Evaluation and management of patients with chronic thromboembolic pulmonary hypertension: consensus statement from the ISHLT

Perrot, M. de; Gopalan, D.; Jenkins, D.; Lang, I.M.; Fadel, E.; Delcroix, M.; ... ; Auger, W.R.

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

Evaluation and management of patients with chronic thromboembolic pulmonary hypertension - consensus statement from the ISHLT

Marc de Perrot, MD,[a] Deepa Gopalan, MD,[b] David Jenkins, MD,[c] Irene M. Lang, MD,[d] Elie Fadel, MD,[e] Marion Delcroix, MD,[f,g] Raymond Benza, MD,[h] Gustavo A. Heresi, MD,[i] Manreet Kanwar, MD,[j] John T. Granton, MD,[k] Micheal McInnis, MD,[l] Frederikus A. Klok, MD,[m] Kim M. Kerr, MD,[n] Joanna Pepke-Zaba, MD,[o] Mark Toshner, MD,[o,p] Anastasia Bykova, RN, NP,[a] Andrea M. D'Armini, MD,[q] Ivan M. Robbins, MD,[r] Michael Madani, MD,[s] David McGiffin, MD,[t] Christoph B. Wiedenroth, MD,[u] Sebastian Mafeld, MD,[v] Isabelle Opitz, MD,[w] Olaf Mercier, MD,[e] Patricia A. Uber, PharmD,[x] Robert P. Frantz, MD,[y] and William R. Auger, MD[z]

From the [a]Division of Thoracic Surgery, Toronto General Hospital, Toronto, Ontario, Canada; [b]Department of Radiology, Imperial College Healthcare NHS Trust, London & Cambridge University Hospital, Cambridge, UK; [c]National Pulmonary Endarterectomy Service, Department of Cardiothoracic Surgery, Papworth Hospital, Cambridge, UK; [d]Department of Cardiology, Pulmonary Hypertension Unit, Medical University of Vienna, Vienna, Austria; [e]Department of Thoracic and Vascular Surgery and Heart Lung Transplantation, Marie-Lannelongue Hospital, Paris Saclay University, Le Plessis-Robinson, France; [f]Clinical Department of Respiratory Diseases, Pulmonary Hypertension Centre, UZ Leuven, Leuven, Belgium; [g]Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department of Chronic Diseases and Metabolism (CHROMETA), KU, Leuven, Belgium; [h]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio; [i]Department of Pulmonary and Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio; [j]Cardiovascular Institute, Allegheny Health Network, Pittsburgh, Pennsylvania; [k]Division of Respirology, University Health Network, Toronto, Ontario, Canada; [l]Joint Department of Medical Imaging, University Health Network, Toronto, Ontario, Canada; [m]Department of Medicine, Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; [n]University of California San Diego Medical Health, Division of Pulmonary Critical Care and Sleep Medicine, San Diego, California; [o]Pulmonary Vascular Disease Unit, Royal Papworth Hospital NHS foundation Trust, Cambridge, Cambridgeshire, UK; [p]Heart Lung Research Institute, University of Cambridge, Cambridge, UK; [q]Unit of Cardiac Surgery, Intrathoracic-Trasplantation and Pulmonary Hypertension, University of Pavia, Foundation I.R.C.C.S. Policlinico San Matteo, Pavia, Italy; [r]Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [s]Department of Cardiovascular and Thoracic Surgery, University of California San Diego, La Jolla, California; [t]Department of Cardiothoracic Surgery, The Alfred Hospital and Monash University, Melbourne, VIC, Australia; [u]Department of Thoracic Surgery, Campus Kerckhoff of the University of Giessen, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany; [v]Division of Vascular and Interventional Radiology, Joint Department of Medical Imaging, University Health Network, Toronto, Ontario, Canada; [w]Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland; [x]Pauley Heart Center, Virginia Commonwealth University Health System, Richmond, Virginia; [y]Department of Cardiovascular Disease, Mayo Clinic College of Medicine, Rochester, Minnesota; and the [z]Pulmonary Hypertension and CTEPH Research Program, Temple Heart and Vascular Institute, Temple University, Lewis Katz School of Medicine, Philadelphia, Pennsylvania.

Reprint requests: Marc de Perrot, MD, Toronto CTEPH Program, Division of Thoracic Surgery, Toronto General Hospital, 9N-961, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada
E-mail address: marc.deperrot@uhn.ca

https://doi.org/10.1016/j.healun.2021.07.020

KEYWORDS:
pulmonary emboli;
CTEPH;
pulmonary thromboendarterectomy;
balloon pulmonary angioplasty;
pulmonary hypertension;
guidelines

ISHLT members have recognized the importance of a consensus statement on the evaluation and management of patients with chronic thromboembolic pulmonary hypertension. The creation of this document required multiple steps, including the engagement of the ISHLT councils, approval by the Standards and Guidelines Committee, identification and selection of experts in the field, and the development of 6 working groups. Each working group provided a separate section based on an extensive literature search. These sections were then coalesced into a single document that was circulated to all members of the working groups. Key points were summarized at the end of each section. Due to the limited number of comparative trials in this field, the document was written as a literature review with expert opinion rather than based on level of evidence.
J Heart Lung Transplant 2021;40:1301−1326

Definition, epidemiology and clinical presentation

Definition

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct pulmonary vascular disease classified as group 4 in the classification of pulmonary hypertension.[1] It is characterized by chronic stenosis and occlusion of the pulmonary arteries due to obstructive intraluminal organized thromboembolic material.[2,3]

The diagnosis of CTEPH requires a mean pulmonary artery pressures (PAP) ≥25 mmHg with a pulmonary arterial wedge pressure (PAWP) of ≤ 15 mmHg documented at invasive right heart catheterization with radiographic evidence of organized thrombi involving the pulmonary arteries after 3 months of anticoagulation.[4]

At the 6th World Symposium on Pulmonary Hypertension in Nice, a new definition was presented with a mean PAP >20 mmHg combined with a pulmonary vascular resistance (PVR) ≥ 3 WU and PAWP ≤ 15 mmHg.[5]

Incidence

The exact incidence of CTEPH in the general population is not well defined as the disease remains largely underdiagnosed.

CTEPH has been reported with a cumulative incidence ranging between 0.1% and 9.1% within the first 2 years after an acute PE event.[6,7] The large range in incidence is due to referral bias, variability in diagnostic criteria, paucity of early symptoms, and the difficulty in differentiating acute PE from CTEPH.

A meta-analysis revealed a 2.8% incident rate of CTEPH in survivors of acute PE.[7]

Epidemiological studies estimate an annual incidence in the United States and Europe as high as 3-5 cases per 100,000 population, with a lower rate of 1.9 case per 100,000 in Japan.[8]

As disease awareness increases in the medical community, the incidence and prevalence of CTEPH in the general population should progressively become more accurate.

Genetics

Although known contributors to pathways of coagulation and fibrinolysis dominate the genetic risk factors for venous thromboembolic (VTE) disease,[9-12] their contribution to the development of CTEPH is currently considered to be limited.[13-19]

Non-blood group 0, lupus anticoagulant, antiphospholipid antibodies, fibrinogen polymorphism, and possibly factor V Leyden can be associated with a higher risk of CTEPH.[7,17-23] BMPR2 is not mutated in CTEPH.[24-26]

Recent studies have shown that CTEPH is associated with elevated plasma concentrations of factor VIII and increased level of von Willebrand factor (VWF) that are persistent after PEA, suggesting that they play a role in the pathogenesis of CTEPH.[19,27,28]

Pathophysiology

CTEPH has a complex pathophysiology due to vascular derangement in both the elastic and the resistive pulmonary arteries.[29-45] Unlike acute PE, there is no linear correlation between the extent of mechanical obstruction on imaging and the severity of PVR.[30] CTEPH is characterized by a progressive pulmonary vascular remodeling that develops in both occluded and non-occluded small pulmonary arteries. In its most severe form, CTEPH can also present with focal capillary haemangiomatosis and post-capillary venous remodeling as a consequence of the bronchial-to-pulmonary shunting.[46] Experimental investigations have shown that staphylococcal infection, endothelial dysfunction, unbalanced fibrinolysis, dysfunctional angiogenesis and inflammatory or immunological mechanisms can be associated with CTEPH.[37-44] One of the major limitations in CTEPH studies is the difficulty to reproduce the disease in animal models.[47-66]

Clinical presentation

The clinical presentation of CTEPH always involves dyspnea at rest or with exertion.[67-71] Other symptoms can include fatigue, chest pain, syncope, dizziness, and hemoptysis.[68,69]

Symptoms are not specific and consequently the median time between the beginning of symptoms and diagnosis of CTEPH is about 14 months.[27,68] Therefore, it is essential to keep a high index of suspicion for CTEPH particularly in the context of an acute PE, a new diagnosis of PH, or in the presence of unexplained dyspnea.

Delayed diagnosis of CTEPH results in unnecessary suffering and monetary waste on inappropriate treatments.[72-83] Progression of disease can also lead to worsening of the small vessel vasculopathy and the development of right heart failure, which can be associated with worse surgical outcomes in terms of operative risks and PH resolution.[84,85]

The initial investigations in suspected CTEPH should include an echocardiogram and a ventilation-perfusion (VQ) scan. These tests are easy to perform and interpret, widely available, non-invasive, and acceptable to patients.[70,81] Echocardiogram is generally the first choice since it will provide an estimation of the PH, and information on other parameters of cardiac function, which may contribute to dyspnea.[82-90] A VQ scan is important in the presence of residual symptoms after acute PE and in patients with newly diagnosed PH to demonstrate the presence of perfusion defects. Additional testing with cardiopulmonary exercise testing and/or right heart catheterization with exercise may be helpful to investigate the possibility of CTEPH, particularly in the absence of PH on echocardiogram despite persistent VQ mismatches.[3,91-94] Of importance, CTEPH often coexists with other comorbidities such as COPD or left heart failure with preserved ejection fraction and therefore these comorbidities should not prevent further investigations for CTEPH.[27,68,95-102]

CTEPH in the context of acute PE

CTEPH can mimic acute PE at presentation.[80] Thus, CTEPH can be mislabeled as acute PE, which is one of the reasons for delayed diagnosis. It is therefore essential to keep a high index of suspicion for CTEPH in the context of acute PE. Although there is currently no indication to routinely screen for CTEPH after an acute PE, follow-up imaging with echocardiogram and VQ scan is indicated in some specific situations. These include evidence of PH on echocardiogram, CT scan findings suggestive of CTEPH, large clot burden, recurrent PE, and persistent dyspnea despite anticoagulation. Other factors that can increase the risk of CTEPH include history of splenectomy, infected pacemaker leads, ventriculo-atrial shunts, chronic inflammatory disease, antiphospholipid syndrome, and hypothyroidism.[19,33,34,71]

The initiation of anticoagulation is frequently associated with clinical improvement as the acute component of the clot burden resolves. However, CTEPH does persists and it is prudent to pursue further investigations in the presence of persistent symptoms despite clinical improvement. The optimal moment for investigating the presence of CTEPH is after 3 months of anticoagulation, but earlier work-up may be necessary in highly symptomatic or deteriorating patients.[72-79] A CTEPH risk score has been developed[81,82,102] to help stratify the risk of CTEPH and guide the need for further investigations (Table 1). A strategy using this score accurately excluded CTEPH without the need for echocardiography in the overall majority of PE patients. Moreover, CTEPH was identified early after acute PE, resulting in a substantially shorter diagnostic delay than in current practice. Table 2 provides an overview of initial diagnostic tests that are relevant for patients with functional impairment in the clinical follow-up of acute PE and unexplained dyspnea.

Table 1 CTEPH Prediction Score; a Score of More Than 6 Points Denotes a 'high risk'

Points for score	
Unprovoked PE	+6
Known hypothyroidism	+3
Symptom onset greater than 2 weeks before PE diagnosis	+3
Right ventricular dysfunction on CT or echocardiogram	+2
Known diabetes mellitus	-3
Thrombolytic therapy or embolectomy	-3
A Score greater than 6 points denotes a "high risk" for CTEPH	

CT, computed tomography; PE, pulmonary embolism; VTE, venous thromboembolism.

Thrombolysis and CTEPH

Currently, there is no indication to administer thrombolytic therapy to prevent CTEPH. Thrombolytic therapy should remain an indication for the management of patients with acute PE only.[103-106]

The impact of early thrombolytic treatment to decrease the risk of CTEPH in the long term was prospectively addressed in the international PEITHO (Pulmonary Embolism Thrombolysis) trial, which compared a single intravenous bolus of the thrombolytic agent tenecteplase to placebo in the context of submassive PE.[105] A total of 290 patients from the PEITHO trial had long-term echocardiographic follow-up with a median follow-up exceeding 3 years.[106] There was no difference in the incidence of CTEPH between the two groups in the long-term. The diagnosis of CTEPH was confirmed in 2.1% and 3.2% of the patients randomized to tenecteplase and placebo, respectively.

Key points

1. The exact incidence of CTEPH in the general population is not well defined as the disease remains largely underdiagnosed.
2. The clinical presentation is not specific and can mimic acute PE diagnosis. As a consequence, the diagnosis is frequently delayed.
3. It is essential to keep a high index of suspicion for CTEPH: (1) In patients with risk factors for CTEPH in the context of an acute PE, (2) In patients with a new diagnosis of PH, and (3) In patients with unexplained dyspnea.
4. Risk factors for CTEPH in the context of acute PE include CT findings suggestive of CTEPH, evidence of PH on echocardiogram, large clot burden, recurrent PE, unprovoked PE, history of splenectomy, infected pacemaker leads, chronic inflammatory disease,

Table 2 Overview of Initial Diagnostic Tests That May Point to CTEPH and are Relevant for Patients With Functional Impairment in the Clinical Follow-up of Acute PE or With Unexplained Dyspnea in General

	Indication	Limitation
ECG	Evaluation of heart rhythm and function, may be used in combination with NT-proBNP to rule out CTEPH	Not sufficiently sensitive to be used as single test to rule out CTEPH; signs of PH include P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block and QTc prolongation.
NT-proBNP	Evaluation of heart failure, may be used in combination with ECG to rule out CTEPH	Non-specific test in general, not sufficiently sensitive to be used as single test to rule out CTEPH.
Spirometry	Evaluation of pulmonary function to explain symptoms	Not sensitive for CTEPH; many patients with PAH have mild to moderate reduction of lung volumes and decreased lung diffusion capacity for carbon monoxide.
Cardiopulmonary exercise testing	Assessment of the exercise responses of the pulmonary and cardiovascular system to explain symptoms	Not sensitive for CTEPH; signs of PH include a typical pattern with a low end-tidal partial pressure of carbon dioxide, high ventilatory equivalents for carbon dioxide, low oxygen pulse and low peak oxygen uptake.
Chest X-ray	General screening for cardiopulmonary conditions to explain symptoms	Not sensitive or specific for CTEPH; Signs of PH include central pulmonary arterial dilatation and RA and/or RV enlargement and RV hypertrophy
Ventilation perfusion scintigraphy	Rule out CTEPH with high certainty.	Radiation exposure. Not specific for CTEPH. Will not demonstrate alternative diagnoses; Mismatched perfusion defect is indicative of thromboembolic disease until proven otherwise.
Echocardiography	Suspected CTEPH, screening for other cardiac comorbidities to explain symptoms	Less sensitive for CTEPH than ventilation perfusion scintigraphy. Can miss the diagnosis in patients with mild PH or with exercise induced PH

CTEPH, chronic thromboembolic pulmonary hypertension; ECG, Electrocardiography; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RA, right atrial; RV, right ventricular.

antiphospholipid syndrome, hypothyroidism, ventriculo-atrial shunt, and persistent symptoms despite anticoagulation.

5. There is no indication to administer thrombolytic therapy to prevent CTEPH.
6. If CTEPH is suspected, screening investigations should be performed after 3 months of anticoagulation with echocardiogram and VQ scan. Earlier assessment can be performed in the presence of worrisome signs or symptoms of heart failure.

Diagnostic approach to CTEPH

Blood markers

Several inflammatory biomarkers can be elevated in CTEPH.[107-124] However, none of them are validated for routine clinical use. Brain natriuretic peptide (BNP) and NT-pro-BNP are most frequently used for prognosis of CTEPH.[100,102,116-118,124]

Inflammatory biomarkers can correlate with the severity of disease. For instance, IP-10 negatively correlated with cardiac index, 6-min walk distance and carbon monoxide diffusion capacity, while IL-6 positively correlated with PVR, right atrial pressure and NT-proBNP.[116] These correlations were observed in CTEPH, but not in idiopathic PAH, suggesting that persistent inflammation may be more important in the pathophysiology of CTEPH than PAH.[116] One major limitation in biomarkers evaluation for CTEPH is that most studies are single center series with small cohorts of patients.

