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Chronic Thromboembolic Pulmonary Hypertension

JACC Focus Seminar

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is the result of pulmonary arterial obstruction by organized thrombotic material stemming from incompletely resolved acute pulmonary embolism. The exact incidence of CTEPH is unknown but appears to approximate 2.3% among survivors of acute pulmonary embolism. Although ventilation/perfusion scintigraphy has been supplanted by computed tomographic pulmonary angiography in the diagnostic approach to acute pulmonary embolism, it has a major role in the evaluation of patients with suspected CTEPH, the presence of mismatched segmental defects being consistent with the diagnosis. Diagnostic confirmation of CTEPH is provided by digital subtraction pulmonary angiography, preferably performed at a center familiar with the procedure and its interpretation. Operability assessment is then undertaken to determine if the patient is a candidate for potentially curative pulmonary endarterectomy surgery. When pulmonary endarterectomy is not an option, pulmonary arterial hypertension–targeted pharmacotherapy and balloon pulmonary angioplasty represent potential therapeutic alternatives. (J Am Coll Cardiol 2020;76:2155–69)

Chronic thromboembolic pulmonary hypertension (CTEPH) represents an important form of pulmonary hypertension (PH) in that it represents the only variant of PH for which there is a potential cure, in the form of pulmonary endarterectomy (PEA).

The recognition of chronic pulmonary thromboembolic disease as a discrete disease entity dates back to the early aspect of the 20th century (1). The development of diagnostic and surgical techniques including cardiac catheterization, contrast angiography, and cardiopulmonary bypass made CTEPH potentially remedial and accelerated interest in the disease process. However, as recently as 1984, Chitwood et al. (2) identified only 85 patients worldwide who underwent attempted surgical correction for chronic thromboembolic disease between 1960 and 1983 with an overall peri-operative mortality rate of 22%. In 1990, Jamieson et al. (3) reported results in 150 patients undergoing PEA at the University of California, San Diego where the modern era of the management of this disease was pioneered under the leadership of Kenneth M. Moser, MD (3).

Mortality in this series using what has become the standardized surgical approach of sternotomy, cardiopulmonary bypass, deep hypothermia, and

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ABBREVIATIONS AND ACRONYMS

6-MWD = 6-min walk distance

BPA = balloon pulmonary angioplasty

CI = confidence interval

CTED = chronic thromboembolic disease

CTEPH = chronic thromboembolic pulmonary hypertension

CTEPVD = chronic thromboembolic pulmonary vascular disease

CT-PA = computed tomographic pulmonary angiogram

IPAH = idiopathic pulmonary arterial hypertension

mPAP = mean pulmonary arterial pressure

OR = odds ratio

PAH = pulmonary arterial hypertension

PEA = pulmonary endarterectomy

PH = pulmonary hypertension

PVR = pulmonary vascular resistance

RV = right ventricular

V/Q = ventilation/perfusion

circulatory arrest was 8.7%. At present, over 4,200 procedures have been performed at the University of California, San Diego, and expert centers have been developed worldwide with reported in-hospital mortality rates of <5% and survival of >90% at 1 year (4). In parallel with the advances in the diagnostic and surgical techniques for patients with operable CTEPH, considerable therapeutic advances including targeted medical therapy and balloon pulmonary angioplasty (BPA) have also been introduced for those deemed to have inoperable CTEPH due to the distal location of the chronic thromboembolic obstruction, severity of the hemodynamic impairment, presence of severe comorbid conditions, or personal preference (5–8).

Although many unanswered questions remain about the pathogenesis and optimal management of the disease process, much has been accomplished over the past several decades. Risk factors have been identified; recognition has been enhanced; post-PEA mortality has been substantially reduced; and therapeutic interventions, both pharmacological and interventional, have been developed for patients deemed inoperable and those with post-PEA residual PH. In this article, we review the current state of understanding of the epidemiology, diagnosis, and management of CTEPH.

HIGHLIGHTS

- CTEPH, a consequence of unresolved pulmonary embolism, represents a potentially curable form of pulmonary hypertension.
- Operability assessment includes right heart catheterization and pulmonary angiography, preferentially performed at an expert center, to define the location and extent of vascular obstruction and the degree of hemodynamic impairment.
- PEA is the treatment of choice for CTEPH and is potentially curative.
- For patients with CTEPH who are not candidates for PEA, pharmacotherapy targeting pulmonary artery hypertension and balloon angioplasty are alternative therapeutic options.

PATHOPHYSIOLOGY AND PATHOGENESIS

CTEPH is the result of single or recurrent pulmonary emboli arising from sites of deep vein thrombosis, most commonly originating from the veins of the lower extremities although any site of venous thrombosis may be involved including those associated with long-term indwelling catheters, pacemaker leads, or ventriculoatrial shunts. The natural history of most acute pulmonary emboli is typically resolution, either complete or partial, leaving minimal, organized residual abnormalities with restoration of normal pulmonary hemodynamics, gas exchange, and exercise tolerance. Patients who ultimately develop CTEPH experience an alternative clinical course in which incomplete embolic resolution results in either complete obstruction or significant narrowing of the central pulmonary vessels by organized scar tissue sufficient to cause an increase in right ventricular (RV) afterload and compromise RV function (9). If left untreated, progressive RV failure and death may ensue. The basis for this abnormal resolution remains unclear and has been variably ascribed to the initial extent of pulmonary vascular obstruction, patient age, coexisting pulmonary disease, the quality of anticoagulation control and duration of therapy, unprovoked or recurrent embolic events, or a defect in plasmin-mediated fibrinolysis (10).

On the spectrum of chronic unresolved pulmonary embolism is the more recently designated clinical entity of chronic thromboembolic disease (CTED) or chronic thromboembolic pulmonary vascular disease (CTEPVD), which includes patients with unresolved embolism, chronic functional limitations, and a decreased quality of life in the absence of PH at rest (11).

Although incomplete recovery of perfusion after an episode of acute pulmonary embolism appears to be necessary for the initial development of CTEPH, changes in the distal pulmonary vascular bed appear to be involved in its progression. Histological studies have revealed changes in the pulmonary microvasculature similar to other forms of severe PH (12,13). Therefore, it appears to be both the central pulmonary vascular occlusion as a result of unresolved embolism and the development of secondary small-vessel vasculopathy that contribute to the progressive PH, deterioration of RV function, and decline in functional status associated with the disease.

The pathogenesis of CTEPH has yet to be fully defined. The failure of resolution of acute embolism,

which is the main event precipitating CTEPH, may be related to multiple factors including impaired fibrinolysis and fibrinogen mutations, endothelial dysfunction and defects in neoangiogenesis, differential gene expression, platelet dysfunction, and inflammation.

