Review Article

Clinical Updates on the Diagnosis and Management of Chronic Thromboembolic Pulmonary Hypertension

Wen Ruan, *[1] MD, MRCP (UK), MMed (Int Med), Jonathan JL Yap, *[1] MBBS, MRCP (UK), MMed (Int Med), Kevin KH Quah, [1] MBBS, Foong Koon Cheah, [1,4] MB ChB, MRCP (UK), FRCR, Ghee Chee Phua, [5] MBBS, MMed (Int Med), MRCP (UK), Duu Wen Sewa, [5] MBBS, MRCP(UK), Aidila Binte Ismail, [3], Alicia XF Chia, [2] BM (UK), MRCS (Ed), FRCSEd (CTh), David Jenkins, [3] MBBS, FRCS, Ju Le Tan, [1] MBBS (Newcastle-u-Tyne,UK), MRCP (London), FACC, Victor TT Chao, [2] MBBS, FRCS, FRCSEd (CTh), Soo Teik Lim, [1] MBBS, MMed (Int Med), MRCPE (Int Med)

Abstract

Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a known sequela after acute pulmonary embolism (PE). It is a debilitating disease, and potentially fatal if left untreated. This review provides a clinically relevant overview of the disease and discusses the usefulness and limitations of the various investigational and treatment options. Methods: A PubMed search on articles relevant to pulmonary embolism, pulmonary hypertension, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, and balloon pulmonary angioplasty were performed. A total of 68 articles were found to be relevant and were reviewed. Results: CTEPH occurs as a result of non-resolution of thrombotic material, with subsequent fibrosis and scarring of the pulmonary arteries. Risk factors have been identified, but the underlying mechanisms have yet to be fully elucidated. The cardinal symptom of CTEPH is dyspnoea on exertion, but the diagnosis is often challenging due to lack of awareness. The ventilation/perfusion scan is recommended for screening for CTEPH, with other modalities (eg. dual energy computed tomography pulmonary angiography) also being utilised in expert centres. Conventional pulmonary angiography with right heart catherisation is important in the final diagnosis of CTEPH. Conclusion: Operability assessment by a multidisciplinary team is crucial for the management of CTEPH, as pulmonary endarterectomy (PEA) remains the guideline recommended treatment and has the best chance of cure. For inoperable patients or those with residual disease post-PEA, medical therapy or balloon pulmonary angioplasty are potential treatment options.

Keywords: Balloon pulmonary angioplasty, Chronic thromboembolic pulmonary hypertension, Pulmonary embolism, Pulmonary endarterectomy, Pulmonary hypertension

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pre-capillary pulmonary hypertension and is classified under group 4 of pulmonary hypertension (PH).[1] While CTEPH portends significant mortality and morbidity, it is often under-recognised and under-diagnosed.[2] In this review, a pertinent overview of the topic is provided and the usefulness and limitations of the various investigational and treatment options are covered.

Epidemiology

The incidence of venous thromboembolic disease (VTE) varies in different populations. In Asian countries like Singapore, the population-based incidence of VTE and pulmonary embolism (PE) was noted to be 57 and 15 per 100,000 respectively, compared to more than 100 per 10,000 in Caucasians.[3] CTEPH is a known complication after acute PE and this may account for the different incidences in different countries. In the USA and Europe, the crude annual incidence of CTEPH was 3 to 5 cases per 100,000 population, while

[1]Department of Cardiology, National Heart Centre Singapore, Singapore
[2]Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore
[3]Nursing Specialty Care Unit, National Heart Centre Singapore, Singapore
[4]Department of Diagnostic Radiology, Singapore General Hospital, Singapore
[5]Department of Respiratory Medicine and Critical Care, Singapore General Hospital, Singapore
[6]Department of Cardiothoracic Surgery, Royal Papworth Hospital NHS Foundation Trust, United Kingdom
Address for Correspondence: Dr Wen Ruan, Department of Cardiology, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609
Email: ruan.wen@singhealth.com.sg

in Japan the incidence was noted to be 1.9 cases per 100,000 population.[4] Among survivors of acute PE, between 0.4–6.2% will develop CTEPH by invasive haemodynamic definition.[1,5] A significant proportion of patients diagnosed with CTEPH have no known history of PE. Historical retrospective data reported as high as 40-60% of CTEPH subjects having no prior history of VTE.[6] A recent prospective international registry reported 25.2% and 43.9% of CTEPH patients without prior PE or VTE respectively.[7] This may partly be a result of under diagnosis of VTE. In an old autopsy study of over 100 patients who passed away from PE, the diagnosis was only discovered at autopsy in 77.1%,[2] with the deaths initially attributed to ischemic heart disease.

Pathophysiology

CTEPH is defined as symptomatic PH due to incomplete or non-resolution of PE despite anticoagulation. The pathogenesis is mutifactorial, including inflammation and infection, biological and genetic factors, fibrinogen and fibrinolytic abnormalities, platelet dysfunction and impaired angiogenesis.[8] These lead to the reorganisation of thrombi into collagen deposits, which become incorporated into the vessel wall and become endothelialised, impeding blood flow and increased pulmonary vascular resistance (PVR). In addition, small vessel disease may also play a role in the genesis of PH. This occurs when the pulmonary flow is redistributed into non-obstructed pulmonary arteries, causing high pressure and shear stress which results in endothelial dysfunction.[8] Altered mutations in bone morphogenetic protein receptor type II (BMPR2) and the transcription factor, Forkhead box class O transcription factor 1 (FoxO1), have also been implicated in the process of abnormal vascular remodelling.[9]

