

REVIEW ARTICLE

CURRENT CONCEPTS

Chronic Thromboembolic Pulmonary Hypertension

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CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION IS DEFINED AS mean pulmonary-artery pressure greater than 25 mm Hg that persists 6 months after pulmonary embolism is diagnosed. The 2008 World Symposium on Pulmonary Hypertension¹ emphasized the importance of chronic thromboembolic pulmonary hypertension, which occurs in 2 to 4% of patients after acute pulmonary embolism.^{2,3} The frequency of this condition among patients with pulmonary hypertension is unknown. Patients with chronic thromboembolic pulmonary hypertension generally present in their 40s, although this condition has been reported in patients in other age groups.² The diagnosis is often overlooked because many patients do not have a history of clinically overt pulmonary embolism.⁴

The natural history of chronic thromboembolic pulmonary hypertension has been difficult to determine because a subgroup of patients have had occult pulmonary embolism, with subtle clues to the diagnosis that became apparent only in retrospect. Patients with chronic thromboembolic pulmonary hypertension typically have a honeymoon period after acute pulmonary embolism, during which symptoms are absent despite the onset of pulmonary hypertension. Long-term follow-up of patients with chronic thromboembolic pulmonary hypertension, including those with mild symptoms and those who are asymptomatic, is needed to elucidate the natural history of this disease.

Although symptomatic disease develops in a substantial proportion of patients, the clinical importance of asymptomatic chronic thromboembolic pulmonary hypertension remains controversial. This condition is usually detected when pulmonary hypertension worsens and causes dyspnea, hypoxemia, and right ventricular dysfunction. Death is usually due to progressive pulmonary hypertension culminating in right ventricular failure. The risk of the development of chronic thromboembolic pulmonary hypertension is increased by factors associated with pulmonary embolism, certain chronic medical conditions, thrombophilia, and a genetic predisposition (Table 1).^{2,3,5-9} Thyroid disease is a risk factor for both chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension.^{8,10}

Currently, no pharmacologic regimen helps prevent chronic thromboembolic pulmonary hypertension, except anticoagulation with or without fibrinolysis. When administered in hemodynamically stable patients with right ventricular dysfunction due to acute pulmonary embolism (submassive pulmonary embolism), fibrinolytic therapy has been shown to reduce the frequency of chronic thromboembolic pulmonary hypertension.¹¹ Such therapy, which is most effective if administered within 2 weeks after acute pulmonary embolism is detected, is considered a life-saving intervention in patients with massive pulmonary embolism but remains

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Table 1. Risk Factors for Chronic Thromboembolic Pulmonary Hypertension.**Factors specific to pulmonary embolism**

- Recurrent or unprovoked pulmonary embolism
- Large perfusion defects when pulmonary embolism detected
- Young or old age when pulmonary embolism detected
- Pulmonary-artery systolic pressure >50 mm Hg at initial manifestation of pulmonary embolism
- Persistent pulmonary hypertension on echocardiography performed 6 mo after acute pulmonary embolism detected

Chronic medical conditions

- Infected surgical cardiac shunts or pacemaker or defibrillator leads
- Postsplenectomy
- Chronic inflammatory disorders
- Thyroid-replacement therapy
- Cancer

Thrombotic factors

- Lupus anticoagulant or antiphospholipid antibodies
- Increased levels of factor VIII
- Dysfibrinogenemia

Genetic factors

- ABO blood groups other than O
- HLA polymorphisms
- Abnormal endogenous fibrinolysis

humoral factors, including endothelin-1, play a central role in chronic thromboembolic pulmonary hypertension as potent vasoconstrictors and as triggers of microvascular changes.¹⁷ Reductions in the cross-sectional area of the pulmonary arteries due to thrombosis and vasoconstriction cause further abnormal vascular remodeling. In situ thrombosis may also accompany secondary small-vessel arteriopathy. The combination of persistent macrovascular obstruction, small-vessel arteriopathy, and vasoconstriction results in pulmonary hypertension and right ventricular pressure overload that exceeds the level expected from macrovascular obstruction alone. Persistent increases in pulmonary vascular resistance due to continued vascular remodeling and vasoconstriction in chronic thromboembolic pulmonary hypertension result in pulmonary-artery systolic pressures that are typically greater than those in acute pulmonary embolism.