When fibrinogen from patients with CTEPH was compared with healthy controls, increased resistance of fibrin to plasmin-mediated lysis was noted (14). Considering there is a higher prevalence of dysfibrinogenemia in CTEPH patients resulting in irregular fibrin structure, it has been theorized that this could be part of the mechanism of thrombus nonresolution and impaired thrombolysis (15). Moreover, endothelial-related neoangiogenesis impairment in a mouse model deficient of the predominant endothelial cellular receptor for vascular endothelial growth factor resulted in incomplete thrombus resolution. Similar pathological findings in post-surgical CTEPH specimens suggest this could represent another mechanism of CTEPH pathogenesis (16). Although multiple changes in gene expression of pulmonary artery endothelial cells have been reported in CTEPH compared with normal controls, there is a paucity of data regarding the possible genetic substrate associated with CTEPH (17).

EPIDEMIOLOGY AND RISK FACTORS

Estimates of CTEPH incidence are derived from studies in which patients with acute pulmonary embolism are followed serially for the development of persistent perfusion defects and PH. The rates of case finding vary depending on the study design, geographic location of the patients involved, and the definition used (18–22). Additionally, an unknown number of patients with CTEPH may present with acute-on-chronic thrombosis, and many of the patients included in the numbers for incident CTEPH cases may represent acute presentations of an already prevalent disease (23).

In order to develop CTEPH, patients with pulmonary embolism must survive the initial event and complete adequate anticoagulation to allow resolution of the initial thrombus burden. The resolution of the initial clot after a pulmonary embolism exists on a spectrum ranging from complete restoration of normal perfusion to significant residual chronic clot that results in PH. After 6 months of anticoagulation, estimates of abnormal perfusion scans range from 30% to 50% (24,25). These persistent perfusion defects representing unresolved embolism are requisite to the development of CTEPH, and those with larger defects are more likely to develop CTEPH (25). However, the majority of these patients with persistent perfusion defects after an episode of pulmonary embolism are either asymptomatic or mildly limited with no evidence of resting PH. In approximately 10% of patients with persistent defects, resting PH develops (24).

In studies that used active surveillance after pulmonary embolism to estimate CTEPH incidence, estimates ranged between 0.1% and 8.8% within 2 years of embolism diagnosis (18–22). In 2017, Ende-Verhaar et al. (22) published a large meta-analysis of 16 studies that included 4,047 patients followed after an episode of pulmonary embolism. The overall weighted pooled incidence of CTEPH across all 16 studies was 2.3% (95% confidence interval [CI]: 1.5% to 3.1%). Two studies reported the CTEPH incidences in 1,186 “all comers” (consecutive patients with symptomatic embolism and no exclusion criteria) who had been followed for 2 to 3 years. The weighted pooled incidence of CTEPH in this group was 0.56% (95% CI: 0.13% to 0.98%). Four studies focused on unselected consecutive patients who were alive after an initial treatment period of at least 3 months. The weighted pooled incidence of CTEPH in these 999 survivors followed for a period varying from 3 months to 8 years was 3.2% (95% CI: 2.0% to 4.4%). When the 12 studies that did not include objective testing such as right heart catheterization in the case definition of CTEPH were analyzed, the CTEPH incidence increased to 6.3% (95% CI: 4.1% to 8.4%).

Although estimates vary widely and the true incidence of pulmonary embolism remains unknown, it is estimated that there are approximately 300,000 incident pulmonary embolic events per year in the United States (26). Using even the most conservative estimates of the incidence of CTEPH in survivors of acute pulmonary embolism, approximately 3,000 new cases of CTEPH should be identified per year. This conservative estimate of the incidence does not account for the 25% of CTEPH cases without an identified preceding pulmonary embolism (27). The total annual number of pulmonary endarterectomy procedures, BPA procedures, and new referrals for riociguat (the only Food and Drug Administration–approved therapy for inoperable CTEPH) does not appear to approach the expected incidence, suggesting that this condition is substantially underdiagnosed.

The risk factors associated with CTEPH can be divided into those associated with the original episode of pulmonary embolism and those factors that occur with a higher prevalence in patients with CTEPH compared with patients with idiopathic pulmonary arterial hypertension (IPAH). Two important

risk factors for CTEPH development are an unprovoked pulmonary embolism (odds ratio [OR]: 20.0; 95% CI: 2.7 to 100) and a delay in diagnosis of >2 weeks from symptom onset (OR: 7.9; 95% CI: 3.3 to 19.0) (28). RV dysfunction at the time of acute pulmonary embolism also has been associated with higher odds for CTEPH development. At the time of embolism diagnosis, an initial estimated RV systolic pressure by transthoracic echocardiography >50 mm Hg was associated with a 3.3 times higher odds of persistent PH at 12 months (29). Although unprovoked embolism, delay in diagnosis, and initial RV dysfunction are important and associated with higher ORs for the development of CTEPH, they also reiterate the difficulty of differentiating incident and prevalent CTEPH. Many patients with any of these risk factors may include an acute presentation of preexisting CTEPH rather than a true incident case or even simply an acute pulmonary embolus.

Several medical conditions are over-represented in CTEPH compared with IPAH. Although certain inherited thrombophilias such as factor V Leiden mutation and the prothrombin G20210A gene mutation increase the risk of acute venous thromboembolism, these thrombophilias are not over-represented among patients diagnosed with CTEPH (30). The only hypercoagulable state over-represented in CTEPH is the presence of antiphospholipid antibodies or the lupus anticoagulant (31). A history of infected ventriculoatrial shunts and splenectomy are both associated with high odds of CTEPH and are associated with significant inflammation and increased risk for VTE development (32). A history of malignancy is also seen more commonly with CTEPH than IPAH and is likely driven by both the hypercoagulable state associated with cancer and the risk conferred by the common use of indwelling catheters in this population. Finally, hypothyroidism is observed with increased prevalence in CTEPH compared with both acute pulmonary embolism and IPAH. The exact mechanism of hypothyroidism affecting the risk of CTEPH is unknown, but this finding is consistent in several epidemiologic surveys of CTEPH (28,31).

EVALUATION OF THE PATIENT WITH SUSPECTED CTEPH

CTEPH is defined by the presence of chronic thromboembolic material obstructing the pulmonary arteries in the setting of confirmed pre-capillary PH defined as a mean pulmonary artery pressure >20 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units in the setting of a pulmonary artery occlusion pressure <15 mm Hg (33). A high index of suspicion for CTEPH is key in initiating patient evaluation. In the international prospective registry, a median time of 14.1 months passed between symptom onset and diagnosis, and a delay in diagnosis has been demonstrated to negatively impact the prognosis from the disease process (27,32). It is likely that diagnostic delay contributes to the progression of the secondary vasculopathy that develops during the course of the disease. Given that PEA will relieve only that portion of the PH arising from the accessible component of the CTED, this component of the elevated PVR would not be correctable by surgical intervention. Approximately 25% of patients will not provide a prior history of acute embolism (27).

