomy, and in these cases the pulmonary artery pressures did not improve, often resulting in death.

### **Surgical Technique**

After a median sternotomy incision is made, the pericardium is incised longitudinally and attached to the wound edges. Typically the right heart is enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation. There is usually severe right ventricular hypertrophy, and with critical degrees of obstruction, the patient's condition may become unstable with the manipulation of the heart. Anticoagulation is achieved with the use of beef-lung heparin sodium (400 units/kg, intravenously) administered to prolong the activated clotting time beyond 400 seconds. Full cardiopulmonary bypass is instituted with high ascending aortic cannulation and two caval cannulae. These cannulae must be inserted into the superior and inferior vena cavae sufficiently to enable subsequent opening of the right atrium. The heart is emptied on bypass, and a temporary pulmonary artery vent is placed in the midline of the main pulmonary artery 1 cm distal to the pulmonary valve. This will mark the beginning of the left pulmonary arteriotomy.

When cardiopulmonary bypass is initiated, surface cooling with both the head jacket and the cooling blanket is begun. The blood is cooled with the pump-oxygenator. During cooling a 10°C gradient between arterial blood and bladder or rectal temperature is maintained.<sup>17</sup> Cooling generally takes 45 minutes to

an hour. When ventricular fibrillation occurs, an additional vent is placed in the left atrium through the right superior pulmonary vein. This prevents atrial and ventricular distension from the large amount of bronchial arterial blood flow that is common with these patients. It is most convenient for the primary surgeon to stand initially on the patient's left side. During the cooling period, some preliminary dissection can be performed, with full mobilization of the right pulmonary artery from the ascending aorta. All dissection of the pulmonary arteries takes place intrapericardially, and neither pleural cavity should be entered. An incision is then made in the right pulmonary artery from beneath the ascending aorta out under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the take-off of the middle lobe artery.

Any loose thrombus, if present, is now removed. It is most important to recognize, however, that first, an embolectomy without subsequent endarterectomy is quite ineffective and, second, that in most patients with chronic thromboembolic hypertension, direct examination of the pulmonary vascular bed at operation generally shows no obvious embolic material. Therefore, to the inexperienced or cursory glance, the pulmonary vascular bed may well appear normal even in patients with severe chronic embolic pulmonary hypertension. If the bronchial circulation is not excessive, the endarterectomy plane can be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained because the development of a correct plane is essential.

When the patient's temperature reaches 20°C, the aorta is crossclamped and a single dose of cold cardioplegic solution (1L) is administered. Additional myocardial protection is obtained by the use of a cooling jacket. The entire procedure is now performed with a single aortic crossclamp period with no further administration of cardioplegic solution. A modified cerebellar retractor is placed between the aorta and superior vena cava. When blood obscures direct vision of the pulmonary vascular bed, thiopental is administered (500 mg to 1 g) until the electroencephalogram becomes isoelectric. Circulatory arrest is then initiated, and the patient undergoes exsanguination. It is rare that one 20-minute period for each side is exceeded. Although retrograde cerebral perfusion has been advocated for total circulatory arrest in other procedures, it is not helpful in this operation because it does not allow a completely bloodless field, and with the short arrest times that can be achieved with experience, it is not necessary.

### **Removing Thromboembolic Material**

Any residual loose thrombotic debris encountered is removed. Then, a microtome knife is used to develop the endarterectomy plane posteriorly. Dissection in the correct plane is critical because if the plane is too deep the pulmonary artery may perforate, with fatal results, and if the dissection plane is not deep enough, inadequate amounts of the chronically thromboembolic material will be removed. Once the plane is correctly developed, a full-thickness layer is left in the region of the incision to ease subsequent repair. The endarterectomy is then performed with an eversion technique. Because the vessel is everted and subsegmental branches are being worked on, a perfora-

tion here will become completely inaccessible and invisible later. This is why absolute visualization in a completely bloodless field provided by circulatory arrest is essential. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction. Residual material should never be cut free; the entire specimen should "tail off" and come free spontaneously. Once the right-side endarterectomy is completed, circulation is restarted, and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. The hemostatic nature of this closure is aided by the nature of the initial dissection, with the full thickness of the pulmonary artery being preserved immediately adjacent to the incision.

After the completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, and an arteriotomy is made from the site of the pulmonary vent hole laterally to the pericardial reflection, avoiding entry into the left pleural space. Additional lateral dissection does not enhance intraluminal visibility, may endanger the left phrenic nerve, and makes subsequent repair of the left pulmonary artery more difficult. The left-sided dissection is virtually analogous in all respects to that accomplished on the right. The duration of circulatory arrest intervals during the performance of the left-side dissection is subject to the same restriction as the right. After the completion of the endarterectomy, cardiopulmonary bypass is reinstated and warming is commenced. Methylprednisolone (500 mg, intravenously) and mannitol (12.5 g, intravenously) are administered, and during warming a 10°C temperature gradient is maintained between the perfusate and body temperature. If the systemic vascular resistance level is high, nitroprusside is administered to promote vasodilatation and warming. The rewarming period generally takes approximately 90 minutes but varies according to the body mass of the patient.

When the left pulmonary arteriotomy has been repaired, the pulmonary artery vent is replaced at the top of the incision. The right atrium is then opened and examined, unless prior to cardiopulmonary bypass, a negative "bubble" test was confirmed on transthoracic echocardiography. Otherwise, any intraatrial communication (present in about 20% of patients) is closed at this point. Although tricuspid valve regurgitation is invariable in these patients and is often severe, tricuspid valve repair is not performed. Right ventricular remodeling occurs within a few days, with the return of tricuspid competence. If other cardiac procedures are required, such as coronary artery or mitral or aortic valve surgery, these are conveniently performed during the systemic rewarming period. Myocardial cooling is discontinued once all cardiac procedures have been concluded. The left atrial vent is removed, and the vent site is repaired. All air is removed from the heart, and the aortic crossclamp is removed.