Risk Stratification

Predicting CTEPH after pulmonary embolism is challenging. Universal screening of all post PE patients with echocardiogram has not proven to be cost-effective and remains controversial.[10] Some risk factors which predispose patients to CTEPH have been identified: 1) Related to the acute PE event: younger age, larger perfusion defects, unprovoked PE, PH at presentation (right ventricular (RV) systolic pressure above 50 mmHg);[11] 2) Autoimmune or haematological disorders: lupus anticoagulant, antiphospholipid syndrome, non-O blood group; 3) Associated medical conditions: cancer, ventriculoatrial shunts, infected pacemaker leads, splenectomy, chronic inflammatory disorders and hypothyroid.[12,13] Klock et al. studied 772 consecutive patients with acute PE and CTEPH was confirmed in 22 patients (2.8%) on follow-up. Four significant risk factors: unprovoked PE, known hypothyroidism, symptom onset >2 weeks before PE diagnosis and RV dysfunction on computed tomography (CT)/echocardiography and 2 protective factors- diabetes mellitus and thrombolytic therapy/ embolectomy were identified. A "CTEPH prediction score" was developed based on the 6 variables, yielding an area under the receiver operating characteristic curve (AUC) of 0.89 in predicting PE patients with a high risk of CTEPH diagnosis after PE.[14]

Symptoms and Outcomes

The primary symptoms of CTEPH include dyspnoea (99.1%), edema (40.5%), fatigue (31.5%), chest pain (15.3%) and/or syncope (13.7%).[7] However, these symptoms are often non-specific. Hence, together with the lack of awareness of this disease entity, the diagnosis is frequently missed. It has been reported that average delay from the embolic event to symptom onset was about 18 months[15] and at diagnosis, the majority of patients were in New York Heart Association (NYHA) functional class III or IV.[7] If untreated, historically, the 3-year survival was 30% and 5-year survival of 10% in those with a mean pulmonary artery pressure (mPAP) >30 mmHg;[16] and 2-year survival was only 20% in those with mPAP >50 mm Hg.[17]

Methods

Definition

CTEPH is categorised as Group 4 in the classification of PH. The diagnosis of CTEPH is based on the following criteria:[18]

- Pre-capillary PH (combination of mPAP ≥25 mmHg, pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) ≥3 Wood Units. at rest and
- Mismatch on ventilation/perfusion (V/Q) scintigraphy (usually V/Q single-photon emission computed tomography [SPECT]) with at least one large perfusion defect in one segment or in two subsegments, or evidence of pulmonary vascular lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI) or pulmonary angiography.
- These findings should be obtained after at least 3 months of effective anticoagulation.

Chronic thromboembolic disease (CTED) is a similar entity to CTEPH, but without PH at rest (mean PAP <25 mmHg).[19] Currently a new threshold for PH (mean PAP (mPAP) >20 mmHg, and PVR ≥3 Wood units) has been proposed to diagnose pulmonary hypertension.[20] The impact on the diagnosis of CTEPH and CTED has not yet been established.

Investigational Modalities

Due to the non-specific nature of symptoms and the heterogenicity of the aetiologies, diagnosing CTEPH has been challenging. The varying availability of the different investigations as well as the ability to interpret these investigations across different centres add to this challenge. In the following section, the utility and limitations of these investigations are discussed.

Echocardiography

Echocardiography serves as a first-line screening tool. Although it is not specific for the diagnosis of CTEPH, it enables indirect assessment of PA pressure and permits exclusion of intracardiac shunt or left heart disease as a cause for PH. Patients with intermediate to high echocardiographic probability of PH will be further evaluated to exclude CTEPH.[21] This is determined by a tricuspid regurgitant (TR) velocity of more than or equal to 2.8 m/s, or, if the TR velocity is less than 2.8 m/s or unmeasurable, with additional features of pulmonary hypertension, which comprises abnormalities in two out of the three categories: 1) abnormal right ventricle (dilated right ventricular size, or left-shifting of the interventricular septum); 2) abnormal pulmonary artery (shortened acceleration time of the systolic flow in right ventricular outflow tract, increased early diastolic pulmonary regurgitant velocity, or dilated pulmonary artery); 3) abnormal inferior vena cava or right atrium (dilated and plethoric inferior vena cava, or enlarged right atrial area) (Figure 1a).[21]

A clinical screening protocol has been established at the authors' institution to identify patients with CTEPH post-PE. In summary, a follow-up echocardiogram is recommended in all acute PE patients with high risk features defined as any one of the following a) acute massive PE (Systolic BP <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to other causes), b) acute PE with RV dysfunction, or echo features of pulmonary hypertension and c) acute PE with CTEPH clinical prediction score >6.[14] In patients without high risk features but continue to be symptomatic at follow-up, an echocardiogram is also recommended. The follow-up echocardiogram is recommended to be performed after at least 3 months of anticoagulation. If there is intermediate to high echocardiographic probability of pulmonary hypertension, these patient will be referred to pulmonary hypertension clinic. If the clinical suspicion is high and the echocardiogram does not show pulmonary hypertension, a dual energy computed tomography pulmonary angiogram (discussed below) to exclude recurrent acute PE or symptomatic chronic thromboembolic disease (CTED) without PH is considered.

Ventilation/Perfusion (V/Q) Scan

The V/Q scan is the gold standard screening modality for the exclusion of CTEPH in patients with PH.[21, 22] Despite this, the V/Q scan is underutilised, with registry data showing only 57% of patients with a diagnosis of pulmonary arterial hypertension (PAH) having had a V/Q scan done leading up to their diagnosis. This could potentially lead to misdiagnosis of CTEPH cases as PAH.[23] A normal V/Q scan rules out CTEPH with a sensitivity of 90-100% and a specificity of 94_100%.[24] In addition, V/Q scan interpretation requires less additional training beyond what is standard of care. In contrast, inexperienced CT readers might miss distal segmental or subsegmental disease; misinterpret pulmonary artery sarcoma,[25] or misdiagnose proximal lining thrombi associated with PAH.[26]

CTEPH features on V/Q scans include one or more segmental or larger mismatched perfusion defects (Figures 1b, 1c). Other causes of PH (e.g., PAH and pulmonary veno-occlusive disease) generally present with normal scans or unmatched/non-segmental perfusion abnormalities (i.e., "mottled" perfusion scans) secondary to diffuse narrowing of small vessels.[27,28] However, false interpretation of matched V/Q defects can happen in areas that reflect compensatory hypoventilation from chronic lung hypoperfusion. Another pitfall of planar V/Q is "shine-though", which occurs when normally perfused areas overlap hypoperfused areas, resulting in underestimation of the presence and extent of PE.[29,30] The latter can be improved using SPECT V/Q scanner.[31,32]