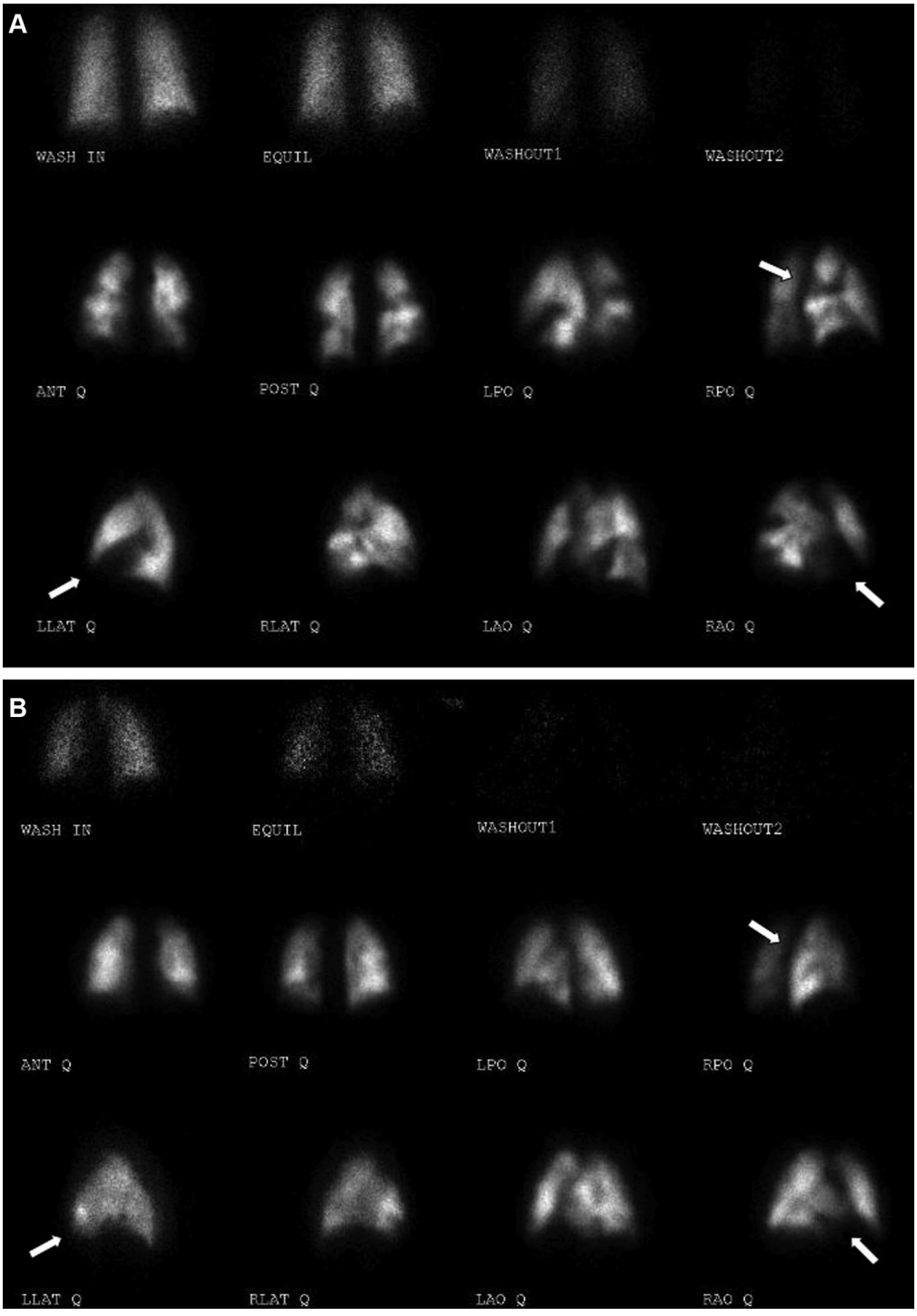
As in other forms of PH, the complaint common to patients with CTEPH is progressive exercise intolerance and/or exertional dyspnea, which physiologically appear related to a limitation in cardiac output as well as to an increased dead space ventilation (34). As the disease progresses and RV dysfunction worsens, lower extremity swelling, abdominal distention, early satiety, chest pain or pressure, and exertional light-headedness with or without syncope may also present. Hemoptysis may occur and is likely related to bronchial artery collateral circulation.

Physical examination findings early in the course of the disease may be subtle and involve little more than an accentuated second heart sound with a prominent pulmonic component. Turbulent blood flow through obstructed pulmonary arteries can cause a pulmonary flow bruit heard over the lung fields in up to 30% of patients (35). With disease progression, a murmur of tricuspid regurgitation, an RV lift or gallop, fixed splitting of S2, elevated jugular venous pressure, hepatojugular reflux, ascites, hepatomegaly, and peripheral edema may be noted.

The primary goals in the evaluation of patients with suspected CTEPH are to determine cardiac function and the degree of PH and to exclude competing diagnoses such as pulmonary artery sarcomas or other endovascular tumors; pulmonary vasculitis or congenital stenosis; in situ thrombosis associated with IPAH or structural lung disease; or extrinsic vascular compression from mediastinal fibrosis, adenopathy, or neoplasm (36).