Echocardiography

Echocardiogram is generally the first step in evaluating patients with suspected PH. The potential signs of PH based on established guidelines[89] are summarized in Table 3.

Echocardiogram can miss CTEPH diagnosis in patients with mild PH or with exercise induced PH.[83,91] Therefore, patients with persistent symptoms after an acute PE should undergo further investigations despite a normal echocardiogram.

Table 3 Echocardiographic Signs Suggesting Pulmonary Hypertension (based on Reference [89])

Ventricles:
• Peak tricuspid regurgitation velocity >2.8 m/s
• Right ventricle/left ventricle basal ratio >1.0
• Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)
Pulmonary artery:
• Right ventricular outflow acceleration time <105 msec and/or midsystolic notching
• Early diastolic pulmonary regurgitation velocity >2.2 m/sec
Inferior vena cava and right atrium:
• Inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
• Right atrial area (end-systole) >18 cm^2

Echocardiogram is also an important test to determine right ventricular function in patients with PH. Recent work has shown that the peak velocity combined with RV end−systolic area index (RVESAi) could be a good surrogate of RV-PA coupling and thus potentially be a valuable clinical parameter to predict PH outcome by echocardiography.[125]

Echocardiographic parameters to predict outcome may be different in PAH than CTEPH. Parameters of RV pressure overload such peak tricuspid regurgitation, right ventricular acceleration time and LV systolic eccentricity index are better to risk stratify CTEPH patients, while parameters of RV systolic function such as global right ventricular longitudinal strain, free-wall right ventricular longitudinal strain, RV FAC, and TAPSE are better to risk stratify PAH patients.[126]

Further work will be required to determine the importance of echocardiographic parameters on the surgical risks before PEA.

Cardio-pulmonary exercise testing

Cardio-pulmonary exercise testing (CPET) provides important insights into the pulmonary vascular reserve and imparts additional understanding into the cause of patient limitations. CTEPH has specific features on CPET characterized by a dramatic reduction in ventilatory efficiency, which can be helpful to assess patients after acute PE as well as before and after PEA.[127,128-133] Ventilatory efficiency is quantified by an increase in ventilation relative to CO2 production (VE/VCO2) and higher physiologic deadspace fraction (VD/VT).[127] The degree of dead space ventilation and ventilatory efficiency have been associated with exercise impairment and survival in CTEPH.[134,135] In comparison to other forms of PH, patients with CTEPH appear to have a lower heart rate response, which may account for some of the differences observed during exercise, even after PEA.[134] The degree to which abnormalities in exercise response during CPET can inform treatment choice for patients with CTEPH remains to be studied.

SPECT VQ

VQ scintigraphy remains the imaging technique of choice for CTEPH screening.[1] In CTEPH, VQ SPECT has been demonstrated to be significantly more sensitive than planar imaging for detecting regional lung mismatched perfusion defects.[136] Evolving dual modality techniques (Figure 1) with varying combinations of hybrid SPECT/CT pulmonary imaging can improve VQ SPECT specificity by promoting the identification of lung diseases other than PE in patients with perfusion abnormalities.[137,138] In-spite of the many obvious advantages, VQ SPECT and hybrid pulmonary imaging are not necessarily available in every department and hence there will be geographical variation in its usage.

CT pulmonary angiogram

Computed tomography pulmonary angiography (CTPA) is commonly used in CTEPH evaluation because of its ability to visualize chronic thromboembolic disease. In a meta-analysis, CTPA was shown to be sensitive and specific for the identification of chronic PE, with pooled high-quality studies demonstrating a sensitivity of 99% and specificity of 97%.[139] All studies required optimal imaging quality and expert radiology readers. These direct signs of chronic PE include slits/webs, eccentric thrombus, and occlusions/pouch defects.[140] The CT appearances are analogous to findings at conventional angiography.[141] Other CT signs of CTEPH include enlarged bronchial arteries with vascularized adhesions from the mammary and intercostal arteries, under-perfused lung with a mosaic lung attenuation pattern, cylindrical bronchial dilatation and chronic infarcts. CTPA is also useful for evaluation of generic features of PH (Figure 2).

Recognition of CTEPH signs requires a high quality diagnostic CTPA, particularly for disease located at the segmental level. We recommend reviewing multiplanar images in mediastinal windows using a slice thickness of ≤ 1 mm. Webs and wall thickening can measure < 1 mm in thickness and may not be visible using thick slice reconstructions. A lung algorithm is useful for identification of mosaic lung attenuation. Occasionally, the protocol will need to be modified to account for artifacts.[142]

Dual energy CT (DECT) and lung subtraction iodine mapping (LSIM) have yielded promising results for the concomitant visualisation of the morphological changes in the pulmonary vasculature as well as lung perfusion abnormalities.(Figure 3) In CTEPH, segmental perfusion defects on pulmonary arterial phase demonstrate delayed parenchymal enhancement as a consequence of the systemic collateral supply.[143] Perfusion alterations are more frequent and heterogeneous in CTEPH compared to PAH.[144] DECT has been shown to be accurate at the segmental level and identifies more peripheral emboli than CTPA.[98,145] The pulmonary perfused blood volume (PBV) score on DECT can be

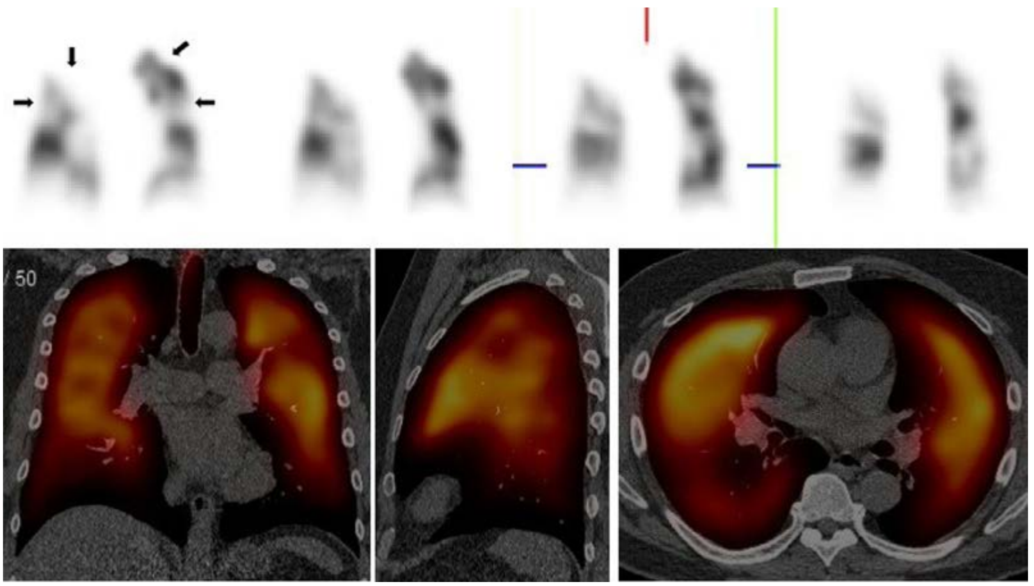

Figure 1 VQ-SPECT CT in a 38 year old male with CTEPH. Coronal perfusion views from the SPECT series (Top) demonstrates multiple segmental perfusion defects in both lungs (black arrows). Coronal, sagittal and axial reconstructions (Bottom) delineates the perfusion component overlaid on the axial low dose CT. The addition of CT to SPECT improves the specificity of the VQ by promoting the identification of lung diseases. CTEPH, Chronic thromboembolic pulmonary hypertension. VQ, ventilation-perfusion.

a useful and non-invasive measure of CTEPH severity with inverse correlation to mean PAP and PVR.[146,147] It has also been used to demonstrate improvement in perfusion post-BPA.[148] Whilst the information obtained from DECT is no-doubt useful, its utility in the diagnosis and prognosis of CTEPH must further be investigated in larger patient groups before it can be properly integrated into routine clinical practice.

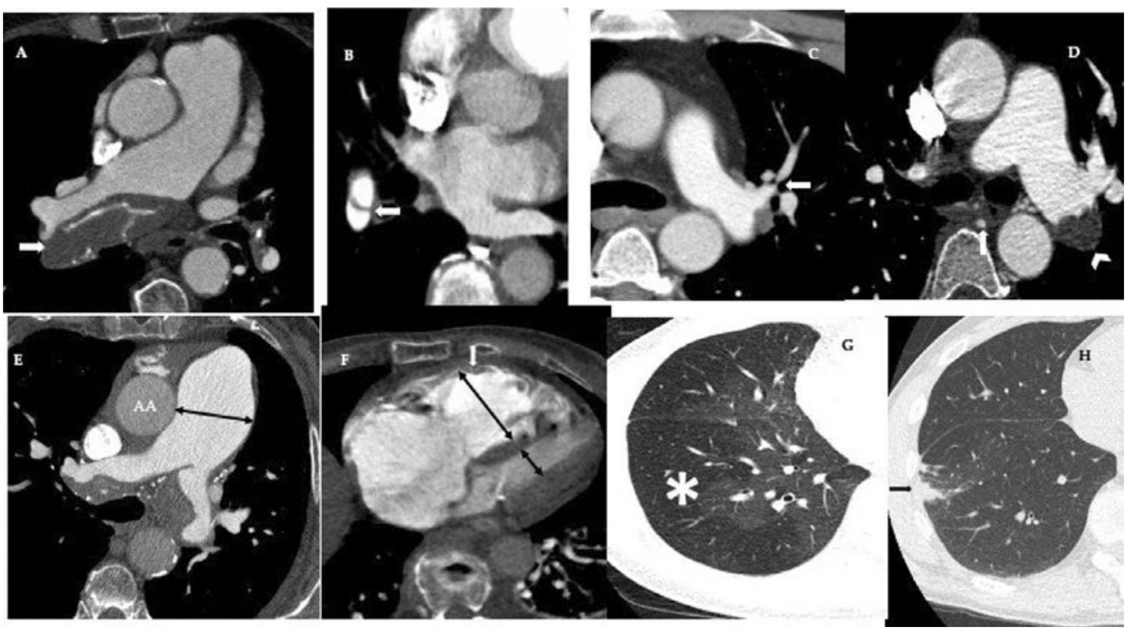

Figure 2 Signs of CTEPH on CTPA. (A) Eccentric calcific thrombus (arrow) in distal right main pulmonary artery. (B) Magnified view of the right lower lobe demonstrates a slit (arrow) in the segmental artery. Multiple slits are termed a web. (C) Stenosis (arrow) in left upper lobe artery (D) Dilated and tortuous bronchial artery collaterals (arrow) & occlusive thrombus (chevron) in the left interlobar artery. (E) Dilatation of the main pulmonary artery measuring 37 mm, larger than the accompanying ascending aorta (AA). (F) Dilated right ventricle (long double-ended arrow) relative to the left ventricle (short double-ended arrow). Also note hypertrophy of the right ventricular wall (white arrow). (G) Mosaic attenuation. The hypodense lung (*) corresponds to areas of decreased perfusion. (H) Curvilinear subpleural band opacities (arrow) corresponding to chronic pulmonary infarct. CTEPH, Chronic thromboembolic pulmonary hypertension; CTPA, Computed tomography pulmonary angiography.

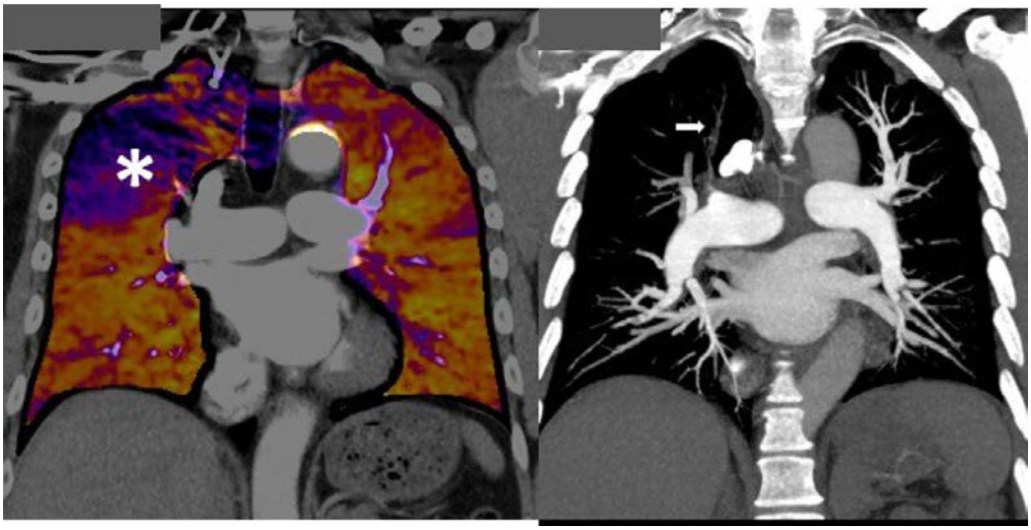

Figure 3 Coronal views of a dual Energy CTPA in a 55 year old with CTEPH. There is a large perfusion defect (*) in the anterior segment of the right upper lobe (Left) with corresponding occlusion (arrow) of the anterior right upper lobe pulmonary artery (Right). CTEPH, Chronic thromboembolic pulmonary hypertension; CTPA, Computed tomography pulmonary angiography.

Magnetic Resonance Imaging (MRI)

Cardiac MRI is the reference standard for the non-invasive assessment of RV function with high observer variability and interstudy reproducibility,[149] but its role in the CTEPH diagnostic algorithm is profoundly influenced by the availability of local expertise resulting in wide institutional variation in its usage.

The evaluation of the pulmonary circulation involves a two-step approach for the lung parenchyma and the pulmonary vasculature (Figure 4). Three-dimensional contrast enhanced lung perfusion MR has been demonstrated to have a high sensitivity equivalent to perfusion scintigraphy in diagnosing CTEPH.[150] High resolution contrast-enhanced angiography (CE-MRA) is the most effective MR technique for delineation of the pulmonary macrocirculation. The sensitivity and specificity of CE-MRA is 98% and 94% respectively in diagnosing proximal and distal CTEPH.[151] Whilst post-processing techniques such as rotating maximum intensity projections provide a comprehensive overview, it is also necessary to interrogate the source data and review multiplanar reformations to elicit all the morphological findings.

Emerging applications for tissue characterisation such as late gadolinium enhancement,[152] myomaps,[153] myocardial tissue tagging,[154] and 3-D strain imaging[155] have the potential to enhance the value of MRI in CTEPH by providing better evaluation of the RV performance. The paramagnetic properties of molecular oxygen as contrast medium is another promising tool for assessing ventilation on

Figure 4 MR of the pulmonary circulation in CTEPH. Coronal perfusion (left panel) dataset reveals lobar perfusion defect in the right upper and segmental perfusion defects in the right middle and left lower lobes (white star). On the angiography volume rendered technique (right panel), note the corresponding lobar occlusion in right upper and segmental disease in the right middle and left lower lobes (white arrow). CTEPH, Chronic thromboembolic pulmonary hypertension.

MRI[156,157] but its use in CTEPH is yet to be established. Parameters such as flow vortices in the main PA as well as metrics such as wall shear stress and kinetic energy losses measured by 4-D flow MR technique are not available from routine right heart catheterization and therefore have great potential for early recognition of PH and longitudinal follow-up.[158,159] A case report of a patient with CTEPH showed substantial late-systole vortex flow in the main PA with complete normalization of the flow patterns after successful BPA.[160] As the utility of these novel MR parameters in CTEPH continues to evolve, multicentre prospective clinical trials are needed to determine their clinical usefulness.

Right heart catheterization

Formal hemodynamic assessment is critical to establish the diagnosis of PH.[1] In CTEPH, it is also useful to inform on the severity of the PVR and facilitate triage of these patients for PEA.

Current recommendations for the diagnosis of CTEPH require a mean PAP ≥ 25 mmHg at rest without the hemodynamic influence of left sided cardiac disease inferenced by a PAWP < 15 mmHg.[1] A mean PAP >20 mmHg in combination with PVR> 3WU and PAWP <15 mmHg can be accepted for CTEPH diagnosis based on the 6th World Symposium on PH.[5] The impact of this new definition on CTEPH management is unknown, but possibly limited considering that some of these patients were already considered for PEA.[3] Of note, the PAWP is not always reliable in CTEPH due to the occlusion of pulmonary artery branches, and left sided heart disease may need to be ruled out by left ventricular end diastolic pressure (LVEDP) during left heart catheterization or with echocardiogram.

