

Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) has emerged as one of the leading causes of severe pulmonary hypertension. The disease is notoriously underdiagnosed, and the true prevalence is still unclear. CTEPH is characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of pulmonary arteries.¹ The consequence is an increased pulmonary vascular resistance resulting in pulmonary hypertension and progressive right heart failure. Vascular disobliteration by pulmonary endarterectomy (PEA) is the preferred treatment for patients with CTEPH,² but not all patients are eligible for surgery. Recent research has provided evidence suggesting that the mechanistic view of CTEPH as a disease caused solely by obliteration of central pulmonary arteries due to organized thrombi may have been too simplistic. Pulmonary embolism, either as a single episode or as recurrent episodes, is thought to be the initiating event followed by progressive pulmonary vascular remodeling. This concept explains the clinical observation that CTEPH patients may have severe pulmonary hypertension out of proportion to the pulmonary vascular obliteration seen on a pulmonary angiogram. Thus, treatment of CTEPH often requires a multidisciplinary approach and may involve surgery, medical treatment, or both. However, many aspects of the pathogenesis of CTEPH are poorly understood, the diagnostic approach to these patients has not been standardized, and neither randomized controlled trials nor guidelines have been published in this field.

In July 2005, a group of international experts met in Zurich, Switzerland, for a comprehensive discussion of CTEPH. The members of this group are listed in the Appendix (in the online-only Data Supplement). This report will review the issues surrounding CTEPH that were discussed during that meeting: its etiology and pathogenesis, epidemiology, diagnosis, treatment options, and associated prognosis. Current issues, including challenges in assessing surgical candidacy and predicting postoperative outcome, will be introduced. Finally, potential ways of resolving uncertain and controversial issues, such as the role of medical therapy and the requirement for randomized controlled trials, will be discussed. Algorithms for the diagnosis and management of CTEPH will be proposed.

Epidemiology

The true incidence and prevalence of CTEPH are unknown. Originally, it was believed that 0.1% to 0.5% of patients who survive an episode of acute pulmonary embolism develop CTEPH.³⁻⁵ However, in a prospective follow-up study of 78 survivors of acute pulmonary embolism, echocardiographic findings suggestive of persistent pulmonary hypertension and/or right ventricular dysfunction were present in 44% of the patients after 1 year.⁶ Four patients (5.1%) developed definite CTEPH, and 3 of these subsequently underwent successful PEA. The only identifiable risk factors for persistent pulmonary hypertension were an age >70 years and a systolic pulmonary artery pressure >50 mm Hg at the initial presentation. An echocardiogram at week 6 after diagnosis of an acute pulmonary embolism was capable of distinguishing between patients with persistent pulmonary hypertension and those with complete recovery. In another prospective follow-up study of 223 patients who presented with acute pulmonary embolism, the incidence of symptomatic CTEPH was 3.1% at 1 year and 3.8% at 2 years.⁷ Risk factors for CTEPH were previous episodes of acute pulmonary embolism, larger perfusion defects at the initial presentation, and a younger age. The incidence of CTEPH in both studies was higher than expected, and it is possible that some of the patients had preexistent unidentified CTEPH when they presented with the clinical picture of acute pulmonary embolism.

Defining the true incidence of CTEPH is hampered by the observation that up to two thirds of these patients have no history of clinically overt acute pulmonary embolism.⁸ Thus, the only way to define the true incidence and prevalence of CTEPH will be a combination of large-scale multicenter studies prospectively following patients after pulmonary embolism in combination with subtle case studies of patients without a history of acute pulmonary hypertension in whom a diagnosis of CTEPH is made during a diagnostic workup for unexplained pulmonary hypertension.

Natural History

The natural history of untreated CTEPH must be determined from historical data because today most patients will be referred for surgery or medical treatment. In 1982, ie, before PEA

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The online-only Data Supplement, which contains the Appendix, can be found at <http://circ.ahajournals.org/cgi/full/113/16/2011/DC1>.

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became widely available, Riedel et al⁹ published a series of 26 patients with CTEPH who were followed up for up to 15 years. Patients who had a mean pulmonary artery pressure >30 mm Hg at the initial presentation invariably had progressive pulmonary hypertension. Survival at 2 years was <20% when the mean pulmonary artery pressure was >50 mm Hg. Another study of 49 CTEPH patients treated only with anticoagulants reported a 3-year mortality of 90% when the mean pulmonary artery pressure was >30 mm Hg.¹⁰ In contrast, a similar follow-up study from Japan of 48 CTEPH patients with mean pulmonary artery pressures of 50 mm Hg found a mean survival of 6.8 years after the diagnosis.¹¹ Despite these conflicting data, it is clear that most patients who present with persistent pulmonary hypertension after pulmonary embolism will have progressive disease despite adequate anticoagulation and that these patients carry a high risk of dying from right heart failure if left untreated.

