Contemporary Reviews in Cardiovascular Medicine

Update on Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct pulmonary vascular disease caused by chronic obstruction of major pulmonary arteries that is amenable to cure by pulmonary endarterectomy (PEA). Main features of CTEPH as opposed to pulmonary arterial hypertension (PAH) are a nonhomogeneous distribution of disease in segments of the pulmonary vascular tree and its association with venous thromboembolism (VTE). Although the exact prevalence and annual incidence of CTEPH are unknown, recent data from the United Kingdom suggest that this condition may occur in ≈5 individuals per million per year,[1] making CTEPH one of the most common subsets of precapillary pulmonary hypertension (PH). Still, CTEPH remains an orphan disease. Given that CTEPH is potentially curable by a complete PEA, the authors surveyed all major centers in Europe and the United States, and the results confirm prior concerns regarding adequate diagnosis and treatment of CTEPH. There are currently 1.7 PEAs per million of population performed in Europe annually compared with 0.9 in the United States. Although these numbers represent a steady increase over the last several years, they underscore the underdiagnosis of the disease, as well as a common delay or lack of referral to expert centers for surgery. Education of physicians to identify CTEPH as a potential diagnosis and training of PEA surgeons to master the techniques of a complex and challenging operation must be supported by worldwide educational activities.

Since the last comprehensive review on CTEPH in *Circulation* in 2006,[2] several milestones in CTEPH research and management have been reached. Those have been set by (1) the International CTEPH Association, which was founded in 2006 as "Association for Research in CTEPH" with the goal to increase awareness, foster worldwide collaboration among centers, provide a platform for surgical centers, establish the European and International CTEPH registries, facilitate training of emerging centers, and advance basic and translational research in CTEPH; (2) the 2008, 2011, and 2014 International Scientific and Educational Workshops in CTEPH in Vienna, Austria, Cambridge, UK, and Paris, France bringing together international groups of experts in the field of CTEPH research; (3) modification and refinement of surgical techniques in addressing patients with distal disease, thereby improving outcomes and availability of the procedure for patients who

may have been considered nonoperable in the past; (4) the Fifth World Symposium on Pulmonary Hypertension in Nice, France, in February 2013; and (5) the approval of the first drug for the treatment of nonoperable CTEPH and persistent/recurrent PH after PEA in October 2013. Scientific advances have been spearheaded by deeper insights into the biology of thrombus resolution,[3,4] the characterization of the European CTEPH population,[5] the definition of the "CTEPH team,"[6] the proof of safety of deep hypothermic circulatory arrest during PEA,[7,8] and the technical refinement of balloon pulmonary angioplasty (BPA)[9] by Japanese investigators.[10–13] It is to be expected that these milestones will lead to a better understanding of CTEPH. In addition, a change in treatment paradigms may evolve that may particularly benefit nonoperable patients[5] who have been labeled as "no-option" patients in the past.

Epidemiology and Definition

CTEPH has been reported as a long-term complication of pulmonary embolism (PE) with a cumulative incidence between 0.1% and 9.1% after symptomatic PE (Table 1). CTEPH as a direct consequence of symptomatic PE is rare, and a significant number of CTEPH cases develop in the absence of previous acute PE. The low incidence after acute PE and the large margin of error are due to referral bias, paucity of early symptoms, and difficulty in differentiating acute PE from an acute episode of PE on top of preexisting CTEPH. Therefore, routine screening for CTEPH in asymptomatic patients after acute PE is not reasonable and not feasible. Still, the thromboembolic nature of the disease is not questioned today.[26] In the large European database, a history of acute PE was evident in 74.8% of patients.[5]

In the recent Nice classification, CTEPH again represents group 4 PH.[27] CTEPH is defined as precapillary PH by invasive right heart catheterization (mean pulmonary artery pressure ≥25 mm Hg, mean pulmonary arterial wedge pressure ≤15 mm Hg) in the presence of chronic/organized flow-limiting thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least 3 months of effective anticoagulation.[28] Appositional red thrombus may be present (Figure 1). Some patients, particularly those with complete unilateral obstruction, may present with normal pulmonary hemodynamics at rest despite symptoms. This is an important, although small, group of patients that can benefit from

PEA. They might be classified as cases of chronic thromboembolic pulmonary vascular disease. Although current practice in major centers is to perform exercise tests, there is still insufficient evidence to add an exercise criterion to the definition of CTEPH in this population. However, recent data suggest that even at rest, the right ventricle is not adapted to its afterload in chronic thromboembolic pulmonary vascular disease despite normal pressures at rest.[30]

Mechanisms of Disease

One of the limitations of CTEPH research is the difficulty to reproduce the disease in animal models.[31] Repeated thromboemboli resolve quickly,[32,33] necessitating clot modification before pulmonary embolization in both the canine[34] and the porcine models.[35]

The hallmark of CTEPH is fibrotic transformation of pulmonary arterial thrombus, leading to mechanical obstruction of pulmonary arteries.[28] Unlike in acute PE, there is no linear correlation between the degree of mechanical obstruction and hemodynamics[36] because of a concomitant small-vessel pulmonary arteriopathy (Figure 2). Although rare cases of combined coagulation defects[38] suggest a genetic trait, no PAH-specific mutations have been identified in CTEPH.[39]