Computed Tomography Pulmonary Angiogram (CTPA)

Despite V/Q scan being a good screening tool, its non-specificity limits its use in the definitive diagnosis of CTEPH. Pathologies such as PA sarcoma, fibrosing mediastinitis, vasculitis and extrinsic compression of pulmonary vasculature may also produce large segmental perfusion defects that cannot be

differentiated from CTEPH on V/Q scan. Hence, any abnormal perfusion scan requires additional diagnostic imaging to allow determination of the magnitude, location and extent of disease.[33] Recent evidence suggests high sensitivity and specificity of CTPA for detecting CTED at the main/lobar (89–100% and 95–100% respectively) and segmental (84–100% and 92–99% respectively) levels.[34] Nevertheless, a negative CTPA does not definitively exclude CTEPH, especially in diseases confined to distal subsegmental level which CTPA may have difficulty in detecting.

Typical CT features of CTEPH includes stenosis with ring-, web- or slit-like filling defects, tapered vessels, or complete absence of the vessel branches (Figure 1d). Besides these, CTPA can detect CTED-associated findings such as mosaic perfusion pattern and bronchial artery collaterals, and lung infarcts. It may also serve as screening for underlying mediastinal disease or parenchymal lung disease.[35]

Dual-Energy Computed Tomography Pulmonary Angiogram (DECTPA)

DECTPA is a newer technology which measures the contrast uptake in the parenchyma as an expression of perfusion (this resembles a V/Q scan perfusion abnormality) in addition to the normal CT findings (Fig. 1e). However, careful interpretation is required. Firstly, although a mosaic perfusion pattern is common in CTEPH, it can also be observed in up to 12% of patients with PAH. Secondly, underlying lung parenchyma disease, such as bullous emphysema can lead to pseudo-defects.[36] Thirdly, unlike 99mTc-macroaggregated albumin in V/Q scan,

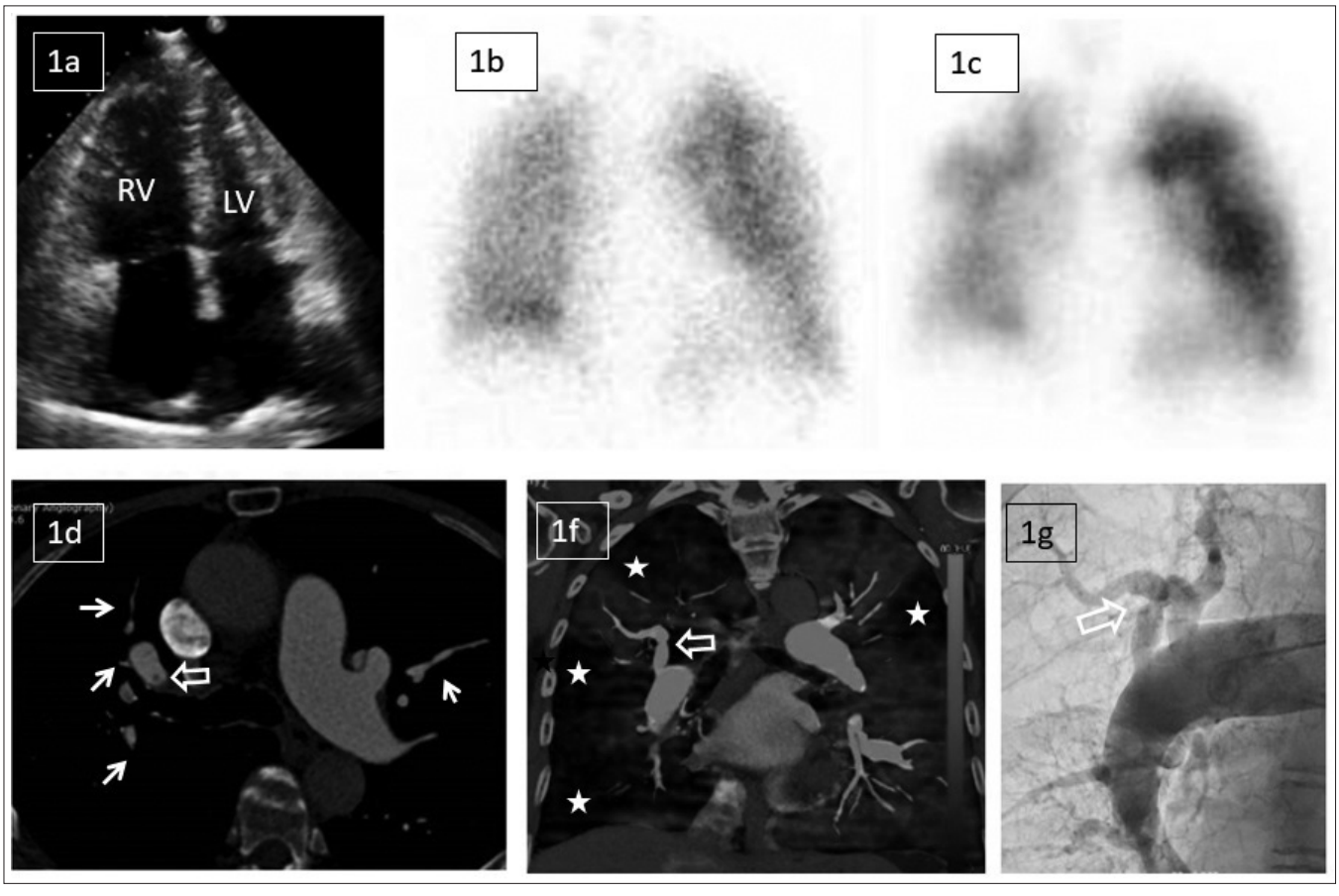

Fig. 1. (a) Echocardiogram demonstrating grossly dilated right heart chambers suggestive of pulmonary hypertension (RV/LV ratio >1); (b) Ventilation portion of V/Q scan showing normal ventilation of both lungs (c) Perfusion portion of the V/Q scan showing wedge-shaped perfusion defects at peripheral lung fields; (d) Conventional CTPA; (e) Dual energy CTPA; (f) Invasive pulmonary angiogram. These images are from an elderly female patient who was diagnosed with CTEPH. Multifocal perfusion defects in both lungs (R>L) are demonstrated on both the V/Q scan and DECTPA (white stars). These perfusion defects correspond to the attenuated and occluded pulmonary arteries (white arrows) on the CTPA. Proximal dilatation and abrupt truncation (hollow arrow) of the distal portion of the right upper lobe branches was noted on both CT and invasive pulmonary angiogram.