CLINICAL PRESENTATION

Exercise intolerance, fatigue, and dyspnea are the most commonly reported symptoms. Subsequently, patients may report chest discomfort, syncope, hemoptysis, light-headedness, or peripheral leg edema. Diagnostic delays are common because many patients do not provide a history of pulmonary embolism. In patients without a history of pulmonary embolism, we recommend that clinicians take the history again to identify any clinical events that might be consistent with venous thromboembolism. If no event suggestive of pulmonary embolism is identified, clinicians should consider diagnoses other than chronic thromboembolic pulmonary hypertension.

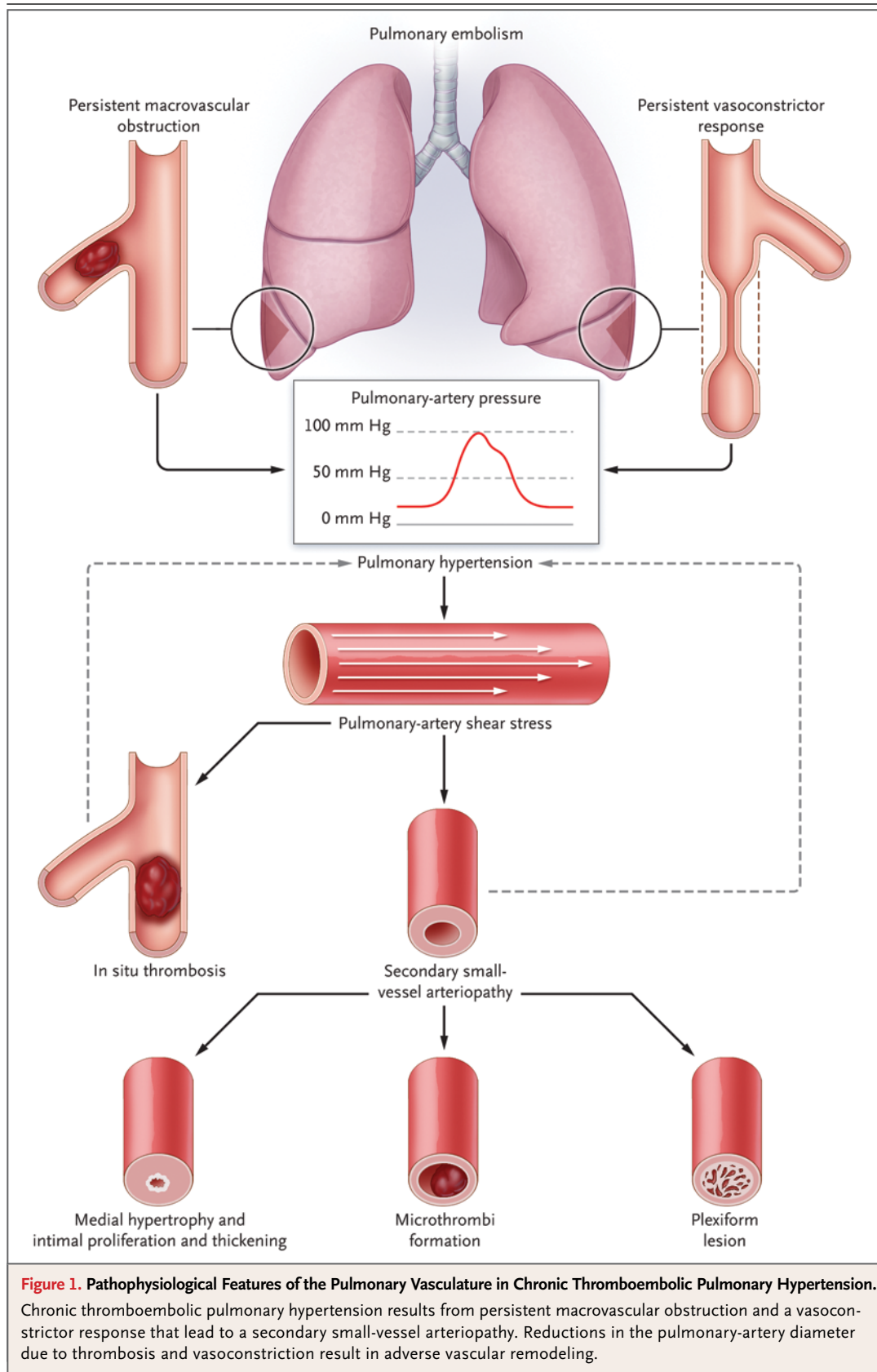
Initial findings of pulmonary hypertension on physical examination, including chronic thromboembolic pulmonary hypertension, may include a reduction in the splitting of the second heart sound (S₂), accentuation of the sound of pulmonic closure (P₂), and a palpable right ventricular heave. Subsequent findings correspond to decreasing right ventricular function: jugular venous distention, fixed splitting of S₂, a right-sided third heart sound (S₃), tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema. Subtle bruits may be heard on auscultation over the peripheral lung fields; they arise from turbulent flow through partially obstructed pulmonary arteries. The 6-minute walk test may be a useful component of the evaluation because it