When the patient has rewarmed, cardiopulmonary bypass is discontinued. Dopamine hydrochloride is routinely administered at renal doses, and other inotropic agents and vasodilators are titrated as necessary to sustain acceptable hemodynamics. The cardiac output is generally high, with a low systemic vascular resistance. Temporary atrial and ventricular epicardial pacing wires are placed. Despite the duration of extracorporeal circulation, hemostasis is readily achieved, and the



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**Fig. 1**—Surgical specimen removed from right and left pulmonary arteries. Evidence of fresh thrombus indicates type I disease. Note that removal of only the fresh material leaves a large amount of disease behind. The ruler measures 15 cm.

administration of platelets or coagulation factors is generally unnecessary. Wound closure is routine. A vigorous diuresis is usual for the next few hours, also a result of the previous systemic hypothermia.

#### Disease Classification: Four Types

There are four broad types of pulmonary occlusive disease related to thrombus that have been described by our group<sup>15</sup>:

- 1) Type I disease (approximately 30% of cases of thromboembolic pulmonary hypertension; **Fig. 1**) refers to the situation in which major vessel clot is present and readily visible on the opening of the pulmonary arteries. As mentioned earlier, all central thrombotic material has to be completely removed before the endarterectomy.
- 2) In type II disease (approximately 60% of cases; **Fig. 2**), no major vessel thrombus can be appreciated. In these cases only thickened intima can be seen, occasionally with webs, and the endarterectomy plane is raised in the main, lobar, or segmental vessels.
- 3) Type III disease (approximately 10% of cases; **Fig. 3**) presents the most challenging surgical situation. The disease is very distal and confined to the segmental and subsegmental branches. No occlusion of vessels can be seen initially. The endarterectomy plane must be carefully and painstakingly raised in each segmental and subsegmental branch. Type III disease is most often associated with presumed repetitive thrombi from indwelling catheters (such as pacemaker wires) or ventriculoatrial shunts, and sometimes represents “burnt out” disease, where most of the embolic material has been reabsorbed.
- 4) Type IV disease does not represent classic chronic thromboembolic pulmonary hypertension and is inoperable. In this entity there is intrinsic small-vessel disease, although secondary thrombus may occur as a result of stasis. Small-vessel disease may be unrelated to thromboembolic events (“primary” pulmonary hypertension) or occur in relation to thromboembolic hypertension as a result of a high flow or



**Fig. 2**—Surgical specimen removed from right and left pulmonary arteries indicating type II disease. Note the extent of dissection down to the tail end of each branch. The ruler measures 6 inches.



**Fig. 3**—Surgical specimen removed from right and left pulmonary arteries. In this patient the dissection plane was raised at each segmental level. The ruler measures 15 cm.

high-pressure state in previously unaffected vessels similar to the generation of Eisenmenger’s syndrome. We believe that there may also be sympathetic “cross-talk” from an affected contralateral side or stenotic areas in the same lung.

#### Postoperative Care

Meticulous postoperative management is essential to the success of this operation. All patients are mechanically ventilated for at least 24 hours, and all patients are subjected to a maintained diuresis with the goal of reaching the patient’s preoperative weight within 24 hours. Although much of the postoperative care is common to more ordinary open-heart surgery patients, there are some important differences. The electrocardiogram, systemic and pulmonary arterial and central venous pressures, temperature, urine output, arterial oxygen saturation,

chest tube drainage, and fluid balance are monitored. A pulse oximeter is used to continuously monitor peripheral oxygen saturation. Management of cardiac arrhythmias and output and treatment of wound bleeding are identical to other open-heart operations. In addition, higher minute ventilation is often required early after the operation to compensate for the temporary metabolic acidosis that develops after the long period of circulatory arrest, hypothermia, and cardiopulmonary bypass. Tidal volumes higher than those normally recommended after cardiac surgery are therefore generally used to obtain optimal gas exchange. The maximum inspiratory pressure is maintained below 30 cm of water if possible. Although we used to believe that prolonged sedation and ventilation were beneficial and led to less pulmonary edema, subsequent experience has shown this not to be so. Extubation should be performed on the first postoperative day, if possible.

**Diuresis.** Patients have considerable positive fluid balance after operation. After hypothermic circulatory arrest, patients initiate an early spontaneous aggressive diuresis for unknown reasons, but this may, in part, be related to the increased cardiac output related to a now lower PVR level. This should be augmented with diuretics, however, with the aim of returning the patient to the preoperative fluid balance within 24 hours of operation. Because of the increased cardiac output, some degree of systemic hypotension is readily tolerated. Fluid administration is minimized, and the patient's hematocrit level should be maintained above 30% to increase oxygen carrying capacity and mitigate the pulmonary reperfusion phenomenon.

**Arrhythmias.** The development of atrial arrhythmias, at approximately 10%, is no more common than that encountered in patients who undergo other types of nonvalvular heart surgery. The small, inferior atrial incision, away from the conduction system of the atrium or its blood supply, may be helpful in the reduction of the incidence of these arrhythmias.

**Transfusion.** Despite the requirement for the maintenance of an adequate hematocrit level, with careful blood conservation techniques used during operation, transfusion is required in a minority of patients.

**Anticoagulation.** A Greenfield filter is usually inserted before operation, to minimize recurrent pulmonary embolism after pulmonary endarterectomy. However, if this is not possible, it can also be inserted at the time of operation. If the device is to be placed at operation, radiopaque markers should be placed over the spine that correspond to the location of the renal veins to allow correct positioning. Postoperative venous thrombosis prophylaxis with intermittent pneumatic compression devices is used, and the use of subcutaneous heparin is begun on the evening of surgery. Anticoagulation with warfarin is begun as soon as the pacing wires and mediastinal drainage tubes are removed, with a target international normalized ratio of 2.5 to 3.