Thrombophilia and CTEPH

Traditional risk factors for VTE include antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, plasminogen deficiency, and anticardiolipin antibodies.[40] However, in 147 consecutive patients with CTEPH, the prevalence of hereditary thrombotic risk factors was not increased compared with 99 consecutive patients with idiopathic PAH or 100 controls.[41] Lupus anticoagulant occurs in ≈10% of CTEPH patients, and 20% of patients carry antiphospholipid antibodies, lupus anticoagulant, or both.[42] Furthermore, plasma level of factor VIII, a protein associated with both primary and recurrent VTE,[43] was elevated in 39% of patients with CTEPH.[42] No abnormalities of systemic fibrinolysis were identified,[44] yet imbalances of cell-bound fibrinolysis-associated proteins were found.[45,46] In a previous pathology series, 15% of patients had an underlying autoimmune or hematologic disorder (eg, polycythemia vera).[47] Blood group types A, B, and AB were significantly more common in patients with CTEPH compared with patients with PAH (88% versus 56%)[48] and compared with the general European population (http://www.redcross.eu). The ABO locus is a known susceptibility locus for VTE,[49] and non-O blood group carriers share a higher risk for VTE than O carriers. Non-O blood group carriers also have higher levels of von Willebrand factor and factor VIII, 2 known risk factors for VTE[50]; this is probably one of the mechanisms by which blood group is related to the risk of VTE[51,52] and CTEPH.[42] Elevated plasma levels of lipoprotein(a), a subgroup of the low-density lipoproteins with high atherogenicity, suggest an overlap of venous and arterial thrombotic risk factors.[53]

Risk Factors and Associated Conditions

Specific risk factors for VTE have been identified as risk factors for CTEPH. Previous splenectomy, the presence or history of infected ventriculoatrial shunts for the treatment of hydrocephalus, indwelling catheters and leads,[54] thyroid replacement

Table 1. Cumulative Incidence of CTEPH Based on Clinical Follow-Up of Patients With Acute Pulmonary Embolism

Reference	No. of Patients With Acute Pulmonary Embolism	Average Observation Time After Acute Event, mo	Cumulative Incidence of CTEPH, %
Long-term outcomes in acute pulmonary thromboembolism: the incidence of chronic thromboembolic pulmonary hypertension and associated risk factors[14]	325	16.3	4.6
Echocardiographic assessment of pulmonary arterial pressure in the follow-up of patients with pulmonary embolism[15]	744	14	8.3
Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension[16]	110	24	9.1
Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism[17]	877	34	0.57
Active search for chronic thromboembolic pulmonary hypertension does not appear indicated after acute pulmonary embolism[18]	110	36	2.7
Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism[19]	239	36	0.4
Prevalence of chronic thrombo-embolic pulmonary hypertension after acute pulmonary embolism: a prospective multicenter study[20]	700	26	4.7
Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism[21]	91	6–12	8.8
Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism[22]	259	46	1.0
Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism[23]	834	25	1.0
Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism[24]	314	94.3	3.8
Pulmonary embolism: one-year follow-up with echocardiography Doppler and five-year survival analysis[25]	78	12	5.0

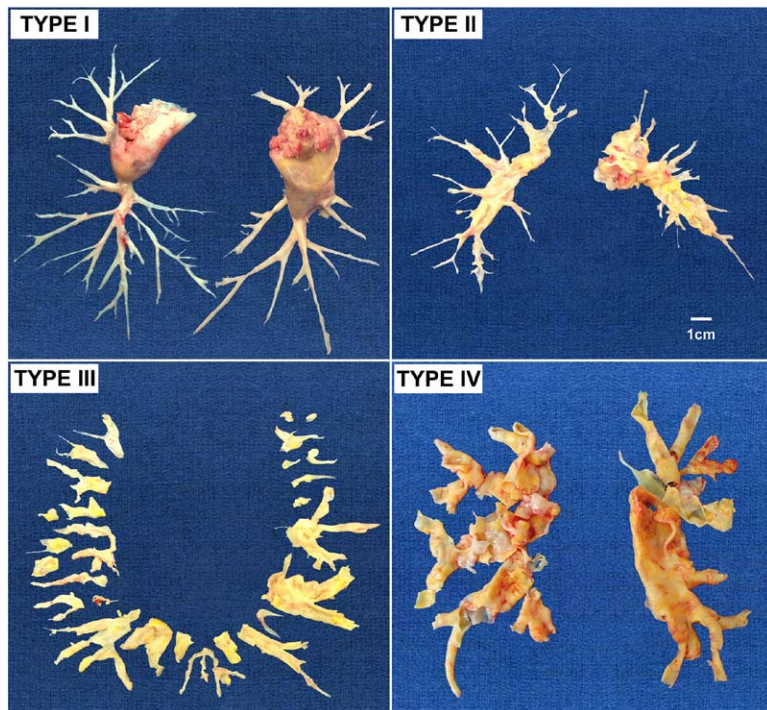CTEPH indicates chronic thromboembolic pulmonary hypertension.

