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.[1]

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.[2] 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.[3] 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.[4] 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.[5]

It is still unclear why acute emboli fail to resolve in a subset 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.[6,7] Inherited deficiencies of protein C, protein S, and antithrombin III, as a group, can be identified in up to 5% of this population.[8] Efforts to identify abnormalities in the fibrinolytic pathway or within the pulmonary endothelium that would account for incomplete thrombus dissolution have been unrevealing.[9-11]

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.[12] 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.[13] In another study, a mean pulmonary artery pressure as low as 30 mmHg was identified as a threshold for poor prognosis.[14]

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 P2, 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.[15]

A delay of two to three years from the onset of symptoms to confirmation of the correct diagnosis is common.[16] 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.[17] 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_2. 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.[18]

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.[19] 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[20] (**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[5] (**Figure 2**). Even a single mis-

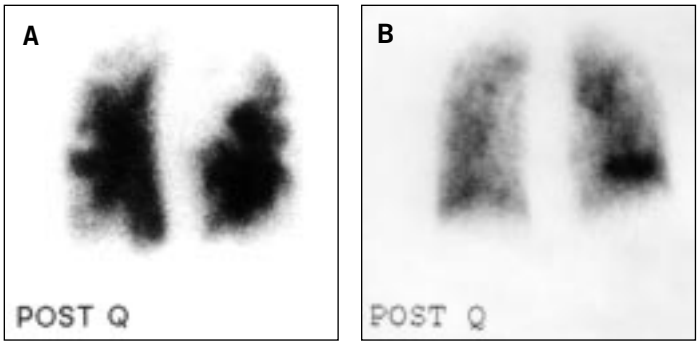
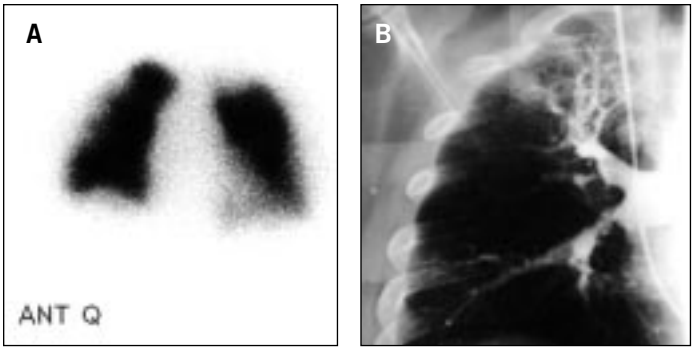


Fig. 1—A. A perfusion scan in a patient with CTEPH demonstrating multiple, bilateral, segmental perfusion defects. B. A patient with PPH with a "mottled" perfusion scan without any segmental perfusion defects.



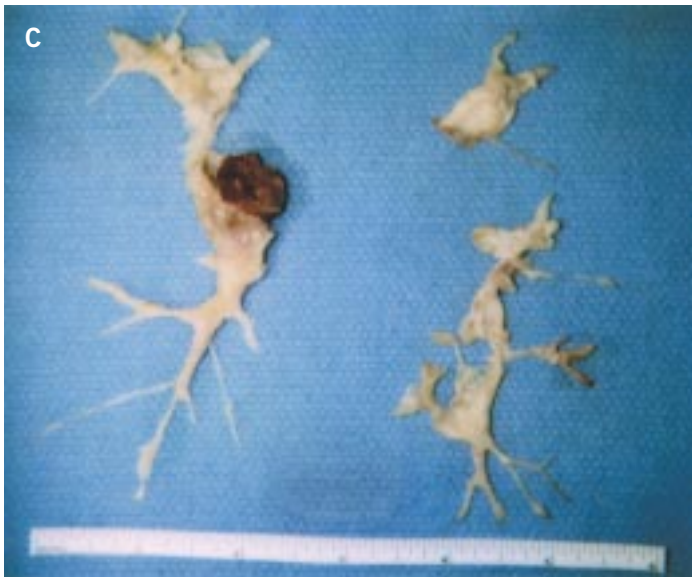


Fig. 2—Due to recanlization of chronic thrombus, the defects seen on the perfusion scan (2A) grossly understate the degree of obstruction seen on the pulmonary angiogram (2B) and the findings at the time of surgery (2C).

