



## Chronic thromboembolic pulmonary hypertension

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### Summary

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) characterized by the persistence of thromboembolic obstructing the pulmonary arteries as an organized tissue and the presence of a variable small vessel arteriopathy. The consequence is an increase in pulmonary vascular resistance resulting in progressive right heart failure. CTEPH is classified as group IV pulmonary hypertension according to the WHO classification of pulmonary hypertension. CTEPH is defined as precapillary pulmonary hypertension (mean pulmonary artery pressure  $\geq 25$  mmHg with a pulmonary capillary wedge pressure  $\leq 15$  mmHg) associated with mismatched perfusion defects on ventilation-perfusion lung scan and signs of chronic thromboembolic disease on computed tomography pulmonary angiogram and/or conventional pulmonary angiography, in a patient who received at least 3 months of therapeutic anticoagulation. CTEPH as a direct consequence of symptomatic pulmonary embolism (PE) is rare, and a significant number of CTEPH cases develop in the absence of history of PE. Thus, CTEPH should be considered in any patient with unexplained PH. Splenectomy, chronic inflammatory conditions such as inflammatory bowel disease, indwelling catheters and cardiac pacemakers have been identified as associated conditions increasing the risk of CTEPH. Ventilation-perfusion scan (V/Q) is the best test available for establishing the thromboembolic nature of PH. When CTEPH is suspected, patients should be referred to expert centres where pulmonary angiography, right heart catheterization and high-resolution CT scan will be performed to confirm the diagnosis and to assess the operability. Pulmonary endarterectomy (PEA) remains the gold standard treatment for CTEPH when organized thrombi involve the main, lobar or segmental arteries. This operation should only be performed by experienced surgeons in specialized centres. For inoperable patients, current ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension recommend the use of riociguat and say that off-label use of drugs approved for PAH and pulmonary angioplasty may be considered in expert centres.

## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) characterized by occlusion of the pulmonary arteries by organized fibrotic thrombi and by a variable small vessel arteriopathy and leading to increased pulmonary vascular resistance. This leads to dyspnoea, and eventually right heart failure and even death. CTEPH is classified as group IV according to the WHO classification of pulmonary hypertension [1].

This disease can be mistaken for acute pulmonary embolism (PE). It is important to differentiate between these, in order to diagnose CTEPH as early as possible. Once a diagnosis of CTEPH is made, careful patient selection in expert centres is required to obtain the best outcomes for these patients.

CTEPH is the only form of pulmonary hypertension, which is potentially curable thanks to pulmonary endarterectomy (PEA). However, this is a complicated operation that many patients are not fit enough to undergo and is only of value in patients with proximal forms of the disease. Recent advances in the treatment of CTEPH mean that there are now three therapeutic options available, with differing levels of success, which are each suited to different forms of the disease. These include PEA, balloon pulmonary angioplasty (BPA) and medical therapies.

This article reviews the data regarding the clinical features, diagnosis and treatment of CTEPH.

## Definition

CTEPH is defined as precapillary pulmonary hypertension (mean pulmonary artery pressure  $\geq 25$  mmHg with a pulmonary capillary wedge pressure  $\leq 15$  mmHg) associated with mismatched perfusion defects on ventilation-perfusion lung scan and signs of chronic thromboembolic disease on computed tomography pulmonary angiogram, magnetic resonance angiogram or conventional pulmonary angiography, in a patient who received at least 3 months of therapeutic anticoagulation [1].

## Epidemiology

CTEPH is a rare disease, which is probably still under-diagnosed. The exact prevalence and incidence of CTEPH are unknown but some data suggest that the annual incidence is of 3–30 per million in the general population [2]. Moreover, the incidence of

CTEPH in patients who have had a symptomatic PE is reported to be in the range of 0.5–9% [3–5]. Median age at diagnosis is 63 years and both genders are equally affected [5].