The mean PAP and PVR in CTEPH tend to be lower than in PAH.[68,161,162] This has been generally attributed to the hemodynamic influence of more proximal pulmonary vascular obstruction that may impart an additional load by altering the propagation of the pressure wave during RV ejection into the PA resulting in an increase in pulse pressure and can be quantified by measuring pulmonary vascular compliance.[163,164] In health and disease (unlike the systemic circuit) there appears to be a predictable relationship between PVR and pulmonary arterial compliance, expressed as the RC time constant; this has been shown to be higher in PAH compared to CTEPH.[165,166]

The degree of recovery after PEA appears to be dependent on improvement in both PVR and pulmonary vascular compliance. Patients who do not have a sufficient improvement in pulmonary vascular compliance (in the face of improved PVR) tend to have worse functional outcomes.[135] Additionally, pulmonary vascular compliance during exercise after PEA is inversely correlated with the degree of exercise impairment.[134] These observations suggests that the elasticity of the pulmonary artery can remain abnormal after PEA despite normalization of the pulmonary pressures.

Pulmonary angiogram

Catheter based pulmonary angiography is still the gold standard for CTEPH diagnosis as well as BPA treatment planning. Whilst a high quality CTPA is adequate for the diagnosis of chronic thromboembolic disease, in the context of a negative CTPA and high index of clinical suspicion for CTEPH, pulmonary angiography remains complementary.

A typical pulmonary angiography procedure includes a right heart catheterization (if not yet performed) followed by individual right and left pulmonary arterial injection in frontal and lateral or oblique views (Figure 5). Selective lobar injections can be performed to better identify treatable lesions. The pulmonary angiogram should be performed in the institution where therapy is planned.

Historical data on diagnostic pulmonary angiography has suggested a major complication rate of <1% and minor complication rate of <5%.[167] Unlike conventional arterial angiography where stenotic lesions are readily identified, CTEPH lesions can be more challenging to recognize. Kawakami and colleagues have described a novel angiographic classification of lesions in CTEPH that includes: (1) ring-like stenosis lesion, (2) web lesion, (3) subtotal occlusion lesion, (4) total occlusion lesion and (5) tortuous lesion.[168] Complementary techniques such as optical coherence tomography (OCT) can be hepful to characterize these lesions, but are yet to be validated in large scale clinical trials.[169]

Artificial intelligence

Technological advances in cardiac imaging coupled with exceptional computing power and innovative analytical

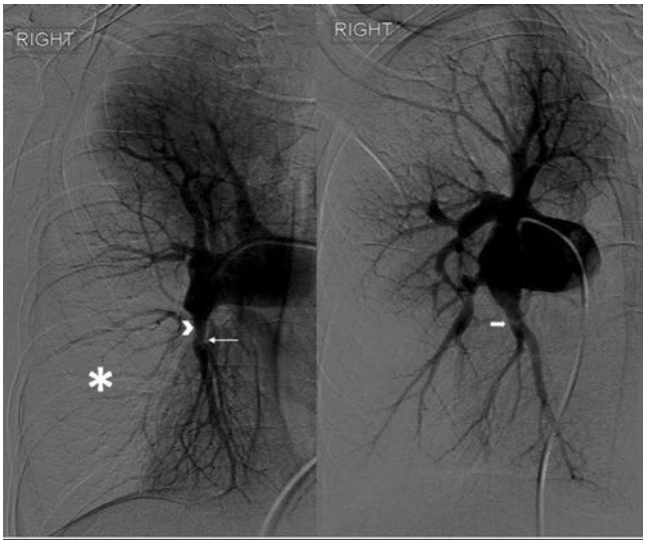

Figure 5 Catheter pulmonary angiography in a 57 year old female with CTEPH. Frontal (left) and Oblique (right) views demonstrates constellation of signs including intimal thrombus (chevron) in right lower lobe pulmonary artery, segmental stenosis with post-stenotic dilatation (thin arrow), proximal web (block arrow) that is only appreciable on the oblique view, abruptly truncated vasculature with loss of perfusion (*) in the parenchymal phase. CTEPH, Chronic thromboembolic pulmonary hypertension.

modelling offer an unprecedented amount of biological data that can contribute to the search for novel imaging biomarkers. Deep learning algorithms have been used in the automatic detection and segmentation of the ventricular chambers and can provide accurate quantitative measurements of RV volumes and ejection fraction.[170,171] A machine-learning based survival model that includes complex motion phenotypes has been shown to have incremental prognostic power when compared with conventional parameters and was able to more accurately predict patient outcomes in different PH groups including CTEPH.[172] Such computational simulations can help in understanding pathophysiological mechanisms of RV failure, risk stratification and identification of imaging end-points following therapeutic interventions.

Key points

1. Echocardiogram can be negative in patients with mild PH or exercise induced PH and it is necessary to consider downstream investigations if there is a high index of suspicion for CTEPH.
2. Cardiopulmonary exercise test is a useful tool for detection of pulmonary vascular disease in patients with suspected PH and normal echocardiography.
3. VQ scan is the screening test of choice to exclude CTEPH. SPECT VQ is superior to planar VQ for the delineation of perfusion defects.
4. High quality CTPA is sufficient for confirming CTEPH diagnosis but a negative CTPA cannot exclude CTEPH.
5. Pulmonary angiography is the gold standard for depicting the pulmonary vasculature. It is best performed in the institution where therapy is planned and often can be done at the same setting as the right heart catheterization.
6. Right heart catheterization is mandated to confirm the diagnosis, determine the severity of the hemodynamic impairment and establish prognosis, thereby informing clinical decision-making in the management of CTEPH.
7. The pulmonary artery wedge pressure is not always reliable in CTEPH due to the occlusion of pulmonary artery branches, and left sided heart disease may need to be ruled out by left ventricular end diastolic pressure (LVEDP) during left heart catheterization or with echocardiogram.

Pulmonary endarterectomy

PEA in segmental and subsegmental CTEPH

PEA using deep hypothermic circulatory arrest is the standard-of-care for CTEPH. The technique has been adopted by the vast majority of the surgical centers performing PEA and progressively refined with increasing experience.[85,173-178]

Currently, patients with disease located in the segmental and subsegmental pulmonary artery on imaging are candidates for PEA with excellent early and long-term outcome in expert centers.[85,178] A key factor of success in segmental and subsegmental disease is excellent quality imaging.[176] These patients can frequently be misdiagnosed if the imaging is not optimal or mislabeled as inoperable in centers with less experience.

Although the subjective correlation between the extent of chronic thromboembolic disease on preoperative pulmonary angiogram and the severity PVR is a reassuring parameter, the imaging tends to underestimate the amount of disease. Therefore, the subjective correlation between the extent of disease on imaging and the severity of the PVR is not a reliable parameter to determine surgical candidacy in segmental and subsegmental disease. Patients can have a dramatic benefit after PEA with normalization of their hemodynamic postoperatively despite limited amount of disease. Imaging tends to underestimate the disease as the chronic thromboembolic material retracts the lumen of the artery and branches of small calibers enlarge after PEA (Figure 6).

Up to 90% of the patients are surgical candidates in expert centers despite potentially higher risks at the time of surgery due to medical comorbidities or severe right heart failure.[177,178] Considering the long-term impact of PEA on functional capacity and quality of life, a second opinion from an expert center is recommended for patients who are deemed not eligible for surgery.[90] The value of the second opinion was demonstrated in the CHEST-1 study where local and central adjudication committees reviewed imaging from inoperable patients.[177] They observed that among the 312 patients considered inoperable, 16% were surgical candidates after local review of the imaging and 25% were surgical candidates after central review of the imaging.

Misdiagnosis and misconception in surgical candidacy

There are a number of conditions that mimic CTEPH and may constitute a diagnostic dilemma (Table 4). The importance of making the distinction between CTEPH and these other conditions is important since PEA is not indicated in these other conditions with the exception of pulmonary artery sarcoma.[179-189]

There are a number of misconceptions related to surgical decision making that are important to clarify. First, there is no evidence that the deep hypothermic circulatory arrest causes cognitive dysfunction in CTEPH patients.[174] The PEACOG trial, which randomized 74 patients between antegrade cerebral perfusion and intermittent periods of DHCA demonstrated that periods of circulatory arrest were necessary to achieve complete clearance of the thromboembolic material with adequate visualization of the distal PA branches.[174] The trial also demonstrated that on average the cognitive function improved at 3 months and 12 months after PEA compared to before the surgery, possibly as a result of better cardiac output and brain perfusion following PEA. Despite deep hypothermic circulatory arrest, a majority of patients do not require any blood transfusion during and after PEA.[85,175]

Second, there is no upper limit of PVR beyond which PEA is contraindicated. The operative risk is higher when

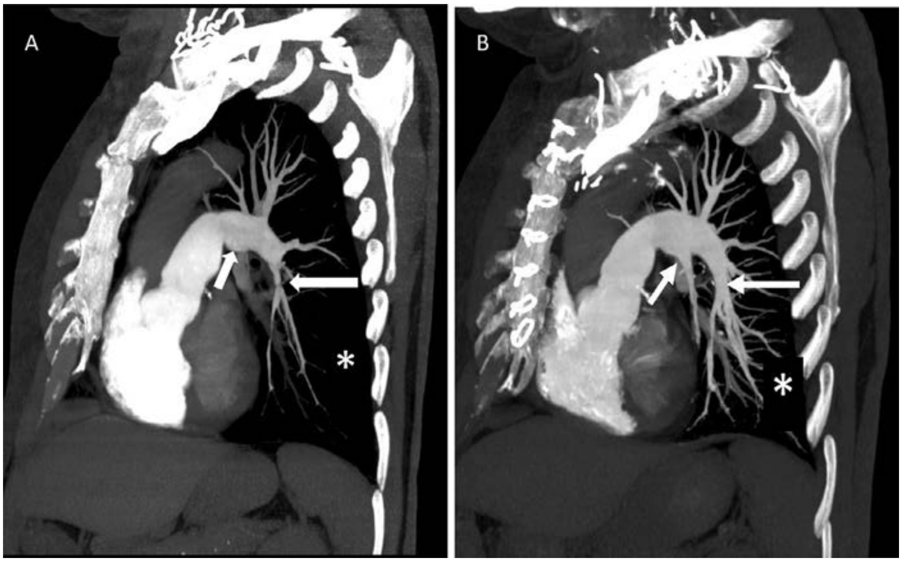

Figure 6 Coronal oblique CTPA MIP reformat of the left pulmonary arteries in a 56 year old man with CTEPH. A. Preoperative CTPA demonstrates a stenosis of the left lower lobe basal trunk (long arrow) due to webs and a complete occlusion of the lingular PA (short arrow). Note the paucity of vessels at the subsegmental level in the lung periphery (asterisk). B. Postoperative CTPA in the same patient demonstrates improved patency of the left lower lobe basal trunk (long arrow), reconstitution of the lingular pulmonary artery (short arrow) and a marked increase in vasculature at the subsegmental level (asterisk). MIP − Maximum intensity projection; CTPA − Computed tomography pulmonary angiogram.

Table 4 Conditions That may be Misdiagnosed as CTEPH

Pulmonary artery sarcoma[179]
Fibrosing mediastinitis[180]
Sarcoidosis[181]
Large vessel vasculitis, including Takayasu[182,183]
Peripheral pulmonary artery stenosis[184]
Congenital pulmonary artery anomalies[185]
In situ pulmonary artery thrombosis[186]
Pulmonary veno-occlusive disease[187]
Moyamoya disease[188]

the PVR is greater than 1,000 dynes.s.cm^{-5} (12.5 Wood Units).[85] However, even with PVR greater than 1,000 dynes.s.cm^{-5} (12.5 Wood Units), PEA is not contraindicated and in fact, these patients often have the most to gain, particularly in the presence of right heart failure. These patients can present with difficulty to wean CPB, but veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has become an important and successful option to bridge these patients to recovery.

Third, evidence demonstrates that patients over the age of 70 years derive as much benefit from PEA as those less than 70 years.[190,191] Although age may not be a contraindication to PEA by itself, the presence of other comorbidities in older patients must be kept in mind.[192]

Role of ECMO in CTEPH

ECMO can be used after PEA as a bridge to recovery in case of persistent PH with difficulty weaning CPB, severe airway hemorrhage, and reperfusion pulmonary edema.

ECMO is required in about 5% of the patients in large surgical series. Currently, over 70% of patients requiring ECMO after PEA are decannulated and up to 79% are discharged home (Table 5). Occasionally, VA ECMO can be used preoperatively to stabilize patients with decompensated right heart failure to transfer them from other institutions for their surgery or to optimize their clinical status before proceeding with PEA.[200-202]

The type of ECMO required is determined by the primary cause of failure. VA ECMO is indicated at the end of PEA in the presence of difficulty weaning CPB or postoperatively in the presence of worsening right heart failure. Central ECMO can be performed by using the sites of cannulation from CPB through the sternotomy. Alternatively, the femoral vessels can be cannulated.

VV ECMO is indicated for respiratory failure due to reperfusion pulmonary edema or severe intrapulmonary shunting with a steal phenomenon leading to severe hypoxemia. VV ECMO can be performed with two single stage venous cannula in the jugular vein and the femoral vein or with a dual lumen catheter (Avalon Elite, Avalon Laboratories, Rancho Dominguez, CA, USA) inserted into the right jugular vein.

The success of ECMO support is determined by the indications so that those with a reversible insult such as airway hemorrhage or reperfusion injury have a higher chance of successful weaning than those with persistent PH and RV failure.

Short and long-term outcome data after PEA

The early results of PEA are well established and described in many case series and registries. In expert centers, this operation is well tolerated and the hospital mortality is almost equivalent to other cardiac surgeries.[84,85,178,191,203-205]

Table 5 Outcome of ECMO After PEA

First author (Reference)	Years	Number of PEA	Number of ECMO	Wean from ECMO	Discharged home
Donahoe, L., et al.[193]	2005-2019	390	19 (4.9%)	17 (89%)	15 (79%)
Sugiyama, K., et al.[194]	2012-2015	35	4 (11%)	4 (100%)	3 (75%)
Kelava, M., et al.[195]	1997-2015	150	14 (9.3%)	NA	6 (43%)
Nierlich, et al.[196]	2001-2013	161	31 (19.3%)	28 (90%)	20 (65%)
Boulate, D., et al.[197]	2005-2013	829	31 (3.7%)	NA	15 (48%)
Berman, M., et al.[198]	2005-2007	127	7 (5.5%)	5 (73%)	4 (57 %)
Thistlethwaite, P.A., et al.[199]	1990-2006	1,790	20 (1.1%)	8 (40%)	6 (30%)

Improved hemodynamic parameters is the most important variable that has been shown to change immediately after PEA.[89] Improvement in functional status and exercise capacity take longer than hemodynamic changes as the right heart remodels over 3 to 12 months after PEA. The International CTEPH Registry[27,84] demonstrated that bridging therapy with PH-targeted therapy before PEA, NYHA class IV, history of cancer, and dialysis-dependent renal failure were independent risk factors for death after PEA. The most important predictor of mortality was functional class IV at registry entry.

There are now increasing reports describing the long-term outcome after PEA.[25,36,206-214] Normal quality of life, sustained improvement in hemodynamics, good functional class and excellent survival rates are the most important results of these studies. The long-term national cohort study from the UK, which included 880 consecutive patients, demonstrated that the cumulative 30-day mortality decreased from 13.2% for the earliest fraction of the cohort to 2.4% for the most recent cohort with an overall survival of 72% at 10 years for the whole cohort.[214]

Residual PH following PEA

Despite significant improvement in all haemodynamic parameters, residual PH is frequent after PEA.[84,197,198,214-219] However, there is no clear definition of what constitutes residual PH after PEA and thus the actual incidence of residual PH has been difficult to quantify.

The data from the UK cohort demonstrated that a mean PAP >38 mmHg and PVR > 425 dynes.sec.cm^{-5} /5.3 Units were associated with an increased risk of death due to right heart failure.[214] This data thus suggests that in patients surviving PEA, moderate residual PH is well tolerated and clinically meaningful residual PH after PEA mainly occur when the mean PAP is greater than 30-35 mmHg.

The lack of data on PH after PEA in the literature is leading to variability in practice between centers in terms of monitoring and reinvestigations after PEA as well as implementation of medical therapy or initiation of BPA. The risk of recurrent PH in the long-term underlines the importance of formally re-evaluating patients after PEA and to follow them in the long term.

Currently, it is recommended to proceed with repeat investigations including exercise testing (6 minute walk test and/or cardiopulmonary exercise testing), right heart catheterization and imaging such as VQ scan and CTPA within the first year after PEA. Patients should then be monitored on a yearly basis, or more frequently depending on their clinical condition. Long-term follow-up is also important due to the risk of progression of PH.

Surgery in patients without PH at rest

Major improvement in early outcome after PEA have led several centres to extend the indication of PEA to patients without evidence of PH at rest.

