



# Chronic thromboembolic pulmonary disease

Nick H. Kim <sup>1</sup>, Andrea M. D'Armini<sup>2</sup>, Marion Delcroix <sup>3</sup>, Xavier Jaïs<sup>4</sup>, Mitja Jevnikar<sup>4</sup>, Michael M. Madani<sup>5</sup>, Hiromi Matsubara <sup>6</sup>, Massimiliano Palazzini<sup>7</sup>, Christoph B. Wiedenroth<sup>8</sup>, Gérald Simonneau<sup>9</sup> and David P. Jenkins<sup>10</sup>

<sup>1</sup>Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, La Jolla, CA, USA. <sup>2</sup>Department of Cardio-Thoracic and Vascular Surgery, Heart and Lung Transplantation and Pulmonary Hypertension Unit, Fondazione IRCCS Policlinico San Matteo, University of Pavia School of Medicine, Pavia, Italy. <sup>3</sup>Clinical Department of Respiratory Disease, Pulmonary Hypertension Center, UZ Leuven, Leuven, Belgium. <sup>4</sup>AP-HP, Department of Respiratory and Intensive Care Medicine, Bicêtre Hospital, University of Paris-Saclay, Le Kremlin-Bicêtre, France. <sup>5</sup>Division of Cardiovascular and Thoracic Surgery, University of California San Diego, La Jolla, CA, USA. <sup>6</sup>Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan. <sup>7</sup>Dipartimento DIMEC (Dipartimento di Scienze Mediche e Chirurgiche), Università di Bologna, Bologna, Italy. <sup>8</sup>Department of Thoracic Surgery, Kerckhoff Heart and Thorax Centre, Bad Nauheim, Germany. <sup>9</sup>Pneumologie Kremlin Bicetre University Hospital, National Reference Center for Pulmonary Hypertension, Paris Saclay University, Paris, France. <sup>10</sup>Cardiothoracic Surgery and Transplantation, Royal Papworth Hospital, Cambridge, UK.

Corresponding author: Gérald Simonneau ([gerald.simonneau@gmail.com](mailto:gerald.simonneau@gmail.com))



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**Treatment of chronic thromboembolic pulmonary hypertension requires a multidisciplinary team approach with tailored treatment across three therapeutic modalities: pulmonary endarterectomy, balloon pulmonary angioplasty and PH targeted medical therapy** <https://bit.ly/4cH37WC>

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## Abstract

Chronic thromboembolic pulmonary hypertension is a complication of pulmonary embolism and a treatable cause of pulmonary hypertension. The pathology is a unique combination of mechanical obstruction due to failure of clot resolution, and a variable degree of microvascular disease, that both contribute to pulmonary vascular resistance. Accordingly, multiple treatments have been developed to target the disease components. However, accurate diagnosis is often delayed. Evaluation includes high-quality imaging modalities, necessary for disease confirmation and for appropriate treatment planning. All patients with chronic thromboembolic pulmonary disease, and especially those with pulmonary hypertension, should be referred to expert centres for multidisciplinary team decision on treatment. The first decision remains assessment of operability, and the best improvement in symptoms and survival is achieved by the mechanical therapies, pulmonary endarterectomy and balloon pulmonary angioplasty. With the advances in multimodal therapies, excellent outcomes can be achieved with 3-year survival of >90%.

## Introduction

Chronic thromboembolic pulmonary disease (CTEPD) is the umbrella term describing a treatable form of chronic pulmonary vascular obstruction. CTEPD includes chronic thromboembolic pulmonary hypertension (CTEPH) and CTEPD without pulmonary hypertension (PH) [1]. CTEPH is the main diagnosis within PH classification group 4 [2]. Its incidence, which had been estimated at 5–6 cases per million inhabitants per year, is reaching 13 cases per million inhabitants per year when a systematic pulmonary embolism follow-up is organised [3]. The haemodynamic thresholds defining PH in CTEPH are adopted from the revised and now accepted thresholds based on definition of normal *versus* abnormal pulmonary haemodynamic parameters [4, 5]. Without effective treatment, patients with CTEPH can progress to right heart failure and premature death. CTEPD without PH may not necessarily progress to CTEPH [6]. However, select cases may achieve symptomatic benefit with treatments developed for CTEPH including pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA) [7, 8].

Since the last World Symposium on Pulmonary Hypertension (WSPH) in 2018, there have been ongoing advances across broad topics pertaining to CTEPD. This article highlights these advances, points out



remaining gaps and emphasises key reminders paramount in the optimal diagnosis and management of patients with CTEPH.

### Components of disease

The development of CTEPH involves several components and factors that contribute to its manifestation and progression. Anatomically, two different vascular lesions participate in the increase in pulmonary vascular resistance (PVR) in CTEPH patients: an obstruction of pulmonary arteries by unresolved organised fibrothrombotic clots and a secondary microvasculopathy observed in both obstructed and nonobstructed lung areas [9]. While after acute pulmonary embolism (PE) most thrombi resolve with treatment, in some cases, clots fail to dissolve completely. In CTEPH, incomplete thrombus resolution triggers an abnormal healing response in the pulmonary arteries. This response involves the formation of scar-like tissue and vascular remodelling, which narrows and stiffens the arteries, further obstructing pulmonary blood flow, resulting in a persistent obstruction of pulmonary arteries. Different mechanisms are potentially responsible for incomplete clot resolution: abnormalities in fibrinogen structure and function, inflammatory thrombosis and inhibition of intrathrombus angiogenesis [10]; a component of *in situ* thrombosis is potentially also contributing to CTEPH pathogenesis [11, 12]. These fibrothrombotic lesions are visualised as slits/tails, webs, stenoses or pouching on vascular imaging and are the target of mechanical treatment with PEA or BPA.

The secondary microvasculopathy, resembling changes seen in pulmonary arterial hypertension (PAH), predominates in nonobstructed lung regions and results from a redistribution of flow and increased pressure and shear stress [13]. A microvasculopathy is also observed in completely or partially obstructed lung areas and is attributed to the development and hypertrophy of systemic bronchial arteries anastomosing with pulmonary arterioles and venules [14]. The presence of microvasculopathy is suspected when mechanical obstruction does not correlate with the haemodynamic severity [15]. The microvasculopathy may explain clinical deterioration of some patients in the absence of PE recurrence, and the persistence of PH after PEA. Medical therapy with PH drugs in CTEPH aims to target the microvasculopathy.

