

# Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Chronic thromboembolic pulmonary hypertension

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**Abstract:**

Chronic thromboembolic pulmonary hypertension (CTEPH) is categorized as group IV in the WHO classification for pulmonary hypertension. The disease requires a very low index of suspicion for identification and needs a special diagnostic approach utilizing clinical, radiological, and hemodynamic tools. As CTEPH is potentially curable, all efforts should be consumed to reach the accurate diagnosis and subsequently evaluated for operability.

Although pulmonary endarterectomy (PEA) is the only curative tool so far, recent updates concerning medical and interventional therapy have made significant advances in inoperable patients.

In this review, we provide a detailed discussion on diagnostic algorithm, surgical operability criteria, PEA, and the medical therapy.

**Key words:**

Chronic thromboembolic pulmonary hypertension, endarterectomy, riociguat, Saudi association for pulmonary hypertension guidelines

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subset of pulmonary hypertension (PH), which can be cured by surgical pulmonary endarterectomy (PEA). CTEPH is widely underdiagnosed and diagnosis and treatment of the disease are frequently suboptimal. Any patient with unexplained dyspnea due to PH should be screened for CTEPH. Following echocardiographic detection of PH and right heart dysfunction, ventilation perfusion (V/Q) lung scanning is recommended as a screening method of choice. If the V/Q scan shows mismatched perfusion defects suggesting CTEPH, the patient should be referred to a center with expertise in the diagnostic and surgical management of CTEPH. Following high quality imaging (pulmonary angiography) every patient has to be evaluated by an experienced interdisciplinary team and PEA surgeon for the assessment of operability. Two-thirds of CTEPH patients are considered operable. PEA is a complex cardiothoracic operation, which is performed in very few expert centers worldwide. Early and long-term results after PEA surgery are very favorable with regard to pulmonary hemodynamics, exercise capacity and life expectancy. Until lately, the value of specific medical PH treatment in CTEPH patients was unclear. In this review article, important recommendations gathered from many international guidelines are included.<sup>[13]</sup>

## Definition and Pathogenesis

CTEPH is defined as symptomatic PH (mean pulmonary artery pressure  $\geq 25$  mmHg and pulmonary artery wedge pressure  $\leq 15$  mmHg) with persistent pulmonary perfusion defects after a period of at least 3 months of adequate anticoagulation.<sup>[1]</sup> Single or recurrent episodes of acute pulmonary embolisms are considered to be the primary events followed by intraluminal thrombus organization and fibrous obstructions of pulmonary artery (PA) branches with consequent development of PH and progressive right heart dysfunction and failure.<sup>[1]</sup> The pathogenesis involves coagulation and fibrinolytic disorders, which contribute to the development of the disease and other factors, such as abnormal fibrinogen and immunological, inflammatory, or infectious mechanisms trigger pathological remodeling of major and small pulmonary vessels as a response to misguided thrombus resolution.<sup>[2,4]</sup> Vascular remodeling occurs in areas with maintained pulmonary perfusion and leads to microvasculopathy and further deterioration of hemodynamics and exercise capacity. Therefore, CTEPH is a disease with a mechanical component judged amenable to surgery and a variable degree of microvasculopathy.

The incidence of CTEPH is much higher than previously assumed.<sup>[5-7]</sup> However, the overall

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prevalence of CTEPH is unknown, as acute pulmonary embolism is frequently overseen and not all CTEPH patients have a history of acute PE.<sup>[8]</sup> In addition to thrombophilia, other conditions including splenectomy, ventriculo-atrial shunts and chronic inflammatory diseases are associated with an increased risk for CTEPH [Table 1].<sup>[2,9]</sup>

### Diagnosis and Evaluation of Operability

Any patient with unexplained PH should be evaluated for CTEPH, especially in the presence of a medical history of recurrent thromboembolism. All survivors of severe acute idiopathic pulmonary embolism with symptoms of PH and right ventricular (RV) dysfunction should be screened for CTEPH.

In patients with unexplained dyspnea due to PH, a V/Q lung scan (planar images on at least six views + single-photon emission computed tomography) is recommended as the method of choice to exclude or suggest CTEPH [Figure 1]. A

normal ventilation/perfusion lung scan virtually rules out CTEPH.<sup>[10]</sup>

Computed tomography (CT) angiography or conventional pulmonary angiography may show complete PA obstructions, stenosis, strictures, or intimal irregularities and parenchymal lesions and hypertrophic bronchial collaterals [Figure 2]. These tests are considered complementary to the V/Q scanning.

