Review

Management of chronic thromboembolic pulmonary hypertension: current status and emerging options

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Practice Points

- Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to be a complication of pulmonary embolism; it remains underdiagnosed, and is the only potentially curable form of pulmonary hypertension.
- Exertional breathlessness is the most common presenting symptom and there are no specific symptoms or signs.
- Radiological investigations are central to diagnosing CTEPH.
- Interpretation of diagnostic tests is best performed in experienced centers.
- Anticoagulation is essential to prevent further thrombosis.
- Endothelin antagonists, phosphodiesterase-5 inhibitors and prostanoids are used to improve symptoms in some patients with inoperable CTEPH but, to date, these drugs are not licensed as trials have not confirmed benefit.
- Pulmonary endarterectomy is the gold standard treatment for CTEPH and is potentially curative.
- In experienced centers, in-hospital mortality approaches that for conventional cardiac surgery.
- Increase awareness of CTEPH to ensure earlier referral to specialist centers, improving patient access to potentially curative therapies.

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SUMMARY Chronic thromboembolic pulmonary hypertension (CTEPH) is the only cause of pulmonary hypertension for which there is a potential cure, in the form of surgical pulmonary endarterectomy. There is a strong link between pulmonary embolism and the development of CTEPH. Although initially felt to be a rare complication, this position has been reviewed, following several studies suggesting that up to 8.8% of patients develop CTEPH within the 2 years following pulmonary embolism. However, there is a significant discrepancy in the number of patients being diagnosed, referred and treated for CTEPH. In this review, we discuss the challenges of diagnosing CTEPH and present the current and emerging medical and surgical management options available for patients suffering with CTEPH.

Chronic thromboembolic pulmonary hypertension (CTEPH) is an underdiagnosed and frequently overlooked cause of pulmonary hypertension (PH). It is thought to be a late complication after pulmonary embolism (PE) [1]. Unfortunately there is often a delay in making the diagnosis of CTEPH, resulting in a delayed referral to specialist centers with expertize in the medical and surgical management of these patients. The significance of this lies in the fact that CTEPH is the only potentially curable form of PH, with excellent symptomatic and prognostic benefit from pulmonary endarterectomy (PEA) [2,3]. Untreated, the 3-year mortality has been reported to be as high as 90% [4–6]. This article aims to review the current diagnostic pathway, and available and emerging management options for patients with CTEPH.

CTEPH

CTEPH is classified in Group 4 of the recently updated Dana Point classification of PH [7]. It is defined clinically as symptomatic, precapillary PH (mean pulmonary arterial pressure ≥25 mmHg, pulmonary capillary wedge pressure ≤15 mmHg as assessed by right heart catheterization) in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (i.e., main, lobar, segmental or subsegmental arteries) after at least 3 months of effective anticoagulation [8].

Pathogenesis

The pathogenesis of CTEPH is incompletely understood. It is widely believed that CTEPH is a complication of PE [9]. It is postulated that residual thromboembolic masses that are not completely cleared following a PE undergo fibrosis, leading to mechanical obstruction of the pulmonary arteries, either by narrowing or occluding the vessels [10,11]. However, this embolic hypothesis has been questioned, as in some series a significant proportion of patients with CTEPH report no history of previous PE. There is the possibility though, that these patients suffered an occult embolic event. Although the recent prospective European CTEPH registry demonstrated that 80% of patients undergoing PEA did have a history of PE [9], there is always the possibility that previous ventilation/perfusion (V/Q) scans and computed tomography pulmonary angiograms (CTPAs) have been misinterpreted as acute when chronic disease was present at presentation.

An alternative hypothesis has been proposed. The thrombotic hypothesis suggests that CTEPH is initiated by *in situ* thrombotic events within the pulmonary vasculature secondary to arteriopathy with abnormalities in the clotting cascade, platelets or endothelial cells [12,13]. Progressive development of thrombi with incomplete resolution results in partial or complete obstruction of the lumen. It is unclear why there is ineffective resolution of these thrombi, but several hypotheses include: chronic staphylococcal infection [13], abnormal fragmentation of fibrinogen [14], abnormal sialylation of fibrinogen γ-chains [15] and abnormalities with fibrinolysis [16].