This group of patients currently represent 6 to 7% of all patients undergoing PEA in large programs.[3,91,220] Patient selection for PEA in the absence of PH at rest can be challenging and an extensive work-up to rule out other causes of shortness of breath is important. Several reports have shown that adequately selected patients without PH at rest can have significant improvement in their quality of life and exercise performance after PEA.[3,221,222]

CPET and right heart catheterization on exercise are helpful to select surgical candidates in the absence of PH at rest. CPET can document the reduction in ventilatory efficiency (VE/VC02) on exercise.[92,130] CPET also helps to evaluate the degree of deconditioning, which is a frequent cause of dyspnea after acute PE and may warrant referral to a rehabilitation program.[132]

Right heart catheterization during exercise provides an excellent means to evaluate the physiological impact of the pulmonary vascular disease.[93] The mean PAP can rise rapidly during exercise in relation to the cardiac output (CO) with a ratio mean PAP-CO slope >3.0 mmHg/min/l, suggestive of exercise induced PH.

The final decision about whether to proceed with PEA or not in these patients must be done after careful discussion with the patient on the risks and benefit of the surgery. The surgery is predominantly performed for quality of life and must be balanced against the risks of PEA.[221] Although cases of progression to CTEPH have been described, the risk is extremely low.[91]

What constitutes standard-of-care in PEA

Early and long-term outcomes after PEA are excellent when performed in expert CTEPH centers.

The hospital mortality is currently 2 to 3% and the 5-year survival greater than 70% in surgical centers performing more than 50 PEAs per year.[84,85,214,220,223-225] The risks of PEA depends on the location of the disease in the pulmonary artery, the severity of right heart failure and the degree of comorbidities.

Jenkins et al[224] on behalf of the International CTEPH Association proposed criteria to determine centers with surgical expertise based on the annual number of PTEs performed (>50/year), outcomes (in-hospital mortality <5%) and availability of specialists for medical and interventional therapies for CTEPH, recognizing that international networks is important for improving education in smaller centres to limit the learning curve of this demanding operation.

Key points

1. PEA under deep hypothermic circulatory arrest is the standard-of-care for CTEPH.
2. Excellent quality imaging is a key factor for surgical evaluation.
3. Segmental and subsegmental disease is accessible to PEA in experienced centers with excellent short and long-term outcome. These patients can be misdiagnosed if the imaging is not optimal or mislabeled as inoperable in centers with less experience. Second opinion should be sought from expert centers if necessary.
4. Imaging tends to underestimate the amount of disease. Therefore, the subjective correlation between the extent of disease on imaging and the severity of the pulmonary vascular resistance is not a reliable parameter to determine surgical candidacy, particularly in segmental and subsegmental disease.
5. ECMO provides an important back-up strategy for patients with postoperative complications.
6. PEA leads to excellent functional results and quality of life. However, residual PH is common and therefore patients should be reassessed with exercise testing (6 minute walk test and/or cardiopulmonary exercise testing), imaging and right heart catheterization within the first year after PEA. Long-term follow-up is also important due to the risk of progression of PH.
7. Chronic thromboembolic disease in the absence of PH at rest can be an indication for PEA in expert centers after careful patient selection.

Medical therapy for patients with CTEPH

Indications for targeted PH therapy

The histopathological remodeling of the precapillary pulmonary arteries in CTEPH are similar to those observed in idiopathic PAH. Hence, PH-targeted therapies have been studied in CTEPH patients, particularly in those who are deemed inoperable.[218,226-237]

Randomized controlled trials with targeted PH therapy in non-surgical CTEPH

A total of 5 randomized clinical trials have been completed and one is in progress in patients with CTEPH who were not candidates for PEA or presented with residual PH after PEA (Table 6).

A double-blind, placebo-controlled pilot study randomized 19 patients with inoperable CTEPH to sildenafil vs placebo for 12 weeks.[228] The overall severity of CTEPH at baseline was lower in the placebo arm than in the sildenafil arm. Although the study showed no significant improvement in 6MWD (p = 0.38, primary endpoint), significant improvement was seen in the secondary endpoints of WHO-FC ($p = 0.02$) and PVR ($p = 0.04$). When transitioned to open label sildenafil for 12 months, significant improvement was noted in 6MWD and PVR.

The BENEFiT study evaluated the safety and efficacy of dual endothelin receptor antagonist bosentan in 157 patients with inoperable CTEPH or persistent/ recurrent PH post PEA.[229] This 16-week randomized placebo-controlled trial demonstrated advantages with bosentan in terms of PVR (24% reduction, $p < 0.0001$) and NT-pro BNP levels ($p = 0.003$), but the primary combined end point of a reduction in PVR and an increment in 6MWD was not met. There was no statistically significant decrease in time to clinical worsening with bosentan versus placebo (hazard ratio 0.63, 95% CI 0.15-2.64).

In the double-blind CHEST-1 trial, oral soluble guanylate cyclase stimulator, riociguat, was randomly assigned to 173 of 261 enrolled patients with inoperable CTEPH or persistent/ recurrent PH post PEA for 16 weeks.[218] There was a mean increase of 39 meters in the 6MWD ($p < 0.001$, primary endpoint) and a drop in PVR of 246 dynes/cm/sec^5 ($p < 0.001$, secondary endpoint). Riociguat was also associated with significant improvements in NT-pro BNP level ($p < 0.001$) and WHO FC ($p = 0.003$), although the time to clinical worsening remained unchanged. Following CHEST-1, 237 of these patients entered the open label extension arm of the study (CHEST-2).[230] Improvements in 6MWD and WHO FC observed in CHEST-1 persisted up to 1 year. Riociguat is currently the only approved medical therapy in many countries for inoperable CTEPH and for residual PH after PEA.

MERIT-1 is a phase 2, double-blind, randomized, placebo controlled trial assessing macitentan in CTEPH patients adjudicated as inoperable.[231] Of importance, this trial allowed treatment with phosphodiesterase-5 inhibitors and oral or inhaled prostanoids for WHO functional class III/IV patients, thus supporting combination therapy in CTEPH.[212] There was a mean PVR reduction to 73% of baseline in the macitentan group and to 87% in the placebo group ($p = 0.041$), and improvement in 6MWD ($p = 0.033$) and NT-pro BNP ($p = 0.040$). The open label extension arm (MERIT-2) to assess the long-term safety, efficacy and tolerability of macitentan in inoperable CTEPH is ongoing.

More recently, the randomized double-blind controlled CTREPH (ClinicalTrials.gov, NCT01416636) trial

Table 6 Summary of Randomized Trials Looking at Medical Treatment for CTEPH

	Sildenafil	BENEFiT	Chest 1	MERIT 1	CTREPH
Drug	Sildenafil	Bosentan	Riociguat	Macitentan	Treprostinil
Trial design	Randomized, placebo controlled, double blind	Randomized, multi-center, placebo controlled, double blind	Randomized, multi-center, placebo controlled, double blind	Randomized, multi-center, placebo controlled, double blind	Randomized, double blind, randomized to high versus low dose
Author (Year) (Ref)	Suntharalingam et al. (2008)[228]	Jais et al. (2008)[229]	Ghofrani et al. (2013)[218]	Ghofrani et al. (2017)[231]	Sadushi-Kolici et al. (2018)[232]
Number of patients randomized to active drug/ enrolled	9/19	77/ 157	173/ 261	40/80	53/52 (high/low dose)
CTEPH patients included	Inoperable	Inoperable, persistent/ recurrent PH post PEA	Inoperable, persistent/ recurrent PH post PEA	Inoperable	Inoperable, persistent/ recurrent PH post PEA
Goal drug dose	40 mg TID	125 mg BID	2.5 mg TID	10 mg daily	Low dose – 3ng/kg/min High dose – 30 ng/kg/ min
Study duration	3 months	16 weeks	16 weeks	16 weeks	24 weeks
Primary endpoint	6MWD	6MWD, PVR	6 MWD	PVR	6MWD
Secondary endpoints	WHO FC, NT-pro BNP, hemodynamics, QOL scores	WHO FC, hemodynamics, Borg index, QOL scores, time to clinical worsening	WHO FC, PVR, NT-pro BNP, time to clinical worsening, Borg index, QOL, safety	WHO FC, 6MWD	WHO FC, Borg index, QoL, clinical worsening, HR
Change in endpoints					
noted	+17.9 m (0.38)	+2.9 m ($p = 0.54$)	+39 m ($p < 0.001$)	+35 m ($p = 0.03$)	High/Low dose
- 6MWD	-5.8 ($p = 0.052$) -179	-2.5 ($p = 0.06$)	-4 ($p < 0.001$)	-17% ($p = 0.04$)	+45/+3.8 ($p = 0.0002$)
- PAP mean	(p=0.044)	-24.1% ($p < 0.0001$)	-226 ($p < 0.001$)	$p = 0.10$	-3.4/-0.4 ($p = 0.04$)
- PVR	-0.1 ($p = 0.7$)	-0.8 ($p = 0.63$)	-1 ($p = 0.4$)		-214/+73 ($p < 0.001$)
- RAP	44% ($p = 0.025$)	-622 ($p = 0.003$)	$p < 0.003$		+0.7/+2.9 ($p = 0.23$)
- WHO-FC improved	-355 ($p = 0.24$)	+0.3 ($p = 0.0007$)	-444 ($p < 0.001$)		0 = 0.001
- NT-pro BNP	-0.1($p = 0.99$)	-0.4 ($p = 0.038$)	-0.8 ($p = 0.004$)		-157/+330 ($p = 0.03$)
- Cardiac Index	-0.7 ($p = 0.2$)				+0.4/-0.2 ($p < 0.001$)
- Borg index					-0.4/-0.1 ($p = 0.3$)

demonstrated safety and efficacy of high dose subcutaneous treprostinil compared to low dose in inoperable CTEPH or recurrent PH after PEA. At week 24, the mean 6-minutes walk distance improved by 44.98 m (95% CI 27.52 – 62.45) in the high-dose group, and by 4.29 m (95% CI -13.34 – 21.92) in the low-dose group (treatment effect 40.69 m, 95% CI 15.86 to 65.53, $p = 0.0016$).[232]

The SELECT study (ClinicalTrials.gov NCT03689244) assessing the efficacy and safety of selexipag in subjects with inoperable or persistent/recurrent CTEPH is ongoing.

Bridging therapy for PEA with targeted PH therapy

There have been two small randomized, prospective studies of bridging therapy before PEA, both using bosentan,[233,234] although only one of them reported post-PEA results (Table 7). Thirteen of 25 patients received bosentan for 16 weeks prior to PEA.[214] Hemodynamics and exercise capacity were significantly improved in the bosentan group compared to baseline and to the placebo group. However, hemodynamic improvement following PEA was similar between the 2 groups with no additional benefit related to the use of bosentan.

Two retrospective studies analyzed the outcome after bridging therapy for PEA using epoprostenol. These studies included 21 patients in total, the majority with PVR >12 Wood Units and reported improvement in hemodynamics prior to PEA following treatment with IV epoprostenol.[235,236] Post-operatively, there was significant hemodynamic improvement from PEA with similar results between patients treated or not with epoprostenol.

A large retrospective single center study found minimal pre-operative hemodynamic benefit in 111 patients who received targeted PH therapies before PEA compared to 244 patients who did not. Both groups had similar hemodynamic benefit and outcome following PEA.[227] However, those treated with medical therapy had a significant delay in the time to referral for PEA.[227]

The International CTEPH Registry reported that bridging therapy was associated with higher mortality after PEA (HR 2.62, 95%CI, 1.30-5.28, $p = 0.007$).[27] Although this observation could be due to the use of targeted PH therapies predominantly in higher risk patients before PEA, it also point out to a possible deleterious effect from delayed PEA.

An ongoing randomized trials (ClinicalTrials.gov NCT03273257) with bridging therapy before PEA was initiated, but closed early due to the lack of accrual.[237]

Overall, currently there is no indication for targeted PH therapy before PEA in surgical candidates.

Targeted PH therapy in BPA candidates

BPA candidates with mean PAP greater than 35 mmHg are treated with targeted PH therapy before BPA to reduce the risk of reperfusion injury during BPA (Table 8). This approach is supported by 2 recent studies demonstrating

Table 7 Studies of Bridging Therapy Prior to PEA

Author	Year	Study	Patients (n)	Medical treatment before PEA (%)
Nagaya, N., et al.,[235]	2003	Prospective	33	36
Bresser, P., et al.[236]	2004	Retrospective	246	4
Jensen, K.W., et al.[227]	2009	Retrospective	355	31
Reesink, H.J., et al.[233]	2010	Randomized	23	52
Surie, S., et al.[234]	2013	Randomized	15	53
Delcroix, M., et al.[27]	2016	Prospective	404	29

that high mean PAP predicts the occurrence of lung injury as a complication of BPA.[251,252] In addition, since multiple sessions of BPA are usually necessary, PH medications can improve symptoms while the sessions of BPA are being completed. The soluble guanylate cyclase inhibitor riociguat is most commonly utilized,

The RACE study (ClinicalTrials.gov NCT02634203) randomized CTEPH patients who are not eligible for PEA to riociguat or BPA with a cross over. The results from this trial will provide important information on the role of targeted PH therapy in patients who are candidates for BPA. Preliminary results found that PVR is reduced by 68% with BPA and by 41% with riociguat.

IVC filters in the management of CTEPH

Routine use of vena-cava filters in CTEPH is not justified by available evidence. Initially recommended for patients undergoing PEA, this practice has been abandoned by most expert centers. The International CTEPH Registry showed that 40% of patients had IVC filters, but there was no evident benefit in long-term outcome.[27]

Use of anti-coagulants in CTEPH

Vitamin K antagonists are the standard of care for patients with CTEPH targeting an INR between 2 and 3 to prevent both recurrent venous thromboembolism and in situ pulmonary artery thrombosis.[89]

Although DOACs are increasingly used in CTEPH, there is limited data published in this patient population. DOACs presently are indicated only in the treatment of acute PE and deep vein thrombosis, atrial fibrillation, and acute coronary syndromes.[253,254] They have been shown to be inferior to vitamin K antagonists for anticoagulation in patients with mechanical valves.[253,254] A recent retrospective multicenter study comparing 794 patients treated with vitamin K antagonists to 206 patients with DOACs demonstrated a small but significant increase in the rate of VTE recurrence with DOACs.[255] The rate of major bleeding was otherwise equivalent between the 2 groups.

No recommendation can be made at this time regarding the use of DOACs in CTEPH before or after PEA. The full dose of DOACs should be used. There is no data to support the use of low dose DOACs in CTEPH. These observations provide a strong rational for prospective registry data to evaluate the safety of DOACs in CTEPH compared to vitamin K antagonist.

Multidisciplinary management of CTEPH patients

It has been well established that patients with CTEPH require multidisciplinary care at expert CTEPH centers.[113,204] CTEPH coordinators are helpful to provide comprehensive patient care and coordination between PEA centers and

Table 8 Studies of Bridging Therapy Prior to BPA

Author	Year	Study	Patients (n)	Medical treatment before BPA (%)
Sugimura, K., et al.[238]	2012	Prospective	12	100
Mizoguchi, H., et al.[239]	2012	Retrospective	68	100
Andreassen, A.K., et al.[240]	2013	Retrospective	20	10
Inami, T., et al.[241]	2014	Retrospective	68	88
Taniguchi, Y., et al.[242]	2014	Retrospective	29	100
Fukui, S., et al.[243]	2014	Retrospective	20	75
Tsugu, T., et al.[244]	2015	Prospective	25	100
Roik, M., et al.[245]	2016	Prospective	11	55
Inami, T., et al.[246]	2016	Retrospective	170	91
Kurzyna, M., et al.[247]	2017	Retrospective	56	80
Ogo, T., et al.[248]	2017	Retrospective	80	61
Aoki, T., et al.[249]	2017	Prospective	84	96
Olsson, K.M., et al.[250]	2017	Prospective	56	95

community-based referring practitioners.[256] These coordinators are typically registered nurses who provide smooth transition for the patients and their families in the CTEPH journey. The CTEPH team should also have accessed to extended multidisciplinary teams including social worker, psychiatrist, physiotherapist and occupational therapist to address unique patient needs or situations.