Pathophysiology

It has been appreciated for many years that CTEPH may not be explained simply by pulmonary vascular obliteration due to unresolved thromboemboli.¹² Persistent obstruction of pulmonary arteries may result in elevated pulmonary artery pressures and high shear stress in those areas of the pulmonary vasculature that were spared from thromboembolic occlusion. In that scenario, acute pulmonary embolism would be the initiating event, but progression of pulmonary hypertension would result from progressive pulmonary vascular remodeling, ie, small-vessel disease. This concept was proposed by Drs Kenneth Moser and Nina Braunwald after Dr Braunwald's first surgical PEA at the University of California at San Diego in 1971.¹² Moser and Braunwald noted that the patient had "a two compartment pulmonary vascular bed." The open pulmonary arteries had marked structural changes of chronic pulmonary hypertension, whereas the vascular bed distal to the obliterated segments, which had not been exposed to high pressure and high shear stress, appeared to be completely normal. This observation was later confirmed by clinical and histological studies revealing changes in the pulmonary microvasculature very similar to other forms of severe pulmonary hypertension including the formation of plexiform lesions.^{13–17} Both the extent of proximal occlusion of pulmonary arteries and secondary small-vessel arteriopathy contribute to the elevated pulmonary vascular resistance (Figure 1). The more pronounced the distal vascular changes are, the higher is the risk of surgery and the less likely is hemodynamic improvement after surgery.^{2,18}

When attempting to elucidate the mechanisms driving the development of CTEPH, one must distinguish between factors that prevent complete recanalization of pulmonary arteries after acute pulmonary embolism and those that are involved in the remodeling of small pulmonary vessels. The reasons for incomplete resolution of pulmonary emboli have not been identified. The normal pulmonary vascular bed carries a high fibrinolytic potential, but alterations in the fibrinolytic system have not yet been identified in patients with CTEPH. Secretion by pulmonary vascular endothelial cells of tissue plasminogen activator and plasminogen activator inhibitor-1 is not different between lungs from CTEPH

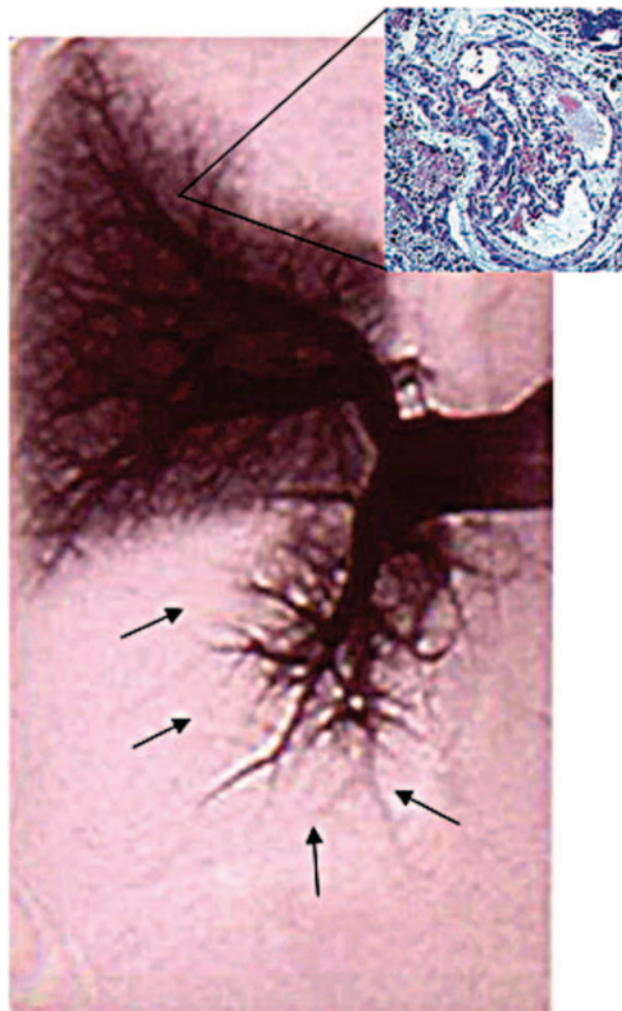


Figure 1. Pulmonary angiogram (capillary phase) of the right lung of a patient with CTEPH. The right middle and upper lobe arteries are almost completely obstructed by central thromboemboli, which are not directly visible on this radiograph. The peripheral arteries and arterioles in these areas (arrows) are not perfused, resulting in protection from high intravascular pressures and high shear stress. The peripheral vessels in these areas usually appear normal on histological examination (not shown). In contrast, the right upper lobe is exposed to high intravascular pressures and receives almost the complete blood flow of the right lung. High pressure, high shear stress, inflammation, and an imbalance of vasoactive mediators result in vascular remodeling including the formation of plexiform lesions (inlet).