Risk factors for CTEPH include 1) thrombotic risk factors with a predominance of antiphospholipid syndrome and increased factor VIII, as opposed to acute PE; 2) medical conditions such as splenectomy, chronic inflammatory disorders, ventriculoatrial shunts, infections and cancer; and 3) non-O blood groups [16]. When acute PE is diagnosed and thrombus load is considerable, it has been hypothesised that systemic thrombolysis could prevent the development of CTEPH. However, it did not in intermediate high-risk PE patients treated in the Pulmonary Embolism Thrombolysis (PEITHO) trial [17]. Consequently, we have currently no preventive strategy available for CTEPH. Earlier recognition and diagnosis of CTEPH at milder stages may be feasible with a systematic strategy and follow-up after acute PE [3]. In the region with proximity to the centre utilising such a screening strategy after PE, the diagnostic rate of CTEPH and referral for PEA were both notably higher [3].

Concerning the haemodynamic alterations in CTEPH, it has been shown that patients may have left ventricular (LV) dysfunction and somewhat increased LV filling pressures contributing to PH in older age [18]. With regard to CTEPH molecular and cellular mechanisms, additional evidence has been reported on 1) the inflammatory thrombosis hypothesis with involvement of neutrophil extracellular traps, elevated plasma concentration of von Willebrand factor, NF- $\kappa$ B signalling and upregulation of inflammatory signalling by macrophages and T-cells identified by single-cell RNA sequencing [12, 19–22]; 2) the angiogenesis-driven clot resolution hypothesis; 3) the genetic hypothesis [23]; and 4) a potential role of air pollution [24]. Concerning risk factors, a CTEPH prevalence of 3.8% has been observed in patients with antiphospholipid syndrome (APS) [25]. Primary APS, prior PE, recurrent venous thromboembolism (VTE), thrombocytopenia and specific antiphospholipid antibodies predict CTEPH in APS. Active assessment for CTEPH in APS patients may be considered.

Further research is ongoing to identify biomarkers of fibrotic thrombus transformation that could help to identify patients with CTEPH earlier. Integration of clinical and -omic measurements is needed to identify clinically valuable diagnostic signatures and pathways for potential future therapeutic interventions. It is still unclear whether the systemic collateral circulation, supposedly developed to preserve pulmonary parenchyma and airways from ischaemia/infarction, is a friend or foe due to competing flow in pulmonary arteries. It is not known whether bronchial collateral coiling before or after PEA is beneficial or harmful, and in which circumstances, apart from haemoptysis, it should be considered. Advanced imaging modalities may allow separate analyses of pulmonary and systemic collateral circulations, and changes if any after treatments. While systemic thrombolysis does not reduce CTEPH incidence after acute submassive PE [17], it is not known whether mechanical intervention by aspiration or by combined local

thrombolysis and ultrasonic clot disruption will do. Catheter-based therapy studies need long-term evaluation for CTEPH incidence and careful adjudication of acute PE *versus* acute clot on top of existing CTEPH at time of initial intervention.

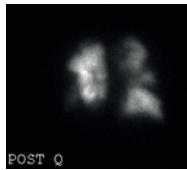


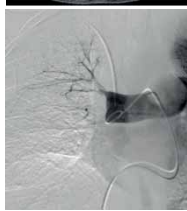

### **Diagnostic directions and considerations**

Despite improvements in imaging techniques (figure 1), a ventilation/perfusion (V/Q) lung scan should be performed as the first examination when suspecting CTEPD [26, 27]. In some regions, and also due to post-pandemic practice, the ventilation portion may not be available. In such a scenario, the perfusion scan alone would still be of value when evaluating patients with PH. In the 6th WSPH, the V/Q scan was confirmed as a first step in the diagnosis of CTEPH, and since then, this role has been incorporated into the ERS statement [1]. The guidelines for the diagnosis and management of acute PE support V/Q lung scan as the first-line test for diagnosing CTEPH following PE in the presence of dyspnoea or functional limitation and high probability of PH by echocardiography [28]. However, additional diagnostic imaging is required, as unmatched perfusion defects may also be seen in other pulmonary vascular disease such as acute PE, pulmonary veno-occlusive disease, pulmonary artery tumours, pulmonary vasculitis, peripheral pulmonary artery stenosis and pulmonary vein stenosis [29, 30]. Single photon emission computed tomography (SPECT) V/Q has been shown to be superior to planar V/Q scan in the detection of both acute PE and CTEPD, because of its ability to generate three-dimensional imaging data (resolving the problem of overlapping structures).

Although computed tomography pulmonary angiography (CTPA) may not be the initial test for the evaluation of CTEPH, it is important in the next step of the diagnostic algorithm and for treatment decision-making. In everyday clinical practice, CTPA is easily available. Mural thrombus, complete arterial occlusions, intravascular webs or bands, and artery narrowing or retraction are all signs of CTEPD and can be visualised accurately on CTPA [31]. In addition to CTEPD, obstructive defects involving the proximal pulmonary arteries can be seen with pulmonary artery sarcoma, and less commonly other tumours, pulmonary vasculitis, congenital pulmonary artery stenoses and hydatidosis [5]. Very peripheral disease is difficult to recognise on CTPA due to the small calibre of the vessels, but visualisation is very important for optimal treatment planning, and perfusion defects can be detected even in the absence of a visible arterial abnormality [32]. In this respect, advanced computed tomography (CT) technologies, such as dual-energy CT (DECT), can provide excellent morphological images of the pulmonary arteries with perfusion images of the lungs based on iodine maps which have been considered surrogate markers of lung perfusion [33]. When an analysis of iodine maps is combined with standard CT images of pulmonary arterial morphology, DECT has a sensitivity and specificity of 100% for a diagnosis of CTEPH [33]. Despite what guidelines recommend and the improvement in technology, the infrequent use of V/Q lung scanning in daily practice and the lack of expertise required to evaluate CTPA are still responsible for the underdiagnosis of CTEPH. Indeed, it is still frequent that patients initially referred as idiopathic PAH may have their diagnosis changed to CTEPH after obtaining a perfusion scan or re-evaluation of a CTPA by an expert radiologist.