iodine is capable of entering collateral vessels. Hence, perfusion defects can be missed (i.e. false negative) in areas of lung distal to affected vessel due to collateralisation or sub-occlusive thrombi.[37] Despite these limitations, the sensitivity and specificity of DECTPA in diagnosis of CTEPH were reported as 96–100% and 76–92% respectively.[38,39] In cases with severe lung parenchymal disease, poor blood flow to the scarred areas may lead to artefactual filling defects on conventional CTPA, and hence false positive results. DECTPA is a potentially useful tool that incorporates both anatomical and functional abnormalities, allowing for the differentiation of true versus false filling defects. Its role in the diagnosis of CTEPH is currently evolving.

Magnetic Resonance Pulmonary Angiogram (MRPA)

MRPA allows for not only the anatomical assessment of the PA circulation with no radiation exposure, but also the evaluation of pulmonary perfusion and haemodynamics.[40] The diagnostic performance of MRPA for CTEPH diagnosis is still inferior to CTPA.[21,34,41] Ley et al.[34] compared CTPA, MRPA, and digital subtraction angiography (DSA), showing the sensitivity and specificity of MRPA for diagnosing disease at the main/lobar level to be 83.1% and 98.6%, and at the segmental level 87.7% and 98.1%, respectively. Subsegmental arteries were demonstrated in only 75% of cases, compared with 87% by DSA. Usage of MRPA is highly dependent on local practice and is not yet integrated in the guidelines. A longer scan time and the association with nephrogenic systemic fibrosis in renally impaired subjects are some of the disadvantages of this method.

Catheter-based Pulmonary Angiogram

Catheter based pulmonary angiography while invasive has a generally low complication rate. It has the advantage of being able to combine imaging with haemodynamic assessment via right heart catheterisation, and accurately localise or "map out" lesions in the determination of surgical accessibility.[43] In addition, assessment of central and subpleural capillary perfusion score is possible. Poor subpleural perfusion in the context of PH is associated with distal vessel angiopathy or other primary lung disease. This is associated with a higher surgical risk.[44]

A disadvantage is the higher contrast load needed compared to a conventional CTPA. This can be improved by using cardiac output tailored minimal contrast exposure, or rotational pulmonary angiogram. It is not used as a routine screening tool for patients under investigation for PH, but as one of the final step to determine CTEPH operability. This requires relevant experience. Typical signs of CTEPH (Figure 1f) include bands, intimal irregularities, pouch defects, abrupt vascular narrowing, and complete obstruction of pulmonary arteries.[45] A classification system based on the lesion opacity and the blood flow distal to it has been described–Type A: ring-like stenosis, Type B: web lesion, Type C: subtotal lesions, Type D: total occlusion, and Type E: tortuous lesion.[46] These has implications on the success of balloon angioplasty (see below).

Cardiopulmonary Exercise Testing (CPET)

Exertional dyspnoea can be multifactorial in origin. CTEPH may be difficult to diagnose especially when there is chronic pulmonary vascular obstruction but normal PA haemodynamics at rest. CPET as an indirect marker of cardiopulmonary function is a promising additional tool to assess patients in this special category.[42] Firstly, it helps exclude other causes of dyspnea such as ventilatory limitation from lung or musculoskeletal disease or deconditioning. Secondly, it is able to demonstrate symptom and cardiovascular limitation on exercise in a patient with otherwise normal resting haemodynamics. Typical findings of CTED/CTEPH show evidence of ineffective ventilation caused by elevated alveolar-capillary gradients of oxygen and carbon dioxide: (a) elevated slope of minute ventilation (V′E) / carbon dioxide output (V′CO2) ratio showing hyperventilation; (b) elevated ventilator equivalents for oxygen and carbon dioxide showing ineffective ventilation; (c) low and decreasing end-tidal carbon dioxide tension (PETCO2), elevated alveolar-arterial oxygen tension gradient (PA-aO2) and elevated arterial end-tidal carbon dioxide gradient (Pa-ETCO2).[47]

Understanding the limitations of each type of imaging and having the ability to perform and interpret different modalities of imaging is crucial at a tertiary PH centre. Figure 2 shows a case of a young female with history of systemic sclerosis and interstitial lung disease involving bilateral lower lobes. The conventional CTPA demonstrated a linear filling defect within the lumen of the right lower lobe pulmonary artery, suspicious of chronic thromboembolic disease (Figure 2a). However, the perfusion of the right lower lobe was normal in both the VQ scan (Figure 2b) and the DECTPA iodine