patients and donor lungs.^{19,20} Interestingly, thrombophilia resulting from mutations in protein C, protein S, antithrombin, prothrombin, or factor V has not been associated with CTEPH.^{21,22} The only factors that have been linked to CTEPH thus far are anticardiolipin antibodies, which are found in 10% to 20% of these patients,²² and elevated levels of factor VIII,²³ but similar findings have been reported in patients with other forms of pulmonary hypertension.²⁴

Several risk factors for the development of CTEPH have been identified, including chronic inflammatory disorders, myeloproliferative syndromes, the presence of a ventriculoatrial shunt, and splenectomy.²⁵ The association with these distinct conditions suggests that chronic infection and/or chronic inflammatory processes are involved in the pathogen-

esis of CTEPH. This hypothesis is supported by numerous experimental findings showing that inflammation may cause a prothrombotic state and impair resolution of pulmonary thrombemboli.^{26–29}

The high proportion of splenectomized patients in the CTEPH population has gained considerable attention.^{30–32} The interval between splenectomy and diagnosis of CTEPH ranges between 2 and 34 years, and the pathogenetic link between these conditions remains unclear. Current hypotheses include prothrombotic activity of abnormal erythrocytes, interactions between abnormal erythrocyte membranes and the pulmonary vasculature, or abnormal platelet activation.^{25,32,33}

Despite the overwhelming evidence linking CTEPH to previous events of pulmonary embolism, an alternative hypothesis of the pathogenesis of CTEPH disputes the role of acute or recurrent pulmonary embolism but suggests a primary arteriopathy of pulmonary vessels and secondary in situ thrombosis as causes of pulmonary vascular occlusion.³⁴ This hypothesis is driven by pathophysiological considerations and experimental data raising doubts that a single episode of pulmonary embolism or even recurrent events may result in pulmonary vascular obliteration sufficiently severe to cause pulmonary hypertension. In fact, in situ thrombosis of pulmonary vessels is a well-recognized complication in patients with severe pulmonary hypertension of other etiologies.³⁵ The observation of different risk constellations for acute venous thromboembolism and CTEPH has fueled this discussion. It has also been argued that venous thrombosis can be found in <50% of patients with CTEPH,² although this number is similar to the rate of detectable venous thrombosis in patients presenting with acute pulmonary embolism.^{36,37} The vast majority of experts agree that there is compelling evidence supporting the concept of pulmonary embolism, either overt or occult, triggering a cascade of events that eventually result in CTEPH.³⁶ However, distinguishing patients with idiopathic PAH and in situ thrombosis of peripheral vessels from patients with a distal type of CTEPH may be impossible, and there may be an overlap between both disorders.

Some but clearly not all of the mechanisms involved in pulmonary vascular remodeling after acute or recurrent pulmonary emboli have been identified. The system is complex and consists of a large spectrum of biological molecules. As in other forms of pulmonary hypertension, it is widely believed that some patients are genetically susceptible to developing this complication, but genetic variants associated with a heightened risk of CTEPH have yet to be determined. Mutations in bone morphogenetic protein receptor type 2 (BMPR-2) have been found in familial and idiopathic pulmonary arterial hypertension.^{38,39} These mutations have been linked to vascular remodeling because they promote smooth muscle cell proliferation. Similar mutations have not been described in CTEPH. In fact, it has been shown that BMPR-2 expression is not diminished in lungs from CTEPH patients.⁴⁰ However, expression of BMPR-1A, a transmembrane protein required for BMPR-2 signaling, is markedly downregulated in lungs from patients with CTEPH as well as other forms of pulmonary hypertension.⁴⁰ Angiopoetin-1, a signaling molecule involved in angiogenesis and smooth muscle cell prolif-

eration that has been experimentally linked to pulmonary hypertension,⁴¹ is upregulated in the lungs from CTEPH patients. Angiopoetin-1 shuts off BMPR-1A expression and thereby blocks BMPR-2 signaling even in the absence of germline BMPR-2 mutations. This mechanism seems to play a role in several forms of pulmonary hypertension including but not restricted to CTEPH.⁴⁰

Inflammatory mechanisms have also been implicated in the pathogenesis of CTEPH. Plasma levels of the proinflammatory cytokine macrophage chemoattractant protein-1 are elevated in patients with CTEPH and correlate with the magnitude of pulmonary hypertension.⁴² Elevations of proinflammatory molecules have also been reported in patients with idiopathic pulmonary arterial hypertension.^{43–46}

As in other forms of severe pulmonary hypertension, the endothelin system is activated in patients with CTEPH and may contribute to pulmonary vasoconstriction as well as vascular remodeling. Plasma levels of endothelin-1 are elevated in this group of patients, and upregulation of type B endothelin receptors on pulmonary arterial smooth muscle cells has been demonstrated.⁴⁷ In a canine model of chronic pulmonary embolism, pulmonary vascular remodeling was attenuated by bosentan, an endothelin receptor antagonist that blocks both ET_A and ET_B receptors.⁴⁸

Taken together, the molecular mechanisms involved in pulmonary vascular remodeling in CTEPH appear to be similar to those seen in severe pulmonary hypertension of other etiology. However, further studies are required for a full understanding of the sequence of events that eventually result in pulmonary vascular remodeling.