It is probable that both the embolic and thrombotic hypotheses are valid, and may even both contribute to CTEPH in a single patient in some instances. The outcome of the embolic and thrombotic hypotheses is the same, a decrease in the total cross-sectional area of the pulmonary vasculature leading to an increase in pulmonary vascular resistance (PVR) and subsequent PH. Abnormal vascular remodeling aggravates the progression of the disease even in the absence of further thrombi [13]. Within the non-occluded vessels, a pulmonary arteriopathy sometimes develops similar to that seen in Group 1 PH,

perhaps due to increased shear stresses, which contributes to disease progression. This two-compartment model to account for the PVR resistance in CTEPH was first proposed by Moser and Braunwald [17] and is still important when considering assessment of operability, as the distal vasculopathy will not be immediately relieved by endarterectomy. This model also supports the concept of the importance of early diagnosis of the disease with the expectation that early treatment will reduce the pulmonary arteriopathy in the unobstructed vessels.

Risk factors

Various predisposing factors have been associated with the development of CTEPH and are summarized in **Box 1**. Interestingly, hereditary prothrombotic conditions such as antithrombin III deficiency, protein C and S deficiency and factor V Leiden have not been found to be strongly associated with the development of CTEPH [13,18–20]. There is some evidence to suggest that patients having undergone a splenectomy are at higher risk of CTEPH. In an observational study looking at 257 patients with CTEPH, 8.6% had a history of splenectomy compared with 2.5 and 0.5% in patients with idiopathic PH and other chronic pulmonary conditions, respectively [21]. However, the majority of patients have no known precipitating factors.

Incidence

The true incidence and prevalence of CTEPH has not been clearly established and current estimates are based on referral to specialist centers, which may underestimate the true extent of the disease in the population. One such estimate comes from a recently completed national PH audit in the UK, which demonstrated a prevalence of 16.6 per million population per annum based on patients referred to specialist tertiary referral centers [22]. In the USA, attempts to estimate the prevalence of CTEPH have been performed using claims data from their insurance-based healthcare system with an estimate of 63 per million individuals among those privately insured under the age of 65 years and 1007 per million individuals under the Medicare population (aged 65 years and above) [23].

CTEPH was initially thought to be a rare, late, sequelae following PE with an estimated incidence of 0.1–0.5% in patients surviving the initial PE [24]. More recently there have been several prospective studies following patients surviving an episode of PE, which suggest a much higher incidence of CTEPH, ranging from 0.4 to 8.8% [1,10,11,25–28]. One of these studies also observed that patients suffering recurrent PEs had an even higher incidence, with 37.5% developing CTEPH [11].

Clinical presentation

The majority of patients complain of exertional breathlessness, reduced exercise capacity and fatigue. There is no constellation of symptoms or signs that is diagnostic of CTEPH. As a result, misdiagnosis is frequent and patients are often initially diagnosed with other common cardiopulmonary disease such as chronic obstructive pulmonary disease or ischemic heart disease. Alternatively the symptoms are incorrectly assigned to advancing age and deconditioning. A prospective international registry of patients with CTEPH identified that there had been a median delay of 14.1 months from presentation with initial symptoms to diagnosis [29]. This diagnostic delay in turn leads to a therapeutic delay.

Box 1. Risk factors for chronic thromboembolic pulmonary hypertension.

Medical associations
- Splenectomy
- Ventriculo-atrial shunts
- Infected indwelling central venous catheters or pacemaker leads
- Osteomyelitis, inflammatory bowel disease
- Thyroid replacement therapy
- Malignancy

Thrombotic associations
- Antiphospholipid antibody or lupus anticoagulant
- Elevated factor VIII
- Dysfibrinogenemia
- Abnormal endogenous fibrinolysis

Associations with the development of CTEPH after PE
- Reccurent PE
- Large perfusion defect
- Young or old age at time of PE
- Idiopathic PE
- Raised pulmonary arterial pressure >50 mmHg at time of presentation with PE

CTEPH: Chronic thromboembolic pulmonary hypertension; PE: Pulmonary embolism.
Data taken from [13,18–20].