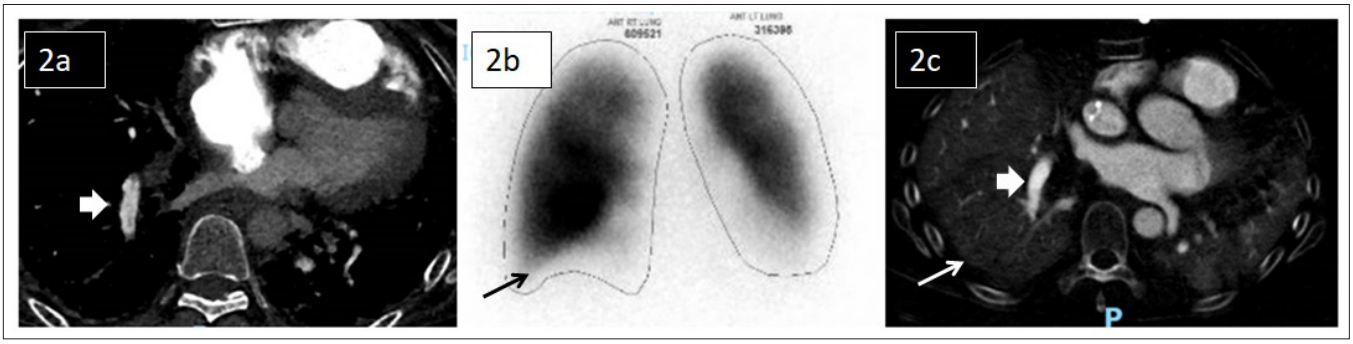

Fig. 2. (a) Conventional CTPA; (b) VQ scan; and (c) DECTPA. These are images from a young female with history of systemic sclerosis and interstitial lung disease involving bilateral lower lobes. The conventional CTPA demonstrated a linear filling defects within the lumen of the right lower lobe pulmonary artery (white arrow), suspicious of chronic thromboembolic disease. However, the perfusion of the right lower lobe was normal in both VQ scan (black arrow) and DECTPA iodine perfusion map (white arrow). The filling defect was also not present on the repeat DECTPA. The initial linear filling defect on conventional CTPA was likely a result of artefacts from poor flow to the scarred lung.

perfusion map (Figure 2c). The initial linear filling defect on conventional CTPA was likely a result of artefacts from poor flow to the scarred lung. Figure 3 shows a case of middle-aged male presented with dyspnoea on exertion whose lung perfusion on the initial VQ scan was normal. Due to previous history of PE and high clinical suspicion, a CTPA was performed which showed extensive chronic thromboembolic diseases at multiple pulmonary artery segments. This was in keeping with a subsequent DECTPA which demonstrated patchy perfusion defects corresponding to the areas supplied by these narrowed or occluded arteries. These cases highlight the importance of multimodality imaging to avoid misdiagnosis.

Management

Pulmonary endarterectomy (PEA) is considered the treatment of choice and affords potential cure.[48] In inoperable patients or those with residual disease post-PEA, medical therapy remains an option. In recent times, balloon pulmonary angioplasty (BPA) has emerged as a potential treatment modality for such patients in experienced centres.[49-51,21,52]

Pulmonary Endarterectomy (PEA)

The primary treatment for patients with CTEPH is surgical PEA, which is regarded as a curative treatment of choice (Figure 4a). Operability assessment by a multidisciplinary team is crucial for the management in all CTEPH patients. In general, at least moderate disease burden with a distribution at lobar and proximal segmental level is better suited for PEA. Besides technical considerations, surgical risk based on invasive haemodynamics, other comorbidities, as well as the experience level of the PEA surgeon and supporting CTEPH team, plays an important role in the decision making for the suitability for PEA.

The standard surgical technique for PEA was established by the group from San Diego.[53] Deep hypothermic circulatory arrest is necessary to provide a clear operating field to enable a complete endarterectomy with dissection into subsegmental branches. This technique has proven safe and reproducible and is used at most centres performing PEA surgery. Successful PEA in suitable patients can lead to significantly improved symptoms and functional status, haemodynamics (mPAP reduction by about 65%), remodelling of the PAs, improvement of RV function, quality of life and survival.[8] The international registry of incident cases of CTEPH reported 3-year survival of 90% in those operated compared to 70% in those who were not. Residual PH with PVR $\geq$5.3 Woods correlated with worse survival. Survival rates of >90% at 1 year, >80% at 5 years, and >70% at 6–10 years have been reported.[54]

Common risks of surgery include bleeding, reperfusion pulmonary edema, wound infection, and arrhythmias. Severe cases of reperfusion lung injury can be quite challenging to manage. For reperfusion lung injury with severe hypoxemia, veno-venous extracorporeal membrane oxygenation (ECMO) support may be instituted to maintain arterial oxygenation and to prevent further lung injury by allowing for the use of protective ventilatory settings.[55] In cases with haemodynamic instability, veno-arterial

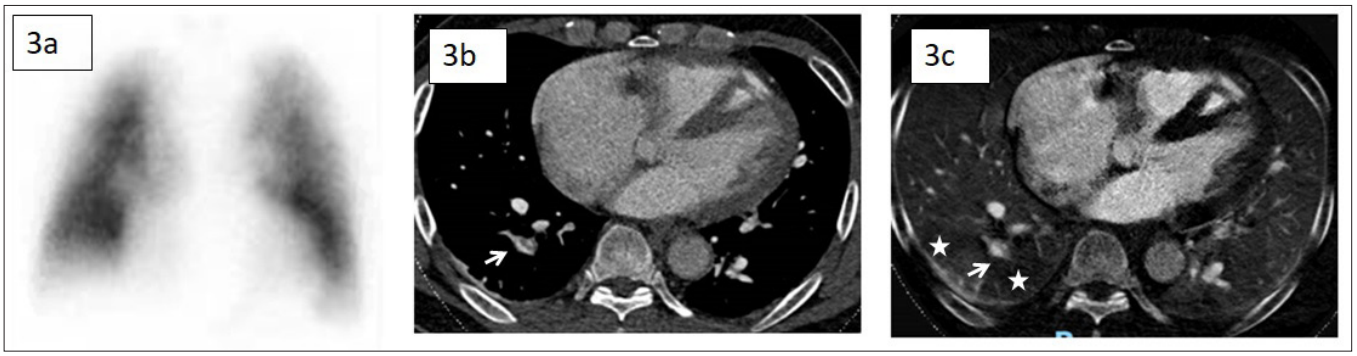

Fig. 3. (a) VQ scan; (b) conventional CTPA; (c) DECTPA. These are images from a middle-aged male who presented with dyspnoea on exertion. The perfusion on the initial VQ scan was normal. The diagnosis of CTEPH was subsequently confirmed by CTPA and DECTPA. 3b shows on CTPA chronic emboli with linear band-like appearance (white arrow) at the bifurcation of right lower lobar pulmonary artery. 3c demonstrates on DECTPA patchy areas of reduced perfusion in basal segments of the right lower lobe (white stars) corresponding to the obstructed blood flow.