## Pathophysiology

In CTEPH, both the proximal and distal pulmonary arteries can be affected whereas in group I pulmonary arterial hypertension (PAH), only the small pulmonary vessels are affected. CTEPH is characterized by the presence of organized fibrotic thrombi in the pulmonary arteries, causing occlusion, the presence of bands and webs, and there may be partial recanalisation [6]. Fibrous and atherosclerotic plaques cause vessel wall thickening [7].

In addition to the chronic fibrotic vascular occlusive lesions, some patients develop an arteriopathy with remodelling of both distal obstructed and nonobstructed vessels. This may be due to shear stress in the well-perfused vessels and the inflammatory milieu, and may contribute to persistent pulmonary hypertension after removal of chronic thrombotic material. This arteriopathy is similar to that found in group I PAH with intimal fibrosis, medial hypertrophy and plexiform lesions [2]. Like in PAH, neurohumoral factors such as endothelin-1 act as potent vasoconstrictors and mediators of microvascular changes [8].

Animal models of CTEPH have been difficult to produce and this has impeded progress with regards to understanding the pathogenesis of the disease. However, it appears that CTEPH patients have either incomplete resorption of clots or they have recurrent disease, leading to incomplete thrombus resolution, formation of fibrosis and remodeling of pulmonary blood vessels [9]. It is not clear if this is due to genetic defects, defective fibrinolysis, prothrombotic factors and/or deficient angiogenesis. The thickened pulmonary artery walls seen in CTEPH consist of fibrous and atherosclerotic plaques, which could be due to aberrant proliferation of adventitial fibroblasts, circulating progenitor cells and myofibroblasts [7]. A study of 22 CTEPH patients found that 15% of patients had genetic mutations for dysfibrinogenaemia [10]. But data on these mutations in the general population is lacking [11]. There is also evidence of a downregulation of angiogenic gene expression and dysfunctional endothelial cells, which may also impair thrombus resolution [6].

The usual thrombophilic mutations such as factor V Leiden and protein C and S deficiency are not associated with CTEPH. There is however an increased incidence of elevated factor VIII levels in CTEPH [2].

Systemic inflammation seems to play a part in the development of CTEPH [12]. It is associated with certain chronic inflammatory diseases and C-reactive protein, tumour necrosis factor- $\alpha$ , interleukin-1b, interleukin-2, interleukin-4, interleukin-8, interleukin-10, matrix metalloproteinase-9, macrophage inflammatory protein-1 $\alpha$ , and monocyte chemoattractant protein-1 have been found to be elevated in the plasma and thrombus tissues of

## Glossary

<b>CTEPH</b>	chronic thromboembolic pulmonary hypertension
<b>PH</b>	pulmonary hypertension
<b>PE</b>	pulmonary embolism
<b>PEA</b>	pulmonary endarterectomy
<b>BPA</b>	balloon pulmonary angioplasty
<b>PAH</b>	pulmonary arterial hypertension
<b>CTPA</b>	computed tomography pulmonary angiogram

patients with CTEPH [2]. In addition, inflammatory cell infiltrates have been found on proximal pulmonary arteries of CTEPH patients [2]. Quarck et al. also hypothesized that deficient angiogenesis is involved in the pathogenesis of CTEPH. Indeed, they observed recanalised lesions with the presence of neovessels and vascular neoangiogenesis in pulmonary vascular lesions of 52 patients who underwent PEA and showed that patients with adverse outcomes displayed fewer neovessels and that low angiogenesis scores could predict adverse outcomes [12].

## Risk factors and associated conditions

Risk factors for the disease include PE related risk factors, medical conditions, abnormalities of coagulation or fibrinolysis and genetic risk factors. PE related risk factors include the size of the initial PE, idiopathic PE, and recurrent PE. Medical conditions which increase the risk of CTEPH include antiphospholipid syndrome (up to 20% of CTEPH patients) [13], splenectomy, chronic inflammatory conditions such as inflammatory bowel disease, osteomyelitis, malignancy, myeloproliferative disorders, thyroid replacement therapy, indwelling catheters and cardiac pacemakers [2,5]. Patients with malignancy, inflammatory bowel disease, splenectomy and indwelling catheters are more at risk of distal forms of the disease [14]. In experimental models, staphylococcal infection has been shown to delay thrombus resolution, which may explain the increased risk of CTEPH with indwelling catheters and pacemakers [15]. In splenectomy patients, abnormal circulating erythrocytes and thrombocytosis, which would normally have been filtered by the spleen may lead to a hypercoagulable state.