The interval between the initial acute event and the development of clinically apparent CTEPH can range from a few months to several years. During this asymptomatic, lag phase the disease progresses and PVR increases. It is thought that the development of right ventricular dysfunction is the critical point when patients become symptomatic. Patients commonly present with exertional dyspnea and the majority of patients have New York Heart Association (NYHA) class III or IV symptoms at the time of diagnosis. Other common symptoms include fluid retention, fatigue, chest pain and syncope [29]. Subtle physical signs may also be evident once right ventricular dysfunction develops, such as a left parasternal heave, a prominent pulmonary component of the second heart sound or a systolic murmur on auscultation [30]. Other signs of right heart failure including distended neck veins, peripheral edema, ascites and acrocyanosis may be evident late in the course of CTEPH [30].

The nonspecific presentation and common misdiagnosis lead some to suggest that patients who have survived an episode of PE should be screened for the development of CTEPH to permit an earlier diagnosis [26,31]. However, to date there is no evidence that this approach is beneficial to patients, no consensus over the best screening method and it will miss patients that do not present with PE.

CTEPH diagnosis

Radiological investigations are central to the diagnosis of CTEPH. The use of appropriate imaging modalities is important to distinguish CTEPH from other forms of PH and to additionally assess the distribution of the clot burden. However, one of the suggested reasons for the underdiagnosis of CTEPH is the misinterpretation of imaging studies by radiologists not familiar with the condition [10,32]. For example, V/Q scans and computed tomography (CT) angiograms can both underestimate the clot burden [30]. Conventional pulmonary angiography has been considered the gold standard test for some time but is rarely performed in most hospitals, and obtaining high-quality images to interpret the anatomy is a skill. Access to a variety of radiological studies is essential to thoroughly assess patients and make the initial diagnosis, and this is best achieved in specialist centers where interpretation of imaging and decisions on clinical management are made by members of a multidisciplinary team experienced in this condition.

The range of imaging studies that are available to investigate suspected cases of CTEPH are discussed below.

Chest radiography

Chest radiography may be performed as part of the initial assessment of suspected PH. Enlargement of the central pulmonary arteries and right atrium on a chest radiograph is suggestive of PH. It may also be possible to detect evidence of a thromboembolic etiology, which includes attenuation and amputation of the lobar or segmental pulmonary arteries [33]. Pulmonary infarcts may also be visible on a chest radiograph.

Echocardiography

Echocardiography is not specific for CTEPH, but is performed to assess patients suspected of having PH. Echocardiography enables indirect assessment of pulmonary systolic pressures and helps to exclude intracardiac shunts or left heart disease as a cause of PH. PH may be evidenced by demonstrating right ventricular dilatation, hypertrophy and hypokinesis, right atrial enlargement, right ventricular pressure overload and tricuspid regurgitation. The left heart is often underfilled and compressed. The absence of signs of right ventricular overload observed by echocardiography in conjunction with a normal N-terminal pro-brain natriuretic protein level virtually excludes significant PH [34].

The European Society of Cardiology and European Respiratory Society guidelines for the diagnosis and treatment of PH recommend a follow-up echocardiogram in patients with acute PE showing signs of PH or right ventricular dysfunction to determine whether or not the PH has resolved [8].

V/Q scans

V/Q lung scans are recommended as a screening method for CTEPH in patients with unexplained PH **(Figure 1)**. Although V/Q scanning is a functional technique, it has limited spatial resolution [35]. However, large vessel disease with multiple mismatched wedge-shaped perfusion defects can be distinguished from small vessel disease with a patchy mottled appearance [36]. A completely normal V/Q scan virtually excludes the diagnosis of CTEPH, although there are very rare cases with isolated nonocclusive web disease

and normal perfusion. V/Q scans may also be useful in operability assessment as large segmental perfusion defects often predict a good result from PEA.

Right heart catheterization

Right heart catheterization should be performed in all patients to obtain right-sided pressures and to calculate PVR. It is a mandatory investigation for confirming the diagnosis of PH and provides data of prognostic value.

A mean pulmonary pressure ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg confirms the diagnosis of CTEPH in patients known to have chronic or organized thromboembolic obstructions of the pulmonary vasculature [8]. A PVR that is disproportionately elevated compared with the observed pulmonary arterial obstruction is generally indicative of a more distal vasculopathy, which is likely to be accompanied by a proximal occlusion and is not necessarily a contraindication to surgical management. Analysis of the decay curve of the wedge tracing following balloon occlusion may help distinguish more distal small vessel disease from more proximal by partitioning the PVR [37], but at present these techniques are experimental and single occlusion results may not be reproducible [38].