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.[21] 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. Interpre-tation of these angiograms can be difficult in large measure because the appearance of chonic 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[22] (**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 obstuction 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

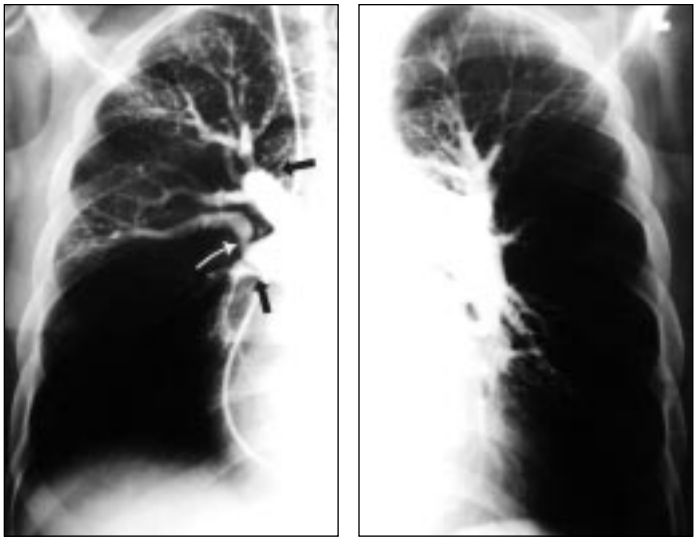


Fig. 3—Angiographic findings of chronic thromboembolic disease: pouches in the right upper lobe and interlobar artery (black arrows), a band with post-stenotic dilatation (white arrow), and rapid tapering of the left descending pulmonary artery.

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 angioscopy 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 thromboemblic 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.[23] 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.[24,25] 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^{-5}, typically in the range of 800-1000 dynes/sec/cm^{-5}.[26] 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.

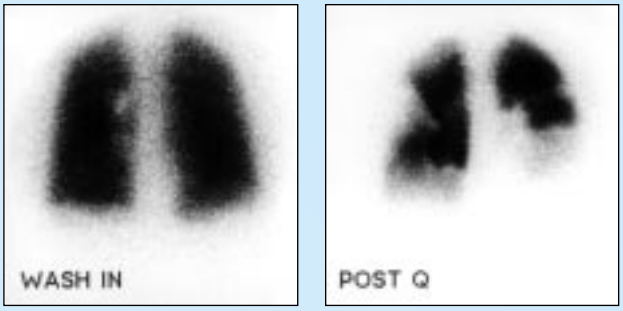
Operability is determined by the location and extent of proximal thromboemboli. The experience of the surgical team will determine what is considered surgically accessible. Thrombi must involve the main, lobar, or proximal segmental arteries; disease originating more distally is not accessible with current 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.[27]

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 morbity 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.[28] 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.

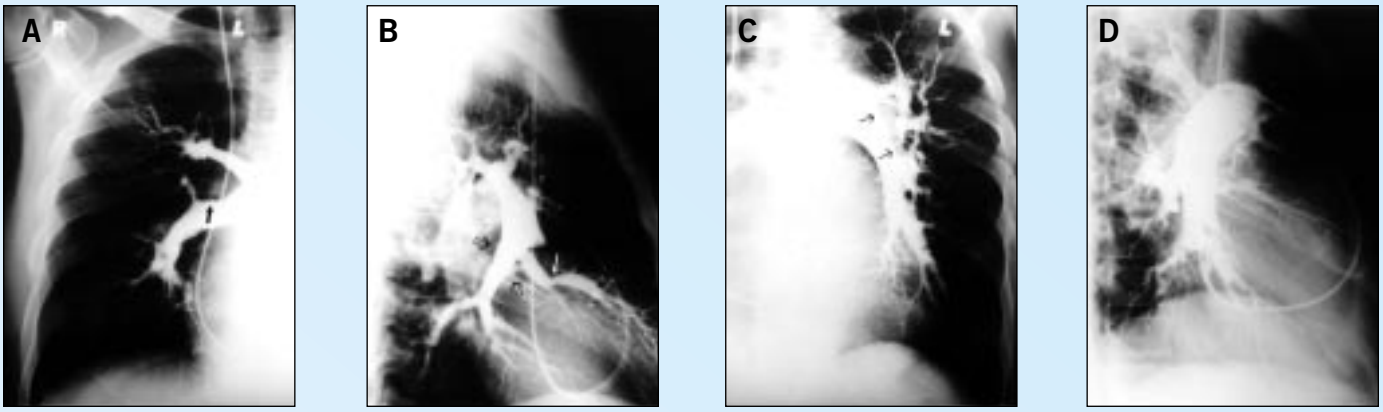
(continued on page 10)