Figure 1. University of California–San Diego surgical classification (Jamieson) of pulmonary endarterectomy specimens.[29] Typical surgical specimens classified by the most proximal level of obstruction for types I through III are shown. In type I disease (12% of cases), major-vessel clot is present and readily visible on opening the pulmonary artery. In type II disease (38% of cases), no major-vessel thrombus is present, but there is evidence of thickened intima with webs in the lobar branches. In contrast, in type III disease (39.4% of cases,) very distal disease, confined only to segmental and subsegmental branches, is encountered. Type IV disease refers to a very small subgroup of patients (7.6%) in whom despite a complete surgical exploration and intimectomy of the vascular tree, there is no evidence of thromboembolic material.

therapy, cancer, and chronic inflammatory disorders, such as osteomyelitis and inflammatory bowel diseases, are significantly associated with CTEPH[48,55] and have a negative impact on survival.[56] Experimentally, it has been demonstrated in an animal model that staphylococcal infection delays thrombus resolution.[57] Patients suffering from moderate hypothyroidism are at an increased risk of thrombosis.[58] In addition, treatment with levothyroxin increases von Willebrand factor levels and shortens in vitro platelet plug formation, measured as collagen/epinephrine-induced closure time.[59]

Vascular Biology
CTEPH is a dual vascular disorder, with major-vessel vascular obliteration (Figure 2C) and, in an unknown proportion of patients, a peripheral pulmonary arteriopathy resembling classic PAH (Figure 2A). A current understanding of CTEPH pathogenesis is that of "inflammatory thrombosis,"[28] in which disorders of coagulation,[38,42,60–62] sticky red blood cells,[63] and uncleavable fibrinogen variants[62] are modified by immunologic, inflammatory, or infectious mechanisms that trigger pathological remodeling of major (Figure 2C and 2D) and small pulmonary vessels (Figure 2A and 2B). One of the explanations for abnormal thrombosis in CTEPH may be increased plasma levels of microparticles and anionic phospholipids as a consequence of splenectomy[64] and presumably as a consequence of infection and cancer.

The pathogenesis of "secondary vascular disease" in CTEPH is much less explored.
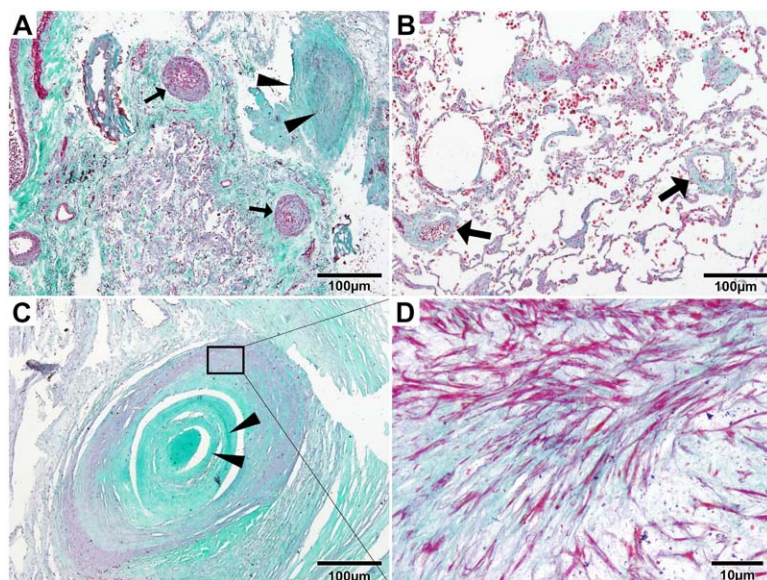

Figure 2. Fibrotic vascular remodeling of chronic thromboembolic pulmonary hypertension. Lung biopsies (**A** and **B**) from a patient undergoing pulmonary endarterectomy and the respective pulmonary endarterectomy specimens (**C** and **D**) were fixed, sectioned, and treated with a modified trichrome stain in which collagen is green and smooth muscle cells and fibroblasts appear red. Severe concentric intimal hyperplasia is seen in lung sections of "open" vascular areas (**A**, small arrows). By contrast, vascular changes are mild in areas distal to an occluded pulmonary artery (**B**, large arrows). Vascular occlusions also occur within thrombus vessels (**A**; arrowheads point to concentric layers of collagen that can also be seen in vessels of the lung). Magnification of the boxed area in **C** shows cells resembling myofibroblasts[37] that are embedded in a collagen matrix (green staining in **D**).

Major-Vessel Disease

In contrast to the almost complete resolution of acute pulmonary thromboemboli commonly within 6 months,[65] thromboemboli in CTEPH undergo an organization process with permanent fibrotic obstruction of the pulmonary vascular bed (Figure 2), which has led to speculations about a nonthromboembolic intrinsic pulmonary vascular process.[66] Vascular lesions are characterized by organized thrombi tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries, replacing the normal intima and expressing high levels of plasminogen activator inhibitor type 1, a major fibrinolysis inhibitor in endothelial cells adjacent to in situ thrombi.[45] Collateral vessels from the systemic circulation (from bronchial, costal, diaphragmatic, and coronary arteries) can grow to reperfuse areas distal to complete obstructions[67] and have been shown to contribute to vascularization of major-vessel organizing thrombus.