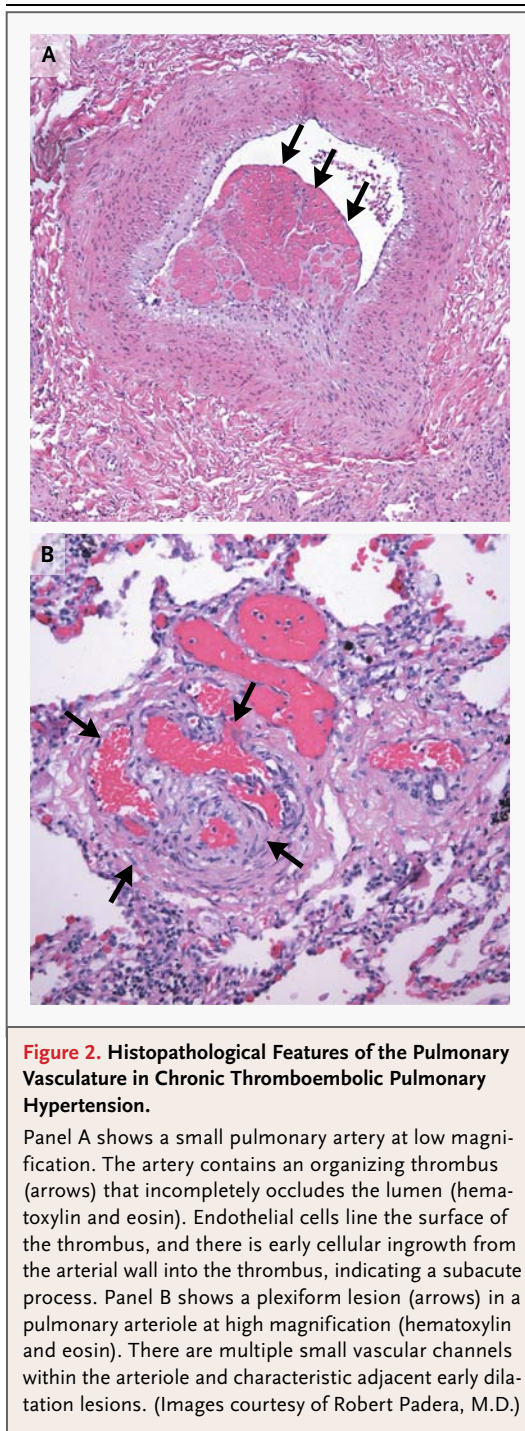
controversial in the treatment of patients with submassive pulmonary embolism.¹²

PATHOPHYSIOLOGY

In 1973, Moser and Braunwald¹³ discovered a paradox when they examined the histopathological features of specimens obtained from patients who had undergone pulmonary thromboendarterectomy. They detected marked small-vessel abnormalities that appeared similar to idiopathic pulmonary arterial hypertension distal to patent pulmonary arterial segments, whereas tissue distal to occluded segments appeared to be normal (Fig. 1). The small-vessel arteriopathy is characterized by medial hypertrophy and intimal proliferation, microvascular thrombosis, and plexiform-lesion formation (Fig. 2).