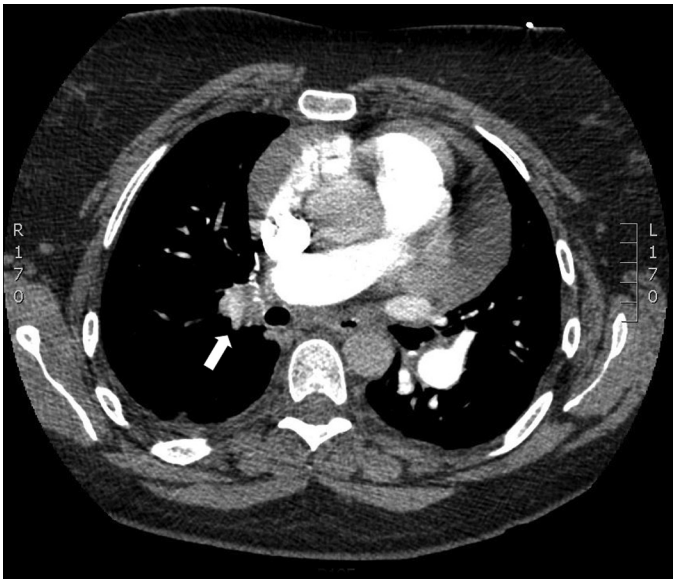
Routine laboratory tests are not particularly helpful early in the disease process but may provide prognostic information in the setting of RV or end-organ dysfunction. Electrocardiography is neither sensitive nor specific, albeit it may provide right cardiac chamber information in more advanced disease states. Chest radiography is usually unrevealing at early stages but may demonstrate enlargement of

FIGURE 1 **Pre-Operative and Post-Operative Ventilation/Perfusion Scan in Chronic Thromboembolic Pulmonary Hypertension**



(A) The pre-operative ventilation/perfusion scan reveals normal ventilation and evidence of multiple segmental defects, most notable in the anterior aspect of the left lower lobe, the right middle lobe, and the posterior aspect of the right upper lobe (**arrows**). **(B)** The post-operative scan demonstrates substantial improvement in perfusion to the affected areas.

FIGURE 2 Computed Tomography in Chronic Thromboembolic Pulmonary Hypertension



Computed tomographic pulmonary angiogram demonstrating chronic thrombus with evidence of contrast within recanalized channels in the proximal right descending pulmonary artery **(arrow)**.

the central pulmonary arteries and right cardiac chambers or asymmetry of pulmonary vasculature (37). Pulmonary function testing is mostly helpful in ruling out functional lung disease, with some CTEPH patients exhibiting mild restriction or mild to moderate decrease of their lung diffusing capacity of carbon monoxide (DLCO) (38,39).

Transthoracic echocardiography commonly provides the initial objective evidence for the presence of PH as well as estimates of RV size and function. It also can disclose valuable information regarding left cardiac chamber size and function, valvular structures, and the presence of intracardiac shunts (40,41). Although routine screening for PH in all patients after pulmonary embolism is not recommended, such a strategy should be considered in the setting of persisting symptoms (42,43).

Ventilation/perfusion (V/Q) scintigraphy continues to play a central role in the evaluation of patients with suspected CTEPH (**Figure 1**). In CTED, at least 1, and more commonly several, segmental or larger mismatched perfusion defects are present. It should be emphasized that the scan findings may underestimate the extent of pulmonary artery obstruction in cases of recanalized occlusions with re-established distal perfusion (44). In disorders of the distal pulmonary vascular bed, perfusion scans either are normal or exhibit a "mottled" appearance characterized by nonsegmental defects (45). An exception to this observation is pulmonary veno-occlusive disease in which segmental defects have been reported (46).

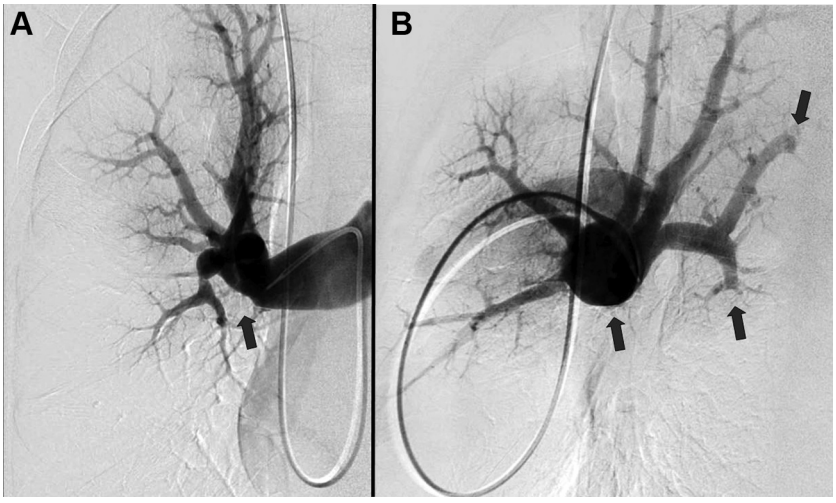
Recent studies have shown that computed tomographic pulmonary angiography (CT-PA) is an accurate method for the detection of CTEPH with excellent diagnostic efficacy (47,48). Scan findings capable of differentiating CTEPH from other variants of PH include evidence of chronic intraluminal thrombi, segmental vessel size disparity, mosaic perfusion, and collateral arteries (49) (**Figure 2**). Interpretive difficulties with CT-PA scanning persist. A recent study demonstrated that radiologists frequently miss CTEPH findings, leading to a falsely low sensitivity for CT-PA (50). Even when interpreted properly, a negative computed tomographic scan cannot exclude the possibility of CTEPH, and for this reason, V/Q scanning remains the preferred initial imaging test for screening.

Other imaging modalities including magnetic resonance pulmonary angiography and dual-energy and cone-beam computed tomography have also shown promise for detailing the pulmonary vasculature (51–53).

The final step in confirming the diagnosis of CTEPH and assessing technical suitability for surgery is right heart catheterization with selective digital subtraction pulmonary angiography (DS-PA) because it provides combined hemodynamic and radiographic disease assessment. In patients with only modest levels of PH at rest or those with CTED/CTEPVD, exercise hemodynamics with or without exhaled gas analysis can provide evidence of increasing dead space ventilation or pulmonary pressures during activity. This hemodynamic information provides objective evidence to explain an individual's symptoms and may reflect a clinically relevant stage in the development of CTEPH.

The angiographic appearance of CTED is distinct from that of acute pulmonary embolism (**Figure 3**). Well-defined, intraluminal filling defects found in acute disease are not present. Instead, the angiographic patterns encountered in CTED reflect the complex patterns of organization and recanalization that occur after an acute thromboembolic event. Angiographic findings associated with CTEPH include irregular vessel wall contour, bandlike vessel narrowing, weblike structures within the vessel lumen, early vessel tapering or disappearance, and "pouch" defects with complete obstruction and absence of large vessels (54). Because of the 3-dimensional

FIGURE 3 Digital Subtraction Pulmonary Angiogram in Chronic Thromboembolic Pulmonary Hypertension



(A) Anterior-posterior and **(B)** lateral still images from digital subtraction pulmonary angiogram are depicted. Irregularity of the inferior margin of the proximal descending right pulmonary artery with complete occlusion is shown **(arrow in A)**. The same finding is depicted in the lateral view **(central arrow, B)** as well as more distal-level obstructions in the subsegments of a large, posterior segment of the right upper lobe artery **(peripheral arrows, B)**.

nature of the pulmonary vascular bed and the 2-dimensional images generated by DS-PA, biplane imaging has been shown to be useful in affected area identification. It is strongly recommended that right heart catheterization with DS-PA be performed at a CTEPH center with relevant procedural and interpretive expertise in order to obtain optimal data and to avoid the need for repetition of invasive testing (55).