In a large series of thromboembolic obstructions analyzed at the University of California–San Diego, remodeling of thrombi at various stages was observed.[68] In 13% of cases, significant inflammation was noted.[69] Inflammatory cells appear at the thrombus attachment sites to the endothelium.[70] Recently, the sequence of events that promote deep vein thrombosis was analyzed with the use of variations of the murine vena cava ligation model.[3] In the same model, genetic deletion of platelet endothelial cell adhesion molecule 1[4] illustrated the crucial roles of leukocyte migration and angiogenesis[71] in resolution of deep vein thrombosis and resolution of thrombus in CTEPH. Despite all of this evidence, one must bear in mind the limitations of studying thrombosis and thrombus resolution in animals or in in vitro models.

Microvascular Disease

Microvascular disease is generally considered a major contributor to the progression of disease over time and is a major determinant of postoperative outcome after PEA. Mechanisms for disease may involve the following processes: (1) predominant obstructions of subsegmental elastic pulmonary arteries (Figure 2A, arrowheads); (2) classic pulmonary arteriopathy of small (<100 μm in diameter) arteries and arterioles distal to nonobstructed vessels (Figure 2A, small arrows); and (3) pulmonary arteriopathy of small muscular arteries and arterioles distal to totally or partially obstructed vessels (Figure 2B). Commonly, intermediate forms between plexiform and thrombotic lesions are found.[72] Shear stress, pressure, inflammation, and the release of cytokines and vasculopathic mediators may be triggers of arteriopathy. Details remain unclear, however, deserving further investigation on lung biopsies from patients undergoing PEA.[68,73]

Hemodynamics and Right Ventricular Function

As a general rule, mean pulmonary artery pressure is lower in CTEPH than it is in PAH,[74] despite similar pulmonary vascular resistance (PVR),[74] which has led to the assumption that right ventricular adaptation may be poorer than in PAH patients, presumably because of the generally older age of CTEPH patients.[75] A higher pulse pressure has been reported in CTEPH patients[76] as a result of obstruction and increased stiffness of the proximal arteries, corresponding to increased exponential pressure decay in the pulmonary artery during diastole. Therefore, right ventricular stroke work is increased,[77] which may explain differences in mean pulmonary artery pressures and a decreased RC time constant in CTEPH compared with PAH patients.[78] PEA has been shown to lead to an immediate decrease in PVR and concordant increase in pulmonary arterial compliance under a mild further decrease of RC time.[78,79] PVR measured immediately after surgery was identified as the only independent predictor of long-term survival/freedom of lung transplantation after PEA. Patients with immediate postoperative PVR <590 dyne·s/cm^5 had better long-term outcomes than patients with PVR ≥590 dyne·s/cm^5.[79] In other series, patients with a

Table 2.   Patient Characteristics: Japanese Compared With European and University of California–San Diego CTEPH Populations

Parameters	Japanese Registry[12]	International Registry[5]	University of California–San Diego Pulmonary Endarterectomy Registry[90]
No. of patients	519	679	2700
Sex, % male	28.1	50.1	49.7
Age, y	67 (53, 75)*	63 (51, 72)*	52 (40, 63)* (8–88)†
World Health Organization class, % I/II/III/IV	5.2/41.9/47.7/5.2	0.7/17.8/68.6/12.8	1.5/9.7/80.3/8.6
History of deep vein thrombosis, %	50.4	56.1	49.2
History of acute pulmonary embolism, %	37.2	74.8	70.6
Coagulopathies, %	11.7	31.9	30.1
Mean pulmonary arterial pressure, mm Hg, median	38 (33, 46)*	47 (38, 55)*	46 (38, 53)*
Pulmonary vascular resistance, dyne·s/cm^5, median	621 (439, 916)*	709 (480, 988)*	814 (476, 1018)*
Pulmonary endarterectomy, %	13.9	56.8	100
Inferior vena cava filter, %	26.9	12.4	>90
PAH-targeted therapy, %	52.2	37.9‡	37.0‡

CTEPH indicates chronic thromboembolic pulmonary hypertension; and PAH, pulmonary arterial hypertension.

*Medians and quartiles (quartile 1, quartile 3).

†Range.

‡Preoperative treatments.

postoperative PVR ≥500 dyne·s/cm[5] had a 30-day mortality of ≈10.3% compared with a 0.9% mortality rate for patients with postoperative PVR of <500 dyne·s/cm[5]. Patients with persistent exertional dyspnea after successful PEA still display an abnormal pulmonary hemodynamic response to exercise.[80]

PVR in CTEPH can be partitioned into larger arterial (upstream) and small arterial plus venous (downstream) components[81–83] with the use of the pulmonary artery occlusion technique. Patients with higher downstream and lower upstream resistance appear to be at increased risk for persistent PH and poor outcome after PEA. Data indicate that patients with upstream resistance <60% are at highest risk for adverse outcomes after PEA,[84] possibly because of concomitant small-vessel disease. This technique would allow for preoperative assessment of small-vessel disease, but its reproducibility has recently been questioned.[85]