Even in the era of modern dual-source CT scanners, there is not enough evidence that a normal CT angiography excludes CTEPH. Therefore, CT and also magnetic resonance (MR) imaging are not adequate modalities to refute the diagnosis or inoperability of a patient with CTEPH. It is a common observation in PEA centers that CTEPH patients are referred late, after previous misdiagnoses that were based on “negative” CT-scans. However, CT and MR imaging can provide relevant adjunctive information on PA morphology and right heart function before PEA.<sup>[11]</sup>

Upon suspicion of CTEPH, the patient should be referred to a center with expertise in the medical and surgical management of CTEPH. To determine the further therapeutic strategy, evaluation of operability and surgical risk stratification, right heart catheterization (RHC) and conventional traditional pulmonary angiography in two projections are still representing the gold standard of diagnostics. These investigations should be performed at an expert center rather than at the referring center. A coronary angiography is indicated in candidates for PEA, and in those carrying risk for coronary heart disease.

The final diagnosis of CTEPH and the decision about PEA is based on the review of the patient history and functional class, V/Q lung scan, echocardiography, RHC, and selective bi-planar pulmonary angiography.

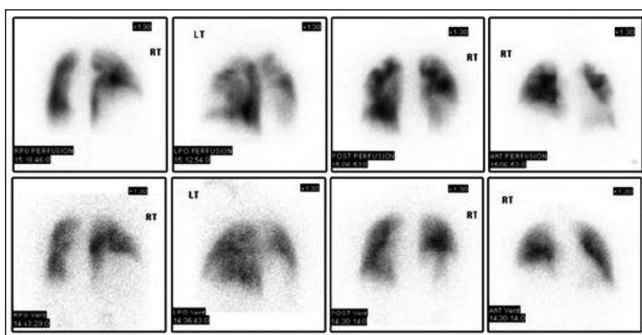
### Treatment of Chronic Thromboembolic Pulmonary Hypertension

Patients with CTEPH should receive life-long anticoagulation, usually with vitamin K antagonist adjusted to a target

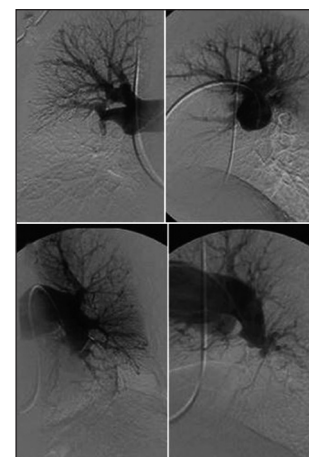
**Table 1: Risk factors for CTEPH**

Risk factors
<b>Independent clinical risk factors for CTEPH</b>
Splenectomy
VA shunts
Pacemaker leads
Indwelling central venous catheters (e.g., Port, Hickman catheter)
Chronic inflammatory diseases (osteomyelitis, inflammatory bowel diseases)
Malignant diseases
Thyroid hormone replacement therapy
<b>Risk factors associated with CTEPH after symptomatic PE</b>
Previous pulmonary embolism
Early age
Large perfusion defect
Idiopathic PE at presentation
<b>Plasmatic risk factors associated with CTEPH</b>
Elevated factor VIII levels >250%
APA/LAC (antiphospholipid/cardioliipin antibody)
Combined coagulation defects
Fibrinogen mutations

CTEPH = Chronic thromboembolic pulmonary hypertension, VA = Ventriculo-atrial, PE = Pulmonary embolism, APA = Antiphospholipid antibody, LAC = Lupus anticoagulant antibody



**Figure 1:** Ventilation/perfusion scan for chronic thromboembolic pulmonary hypertension patient



**Figure 2:** Pulmonary angiography in chronic thromboembolic pulmonary hypertension

international normalized ratio of 2-3. The need for lifelong inferior vena cava filter is a controversial issue and is adopted by some treating centers.

### Surgical treatment

The decision on specific therapy of CTEPH patients should be made in an individual fashion at an expert center based on interdisciplinary discussion between PH physicians, radiologists, and expert surgeons. PEA is the treatment of choice for patients with CTEPH as it is the only potentially curative treatment option. As experience is the most important prognostic factor for short and long-term outcome, no patient should be considered nonoperable as long as the case has not been reviewed by an experienced PEA surgeon. High quality preoperative imaging, individual patient evaluation and selection, surgical technique and experience, and meticulous postoperative management are essential prerequisites for the success of this intervention.<sup>[4]</sup>