Pulmonary angiography

Pulmonary angiography has been traditionally recommended as the gold standard for the definitive diagnosis of CTEPH, indicating the site and accessibility of the pulmonary arterial obstruction. Findings typically include dilatation of the pulmonary artery, vascular obstructions, vascular webs, postobstructive dilatation and poorly perfused areas of the lungs [39]. Pulmonary angiography is often performed in conjunction with right heart catheterization in some centers [30].

CTPA

CTPAs are increasingly used for diagnosing CTEPH. Characteristic findings include mosaic perfusion pattern, dilatation of proximal pulmonary arteries and right heart chambers together with the presence of vascular stenosis or obstruction [29]. Enlarged bronchial artery collaterals (not usually found with other types of PH) may be seen on CT angiograms and are considered to be a good prognostic sign in operable patients [32,39–41]. Scans can be misinterpreted

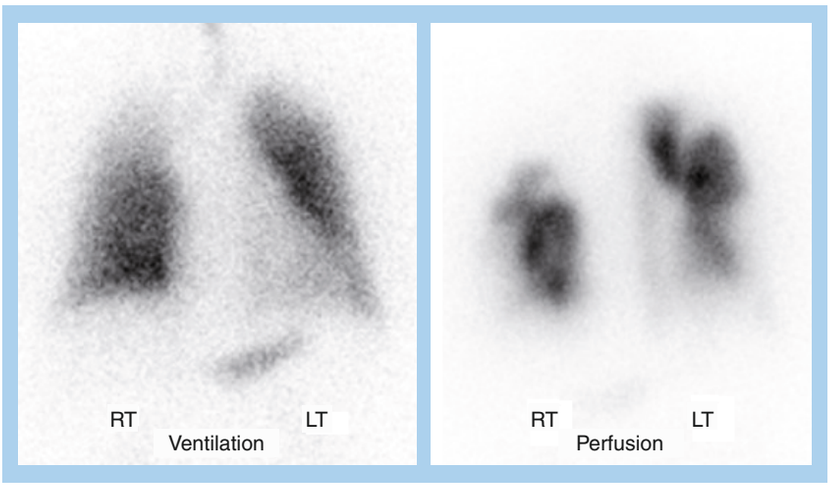

Figure 1. Ventilation/perfusion scan with multiple mismatch defects.
LT: Left; RT: Right.

and it is important to emphasize that the presence of proximal pulmonary artery thrombus does not confirm the diagnosis of CTEPH and more importantly the absence does not exclude CTEPH. Other conditions that can be mistaken for CTEPH include pulmonary vasculitis, *in situ* thrombosis associated with congenital heart defects, extrinsic compression of the pulmonary artery by lymphadenopathy (e.g., sarcoidosis) and pulmonary artery sarcoma.

The recent development of dual-energy CT permits the identification of perfusion defects distal to proximal vascular obstruction and therefore, has the potential to improve the detection of distal CTEPH [42].

MRI angiogram

MRI angiograms can provide excellent 3D views and offer a radiation free alternative to CT angiograms. They can be used for morphological, anatomical and functional assessment of both the cardiac and pulmonary circulations. They provide information on right and left ventricular function and can be used to estimate cardiac output, and its use in the diagnosis of CTEPH is increasing [43].

Management of patients with CTEPH

Although CTEPH is responsible for significant morbidity and mortality, it is a potentially curable disease. The natural history of the condition is poorly characterized, but patients ultimately progress to right ventricular failure and, historically, the 3-year mortality has been reported to be as high as 90% [5,6].

The most effective therapy for CTEPH is surgical PEA, which is the only potentially curative treatment available and is now the gold standard. It offers both excellent symptomatic and prognostic benefit to patients with CTEPH. Despite the existence of this potentially life-saving cure, underdiagnosis continues to prevent patients accessing PEA.

Upon suspected diagnosis of CTEPH, patients should be referred to tertiary specialist centers where a multidisciplinary team, led by experienced PEA surgeons, can decide whether the disease is amenable to surgery. Although there are drugs for Dana Point Group 1 (pulmonary arterial hypertension), there are currently no drugs licensed for the treatment of CTEPH (Group 4 PH). However, there is international experience of using pulmonary arterial hypertension licensed drugs to treat CTEPH where surgery is not possible or has not been curative.