Clinical Characteristics

Clinical symptoms and signs are nonspecific or absent in early CTEPH, with signs of right heart failure only in advanced disease stages. Thus, early diagnosis is difficult, with a median time of 14 months between symptom onset and diagnosis in expert centers.[5] The major clinical challenge is to differentiate CTEPH from PAH. When present, the clinical symptoms of CTEPH may resemble those of acute PE or PAH. Hemoptysis occurs more frequently in CTEPH compared with idiopathic PAH (4.8% versus 0.6%).[74] Another distinctive feature is the episodic disease course in CTEPH. Typically, a symptomatic thromboembolic event is followed by a so-called honeymoon period, characterized by absence of symptoms. Comparative survival after diagnosis in CTEPH has been reported to be twice that of patients with PAH[86] but is still dismal. In the European CTEPH Registry, operated patients had a much better survival than nonoperated patients, with a 89.3% and 70.5% survival rate at 3 years, respectively (P=0.001).[87] However, all registry comparisons of outcomes in operated and nonoperated cohorts suffer from significant selection bias favoring patients undergoing PEA. Significant functional and hemodynamic improvements are seen in surgically treated patients from major PEA centers, with an increase in 6-minute walking distance in the range of 100 m at 3 to 12 months[88–91] and overall long-term survival rates at 5 and 10 years of 82% and 75%, respectively, in most recent series from San Diego.[90]

Median age of patients at diagnosis is 63 years, and surgical cases are younger (57 years[91]; Table 2). CTEPH is rare in children.[92,93] In Europe, both sexes are equally affected,[5] whereas there appears to be a preponderance of women in Japan[12] (Table 2). In a recent substudy of the European CTEPH registry, comparing 436 CTEPH patients with 158 idiopathic PAH patients collected in the same centers, older age, history of acute VTE, and non-O blood groups were independent risk factors for CTEPH.[74]

Diagnostic Procedures

Any patient with unexplained PH should be subjected to a CTEPH evaluation (Figure 3, top). Suspicion should be high, particularly when the patient presents with a history of previous VTE, although many patients do not present with such history. CTEPH should be ruled out in PE survivors with persistent dyspnea and >15% persistent perfusion defects.[23,94] Despite advances in computed tomography (CT) and magnetic resonance imaging, ventilation/perfusion scan planar images

on at least 6 views combined with single-photon emission CT remain the preferred initial diagnostic test for CTEPH (Figures 3 and 4). CT pulmonary angiography had a sensitivity of detecting CTEPH of 51% compared with a >96% sensitivity of ventilation/perfusion scan.[95] A normal ventilation/perfusion scan virtually excludes CTEPH, although scans tend to normalize as disease progresses.[96] Despite modern multidetector CT technology, a normal CT pulmonary angiogram alone cannot safely exclude the diagnosis of CTEPH. Additional concern regarding reliance on CT includes false-positive cases from conditions mimicking CTEPH, such as mural pulmonary arterial thrombi in congenital heart disease or in severe idiopathic PAH. Multidetector CT pulmonary angiography may help to identify complications of the disease such as pulmonary artery distension with left main coronary artery compression and may help to tease out unilateral pulmonary artery agenesis. High-resolution CT of the chest delivers images of the lung parenchyma and identifies emphysema, bronchial disease, and mediastinal or interstitial lung disease, as well as infarcts, vascular and pericardial malformations, and thoracic wall deformities. Rare cases of pulmonary artery sarcoma may only be diagnosed at PEA.[69] Perfusion inequalities manifest as a mosaic parenchymal pattern with dark areas corresponding to relatively decreased
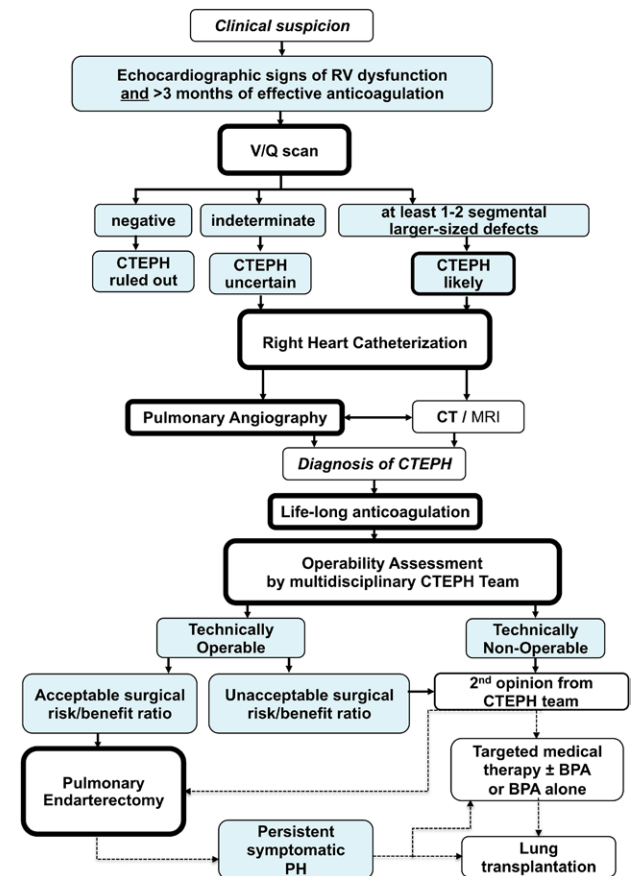