Although there is increasing interest in noninvasive haemodynamic evaluation, given the complexity of pathophysiological changes occurring in CTEPH, right heart catheterisation (RHC) and catheter-based pulmonary angiography are still mandatory to confirm the diagnosis. Indeed, despite advanced imaging, the degree of pre-capillary microvasculopathy can only be estimated by considering the discrepancy between obstructive disease seen on imaging and haemodynamic severity. In this regard, a complete haemodynamic evaluation by RHC including cardiac output is recommended, because the calculated PVR is important to assess the prognosis and the risks associated with PEA [34]. Measurement of pulmonary arterial wedge pressure (PAWP) is necessary to exclude post-capillary PH resulting from comorbidities. Intravascular obstructions might confound the correct estimation of PAWP in some patients, and if unreliable, left ventricular end-diastolic pressure should be obtained by left ventricular catheterisation. High-quality pulmonary angiography, with or without digital subtraction, is still considered valuable especially for planning BPA [27]. In terms of angiographic technique, multiple selective injections are not required for the diagnosis of CTEPH, whereas they are essential for BPA planning and during treatment sessions. Biplane acquisition provides optimal anatomical detail; the lateral projection providing more detailed definition of lobar and segmental anatomy compared to the anteroposterior view alone.

CTPA is still the initial imaging test of choice for acute PE, but not for CTEPH. Whenever CTPA is performed in the suspicion of acute PE, signs such as increased calibre of the pulmonary artery with intravascular bands or webs, the presence of mosaic oligemia, hypertrophy of the bronchial arteries and right ventricle are suggestive of a pre-existing CTEPH [35, 36]. For the first time, guidelines for the diagnosis and management of acute PE have provided awareness of imaging characteristics of chronic

Test	Pros	Cons	Examples
<b>V/Q scan</b>	<ul style="list-style-type: none"> <li>• Screening test of choice</li> <li>• Specific to pulmonary arterial blood flow</li> <li>• Normal or abnormal</li> </ul>	<ul style="list-style-type: none"> <li>• Perception of being an outdated test or phasing out</li> <li>• Ventilation may not be available (e.g. accessibility, pandemic effect)</li> </ul>	
<b>SPECT scan</b>	<ul style="list-style-type: none"> <li>• More sensitive than planar radionuclide perfusion scan</li> <li>• May become more readily available than V/Q</li> </ul>	<ul style="list-style-type: none"> <li>• Not additive if planar scan already available</li> </ul>	
<b>CT pulmonary angiogram (with or without dual energy)</b>	<ul style="list-style-type: none"> <li>• Most widely available</li> <li>• Detailed information about pulmonary circulation but also lung parenchyma and mediastinum</li> <li>• Dual energy capable of perfusion map</li> </ul>	<ul style="list-style-type: none"> <li>• False negative results (e.g. chronic segmental/subsegmental disease)</li> <li>• Requires radiologist with CTEPD awareness and experience</li> <li>• Contrast necessary</li> </ul>	
<b>Pulmonary angiogram</b>	<ul style="list-style-type: none"> <li>• Direct injection into pulmonary arteries can offer details of the lumen including sequential views as contrast passes</li> <li>• Helpful for surgical or BPA planning</li> </ul>	<ul style="list-style-type: none"> <li>• Requires right heart catheterisation with devices allowing for rapid injection without catheter migration</li> <li>• Limited access to expertise</li> <li>• Can underestimate disease</li> </ul>	
<b>MRI</b>	<ul style="list-style-type: none"> <li>• No radiation</li> <li>• Can offer views of pulmonary circulation, perfusion map and surrounding soft tissues</li> <li>• Valuable for pulmonary arterial tumour evaluation</li> <li>• Additional cardiac morphology and functional assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Requires radiologist with CTEPD awareness and experience</li> <li>• Limited access to expertise</li> </ul>	

**FIGURE 1** Chronic thromboembolic pulmonary disease (CTEPD) imaging modalities. V/Q: ventilation/perfusion; SPECT: single photon emission computed tomography; CT: computed tomography; MRI: magnetic resonance imaging; BPA: balloon pulmonary angioplasty.

thromboembolism, and these have supported the awareness of the diagnosis of CTEPH at the time of “acute” PE [28]. When obtaining CTPA for the workup of CTEPH, proper protocol and acquisition are critical to ensure visualisation of the more subtle findings in CTEPH compared with PE.

Cone beam and area detector CT allow for more accurate visualisation of subsegmental vasculature and have been shown to be more useful for procedural guidance for BPA rather than for diagnosis of CTEPH. However, the benefits of the technology require validation in prospective trials before recommendation for routine clinical use [1]. Three-dimensional contrast-enhanced lung perfusion magnetic resonance imaging (MRI) is a more recent and advanced imaging technique that can be deployed to search for perfusion defects in the pulmonary vascular bed. MRI was compared with SPECT lung scintigraphy in a series of 74 patients with PH (30 of the patients had CTEPH and 10 had CTEPD without PH). MRI showed a trend to increased sensitivity when compared to SPECT perfusion scintigraphy in the detection of CTEPH (97% SPECT, 100% MRI) [37]. Despite being a reliable and safe diagnostic tool (no radiation exposure in comparison with CTPA), its use is still restricted to specialised centres.

#### **Multidisciplinary team definition and role**

The concept of importance of a “CTEPH team” for determining operability was first stated at the 5th WSPH and was incorporated into the CTEPH treatment algorithm. We stated the team should consist of an experienced surgeon and CTEPH physicians. This predated the acceptance of BPA as an established treatment modality [26]. Although there is no scientific evidence for the multidisciplinary team (MDT) definition, the MDT concept is used successfully in all experienced CTEPH centres internationally and is arguably more important today compared with 2013, as the treatment options and combinations for CTEPH patients have increased. This was expanded in the 6th WSPH to include the need for a

multidisciplinary assessment in the treatment algorithm, with a larger “expert CTEPH team” including an experienced surgeon, PH specialist, BPA interventionalist and CTEPH-trained radiologist to reflect the additional treatment modalities [38]. The critical importance of the contribution of an expert radiologist is perhaps under-recognised with respect both to the CTEPH diagnosis and determining treatment options, and CTEPH is sometimes misdiagnosed on CTPA [39]. MDT decision-making is still mainly based on relatively subjective clinical experience.