Clinical Presentations and Diagnosis

The symptoms and signs of pulmonary hypertension have been reviewed elsewhere.^{49–51} Patients with CTEPH typically present in either of 2 scenarios: patients may complain of progressive dyspnea on exertion, hemoptysis, and/or signs of right heart dysfunction including fatigue, palpitations, syncope, or edema after a single episode or recurrent episodes of overt pulmonary embolism. A “honeymoon period” between the acute event and the development of clinical signs of CTEPH is common and may last from a few months to many years. However, up to 63% of patients have no history of acute pulmonary embolism.⁸ In these patients, progressive dyspnea on exertion, rapid exhaustion, and fatigue are the most common symptoms, and the clinical course is often indistinguishable from other forms of severe pulmonary hypertension, especially idiopathic pulmonary arterial hypertension. Physical findings are often subtle and may include a left parasternal heave, a prominent pulmonary component of S₂, and a systolic murmur of tricuspid regurgitation. Signs of right heart failure, ie, extended neck veins, edema, ascites, and acrocyanosis, occur late in the course of the disease and may signal a life-threatening situation. A rare clinical finding that is virtually pathognomonic for CTEPH is bruits over peripheral lung fields,⁵² typically over the lower lobes, which result from turbulent blood flow in partially occluded areas. According to most experts, these bruits can be found in ≈10% of patients with CTEPH, making this sign one of low sensitivity but probably very high specificity.

As outlined below, the therapeutic approach to CTEPH differs substantially from that to pulmonary arterial hypertension. Thus, it is crucial to clarify the presence or absence of CTEPH in any patient presenting with unexplained pulmonary hypertension. The fact that many CTEPH patients have no history of acute pulmonary embolism together with uncertainties about the appropriate diagnostic approach to these patients contributes to a substantial rate of diagnostic misclassifications in this patient population. However, the most promising means to improve the diagnosis of CTEPH is increased awareness by physicians.

Echocardiography is widely used as the initial diagnostic tool when pulmonary hypertension is suspected, and routine echocardiography 6 weeks after pulmonary embolism has been suggested to identify patients at risk for developing CTEPH.⁶ However, the ideal timing of echocardiography, the need for long-term follow-up in symptomatic or asymptomatic patients, and the cost-effectiveness of wide-scale echocardiographic screening of patients after acute pulmonary embolism remain to be determined.

Imaging technologies including ventilation-perfusion scanning, computed tomography (CT), MRI, and pulmonary angiography are a fundamental part of the diagnostic workup of patients with suspected CTEPH. No prospective studies have evaluated the most appropriate diagnostic approach to CTEPH, and ventilation-perfusion scanning as well as CT angiography may underestimate clot burden. Nevertheless, ventilation-perfusion scanning is a useful tool to start searching for possible CTEPH. There is consensus among experts that a normal ventilation-perfusion scintigram practically rules out the presence of CTEPH.^{3,53-56} In contrast, the presence of multiple bilateral perfusion defects makes CTEPH the most likely diagnosis, although other conditions including pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, fibrosing mediastinitis, pulmonary vasculitis, or sarcomas of the pulmonary arteries may cause similar findings.^{3,57-60}

If scintigraphy shows indeterminate results, ie, whenever the perfusion scan is not completely normal or reveals findings suggestive of CTEPH, the next diagnostic step is usually CT angiography, which may reveal eccentric thrombotic material within the pulmonary arteries, subpleural densities, and a characteristic mosaic attenuation of the pulmonary parenchyma (Figure 2).⁶¹⁻⁶⁴ It is important to note that patients with pulmonary arterial hypertension can develop secondary thrombosis of the central pulmonary arteries, a condition mimicking CTEPH.³⁵ In addition, neoplasms involving the pulmonary arteries or pulmonary large-vessel vasculitis may present with a similar CT picture.^{59,60,65} In these cases, ventilation-perfusion scanning usually does not show the typical bilateral segmental and subsegmental perfusion defects but rather normal findings, an inhomogeneous perfusion pattern, or unilateral abnormalities. Large bronchial artery collaterals are typically visible in patients with CTEPH and may be of diagnostic value because these collaterals are rarely found in other forms of pulmonary hypertension except for some cases associated with congenital heart disease.⁶⁶⁻⁶⁸ Of note, the absence of visible lesions in central pulmonary arteries does not exclude the presence of CTEPH, especially