The selection of symptomatic patients for surgery depends on the extent and location of the organized thrombi in relation to the degree of PH and comorbidities, like severe chronic obstructive pulmonary disease and systolic left ventricular dysfunction. Proximal PA obstructions at the lobar and segmental level represent the ideal indication, while more distal obstructions may increase the risk of surgery dependent on the personal experience of the surgeon [Table 2].<sup>[12-14]</sup>

Currently, advanced age, concomitant cardiac disease (e.g., coronary artery disease), severe RV failure, renal or hepatic insufficiency, and malignancy with reasonable survival expectations are not considered absolute contraindications for PEA. However, patients with severe left ventricular dysfunction or significant obstructive or restrictive lung diseases are generally not acceptable for surgery. All patients over 45 years should undergo coronary angiography before PEA to rule out coronary disease. If necessary, coronary artery bypass grafting can be performed at the time of PEA. Finally, patients with supra-systemic PAP and very high pulmonary vascular resistance (PVR) ( $>1500$  dynes/s/cm<sup>5</sup>) are considered significantly high operative risk.<sup>[15]</sup>

Although PEA has proved to be a curative option for patients with severe CTEPH, only approximately 5000 operations have been performed in a limited number of centers worldwide with the largest experience accumulated at the University of California San Diego Medical Center followed by four major European PEA programs.

The rationales of operation are restoration of pulmonary perfusion, ventilation perfusion balance and oxygenation,

reduction of RV afterload and recovery of right heart function and avoidance of secondary microvasculopathy. The operation is not an embolectomy but a true endarterectomy removing the organized fibrous obstructive material with its neointima.

As a good visibility in a bloodless field is mandatory for a complete endarterectomy of segmental and subsegmental PA branches, use of extracorporeal circulation and periods of deep hypothermic circulatory arrest (DHCA) is standard.<sup>[16,17]</sup> DHCA has recently been shown to protect neurocognitive function during PEA operations.<sup>[18]</sup>

In contrast to most other cardiothoracic procedures using extracorporeal circulation, the postoperative course after PEA is much more determined by right heart function and pulmonary circulation rather than left heart function and systemic circulation. Postoperative residual PH, RV dysfunction, and a reperfusion response within the endarterectomized areas of the lung are infrequent, but significant problems making a meticulous postoperative management mandatory.

In expert centers, the outcome of PEA surgery with respect to early and late survival, exercise capacity, hemodynamics, RV function, and pulmonary gas exchange is very favorable for most of the patients.<sup>[17,19,20]</sup> A center is considered an expert center if it performs at least 20 PEA operations per year with mortality of  $<10\%$ .<sup>[1]</sup> Large volume centers have even reported in-hospital mortality rates of  $<5\%$ . Therefore, lung transplantation is very rarely considered as a treatment option for highly selected CTEPH patients judged as inoperable by an experienced interdisciplinary PEA team.

The postoperative management of CTEPH patients undergoing PEA can be quite challenging. One of the most significant postoperative complications is persistent PH that can be seen in up to 10% of patients. This can be due to incomplete endarterectomy of inaccessible distal lesion or to significant small vessels remodeling. Rarely, persistent postoperative PH can be related to wrongly selected cases for PEA, e.g., patients with idiopathic PAH with secondary thrombotic lesions wrongly labeled as CTEPH. Another potential postoperative complication is reperfusion edema in the treated territories, which may develop in 10-15% of cases. Optimal fluid management, postoperative mechanical ventilation (high positive end-expiratory pressure) strategy, and avoidance of positive inotropic drugs have been associated with a lower incidence of reperfusion edema and right sided heart failure.<sup>[21]</sup>

The use of postoperative extracorporeal membrane oxygenation has been shown recently to be beneficial in patients with persistent high PVR postoperatively. The use of prostanoids,<sup>[22,23]</sup> and more recently riociguat,<sup>[24]</sup> has also been shown to benefit patients with persistent postoperative PH.

Other rare postoperative complications include nosocomial pneumonia, hemoptysis, or re-thrombosis of the endarterectomized vessels, especially in those patients with inadequate postoperative anticoagulation.