## Clinical presentation and diagnosis

There may be an initial honeymoon period lasting months to years, where the patient is asymptomatic, which usually lasts until more than 40% of the vascular bed has become obstructed [16]. Patients usually present with progressive dyspnoea, which may be associated with lethargy, chest pain, light-headedness, syncope, ankle swelling and haemoptysis. Haemoptysis occurs more frequently in CTEPH (4.8%) than PAH (0.6%) due to bronchial artery dilatation [17]. A diagnosis of CTEPH should be considered in patients with persistent or gradually progressive dyspnoea following an acute PE, although CTEPH is rarely diagnosed during regular follow-up after PE. Around 25% of patients with CTEPH have no history of thromboembolic disease [18]. Thus, CTEPH should be considered in any patient with unexplained PH. Physical signs suggestive of the disease include a pulmonary artery bruit best heard over the midback, which may represent a proximal narrowing of the pulmonary artery. Hypoxemia may be present due to ventilation-perfusion mismatching.

A diagnosis of CTEPH is established in a patient who has been anticoagulated for at least 3 months who has a mean pulmonary

artery pressure  $\geq 25$  mmHg, pulmonary capillary wedge pressure  $\leq 15$  mmHg and evidence of chronic thromboembolic disease with multiple chronic and organized occlusive thrombi. When diagnosing an acute PE, physicians should be aware of the features in favor of CTEPH. These include a mean pulmonary artery pressure  $> 40$  mmHg, right ventricular hypertrophy, a dilated pulmonary artery, dilated bronchial arteries due to development of collateral circulation, pulmonary artery wall thickening, abrupt narrowing of a pulmonary artery, pulmonary artery pouches or webs and mosaic attenuation due to heterogeneous perfusion [19]. In 10% of patients being assessed for PEA there may even be coronary-pulmonary artery collaterals [20]. Selected patients with severe acute PE or elevated right ventricular pressures should be followed for 2 years and serial transthoracic echocardiography used to screen for the development of CTEPH [15]. However, routine testing for CTEPH is not recommended for all acute PE patients [21].

On chest X-ray there may be cardiomegaly, prominent pulmonary arteries and pleural abnormalities or regions of avascularity. These pleural abnormalities represent small pulmonary infarcts. In about 20% of patients there will be a restrictive ventilatory defect also due to small pulmonary infarcts [22]. There may also be a reduced diffusion capacity for carbon monoxide due to a reduction in pulmonary membrane diffusion capacity.

Transthoracic cardiac echo is the screening tool of choice for diagnosing pulmonary hypertension. A tricuspid velocity of  $> 2.8$  m/s or an estimated pulmonary artery systolic pressure  $> 36$  mmHg are indicative of pulmonary hypertension [23]. Other echo findings, suggestive of pulmonary arterial hypertension, include dilated right heart chambers, tricuspid regurgitation, flattening or paradoxical motion of the interventricular septum with normal left ventricular function.

Ventilation-perfusion scan (V/Q) is the best test available for establishing the thromboembolic nature of PH as it has a sensitivity of 95% vs. 51% with computed tomography pulmonary angiogram (CTPA) for detecting CTEPH [24]. V/Q scan usually shows one or several segmental or larger mismatched perfusion defects. This test should be performed in all patients with PH in order to rule out this potentially curable disease. CTPA alone does not have a high enough sensitivity to exclude the diagnosis of CTEPH.