■ Medical management

Anticoagulation

It is considered essential that all patients with CTEPH must be fully anticoagulated, usually with warfarin, life-long to prevent further thrombus formation. This is a rare condition so this is an expert recommendation backed up by evidence that recurrent thrombus is a risk factor for CTEPH. For warfarin a target international normalized ratio of 2–3:1 is recommended by guidelines although, in practice, some centers recommend higher ranges for individual patients.

Newer oral anticoagulant agents are being used for the treatment of venous thromboembolic events. Rivaroxaban is approved for use in treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT/PE [44,45]. Dabigatran and apixaban are approved for prevention of DVT after total hip or knee surgery [46]. It is likely that these drugs will be considered for use in the future for patients with CTEPH. However, because a formal study to evaluate them in this patient group is unlikely, they should be implemented with caution while understanding of the drugs remains limited, as the potential for undercoagulation will have important consequences for these patients.

Supportive treatment

Fluid status should be optimized where appropriate with diuretics and oxygen therapy provided at home as required. Inferior vena cava filters are used in patients with recurrent PEs despite full anticoagulation or in patients with contraindications to anticoagulation to prevent further PE. The role of their use in PEA/CTEPH is debateable and lacking an evidence base. PEA surgical center preference usually dictates whether or not they are used in relation to PEA surgery.

Pulmonary arterial hypertension (Group 1) licensed drugs

At the time of CTEPH diagnosis, 37.9% of patients in an international registry were receiving at least one pulmonary arterial hypertension-licensed therapy as off-licence prescribing [29].

Histologically, PH in CTEPH has similarities with that of idiopathic PH, and a similar therapeutic approach is therefore taken to managing CTEPH [47]. The three main therapeutic agents include endothelin receptor antagonists [48–54], phosphodisterase-5 inhibitors [55–58] and prostanoids [47,59–62].

Endothelin receptor antagonists

Endothelin is an endogenous vasoconstrictor and elevated levels have been shown to correlate with CTEPH and clinical severity [63]. Increased levels of endothelin may also lead to increased vascular remodeling, with inflammation, vasoconstriction and fibrosis [64].

Bosentan and ambrisentan have been shown to improve patient symptoms and exercise capacity in some forms of PH [65,66].

Phosphodiesterase-5 inhibitors

Nitric oxide is a potent vasodilator [67]. Previous studies have shown it to be upregulated in conditions associated with PH [68,69].

Sildenafil and tadalafil are phosphodiesterase type-5 inhibitors. Sildenafil is also thought to have antiproliferative effects on pulmonary vascular smooth muscle cells [70]. Sildenafil has been shown to increase exercise capacity, WHO functional class and hemodynamics in patients with some forms of symptomatic PH [71]. Tadalafil has been shown to improve exercise capacity in patients with some forms of PH [72].

Prostanoids

Endogenous prostacycline induces vasodilation, has antiplatelet activity and antiproliferative effects [73]. Prostanoids have been shown to improve PVR and improve right ventricular function in PH [47]. Epoprostenol, iloprost and

treprostinil are prostanoid drugs that formed the first treatments developed for idiopathic PH [74]. Inhaled iloprost has been studied in patients with idiopathic PH and a mixture of patients with other forms of PH, including a reasonable cohort of patients CTEPH (28% of total study size). This study showed a greater improvement in the idiopathic PH patients compared with the other forms of PH (which included CTEPH) [75].

Evidence for medical treatments in CTEPH

The only multicenter, randomized, double-blind, placebo-controlled trial for any therapeutic agent in specifically managing CTEPH, is the BENEFIT trial for bosentan. This study of 157 patients with inoperable CTEPH or residual disease 6 months post-PEA, showed a decrease in PVR but no improvement in the 6 min walk test or time to clinical worsening after 16 weeks of therapy [48]. Only small, uncontrolled, retrospective evaluations have been undertaken to evaluate the other medical therapies for CTEPH and although demonstrating some benefit, none have proven which therapy is superior.

Sildenafil has shown some benefits in inoperable CTEPH. In a small randomized trial with 19 patients [55], it was shown to improve PVR at 3 months and symptoms and 6-min walk test at 12 months, but was insufficiently powered to show improved exercise capacity at 3 months. Another trial with 12 patients [57], although lacking a control group, showed improvement in pulmonary hemodynamics and exercise capacity after 6 months treatment.