The European Respiratory Society (ERS) statement made clear that some patients with CTEPH benefit from multimodality treatment, but there were few published data, no direct randomised controlled trial (RCT) comparisons and no consensus on eligibility criteria, just the requirement for an expert centre and MDT approach [1]. The International Society for Heart and Lung Transplantation consensus statement on the management of CTEPH patients also suggested that patients with CTEPH require multidisciplinary care at expert CTEPH centres, but with no new evidence [40]. The latest European Society of Cardiology (ESC)/ERS guidelines specified that treatment assessment should be by an expert MDT (class IC), including experienced PEA surgeons, at a CTEPH centre to evaluate operability, and indicated that a multimodality approach should be considered for patients with persistent PH after PEA and for patients with inoperable CTEPH (class IIaC). These recommendations were broadly based on the 6th WSPH conclusions rather than on any new published evidence. The guidelines confirmed that the CTEPH MDT should include PEA surgeons, BPA interventionalists, PH specialists and thoracic radiologists, all trained in high-volume centres [5]. There has been little published on the specific role of the MDT. An article from Switzerland describing the introduction of a national MDT concept has shown feasibility, although the numbers were small and <100 patients were reported [41].

Therefore, further confirmation of the MDT concept was repeated in all major statements, but without significant interval advances or substantial new evidence since the 6th WSPH. Current best practice proposed that the CTEPH MDT include experienced PH radiologists, experienced PEA surgeons, CTEPH/PH physicians, BPA interventionalists, a coordinator, PEA/PH specialist nurses and MDT administration. The latter is required for minuting decision-making. Ideally, the team should have two clinicians from each interventional subspecialty to allow more than one opinion. In principle, the role of CTEPH MDT is 1) confirmation of CTEPH diagnosis; 2) determination of operability; 3) determination of BPA potential; 4) determination of appropriateness of medical therapy and/or multimodal approach; and 5) follow-up/review of previously treated patients, both to determine the need for additional therapy and as a feedback loop for the MDT.

However, there remain numerous gaps regarding CTEPH MDTs: 1) no evidence for a clinically useful objective radiological classification/description tool; 2) no evidence for an accurate pre-operative surgical or BPA risk-scoring system; 3) no trial evidence on objectivity of inter- and intra-MDT decision-making; and 4) no trial evidence for direct comparison between BPA and PEA to aid MDT decision-making. There is a need for more objective radiological reporting to aid MDT decision-making and to help compare treatment outcomes. Furthermore, there should be an emphasis placed on the important feedback loop to the surgeon or BPA team of limits and consequences of their treatments including with longer term follow-up [5].

The application of MDT in CTEPH cannot be overstated and is foundational for optimal management of each case (table 1). The following sections provide overviews of each CTEPH therapy in the current management and based on MDT determination.

### **Pulmonary endarterectomy**

Surgical resection of occlusive chronic thromboembolic material, by means of PEA, also referred to as pulmonary thromboendarterectomy (PTE) is the guideline-recommended treatment of choice (class IB) and the first step when evaluating patients with CTEPH [5] (figure 2). The procedure can normalise pulmonary artery pressures in ~70–75% of patients and carries an operative mortality of ~2% at expert centres [42–44].

**TABLE 1** Steps to recovery in chronic thromboembolic pulmonary hypertension: AMEND

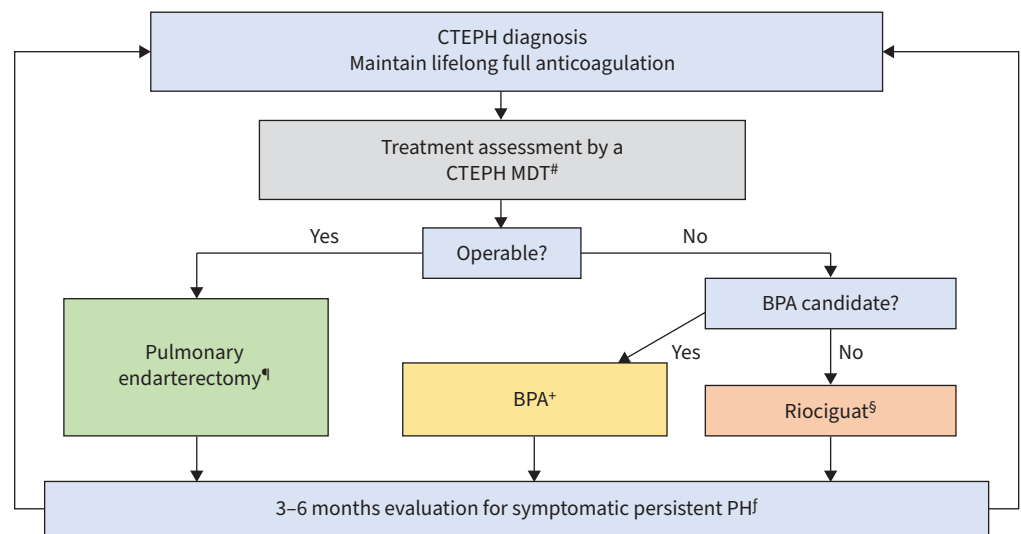
<b>A</b>	<b>Anticoagulation</b>
<b>M</b>	<b>Multidisciplinary team review</b>
<b>E</b>	<b>Pulmonary Endarterectomy</b>
<b>N</b>	<b>Nonsurgical treatments: medical therapy, balloon pulmonary angioplasty</b>
<b>D</b>	<b>Don't forget follow-up assessment after any intervention</b>

Currently, survival for PTE/PEA is >90% at 3 years, 87% at 5 years and 78% at 10 years; however, disease-specific survival is 91% at 5 years and 85% at 10 years [45, 46]. In comparison, survival was only 70% at 3 years in those CTEPH patients not operated and before availability of BPA and riociguat [47]. In the current era of multimodality treatment with BPA and medical therapy, 5-year survival in inoperable patients has improved significantly, and is approaching 90%, but it remains unchanged at ~70% for patients who did not undergo either intervention (M. Delcroix, UZ Leuven, Leuven, Belgium; personal communication) [47]. Operability assessment and patient selection remain the Achilles' heel in prediction of excellent long-term outcome. Certain patient characteristics can help with appropriate treatment strategy [48].