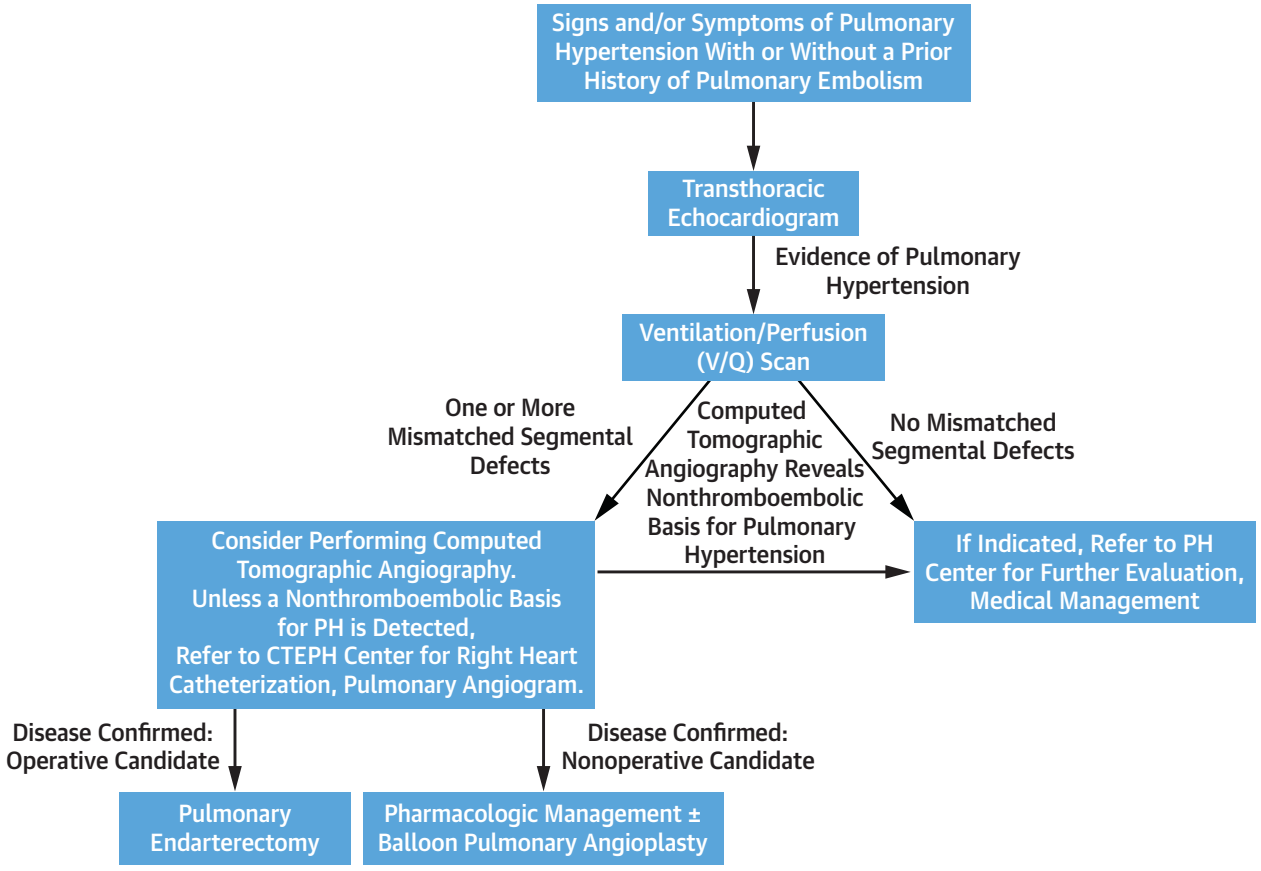
In summary, the possibility of CTEPH should be considered in any patient with unexplained dyspnea regardless of whether there is a documented history of acute embolism and an appropriate evaluation undertaken (**Central Illustration**). Echocardiography can provide a noninvasive assessment of right and left ventricular function, peak pulmonary artery pressure, mean right atrial pressure, and the severity of tricuspid regurgitation. Even a single segmental or larger mismatched defect on V/Q scanning supports the possibility of CTEPH, whereas a normal perfusion scan can exclude it. Computed tomographic scanning can provide complementary information and help exclude competing diagnostic possibilities. Once the diagnosis of CTEPH has been made, referral to a center experienced in determining the potential for PEA or other forms of management should then be undertaken.

SURGICAL SELECTION AND MANAGEMENT

CTEPH has long been recognized as a surgical disease and PEA, variably referred to as pulmonary thromboendarterectomy, offers the potential for cure with peri-operative mortality rates of <5% at experienced surgical centers (56). Guidelines from the World Symposium on Pulmonary Hypertension 2018 and the 2015 European Society of Cardiology/European Respiratory Society recommend PEA be offered to all CTEPH patients who are surgical candidates (42,57).

The evaluation of potential surgical patients should be undertaken by an experienced multidisciplinary team. Determining surgical candidacy involves 2 separate processes: 1) an evaluation of technical operability; and 2) an assessment of the potential risks and benefits of surgery. Technical operability depends on both the anatomic location of the CTED and the skill and experience of the surgeon. An intraoperative classification of the disease based on the most central component of the occluding thrombus, which is reflective of the difficulty of the procedure, has been developed. Level I defines disease involving the main pulmonary arteries, level II the lobar branches, level III the segmental branches, and level IV the subsegmental arteries (58). With advances in imaging and surgical experience, patients

CENTRAL ILLUSTRATION **Diagnostic Algorithm**



Papamatheakis, D.G. et al. J Am Coll Cardiol. 2020;76(18):2155–69.

A diagnostic algorithm for a patient with unexplained dyspnea or suspected chronic thromboembolic disease regardless of whether there is a prior documented history of acute pulmonary embolism.

with more distal disease (levels III and IV) are able to successfully undergo PEA at expert centers.