Right heart catheterization is then performed to precisely assess the severity of the haemodynamics and to confirm that it is precapillary pulmonary hypertension. CTPA is performed to assess for proximal disease (lesions involving segmental, lobar, or main pulmonary arteries) and may show organized thrombi, complete obstruction of pulmonary arteries, webs and bands. However, lesions confined to the distal segmental or subsegmental pulmonary arteries may be missed by CTPA. CTPA may also reveal associated findings suggestive of CTEPH including mosaic perfusion pattern and bronchial artery collaterals (figure 1). Lastly, it may serve to screen for other conditions mimicking CTEPH such as

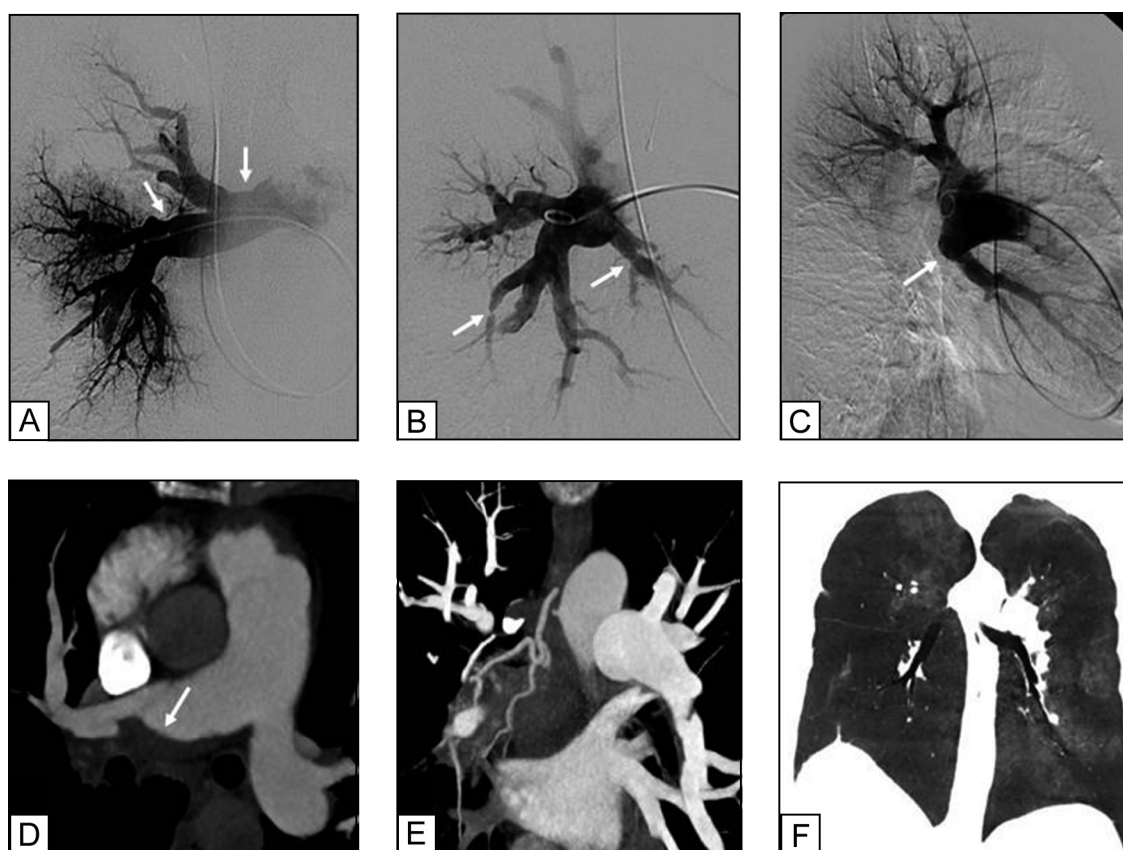


FIGURE 1

### Imaging of chronic thromboembolic pulmonary hypertension

Panels A–C. Digital subtraction pulmonary angiograms.

A. Right anterior view showing intimal irregularities of the main pulmonary artery (arrows). B. Right lateral projection showing multiple vascular webs (arrows). C. Right lateral view demonstrating complete obstruction of the right lower lobe (arrow).

Panels D–F. Computed tomography pulmonary angiograms.