## Complications

Patients are subject to all complications associated with open heart and major lung surgery (arrhythmias, atelectasis, wound infection, pneumonia, mediastinal bleeding, etc.) but also may develop complications specific to this operation. These include

A specific complication that occurs in most patients to some degree is localized pulmonary edema, or the "reperfusion response." Reperfusion injury is defined as a radiologic opacity seen in the lungs within 72 hours of pulmonary endarterectomy.

persistent pulmonary hypertension, reperfusion pulmonary response, and neurologic disorders related to deep hypothermia.

**Persistent Pulmonary Hypertension.** The decrease in PVR level usually results in an immediate and sustained restoration of pulmonary artery pressures to normal levels, with a marked increase in cardiac output. In a few patients, an immediately normal pulmonary vascular tone is not achieved, but an additional substantial reduction may occur over the next few days because of the subsequent relaxation of small vessels and the resolution of intraoperative factors such as pulmonary edema. In such patients, it is usual to see a large pulmonary artery

pulse pressure, the low diastolic pressure indicating good runoff, and yet persistent pulmonary arterial inflexibility still resulting in a high systolic pressure.

There are a few patients in whom the pulmonary artery pressures do not resolve substantially. We do operate on some patients with severe pulmonary hypertension but equivocal embolic disease. Despite the considerable risk of attempted endarterectomy in these patients, since transplantation is the only other avenue of therapy, there may be a point when it is unlikely that a patient will survive until a donor is found. In our most recent 500 patients, more than one third of perioperative deaths were directly attributable to the problem of inadequate relief of pulmonary artery hypertension. This was a diagnostic rather than an operative technical problem. Attempts at pharmacologic manipulation of high residual PVR levels with sodium nitroprusside, epoprostenol sodium, or inhaled nitric oxide are generally not effective. Because the residual hypertensive defect is fixed, it is not appropriate to use mechanical circulatory support or extracorporeal membrane oxygenation in these patients if they deteriorate subsequently.

**The Reperfusion Response.** A specific complication that occurs in most patients to some degree is localized pulmonary edema, or the reperfusion response. Reperfusion injury is defined as a radiologic opacity seen in the lungs within 72 hours of pulmonary endarterectomy. This unfortunately loose definition may therefore encompass many causes, such as fluid overload and infection. True reperfusion injury that directly adversely impacts the clinical course of the patient now occurs in approximately 10% of patients. In its most dramatic form, it occurs soon after operation (within a few hours) and is associated with profound desaturation. Edema-like fluid, sometimes with a bloody tinge, is suctioned from the endotracheal tube. Frank blood from the endotracheal tube, however, signifies a mechanical violation of the blood-airway barrier that has occurred at operation and stems from a technical error. This complication should be managed, if possible, by identification of the affected area by bronchoscopy and balloon occlusion of the affected lobe until coagulation can be normalized.

One common cause of the reperfusion pulmonary edema is persistent high pulmonary artery pressures after operation when a thorough endarterectomy has been performed in certain areas, but there remains a large part of the pulmonary vascular bed affected by type IV change. However, the reperfusion phenomenon is often encountered in patients after a seemingly technically perfect operation with complete resolution of high

pulmonary artery pressures. In these cases the response may be one of reactive hyperemia, after the revascularization of segments of the pulmonary arterial bed that have long experienced no flow. Other contributing factors may include perioperative pulmonary ischemia and conditions associated with high permeability lung injury in the area of the now denuded endothelium. Fortunately, the incidence of this complication is very much less common now in our series, probably as a result of the more complete and expeditious removal of the endarterectomy specimen that has come with the large experience over the last few years.

**Management of the Reperfusion Response.** Early measures should be taken to minimize the development of pulmonary edema with diuresis, maintenance of the hematocrit levels, and the early use of peak end-expiratory pressure. Once the capillary leak has been established, treatment is supportive because reperfusion pulmonary edema will eventually resolve if satisfactory hemodynamics and oxygenation can be maintained. Careful management of ventilation and fluid balance is required. The hematocrit is kept high (32%-36%), and the patient undergoes aggressive diuresis, even if this requires ultrafiltration. The patient's ventilatory status may be dramatically position sensitive. The  $\text{FIO}_2$  level is kept as low as is compatible with an oxygen saturation of 90%. A careful titration of positive end-expiratory pressure is carried out, with a progressive transition from volume-limited to pressure-limited inverse ratio ventilation and the acceptance of moderate hypercapnia. Infrequently, inhaled nitric oxide at 20 to 40 parts per million can improve the gas exchange. On occasion we have used extracorporeal perfusion support (extracorporeal membrane oxygenator or extracorporeal carbon dioxide removal) until ventilation can be resumed satisfactorily, usually after 7 to 10 days.

**Delirium.** Early in the pulmonary endarterectomy experience (before 1990), there was a substantial incidence of postoperative delirium. A study of 28 patients who underwent pulmonary endarterectomy showed that 77% experienced the development of this complication.<sup>18</sup> Delirium appeared to be related to an accumulated duration of circulatory arrest time of more than 55 minutes; the incidence fell to 11% with significantly shorter periods of arrest time.<sup>19</sup> With the more expeditious operation that has come with our increased experience, postoperative confusion is now encountered no more commonly than with ordinary open-heart surgery.