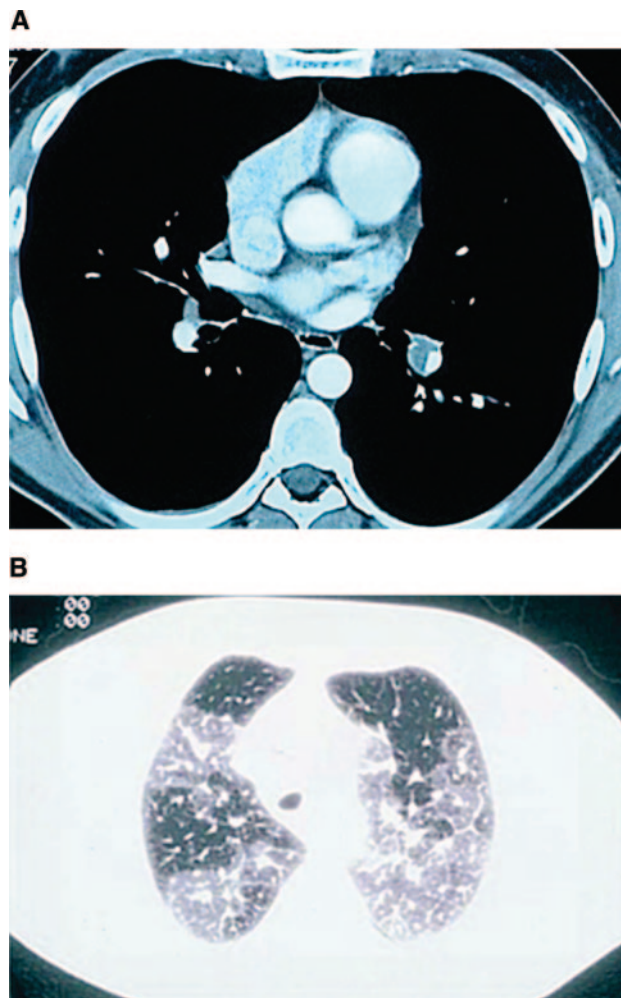


Figure 2. CT scans of the lungs of patients with CTEPH showing eccentric thrombotic material within the pulmonary arteries (arrows) (A) and a characteristic mosaic attenuation of the pulmonary parenchyma with the darker areas corresponding to the hypoperfused lung sections (B).

not with older imaging technology. Sensitivity and specificity of new-generation multidetector row scanners have not yet been sufficiently evaluated.

MRI may also provide a clear diagnosis of CTEPH, but this technique is infrequently used for this indication.⁶⁹⁻⁷² However, contrast-enhanced magnetic resonance angiography may be very useful in discriminating central thromboembolic lesions from tumors because the latter are enhanced with gadolinium, whereas the former are not.⁷³

Pulmonary angiography remains a standard diagnostic tool in the assessment of patients with probable or definite CTEPH both to establish the diagnosis and to assess operability (Figure 3).⁷⁴⁻⁷⁶ Pulmonary angiography is often performed in conjunction with a diagnostic right heart catheterization, which is required to confirm the diagnosis of pulmonary hypertension, rule out pulmonary venous hypertension, and establish the degree of hemodynamic impairment. In many centers it has become a standard procedure to perform the right heart catheterization first and then to use the same introducer sheath for pulmonary angiography, thereby