Figure 3. Contemporary diagnostic and therapeutic algorithm. BPA indicates balloon pulmonary angioplasty; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; MRI, magnetic resonance imaging; PH, pulmonary hypertension; RV, right ventricular; and V/Q, ventilation/perfusion. Diagnostic findings are in light blue boxes, diagnostic and therapeutic measures are in white boxes, and important key measures are in boxes with bold framing.
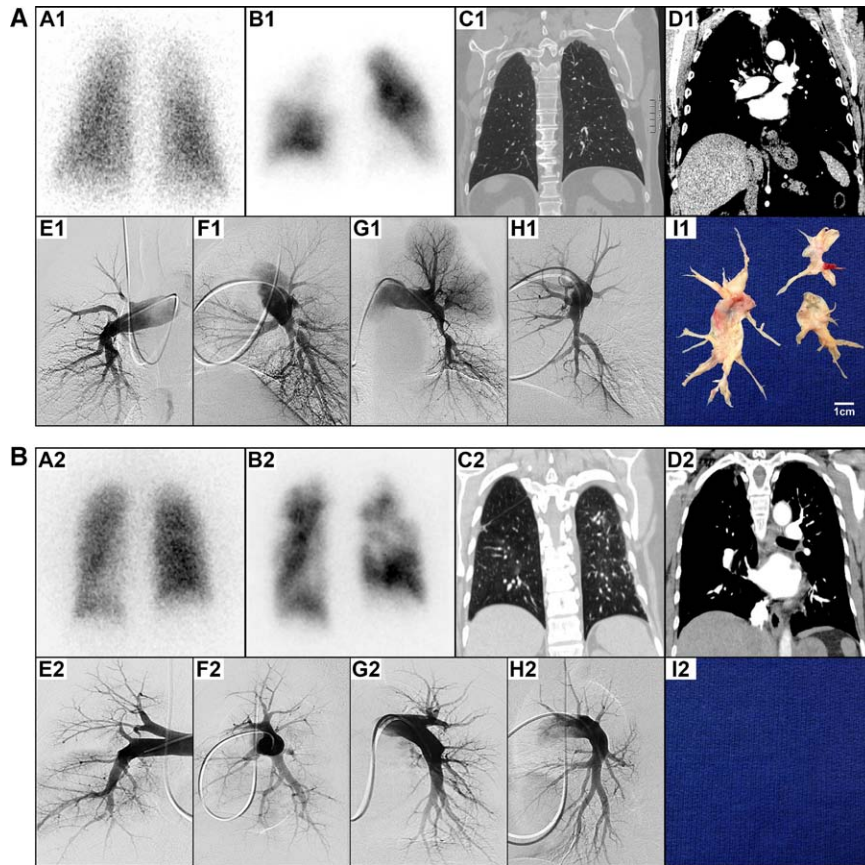
Figure 4. Completed diagnostic pathways of chronic thromboembolic pulmonary hypertension imaging and their therapeutic consequences, according to the algorithm shown in Figure 3, illustrating an operable and a nonoperable patient case. Examples of technetium-99 m–labeled aerosol ventilation (**A**) and perfusion (**B**) images are shown, labeled as high probability under Prospective Investigation of Pulmonary Embolism Diagnosis criteria. High-resolution computed tomographies (**C**) and spiral computed tomographic angiographies (**D**), as well as side-selective pulmonary angiographies in the anteroposterior right (**E**), left (**G**), and lateral projections (**F** and **H**), are shown. Patient 1 in **A1** through **I1** is a 69-year-old man with past medical history of deep vein thrombosis and acute pulmonary embolism. He underwent pulmonary endarterectomy (specimen in **I1**) in addition to coronary artery bypass grafting in the rewarming period. At the time of surgery, type II disease was encountered, with a larger amount of thromboembolic material than was expected on the basis of the imaging studies, which is commonly the case. He was discharged home 1 week postoperatively with normal right ventricular function and pulmonary vascular resistance of 70 dyne·s/cm[5] compared with 450 dyne·s/cm[5] preoperatively. Patient 2 in **A2** through **I2** is 49-year-old woman with history of progressive shortness of breath on exertion for many years. After initiation of pulmonary arterial hypertension therapy, right heart catheterization revealed only moderate pulmonary hypertension and a few distal segmental and subsegmental obstructions. Surgery was not believed to be beneficial for this patient. In contrast to **A**, there is no pulmonary endarterectomy specimen in **B**.

perfusion. Although a mosaic pattern is frequent in CTEPH, it can also be observed in up to 12% of patients with PAH.[97] Magnetic resonance imaging of the pulmonary vasculature is still considered inferior to CT[98] but may be preferred according to local practice. Recent advances such as dual-energy CT,[67] cone-beam CT, ECG-gated 320-row area detector CT, and lung perfusion magnetic resonance imaging are about to change paradigms in pulmonary vascular imaging. Percutaneous interventional approaches have started to utilize intravascular imaging, with ultrasound and optical coherence tomography providing new insights into the vascular obstructions of CTEPH.[99]