Exercise training and physical rehabilitation of CTEPH patients is an evolving topic. All exercise programs for patients with CTEPH should be supervised by a physiotherapist and/or CTEPH specialist due to the possibility of adverse effects such as presyncope, syncope, cardiac arrhythmias, or chest pain secondary to PH. Initially, post PEA patients with no residual PH should engage in cardiopulmonary exercises and slowly increase the intensity until sternal healing takes place. Thereafter, weight based training can be added gradually while monitoring symptoms of fatigue, dyspnea, and chest pain. Pulmonary and cardiac rehabilitation programmes in patients after BPA treatment or after PEA surgery demonstrated improved 6-minute walk distance, peak oxygen consumption, exercise capacity and quality of life.[257-260] Although studies have shown that obesity did not increase the surgical risks in patients undergoing PEA and similar functional outcome can be achieved in obese and non-obese patients after PEA, CTEPH patients should nevertheless still be encouraged to follow adequate nutrition to keep healthy body weight.[261,262]

Key points

1. Pharmacotherapy targeting PH is an option for CTEPH patients who are not candidates for PEA and those with residual PH after PEA.
2. There is currently no evidence to support using targeted PH therapy before PEA in patients with operable CTEPH.
3. Life-long anticoagulation is recommended for patients with CTEPH.
4. Direct oral anti-coagulants (DOACs) are increasingly used in CTEPH, but limited data is available in this specific patient population.
5. There is no data to support the routine use of IVC filter in CTEPH patients.

5. Balloon pulmonary angioplasty

History and current results

The first series of balloon pulmonary angioplasty (BPA) was reported by Feinstein et al[263] in 2001 in 18 patients with inoperable CTEPH. They showed that BPA could improve functional parameters.[263] However, 61% of patients developed reperfusion pulmonary edema including one third requiring mechanical ventilation.

Since then, staged approaches to avoid opening too many segments in one session, use of softer wires to avoid guide wire injury, and careful selection of balloon size in relation to hemodynamic severity have significantly reduced the rate of complications and enhanced the role of BPA as an excellent treatment option for inoperable patients with CTEPH and patients with persistent PH after surgery.[238,239,249,264]

The largest BPA cohort published to date is the Japanese multicenter registry of 308 patients who underwent 1,408 BPA procedures from 2004 to 2013.[265] Twelve patients (3.9%) died during follow-up, including 8 within 30 days after BPA (2.6%). The main causes of death were similar to those post-PEA: right heart failure, multiorgan failure and sepsis. Complications occurred in 36.3% and included predominantly pulmonary injury (17.8%), hemoptysis (14.0%), and pulmonary artery perforation (2.9%). One-year survival was 96.8% (95% CI, 93.7%-98.4%) and 3-year survival 94.5% (95% CI, 89.3%-97.3%). The decrease in PVR after BPA was maintained during follow-up, with a reduction of concomitant use of PH-targeted therapy and need of oxygen supplementation.[265] Information on long-term outcome after BPA was limited.

The French group assessed the evolution of their activity following the initiation of the BPA program in their institution in 2014.[266] The BPA program did not reduce the number of patients who underwent PEA. Patients undergoing PEA in the BPA era, however, appeared to have lower early mortality (although non-significant) at 30- and 90-days despite more distal lesions (type III of the Jamieson's classification), suggesting that PEA and BPA can be complementary therapeutic options.

Since 2017, a large number of centers have reported their results with BPA around the world (Table 9). Around 12% of BPAs were performed for residual PH after PEA. The proportion of women undergoing BPA is higher than men, reaching up to 80% in the Japanese registry.[265] This may be related to the fact that women are at increased risk of residual PH after PEA and have more segmental disease than men.[267]

Mean PA pressures have consistently improved after BPA to an average ranging between 31 and 33 mmHg in all series of patients published in the English literature since 2017 (Table 9). The only notable exception is the Japanese experience with an average dropped in mean PA pressure to 24 mmHg (Table 9). Whether this difference is related to the larger Japanese experience or to different patient's characteristics is unknown. Brenot et al demonstrated that outcome and complication rates improve with growing experience.[252]

In addition to hemodynamic improvements in right atrial pressure, pulmonary artery pressure, cardiac index and PVR, other parameters that have been shown to improve after BPA including 6MWD, functional class, NT-proBNP, and right heart imaging parameters including tricuspid annular plane systolic excursion.[245,250,269-281] In addition, cardiopulmonary exercise testing has proven enlightening, with clear improvement in ventilatory efficiency (VE/VC02) that likely accounts for a significant component of the improvement in dyspnea and physical functioning that have become the hallmark of successful BPA treatment.[272]

This improvement in ventilatory efficiency and its benefits for patient perception of dyspnea provides a strong rationale for preferring BPA over medical therapy for these patients, particularly in the absence of PH at rest.[278] A

Table 9 Summary of Published BPA Experience Around the World Since 2017

Country (References)	Year of publication	Number of patients	% after PEA	Gender	mean PAP (mmHg)		Cardiac index (L/min/m^2)		PVR (Dynes.s.cm^{-5})		6′ walk distance (m)	
				% women	pre-BPA	post-BPA	pre-BPA	post-BPA	pre-BPA	post-BPA	pre-BPA	post-BPA
Japan[265]	2017	308	4.5	80	43±11	24±6	2.6±0.8	2.9±0.7	854±451	360±223	318±122	401±105
Germany[250]	2017	56	13	61	40±12	33±11	2.4±0.6	2.5±0.6	591±286	440±279	358±108	391±108
Korea[268]	2018	15	40	47	41±13	32±10	2.94±0.79	2.96±0.93	607±452	407±265	387±86	453±65
Germany[269]	2018	51	7.8	55	40±12	33±13	2.5±0.6	2.5±0.5	516±219	397±183	375 (281-446)	409 (332-446)
Poland[270]	2019	15	100	40	45±6	31±8	2.9±0.7	2.9±0.9	6.9±2.3 WU	4.35±1.57 WU	383±104	476±107
France[252]	2019	154	8.2	49	44±10	32±9	2.68±0.6	3.07±0.75	604±226	329±177	396±120	441±104
Belgium[271]	2019	18	28	56	44±12	31±12	2.3±0.4	2.7±0.6	8.4±3.6 WU	4.6±3.3 WU	412±167	402±196
United States[272]	2019	31	16	42	40 (29-48)	29 (25-37)	2.4 (2.1-3.1)	2.7 (2.1-3.3)	5.5 (3.0-7.6) WU	3.3 (2.2-5.2) WU	402 (311-439)	439 (366-510)
Netherlands[273]	2020	38	0	61	40±12	31±8	2.9±1.1	3.0±0.8	6.1±4.7 WU	3.3±2.0 WU	374±124	422±125
United Kingdom[274]	2020	30	0	27	45±11	34±8	NA	NA	663±281	436±196	366±107	440±94

recent meta-analysis of published reports of BPA and medical therapy for CTEPH is consistent with greater improvement in hemodynamics and 6-minute walk distance with BPA. The report also showed marked heterogeneity in the incidence of reperfusion injury.[280] The frequency of serious complications from BPA appears to be declining with increasing center experience, so it is anticipated that the role of BPA in management of CTEPH will continue to expand.

Patient selection for BPA

Patients diagnosed with CTEPH should be assessed by expert centers to determine operability for PEA and BPA in a multidisciplinary meeting that includes PEA surgeons, interventional radiologists/ cardiologists experienced in pulmonary vascular imaging and cardiologists/pulmonologists with expertise in PH.[89] Eligibility for BPA is decided on the basis of a consensus among the multidisciplinary team.

Currently, the selection for PEA and BPA is in part dependent on the center expertise. In high volume PEA centers, material that is located in the first subsegmental generation of the pulmonary vasculature can be accessible surgically. Therefore, optimized imaging (0.5-1 mm slices CTPA and selective pulmonary angiography) is crucial for treatment decision making. Furthermore, in highly selected patients, severe comorbidities in technically operable CTEPH may be reasons to decide for BPA.

In very rare situations, patients with upper lobe predominant COPD and lower lobe predominant CTEPH may present with significant problems of hypoxemia resulting from very adverse VQ mismatch (poor perfusion in the lower segments that are reasonably ventilated, and poor ventilation in the upper segments that are reasonably perfused). This can be accompanied by the hemodynamic compromise of pulmonary hypertension (mixed Group III and IV) with impaired cardiac output and right ventricular function at rest and with activity. BPA can be particularly effective in these patients in reducing oxygen requirements, improving dyspnea, and improving hemodynamics and activity tolerance.

Target lesions for BPA

The most common target lesions for BPA are sub-segmentally located stenoses such as “webs” and “slits” (Figure 7). Subtotal obstructions can also be targeted, with careful wire technique and a sense of when to back off. Pouch lesions in more proximal segments are generally avoided since accessing the distal lumen of the vessel is very challenging, with increased risk of vascular perforation.

Selective right and left pulmonary angiography with rotational Dyna CT imaging can be very useful in visualizing the pulmonary vascular tree prior to initiating a series of BPA sessions (272). Visualization of extent of perfusion defects can also be improved with SPECT scan, which provides more volumetric and easily visualized assessment of the perfusion defects. This can also be fused with the CT angiographic images to define the target arears for BPA.[281]

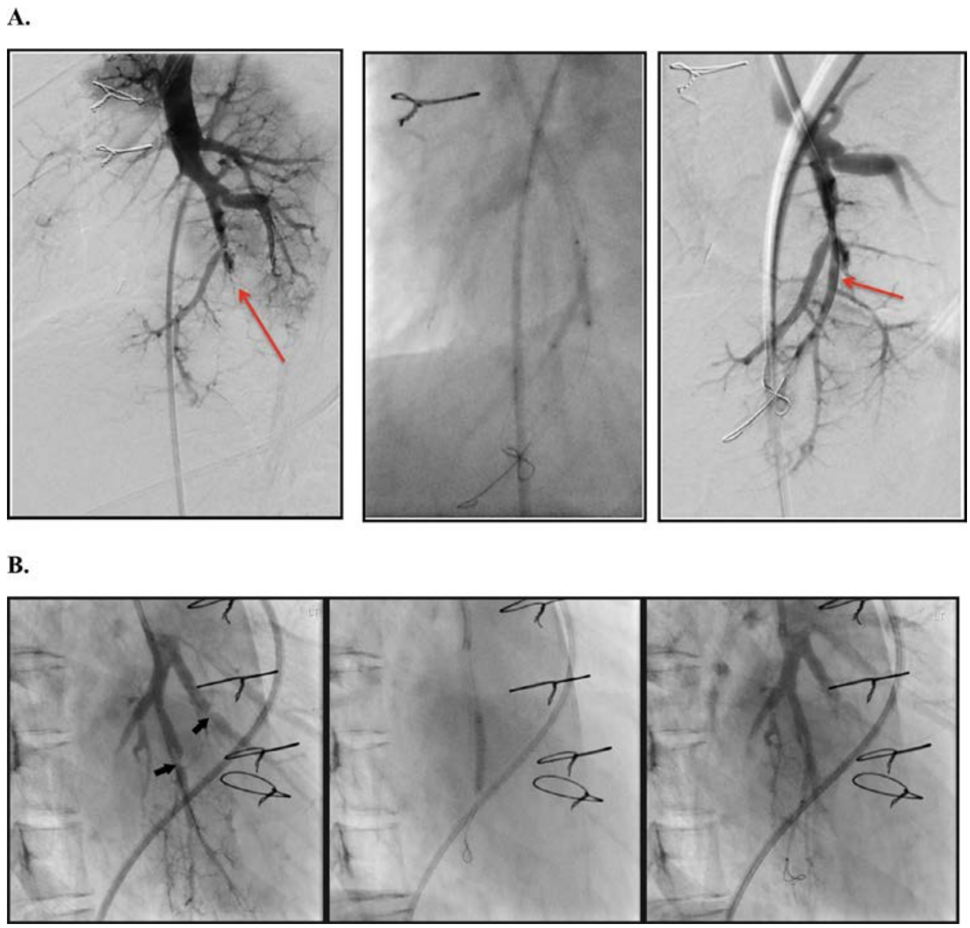

Figure 7 Two patients (A and B) post endarterectomy with residual left lower lobe distal segmental severe stenosis (arrows). Challenging area to reach surgically. Balloon pulmonary angioplasty to 3mm with improvement in angiographic result.

BPA is performed as a staged procedure with a limited number of pulmonary segments per session, depending on disease severity. Factors to be considered with regard to number of segments to dilate at a given session include contrast load which can be significant, presence of renal insufficiency that will impact amount of contrast that can be safely utilized per session, and extent of baseline elevation in PA pressure since that impacts the risk of reperfusion injury.

Dilatation strategies to reduce risk of reperfusion injury include only partially opening segments, utilizing a pressure wire to assess baseline and residual pressure gradient, and then returning on a different occasion to more fully open the segments.[275] An alternative approach is to fully open the segments that are being treated in a particular session, but to limit the number of vessels and size of distribution of the segments so that if reperfusion edema does occur, the extent of lung involved is tolerable.

Because vascular injury causes most complications, including the majority of those that are labeled as reperfusion edema, cautious handling and avoiding advancement of the wire or balloon too far peripherally is useful in preventing complications

Longitudinal assessment

BPA generally aims to treat all target lesions. If patients have been pretreated with riociguat or other pulmonary vasodilators, it can be possible to withdraw the medication following successful completion of the BPA sessions. Reassessment with 6MWD, CPET, echocardiography, NT-proBNP, and right heart catheterization is helpful in confirming extent of improvement and assurance that there is no need for additional BPA sessions or other therapy. Restenosis does not appear to be a problem with BPA, so there does not appear to be need for repeat dilation of previously effectively treated segments.

Combined approach with PEA and BPA

BPA and PEA can be complementary and combined in different sequences. This includes elective BPA in patients with residual PH after PEA (Figure 7). Urgent BPA after PEA does carry high risks of complications due to hemodynamic instability and is generally avoided.[217] BPA before PEA allegedly entails difficulties for surgery as the plane of endarterectomy is fractured by the balloon angioplasty, which may make PEA impossible in segments that have been dilated. Hybrid options are also feasible, either with preoperative BPA for left lower lobe segmental disease that may be more difficult to reach at surgery or with concomitant procedures in the operating room, using BPA during the rewarming period after PEA in an hybrid operating room.[279] Concomitant procedures in the operating room, however, has generally not been recommended due to the complexity and risks.

Limitations and futures studies

The three treatment modalities (PEA, targeted PH therapy, BPA) lead to various possible combinations. Hence, individualized long-term multimodality concepts do play an important role in the treatment of CTEPH patients. Long-term data of BPA treated patients remains limited, so that the ultimate role of BPA in management of CTEH needs to continue to be refined and understood.

Key Points

1. Balloon pulmonary angioplasty should be performed at centers with multidisciplinary expertise in management of CTEPH.
2. Pretreatment with targeted PH therapy in patients with mean PA pressure greater than 35 mmHg may reduce risk of reperfusion pulmonary edema and facilitate earlier symptomatic improvement in CTEPH.
3. Balloon pulmonary angioplasty can result in clinically important improvement in dyspnea, activity tolerance, hemodynamics, right ventricular function, and ventilatory efficiency in appropriately selected patients.
4. Optimal role of BPA and long term outcome requires additional study.

Conclusions

The field of CTEPH is rapidly evolving with regards to diagnosis, therapy and monitoring. Future studies will continue to refine an integrated multidisciplinary approach, analyze the application of new diagnostic options, and evaluate the implementation of new therapies in the management of CTEPH such as for instance pulmonary artery denervation.[282]

Summary of key points

Definition, epidemiology and clinical presentation

1. The exact incidence of CTEPH in the general population is not well defined as the disease remains largely underdiagnosed.
2. The clinical presentation is not specific and can mimic acute PE diagnosis. As a consequence, the diagnosis is frequently delayed.
3. It is essential to keep a high index of suspicion for CTEPH: (1) In patients with risk factors for CTEPH in the context of an acute PE, (2) In patients with a new diagnosis of PH, and (3) In patients with unexplained dyspnea.
4. Risk factors for CTEPH in the context of acute PE include CT findings suggestive of CTEPH, evidence of PH on echocardiogram, large clot burden, recurrent PE, unprovoked PE, history of splenectomy, infected pacemaker leads, chronic inflammatory disease, antiphospholipid syndrome, hypothyroidism, ventriculo-atrial shunt, and persistent symptoms despite anticoagulation.
5. There is no indication to administer thrombolytic therapy to prevent CTEPH.
6. If CTEPH is suspected, screening investigations should be performed after 3 months of anticoagulation with echocardiogram and VQ scan. Earlier assessment can be performed in the presence of worrisome signs or symptoms of heart failure.

Diagnostic approach to CTEPH

1. Echocardiogram can be negative in patients with mild PH or exercise induced PH and so it is necessary to consider downstream investigations if there is a high index of suspicion.
2. Cardiopulmonary exercise testing is a useful tool for detection of pulmonary vascular disease in patients with suspected PH and normal echocardiography.
3. VQ scan is the screening test of choice to exclude CTEPH. SPECT VQ is superior to planar VQ for the delineation of perfusion defects.
4. High quality CTPA is sufficient for confirming CTEPH diagnosis but a negative CTPA cannot exclude CTEPH.
5. Pulmonary angiography is the gold standard for depicting the pulmonary vasculature. It is best performed in the institution where therapy is planned and often can be done at the same setting as the right heart catheterization.
6. Right heart catheterization is mandated to confirm the diagnosis, determine the severity of the hemodynamic impairment and establish prognosis, thereby informing clinical decision-making in the management of CTEPH.
7. The pulmonary artery wedge pressure is not always reliable in CTEPH due to the occlusion of pulmonary artery branches, and left sided heart disease may need to be ruled out by left ventricular end diastolic pressure (LVEDP) during left heart catheterization or with echocardiogram.