## Results

More than 1575 pulmonary thromboembolism operations have been performed at UCSD Medical Center since 1970. Nearly 1400 have been completed since 1990, when the surgical procedure was modified as described earlier. The mean patient age in the last 1300 patients was 52 years, with a range of 8 to 85 years. There was a very slight male predominance. In nearly one third of these cases, at least one additional cardiac procedure was performed at the time of operation. Most commonly, the adjunct procedure was closure of a persistent foramen ovale or atrial septal defect (26%) or coronary artery bypass grafting (8%).

It is increasingly apparent that pulmonary hypertension caused by chronic pulmonary embolism is a condition that is underrecognized and carries a poor prognosis. Medical therapy is ineffective in prolonging life and only transiently improves the symptoms. The only therapeutic alternative to pulmonary thromboendarterectomy is lung transplantation.

**Hemodynamic Results.** A reduction in pulmonary pressures and resistance to normal levels and a corresponding improvement in pulmonary blood flow and cardiac output are generally immediate and sustained. In general, these changes can be assumed to be permanent. Before the operation, more than 95% of the patients are in NYHA functional class III or IV; at 1 year after the operation, 95% of patients remain in NYHA functional class I or II.<sup>20, 21</sup> In addition, echocardiographic studies have demonstrated that, with the elimination of chronic pressure overload, right ventricular geometry rapidly reverts toward normal. Right atrial and right ventricular enlargement regresses. Tricuspid valve function returns to normal within a few days as a result of restoration of tricuspid annular geometry after the remodeling of the right ventricle, and tricuspid repair is not therefore part of the operation.

**Operative Morbidity.** Severe reperfusion injury was the single most frequent complication in the UCSD series, occurring in 10% of patients. Some of these patients did not survive, and other patients required prolonged mechanical ventilatory support. A few patients were salvaged only by the use of extracorporeal support and blood carbon dioxide removal. Neurologic complications from circulatory arrest appear to have been eliminated, probably as a result of the shorter circulatory arrest periods now experienced, and perioperative confusion and stroke are now no more frequent than with conventional open-heart surgery. Early postoperative hemorrhage required reexploration in 2.5% of patients, and only 50% of patients required intra- or postoperative blood transfusion. Despite the prolonged operation, wound infections are relatively infrequent. Only 1.8% experienced the development of sternal wound complications, including sterile dehiscence or mediastinitis.

**Deaths.** In our experience, the overall mortality rate (30 days or in-hospital if the hospital course is prolonged) was 9% for the entire patient group, which encompasses a time span of 30 years. The mortality rate was 9.4% in 1989 and has been 5% to 7% for the more than 1300 patients who have undergone the operation since 1990. In the most recent series of 500 patients (June 1998 to July 2002), the mortality rate was 4.4%. We generally quote an operative risk of approximately 5%, but some patients predictably fall within a much higher risk. With our increasing experience and many referrals, we continue to accept the occasional patient who, in retrospect, was unsuitable for the procedure. We also accept patients in whom we know that the entire degree of pulmonary hypertension cannot be explained by the occlusive disease detected by angiography but feel that they will be benefited by operation, albeit at higher risk. Residual causes of death are operation on patients in whom thromboembolic disease was not the cause of the pulmonary hypertension (50%) and the rare case of reperfusion pulmonary edema that progresses to a respiratory distress syndrome of long standing, which is not reversible (25%).

## Summary

It is increasingly apparent that pulmonary hypertension caused by chronic pulmonary embolism is a condition that is underrecognized and carries a poor prognosis. Medical therapy is inef-

fective in prolonging life and only transiently improves the symptoms. The only therapeutic alternative to pulmonary thromboendarterectomy is lung transplantation. The advantages of thromboendarterectomy include a lower operative mortality and excellent long-term results without the risks associated with chronic immunosuppression and chronic allograft rejection. The mortality for thromboendarterectomy at our institution is now in the range of 4.5%, with sustained benefit. These results are clearly superior to those for transplantation both in the short and long term.

Although pulmonary thromboendarterectomy is technically demanding for the surgeon, and requires careful dissection of the pulmonary artery planes and the use of circulatory arrest; excellent short- and long-term results can be achieved. Successive improvements in operative technique developed over the last four decades allow pulmonary endarterectomy to be offered to patients with an acceptable mortality rate and excellent anticipation of clinical improvement. With this growing experience, it has also become clear that unilateral operation is obsolete and that circulatory arrest is essential. The primary problem remains that this is an under-recognized condition. Increased awareness of both the prevalence of this condition and the possibility of a surgical cure should avail more patients of the opportunity for relief from this debilitating and ultimately fatal disease.

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## Surgically Curable Pulmonary Hypertension: A View From the Experts



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William Auger, MD



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Christopher McGregor, MD

*Five physicians addressed important issues in the diagnosis and management of patients with pulmonary thromboembolic disease. The roundtable discussion was moderated by Victor F. Tapson, MD, Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina, and included William Auger, MD, Professor of Clinical Medicine, University of California, San Diego, Medical Center, San Diego, California; Peter Fedullo, MD, Clinical Professor of Medicine, University of California, San Diego, Medical Center; Eckhard Mayer, MD, Professor of Thoracic Surgery, Department of Cardio-Thoracic Surgery, University Hospital, Mainz, Germany; and Christopher McGregor, MD, Professor of Surgery, Consultant in Cardio-Thoracic Surgery, and Director of the Mayo Clinic William J von Liebig Transplant Center, Rochester, Minnesota.*

**Dr Tapson:** Let's start with a general statement. If we start with the US, how many centers can do thromboendarterectomy for chronic pulmonary embolism?

**Dr Auger:** It's hard to get a handle on that. It seems some groups are trying to perform thromboendarterectomies on an irregular basis. If you look at the centers that are set up to do these surgeries on a regular basis, one thinks of the Mayo Clinic, and I would probably include the Cleveland Clinic, and the UCSD Medical Center—about three to four centers in the United States.