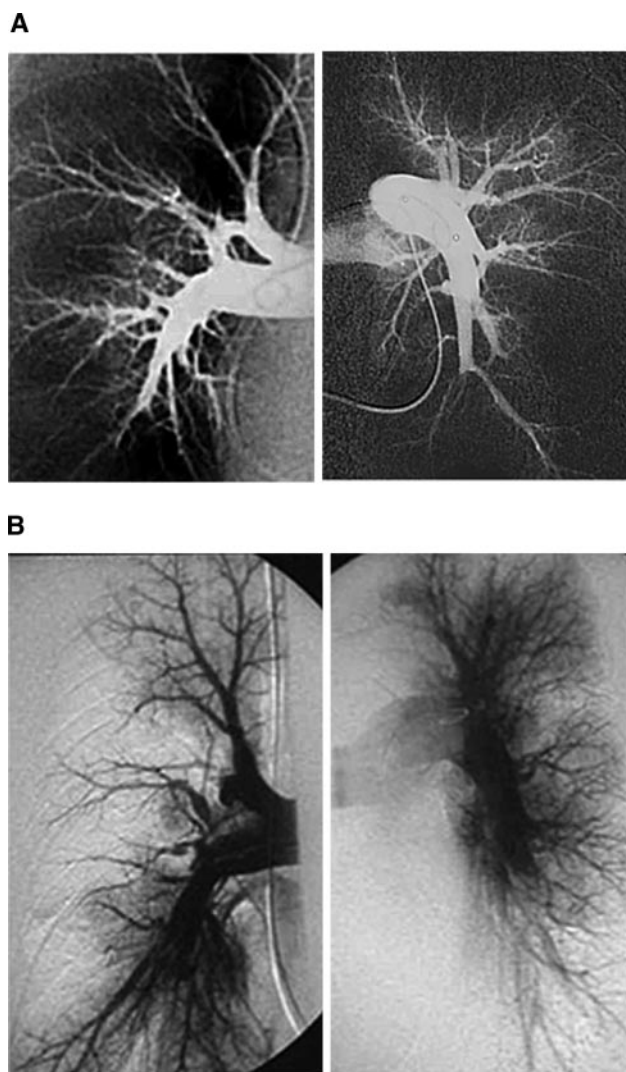


Figure 3. Pulmonary angiographies of 2 patients with CTEPH. The first patient (A) has extensive central pulmonary vascular obliterations and a pulmonary vascular resistance of ≈ 900 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ that is fully attributable to the visible lesions, making PEA the treatment of choice. The therapeutic decision is much more difficult in the second patient (B), who also has typical lesions of chronic thromboembolic pulmonary hypertension with a more distal distribution and a pulmonary vascular resistance of $2000 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$. With this constellation, the risk of surgery is markedly elevated, and the optimal treatment is uncertain (see text for details).

minimizing risks and inconveniences for the patient. Both right heart catheterization and pulmonary angiography should be performed by experienced staff. The use of nonionic contrast media, right and left main branch selective injections, serial pictures, and multiples views is recommended. If PEA is considered, pulmonary angiography might best be done at the institution where surgery would be performed.

A proposed algorithm for the diagnostic workup of patients with potential CTEPH is shown in Figure 4.

Treatment

CTEPH patients should receive lifelong anticoagulation adjusted to a target international normalized ratio between 2.0

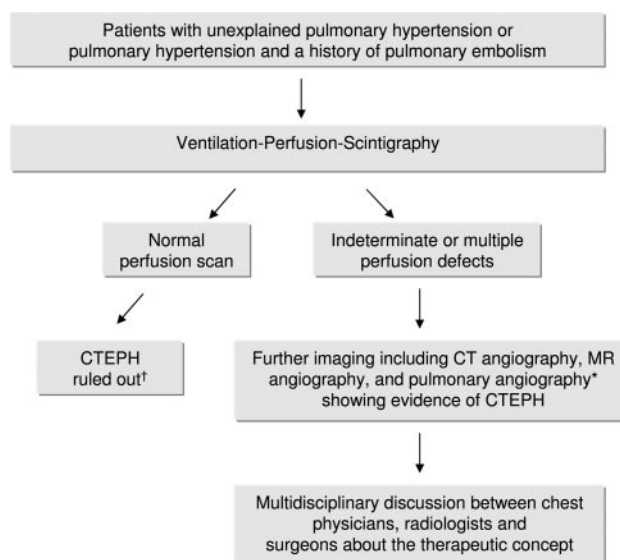


Figure 4. Proposed algorithm for the diagnostic approach to patients with CTEPH. Ventilation-perfusion scanning is the recommended screening procedure because a normal perfusion scan virtually rules out CTEPH. When perfusion scans show indeterminate results or bilateral segmental and subsegmental perfusion defects, CTEPH is the most likely diagnosis, and further imaging of the pulmonary vascular tree is required. *Pulmonary angiography should be performed only if PEA is considered a potential therapeutic option. A center experienced in PEA should be contacted before pulmonary angiography because most of these centers prefer to have pulmonary angiography performed at their institution. To plan the therapeutic concept, right heart catheterization with assessment of hemodynamics is often performed in conjunction with pulmonary angiography. †CTEPH despite a normal or nearly normal perfusion scan has been reported on rare occasions. Thus, further diagnostic workup may be warranted if there is a high clinical suspicion of CTEPH.

and 3.0. The rationale for anticoagulation is the prevention of recurrent thromboembolic events; once CTEPH is fully established, one should not expect significant regression of pulmonary hypertension from anticoagulation.

It is unclear how to proceed with patients presenting with mild pulmonary hypertension and no or only mild clinical impairment and normal right ventricular function after incomplete resolution of pulmonary emboli. Although some surgeons advocate early surgery in those patients to prevent progressive pulmonary vascular remodeling, the natural history of these patients has never been studied prospectively. Thus, anticoagulation and watchful waiting with regular clinical assessment and echocardiographic monitoring is an acceptable alternative to immediate surgery.