Pulmonary endarterectomy

1. PEA under deep hypothermic circulatory arrest is the standard-of-care for CTEPH.
2. Excellent quality imaging is a key factor for surgical evaluation.
3. Segmental and subsegmental disease is accessible to PEA in experienced centers with excellent short and long-term outcome. These patients can be misdiagnosed if the imaging is not optimal or mislabeled as inoperable in centers with less experience. A second opinion should be sought from expert centers if necessary.
4. Imaging tends to underestimate the amount of disease. Therefore, the subjective correlation between the extent of disease on imaging and the severity of the pulmonary vascular resistance is not a reliable parameter to

determine surgical candidacy, particularly in segmental and subsegmental disease.

5. ECMO provides an important back-up strategy for patients with postoperative complications.
6. PEA leads to excellent functional results and quality of life. However, residual PH is common and therefore patients should be reassessed with exercise testing (6 minute walk test and/or cardiopulmonary exercise testing), imaging and right heart catheterization within the first year after PEA. Long-term follow-up is also important due to the risk of progression of PH.
7. Chronic thromboembolic disease in the absence of PH at rest can be an indication for PEA in expert centers after careful patient selection.

Medical therapy for patients with CTEPH

1. Pharmacotherapy targeting PH is an option for CTEPH patients who are not candidates for PEA and those with residual PH after PEA.
2. There is currently no evidence to support using targeted PH therapy before PEA in patients with operable CTEPH.
3. Life-long anticoagulation is recommended for patients with CTEPH.
4. Direct oral anti-coagulants (DOACs) are increasingly used in CTEPH, but limited data is available in this specific patient population.
5. There is no data to support the routine use of IVC filter in CTEPH patients.

Balloon pulmonary angioplasty

1. Balloon pulmonary angioplasty should be performed at centers with multidisciplinary expertise in management of CTEPH.
2. Pre-treatment with targeted PH therapy in patients with mean PA pressure greater than 35 mmHg may reduce risk of reperfusion pulmonary edema and facilitate earlier symptomatic improvement in CTEPH.
3. Balloon pulmonary angioplasty can result in clinically important improvement in dyspnea, activity tolerance, hemodynamics, right ventricular function, and ventilatory efficiency in appropriately selected patients.
4. The optimal role of BPA and long-term outcome requires additional study.

Disclosures

Anastasia Bykova , Elie Fadel, Deepa Gopalan, Sebastian Mafeld , David McGiffin and Patricia A Uber has nothing to disclose.

William R Auger received personal fees from Bayer, Actelion, Cereno Scientific and non-financial support from Bayer outside the submitted work. Raymond Benza received personal fees and institution grants from Bayer and Janssen outside the submitted work. Andrea M D'Armini received personal fees from MSD outside the submitted work. Marion Delcroix reports grants from Actelion and other support from Actelion, Bayer, MSD, Acceleron outside the submitted work. Marc de Perrot received personal fees from Actelion, AstraZeneca, Bayer, Merck, Roche and unrestricted financial support provided to his institution from Bayer outside the submitted work,. Robert P Frantz received personal fees from Janssen, Liquidia, Shouti, and Up-To-Date, institutional grant from Bayer, and institutional payment from United Therapeutics and Gossamer Bio. John T Granton received unrestricted financial support provided to his institution from Bayer and Janssen Pharmaceuticals outside the submitted work. Gustavo A Heresi received personal fees from Bayer, and Janssen outside the submitted work. David Jenkins received personal fees from Actelion and grant from Bayer outside the submitted work. Manreet Kanwar received personal fess from Amiomed, Bayer and CareDx (Advisory Board) outside of the submitted work. Kim M Kerr receives personal fees from Actelion and grants from Bayer outside the submitted work. Erik A Klok received research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Actelion, the Dutch thrombosis association, The Netherlands Organisation for Health Research and Development and the Dutch Heart foundation, all outside the submitted work. Irene M Lang received personal fees from Janssen, AOP Orphan Pharma, United Therapeutics, and grants from Janssen, AOP Orphan Pharma, Neutrolis, and non-financial support from AOP Orphan Pharma, outside of the submitted work. Michael M Madani received personal fees as a consultant for Wexler Surgical outside the submitted work. Micheal McInnis received personal fees from Bayer outside of the submitted work. Olaf Mercier received personal fees from MSD outside the submitted work. Isabelle Opitz received personal fees from AstraZeneca, MSD, Roche, and AstraZeneca, and grants from Roche, and Medtronic, outside the submitted work. Joanna Pepke-Zaba received personal fess from Actelion, Merck and Bayer. Ivan M Robbins received personal fees from Bayer and Acceleron. His institution received payment for participating in multicenter registry studies and studies evaluating treatment of patients with pulmonary arterial hypertension. Mark Toshner received personal fees from Bayer, MSD, GSK as well as grants and personal fees from Actelion/J&J outside the submitted work. Christoph B Wiedenroth received personal fees Actelion, Bayer, Pfizer, MSD, AOP Orphan Pharmaceuticals, BTG outside the submitted work.

References

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.

2. Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. Circulation 2014;130:508-18.
3. Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J 2014;44:1635-45.
4. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26:160108.
5. Galie N, McLaughlin VV, Rubbin LI, et al. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J 2019;53:1802148.
6. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014;34:2363-71.
7. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 2017;49.
8. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. Eur Respir Rev 2017;26.
9. Tregouet DA, Morange PE. What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. Br J Haematol 2018;180:335-45.
10. Franchini M, Marano G, Vaglio S, Catalano L, Pupella S, Liumbruno GM. The Role of ABO Blood Type in Thrombosis Scoring Systems. Semin Thromb Hemost 2017;43:525-9.
11. O'Donnell J, Boulton FE, Laffan MA. The relationship between plasma concentration of alpha2-macroglobulin and ABO blood group. Thromb Haemost 2002;88(1):167-8.
12. Germain M, Chasman DI, de Haan H, et al. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. Am J Hum Genet 2015;96:532-42.
13. Desmarais J, Elliott CG. Familial chronic thromboembolic pulmonary hypertension. Chest 2016;149:e99-e101.
14. Roik M, Wretowski D, Irzyk K, Łabyk A, Dzikowska-Diduch O, Pruszczyk P. Familial chronic thromboembolic pulmonary hypertension in a mother and a son: successful treatment with refined balloon pulmonary angioplasty. Pol Arch Med Wewn. 2016;126:1014-6.
15. Kataoka M, Momose Y, Aimi Y, Fukuda K, Gamou S, Satoh T. Familial chronic thromboembolic pulmonary hypertension in a pair of Japanese brothers. Chest 2016;150:748-9.
16. Dodson MW, Desmarais J, Best DH, et al. Heritability in chronic thromboembolic pulmonary hypertension: Pedigree analysis suggests a high prevalence of venous thromboembolism in family members of CTEPH patients, but a low prevalence of CTEPH. Am J Crity Care Respir Med 2016;193:A28.
17. Moser KM, Auger WR, Fedullo PF. Chronic major-vessel thromboembolic pulmonary hypertension. Circulation 1990;81(6):1735-43.
18. Wolf M, Boyer-Neumann C, Parent F, et al. Thrombotic risk factors in pulmonary hypertension. Eur Respir J 2000;15:395-9.
19. Lang IM, Simonneau G, Pepke-Zaba JW, et al. Factors associated with diagnosis and operability of chronic thromboembolic pulmonary hypertension. A case-control study. Thromb Haemost 2013;110:83-91.
20. Wong CL, Szydlo R, Gibbs S, Laffan M. Hereditary and acquired thrombotic risk factors for chronic thromboembolic pulmonary hypertension. Blood Coagul Fibrinolysis 2010;21:201-6.
21. Suntharalingam J, Goldsmith K, van Marion V, et al. Fibrinogen Aalpha Thr312Ala polymorphism is associated with chronic thromboembolic pulmonary hypertension. Eur Respir J 2008;31:736-41.
22. Li JF, Lin Y, Yang YH, et al. Fibrinogen Aalpha Thr312Ala polymorphism specifically contributes to chronic thromboembolic pulmonary hypertension by increasing fibrin resistance. PLoS One 2013;8:e69635.
23. Morris TA, Marsh JJ, Chiles PG, et al. High prevalence of dysfibrinogenemia among patients with chronic thromboembolic pulmonary hypertension. Blood 2009;114(9):1929-36.
24. Suntharalingam J, Machado RD, Sharples LD, et al. Demographic features, BMPR2 status and outcomes in distal chronic thromboembolic pulmonary hypertension. Thorax 2007;62(7):617-22.
25. Ulrich S, Szamalek-Hoegel J, Hersberger M, et al. Sequence variants in BMPR2 and genes involved in the serotonin and nitric oxide pathways in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: relation to clinical parameters and comparison with left heart disease. Respiration 2010;79:279-87.
26. Machado RD, Aldred MA, James V, et al. Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterial hypertension. Hum Mutat 2006;27:121-32.
27. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-Term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 2016;133:859-71.
28. Newnham M, South K, Bleda M, et al. The ADAMTS13-VWF axis is dysregulated in chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1801805.
29. Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 2013;41:462-8.
30. Azarian R, Wartski M, Colligon MA, et al. Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. J Nucl Med. 1997;38:980-3.
31. Laczika K, Lang IM, Quehenberger P, et al. Unilateral chronic thromboembolic pulmonary disease associated with combined inherited thrombophilia. Chest 2002;121:286-9.
32. Natali D, J.X Abraham M, Savale L, et al. Chronic thromboembolic pulmonary hypertension associated with indwelling Port-A-Cath® central venous access systems. A106. Chronic thromboembolic pulmonary hypertension: bench to bedside. Am J Respir Crit Care Med; 2011 A2409-A2409.
33. Bonderman D, Jakowitsch J, Adlbrecht C, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost 2005;93:512-6.
34. Bonderman D, Wilkens H, Wakounig S, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 2009;33:325-31.
35. Guilpain P, Montani D, Damaj G, et al. Pulmonary hypertension associated with myeloproliferative disorders: a retrospective study of ten cases. Respiration 2008;76:295-302.
36. Bonderman D, Skoro-Sajer N, Jakowitsch J, et al. Predictors of outcome in chronic thromboembolic pulmonary hypertension. Circulation 2007;115:2153-8.
37. Bonderman D, Jakowitsch J, Redwan B, et al. Role for staphylococci in misguided thrombus resolution of chronic thromboembolic pulmonary hypertension. Arterioscler Thromb Vasc Biol 2008;28:678-84.
38. Chibana H, Tahara N, Itaya N, et al. Pulmonary artery dysfunction in chronic thromboembolic pulmonary hypertension. Int J Cardiol Heart Vasc 2017;17:30-2.
39. Lang IM, Marsh JJ, Olman MA, Moser KM, Schleef RR. Parallel analysis of tissue-type plasminogen activator and type 1 plasminogen activator inhibitor in plasma and endothelial cells derived from patients with chronic pulmonary thromboemboli. Circulation 1994;90(2):706-12.
40. Lang IM, Marsh JJ, Olman MA, Moser KM, Loskutoff DJ, Schleef RR. Expression of type 1 plasminogen activator inhibitor in chronic pulmonary thromboemboli. Circulation 1994;89:2715-21.
41. Lang IM, Moser KM, Schleef RR. Expression of Kunitz protease inhibitor−containing forms of amyloid beta-protein precursor within vascular thrombi. Circulation 1996;94:2728-34.
42. Satoh T, Satoh K, Yaoita N, et al. Activated TAFI promotes the development of chronic thromboembolic pulmonary hypertension: a possible novel therapeutic target. Circ Res 2017;120:1246-62.
43. Alias S, Redwan B, Panzenboeck A, et al. Defective angiogenesis delays thrombus resolution: a potential pathogenetic mechanism underlying chronic thromboembolic pulmonary hypertension. Arterioscler Thromb Vasc Biol 2014;34:810-9.

44. Frey MK, Alias S, Winter M.P, et al. Splenectomy is modifying the vascular remodeling of thrombosis. J Am Heart Assoc 2014;3:e000772.
45. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993;103:685-92.
46. Dorfmuller P, Günther S, Ghigna MR, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. Eur Respir J 2014;44:1275-88.
47. Waltham M, Burnand KG, Collins M, Smith A. Vascular endothelial growth factor and basic fibroblast growth factor are found in resolving venous thrombi. J Vasc Surg 2000;32:988-96.
48. Modarai B, Humphries J, Burnand KG, et al. Adenovirus-mediated VEGF gene therapy enhances venous thrombus recanalization and resolution. Arterioscler Thromb Vasc Biol 2008;28:1753-9.
49. Waltham M, Burnand K, Fenske C, Modarai B, Humphries J, Smith A. Vascular endothelial growth factor naked DNA gene transfer enhances thrombus recanalization and resolution. J Vasc Surg 2005;42:1183-9.
50. McGuinness CL, Humphries J, Waltham M, Burnand KG, Collins M, Smith A. Recruitment of labelled monocytes by experimental venous thrombi. Thromb Haemost 2001;85:1018-24.
51. Wakefield TW, Linn MJ, Henke PK, et al. Neovascularization during venous thrombosis organization: a preliminary study. J Vasc Surg 1999;30:885-92.
52. Varma MR, Varga AJ, Knipp BS, et al. Neutropenia impairs venous thrombosis resolution in the rat. J Vasc Surg 2003;38:1090-8.
53. Henke PK, Varga A, De S, et al. Deep vein thrombosis resolution is modulated by monocyte CXCR2-mediated activity in a mouse model. Arterioscler Thromb Vasc Biol 2004;24:1130-7.
54. Xie H, Kim K, Aglyamov SR, et al. Staging deep venous thrombosis using ultrasound elasticity imaging: animal model. Ultrasound Med Biol 2004;30:1385-96.
55. Wakefield TW, Strieter RM, Wilke CA, et al. Venous thrombosis-associated inflammation and attenuation with neutralizing antibodies to cytokines and adhesion molecules. Arterioscler Thromb Vasc Biol 1995;15:258-68.
56. Quarck R, Wynants M, Verbeken E, Meyns B, Delcroix M. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J 2015;46:431-43.
57. Bonderman D, Turecek PL, Jakowitsch J, et al. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb Haemost 2003;90:372-6.
58. Morris TA, Marsh JJ, Chiles PG, Auger WR, Fedullo PF, Woods W. L. Jr.. Fibrin derived from patients with chronic thromboembolic pulmonary hypertension is resistant to lysis. Am J Respir Crit Care Med 2006;173:1270-5.
59. Gandara E, Kovacs MJ, Kahn SR, et al. Non-OO blood type influences the risk of recurrent venous thromboembolism. A cohort study. Thromb Haemost 2013;110:1172-9.
60. Mercier O, Fadel E. Chronic thromboembolic pulmonary hypertension: animal models. Eur Respir J 2013;41:1200-6.
61. Lang IM, Marsh JJ, Konopka RG, et al. Factors contributing to increased vascular fibrinolytic activity in mongrel dogs. Circulation 1993;87:1990-2000.
62. Lang IM, Marsh JJ, Moser KM, et al. Presence of active and latent type 1 plasminogen activator inhibitor associated with porcine platelets. Blood 1992;80:2269-74.
63. Marsh JJ, Konopka RG, Lang IM, et al. Suppression of thrombolysis in a canine model of pulmonary embolism. Circulation 1994;90:3091-7.
64. Modarai B, Burnand KG, Humphries J, et al. The role of neovascularisation in the resolution of venous thrombus. Thromb Haemost 2005;93:801-9.
65. von Bruhl ML, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J Exp Med 2012;209:819-35.
66. Boulate D, Perros F, Dorfmuller P, et al. Pulmonary microvascular lesions regress in reperfused chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2015;34:457-67.
67. Ende-Verhaar YM, Meijboom IJ, Kroft LJM, et al. Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study. J Heart Lung Transplant 2019;38:731-8.
68. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973-81.
69. Delcroix M, Kerr K, Fedullo P. Chronic Thromboembolic Pulmonary Hypertension. Epidemiology and Risk Factors, 13. Ann Am Thorac Soc; 2016:S201-6.
70. Ende-Verhaar YM, Huisman MV, Klok FA. To screen or not to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Res 2017;151:1-7.
71. Boon GJAM, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax 2021: Published online March 23, 2021. https://doi.org/10.1136/thoraxjnl-2020-216324.
72. Klok FA, van Kralingen KW, van Dijk AP, et al. Quality of life in long-term survivors of acute pulmonary embolism. Chest 2010;138:1432-40.
73. Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007;28:2517-24.
74. Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. Chest 2009;136:1202-10.
75. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. Eur Respir J 2018;52:1801687.
76. Klok FA, van Kralingen KW, van Dijk APJ, Heyning FH, Vliegen HW, Huisman MV. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010;104:1744-9.
77. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vasc Med. 2017;22:37-43.
78. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014;28:221-6.
79. Sista AK, Klok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. Thromb Res 2018;164:157-62.
80. Guerin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014;112:598-605.
81. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016;14:121-8.
82. Ende-Verhaar YM, Ruigrok D, Bogaard HJ, et al. Sensitivity of a Simple Noninvasive Screening Algorithm for Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism. TH Open 2018;2:e89-95.
83. Dzikowska-Diduch O, Kostrubiec M, Kurnicka K, et al. The post-pulmonary syndrome - results of echocardiographic driven follow up after acute pulmonary embolism. Thromb Res 2020;186:30-5.
84. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg 2011;141:702-10.
85. Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg 2012;94:97-103. [discussion 103].