**Dr Tapson:** Dr Mayer, how about in Europe? How many centers do this and would you be able to name them?

**Dr Mayer:** I think there are approximately five to seven centers all over Europe. There is an active center in Paris, one in northern Italy, one in Austria, one in England, and three centers in Germany. In Europe, I think we have the largest experience in Mainz, with approximately 300 cases over the last 12 years, although these numbers are not comparable to the experience in San Diego.

**Dr Fedullo:** Now that you've raised that question, Vic, I think it raises another question and that is, how many centers should be doing this procedure and how do the other members of the panel feel about the minimum number of cases that are required on an annual basis to optimize outcome? There are good data regarding other high-risk procedures that volume

is related to outcome. The issue is, can the procedure be done with optimal safety? There's a huge learning curve with this procedure. Perhaps Dr Mayer could comment on what he thinks about the volume of procedures and its relationship to outcome.

**Dr Mayer:** We had a very significant learning curve during the first 5 years of our program when we started in 1989. The results were much worse compared with the last 5 to 8 years. I do believe that a center should have a multidisciplinary team and there should be at least 20 operations per year. That means 30 to 40 patients are referred for surgery and at least 20 patients per year should be operated on to gain enough experience. Even with 20 patients a year, it will take a little time until the results can reach a level comparable to the San Diego results.

**Dr Tapson:** What do you think about that, Chris?

**Dr McGregor:** I think I agree with what people have said. Clearly, there is a learning curve. For the first patients, the mortality for us was around 19% and in the subsequent 42 patients it fell to less than 4.6%. I think there are two aspects to this operation in terms of outcomes. I agree totally with Dr Mayer that this operation should be part of a pulmonary hypertension multidisciplinary group. In terms of surgical outcomes, there are multiple reports where people have not gotten over that early learning curve and have a mortality rate of anywhere from 20% to 40% and there's no point in people doing that unless they're going to see it through so that patients down the line benefit from that learning curve. Regarding the number per year, one could argue, but I would say that the minimum of one a month or 12 per year—that kind of number, although the more the better. There is a second issue: once there is significant experience with this surgery the mortality you achieve is dictated by patient selection and how aggressive you will be in accepting patients with distal disease for surgery. There will always be a mortality for this surgery if you are going to be very aggressive in the pursuit of distal disease. I would be interested in what Professor Mayer thinks about that.

**Dr Mayer:** I totally agree with that. During the first phase of our learning curve we had a mortality rate of approximately 20% to 24%. There was a lot of criticism and all the cardiologists and respiratory physicians told us this procedure is too risky for our patients. Therefore, we changed the patient selection

for a phase of 2 or 3 years and we accepted only patients with proximal disease who were considered surgically accessible. We were able to reduce our mortality rate to less than 5%. But with increasing experience we started to accept patients with very distal disease during the last couple of years and those patients do have a higher risk than 5%. So it's really true that you can influence the mortality rate by changing the patient selection. However, the patients with very distal disease do not have good surgical or medical alternatives so I think someone with adequate surgical experience should also do the high-risk operations in patients with very distal disease.

**Dr McGregor:** And I would add that if you're not occasionally—and I'm talking about mortality of less than 5% here—if you're not occasionally having a suboptimal outcome, maybe you're not going to help a large number of people with relatively distal disease who could be helped. So I think there's a balance that could be reached here.

**Dr Fedullo:** I agree completely. There are always those cases that really surprise us in terms of suspecting that the patient had distal disease during their evaluation phase and who have just a wonderful hemodynamic outcome.

**Dr Auger:** It certainly has been one of our challenges as diagnosticians in selecting appropriate patients to have surgery. What constitutes distal disease? Those of us who see these patients on a regular basis are occasionally surprised by what we have assessed as distal disease turns out to be resectable while patients who we feel have accessible disease can sometimes be very difficult cases. So there are still some diagnostic problems for us in this patient population.

**Dr Fedullo:** Absolutely. The correlation between the angiographic and hemodynamic findings is a critical part of the referral process. A procedure in someone with distal disease with a PVR of 1500 carries a much higher risk than one in a patient with a PVR of 500, who would probably tolerate the procedure, even if very minimal amounts of clot were removed at the time of surgery.

**Dr Tapson:** How do you define distal disease? Is it a relative term or fairly absolute?

**Dr McGregor:** Therein lies the problem, Vic, as Bill just outlined. As a surgeon, I go in sometimes to what is billed as distal disease and it's surprisingly amenable to surgery. At other times I go in expecting to be able to have a good surgical outcome and it turns out to be very difficult, with more distal disease than anticipated. I think there's a certain sort of art to defining distal disease and I don't think diagnostically we're as good as we'd like to be.

**Dr Mayer:** I completely agree. Even if you think you have a lot of experience it sometimes happens that the operation is a real surprise in a good way and also in a bad way. Sometimes the

**The correlation between the angiographic and hemodynamic findings is a critical part of the referral process. A procedure in someone with distal disease with a PVR of 1500 carries a much higher risk than one in a patient with a PVR of 500, who would probably tolerate the procedure, even if very minimal amounts of clot were removed at the time of surgery.**

operation and the postoperative course are very difficult in patients who were considered very good candidates preoperatively while other patients considered to have very distal peripheral disease are easily operable. Even with a lot of experience and good diagnostic tools we are never sure before we are at the end of the operation.

**Dr Fedullo:** It raises two points. First, it's a shame that angiography is not more widely available because we find it useful in determining operability and we've been having a problem obtaining angioscopes. The other issue is that in certain patients this is clearly both a medical and surgical disease. We thought of it somewhat simplistically in the early years as nothing more than mechanical obstruction of the major pulmonary arteries—but it's clear that there can be a small-vessel component to the disease process and the future approach to the disease under that circumstance may involve both surgical and medical therapy.