D. Cross-sectional view showing eccentric thromboembolic material (arrow). E. Coronal view showing enlarged bronchial arteries. F. Minimum Intensity Projection (minMIP) coronal thoracic view showing mosaic perfusion.

pulmonary artery sarcoma, vasculitis and fibrosing mediastinitis. Pulmonary angiography remains the gold standard investigation for confirming the diagnosis of CTEPH and evaluating the location and extent of chronic thromboembolic disease. This study reveals direct signs of CTEPH including webs, bands, intimal irregularities, stenoses, obstruction of vessels and pouch defects (*figure 1*). Magnetic resonance angiography also has high sensitivity for diagnosing CTEPH [25]. This has the advantage of not causing exposure to irradiation, but is a costly investigation, which is not widely available. Newer techniques, which are under investigation, include optical coherence tomography and intravascular ultrasound. These allow improved views of small vessels and the interior arterial walls. These may be useful in helping to differentiate between distal CTEPH and PAH and during balloon angioplasty to determine the size of target lesions [26].

Finally for patients who are considered operable and at risk of ischaemic heart disease, coronary angiography is performed. Coronary artery bypass grafting can be performed during PEA with no increased operative risk [27].

### Treatment

All patients should be treated with life-long anticoagulant therapy with a target international normalized ratio of 2:3. There is insufficient evidence at present to recommend the use of new oral anticoagulants in CTEPH [28]. The use of inferior vena cava filters is controversial. There is no prospective data to confirm the benefits of their use in CTEPH. Indeed, the presence or absence of vena cava filters had no effect on 1-year survival post-PEA in the International CTEPH Association registry [29]. In addition, these filters are associated with complications such as

misplacement of the filter, haematoma/bleeding, inferior vena caval thrombosis and inferior vena caval penetration. Therefore, the routine vena cava filter placement is not recommended.

### Surgical treatment

PEA remains the gold standard treatment for CTEPH when organized thrombi involve the main, lobar or segmental arteries. This operation should only be performed by experienced surgeons in specialized centres. It requires a median sternotomy, cardiopulmonary bypass and periods of deep hypothermic circulatory arrest. The circulatory arrest allows a clear field of vision when dissecting the pulmonary artery. During PEA, the obstructing material is removed from the pulmonary arteries as far as the segmental branches. The challenge is to find the correct endarterectomy plane without causing vascular injury during the brief periods of circulatory arrest (usually about 20 min) [30]. Therefore, careful selection of the patients who undergo this procedure by expert centres is required, along with meticulous surgical technique and postoperative management. Patients who are likely to benefit from the procedure will have proximal chronic thromboembolic material up to the level of the segmental arteries with a proportional pulmonary vascular resistance (indicating the PVR is not due to small vessel disease) and absence of severe co-morbidities [31]. Some patients will have severe dyspnoea with only mild pulmonary hypertension or pulmonary hypertension only with exercise but can derive great benefit from PEA [32]. This is due to increased dead space ventilation and limitation of the cardiac output. On the other hand, patients with chronic thromboembolic disease and severe parenchymal disease may not be good candidates as it may lead to the perfusion of poorly ventilated areas. For the above reasons, about 40% of patients will not be candidates for PEA [33]. PEA is associated with improved survival, pulmonary haemodynamics and exercise capacity [18]. A mean reduction in pulmonary vascular resistance of 65% can be achieved with PEA [29,34]. With the improved haemodynamics post-PEA, the heart is able to remodel itself to reduce the dilatation and tricuspid regurgitation and regain a more normal systolic and diastolic function [35]. In-hospital mortality has been reported at 4.7% and 1-year postoperative mortality at 7% in the international prospective CTEPH registry [29]. This may be due to cardiac arrest, multi-organ failure, massive haemorrhage, sepsis, right ventricular failure or acute lung injury. Risk factors for poor outcomes with PEA include high pulmonary vascular resistance before and immediately after surgery, poor preoperative exercise capacity, and advanced age [29,36]. However, advanced age alone is not a contraindication to surgery. There is no recommended cut-off for pulmonary vascular resistance above which surgery is not performed as it depends on many other factors. However, there is data showing an increased perioperative mortality and less than optimal postoperative haemodynamics in patients with preoperative pulmonary vascular