Chronic thromboembolic pulmonary hypertension results in persistent macrovascular obstruction and vasoconstriction. Chronic staphylococcal infection,¹⁴ abnormal sialylation of fibrinogen γ -chains,¹⁵ and abnormal fragmentation of fibrinogen¹⁶ have been proposed as mechanisms for ineffective fibrinolysis. Neuro-





reflects the clinical and hemodynamic severity of disease.¹⁸ Specific levels for distance walked or desaturation have not been standardized. At specialized centers, the 6-minute walk distance is used to assess the prognosis and gauge the patient's response to therapy.

DIAGNOSIS

After a thorough history taking and physical examination, patients with symptoms and signs of pulmonary hypertension and a clinical history compatible with pulmonary embolism or pulmonary hypertension of unexplained cause should be evaluated for chronic thromboembolic pulmonary hypertension with the use of imaging tests (Fig. 3). A broad workup for causes of pulmonary hypertension, including a rheumatologic panel, polysomnography, and thrombophilia testing, is unnecessary if there is a reasonable suspicion of chronic thromboembolic pulmonary hypertension. Referral to specialized centers for additional invasive testing, such as right heart catheterization and pulmonary angiography, may be advisable to define the anatomical location and extent of obstruction and to quantify the degree of pulmonary hypertension. Although not required for the diagnosis, invasive coronary angiography, pulmonary-function tests, and cardiopulmonary exercise testing may occasionally be useful to evaluate certain patients with established chronic thromboembolic pulmonary hypertension or to rule out alternative or concomitant diagnoses. Among patients with this condition, coronary angiography is typically unremarkable, whereas pulmonary-function tests and cardiopulmonary exercise testing are frequently abnormal.

Routine echocardiographic evaluation to detect persistent pulmonary hypertension within 6 months after acute pulmonary embolism may help to identify patients who are at increased risk for chronic thromboembolic pulmonary hypertension.¹⁹ Such testing may lead to early diagnosis of this disease and therefore may improve management and outcomes. However, this hypothesis remains to be proved.

Differentiating chronic thromboembolic pulmonary hypertension from recurrent pulmonary embolism can be challenging because there is an overlap among risk factors for the two conditions. Clues that suggest chronic thromboembolic pulmonary hypertension (as opposed to recurrent pulmonary embolism) include a gradual progression of symptoms and signs of pulmonary hypertension and right ventricular failure (rather than profound episodic exacerbations) and lack of a response to fibrinolytic therapy or at least 6 months of antithrombotic therapy. Differentiating persistent elevation of pulmonary-artery

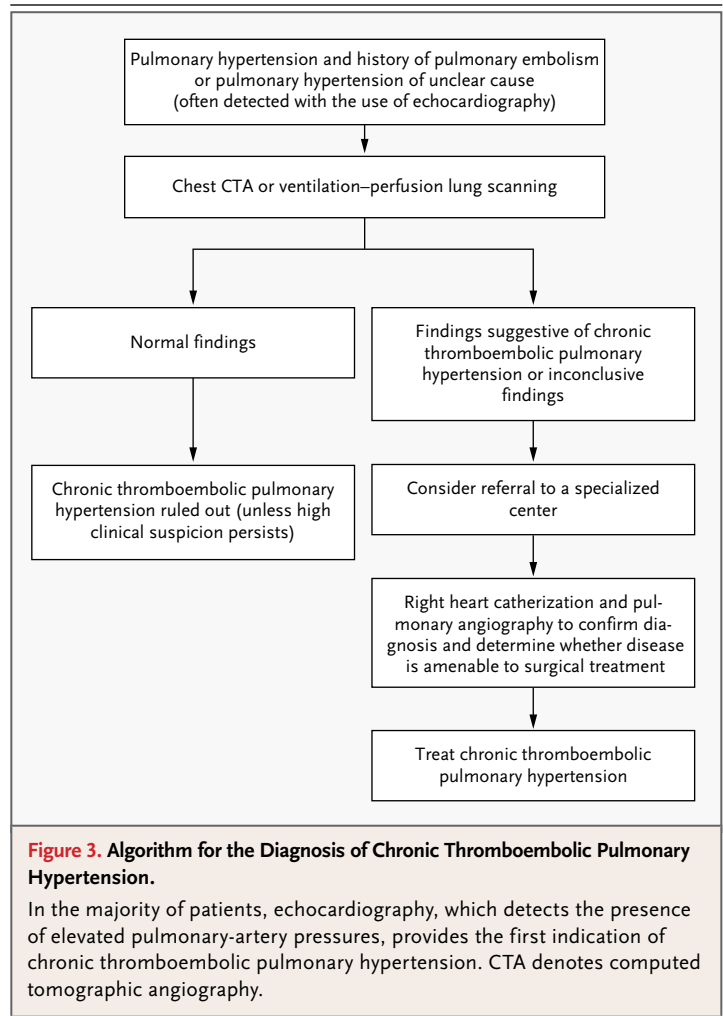
pressures from preexisting pulmonary-artery hypertension with acute pulmonary embolism and subsequently elevated pulmonary-artery pressures is a common problem. Clinicians should look for stepwise increases in pulmonary-artery pressures and episodic changes in symptoms as indicators of an intercurrent pulmonary embolism.