ECMO is necessary to support patient. Blood is diverted away from the heart and lungs, allowing reduction in PA pressure and offloading of the RV. At the same time, the ECMO circuit provides cardiac output and gas exchange. Average support duration is a median of 5 days in most series, and reported survival is up to 57% in those requiring ECMO support.[56]

The patient can also develop subdural haematoma, renal and heart failure, as well as residual PH.[57] Other complications include that of perforation of the PA, stroke, and death. The in-hospital mortality rate ranges from as low as ≤3.5% in specialised high-volume centres (n >50 PEAs/year), to 4.7% in medium volume (11-50 PEAs per year) and 7.4% in low volumes centres (<11 PEAs per year).[58]

Balloon Pulmonary Angiogram (BPA)

BPA involves the wiring of target lesions and the use of small size balloons at low pressures to expand these lesions (Figure 4b–d). Generally, BPA is more appropriate for diseases distributed at the distal segmental and subsegmental levels.[59] The types of lesions usually tackled by BPA include webs and stenosis. Sub-total or total occlusions should not be attempted by the inexperienced operator. In the recent few years, numerous studies have emerged in the use of BPA to treat CTEPH that is inoperable. [51,52,59,60] There were significant improvements in the reported haemodynamic results (reduction of PVR and improvement of cardiac output) as well as improvements in the 6-min walk distance (6MWD) and NYHA/WHO functional class, almost equivalent to the results from PEAs by experienced centres.[49] This technique carries risks of complications including periprocedural mortality ranging from 0 to 10%,[13] vessel rupture (0 to 7%), and reperfusion lung injury. Reperfusion lung injuries range from desaturations, haemoptysis and infiltrations to more severe events like acute respiratory distress syndrome requiring ECMO support. In experienced hands, BPA has emerged as a promising treatment for inoperable CTEPH and those with residual disease after PEA with recent publications showing lower complication rates than initial publications.[22]

Medical Therapy

The International CTEPH registry reported that about 40% of the patients were considered inoperable due to concern for inaccessible distal vascular obstruction, PH out of proportion to morphological lesions and significant comorbidities; around 20% of the patients had residual PH post-PEA.[7] It is plausible to use PAH-targeted therapy in CTEPH cases, as they share many similar histopathological features.[61–64]

Before the publication of several important randomised controlled trials, PAH-targeted therapies were widely used “off label” in the treatment of CTEPH. In the BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) trial, Bosetan, an oral dual endothelin receptor antagonist, was given to patients with either inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA (>6 months after PEA). This study demonstrated a positive treatment

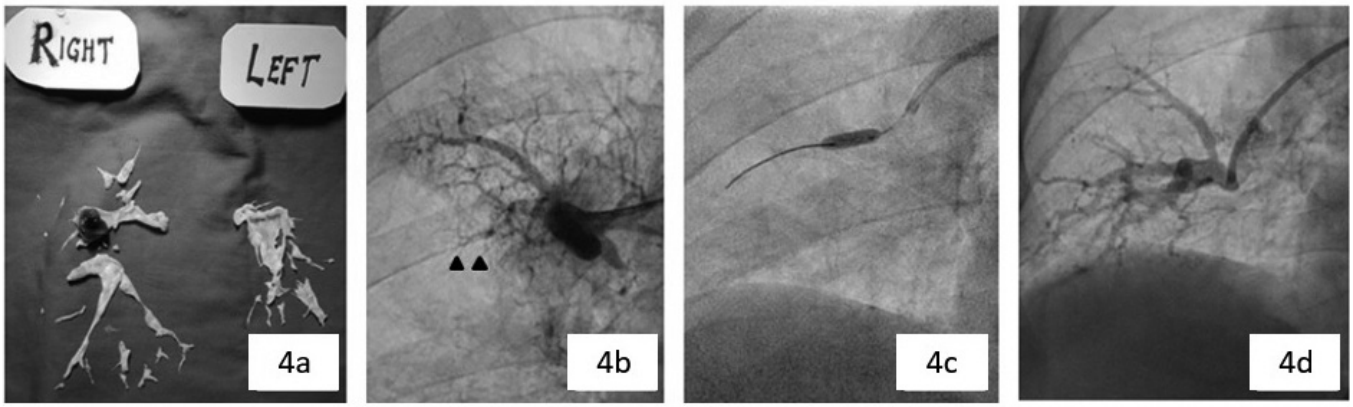

Fig. 4. (a) Resected tissue from pulmonary endarterectomy surgery (PEA); (b) Subtotally occluded right middle lobe segmental pulmonary artery (black triangles); (c) Balloon pulmonary angioplasty of the segment (d) Restored flow post balloon dilatation.

effect of Bosentan on haemodynamics (reduction of PVR by 24% and improvement of cardiac index by 0.3 L/min) in this patient population. However, no improvement was observed in exercise capacity after 16 weeks of treatment.[65] Subsequently, in the CHEST-1 (Riociguat for the treatment of chronic thromboembolic pulmonary hypertension) trial, Riociguat, a direct soluble guanylate cyclase stimulator, achieved clinically meaningful primary endpoints including an improved WHO functional class, improved 6MWD by an average 46 m, reduction in plasma brain natriuretic peptide levels, and reduction in PVR by 31% after 16-weeks of treatment.[62] This improvement persisted at 1 year. More recently, the MERIT- 1 (Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension) trial provided evidence of using macitentan, a endothelin receptor antagonist, in the treatment of CTEPH. CTEPH patients treated with macitentan had a significant reduction in PVR by 16%, as well as improvements in functional class and 6MWD. This study provided some evidence for using combination therapy as 51% of the recruited patient were already treated with baseline phosphodiesterase type 5 inhibitors and/or oral/inhaled prostanoids at inclusion.[64] There are several ongoing clinical trials that will shed further important knowledge on the medical management of CTEPH. The SELECT trial (Study to Find Out if Selexipag is Effective and Safe in Patients With Chronic Thromboembolic Pulmonary Hypertension When the Disease is Inoperable or Persistent/Recurrent After Surgery) aims to evaluate the efficacy of Selexipag, a prostacyclin receptor agonist, in treating inoperable CTEPH or persistent/recurrent PH after PEA, while the SOPHA trial (The Effect of Oxygen Therapy on 6MWD in PAH and CTEPH Patients With Hypoxemia) aims to study the effect of long term oxygen therapy in CTEPH and PAH patients with oxygen deficiency (See Table 1).[66]