Historically, high PVR was considered a potential contraindication to surgery [49]; however, even in patients with the most severe forms of disease, characterised by a pre-operative PVR of >1000 dyn·s·cm<sup>-5</sup>, the operative mortality has decreased to <5% [43, 46]. Furthermore, advanced age (>80 years), morbid obesity or repeat operations are not considered contraindications to surgery [50–55]. In addition, recent data show that although females have similar short- and long-term outcomes, there is slightly higher incidence of residual PH requiring medical therapy [56]. There is now clear evidence that in expert centres and with advancements in diagnosis, imaging, surgical techniques and instruments, distal endarterectomy in segmental and subsegmental vessels is feasible with comparable short- and long-term outcomes [45, 57]. As a result, a new intraoperative surgical classification is now widely accepted to better designate the location of thromboembolic disease and surgical resection [57, 58].

Advancements in extracorporeal membrane oxygenation (ECMO) technology, utilisation and management has had a significant impact on treatment of patients with CTEPH. This has also translated into improved outcomes, not only in high-risk surgical patients allowing better pre-operative optimisation and perioperative management, but also in rare circumstances when devastating post-operative complications such as severe reperfusion injury or airway haemorrhage are encountered [46, 59–64]. Pioneered at the University of California San Diego, minimally invasive PEA is a new technique where the procedure is performed through bilateral or occasionally unilateral mini-anterior thoracotomy incisions, and can be offered to patients to avoid sternotomy, or are otherwise considered at high risk of wound-healing complications [58, 65, 66].

What determines operability is multifactorial, complex and dependent on centre expertise [28, 67]. Patients can be technically operable, but refuse surgery or have prohibitive comorbidities. Some may have severe discordance between amount of disease and severity of PH, and yet others may have disease that is beyond



**FIGURE 2** Chronic thromboembolic pulmonary hypertension (CTEPH) treatment algorithm. MDT: multidisciplinary team; BPA: balloon pulmonary angioplasty; PH: pulmonary hypertension. #: CTEPH MDT requires pulmonary endarterectomy surgeon, PH expert, BPA specialist and chest radiologist; ¶: treatment of choice for technically operable disease; †: riociguat therapy prior to BPA: mean pulmonary arterial pressure ≥40 mmHg or pulmonary vascular resistance >4 Wood Units; §: other PH medications approved in select regions; f: structured follow-up; may include imaging and haemodynamic assessment.

the reach of expert surgeons. There is no evidence that operable patients benefit from delaying surgery for a trial of bridging therapy with either PH drugs or with BPA [47, 68]. There are now reports of combining PEA with BPA, both sequentially [69–71] or in a hybrid manner [72] where surgery is performed on the operable side and BPA on the inoperable side. However, caution is advised in interpreting these reports, as despite significant advancement in imaging, it is hard to predict the exact level of disease; and obstruction within pulmonary vasculature may be underestimated, thereby potentially denying the patient the opportunity for complete resection of disease.

What constitutes the definition of a CTEPH surgical expert centre at a regional or at a national level is debatable, challenging and may depend on paucity or surplus of other CTEPH centres. But there are certain important characteristics and goals which must be taken into consideration. This has become even more relevant with wide availability of medical therapy and easy access to percutaneous therapies such as BPA for all patients, including those who would clearly benefit from surgery. A three-step stratified definition of expert surgical centre is proposed which factors the following important goals: surgical mortality (<3%), surgical volume (>50 per year), ability to perform segmental endarterectomy [34, 45, 57] and availability of ECMO support if necessary. Furthermore, in this era of a multidisciplinary approach and multimodality treatment of CTEPH, an expert centre should be capable of evaluating and offering any/all established treatment modalities according to individual need.

### **Balloon pulmonary angioplasty**

At the 6th WSPH, BPA was described as “an important component of the CTEPH treatment algorithm”, mainly based on single-centre trials from Japan [73–75], showing promising improvements of haemodynamics, symptoms, exercise capacity and right ventricular function. Shortly before the 6th WSPH, publications from European centres confirmed the lower rates of severe complications compared to the first series published in 2001 [76–82]; however, the benefits were less pronounced than those achieved in Japanese centres. A steep learning curve with extensive training and case experience led to the recommendation of treatment in expert centres [83]. BPA should be considered for symptomatic patients ineligible for PEA due to distally localised pulmonary artery lesions or patients with persistent/recurrent PH after surgery. Therefore, the MDT is deemed obligatory for treatment decision-making. Target lesions for BPA are visualised by pulmonary angiography [84]; the intervention may be augmented using intravascular imaging and pressure gradient analysis [85]. The 6th WSPH summarised the most common complications of BPA and pointed out that vascular injury (mostly caused by wire perforation) may be far more common than the capillary leak syndrome known from PEA surgery [84, 86, 87]. Mid-term results were promising, but the according evidence was scarce, and all trials derived from Japanese centres [88, 89].