IMAGING

In the majority of patients with chronic thromboembolic pulmonary hypertension, echocardiography provides the first clues to the diagnosis by detecting the presence of pulmonary hypertension. Pulmonary hypertension with or without right ventricular dysfunction should raise concern about chronic thromboembolic pulmonary hypertension in a patient with a compatible history. Transthoracic echocardiography with Doppler imaging is sensitive for the detection of pulmonary hypertension and right ventricular dysfunction, but it is not specific for the diagnosis of chronic thromboembolic pulmonary hypertension. Common echocardiographic findings include right ventricular dilatation, hypertrophy, and hypokinesis; right atrial enlargement; right ventricular pressure overload as suggested by interventricular septal deviation toward the left ventricle during systole; and tricuspid regurgitation. The tricuspid regurgitant jet gradient provides an estimate of the pulmonary-artery systolic pressure. In rare cases, transthoracic echocardiography shows proximal pulmonary-artery thrombus.²⁰ However, echocardiography cannot be used to reliably differentiate among acute, subacute, and chronic pulmonary embolism.

Ventilation–perfusion lung scanning may be used to differentiate chronic thromboembolic pulmonary hypertension from other causes of pulmonary hypertension.²¹ Normal findings on ventilation–perfusion lung scanning practically rule out the diagnosis, whereas multiple bilateral perfusion defects suggest chronic thromboembolic pulmonary hypertension as a likely diagnosis. Ventilation–perfusion lung scanning does not anatomically localize the extent of disease and cannot be used to determine surgical accessibility.

Chest computed tomographic angiography (CTA) may show eccentric thromboembolic material, subpleural densities, right ventricular enlargement, and a mosaic parenchymal pattern. CTA may complement the information obtained from ventilation–perfusion lung scanning by pro-



viding additional data regarding anatomical localization and surgical accessibility. The accuracy of CTA for detecting abnormalities is greatest in the main and lobar pulmonary arteries and subsequently decreases in the segmental and subsegmental vessels.²² Magnetic resonance angiography is an alternative form of imaging that remains unproven for the diagnosis of chronic thromboembolic pulmonary hypertension, but it has shown limited sensitivity (78%) for the diagnosis of acute pulmonary embolism.^{23,24}

We prefer CTA as the initial imaging test because expertise in the interpretation of ventilation–perfusion lung scanning is waning. If either CTA or ventilation–perfusion lung scanning is inconclusive for chronic thromboembolic pulmonary hypertension or if surgery is being considered, right heart catheterization and pulmonary angiography are typically performed to

confirm the diagnosis and further define the physiological and anatomical characteristics. Invasive pulmonary angiography is not used as the initial test of choice because noninvasive forms of imaging, in particular CTA, provide information regarding alternative diagnoses and show baseline abnormalities that may be compared in serial follow-up studies. Right heart catheterization with pulmonary angiography continues to be the standard for establishing the diagnosis and assessing operability. Specific angiographic patterns that correlate with operative findings include pulmonary-artery webs or bands, intimal irregularities, abrupt stenoses of major pulmonary arteries, and obstruction of lobar or segmental arteries at their origins.^{25,26}

HEMODYNAMIC EVALUATION

Right heart catheterization performed in conjunction with invasive pulmonary angiography quantifies the degree of pulmonary hypertension and can be used to assess responsiveness to vasodilator therapy. A reduction in pulmonary-artery pressure after administration of a vasodilator, inhaled nitric oxide, may be indicative of increased long-term survival among patients with chronic thromboembolic pulmonary hypertension who undergo pulmonary thromboendarterectomy.²⁷