Evaluation of Patient With CTEPH

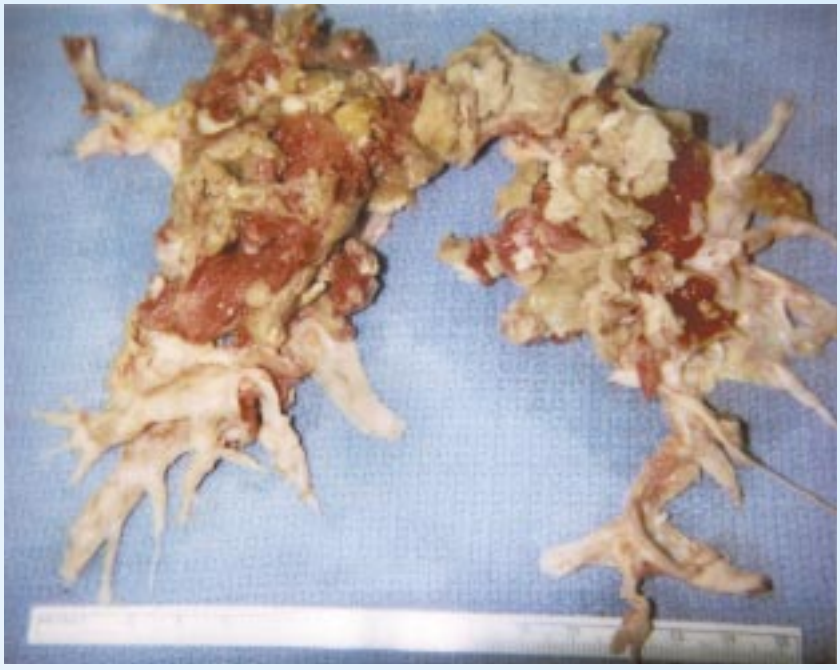
Fifty-six-year-old man *with a history of recurrent DVT/pulmonary embolism starting 18 years prior to admission. The preoperative ventilation-perfusion scan demonstrated multiple unmatched perfusion defects. Right heart catheterization revealed pulmonary artery pressure of 82/35 (mean 54) mmHg with a 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.*



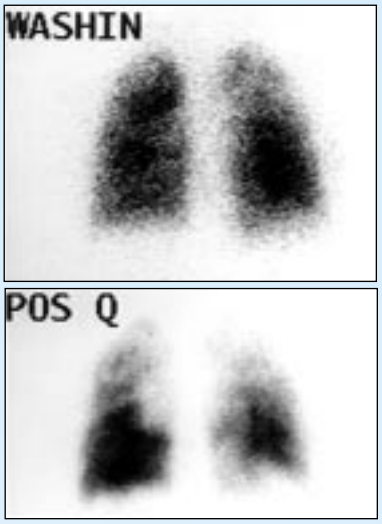
Preoperative ventilation-perfusion scan: the ventilation scan (left) is normal. The perfusion scan (right) demonstrates absence of perfusion to the right lower lobe and segmental defects in the right middle lobe, lingula, and left lower lobe.



Preoperative pulmonary angiogram: Note the intimal irregularities of the interlobar (solid black arrow) and descending pulmonary arteries on the 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.

(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.[29] 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.[1] 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.[30] The long-term efficacy of prostacyclin analogs, endothelin-receptor antagonists, and sildenafil has yet to be determined.