Patients presenting with systolic pulmonary artery pressures >50 mm Hg at the time of acute pulmonary embolism are very likely to suffer from CTEPH even if the diagnosis has not been established earlier. If these patients are in a stable condition, anticoagulation and watchful waiting for a period of 3 months is appropriate. Hemodynamic improvement sometimes occurs during this period. In addition, surgery may be much more difficult and less successful if thromboemboli have not been completely organized. If persistent pulmonary hypertension is present after 3 months, a full diagnostic workup is warranted. However, in patients



Figure 5. Material removed from the right and left pulmonary artery by PEA.

presenting with persistent hemodynamic instability, immediate surgery may be life-saving.

The treatment of choice for symptomatic patients with CTEPH is PEA. This surgical procedure has been described in detail elsewhere.^{1–4,12,18,77,78} Briefly, after cardiopulmonary bypass is established, deep hypothermia between 18°C and 20°C is induced. The endarterectomy is performed during complete circulatory arrest to avoid bleeding from systemic-to-pulmonary collaterals. The surgeon establishes the correct endarterectomy plane, which is followed down to lobar, segmental, or subsegmental branches of each lobe (Figures 5 and 6). When performed in experienced centers and in carefully selected patients, PEA provides remarkable results with a periprocedural mortality rate of <5% to 11%, nearly normalized hemodynamics, and substantial improvement in clinical symptoms.^{1,2,18} In a comprehensive review of 1500 PEA procedures performed at University of California at San Diego, Jamieson et al² stated that “there is no degree of embolic occlusion within the pulmonary vascular tree that is inaccessible and no degree of right ventricular impairment or any level of pulmonary vascular resistance that is inoperable.” However, there is an almost linear relationship between preoperative pulmonary vascular resistance and perioperative mortality. In a series from France, the mortality rate was 4% when the preoperative pulmonary vascular resistance was <900 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ but increased to 10% in patients with resistances between 900 and 1200 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ and to 20% for higher resistances.¹⁸ Postoperative residual pulmonary hypertension has been identified as the most important predictor of death. In the largest series published thus far, patients with a postoperative pulmonary vascular resistance >500 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ had a mortality rate of 30.6% (15 of 49 patients), whereas those with a postoperative resistance <500 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ had a mortality rate of 0.9% (4 of 434 patients).²

Taken together, these data suggest that technical operability must not necessarily confer a benefit to every patient with

A



B



Figure 6. Preoperative (A) and postoperative (B) MR tomography pulmonary angiogram of a patient with CTEPH. The central vascular lesions that are visible preoperatively (arrows) have been almost completely removed. The preoperative MR tomography angiogram was obtained 5 days before surgery when the pulmonary vascular resistance was 768 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$. Three days postoperatively, the pulmonary vascular resistance was 196 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$. The postoperative MR tomography angiogram was obtained 10 days after surgery.

CTEPH. Darteville et al¹⁸ have suggested that patients should be selected for PEA only if a reduction in pulmonary vascular resistance by >50% can be predicted. A multidisciplinary approach involving pulmonologists, radiologists, and surgeons is necessary to estimate the likelihood of a major

hemodynamic improvement after surgery. These decisions are still based on clinical experience. Patients with a disproportionately high preoperative pulmonary vascular resistance unexplained by the visible central vascular obliterative lesions are very likely to have a high degree of peripheral vasculopathy and therefore an elevated perioperative risk. A balloon occlusion technique has recently been developed to determine the relative proportions of central and peripheral components of elevated pulmonary resistance.^{79,80} Preliminary data are promising, but this technique needs further evaluation before routine clinical use. Pulmonary angiography can sometimes be helpful to assess operability in patients with unclear angiographic findings, but this technique is not widely available.^{81,82}

Although there is no doubt that eligible CTEPH patients should undergo PEA, it is uncertain how to best approach patients without surgically accessible disease. Patients may not be considered candidates either because of substantial small-vessel involvement or because of comorbid illness. Balloon pulmonary angioplasty has been performed successfully in some of these patients,^{83,84} but this technique must be considered experimental and requires further investigation. Lung transplantation may be an option for selected patients who are not candidates for PEA.¹⁸

On the basis of pathophysiological considerations, medical treatment is now being studied for CTEPH patients. Intravenous epoprostenol has been used with varying results to achieve hemodynamic stabilization before surgery, but at least some patients seemed to have had significant hemodynamic and clinical improvement.^{85–87} Uncontrolled studies suggest a potential role of both the phosphodiesterase-5 inhibitor sildenafil and the endothelin receptor antagonist bosentan for inoperable CTEPH patients.^{88–91} In 12 patients with inoperable CTEPH, 6 months of sildenafil treatment resulted in an average increase of 6-minute walk distance of 54 m and a drop in pulmonary vascular resistance of 30% from baseline.⁸⁸ Comparable results were achieved with 3 months of bosentan therapy in 18 patients, which resulted in a mean increase of 6-minute walk distance of 73 m and a fall in pulmonary vascular resistance of 33%.⁸⁹ The only controlled clinical trial thus far to include CTEPH patients was the Aerosolized Iloprost Randomization (AIR) study.⁹² This study included 57 patients with CTEPH, but subgroup analysis failed to show a significant benefit of inhaled iloprost on hemodynamics or exercise capacity. A randomized, placebo-controlled trial is currently under way to determine the safety and efficacy of bosentan in patients with inoperable CTEPH. A proposed algorithm for the therapeutic approach to CTEPH is shown in Figure 7.