ROLE OF SPECIALIZED CENTERS IN DIAGNOSIS

Patients with pulmonary hypertension and findings of pulmonary embolism on CTA or ventilation-perfusion lung scanning and those with unexplained elevations in pulmonary-artery systolic pressure should be referred to specialized centers. Additional testing, such as right heart catheterization with vasodilator challenge and pulmonary angiography to establish the diagnosis of chronic thromboembolic pulmonary hypertension and to determine suitability for pulmonary thromboendarterectomy, is best performed at centers that are experienced in such procedures. Furthermore, specialized centers can offer advanced therapy such as pulmonary thromboendarterectomy as well as enrollment in clinical trials of medical therapy for patients who are ineligible for surgery.

TREATMENT

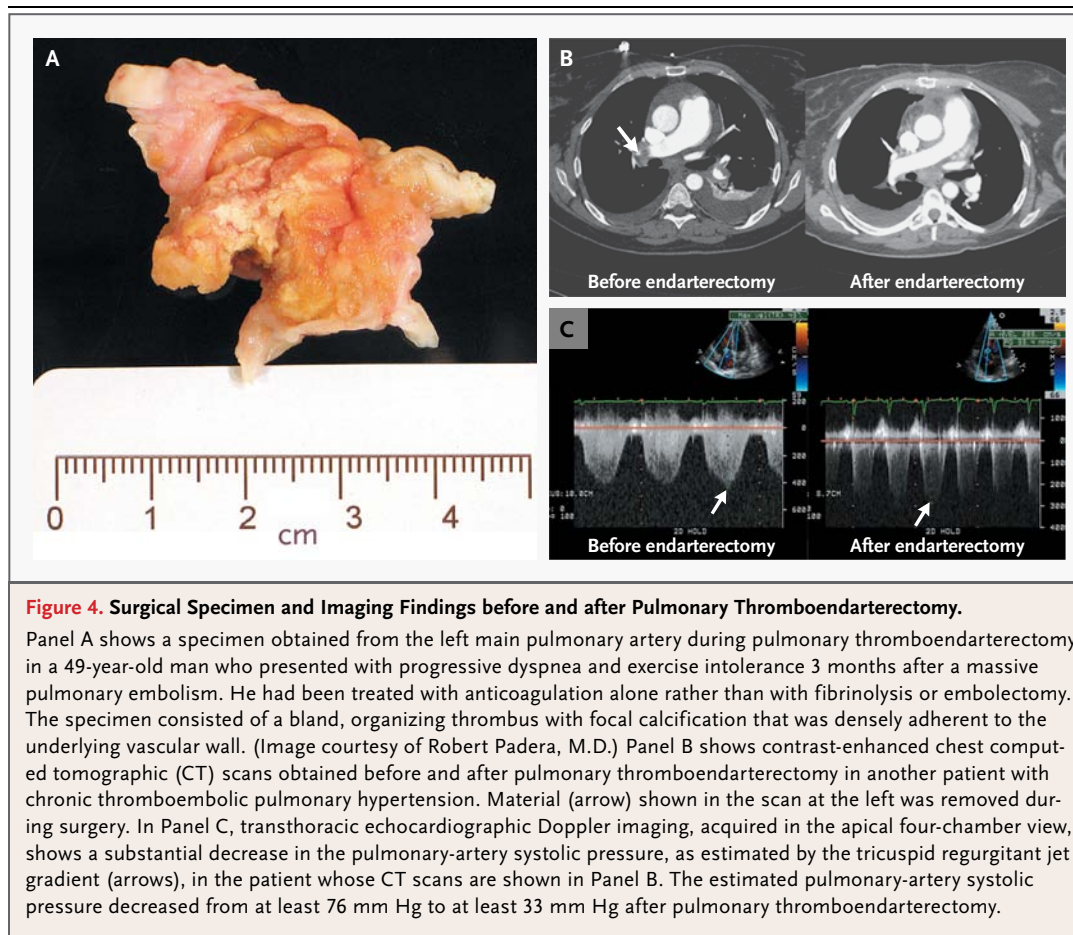
The most effective therapy for chronic thromboembolic pulmonary hypertension is pulmonary thromboendarterectomy.²⁸ Advanced medical

therapy, which includes any medical intervention in addition to anticoagulation, is considered in patients with inoperable disease or those with persistent or recurrent pulmonary hypertension after pulmonary thromboendarterectomy.