resistance beyond 1000 dyne s/cm<sup>5</sup> [37]. In the international CTEPH registry, 16.7% of the patients had persistent pulmonary hypertension after the procedure [29]. Thus, patients should undergo PEA as soon as possible after the diagnosis, in order to reduce the risk of developing an arteriopathy and having persistent pulmonary hypertension postoperative. Postoperative residual pulmonary hypertension can be due to incomplete endarterectomy, inaccessible chronic thromboembolic material or small vessel arteriopathy. The presence of persistent pulmonary hypertension is itself an important predictor of late postoperative adverse events [38]. Other complications of the procedure include pulmonary artery reperfusion injury, pulmonary artery steal syndrome, neurological complications, atelectasis, pleural or pericardial effusions and dysrhythmias. Reperfusion oedema occurs in 10–40% of patients, for which the treatment is supportive with diuretics, oxygen, mechanical ventilation and if necessary nitric oxide and extracorporeal membrane oxygenation [39]. Pulmonary artery steal syndrome occurs when newly reopened vessels lead to redistribution of blood flow from previously well-perfused segments to newly opened ones, leading to ventilation-perfusion mismatching and hypoxia.

### Targeted medical treatment

Small vessel disease in CTEPH has provided the rationale for the use of PAH-targeted medical therapy in non-operable patients with CTEPH or patients with persistent PH after PEA. Some case series or uncontrolled studies have provided evidence for improvement in exercise capacity and haemodynamics with the use of bosentan, epoprostenol, sildenafil, treprostinil [40–43]. The positive experience gained from these studies led to the first randomized, placebo-controlled trial in patients with inoperable CTEPH. The BENEFIT study investigated Bosentan Effects in iNoperable Forms of CTEPH [44]. This study compared the use of bosentan to placebo in 157 patients with either inoperable CTEPH or persistent/recurrent PH after PEA over 16 weeks. Coprimary endpoints included change in PVR and change in 6-minute walk distance. There was a significant decrease in PVR (by 24%,  $P < 0.001$ ) for bosentan treated patients, but no significant improvement in 6-minute walk distance.

The use of sildenafil was also evaluated in one randomized placebo-controlled study including 19 patients with inoperable or persistent PH after PEA [45]. The primary end point was change in 6-min walk distance. After 12 weeks of treatment with sildenafil, improvement in haemodynamics was found but no improvement in exercise capacity was observed.

More recently, in the CHEST study, a 16-week double-blind multicenter randomized placebo-controlled phase III study of 261 patients with inoperable CTEPH or persistent CTEPH postoperative, patients were randomized to receive a placebo or up to 2.5 mg three times a day of riociguat, an oral soluble guanylate



cyclase stimulator [46]. There was a significant improvement in six-minute walk test (the primary endpoint) of 39 m in the riociguat group ( $P < 0.001$ ). The patients on riociguat also had significantly reduced pulmonary vascular resistance ( $-246 \text{ dyn}\cdot\text{cm}\cdot\text{s}^{-5}$ ,  $P < 0.001$ ). This effect was maintained in the 1-year open-label extension study [47]. Currently, riociguat is the only approved drug in the USA and Europe for the treatment of inoperable CTEPH or persistent PH after PEA (class I recommendation) based on the phase III CHEST study results [21]. Adverse effects of the drug include hypotension, haemoptysis, headache and dyspepsia. The drug is contraindicated in pregnancy due to fetal harm and in severe renal insufficiency [48].

Current ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension also say that off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable disease by a CTEPH team including at least one experienced PEA surgeon (class IIb recommendation).

Lastly, there is no strong evidence supporting the use of targeted therapy before PEA in patients with severe haemodynamic impairment [21].