Over the past 5 years, BPA has become a guideline-recommended treatment (class IB) for inoperable CTEPH patients or patients with residual PH after PEA [5]. Two randomised controlled trials have been published, comparing the effectiveness of the interventional treatment with drug therapy using riociguat [90, 91]. Furthermore, two multicentre registries [89, 92] have confirmed the findings of several single centre reports [69, 71, 93, 94]. In conclusion, BPA leads to significant improvements of pulmonary haemodynamics and physical capacity with 3-year survival rates of 92–95% [10, 90, 91, 95]. Importantly, it has been shown that the number of successfully treated lesions predicts treatment response, and especially the number of successfully treated occlusions (particularly chronic total occlusions) have the largest impact on relative change in mean pulmonary artery pressure (mPAP) [93]. The rate of restenosis was very low with 0.6% of the treated lesions in a median follow-up of 1.9 years [96]. By far the most common peri-interventional complication with a rate of ~10% (of the sessions) is lung injury, usually caused by wire perforation [69, 95, 97], with more severe lung injury occurring in cases with mPAP  $\geq$ 40 mmHg [98]. Accordingly, extra caution has been advised for BPA intervention, including balloon sizing for patients with mPAP  $\geq$ 40 mmHg [95]. In a systematic review of BPA publications, the rate of lung injury complication was down to 7.7% in the more recent period spanning from 2018 to 2022 [99]. The improved complication rate is probably associated with the learning curve previously reported from the major French series [69]. Importantly, the occurrence of this complication does not affect the outcome of BPA in expert centres [97]. As a promising management strategy, the instillation of gel foam has been described besides proximal vessel occlusion (using a guiding or balloon catheter) [100]. Another important finding was that medical pre-treatment reduced the rate of severe complications of BPA in patients with a PVR >4 Wood Units (WU) in a randomised controlled trial [90]. Furthermore, the combination of riociguat and BPA leads to long-term survival rates of 92.9% after 3 years and 90% after 5 years in inoperable CTEPH patients with significant improvement in quality of life [94, 101].

Not all patients with technically operable disease are amenable to PEA. Treating surgically accessible lesions by BPA leads to significantly less improvement of pulmonary haemodynamics and physical

capacity compared to interventional treatment of technically inoperable CTEPH. However, the cumulative survival rates at 1, 5 and 10 years after BPA were not significantly different (92.5%, 86.1%, 84.3%, respectively, *versus* 96.5%, 92.9%, 90.1%) [102, 103]. As a certain strategy for patients with high-risk for PEA, pre-operative BPA has been used to decrease right ventricular afterload and thus to reduce the perioperative risk: in nine selected CTEPH patients with mixed (proximal and distal) anatomical lesions and baseline PVR >10 WU, all three therapeutic modalities were combined in a sequential multimodal treatment concept [70]. The intraoperative use of BPA in regions that could not be surgically cleared has already been described, but remains a single-centre experience [72]. However, BPA for residual/recurrent PH after PEA appears promising with growing evidence [104–106]. Lastly, a first consensus paper driven by European and Japanese centres summarises a standardised approach to BPA including diagnostic workup, treatment decision-making, procedural techniques and treatment goals [95].

In the 2022 ESC/ERS guidelines [5], BPA was recommended in patients who are technically inoperable or have residual PH after PEA. However, BPA has a weaker recommendation (class IIbC) in patients who are technically operable, but have a high proportion of distal disease and an unfavourable risk/benefit ratio for PEA. In this regard, an ongoing prospective randomised trial (GO-CTEPH; clinicaltrials.gov identifier NCT05110066) compares surgery and intervention in patients eligible for both PEA and BPA [107]. Although current guidelines recommend medical therapy prior to intervention, they do not address whether medical therapy should be continued after achieving normal haemodynamics with BPA. Another ongoing prospective randomised trial (THERAPY-HYBRID-BPA; clinicaltrials.gov identifier NCT04600492) may contribute to developing future recommendations for the long-term treatment strategy after BPA [108]. Although BPA has been expanding globally over the past 5 years, no specific interventional equipment has yet been developed for worldwide use. This is one reason why the interventional technique and its appropriate training has not yet been fully standardised. BPA programmes in most centres developed according to initial reports of refined BPA in 2012, and therefore, long-term survival >10 years after BPA and its determinants have not yet been elucidated. To entirely standardise BPA-specific treatment goals, it is necessary to determine to what extent improvements in haemodynamic parameters after BPA, such as mPAP and PVR values, are sufficient to improve long-term survival in CTEPH patients.

The experience in performing BPA has grown worldwide with numerous single-centre reports, several national registries and RCTs comparing riociguat with BPA. Due to the global expansion of BPA programmes, differences in technical performance, treatment goals and nomenclature of complications need to be addressed. Hopefully, the international BPA registry will shed some light and help guide more uniformity (clinicaltrials.gov identifier NCT03245268) [109].

### Medical therapy

In the management of CTEPH, lifelong therapeutic anticoagulation is recommended to prevent recurrent VTE. The established standard of care for anticoagulation in CTEPH involves the utilisation of vitamin K antagonists (VKAs), which have garnered widespread acceptance for this purpose. VKAs are particularly recommended for anticoagulation in CTEPH patients who also present with antiphospholipid syndrome, a condition affecting ~10% of individuals with CTEPH [5]. In recent years, there has been a rising trend in the utilisation of non-vitamin K oral anticoagulants (NOACs) in the management of CTEPH. Both retrospective and prospective studies have consistently demonstrated comparable major bleeding rates between VKAs and NOACs in CTEPH patients [110–112]. However, specific investigations have reported higher recurrence rates of VTE with NOACs in comparison to VKAs [111, 113]. In particular, a study conducted by BUNCLARK *et al.* [113] identified a higher recurrence of VTE in patients treated with NOACs following PEA. A study conducted by JEONG *et al.* [114] revealed a significant correlation between the use of NOACs and the presence of acute or subacute thrombi at the time of surgery. Furthermore, the prospective EXPERT study reported a higher incidence of embolic or thrombotic events in the NOAC group compared to the VKA group [111]. Importantly, RCTs such as the KABUKI trial and registry data have not demonstrated any significant impact on haemodynamics or survival in patients with CTEPH receiving anticoagulant treatment with VKAs or NOACs [110, 112, 113, 115].

Treating hypoxaemia is suggested for patients with CTEPH to mitigate the consequences of reduced oxygen delivery to organs and potentially prevent worsening of PH by inducing pulmonary vasoconstriction [116, 117]. Additionally, hypoxaemia negatively affects the exercise capacity of patients with PH [116]. A RCT has demonstrated that administering oxygen to patients who experience exercise-induced oxygen desaturation (defined as a decrease of  $\geq 4\%$  in peripheral oxygen saturation to  $\leq 92\%$  during a 6-min walk test) can lead to improvements in exercise capacity and quality of life [118]. An emerging perspective suggests that de-escalation of oxygen therapy is feasible in some patients following de-obstructive treatment [119].