Today catheter-based pulmonary digital subtraction angiography remains the gold standard for diagnosis and assessment of pulmonary revascularization. A major advantage of digital subtraction angiography is the combination of imaging with the indispensable hemodynamic assessment. Angiographic appearance (ie, ring-like stenosis, pouches, webs, occlusions, and distal lesions) and the distribution of disease (ie, subpleural perfusion) have been associated with postoperative

outcome.[100] Wedge angiograms are the basis for catheter-directed interventions.[12]

Treatment Algorithm

Interventional Treatments

Surgical Treatments

Pulmonary Endarterectomy
PEA is the only curative treatment for CTEPH, with periprocedural mortality <2% to 5% in experienced centers,[90] nearly normalized hemodynamics (Table 3), and substantial improvement in clinical symptoms in the majority of patients (Figure 3, bottom). In recent series from the University of California–San Diego, the overall 30-day mortality after PEA has declined to ≈2.2%, despite an increase in patients with distal type III disease[90] (Figure 1).

The decision of the manner in which to treat patients with CTEPH should be made by a CTEPH team on the basis of

Table 3.   Comparison of PEA and Emerging Treatments (Medical and BPA) for CTEPH

	PEA		Medical Treatment		BPA	
Concept	Cure		Palliation		Palliation, cure possible	
Evidence	>7000 cases; multiple publications		CHEST I/II		≈350 documented cases (>1300 procedures)	
Indication	Operable disease		Nonoperable disease		Nonoperated disease (not established for cases with previous PEA)	
6-Min walking distance, change from baseline, m	+100[88]		+39[101]		+100[13,102]	
Availability of quality of life data	Yes[8]		Yes[101]		No	
Long-term outcome, %	82 at 5 y		60 at 5 y		Pending	
Hemodynamic parameters, mean±SD						
	Preoperative	Postoperative	Baseline	Change From Baseline	Baseline	After Intervention
PVR, dyne·s/cm^5	719.0±383.2[90]	253.4±148.6[90]	779±401	−226±248[101]	942±367[11]	327±151[11]
sPAP, mm Hg	75.5±19.1[90]	41.7±14.1[90]			81.3±16.9[11]	42.3±11.9[11]
mPAP, mm Hg	45.5±11.6[90]	26.0±8.4[90]	44±10	−4±7[101]	45.4±9.6[11]	24.0±6.4[11]
CO, L/min	4.3±1.4[90]	5.6±1.4[90]	4±1	0.8±1.1[101]		
Cardiac index, L/min per m^2					2.2±0.7[11]	3.2±0.6[11]
Comparative assessment						
Pros	Accepted standard, reproducible results, recommended in guidelines, potentially curative		Entirely noninvasive		Percutaneous procedure according to interventional standards (average of 2.6 procedures [range, 1–5] per patient)[12]	
Cons	Invasive surgical procedure; wound infection (1.2%), pneumonia (9.2%), CVA (0.2%), perioperative bleeding (3.7%), pulmonary reperfusion edema (13.5%)[90]		Life-long treatment, evidence currently based on a single positive trial, only approved for nonoperable patients and patients with persistent/recurrent PH after PEA; syncope (2%), headache (25%), dizziness (23%), dyspepsia (18%), peripheral edema (16%)[101]		Emerging technique, comparative trials lacking, not established outside of Japan; clinically apparent "reperfusion pulmonary edema," most likely due to wire injury and bleeding (34%[11] or, more recently, 2%; oral communication, H. Matsubara and T. Satoh, 2013)	

BPA indicates balloon pulmonary angioplasty; CHEST, Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial; CTEPH, chronic thromboembolic pulmonary hypertension; CVA, cerebrovascular accident; mPAP, mean pulmonary artery pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and sPAP, systolic pulmonary artery pressure.

interdisciplinary discussions among internists, radiologists, and expert surgeons. A patient should not be considered nonoperable as long as the case has not been reviewed by at least 2 independent experienced PEA surgeons (Figure 3). Detailed preoperative patient evaluation and selection, surgical technique and experience, and meticulous postoperative management are essential for surgical success. Patient selection for PEA is a complex process that is dependent on the extent and most proximal location of obstructive material in relation to hemodynamic severity, parenchymal lung function, age, and comorbidities. After complete endarterectomy, a significant drop of PVR can be expected, with near normalization of pulmonary hemodynamics (Table 3).

A center can be considered to have adequate expertise if it performs at least 20 PEAs per year with a mortality rate <10%,[103] although an expert center typically performs well over 50 such operations annually and has a mortality rate of <4% to 5% while achieving excellent outcomes even in patients with distal disease.