Intravenous (iv.) epoprostenolol has also been shown to improve pulmonary hemodynamics and exercise capacity after long-term treatment in a retrospective study of 27 patients with inoperable CTEPH [58]. Similar results were found in another study of patients with inoperable CTEPH after 12 months of iv. epoprostenolol [59].

Subcutaneous treprostinil has been shown in an open-label uncontrolled study of 25 patients to improve exercise capacity, pulmonary hemodynamics and survival outcome at 19 months follow-up in patients were severe inoperable CTEPH [60].

There is early indication that a new drug, riociguat [76], that has recently completed a Phase III study in patients with CTEPH successfully meeting the primary outcome measure (based on the 6-min walk performance). This was a placebo-controlled study in patients who had CTEPH that was not treatable by surgical methods (CHEST-1 trial) [77]. Riociguat is a soluble guanylate cyclase stimulator that acts via cyclic GMP to affect the pulmonary vasculature.

There is currently no evidence from randomized clinical trials to support medical treatment of CTEPH as an alternative to PEA. As a result, medical management of CTEPH is reserved for those deemed not suitable for surgical intervention or for those with residual PH postsurgery. Although there is no clear evidence for the use of medical therapy as a bridge to PEA, it is frequently initiated prior to surgery for those with CTEPH [78]. One study of 12 patients [61], with severe PH awaiting PEA, treated with iv. prostacyclin for 46 days showed improvement in PVR by 28%. However, there has been some concern that this strategy may delay surgical referral and does not improve outcome [79].

Surgical management

The most effective therapy for CTEPH is PEA surgery, which is the only potentially curative treatment available. It provides excellent symptomatic and prognostic benefit to patients with CTEPH [2,80]. A recent systematic review of outcomes after PEA was favorable with 30-day mortality as low as 1.3% in high-volume centers [81].

Assessment of operability

Assessment for PEA surgery should always be performed when there is evidence of thromboembolic disease [28]. The decision to proceed to surgery is made by multidisciplinary teams in expert centers. There are several aspects determining the operability of patients confirmed to have CTEPH, but this has not been formally defined and relates, to some extent, to the experience of the individual center.

The pattern of thromboembolic disease must be assessed, regarding both clot burden and its accessibility. Thromboembolic disease has been classified into four types [82]:

- Type 1: thrombus in the main/lobar pulmonary arteries;
- Type 2: intimal thickening and fibrosis, with or without organized thrombus proximal to segmental arteries;

- Type 3: fibrosis, intimal webbing and thickening with or without organized thrombus within distal segmental arteries only;
- Type 4: microscopic distal arteriolar vasculopathy without visible thromboembolic disease.

However, it is important to understand that this is an intraoperative classification, and cannot be applied to case selection. Typically, proximal disease is potentially curable with surgery, while distal disease (type 4 disease) is not amenable to surgery, and is often associated with small vessel arteriopathy and poor surgical outcome [7,83]. Type 3 disease is the most challenging technically, and surgical experience has a major impact on the completeness of clearance in these patients, therefore, decisions on operability may vary from center to center. The experience of the PEA team also determines which lesions are considered surgically treatable; for example, accessibility is dependent on the skills and experience of the surgeon, in addition to the angiographic appearance [36]. Surgical assessment can therefore be challenging due to the limitations of current imaging techniques [35]. The degree of thromboembolic disease demonstrated on imaging doesn't always correlate with the extent of disease found during surgery.

In conjunction with the extent of thromboembolic disease, the other key consideration is the severity of the PH. A PVR of 1000 dynes/s/cm^{-5} distinguishes those at higher and lower surgical risk [42,84]. Dartevelle showed increasing operative risk proportional to PVR [3], but it is important to realize that even patients with high PVR (>1500 dynes/s/cm^{-5}), benefit from PEA and the prognosis in these patients without surgery is poor. In a recent cohort of patients in-hospital mortality was only 1.6% when PVR was <1000 dynes/s/cm^{-5} and 4.1% when it was over [85]. Some patients with very high PVR may get less benefit from surgery and be at higher risk of death and residual PH if the distribution of disease is limited to subsegmental pulmonary artery branches [24].