Another important aspect of medical therapy is the pre-treatment of patient as a bridging therapy to PEA. Retrospective data from a single centre suggested that pre-treating patients with PAH-targeted therapy had no impact on surgical outcomes but was associated with a delay in referral for surgical evaluation.[67] Efforts are currently underway to prospectively study the impact of "bridging therapy" or pre-treating patients with PAH therapies before PEA (PEA Bridging Study).[68]

Conclusions

CTEPH is a debilitating disease with significant morbidity and mortality. It is often under-recognised with resultant delays in treatment. Understanding the utility and limitations of the different imaging modalities is crucial. There are effective treatment options available. PEA is a complex surgery that requires both good surgical technique as well as a comprehensive multi-disciplinary team care approach. In CTEPH patients who are ineligible for PEA and in those with residual disease post-PEA, medical therapy and BPA remain potential alternatives.

Table 1. Summary of completed and ongoing trials on medical therapy in CTEPH

Name	Year	Follow-up duration (weeks)	Numbers	Inclusion criteria	Treatment vs Comparator	Design	Effects vs comparator	*P*
BENEFiT (65)	2008	16	157	Inoperable CTEPH or persistent/ recurrent PH after PEA (>6m after PEA)	Bosentan vs placebo	DB, R	6MWD +2m PVR -24% - NT-proBNP + WHO class	NS *P*<0.0001 *P*=0.0034 NS
CHEST-1(62)	2013	16	261	Inoperable CTEPH or persistent/ recurrent PH after PEA	Riociguat vs placebo	DB, R	6MWD +46m PVR - 31% - NT-proBNP + WHO class	*P*<0.001 *P*<0.001 *P*<0.001 *P* =0.003
MERIT-1(64)	2017	16 [24*]	80	Inoperable CTEPH	Macitentan vs placebo	DB, R	6MWD +34m PVR -16% - NT-proBNP + WHO class	*P* =0.033 *P*=0.041 *P*=0.040 NS
SELECT (69)	2019	52	236	Inoperable CTEPH or persistent/ recurrent PH after PEA	Selexipag vs placebo	DB,R	6MWT PVR	Ongoing
SOPHA (66)	2019	24	40	PAH and CTEPH patients with O2 deficiency (PaO2 < 8kpa)	Oxygen	R, Cross over Assignment	6MWT QOL Clinical worsening RHC, Echo, CPET parameters	Ongoing
PEA bridging study (68)	2017	39	80	Operable CTEPH prior to PEA With high preoperative PVR	Riociguat vs placebo	DB, R	PVR before and 6m after PEA All-cause death PH hospitalisation Surgery complications, evaluation of specimen, and circulatory arrest time	Ongoing

PEA: Pulmonary Endarterectomy; DB: double-blind; R: randomised-controlled study, PVR: pulmonary vascular resistance, 6MWD: 6-min walk distance; ns: non-significant; -: reduction; +: improvement; *: 6MWT assessed at 24 weeks

REFERENCES

1. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1801915.
2. Lau G. Pulmonary thromboembolism is not uncommon--results and implications of a five-year study of 116 necropsies. Ann Acad Med Singapore 1995;24:356–65.
3. Molina JA, Jiang ZG, Heng BH, Ong BK. Venous thromboembolism at the National Healthcare Group, Singapore. Ann Acad Med Singapore 2009;38:470–8.
4. 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;26:160121.
5. Poli D, Grifoni E, Antonucci E, Arcangeli C, Prisco D, Abbate R, et al. Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism. J Thromb Thrombolysis 2010;30:294–9.
6. Lang IM. Chronic thromboembolic pulmonary hypertension--not so rare after all. N Engl J Med 2004;350:2236–8.
7. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973–81.
8. Simonneau G, Torbicki A, Dorfmuller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26:160112.
9. Opitz I, Kirschner MB. Molecular Research in Chronic Thromboembolic Pulmonary Hypertension. Int J Mol Sci 2019;20:784.
10. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Haematologica 2010;95:970–5.
11. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: a follow-up study of the relation between the degree of right ventricle overload and the extent of perfusion defects. J Intern Med 1999;245:601–10.
12. Bonderman D, Wilkens H, Wakounig S, Schafers HJ, Jansa P, Lindner J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 2009;33:325–31.
13. Mahmud E, Madani MM, Kim NH, Poch D, Ang L, Behnamfar O, et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. J Am Coll Cardiol 2018;71:2468–86.
14. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuss G, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2015;14:121–8.
15. Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. Pulm Circ 2013;3:89–94.
16. Lewczuk J, Piszko P, Jagas J, Porada A, Wojciak S, Sobkowicz B, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 2001;119:818–23.
17. Riedel M, Widimsky J. [Prognosis of pulmonary hypertension in chronic thromboembolic disease]. Vnitr Lek 1980;26:729–36.
18. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019 Jan;53:1801904.
19. Taboada D, Pepke-Zaba J, Jenkins DP, Berman M, Treacy CM, Cannon JE, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J 2014;44:1635–45.
20. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
21. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, 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.
22. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013;62:D92–9.
23. Clements PJ, Tan M, McLaughlin VV, Oudiz RJ, Tapson VF, Channick RN, et al. The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. Ann Rheum Dis 2012;71:249–52.
24. Best DH, Sumner KL, Austin ED, Chung WK, Brown LM, Borczuk AC, et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. Chest 2014;145:231–6.
25. Kauczor HU, Schwickert HC, Mayer E, Kersjes W, Moll R, Schweden F. Pulmonary artery sarcoma mimicking chronic thromboembolic disease: computed tomography and magnetic resonance imaging findings. Cardiovasc Intervent Radiol 1994; 17:185–9.
26. Perloff JK, Hart EM, Greaves SM, Miner PD, Child JS. Proximal pulmonary arterial and intrapulmonary radiologic features of Eisenmenger syndrome and primary pulmonary hypertension. Am J Cardiol 2003;92:182–7.
27. Powe JE, Palevsky HI, McCarthy KE, Alavi A. Pulmonary arterial hypertension: value of perfusion scintigraphy. Radiology 1987;164:727–30.
28. Lisbona R, Kreisman H, Novales-Diaz J, Derbekyan V. Perfusion lung scanning: differentiation of primary from thromboembolic pulmonary hypertension. AJR Am J Roentgenol 1985;144:27–30.
29. Meignan MA. Lung ventilation/perfusion SPECT: the right technique for hard times. J Nucl Med 2002;43:648–51.
30. Morrell NW, Nijran KS, Jones BE, Biggs T, Seed WA. The underestimation of segmental defect size in radionuclide lung scanning. J Nucl Med 1993;34:370–4.
31. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med 2004;45:1501–8.
32. Soler X, Hoh CK, Test VJ, Kerr KM, Marsh JJ, Morris TA. Single photon emission computed tomography in chronic thromboembolic pulmonary hypertension. Respirology 2011;16:131–7.
33. Ryan KL, Fedullo PF, Davis GB, Vasquez TE, Moser KM. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. Chest 1988;93:1180–5.
34. Ley S, Ley-Zaporozhan J, Pitton MB, Schneider J, Wirth GM, Mayer E, et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Eur Radiol 2012;22:607–16.
35. Bailey CL, Channick RN, Auger WR, Fedullo PF, Kerr KM, Yung GL, et al. "High probability" perfusion lung scans in pulmonary venoocclusive disease. Am J Respir Crit Care Med 2000;162:1974–8.
36. Ferda J, Ferdova E, Mirka H, Baxa J, Bednarova A, Flohr T, et al. Pulmonary imaging using dual-energy CT, a role of the assessment of iodine and air distribution. Eur J Radiol 2009;77:287–93.