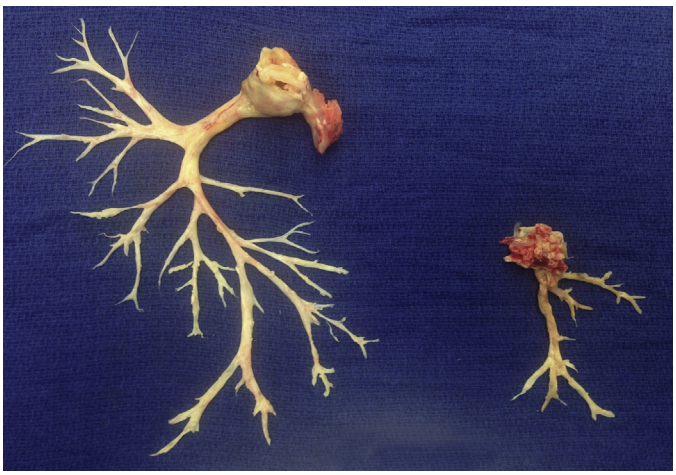
If the CTED is determined to be technically operable, the next consideration is to estimate the potential likelihood of hemodynamic and symptomatic improvement. Initially, symptomatic PH represented the sole indication for surgery. Recently, there has been increased interest in applying the procedure to patients with CTED or CTEPVD (11). Even in the absence of resting PH, these patients may have functional limitations due to increased dead space ventilation or an abnormal pulmonary hemodynamic response during exercise and may benefit from the procedure (59-61).

The assessment of surgical candidacy must also include an evaluation of peri-operative risk. Absolute contraindications are few and include the presence of significant parenchymal lung disease in areas that would reperfuse with surgery. The presence of comorbid conditions, with the exception of those that are terminal or end stage, do not represent an absolute contraindication to pulmonary endarterectomy. The increased risks imposed by coexisting conditions on both peri-operative and long-term outcomes are weighed against the potential symptomatic benefits of PEA, and these are carefully reviewed with the patient before the decision is made to proceed to surgery. Risk factors for a less favorable outcome after PEA surgery, although not absolute contraindications, include an absent history of deep vein thrombosis or pulmonary embolism, World Health Organization functional class IV, right heart failure, a

PVR >1,200 dynes · s/cm^5 (15 Wood units), inconsistent radiologic testing, absence of appreciable lower lobe disease, and significant pulmonary or left heart disease (57).

Successful resection of organized thromboembolic material tightly adherent to and incorporated within the pulmonary artery wall requires an experienced surgeon able to identify the correct dissection plane and perform a complete endarterectomy typically to the level of the segmental and subsegmental arteries (**Figure 4**). The procedure is performed through a median sternotomy on cardiopulmonary bypass with the use of profound hypothermia. Considerable enhancement of the bronchial arterial circulation is a well-recognized feature of CTEPH, and the endarterectomy procedure is performed during periods of complete circulatory arrest to avoid backflow of blood from these systemic to pulmonary artery collaterals, which can obscure the surgical field (62,63). Closure of atrial septal defects, coronary artery bypass grafting, and valvular procedures can also be performed if necessary at the time of the procedure (64).

FIGURE 4 Pulmonary Endarterectomy Surgical Specimen



An example of thromboembolic material obtained at the time of pulmonary endarterectomy surgery. Note the fibrotic nature of the chronic thrombus and the extension into multiple segmental and subsegmental branches, complete removal of which is required for an optimal hemodynamic outcome.

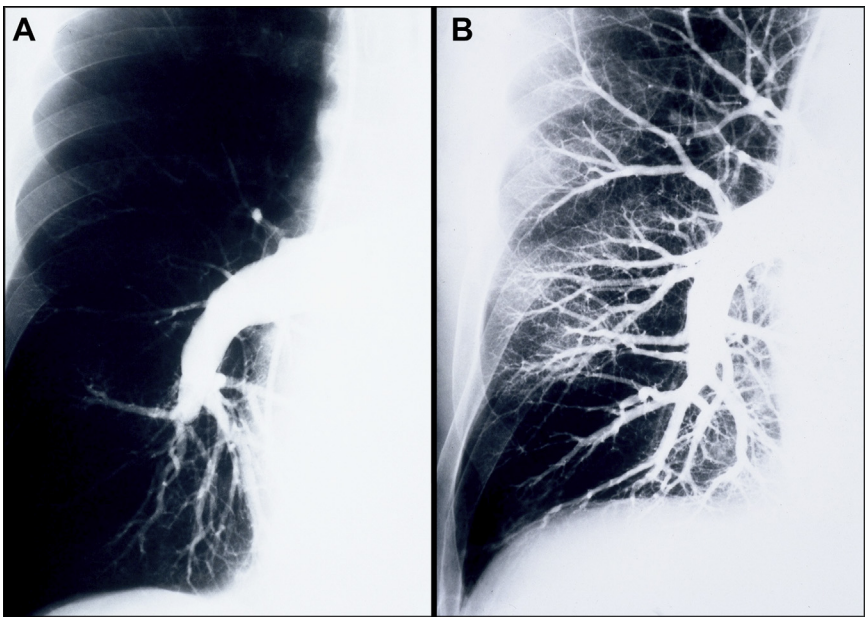
In addition to the usual complications associated with cardiac surgery, hypoxemia is common after PEA surgery and may result from a transient redistribution of blood flow from previously unobstructed arteries to endarterectomized segments resulting in a steal phenomenon and increased V/Q mismatch (65,66). More severe hypoxemia can be seen as a result of reperfusion pulmonary edema, a high permeability edema that develops in segments undergoing reperfusion and that typically develops within the first 72 h of surgery (67). The management of reperfusion pulmonary edema includes diuresis to reduce lung water, avoidance of a high cardiac output, and usual intensive ventilatory and supportive care (68). Inhaled nitric oxide or prostacyclin may improve V/Q matching, and extracorporeal life support may be required when less aggressive interventions fail (69–71).

Surgical resection of the occluding thromboembolic material re-establishes flow to the previously occluded vascular segments (**Figure 5**). Most patients experience significant hemodynamic improvement, and this is seen immediately after surgery (72–74). Post-operative PH, notably a PVR >500 dynes · s/cm^5 (6.25 Wood units) due to an incomplete endarterectomy or distal small-vessel vasculopathy, remains a significant cause of post-operative morbidity and mortality and supports the need for meticulous preoperative evaluation and experienced surgical management (75,76). A single center reported a mortality of 10.3% in those with significant residual PH versus 0.9% in those without, and the European registry reported a higher early mortality (16.7%) in patients with residual PH (73,74).

Less severe residual PH is not uncommon after PEA surgery, but most patients experience significant improvement in symptoms with no adverse effect on medium-term survival (77,78). The threshold that defined clinically significant residual PH was unclear until the publication of a study from Papworth Hospital (Cambridge, UK) in which only a moderate correlation between immediate post-operative hemodynamics and those obtained 3 to 6 months after surgery was observed (79). At that time point, 51% of patients undergoing the procedure had a mean pulmonary artery pressure (mPAP) >25 mm Hg, but the majority maintained a good long-term functional status. However, those with an mPAP >38 mm Hg and a PVR >425 dynes · s/cm^5 (5.3 Wood units) on reassessment had a worse long-term survival, thereby helping stratify patients into a group that requires close follow-up and perhaps additional interventions.