The patient's comorbidities need to be considered. Advancing age, renal failure, hepatic failure and left ventricular dysfunction all affect surgical outcomes, but are not absolute contraindications. Severe parenchymal lung disease is a contraindication to surgery as the underlying disease progression or symptoms will not be improved, better perfusion to areas of severely impaired ventilation will have no benefit [35,86]. Alternative conditions that can mimic CTEPH should be considered (e.g., pulmonary vasculitis, pulmonary sarcoma, *in situ* thrombosis [most commonly seen in patients with congenital heart defects] and extrinsic compression of the pulmonary vasculature [such as sarcoidosis]), as any long-term benefit of surgery may not justify operating.

Based on these considerations, the prospective CTEPH registry demonstrated that as many as 40% of patients diagnosed with CTEPH may not undergo PEA, for multiple reasons [3]. It is hoped that improved education and experience may allow a greater proportion of patients diagnosed with CTEPH to enjoy the potential symptomatic and prognostic benefit of PEA.

PEA

The procedure involves surgical removal of organized thrombus and related fibrous tissue from the pulmonary arterial tree under periods of deep hypothermic circulatory arrest (DHCA) to immediately reduce the PVR **(Figure 2)** [87].

The standard technique utilized in most centers was developed at the University of California at San Diego (USA) [87]. The patient is put onto cardiopulmonary bypass (CPB), to maintain circulation whilst the heart is arrested, through a midline sternotomy, similar to conventional cardiac surgery. The midline sternotomy provides optimal access to both lungs. Arteriotomies are made in the pulmonary arteries within the pericardium to allow for a true endarterectomy to the segmental vessels **(Figure 2)** [13,30,88]. In order to achieve a bloodless field (bronchial circulation continues on CPB), the circulation must be arrested for the duration of the endarterectomy. This is achieved by arresting the circulation, requiring the patient to be cooled to 20°C to protect vital organs from periods of ischemia. Cerebral ischemia limits the duration of DHCA, and 20-min periods of DHCA are alternated with 10-min periods of reperfusion [89]. A multidisciplinary approach to managing periods of DHCA and the cooling and warming phases is essential, with anesthetists and perfusionists being essential parts of the team.

Antegrade cerebral perfusion has recently been proposed as an alternative to DHCA to further minimize the risk of cerebral ischemia [90]. Interestingly, a randomized controlled trial looking at this (PEACOG) suggested that there was no evidence of a superior outcome for antegrade cerebral perfusion. Additionally, 9% of patients required conversion to conventional DHCA to

complete the dissection [90]. Reassuringly, this study was unable to demonstrate any cognitive impairment in patients undergoing PEA, despite prolonged CPB and periods of DHCA [91].

The result after PEA is an immediate reduction in PVR with reduced pulmonary arterial pressure and increased cardiac output.

Postoperative complications

The results of a recent prospective international CTEPH registry, summarizing outcomes for 679 consecutive patients diagnosed over a 2-year period, of which 384 underwent PEA, identified that 49.2% experienced a postoperative complication [3,29]. As well as the expected complications following cardiothoracic surgery, there are specific concerns to be mindful of following PEA. Two important specific postoperative complications are reperfusion pulmonary edema (RPE) and residual PH, which are both associated with increased mortality. RPE occurs in 10–40% of patients, and develops in regions that have been endarterectomized and reperfused [92,93]. Extracorporeal membrane oxygenation can be life saving in severe cases of reperfusion injury [94,95]. Residual PH remains a significant problem in 5–35% [87,95–97] of patients undergoing PEA and is the most common cause of perioperative mortality [3,96]. Reversible postoperative pulmonary vasoconstriction can occur as a result of reduced levels of nitric oxide and prostacyclin and increased levels of endothelin. This condition is often associated with RPE and usually resolves within 72 h [98,99].

Residual PH following PEA surgery is a result of poor surgical clearance or significant small vessel vasculopathy combined with subsegmental occlusions [100]. Some reduction in PVR may be achieved in some patients with inhaled nitric oxide or inhaled illoprost without an associated reduction in systemic blood pressure, and both may be beneficial in cases of residual PH in the perioperative setting [99,101].