**Dr Auger:** I want to underscore what Professor Mayer and Peter have said, that there still remain a number of challenges for us, even in the evaluative or preoperative phase. Peter and I have changed our thinking about how these patients develop pulmonary arterial hypertension over the years. What we once thought was just progressive thrombotic obstruction of the pulmonary vascular bed may indeed not be the major determinant of the severity of pulmonary hypertension over the years. In the unobstructed vascular bed, small-vessel pathology seems to develop over time, eventually leading to a significant rise in pulmonary vascular resistance and cor pulmonale/RV dysfunction. Consequently, our preoperative preparation may sometimes include pulmonary vasodilator therapy for a period of time to improve the hemodynamic profile prior to committing patients to the operating suite.

**Dr McGregor:** When one has a patient with longstanding thromboembolic primary pulmonary hypertension with a PVR in excess of 1200 or 1300 and one has achieved what you would think is a textbook surgical resection and does not have significant reduction in pulmonary artery pressure—it doesn't happen that often but does occasionally—what do you think is happening under those circumstances? Are those secondary changes in the normal vessels?

**Dr Fedullo:** I agree with Bill's point of view entirely. I think these people develop a substantial distal pulmonary arteriopathy and despite a good surgical specimen, some of these patients have considerable postoperative pulmonary hypertension.

**Dr McGregor:** Peter, what happens to the small vessels distal to the obstructive material we remove? Have those vessels been protected or are they subject to the same secondary arteriopathic changes as the unobstructed vessels?

**Dr Fedullo:** You would think they would be protected but in the series that Ken Moser did a number of years ago, looking at this, he found the arteriopathic changes in both the involved

and the uninvolved parts of the lung. Is that correct Bill?

**Dr Auger:** What you're stating is absolutely correct, but there were problems with that study. It was very difficult to correlate accurately the areas from which the lung was biopsied to the areas that were angiographically obstructed by chronic thromboembolic disease versus the areas that were unobstructed. In that study small-vessel arteriopathy occurred in both the obstructed and the unobstructed lung regions. What we would have liked to have seen is a difference, more small-vessel changes in the unobstructed vascular bed versus the obstructed vascular bed. However, I think if you look at preoperative and postoperative lung perfusion scans in patients with major-vessel chronic thromboembolic disease, the increase in perfusion in lung regions that have been endarterectomized relative to those that were not endarterectomized would suggest a lesser degree of small-vessel disease in the obstructed vascular bed.

**Dr Tapson:** What's the latest in the theory of in situ thrombosis? Do we think that a lot of these cases start as embolic disease and then in situ thrombosis develops? What's the theory now?

**Dr Fedullo:** It's almost impossible to say but the data that we have based on sequential lung scan findings is that progressive pulmonary hypertension occurs in the absence of new perfusion scan defects. This suggests that in situ thrombosis isn't a major problem in the progression of the pulmonary hypertension. Actually the progression is felt to be due to progressive small-vessel changes.

**Dr Tapson:** Along those lines, do you all have a fairly consistent approach to evaluating somebody for surgery? In terms of evaluating severity, is it fair to say that everyone undergoing this procedure should at least have an angiogram? What about the CT scan? Are we finding cases where the CT is clearly misleading or misrepresenting what's going on? I guess that would be one of the issues, right?

**Dr McGregor:** We do ultra-fast CT as well as pulmonary angiography in all the patients, and I would not see them as comparative investigations but rather as additive in terms of the information they give. By that I mean the nature of the disease will determine which test is more useful. In other words, if you have a thin transparent veil occluding a segmental pulmonary artery. If that's the nature of the pathology, an ultra-fast CT will miss it totally because of the distance between the cuts. On the other hand, a pulmonary angiogram, if there is circumferential disease, may look better than it should be, considering the extent of the disease and the ultra-fast CT cutting across those vessels at right angles. You will see intimal thickening. So you get different kinds of information from the two tests but I do not believe the ultra-fast CT in any way replaces the necessity of doing a pulmonary angiogram.

**Dr Fedullo:** I agree completely and also agree completely with the point that the two studies provide complementary information and can be very useful when used together.

**Dr Auger:** I also agree that the CT angiogram can be very use-

ful. There have been cases of pulmonary hypertensive patients with clearly defined disease on CT angio and major perfusion defects on lung perfusion scans, in whom we feel it was not necessary to do pulmonary angiography. However, there's an increasing tendency to have it replace conventional pulmonary arteriography. I do not believe it has that power as yet. There are still some unanswered questions as to how useful it is in establishing surgically accessible disease. And I would underscore Chris's statement that this disease can appear very different in the pulmonary vascular bed from one patient to the next. This is a surgically heterogeneous disease.

**Dr Mayer:** Regarding the diagnostics, I completely agree that the combination of CT and angiography is the standard at the moment. However, within the last 2 years we were operating on approximately 30% of our patients without conventional angiography and we do have very good magnetic resonance (MR) angiographies that are comparable to conventional angiographies in most cases. I believe that 2 or 5 years from now MR techniques will replace angiography and CT scanning in many CTEPH patients. MR function tests of the right ventricle can give us even more information than echocardiography. I do believe that there is a future for MR technology in the diagnosis of these patients.

**Dr McGregor:** I agree totally with that. One of the advantages of MR as well as ultra-fast CT is that one can get an estimate of right ventricular ejection fraction that is much more quantitative and reproducible than that achieved with echocardiography because of geometric considerations. It's very useful to know what the right ventricular ejection fraction is going in. We've just completed a series of 30 or 40 consecutive patients where we did right ventricular ejections before and after PTE. All patients were measured while off of vasodilators. It is interesting that as a group the right ventricular ejection fraction (RVEF) improves highly significantly from before to after, verifying that we've achieved something positive. But also what was very interesting to me was that it didn't matter where you started in terms of EF. In other words, even if your EF was 15 or 10 you improved as much as if it was 30. So that's very encouraging that we did see improvement in the low EF and the higher EF groups preoperatively.