86. Stam K, van Duin RW, Uitterdijk A, et al. Pulmonary microvascular remodeling in chronic thrombo-embolic pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2018;315:L951-64.
87. Gall H, Preston IR, Hinzmann B, et al. An international physician survey of chronic thromboembolic pulmonary hypertension management. Pulm Circ 2016;6:472-82.
88. McLaughlin VV, Langer A, Tan M, et al. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. Chest 2013;143:324-32.
89. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
90. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D92-9.
91. Donahoe L, Vanderlaan R, Thenganatt J, et al. Symptoms are more useful than echocardiography in patient selection for pulmonary endarterectomy. Ann Thorac Surg 2017;104:1179-85.
92. McCabe C, Preston SD, Gopalan D, Dunning J, Pepke-Zaba J. Cardiopulmonary exercise testing suggests a beneficial response to pulmonary endarterectomy in a patient with chronic thromboembolic obstruction and normal preoperative pulmonary hemodynamics. Pulm Circ 2014;4:137-41.
93. van Kan C, van der Plas MN, Reesink HJ, et al. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. J Thorac Cardiovasc Surg 2016;152(3):763-71.
94. Klok FA, Delcroix M, Bogaard HJ. Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism. J Thromb Haemost 2018;16:1040-51.
95. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007;48:680-4.
96. He J, Fang W, Lv B, et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. Nucl Med Commun 2012;33:459-63.
97. Johns CS, Swift AJ, Rajaram S, et al. Lung perfusion: MRI vs. SPECT for screening in suspected chronic thromboembolic pulmonary hypertension. J Magn Reson Imaging 2017;46(6):1693-7.
98. Dournes G, Verdier D, Montaudon M, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. Eur Radiol 2014;24:42-51.
99. Rogberg AN, G.D Westerlund E, Lindholm P. Do radiologists detect chronic thromboembolic disease on computed tomography? Acta Radiol 2019;60:1576-83.
100. Klok FA, Surie S, Kempf T, et al. A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Thromb Res 2011;128:21-6.
101. Bonderman D, Wexberg P, Martischnig AM, et al. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. Eur Respir J 2011;37:1096-103.
102. Klok FA, Tesche C, Rappold L, et al. External validation of a simple non-invasive algorithm to rule out chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Res 2015;135:796-801.
103. Piazza G, Goldhaber SZ. Fibrinolysis for acute pulmonary embolism. Vasc Med 2010;15:419-28.
104. Sharma GV, Folland ED, McIntyre KM, Sasahara AA. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. Vasc Med 2000;5:91-5.
105. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-11.
106. Konstantinides SV, Vicaut E, Danays T, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol 2017;69:1536-44.
107. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. Arthritis Care Res (Hoboken) 2013;65:1869-73.
108. Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism−results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost 1997;77:444-51.
109. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995;85:1504-8.
110. Leroyer C, Mercier B, Oger E, et al. Prevalence of 20210 A allele of the prothrombin gene in venous thromboembolism patients. Thromb Haemost 1998;80:49-51.
111. Olman MA, Marsh JJ, Lang IM, Moser KM, Binder BR, Schleef RR. Endogenous fibrinolytic system in chronic large-vessel thromboembolic pulmonary hypertension. Circulation 1992;86:1241-8.
112. Naito A, Tanabe N, Shigeta A, et al. Pentraxin3 in chronic thromboembolic pulmonary hypertension: a new biomarker for screening from remitted pulmonary thromboembolism. PLoS One 2014;9:e113086.
113. Sakamaki F, Kyotani S, Nagaya N, Sato N, Oya H, Nakanishi N. Increase in thrombomodulin concentrations after pulmonary thromboendarterectomy in chronic thromboembolic pulmonary hypertension. Chest 2003;124:1305-11.
114. Yano T, Sogawa K, Umemura H, et al. Serum level of fibrinogen Aalpha chain fragment increases in chronic thromboembolic pulmonary hypertension. Circ J 2011;75:2675-82.
115. Quarck R, Nawrot T, Meyns B, Delcroix M. C-reactive protein: a new predictor of adverse outcome in pulmonary arterial hypertension. J Am Coll Cardiol 2009;53:1211-8.
116. Zabini D, Heinemann A, Foris V, et al. Comprehensive analysis of inflammatory markers in chronic thromboembolic pulmonary hypertension patients. Eur Respir J 2014;44:951-62.
117. Nagaya N, Ando M, Oya H, et al. Plasma brain natriuretic peptide as a noninvasive marker for efficacy of pulmonary thromboendarterectomy. Ann Thorac Surg 2002;74:180-4. [discussion 184].
118. Surie S, Reesink HJ, van der Plas MN, et al. Plasma brain natriuretic peptide as a biomarker for haemodynamic outcome and mortality following pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Interact Cardiovasc Thorac Surg 2012;15:973-8.
119. Lankeit M, Dellas C, Panzenböck A, et al. Heart-type fatty acid-binding protein for risk assessment of chronic thromboembolic pulmonary hypertension. Eur Respir J 2008;31:1024-9.
120. Reesink HJ, Meijer RC, Lutter R, et al. Hemodynamic and clinical correlates of endothelin-1 in chronic thromboembolic pulmonary hypertension. Circ J 2006;70:1058-63.
121. Kato F, Tanabe N, Ishida K, et al. Coagulation-Fibrinolysis System and Postoperative Outcomes of Patients With Chronic Thromboembolic Pulmonary Hypertension. Circ J 2016;80:970-9.
122. Kato F, Tabane N, Urushibara T, et al. Association of plasma fibrinogen and plasminogen with prognosis of inoperable chronic thromboembolic pulmonary hypertension. Circ J. 2014;78:1754-61.
123. Skoro-Sajer N, Mittermayer F, Panzenboeck A, et al. Asymmetric dimethylarginine is increased in chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2007;176:1154-60.
124. Simonneau G, D'Armini AM, Ghofrani HA, et al. Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial. Lancet Respir Med 2016;4:372-80.
125. Boulate D, Amsallem M, Kuznetsova T, et al. Echocardiographic evaluations of right ventriculo-arterial coupling in experimental and clinical pulmonary hypertension. Physiol Rep 2019;7:e14322.

126. Rehman MB, Garcia R, Christiaens L, Larrieu-Ardilouze E, Howard LS, Nihoyannopoulos P. Power of resting echocardiographic measurements to classify pulmonary hypertension patients according to European society of cardiology exercise testing risk stratification cut-offs. Int J Cardiol 2018;257:291-7.
127. Zhai Z, Murphy K, Tighe H, et al. Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Chest 2011;140:1284-91.
128. Godinas L, Sattler C, Lau EM, et al. Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2017;36:1234-42.
129. Richter MJ, Sommer N, Gall H, et al. Pulmonary Hemodynamic Response to Exercise in Chronic Thromboembolic Pulmonary Hypertension before and after Pulmonary Endarterectomy. Respiration 2015;90:63-73.
130. McCabe C, Deboeck G, Harvey I, et al. Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. Thromb Res 2013;132:659-65.
131. Topilsky Y, Hayes CL, Khanna AD, Allison TG. Cardiopulmonary exercise test in patients with subacute pulmonary emboli. Heart Lung 2012;41:125-36.
132. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. Chest. 2017;151:1058-68.
133. Kahn SR, Akaberi A, Granton JT, et al. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. Am J Med 2017;130. 990 e9-990 e21.
134. Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. J Am Heart Assoc 2015;4(3):e001602.
135. de Perrot M, McRae K, Shargall Y, et al. Early postoperative pulmonary vascular compliance predicts outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Chest 2011;140:34-41.
136. Soler X, Kerr KM, Marsh JJ, et al. Pilot study comparing SPECT perfusion scintigraphy with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. Respirology 2012;17:180-4.
137. Gutte H, Mortensen J, Jensen CV, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. J Nucl Med 2009;50:1987-92.
138. Simanek M, Koranda P. The benefit of personalized hybrid SPECT/CT pulmonary imaging. Am J Nucl Med Mol Imaging 2016;6:215-22.
139. Dong C, Zhou M, Liu D, Dong X, Guo T, Kong X. Diagnostic accuracy of computed tomography for chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. PLoS One 2015;10:e0126985.
140. Castaner E, Gallardo X, Ballesteros E, et al. CT diagnosis of chronic pulmonary thromboembolism. Radiographics 2009;29:31-50. [discussion 50-3].
141. Kawakami T, Ogawa A, Miyaji K, et al. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circ Cardiovasc Interv 2016;9:e003318.
142. Wittram C. How I do it: CT pulmonary angiography. AJR Am J Roentgenol 2007;188:1255-61.
143. Hong YJ, Kim JY, Choe KO, et al. Different perfusion pattern between acute and chronic pulmonary thromboembolism: evaluation with two-phase dual-energy perfusion CT. AJR Am J Roentgenol 2013;200(4):812-7.
144. Giordano J, Khung S, Duhamel A, et al. Lung perfusion characteristics in pulmonary arterial hypertension (PAH) and peripheral forms of chronic thromboembolic pulmonary hypertension (pCTEPH): Dual-energy CT experience in 31 patients. Eur Radiol 2017;27:1631-9.
145. Le Faivre J, Duhamel A, Khung S, et al. Impact of CT perfusion imaging on the assessment of peripheral chronic pulmonary thromboembolism: clinical experience in 62 patients. Eur Radiol 2016;26:4011-20.
146. Takagi H, Ota H, Sugimura K, et al. Dual-energy CT to estimate clinical severity of chronic thromboembolic pulmonary hypertension: comparison with invasive right heart catheterization. Eur J Radiol 2016;85:1574-80.
147. Meinel FG, Graef A, Thierfelder KM, et al. Automated quantification of pulmonary perfused blood volume by dual-energy CTPA in chronic thromboembolic pulmonary hypertension. Rofo 2014;186:151-6.
148. Koike H, Sueyoshi E, Sakamoto I, Uetani M, Nakata T, Maemura K. Comparative clinical and predictive value of lung perfusion blood volume CT, lung perfusion SPECT and catheter pulmonary angiography images in patients with chronic thromboembolic pulmonary hypertension before and after balloon pulmonary angioplasty. Eur Radiol 2018;28(12):5091-9.
149. Grothues F, Moon JC, Bellenger NG, et al. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004;147:218-23.
150. Rajaram S, Swift AJ, Telfer A, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. Thorax 2013;68:677-8.
151. Rajaram S, Swift AJ, Capener D, et al. Diagnostic accuracy of contrast-enhanced MR angiography and unenhanced proton MR imaging compared with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. Eur Radiol 2012;22:310-7.
152. Freed BH, Gomberg-Maitland M, Chandra S, et al. Late gadolinium enhancement cardiovascular magnetic resonance predicts clinical worsening in patients with pulmonary hypertension. J Cardiovasc Magn Reson 2012;14:11.
153. Roller FC, Wiedenroth C, Breithecker A, et al. Native T1 mapping and extracellular volume fraction measurement for assessment of right ventricular insertion point and septal fibrosis in chronic thromboembolic pulmonary hypertension. Eur Radiol 2017;27:1980-91.
154. Mauritz GJ, Vonk-Noordegraaf A, Kind T, et al. Pulmonary endarterectomy normalizes interventricular dyssynchrony and right ventricular systolic wall stress. J Cardiovasc Magn Reson 2012;14:5.
155. Kawakubo M, Yamasaki Y, Kamitani T, et al. Clinical usefulness of right ventricular 3D area strain in the assessment of treatment effects of balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension: comparison with 2D feature-tracking MRI. Eur Radiol 2019;29:4583-92.
156. Ohno Y, Iwasawa T, Seo JB, et al. Oxygen-enhanced magnetic resonance imaging versus computed tomography: multicenter study for clinical stage classification of smoking-related chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:1095-102.
157. Nakagawa T, Sakuma H, Murashima S, Ishida N, Matsumura K, Takeda K. Pulmonary ventilation-perfusion MR imaging in clinical patients. J Magn Reson Imaging 2001;14:419-24.
158. Reiter U, Reiter G, Fuchsjäger M. MR phase-contrast imaging in pulmonary hypertension. Br J Radiol 2016;89(1063):20150995.
159. Kheyfets VO, Schafer M, Podgorski CA, et al. 4D magnetic resonance flow imaging for estimating pulmonary vascular resistance in pulmonary hypertension. J Magn Reson Imaging 2016;44:914-22.
160. Ota H, Sugimura K, Miura M, Shimokawa H. Four-dimensional flow magnetic resonance imaging visualizes drastic change in vortex flow in the main pulmonary artery after percutaneous transluminal pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension. Eur Heart J 2015;36:1630.
161. Badesch DB, Raskob GE, Elliott GC, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010;137:376-87.
162. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023-30.