There is a rationale for utilising drugs approved for PAH to address microvasculopathy in inoperable CTEPH patients or in operable patients with residual PH after PEA. For the 6th WSPH, three noteworthy RCTs were available. The BENEFIT study, which evaluated bosentan, a dual endothelin receptor antagonist, reported improvements in PVR, although no significant enhancement in the 6-min walk distance (6MWD) was observed [120]. The CHEST-1 study, evaluating riociguat, an oral soluble guanylate cyclase stimulator, demonstrated improvements in PVR, 6MWD and right ventricular function [121]. Both RCTs included inoperable CTEPH patients or operated patients with residual PH after PEA. The MERIT-1 study investigated macitentan, an endothelin receptor antagonist, in inoperable CTEPH patients and showed improvements in PVR, 6MWD and N-terminal pro-brain natriuretic peptide [122]. Notably, this study provided the initial evidence for combination drug therapy in CTEPH among patients with New York Heart Association functional class III–IV. Subsequently, the long-term benefits of riociguat were confirmed by the CHEST-2 study, and based on these findings, riociguat received approval for the treatment of inoperable CTEPH patients or operable patients with residual PH after PEA [123].

Since the 6th WSPH, two notable RCTs and several studies have provided evidence of the efficacy and safety of PH medical therapy in CTEPH. *Post hoc* analyses demonstrated the sustained long-term benefits of riociguat on right ventricle function [124, 125]. The CTREPH study, utilising subcutaneous continuous infusion of treprostinil, a stable prostacyclin analogue, showcased efficacy in reducing PVR and improving 6MWD in inoperable CTEPH patients or operated patients with residual PH after PEA [126]. Notably, some patients in this study received background therapy. Furthermore, the JapicCTI-163279 study assessed selexipag, an orally selective prostacyclin receptor agonist, revealing improvements in PVR, though no significant enhancement in 6MWD was observed. This study allowed the utilisation of combination medical therapy [127]. Still, several studies in CTEPH either terminated before completion or failed to demonstrate efficacy. The AMBER-1 study, exploring ambrisentan, an endothelin receptor antagonist in inoperable CTEPH patients, was prematurely halted due to insufficient enrolment [128]. A small randomised controlled trial testing sildenafil did not show improvement in 6MWD [129]. Two studies were interrupted due to futility: the SELECT study with selexipag, terminated before completion due to a lack of efficacy in treating inoperable CTEPH or residual PH after PEA (clinicaltrials.gov identifier NCT03689244); and the MACiTEPH study (clinicaltrials.gov identifier NCT04271475) evaluating macitentan in patients with CTEPH faced a similar outcome, closing early due to futility [130, 131].

There is evidence supporting the use of PH medical therapy before BPA in inoperable CTEPH patients with high PVR to mitigate procedural complications [90, 91]. The utilisation of PH medical therapy before PEA in operable CTEPH cases with high PVR is more controversial, and the task force remains divided on its role prior to PEA. Although there has been an interval safety signal using combination of PH targeted therapies in CTEPH from available RCTs, more robust evidence is needed in CTEPH. The ongoing IMPACT-CTEPH study (clinicaltrials.gov identifier NCT04780932) is positioned to provide valuable information to address this gap in the context of inoperable CTEPH before BPA [132]. There is a lack of data guiding withdrawal of medical therapies after successful BPA and/or PEA. A structured long-term follow-up is required to facilitate such an investigation.

### **Multimodal therapy**

Given the availability of three effective treatments targeting different lesions at different levels of the pulmonary vasculature, the current approach to treatment has evolved to incorporate a multimodal management strategy including the sequential combination of at least two of the three treatment modalities. The importance of a multimodal, individualised approach in CTEPH management at expert centres integrating surgical, interventional, imaging and medical PH expertise was first stated at the 6th WSPH [38]. Then, the ERS statement made clear that some patients may have mixed anatomical lesions (*i.e.* organised fibrotic clots, proximally at lobar to segmental level, or distally at subsegmental level and microvasculopathy) and may therefore benefit from multimodal therapy, but without consensus on eligibility criteria [1]. The latest ESC/ERS guidelines advocated for a comprehensive review of all CTEPH patients by a multidisciplinary CTEPH team capable of multimodal management, to formulate an effective therapeutic strategy including a combined approach with PEA, BPA and medical treatment to target the different vascular components of the disease [5].

PEA is the recommended first-line treatment for operable patients [5]. However, despite advancements in the surgical technique, PEA remains a challenging surgery, especially for patients with high pre-operative PVR (table 2), as this has been associated with an increase in early post-operative mortality. However, current evidence does not support the use of pharmacological treatment prior to PEA to improve post-operative outcomes [47, 68]. In contrast, the beneficial effect of a combined approach with BPA (prior to or at the same time as surgery) and PEA has been shown in selected patients with high-risk haemodynamics with unilateral operable and contralateral inoperable disease [70, 72, 133].

**TABLE 2** Approach to chronic thromboembolic pulmonary hypertension with severe pulmonary haemodynamics

	Pros	Cons
<b>PH medical therapy prior to PEA</b>	Improving haemodynamics, perceived lowering the risk of PEA Uncontrolled, anecdotal data Potential strategy to stabilise PH waiting for access	No controlled data Delays in treatment Unknown effects of medications on operable disease
<b>Combined PEA and BPA (hybrid approach)</b>	Feasibility published Access to disease out of reach of PEA at time of surgery	Restricted to expert centres Risk of BPA complication higher than average
<b>BPA prior to planned PEA</b>	Anecdotal data May allow improvements in haemodynamics prior to PEA	Restricted to expert centres Risk of BPA complication higher than average PEA may be more challenging in area of prior BPA
<b>PEA followed by BPA</b>	Clearance of reachable disease bilaterally What remains is inoperable	Restricted to expert centres Higher risk of PEA Delay with BPA due to surgical recovery BPA may be challenging due to surgical changes
<b>PH medical therapy prior to planned BPA</b>	Supported by RCTs Improved haemodynamics before BPA Lower BPA complications	Access/reimbursement of riociguat Mono- versus combination therapies unclear, but being investigated Risk of patients continuing on medical therapy unnecessarily post-BPA

PH: pulmonary hypertension; PEA: pulmonary endarterectomy; BPA: balloon pulmonary angioplasty; RCT: randomised controlled trial.