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Pull-Out Algorithm

Clinical Algorithm

Evaluation of Chronic Thromboembolic Pulmonary Hypertension

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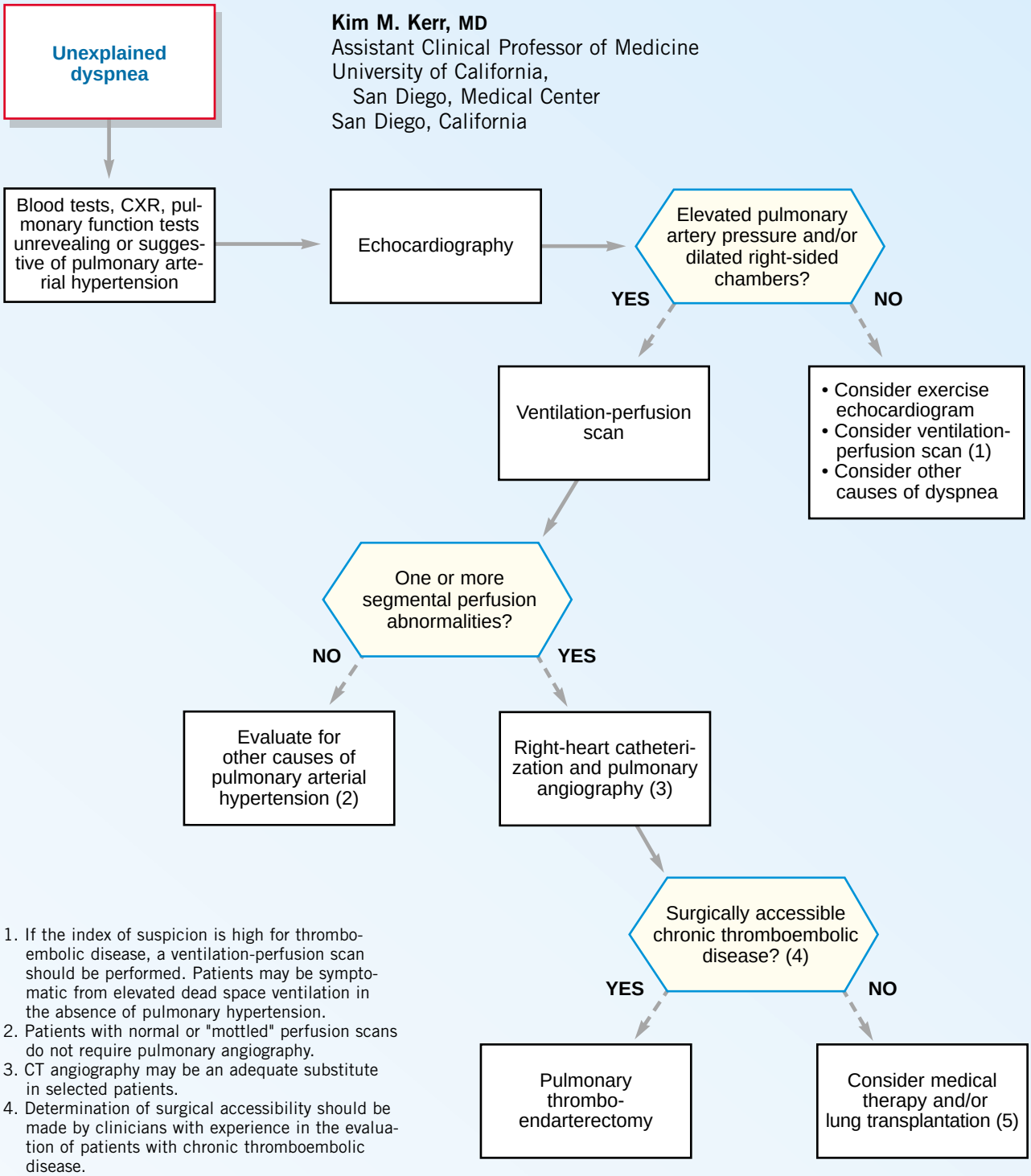

1. If the index of suspicion is high for thromboembolic disease, a ventilation-perfusion scan should be performed. Patients may be symptomatic from elevated dead space ventilation in the absence of pulmonary hypertension.
2. Patients with normal or "mottled" perfusion scans do not require pulmonary angiography.
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.