37. Renard B, Remy-Jardin M, Santangelo T, Faivre JB, Tacelli N, Remy J, et al. Dual-energy CT angiography of chronic thromboembolic disease: can it help recognize links between the severity of pulmonary arterial obstruction and perfusion defects? Eur J Radiol 2011;79:467–72.
38. Nakazawa T, Watanabe Y, Hori Y, Kiso K, Higashi M, Itoh T, et al. Lung perfused blood volume images with dual-energy computed tomography for chronic thromboembolic pulmonary hypertension: correlation to scintigraphy with single-photon emission computed tomography. J Comput Assist Tomogr 2011;35:590–5.
39. Dournes G, Verdier D, Montaudon M, Bullier E, Riviere A, Dromer C, 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.
40. Ruggiero A, Screaton NJ. Imaging of acute and chronic thromboembolic disease: state of the art. Clin Radiol 2017; 72:375–88.
41. Kreitner KF, Ley S, Kauczor HU, Mayer E, Kramm T, Pitton MB, et al. Chronic thromboembolic pulmonary hypertension: pre- and postoperative assessment with breath-hold MR imaging techniques. Radiology 2004;232:535–43.
42. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26:160108.
43. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34:888–94.
44. Tanabe N, Sugiura T, Jujo T, Sakao S, Kasahara Y, Kato H, et al. Subpleural perfusion as a predictor for a poor surgical outcome in chronic thromboembolic pulmonary hypertension. Chest 2012;141:929–34.
45. Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. Radiology 1992;182:393–8.
46. Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, 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.
47. Held M, Grun M, Holl R, Hubner G, Kaiser R, Karl S, et al. Cardiopulmonary exercise testing to detect chronic thromboembolic pulmonary hypertension in patients with normal echocardiography. Respiration 2014;87:379–87.
48. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, 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
49. 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.
50. Fukui S, Ogo T, Morita Y, Tsuji A, Tateishi E, Ozaki K, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. Eur Respir J 2014;43:1394–402.
51. 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.
52. Yamasaki Y, Nagao M, Abe K, Hosokawa K, Kawanami S, Kamitani T, et al. Balloon pulmonary angioplasty improves interventricular dyssynchrony in patients with inoperable chronic thromboembolic pulmonary hypertension: a cardiac MR imaging study. Int J Cardiovasc Imaging 2017;33:229–39.
53. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, 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.
54. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, 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.
55. 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.
56. Berman M, Tsui S, Vuylsteke A, Snell A, Colah S, Latimer R, et al. Successful extracorporeal membrane oxygenation support after pulmonary thromboendarterectomy. Ann Thorac Surg 2008;86:1261–7.
57. Yap J, Ruan W, Chia A, Loh K, Cheah FK, Leen Ang A, et al. Is subdural hemorrhage after pulmonary endarterectomy underrecognized? J Thorac Cardiovasc Surg 2018;156:2039–42.
58. Mayer E. Surgical and post-operative treatment of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2010; 19:64–7.
59. Mahmud E, Behnamfar O, Ang L, Patel MP, Poch D, Kim NH. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. Interv Cardiol Clin 2018;7:103–17.
60. 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.
61. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993;103:685–92.
62. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013; 369:319–29.
63. Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Jansa P, Kim NH, 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.
64. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jais X, 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.
65. Jais X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, 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.
66. clinicaltrials.gov. The effect of oxygen therapy on 6MWD in PAH and CTEPH patients with hypoxemia (SOPHA). Accessed on 25 April 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT04207593.
67. Jensen KW, Kerr KM, Fedullo PF, Kim NH, Test VJ, Ben-Yehuda O, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation 2009;120:1248–54.
68. clinicaltrials.gov. Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy (PEA Bridging Study). Accessed on 25 April 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03273257.