Operative mortality in experienced hand is  $<5\%$  and the main cause of death is persistent PH. The operative mortality, however,

**Table 2: Optimal selective criteria for PEA**

#### Operability criteria

Proximal accessible lesion

Absence of major comorbidity

Preoperative mPAP  $>40$  mmHg

Preoperative PVR  $>300$  dynes/s/cm<sup>5</sup>

Modified NYHA III/IV

Surgical experience

mPAP = Mean pulmonary artery pressure, PVR = Pulmonary vascular resistance, NYHA = New York Heart Association, PEA = Pulmonary endarterectomy

**Table 3: Recommendations for the management of CTEPH**

Recommendation	Class of recommendation	Level of evidence
The diagnostic criteria for CTEPH are met if precapillary PH (mPAP $\geq$ 25 mmHg, PAWP $\leq$ 15 mmHg) is present in patients with chronic/organized thrombi/emboli in the elastic pulmonary arteries (main branch, lobar, segmental or subsegmental level), persisting after effective anticoagulation over a minimum period of 3 months	I	C
In patients with CTEPH, life-long anticoagulation is indicated	I	C
PEA is the recommended therapy for patients with CTEPH	I	C
Once the ventilation/perfusion lung scan or the CT angiography shows signs of CTEPH, the patient should be referred to a center with a PEA program	I	C
The selection of patients for surgery depends on the extent and location of the organized thrombi in relation to the degree of PH, taking into consideration the comorbidities	I	C
Riociguat is indicated in selected patients that include those who are not candidates for surgery or patients with residual PH after PEA	I	A
The role of other PAH-specific drugs is less clear. In selected inoperable patients or those with residual PH after PEA, if riociguat is not available or the patient is still symptomatic, prostanoid or other PAH target therapy might be indicated as an add-on or replacement*	IIb	C
The role of PPA in the treatment of CTEPH needs further evaluation before it can be considered	IIa	B

\*Riociguat should not be used in combination with phosphodiesterase-5 inhibitors. CTEPH = Chronic thromboembolic pulmonary hypertension, PEA = Pulmonary endarterectomy, CT = Computed tomography, PH = Pulmonary hypertension, PAH = Pulmonary arterial hypertension, PPA = Percutaneous pulmonary angioplasty, mPAP = Mean pulmonary artery pressure, PAWP = Pulmonary artery wedge pressure

appears to be closely related to preoperative hemodynamic severity. Those patients with preoperative PVR  $<$ 900 dynes/s/cm<sup>5</sup> have the lowest mortality ( $<$ 5%), while those with preoperative PVR  $>$ 1000 dynes/s/cm<sup>5</sup> have been shown to have a higher mortality.<sup>[15]</sup> Furthermore, high operative mortality has been reported in patients with postoperative PVR  $>$ 500 dynes/s/cm<sup>5</sup>.<sup>[19]</sup>

The survival of PEA appears to be superior to that after lung transplantation, as 75% survival rate up to 15 years has been reported.<sup>[25]</sup>

### Medical treatment

Medical treatment has no role in surgically-candidate patients. Such patients should be sent directly, and without any delay, for surgery once the diagnosis is established. The danger of uncontrolled medical therapy is that potentially operable patients are not referred to a PEA center at all or only after delays and they are therefore denied a potentially curative therapy or are presented for surgery only at a very advanced stage with a significantly increased risk for surgery.<sup>[26]</sup>

Unlike the acute effect on hemodynamics,<sup>[27]</sup> specific PAH drugs have not been shown to be effective in CTEPH in controlled randomized studies.<sup>[28,29]</sup> However, recent data has shown that riociguat, soluble guanylate cyclase stimulators, is effective in patients with inoperable CTEPH or those with recurrent PH after PEA. In phase 3, multicenter, randomized, double-blind, placebo-controlled study, riociguat has significantly improved the exercise capacity and decreased PVR in this group of patients.<sup>[30]</sup> Furthermore, Food and Drug Administration has recently approved riociguat for this indication.

### Percutaneous pulmonary angioplasty (PPA)

Three studies about the use of PPA in CTEPH patients have been recently published. This procedure was mostly considered in patients who were not felt to be surgical candidates or have comorbidities that preclude PEA. The reported functional and hemodynamic improvements are comparable to that achieved PEA by experienced centers.<sup>[30-33]</sup>

However, there are many concerns about PPA for the treatment of CTEPH that need to be addressed. First, patient selection process for this therapy needs to be further clarified. Second, PPA requires multiple procedures and very meticulous follow-up period. Furthermore, the risk and complications, such as vessel rupture and reperfusion lung injury, require more careful risk versus benefit assessment. Third, the durability of the procedure and the long-term risk for restenosis need to be systematically evaluated. Lastly, the procedure is currently limited, with a relatively short follow-up compared with PEA. Hence, although the results of these early reports are encouraging, the role of PPA in CTEPH remains uncertain and requires further evaluation before it can be recommended as an established treatment for CTEPH.

The class of recommendations and the level of evidence for the management of CTEPH patients are summarized in Table 3.

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