PULMONARY THROMBOENDARTERECTOMY

Successful pulmonary thromboendarterectomy removes obstructive, whitish, hardened thromboembolic material and markedly improves the hemodynamic measures of mean pulmonary-artery pressure, pulmonary vascular resistance, and cardiac output (Fig. 4).^{29,30} Improvement in hemodynamics causes reverse right ventricular remodeling, with reductions in tricuspid regurgitation and the return of right ventricular systolic and diastolic function toward normal levels.³¹⁻³³ Hemodynamics and measures of functional capacity, such as the 6-minute walk distance and New York Heart Association (NYHA) class, markedly improve after successful pulmonary thromboendarterectomy, and the beneficial effect usually persists,^{30,34} unless small-vessel arteriopathy or recurrent pulmonary embolism develops. Data are lacking from clinical trials comparing survival among patients with chronic thromboembolic pulmonary hypertension treated with pulmonary thromboendarterectomy with survival among those treated nonsurgically.

When successful, pulmonary thromboendarterectomy improves hemodynamics, symptoms, and functional status. Data are lacking to provide support for the use of advanced medical therapy preoperatively.³⁵ Pulmonary thromboendarterectomy is performed with the use of cardiopulmonary bypass with intermittent circulatory arrest to permit dissection from the main pulmonary arteries to the subsegmental branches. Patients with symptomatic chronic thromboembolic pulmonary hypertension, surgically accessible disease, and an acceptable perioperative risk should be referred for pulmonary thromboendarterectomy. Preoperative predictors of favorable outcomes include a pulmonary vascular resistance of less than $1200 \text{ dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$ and the absence of major coexisting conditions.³⁶ Patients in whom the postoperative pulmonary vascular resistance decreases by at least 50%, to a value of less than $500 \text{ dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$, have a more favorable prognosis after surgery than those who do not.²⁸ In contrast to the short-term response to inhaled nitric oxide, the response to the long-term use of pulmonary vasodilators, such as bosentan, sil-



denafil, or prostacyclin analogues, does not appear to predict hemodynamics or outcomes after pulmonary thromboendarterectomy.³⁵

Contraindications to pulmonary thromboendarterectomy include small-vessel disease as suggested by a pulmonary vascular resistance that is out of proportion to the degree of obstruction noted on imaging, an expected postoperative reduction in pulmonary vascular resistance of less than 50%, and a prohibitive perioperative risk. The perioperative risk is assessed as it is for any intrathoracic procedure requiring cardiopulmonary bypass, and it incorporates center-specific morbidity and mortality associated with pulmonary thromboendarterectomy. The 30-day mortality ranges from less than 5% in the most experienced centers to 10% elsewhere.^{29,30,34}

The two most common anticipated postoperative sequelae are the pulmonary-artery steal syndrome, which occurs when blood flow is redistributed from previously well-perfused seg-

ments to newly opened ones, and reperfusion pulmonary edema. Late adverse events include residual elevation in pulmonary-artery pressure and recurrent pulmonary hypertension in patients who initially had hemodynamic improvement after surgery. Residual pulmonary hypertension, which may result from incomplete endarterectomy, inaccessible chronic thromboemboli, or small-vessel arteriopathy, is itself an important predictor of late postoperative adverse events.³⁰ Postoperative NYHA class III or IV symptoms, unsuccessful pulmonary thromboendarterectomy, high pulmonary vascular resistance, and persistent abnormalities of gas exchange are also associated with an increased risk of late adverse events.³⁰ Inferior vena cava filters are usually implanted perioperatively, but their necessity has been challenged at some centers.

BALLOON PULMONARY-ARTERY ANGIOPLASTY

Balloon pulmonary-artery angioplasty is an alternative therapy in selected patients who have

inoperable disease due to distal surgically inaccessible disease or persistent or recurrent pulmonary hypertension after thromboendarterectomy. Successful balloon pulmonary angioplasty may reduce pulmonary-artery pressure in patients with chronic thromboembolic pulmonary hypertension.³⁷ Improvement in the NYHA functional class and the 6-minute walk distance has also been observed after successful balloon pulmonary angioplasty.³⁷ However, experience with this procedure is very limited, and it is rarely performed.