**Dr Tapson:** Would it be fair to say then that there isn't really an RVEF lower limit with which you couldn't operate? I guess you have to look at the whole patient and the level of other underlying disease, weight, etc. If it were just the RV alone, would an RVEF that was absolutely dismal in a class IV patient ever keep you from doing the procedure?

**Dr McGregor:** My current take on the thing is that I don't care what the pre-op RVEF is, depending on what the likelihood is of getting a good surgical result. In other words, if the EF is 12% but I'm confident that I can get a good outcome surgically, then the EF does not affect my selection. But if I see an RVEF of 10% or 12%, and the disease is "questionable," I'm a little anxious, and maybe I shouldn't be but I still am.

**Dr Fedullo:** I couldn't agree more. That is where experience is

crucial to the evaluation of these patients. The anatomic findings must be correlated with the hemodynamic findings. There's no blueprint but you have a sense that the patient with poor RV function and distal disease will not do well. On the other hand, someone with poor RV function and very accessible disease is much more likely to do well. But it takes a certain experiential base to be able to make that determination.

**Dr Mayer:** I think there's no lower limit of right ventricular function. If the endarterectomy is successful and the findings correlate with the severity of pulmonary hypertension, the preoperative RV function doesn't really make a difference.

**Dr Tapson:** Dr Mayer, I remember your publishing in the last couple of years a series of cases that included a fairly high number of class IV patients. Those patients would fit into the same category as those with poor RV function. It sounds like you had a good outcome with those individuals.

**Dr Mayer:** Yes, we have a good outcome in NYHA class IV patients, if angiographic findings and severity of pulmonary hypertension are proportional and a complete removal of the obstructing material is possible. I am in doubt about the surgical indication if there is only minor unilateral distal disease in the angiography and very severe pulmonary hypertension combined with poor right ventricular function. Those are the cases with a very high risk. But if the disease is surgically accessible, I really believe that every right ventricle can recover.

**Dr Tapson:** What about cases where you have concomitant left ventricular dysfunction or concomitant COPD or other lung disease? How does that play in your decision to do surgery? I guess you have to individualize these cases?

**Dr Auger:** That's absolutely correct. In days past these kinds of cases concerned us a great deal. Let's just take the case of patients with severe COPD or emphysematous lung disease. This is where CT scanning can be very helpful. If someone exhibits significant occlusive vascular disease to the lower lobes and yet much of the emphysematous lung is in the upper lobes, these patients can be helped with a thromboendarterectomy by improving perfusion to relatively normal lung tissue. In the patients with severe left ventricular dysfunction, an endarterectomy can abruptly reduce right ventricular afterload and consequently increase left ventricular preload, which can precipitate heart failure in the postoperative period. These people are at particularly high risk and do not generally do well following the operation.

**Dr Tapson:** Is there any way to gauge what someone's ultimate level of function will be preoperatively or do you get really good results in some sick people and maybe not so good results in some people who do not have such significant obstruction? Can you predict the outcome in any way?

**Dr Mayer:** Not for every patient. For most of the patients we can predict the outcome but there are still some patients in whom

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we are not able to predict the operative and long-term outcome. It can be very difficult to predict the outcome in the individual case.

**Dr McGregor:** I agree with that. The improvement in right ventricular function is dramatic and early. By a week after surgery their EFs increase 20 points. What is also interesting is that there can be continuing improvement at 6 months and a year when you repeat the test and it's even better. So there's an early acute improvement and there may be ongoing more gradual improvement. When you asked about COPD and patient selection, I think one of the biggest problems we deal with are the patients who

have this disease who are missed and have the possibility of getting surgery. When you think that the prognosis of this disease is so bad when they get to class III or IV and the outcomes of surgery are so good, the frustrating thing is that there are patients sitting around major medical centers who are undiagnosed. I would say a third of the patients I see are labeled as having asthma. We have to try and pick out the disease and secondly, if a group is going to do this surgery regularly and establish a program, they have to have reproducible hemodynamic outcomes not only to confirm operative mortality but the success of the surgery

**Dr Fedullo:** Even though it appears that patients are being referred earlier, there is still a large group of patients who are carried for years with the diagnosis of asthma, for example. The patients will say, "I've told the doctor, I've never wheezed, I know what asthma is." And yet they'll be treated with steroids for years until somebody finally stumbles upon the diagnosis. Again, getting the word out to the general community that this disease exists and can be confused with other disease processes is very important.

**Dr McGregor:** I presented at an echo meeting recently and I really made the point that anybody who has an echocardiogram, has elevated pressures, and who does not have morphologic cardiac problems to account for it should have a V/Q scan.

**Dr Tapson:** Chris is making a crucial point. You first have to diagnose the pulmonary hypertension. As we tell our patients, we have to figure out the cause and the severity and that makes all the difference in the world in terms of what we do. But you've got to rule out curable causes of disease. It's so rare that we find a curable cause of pulmonary arterial hypertension. And to find something surgically curable is crucial. I would absolutely echo that, and no pun intended there, that you've got to evaluate patients with abnormal pulmonary artery pressures and exclude the possibility of acute, subacute, or chronic pulmonary embolism.