In contrast, BPA, most often in combination with pharmacological therapy, has become an established treatment for selected patients with residual PH post-PEA. Residual PH after PEA, defined at that time as mPAP  $\geq 25$  mmHg, has been reported in 17–51% of patients [47, 134]. Single-centre series with small numbers of patients have demonstrated improvements in functional class and haemodynamics at follow-up in patients with residual PH post-PEA who were treated by BPA [105, 106, 135–137]. However, haemodynamic improvement was less pronounced than that in primary BPA. In addition, some reports described very hard occlusions after PEA, which were challenging to dilate [106], potentially resulting in BPA-related complications such as haemoptysis [135]. In a single-institution series, clinically relevant residual PH adversely affecting long-term survival after PEA was noted when mPAP was  $\geq 38$  mmHg and PVR was  $\geq 5$  WU 3–6 months after surgery. In the same study, the authors also showed that a mPAP  $\geq 30$  mmHg correlated with the initiation of medical treatment post-PEA and proposed this threshold value to define clinically significant PH post-PEA for which BPA may be considered [134].

Until the RACE RCT, there was no convincing evidence that medical therapy introduced prior to BPA intervention can improve outcome (haemodynamics, exercise capacity and safety during BPA procedures) in inoperable CTEPH [90]. The MR BPA and RACE studies showed that both BPA and riociguat lowered PVR, with mPAP decreasing more with BPA, and cardiac output increasing more with riociguat in patients with inoperable CTEPH [90, 91]. The RACE ancillary study also demonstrated that riociguat and BPA, used sequentially, had complementary effects and that pre-treatment with riociguat for 6 months prior to BPA decreased the incidence of serious adverse events related to BPA by optimising pre-BPA pulmonary haemodynamics [90]. As the rates of interventional complications can be reduced by pharmacological pre-treatment, the latest ESC/ERS guidelines specified that in patients who are candidates for BPA and have a PVR of  $>4$  WU, medical therapy should be considered prior to the intervention, although the quality of evidence is low [5]. Long-term follow-up is recommended by the latest ESC/ERS guidelines. Regular follow-up, including high-quality imaging techniques and RHC 3–6 months after intervention (PEA or BPA), is required for consideration of a multimodal treatment [5]. These significant advancements in multimodal therapeutic management have resulted in a 3-year survival rate  $>90\%$  for both operated and nonoperated patients with CTEPH (M. Delcroix, UZ Leuven, Leuven, Belgium; personal communication) [47, 69, 94, 138].

**TABLE 3** Chronic thromboembolic pulmonary hypertension (CTEPH) multidisciplinary team (MDT) and centre expertise

Requirements	
<b>MDT</b>	PEA surgeon + BPA specialist + PH expert + pulmonary vascular radiologist
<b>PEA centre</b>	≥20 surgeries per year with post-operative mortality rate <5%, ECMO support
<b>Expert PEA centre</b>	50 surgeries per year with mortality <3%, capable of treating segmental/subsegmental disease, ECMO support
<b>BPA centre</b>	≥50 procedures per year with procedure related mortality <3%
<b>Expert BPA centre</b>	>100 procedures per year with mortality <1%, ECMO support
<b>Comprehensive CTEPH centre</b>	Combined PEA + BPA + PH + ECMO expertise available with treatments based on centre MDT

PEA: pulmonary endarterectomy; BPA: balloon pulmonary angioplasty; PH: pulmonary hypertension; ECMO: extracorporeal membrane oxygenation.

Data regarding the therapeutic target after PEA/BPA or medical therapy are scarce. The goals of CTEPH treatment are alleviation of symptoms, improvement in exercise capacity and quality of life and normalisation or near normalisation of pulmonary haemodynamics at rest [5]. Because of the prognostic threshold of a mPAP of 30 mmHg [134, 139], the minimum haemodynamic goal of BPA should aim for final mPAP <30 mmHg. However, this has not been validated and experts may differ on their goal criteria. It is currently unclear if an initial dual oral combination therapy is more effective than a monotherapy, a concept previously established in PAH. This question is being explored in an ongoing study (IMPACT-CTEPH) [132].

### Best practice and expert definitions

The management of CTEPH has become more demanding, but more satisfying, with the advances in multimodal therapies. Once treated primarily with one modality with even the prospect of lung transplantation [26, 140], the field has evolved to obviate the need for lung transplantation. However, successful CTEPH management demands standards which have been reinforced since the last WSPH.

Table 3 summarises best practice recommendations from the expert panel. As emphasised repeatedly, MDT is critical and consists of all four subspecialties attending to each case. The inherent steep learning curve for both PEA and BPA requires proper training and ongoing volume/experience to deliver the best results. A PEA centre should achieve in-hospital mortality rates <5%, with expert centres achieving rates <3% with the capability of treating segmental and subsegmental disease. A BPA centre should achieve procedure-related mortality <3%, with expert BPA centres now reporting mortality rates <1%. For both interventions, higher volume may correlate with improved outcomes. ECMO support should be available for high-risk patients and if needed for major complications. Lastly, a comprehensive CTEPH centre has combined PEA, BPA and PH expertise available to apply any and all modes of CTEPH therapy best suited to the individual case. For any of these centres, a structured follow-up should become standard of care and an important aspect of disease management.

In addition, CTEPH centres ought to work on quality measures. To help achieve some of these goals, CTEPH centres are encouraged to network with expert centres for training opportunities and obtaining second opinion for challenging cases [26, 67]. Interested programmes in countries without an established reference centre should collaborate to conduct a national registry of CTEPH cases. This has the potential benefit of pooling both resources and expertise to optimise approach and management of these patients. Such a disease registry, or other collaborative efforts, may shed light on diagnostic and treatment gaps in need of attention. Some of the most informative work has come from such national and international collaborative efforts (M. Delcroix, UZ Leuven, Leuven, Belgium; personal communication) [49, 141–143].

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