163. MacKenzie Ross RV, Toshner MR, Soon E, Naeije R, Pepke-Zaba J. Decreased time constant of the pulmonary circulation in chronic thromboembolic pulmonary hypertension. Am J Physiol Heart Circ Physiol 2013;305:H259-64.
164. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation 2012;125:289-97.
165. Lankhaar JW, Westerhof N, Faes TJ, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 2006;291:H1731-7.
166. Lankhaar JW, Westerhof N, Faes TJ, et al. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. Eur Heart J 2008;29:1688-95.
167. Zuckerman DA, Sterling KM, Oser RF. Safety of pulmonary angiography in the 1990s. J Vasc Interv Radiol 1996;7:199-205.
168. Kawakami T, Ogawa A, Miyaji K, et al. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circ Cardiovasc Interv 2016;9:e003318.
169. Sugimura K, F.Y Miura Y, Nochioka K, Tatebe S, Yamamoto S, et al. Usefulness of optical coherence tomography for diagnosis and treatment in chronic thromboembolic pulmonary hypertension. Eur Respir J. 2013;42:P2597.
170. Winther HB, Hundt C, Schmidt B, et al. ν-net: deep learning for generalized biventricular mass and function parameters using multicenter cardiac MRI data. JACC Cardiovasc Imaging 2018;11:1036-8.
171. Avendi MR, Kheradvar A, Jafarkhani H. Automatic segmentation of the right ventricle from cardiac MRI using a learning-based approach. Magn Reson Med 2017;78:2439-48.
172. Dawes TJW, de Marvao A, Shi W, et al. Machine Learning of Three-dimensional Right Ventricular Motion Enables Outcome Prediction in Pulmonary Hypertension: A Cardiac MR Imaging Study. Radiology 2017;283:381-90.
173. Jamieson SW, Auger WR, Fedullo PF, et al. Experience and results with 150 pulmonary thromboendarterectomy operations over a 29-month period. J Thorac Cardiovasc Surg 1993;106:116-26. [discussion 126-7].
174. Vuylsteke A, Sharples L, Charman G, et al. Circulatory arrest versus cerebral perfusion during pulmonary endarterectomy surgery (PEA-COG): a randomised controlled trial. Lancet 2011;378(9800):1379-87.
175. McRae K, Shargall Y, Ma M, et al. Feasibility of blood conservation strategies in pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Interact Cardiovasc Thorac Surg 2011;13:35-8.
176. de Perrot M. Operability assessment in chronic thromboembolic pulmonary hypertension (CTEPH): Don't miss the chance of a second opinion!. J Thorac Cardiovasc Surg 2016;152:656-7.
177. Jenkins DP, Biederman A, D'Armini AM, et al. Operability assessment in CTEPH: Lessons from the CHEST-1 study. J Thorac Cardiovasc Surg 2016;152:669-74. e3.
178. D'Armini AM, Morsolini M, Mattiucci G, et al. Pulmonary endarterectomy for distal chronic thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 2014;148:1005-11. 1012 e1-2; [discussion 1011-2].
179. Wong HH, Gounaris I, McCormack A, et al. Presentation and management of pulmonary artery sarcoma. Clin Sarcoma Res 2015;5:3.
180. Seferian A, Jais X, Creuze N, et al. Mediastinal fibrosis mimicking proximal chronic thromboembolic disease. Circulation 2012;125:2045-7.
181. Damuth TE, Bower JS, Cho K, et al. Major pulmonary artery stenosis causing pulmonary hypertension in sarcoidosis. Chest 1980;78:888-91.
182. Dion J, Terrier B, Jais X, et al. Atypical vasculitis mimicking chronic thromboembolic pulmonary hypertension. Am J Med 2015;128:e47-9.
183. Hayashi K, Nagasaki M, Matsunaga N, Hombo Z, Imamura T. Initial pulmonary artery involvement in Takayasu arteritis. Radiology 1986;159:401-3.
184. Kreutzer J, Landzberg MJ, Preminger TJ, et al. Isolated peripheral pulmonary artery stenoses in the adult. Circulation 1996;93:1417-23.
185. Castaner E, Gallardo X, Rimola J, et al. Congenital and acquired pulmonary artery anomalies in the adult: radiologic overview. Radiographics 2006;26:349-71.
186. Levine DJ, Al-Naamani N, Preston I. PH grand rounds: pulmonary artery filling defects: are they all the same? Adv Pulm Hypertens 2014;13:122-4.
187. Bailey CL, Channick RN, Auger WR, et al. High probability" perfusion lung scans in pulmonary venoocclusive disease. Am J Respir Crit Care Med 2000;162:1974-8.
188. Chang SA, Soon JS, Park TK, et al. Nonsyndromic Peripheral Pulmonary Artery Stenosis Is Associated With Homozygosity of RNF213 p.Arg4810Lys Regardless of Co-occurrence of Moyamoya Disease. Chest 2018;153:404-13.
189. Banks DA, Pretorius GV, Kerr KM, Manecke GR. Pulmonary endarterectomy: part I. Pathophysiology, clinical manifestations, and diagnostic evaluation of chronic thromboembolic pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2014;18:319-30.
190. Berman M, Hardman G, Sharples L, et al. Pulmonary endarterectomy: outcomes in patients aged >70. Eur J Cardiothorac Surg 2012;41:e154-60.
191. Vistarini N, Morsolini M, Klersy C, et al. Pulmonary endarterectomy in the elderly: safety, efficacy and risk factors. J Cardiovasc Med (Hagerstown) 2016;17:144-51.
192. Tromeur C, Mercier O, Jaïs X, et al. Factors predicting outcome after pulmonary endarterectomy. PLoS One 2018;13:e0198198.
193. Donahoe L, Granton J, McRae K, et al. Role of extracorporeal life support after pulmonary endarterectomy: a single-centre experience. Interact Cardiovasc Thorac Surg 2016;23:74-8.
194. Sugiyama K, Suzuki S, Fujiyoshi T, Koizumi N, Sato M, Ogino H. Extracorporeal membrane oxygenation after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J Card Surg 2019;34:428-34.
195. Kelava M, Koprivanac M, Smedira N, Mihaljevic T, Alfirevic A. Extracorporeal membrane oxygenation in pulmonary endarterectomy patients. J Cardiothorac Vasc Anesth 2019;33:60-9.
196. Nierlich P, Ristl R. Perioperative extracorporeal membrane oxygenation bridging in patients undergoing pulmonary endarterectomy. Interact Cardiovasc Thorac Surg 2016;22:181-7.
197. Boulate D, Mercier O, Mussot S, et al. Extracorporeal life support after pulmonary endarterectomy as a bridge to recovery or transplantation: lessons from 31 consecutive patients. Ann Thorac Surg 2016;102:260-8.
198. Berman M, Tsui S, Vuylsteke A, et al. Successful extracorporeal membrane oxygenation support after pulmonary thromboendarterectomy. Ann Thorac Surg 2008;86:1261-7.
199. Thistlethwaite PA, Madani MM, Kemp AD, Hartley M, Auger WR, Jamieson SW. Venovenous extracorporeal life support after pulmonary endarterectomy: indications, techniques, and outcomes. Ann Thorac Surg 2006;82:2139-45.
200. Ali JM, Vuylsteke A, Fowles JA, et al. Transfer of patients with cardiogenic shock using veno-arterial extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth 2020;34:374-82.
201. Tahiri M, Bykova A, Dunn B, et al. Preoperative ECMO and plasmapheresis for urgent pulmonary endarterectomy in HIT positive patient. Ann Thorac Surg 2020;110:e231-2.
202. Mydin M, Berman M, Klein A, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary endarterectomy. Ann Thorac Surg 2011;92:e101-3.
203. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003;76:1457-62. [discussion 1462-4].
204. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26(143):160111.
205. Madani M, Mayer E, Fadel E, Jenkins DP. Pulmonary endarterectomy. Patient selection, technical challenges, and outcomes. Ann Am Thorac Soc 2016;13(Suppl 3):S240-7.
206. Corsico AG, D'Armini AM, Cerveri I, et al. Long-term outcome after pulmonary endarterectomy. Am J Respir Crit Care Med 2008;178:419-24.

207. Mellemkjaer S, Ilkjaer LB, Klaaborg KE, et al. Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Ten years experience in Denmark. Scand Cardiovasc J 2006;40:49-53.
208. Saouti N, Morshuis WJ, Heijmen RH, Snijder RJ. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. Eur J Cardiothorac Surg 2009;35:947-52. [discussion 952].
209. Scholzel B, Snijder R, Morshuis W, Saouti N, Plokker T, Post M. Clinical worsening after pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. Neth Heart J 2011;19:498-503.
210. Skoro-Sajer N, Marta G, Gerges C, et al. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. Thorax 2014;69:116-22.
211. Matsuda H, Ogino H, Minatoya K, et al. Long-term recovery of exercise ability after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg 2006;82:1338-43. [discussion 1343].
212. Ishida K, Masuda M, Tanabe N, et al. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 2012;144:321-6.
213. Freed DH, Thomson BM, Tsui SS, et al. Functional and haemodynamic outcome 1 year after pulmonary thromboendarterectomy. Eur J Cardiothorac Surg 2008;34:525-9. [discussion 529-30].
214. Cannon JE, Su L, Kiely DG, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the United Kingdom national cohort. Circulation 2016;133:1761-71.
215. Freed DH, Thomson BM, Berman M, et al. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg 2011;141(2):383-7.
216. Kramm T, Eberle B, Guth S, Mayer E. Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy. Eur J Cardiothorac Surg 2005;28:882-8.
217. Collaud S, Brenot P, Mercier O, Fadel E. Rescue balloon pulmonary angioplasty for early failure of pulmonary endarterectomy: The earlier the better? Int J Cardiol 2016;222:39-40.
218. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369:319-29.
219. Yanaka K, Nakayama K, Shinke T, et al. Sequential hybrid therapy with pulmonary endarterectomy and additional balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. J Am Heart Assoc 2018;7:e008838.
220. Lankeit M, Krieg V, Hobohm L, et al. Pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2017: Published online August 17, 2021. https://doi.org/10.1016/j.healun.2017.06.011.
221. de Perrot M, Mayer E. Chronic thromboembolic pulmonary hypertension: do we need a new definition? Eur Respir J 2014;44:1401-3.
222. Olgun Yildizeli S, Kepez A, Taş S, et al. Pulmonary endarterectomy for patients with chronic thromboembolic disease. Anatol J Cardiol 2018;19:273-8.
223. Condliffe R, Kiely DG, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2008;177:1122-7.
224. Jenkins DP, Madani M, Mayer E, et al. Surgical treatment of chronic thromboembolic pulmonary hypertension. Eur Respir J 2013;41:735-42.
225. Thistlethwaite PA, Madani M, Jamieson SW. Outcomes of pulmonary endarterectomy surgery. Semin Thorac Cardiovasc Surg 2006;18:257-64.
226. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1801915.
227. Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation 2009;120:1248-54.
228. Suntharalingam J, Treacy CM, Doughty NJ, et al. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. Chest 2008;134:229-36.
229. Jais X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008;52:2127-34.
230. Simonneau G, D'Armini AM, Ghofrani HA, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J 2015;45:1293-302.
231. Ghofrani HA, Simonneau G, D'Armini AM, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med 2017;5:785-94.
232. Sadushi-Kolici R, Jansa P, Kopec G, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med 2019;7:239-48.
233. Reesink HJ, Surie S, Kloek JJ, et al. Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 2010;139:85-91.
234. Surie S, Reesink HJ, Marcus JT, et al. Bosentan treatment is associated with improvement of right ventricular function and remodeling in chronic thromboembolic pulmonary hypertension. Clin Cardiol 2013;36:698-703.
235. Nagaya N, Sasaki N, Ando M, et al. Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 2003;123:338-43.
236. Bresser P, Fedullo PF, Auger WR, et al. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. Eur Respir J 2004;23:595-600.
237. Madani M, Ogo T, Simonneau G. The changing landscape of chronic thromboembolic pulmonary hypertension management. Eur Respir Rev 2017;26(146):170105.
238. Sugimura K, Fukumoto Y, Satoh K, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J 2012;76:485-8.
239. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012;5:748-55.
240. Andreassen AK, Ragnarsson A, Gude E, Geiran O, Andersen R. Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Heart 2013;99:1415-20.
241. Inami T, Kataoka M, Andod M, Fukuda K, Yoshino H, Satoh T. A new era of therapeutic strategies for chronic thromboembolic pulmonary hypertension by two different interventional therapies; pulmonary endarterectomy and percutaneous transluminal pulmonary angioplasty. PLoS One 2014;9:e94587.
242. Taniguchi Y, Miyagawa K, Nakayama K, et al. Balloon pulmonary angioplasty: an additional treatment option to improve the prognosis of patients with chronic thromboembolic pulmonary hypertension. EuroIntervention 2014;10:518-25.
243. Fukui S, Ogo T, Morita Y, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. Eur Respir J 2014;43:1394-402.
244. Tsugu T, Murata M, Kawakami T, et al. Significance of echocardiographic assessment for right ventricular function after balloon pulmonary angioplasty in patients with chronic thromboembolic induced pulmonary hypertension. Am J Cardiol 2015;115:256-61.
245. Roik M, Wretowski D, Łabyk A, et al. Refined balloon pulmonary angioplasty driven by combined assessment of intra-arterial anatomy and physiology—Multimodal approach to treated lesions in patients with non-operable distal chronic thromboembolic pulmonary hypertension—Technique, safety and efficacy of 50 consecutive angioplasties. Int J Cardiol 2016;203:228-35.
246. Inami T, Kataoka M, Yanagisawa R, et al. Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Circulation 2016;134:2030-2.

247. Kurzyna M, Darocha S, Pietura R, et al. Changing the strategy of balloon pulmonary angioplasty resulted in a reduced complication rate in patients with chronic thromboembolic pulmonary hypertension. A single-centre European experience. Kardiol Pol 2017;75:645-54.
248. Ogo T, Fukuda T, Tsuji A, et al. Efficacy and safety of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension guided by cone-beam computed tomography and electrocardiogram-gated area detector computed tomography. Eur J Radiol 2017;89:270-6.
249. Aoki T, Sugimura K, Tatebe S, et al. Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension: long-term effects and procedure-related complications. Eur Heart J 2017;38:3152-9.
250. Olsson KM, Wiedenroth CB, Kamp JC, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J 2017;49:1602409.
251. Ejiri K, Ogawa A, Fujii S, Ito H, Matsubara H. Vascular injury is a major cause of lung injury after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2018;11:e005884.
252. Brenot P, Jais X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1802095.
253. Carnicelli AP, O'Gara PT, Giugliano RP. anticoagulation after heart valve replacement or transcatheter valve implantation. Am J Cardiol 2016;118:1419-26.
254. Gomez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol 2015;95:389-404.
255. Bunclark K, Newnham M, Chiu YD, et al. A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. J Thromb Haemost 2020;18:114-22.
256. Sahay S, Melendres-Groves L, Pawar L, et al. Pulmonary hypertension care center network: improving care and outcomes in pulmonary hypertension. Chest 2017;151:749-54.
257. Grunig E, Lichtblau M, Ehlken N, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. Eur Respir J 2012;40:84-92.
258. Fukui S, Ogo T, Takaki H, et al. Efficacy of cardiac rehabilitation after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Heart 2016;102:1403-9.
259. Inagaki T, Terada J, Tanabe N, et al. Home-based pulmonary rehabilitation in patients with inoperable or residual chronic thromboembolic pulmonary hypertension: a preliminary study. Respir Investig 2014;52:357-64.
260. Ehlken N, Lichtblau M, Klose H, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. Eur Heart J 2016;37:35-44.
261. Fernandes TM, Auger WR, Fedullo PF, et al. Baseline body mass index does not significantly affect outcomes after pulmonary thromboendarterectomy. Ann Thorac Surg 2014;98:1776-81.
262. Matthews DT, Le CN, Robbins IM, et al. Severity of pulmonary hypertension and obesity are not associated with worse functional outcomes after pulmonary thromboendarterectomy. Pulm Circ, 6. Pulm Circ; 2016:174-80.
263. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001;103:10-3.
264. Inami T, Kataoka M, Shimura N, et al. Pulmonary edema predictive scoring index (PEPSI), a new index to predict risk of reperfusion pulmonary edema and improvement of hemodynamics in percutaneous transluminal pulmonary angioplasty. JACC Cardiovasc Interv 2013;6:725-36.
265. Ogawa A, Satoh T, Fukuda T, et al. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension: Results of a Multicenter Registry. Circ Cardiovasc Qual Outcomes 2017;10: e004029.
266. Amsallem M, Guihaire J, Arthur Ataam J, et al. Impact of the initiation of balloon pulmonary angioplasty program on referral of patients with chronic thromboembolic pulmonary hypertension to surgery. J Heart Lung Transplant 2018;37:1102-10.
267. de Perrot M, Thenganatt J, McRae K, et al. Pulmonary endarterectomy in severe chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2015;34:369-75.
268. Kwon W, Yang JH, Park TK, et al. Impact of balloon pulmonary angioplasty on hemodynamics and clinical outcomes in patients with chronic thromboembolic pulmonary hypertension: the initial Korean Experience. J Korean Med Sci 2018;33:e24.
269. Kriechbaum SD, Wiedenroth CB, Wolter JS, et al. N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2018;37:639-46.
270. Araszkiewicz A, Darocha S, Pietrasik A, et al. Balloon pulmonary angioplasty for the treatment of residual or recurrent pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol 2019;278:232-7.
271. Godinas L, Bonne L, Budts W, et al. Balloon pulmonary angioplasty for the treatment of nonoperable chronic thromboembolic pulmonary hypertension: single-center experience with low initial complication rate. J Vasc Interv Radiol 2019;30:1265-72.
272. Anand V, Frantz RP, DuBrock H, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: initial single-center experience. Mayo Clin Proc Innov Qual Outcomes 2019;3:311-8.
273. van Thor MCJ, Lely RJ, Braams NJ, et al. Safety and efficacy of balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension in the Netherlands. Neth Heart J 2020;28:81-8.
274. Hoole SP, Coghlan JG, Cannon JE, et al. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience. Open Heart 2020;7:e001144.
275. Wiedenroth CB, Ghofrani HA, Adameit MSD, et al. Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension. Pulm Circ 2018;8:2045894018783996.
276. Kriechbaum SD, Wiedenroth CB, Keller T, et al. Dynamics of high-sensitivity cardiac troponin T during therapy with balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. PLoS One 2018;13:e0204683.
277. Roller FC, Kriechbaum S, Breithecker A, et al. Correlation of native T1 mapping with right ventricular function and pulmonary haemodynamics in patients with chronic thromboembolic pulmonary hypertension before and after balloon pulmonary angioplasty. Eur Radiol 2019;29:1565-73.
278. Wiedenroth CB, Olsson KM, Guth S, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic disease. Pulm Circ 2018;8:2045893217753122.
279. Wiedenroth CB, Liebetrau C, Breithecker A, et al. Combined pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2016;35:591-6.
280. Kalra R, Duval S, Thenappan T, et al. Comparison of balloon pulmonary angioplasty and pulmonary vasodilators for inoperable chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. Sci Rep 2020;10:8870.
281. Yanagisawa R, Fetterly KA, Johnson GB, et al. Integrated use of perfusion SPECT/CTA fusion imaging and pulmonary balloon angioplasty for chronic pulmonary thromboembolism. JACC Cardiovasc Interv 2017;10:532-4.
282. Romanov A, Cherniavskiy A, Novikova N, et al. Pulmonary artery denervation for patients with residual pulmonary hypertension after pulmonary endarterectomy. J Am Coll Cardiol 2020;76:916-26.