**Dr Auger:** Many of us are at centers focusing on pulmonary vascular disorders that are busier than ever. We can all remember the days when this disease was such an oddity; it was rare when we were operating more than once or twice a month. Now many of us are performing a dozen of these surgeries each month, evaluating anywhere from 10 to 20 patients a month as poten-

tial surgical candidates. However, it is still our impression that there are many more folks out there where the diagnosis has not been adequately explored.

**Dr Tapson:** When cases are done, how often is reoperation done or how often is transplant ultimately necessary in these cases? It's amazing what all of you have accomplished with this disease over the years, but there are some cases that will deteriorate no matter what you do.

**Dr Mayer:** I completely agree. Fortunately we have only 1% of PTE reoperations (2 out of 300 patients). In addition I did a lung transplantation 3 or 4 years after primary successful PTE. I don't think that lung transplantation is a good option for patients if they really have CTEPH. However, there are very few patients with primary pulmonary hypertension and in situ thrombosis. We had two cases in the last 2 years in whom we did not have the right diagnosis preoperatively and both patients died. The diagnosis is very difficult if they do have the combination of primary pulmonary hypertension and in situ thrombosis. Lung transplantation is an option for these rare cases.

**Dr Fedullo:** That has been our experience too. I think some minimum level of pulmonary arterial pressure has to be reached postoperatively to assure a good long-term hemodynamic outcome. Unless that minimum level of pressure is reached, 4 to 5 years later the patient may present with recurrent symptoms. When we reevaluate those patients they have developed recurrent pulmonary hypertension that is not due to recurrent thromboembolic disease. They've progressed as a result of small-vessel disease changes. My feeling is that patients who have an incomplete hemodynamic outcome should probably be reevaluated 3 to 6 months after the surgical procedure. If the patient still has pulmonary hypertension then we should strongly consider medical therapy.

**Dr Auger:** Two comments, one of which has to do with the rate of reoperation or redo pulmonary thromboendarterectomies. The numbers that have been discussed are consistent with our experience as well—in the range of less than 1% of operated patients. It also appears that if a patient experienced a successful pulmonary thromboendarterectomy the first time and develops recurrent, chronic thromboembolic disease, a second successful thromboendarterectomy is possible. The second comment relates to our experience with a cohort of patients who do not achieve normalization of pulmonary artery pressures postoperatively. Because of the availability of pulmonary vasodilator therapies, we're more aggressively treating those patients who have a suboptimal hemodynamic response from their pulmonary thromboendarterectomy. We have noted that if the pulmonary vascular resistance achieved postoperatively is in the range of 500 to 600, 4 or 5 years down the road their pulmonary hypertension is typically worse. In many cases, based on angiographic and other diagnostic studies, it appears we're not dealing with recurrent thromboembolic disease but rather progression of small-vessel disease.

**Dr McGregor:** This reemphasizes the point made earlier of why

you need a pulmonary hypertension clinic or center because patients move from the medical site to the surgical site and back to the medical site. This reemphasizes that you need to have multidisciplinary care. Peter and Bill, educate me, what do you think is the hemodynamic outcome in terms of mean PA pressure and PVR that would indicate a good long-term outcome versus naught?

**Dr Fedullo:** I feel absolutely comfortable when the PVR is below 300 and I'm terribly concerned when it is above 500 and uncertain when it is between the two.

**Dr McGregor:** And mean PA?

**Dr Fedullo:** Above 40 I'm concerned, below 30 I'm comfortable and between the two I'm uncertain. These patients have to be evaluated sequentially. If they have a mean PA pressure of 35 after operation, they should undergo repeat right-heart catheterization in 6 months or a year and if there is any evidence that the pulmonary hypertension is progressing then at that point I would initiate medical therapy.

**Dr McGregor:** And what about PA pressure in the same situation? If the PA pressure is 35 at time of discharge?

**Dr Fedullo:** I would do exactly the same thing.

**Dr McGregor:** So anybody who has a mean PA pressure greater than 30 or PVR greater than 300 you would recath them down the line?

**Dr Fedullo:** Yes.

**Dr Auger:** It's important to know the numbers we're talking about. The number of patients who are in the category that Peter is discussing is in the range of 5% to 10% of those undergoing surgery.

**Dr Mayer:** I agree that it's the same numbers, for sure less than 10% of the patients. I think that a less invasive approach for quality control and long-term assessment might be MR angiography and evaluation of right ventricular function. It is a very precise method and you don't have to do a recatheterization.

**Dr Tapson:** One final question. Any perioperative or postoperative care pearls in terms of management, pressor therapy, anything else someone feels strongly about? I visited the San Diego operation before and Bill and Peter certainly have a superlative operation, and it's very clear that there is a substantial amount of input from surgery and the pulmonary staff.

**Dr Auger:** It's hard in a moment or two to come up with a successful formula for postoperative management of these patients. The two most formidable problems we have, comprising 50% of our in-hospital mortality, are persistent pulmonary hypertension with RV dysfunction, and reperfusion lung injury. Meticulous supportive care, particularly as it pertains to dealing with reperfusion lung injury, is critical to getting these patients discharged.

# 2003 Program Announcement: June 1, 2003, Deadline



## The Pulmonary Hypertension Association (PHA) *and the*

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## National Heart, Lung, and Blood Institute (NHLBI)

### *Jointly Sponsored*

### **Mentored Clinical Scientist Development Award (K08)**

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- To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
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- Candidates must be U.S. citizens or noncitizen nationals, or must have been lawfully admitted for permanent residence and possess an Alien Registration Card or some other verification of legal admission as a permanent resident.
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- Candidates must have initiated postgraduate clinical training.
- Candidates must identify a mentor with extensive research experience.
- Candidates must be willing to spend a minimum of 75% of full-time professional effort conducting research and research career development.

#### **Mechanism:**

Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 mechanism.

#### **Funding:\***

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Visit - <http://www.phassociation.org/support/mentored.htm>

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