Multiple case series from experienced centers have confirmed the long-term benefits of PEA surgery reporting sustained improvement in hemodynamics, exercise capacity, and functional status (78–82). Considering the complexity of the procedure and the

FIGURE 5 Pre-Operative and Post-Operative Pulmonary Angiogram



(A) Pre-operative and **(B)** post-operative anterior-posterior contrast pulmonary angiograms are depicted. The pre-operative study demonstrates absent perfusion to the right upper and middle lobes with diminished lower lobe flow. The post-operative study demonstrates a dramatic improvement in right-sided vascular perfusion.

prognosis of the disease without intervention, 30-day mortality rates have fallen to the range associated with coronary artery bypass grafting. The University of California, San Diego group has reported a 2.2% in-hospital mortality and long-term survival rates of 82% at 5 years and 75% at 10 years (74). Similar short-term and long-term survival rates have been reported from the United Kingdom and other national centers.

MEDICAL THERAPY

After the diagnosis of CTEPH, patients should receive standard medical therapy for PH including diuresis for volume overload and supplemental oxygen for hypoxemia when indicated. Lifelong anticoagulation therapy is recommended to avoid recurrent embolism or the possibility of in situ thrombosis in this at-risk group with an already compromised pulmonary vascular bed. The ideal choice of anticoagulation agent has not been established. In patients with concomitant antiphospholipid syndrome, vitamin K antagonist therapy appears safer than the direct oral anticoagulant rivaroxaban (83). Retrospective data suggest that the use of post-PEA direct oral anticoagulant therapy resulted in a higher incidence of venous thromboembolism recurrence compared with vitamin K antagonist (4.62%/person-year vs. 0.76%/person-year) without a survival difference (84). Although there are emerging data regarding the efficacy of direct oral anticoagulant therapy in acute thromboembolic disease, this finding supports the need for a prospective assessment of the optimal anticoagulant regimen in CTEPH, both before and after PEA surgery. Antiplatelet agents and thrombolytic therapy are not indicated in the treatment of CTEPH, and the use of inferior venal cava filters before PEA has not been formally studied. Most expert centers forego the placement of an inferior vena cava filter before PEA, primarily based on international registry data indicating no effect on long-term survival (78).

A major rationale for pulmonary arterial hypertension (PAH)-targeted therapy in CTEPH comes from the recognition of the microvascular arteriopathy that may develop in CTEPH (12,13). Limited access to expert pulmonary endarterectomy centers resulted in a compelling medical treatment rationale for patients experiencing CTEPH. Early clinical trials for inoperable CTEPH included the AIR study (Aerosolized Iloprost Randomized Study) in which 57 patients with inoperable CTEPH were combined with collagen vascular disease and appetite-suppressant PAH

TABLE 1 Randomized Clinical Trials of Pharmacotherapy in Patients With Chronic Thromboembolic Pulmonary Hypertension

Medication	FDA Approved for CTEPH Indication	Medication Class	Study (Ref. #)	Participants	Outcome
Riociguat	Yes	Soluble guanylate cyclase stimulator	Chest-1 (6)	261	Significant improvement in PVR and 6-MWD at 16 weeks
Bosentan	No	Dual endothelin receptor antagonist	Benefit (5)	157	Significant improvement in PVR, no significant improvement in 6-MWD at 16 weeks
Macitentan	No	Dual endothelin receptor antagonist	Merit (7)	80	Significant improvement in PVR and 6-MWD at 16 weeks
Ambrisentan	No	Selective endothelin receptor antagonist	Amber 1 (89)	33*	Trend toward improvement in 6-MWD and PVR at 16 weeks
Sildenafil	No	Phosphodiesterase-5 inhibitor	Suntharalingam (87)	19	Significant improvement in PVR, no significant improvement in 6-MWD at 12 weeks
Subcutaneous treprostinil	No	Prostacyclin analog	CTREPH (88)	105	Significant improvement in PVR and 6-MWD at 24 weeks
Inhaled iloprost	No	Prostacyclin analog	Air Trial (85)	203	Significant improvement in PVR and 6-MWD at 12 weeks

*Trial terminated early due to futility of enrollment.

6-MWD = 6-min walk distance; CTEPH = chronic thromboembolic pulmonary hypertension; FDA = Food and Drug Administration; PVR = pulmonary vascular resistance.

patients and randomized between iloprost versus placebo for 12 weeks (85). Although the treatment arm met the primary endpoint (12.5% vs. 4.3% for the placebo arm), the magnitude of improvement was lower in patients with CTEPH compared with that in the cohort of patients with PAH. Two early clinical trials using sildenafil were also undertaken, one an open-label, uncontrolled trial involving 104 patients and the other a double-blind, placebo-controlled trial involving 19 patients. In both studies, treatment with sildenafil resulted in significant hemodynamic and functional improvement (86,87).

The first randomized controlled trial dedicated to CTEPH was undertaken with the dual endothelin receptor antagonist bosentan in the BENEFIT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) study (5). In this study, 157 patients with technically inoperable CTEPH or residual PH after PEA were randomized to receive either bosentan or placebo for 16 weeks. The coprimary endpoints were changes from baseline in PVR and the 6-min walk distance (6-MWD). Despite a reduction in PVR from baseline (−24.1% treatment effect), there was no significant change in 6-MWD with bosentan therapy compared with placebo.

The CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1) study with the soluble guanylate cyclase stimulator riociguat included 261 patients with inoperable CTEPH or residual PH at least 6 months after pulmonary endarterectomy randomized to receive riociguat or placebo (6). There was a +46 meter treatment effect with riociguat with additional secondary endpoints met, including a reduction in PVR and N-terminal pro-B-type natriuretic peptide and improvement in functional class. This led to riociguat becoming the first medical therapy approved for the treatment of inoperable CTEPH.