### Balloon pulmonary angioplasty

Balloon pulmonary angioplasty (BPA) is another emerging intervention for treating segmental and subsegmental CTEPH, which is gaining popularity. This procedure uses the standard balloon angioplasty technique to dilate selected pulmonary arteries. The main aim is to reopen vessels occluded by webs and bands (figure 2). Initial results were disappointing with 11 out of 18 patients developing reperfusion pulmonary oedema and 3 requiring mechanical ventilation [49]. There were concerns over complications such as vessel rupture and reperfusion lung injury as well as the lack of long-term data on outcomes following this intervention [50]. Since then, in Japan the technique has been refined by limiting the dilatations to only 1 or

2 vascular segments at a time, by using smaller balloons and improving the pressure and inflation time [51,52]. More recent results are encouraging with improved symptoms and haemodynamics, with an incidence of only 2% of reperfusion pulmonary oedema and 10% of pulmonary artery injuries [53–56]. On average 4.8 angioplasty sessions are required for each patient [21]. Periprocedural mortality has ranged from none to 10% but was 1.5% in the largest series. Pulmonary angioplasty now features in the most recent ESC/ERS guidelines for the diagnosis and treatment pulmonary hypertension, as a class IIb recommendation in patients who are inoperable or carry an unfavourable risk:benefit ratio for PEA [21]. Although BPA has never been prospectively evaluated, most of the leading CTEPH centers worldwide have currently added BPA to their therapeutic options. However, no randomized controlled trial comparing safety and efficacy of medical therapy with riociguat versus pulmonary balloon angioplasty has been performed so far. Therefore, the respective places of medical treatment and of BPA in the management of inoperable patients with CTEPH need to be further evaluated.

Finally when there are no other therapeutic options and the patient has severe CTEPH, patients may need to be assessed for their suitability for double lung or heart-lung transplantation.

### Conclusion

A diagnosis of CTEPH should be considered in all patients presenting with pulmonary hypertension, as it is the only potentially curable form of pulmonary hypertension. But once diagnosed, as CTEPH is rare, it is essential for patients to be referred to expert centres to carefully select patients for operability. Early diagnosis is important to reduce the risk of developing distal arteriopathy and to reduce the surgical risk of potentially operable patients. When organized thrombi involved the main, lobar or segmental arteries, PEA is the gold standard treatment with periprocedural mortality  $< 5\%$  in experienced centers, excellent long-term results and high probability of cure

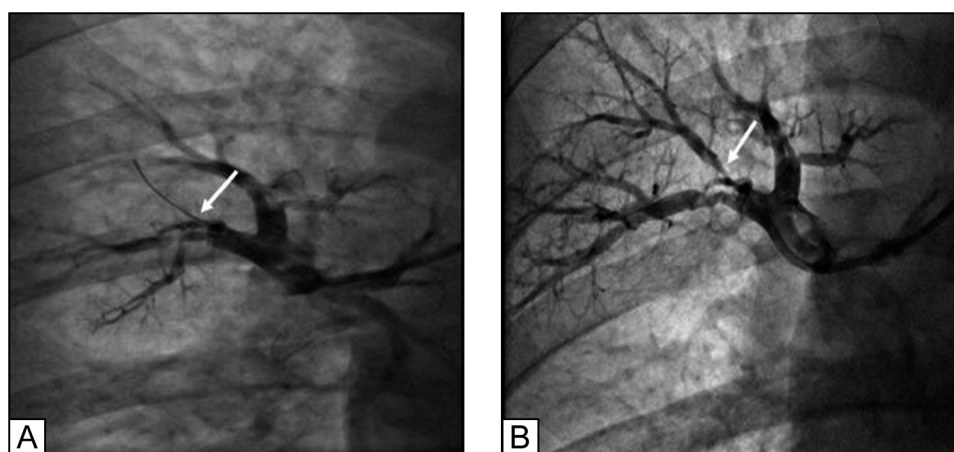


FIGURE 2

**Balloon pulmonary angioplasty in a patient with inoperable distal chronic thromboembolic pulmonary hypertension**

Representative pulmonary angiography (A) before, (B) after angioplasty for a characteristic lesion with complete obstruction.

in the majority of patients. For non-operable patients, current ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension recommend the use of riociguat and say that off-label use of drugs approved for PAH and pulmonary angioplasty may be considered in expert centres.

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