A typical PEA is shown in Movie I in the online-only Data Supplement. The techniques of this procedure have already been well established and described elsewhere.[90,104] The procedure follows 4 basic principles, as follows: (1) The endarterectomy must be bilateral, and therefore the approach is through a median sternotomy. (2) Identification of the correct dissection plane is crucial. (3) Perfect visualization is essential by use of circulatory arrest that is usually limited to 20 minutes at a time and supported by cooling to 18°C. (4) A complete endarterectomy is essential. Patients from whom thrombus with longer tails can be removed have a better improvement in hemodynamics and are less likely to develop persistent/recurrent PH.[79]

Once the endarterectomy is completed on both sides, circulation with warming is restarted. Although tricuspid regurgitation is invariable in these patients, tricuspid repair is not performed unless the valve itself is damaged. Right ventricular remodeling after a reduction in right ventricular pressure usually results in tricuspid competence. At the time of the operation, endarterectomy specimens are categorized according to the Jamieson classification[105] (Figure 1). Recurrent CTEPH after successful PEA is extremely rare as long as patients are adequately anticoagulated. Redo PEA can be offered to patients with recurrent disease, although it is commonly not as successful in patients who previously underwent a true and complete endarterectomy.

Lung Transplantation

Bilateral lung transplantation or heart/lung transplantation for CTEPH is a rare intervention (Figure 3). Although evidence does not exist for different outcomes of transplant in CTEPH compared with PAH, transplantation may be considered for young patients who are not candidates for other treatments.

Balloon Pulmonary Angioplasty

In 2001, Feinstein et al[9] published a series of 18 patients with nonoperable CTEPH whom they subjected to balloon dilatation of the pulmonary arteries. Despite a significant decrease of mean pulmonary artery pressure, 11 patients developed reperfusion pulmonary edema, and 3 required mechanical ventilation. Recently, Japanese investigators have refined BPA by using smaller balloons, by cautiously limiting the number of balloon inflations per session to 1 or 2 pulmonary vascular segments, and by the use of intravascular imaging.[10,11,13] An average number of 4.8 sessions is needed per patient. The use of the Pulmonary Edema Predictive Scoring Index has reduced the incidence of reperfusion pulmonary edema to 2% in individual centers.[102] Although BPA remains largely unexplored in Europe,[106] it is rapidly gaining attention because in the elderly and frail, high-risk cure may be less desirable than low-risk palliation (Table 2).

Medical Treatments

Life-long anticoagulation at an international normalized ratio of 2 to 3 is recommended (Figure 3).

Inferior vena cava filter placement is not mandatory because the origin of clot may also be other sites (eg, upper-extremity veins).[48] According to the European CTEPH Registry, which enrolled 679 patients at 1 Canadian and 26 European expert centers between February 2007 and January 2009, 37% of all patients with CTEPH were classified as nonoperable. Small-vessel disease of CTEPH resembling pulmonary arteriopathy (Figure 2) provides a rationale for exploring the efficacy of PAH-targeted therapies in CTEPH. Endothelin receptor antagonists, phosphodiesterase inhibitors, or prostacyclins are currently initiated in 40% of cases in Europe,[5] regardless of operability and despite the lack of proof of efficacy in controlled trials.[107–109] Vasodilator treatments via intravenous lines carry a risk for worsening CTEPH that may result from complications of permanent catheters.[54] Recently, riociguat, a new class of oral drug and stimulator of soluble guanylate cyclase, met the primary end point of a phase 3, multicenter, randomized, double-blind, placebo-controlled study of 261 patients with adjudicated nonoperable CTEPH or persistent/recurrent PH after PEA as the first medical treatment demonstrating efficacy in this condition.[101] Within 16 weeks, carefully uptitrated doses of riociguat increased 6-minute walking distance by 39 m from baseline, whereas 6-minute walking distance in those on placebo deteriorated by 6 m, and these doses of riociguat improved secondary end points such as World Health Organization functional class, hemodynamics, biomarkers, and quality of life. However, there is a need for more trials targeting (1) patients who need to be bridged to PEA/intervention because available data are uncontrolled and restricted to PEA[110–113]; (2) patients who are technically nonoperable; (3) patients who are technically operable but have an unacceptable surgical risk; and (4) patients with symptomatic

residual/recurrent PH after PEA. In the ongoing Efficacy and Tolerability of Subcutaneously Administered Treprostinil Sodium in Patients With Severe (Nonoperable) Chronic Thromboembolic Pulmonary Hypertension (CTREPH) trial (NCT01416636), subcutaneous treprostinil has confirmed improvement in exercise capacity,[114] hemodynamics, and quality of life at 6 months (unpublished data, Irene Marthe Lang, MD, American Thoracic Society, 2013).

Innovations and Tribulations in CTEPH

More research is necessary to understand the mechanisms of fibrotic vascular remodeling that occur in CTEPH. Important unmet clinical needs remain, including a precise and meaningful definition of postoperative PH and methods to prevent and predict microvascular disease.

We are at the brink of a paradigm shift in treatments: First, riociguat has recently received global approval for the treatment of nonoperable CTEPH and persistent/recurrent PH after PEA; second, BPA has been refined in Japan to be established more widely (Table 3). However, although medical treatment should not delay referral for PEA,[113] some skepticism is warranted regarding BPA until the procedure is reproduced outside of Japan and until there are long-term data. A complete bilateral PEA at an experienced center remains the best treatment option, with excellent long-term outcomes, and can be potentially curative in CTEPH patients.

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