Open Questions and Future Perspectives

Long-term multicenter studies are required to assess the true incidence of CTEPH after acute pulmonary embolism. Such studies will also provide the basis to determine risk factors for the development of CTEPH and for the implementation of preventive strategies. PEA will remain the standard of care for eligible patients. The surgical technique as developed by the San Diego group has been adopted by many centers worldwide. There is clearly a learning curve associated with

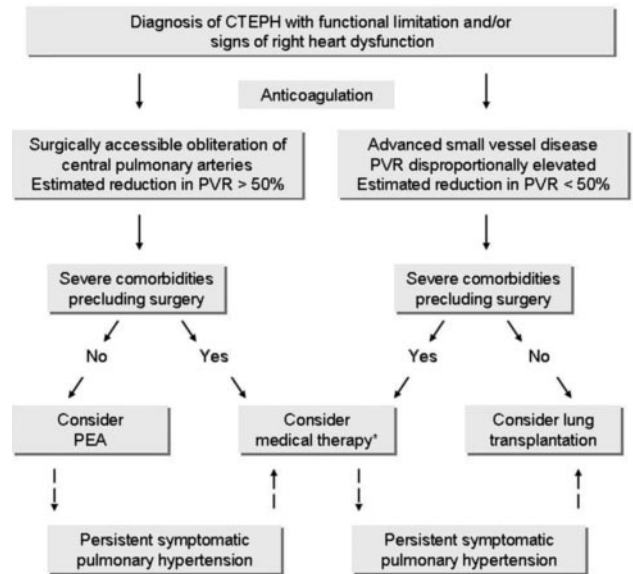


Figure 7. Proposed algorithm for the therapeutic approach to patients with CTEPH. PEA is the preferred treatment for CTEPH, and an experienced surgeon should be involved in deciding whether or not a patient is a candidate for surgery. *Medical therapy refers to prostanoids, endothelin receptor antagonists, or phosphodiesterase-5 inhibitors. The evidence that these substances may exert beneficial effects in selected CTEPH patients is currently limited to uncontrolled clinical trials and case series. No substance has been approved yet in the United States or Europe for CTEPH. The dashed arrows symbolize therapeutic considerations in case the initial approach fails. See text for further details. PVR indicates pulmonary vascular resistance.

PEA, but the results in experienced centers are excellent. Selecting the candidates who will benefit from surgery is still a challenging task, and reliable techniques to define the extent of small vessel involvement need to be developed. Controlled studies are necessary to determine whether patients with high pulmonary vascular resistance derive benefit from preoperative treatment with prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors. It is also an open question whether inferior vena cava filters should be inserted in every patient who undergoes PEA. Insertion of vena cava filters before PEA is still a standard procedure in some centers, whereas more and more centers have abandoned this procedure, apparently without negative consequences, but this approach has never been thoroughly studied. We also do not have sufficient information about the long-term course of patients after PEA, and there is no established strategy for long-term follow-up of these patients. Despite the overall success of PEA, complete normalization of pulmonary hemodynamics is uncommon. Thus, one must expect that at least some patients are at risk of developing late-onset pulmonary hypertension similar to that observed after closure of atrial septal defects. Finally, randomized controlled clinical trials are necessary to define the role of medical treatment in small-vessel arteriopathy accompanying CTEPH.

Disclosures

Dr Hoepfer has received honoraria for lecturing at conferences from Actelion Pharmaceuticals, Pfizer, and Schering and is a member of international advisory boards for Actelion Pharmaceuticals and

Pfizer. Dr Mayer has received honoraria for lecturing at conferences from Actelion Pharmaceuticals and has been a consultant for Actelion Pharmaceuticals. Dr Simonneau has received honoraria for lecturing at conferences from Actelion Pharmaceuticals, Pfizer, Encysive, and United Therapeutics and is a member of international advisory boards for Actelion Pharmaceuticals, Pfizer, Encysive, and United Therapeutics. Dr Rubin has received honoraria for lecturing at conferences from Actelion Pharmaceuticals, Pfizer, Schering, and United Therapeutics and is a member of international advisory boards for Actelion Pharmaceuticals, Pfizer, Myogen, Schering, MondoBiotech, Nitrox, and United Therapeutics.

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