There have been 3 other subsequent randomized trials with PAH therapy in inoperable CTEPH. The MERIT-1 (Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension) trial was a phase 2 study with the dual endothelin receptor antagonist macitentan for technically inoperable CTEPH in which 80 patients were randomized to receive macitentan versus placebo (7). Unlike previous studies, patients were allowed to be on a background phosphodiesterase-5 inhibitor or inhaled/oral prostanoid therapies. The primary endpoint of change from baseline PVR showed a 16% treatment effect in favor of macitentan. The secondary endpoint of 6-MWD was measured at 24 weeks and revealed a +34 meter improvement with treatment. The CTREPH (Subcutaneous Treprostinil for the Treatment of Severe Non-operable Chronic Thromboembolic Pulmonary Hypertension) trial compared low-dose subcutaneous treprostinil infusion therapy (3 ng/kg/min) versus higher dose (30 ng/kg/min) in a mixed CTEPH population including those refusing pulmonary endarterectomy (88). At 24 weeks, the primary endpoint of change in 6-MWD revealed a treatment effect of +40 meters in favor of higher-dose treprostinil. The Amber 1 trial compared ambrisentan versus placebo in 33 patients with inoperable CTEPH. Although the study was terminated early due to futility of enrollment, positive trends in 6-MWD, PVR, and N-terminal pro-B-type natriuretic peptide were noted (89).

In summary, a variety of pharmacological treatment options (**Table 1**) targeting key pathways in the pathology of PAH are available for patients with either inoperable CTEPH or those with residual post-

PEA pulmonary hypertension, although only riociguat is currently Food and Drug Administration approved for these indications (90). There is currently no evidence to support using riociguat or other PAH therapies before PEA in patients with operable CTEPH, and all potentially eligible patients should be referred to an expert center for evaluation, early PEA if they are deemed to be an operative candidate, and consideration of other management strategies if they are not. The next phase of PH-targeted medical therapy in CTEPH will need to address the following areas of interest: 1) the potential for combination medical therapy targeting different pathways; 2) the timing of drug administration and its relationship with BPA; and 3) the benefits of multimodal therapy (medical therapy and/or BPA) compared with PEA for high-risk operable cases.

BALLOON PULMONARY ANGIOPLASTY

Pulmonary endarterectomy is the treatment of choice for patients with CTEPH who are considered operable. However, depending on center experience, up to 40% of patients with CTEPH are not candidates for the procedure (27). For these patients as well as those who have residual PH after PEA surgery, BPA has emerged as an important component of the CTEPH treatment algorithm (57). BPA is a percutaneous treatment performed through central venous access, which disrupts chronic clot, dilates pulmonary blood vessels, and restores blood flow to occluded or flow-limited lung segments. BPA has resulted in durable improvement in hemodynamics, symptoms, exercise capacity, and RV function (8,91–97). Eligibility for BPA should be assessed and the procedure performed at experienced, high-volume CTEPH centers. The rationale for BPA selection includes patients who are technically inoperable, have an unfavorable risk/benefit ratio for PEA, or have persistent/recurrent PH after PEA.

Balloon pulmonary angioplasty is performed under conscious sedation with patients breathing spontaneously. Central venous access is achieved through the femoral (preferred) or internal jugular approach with a short sheath (98,99). A long sheath is placed through the short sheath and positioned in the vascular segment of interest. Target vessels are selected based on perfusion imaging, CT angiography, and selective angiography performed during the procedure. Although lower lobe vessels are preferentially treated, all lung segments should be imaged and treated to gain maximum benefit from the procedure. Patients are anticoagulated during BPA to an activated clotting time of 200 to 250 s. Multiple procedures, typically ranging from 4 to 6, are required to treat all lung segments and to allow time for remodeling to occur in order to achieve the maximal hemodynamic effect.

Pulmonary angioplasty has been demonstrated to improve pulmonary hemodynamics, exercise capacity, functional status, quality of life, and oxygen requirements (8,100–104). Among patients in a multicenter Japanese registry, mPAP decreased from 43.2 ± 11.0 to 24.3 ± 6.4 mm Hg, 6-MWD improved from 318.1 ± 122.1 to 401.3 ± 104.8 meters, BNP was reduced from 239.5 ± 334.2 to 43.3 ± 76.4 pg/ml, and the procedure was associated with a significant reduction of PH-targeted therapy and oxygen supplementation (94). One of the early criticisms of the Japanese BPA experience was that patients selected for BPA had operable CTEPH, and, if available, PEA would have been the appropriate treatment. Despite the differences in patient selection, experienced CTEPH centers in Europe have demonstrated impressive, albeit less robust, results. German centers reported an 18% decline in mPAP, a 26% decline in PVR, and a 33-m improvement in 6-MWD (105). Similar early results were reported from France during their initial BPA experience, and in their most recent series, reductions in mPAP by 30% and PVR by 40% were achieved (106).

The rate of complications associated with BPA has decreased dramatically over time. In the first BPA case series published in 2001, 61% of patients developed reperfusion edema, 17% required mechanical ventilation, and there was a 5.6% procedure-related mortality (107). With refinements in the procedure, the complication rates improved as demonstrated in a multicenter registry of 7 Japanese centers including 308 patients who underwent a total of 1,408 BPA procedures from 2004 to 2013 (95). In this registry, complications occurred in 36% of patients, including vascular injury in 17.8%, hemoptysis in 14%, and pulmonary artery perforation in 2.9%, whereas 30-day, procedure-related mortality was only 2.6%. Current complication rates reported at centers in Japan, Europe, and the United States are even lower, with nonsevere complications ranging from 9% to 12% and procedure-related mortality under 3% (105–110). Complications most frequently occur during the procedure and are related to vascular injury from wire perforation, balloon dilation, and high-pressure contrast injection (98). Less commonly, complications occur after the BPA procedure and can include reperfusion pulmonary edema, hemothorax secondary to unrecognized wire perforation, and complications at the access site.

Compared with PEA, there is less robust long-term follow-up data for patients who undergo BPA, although the available data suggest durability of BPA treatment outcomes. A single Japanese center reported that at a follow-up of more than 3.5 years, improvements in mPAP and PVR were preserved with 3- and 5-year survival of 98% and 95.5%, respectively (93). Similar 3-year survival rates were reported in the multicenter Japanese registry (94). Ongoing BPA registries, international and nation/region specific, will provide additional long-term data in the coming years.

CONCLUSIONS

CTEPH remains the only type of PH that is potentially remedial by surgical intervention. In this review, we described what is currently understood about the pathophysiology and pathogenesis of the disease, examined its epidemiology and risk factors, and delineated the diagnostic approach in patients suspected of having the disease. We also examined disease management including the preferred surgical approach for those deemed operative candidates and PAH-targeted pharmacotherapy and BPA for those who are not operative candidates and for those with post-PEA residual pulmonary hypertension. Nevertheless, multiple questions regarding the disease process and its management remain unanswered. In addition to fostering basic and translational research to better understand the pathogenetic mechanisms of CTEPH, additional clinical studies to improve CTEPH recognition and disease management are still required as an era of multimodal therapy involving pulmonary endarterectomy, pharmacotherapy, and BPA is entered.

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