MEDICAL THERAPY

Anticoagulation is prescribed in most patients with chronic thromboembolic pulmonary hypertension, although data are lacking from randomized clinical trials to support this widespread practice. The rationale is to prevent in situ pulmonary-artery thrombosis and recurrent venous thromboembolism. Among patients with unprovoked or idiopathic pulmonary embolism, an indefinite duration of anticoagulation has reduced the risk of recurrent venous thromboembolism.^{38,39}

Prescription of advanced medical therapy with pulmonary vasodilators may contribute to increased survival among patients with inoperable disease.⁴⁰ The underlying principle for this practice is that the morphologic characteristics of vessels in chronic thromboembolic pulmonary hypertension closely resemble those in idiopathic pulmonary arterial hypertension. Patients with chronic thromboembolic pulmonary hypertension may have acute vasoreactivity to inhaled pulmonary vasodilators, suggesting at least some shared pathophysiological features.⁴¹ Advanced medical therapies include the endothelin-receptor antagonist, bosentan; the phosphodiesterase inhibitor, sildenafil; and prostacyclin analogues, such as epoprostenol or treprostinil.

The Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension trial (ClinicalTrials.gov number, NCT00313222) randomly assigned 157 patients with chronic thromboembolic pulmonary hypertension and persistent or recurrent pulmonary hypertension after thromboendarterectomy or inoperable disease to receive bosentan or placebo.⁴² Bosentan therapy resulted in significant improvements in hemodynamic variables of pulmonary vascular resistance and the cardiac index, levels of pro-brain-type natriuretic peptide, and dyspnea.⁴²

Patients receiving bosentan therapy require periodic monitoring for hepatotoxicity.

In an open-label clinical trial, 104 patients with inoperable chronic thromboembolic pulmonary hypertension received treatment with 50 mg of sildenafil three times daily.⁴³ Long-term treatment with sildenafil was associated with significant improvements in pulmonary vascular resistance, the cardiac index, the 6-minute walk distance, and the World Health Organization (WHO) functional class.⁴³ In a subgroup of patients who underwent initial right heart catheterization, the short-term response to sildenafil was not predictive of the long-term outcome of therapy.⁴³

In an open-label study involving 28 patients with severe, inoperable, chronic thromboembolic pulmonary hypertension, therapy with the subcutaneously administered prostacyclin analogue treprostinil resulted in significant improvements in the 6-minute walk distance, the WHO functional class, levels of brain-type natriuretic peptide, and hemodynamic variables of cardiac output and pulmonary vascular resistance.⁴⁴ Survival among patients who received treatment with treprostinil was longer than that among historical controls.⁴⁴ Inhaled treprostinil⁴⁵ and oral prostacyclin analogues⁴⁶ show promise in patients with severe pulmonary hypertension, including those with chronic thromboembolic pulmonary hypertension.

Newer agents that have been associated with good results in the treatment of pulmonary arterial hypertension include the endothelin-receptor antagonists sitaxsentan and ambrisentan and the phosphodiesterase inhibitor tadalafil.⁴⁷⁻⁴⁹ Evaluation of these agents in the medical treatment of patients with chronic thromboembolic pulmonary hypertension is an important area for further research. A new soluble guanylate cyclase stimulator, riociguat, has been evaluated in chronic thromboembolic pulmonary hypertension and has shown promise.⁵⁰

THERAPEUTIC ALGORITHM

The pivotal decision is to identify patients with surgically accessible chronic thromboemboli in whom pulmonary thromboendarterectomy is expected to result in a substantial reduction in pulmonary vascular resistance. Advanced medical therapy should be reserved for patients with inoperable disease and those with persistent or recur-

rent pulmonary hypertension after pulmonary thromboendarterectomy. Patients with chronic thromboembolic pulmonary hypertension for whom pulmonary thromboendarterectomy or vasodilator therapy is being considered should be referred to centers that have experience in the management of this complex disorder and can offer an array of treatment protocols and enrollment

in clinical trials. Online resources such as the Pulmonary Hypertension Association Web site (www.phassociation.org), which provide information regarding centers of excellence in the management of chronic thromboembolic pulmonary hypertension, are available to patients and providers.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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