Outcomes after surgery

There is early postoperative hemodynamic improvement with an immediate fall in mean PA pressure by approximately 50%, and reduction in PVR to approximately a third of the preoperative level in the majority of patients following weaning from CPB. The recent International CTEPH registry demonstrated a significant reduction in PVR from a median of 698 dyn/s/cm^{-5} before surgery to 235 dyn/s/cm^{-5} within 1 year after surgery for the 384 patients undergoing PEA [3,29]. This improvement in hemodynamics translates into significant symptomatic and prognostic benefits. Changes in perioperative pressures have been remarkably consistent in the reports from the most experienced centers, and despite improved understanding of CTEPH, residual PH with a PVR of >500 dynes/s/cm^{-5} remains an important indicator of increased postoperative mortality [85].

Figure 2. An example of a specimen removed from the pulmonary arteries during pulmonary endarterectomy.

In the last few years, the risk of PEA surgery has continued to decrease with in-hospital mortality approaching that of conventional cardiac surgery in the most experienced centers. The international registry presented an in-hospital mortality rate of 4.7% [3,29]. In more recent update from the University of California at San Diego, mortality was reduced to 2.2% for the current cohort undergoing isolated first time PEA and was only 1.7% in the selected patients entering the PEACOG trial [85].

Fewer studies have examined the functional benefits for patients following discharge from hospital and the longer term outcome. The international registry confirmed that significant functional improvements were achieved in patients undergoing PEA, such as increasing the median 6-min walk distance from 362 to 459 m, and reducing NYHA class with most patients progressing from class III/IV to I/II [3]. In a review of 230 patients surviving to 3-month follow-up in the UK, there was a significant increase in 6-min walk distance compared with preoperation (276.3 ± 17 to 375.8 ± 14 m; $p < 0.001$). Before

surgery there were no patients in NHYA class 1, 12.4% were in NYHA class II, 62.7% were in NYHA class III and 24.9% were in NYHA class IV. At 3 months following endarterectomy, 30.9% were in NYHA class I, 55.9% were in NYHA class II, 12.3% were in NYHA class III and only 0.5% were in NYHA class IV ($p < 0.001$ vs pre-operative). Conditional survival from 3-month follow-up was 94% at 3 years, 92.5% at 5 years and 88.3% at 10 years [2]. In a smaller series from Italy, similar long term benefits have also been demonstrated [102].

It has also been shown that age is not a barrier to PEA surgery with patients over 70 years enjoying similar benefits to younger patients with minimal increased risks [103].

Transplant

Lung or heart–lung transplantation is a treatment option for patients with CTEPH. This is reserved for patients who are unsuitable for PEA surgery or have been left with residual PH after PEA surgery and are deteriorating despite treatment with medical therapies.

■ Balloon angioplasty

There have been a few reports of attempted mechanical treatment of CTEPH without PEA surgery. Although percutaneus transluminal pulmonary angioplasty (PTPA) was reported to improve pulmonary hemodynamics, symptoms and 6-min walking distance [104], the procedure is limited by complications (e.g., pulmonary hemorrhage and pulmonary edema) and remains experimental in highly selected patients at present [31,104]. Safer PTPA procedures have been recently developed with smaller size balloons for fewer lobes per procedure, which may facilitate PTPA with fewer complication [105]. However, the patients reported in the most recent series may have also benefited from conventional PEA and the utility of PTPA relative to PEA remains to be confirmed.

Conclusion & future perspective

With increasing knowledge about CTEPH we will start to have more information about the true epidemiology of the disease.

Currently, the 'gold standard' treatment (i.e., PEA) is performed in only a few specialist centers globally. With increasing experience in the pre-, intra- and post-operative management of these patients we hope to continue to improve in the optimization of patients for surgery and in the technical aspects of the surgery itself.

At present, medical management of patients with CTEPH is either supportive (warfarin/low-molecular-weight heparins, diuretics and oxygen) or off-licence. The next few years may change this picture with the development of drugs with a specific licence for treatment of CTEPH and a move to newer anticoagulants that do not need needles/blood tests.

The increased global awareness of PE and subsequently the advent of surgical and developing medical treatments for CTEPH there has been a push to identify and treat these patients. Nevertheless, these patients are difficult to detect without awareness among clinicians because of the nonspecific nature of the symptoms of CTEPH. Patient follow-up after acute PE will have to become more structured to identify this is a progressive disease as earlier identification can only be to the benefit of the patient.

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■ **Describes the pathophysiology of CTEPH and the recent development in the diagnostic tools available for patients with suspected CTEPH, particularly optical coherence tomography in distal type disease.**