Review of Advances on Management of Chronic Thromboembolic Pulmonary Hypertension

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Abstract

Chronic thromboembolic pulmonary hypertension is rare, underdiagnosed form of pulmonary hypertension. It is caused by intravascular obstruction of pulmonary arteries due to fibrotic transformation of thromboembolic material and microvasculopathy. It is important to diagnose this variant as potentially curative treatment in the form of pulmonary endarterectomy is available. Last two decades have seen rapid advances in targeted medical management and refinement in balloon pulmonary angioplasty technique, which have provided a viable therapeutic option for patients who deemed to be inoperable.

Keywords

- chronic thromboembolic pulmonary hypertension
- pulmonary embolism
- balloon pulmonary angioplasty
- ventilation perfusion scan
- pulmonary endarterectomy
- right heart catheterization
- pulmonary artery pressure

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, progressive pulmonary vascular disease that belongs to Group 4 of pulmonary hypertension classification (PH).[1] CTEPH is caused by obstruction of pulmonary artery vasculature, secondary to pulmonary embolism (PE) with combination of incomplete resolution of thrombus, ineffective fibrinolysis, and endothelial dysfunction, which lead to high pulmonary vasculature resistance and right ventricular pressure overload and ultimately develop right ventricular failure.[2–4] Early diagnosis requires high index of suspicion. CTEPH usually develops within 1 year after an episode of PE.[1] The exact incidence of CTEPH is difficult to quantify, and it is largely underestimated because of nonspecific and variable presenting symptoms, underutilization of lung ventilation/perfusion scintigraphy (V/Q scan), and lack of expertise to report computed tomography pulmonary angiography (CTPA) or V/Q scan.[2–4] The incidence of CTEPH confirmed by right heart catheterization (RHC) is around 0.5 to 5% after a symptomatic episode of PE, and it is reported more frequent in history of recurrent PE.[4]

Diagnostic Evaluation of Chronic Thromboembolic Pulmonary Hypertension

The diagnosis of CTEPH requires at least 3 months of effective anticoagulation, hemodynamic parameters for PH along with evidence of proximal or distal thromboembolic occlusion of the pulmonary vasculature.[5] Diagnostic algorithm of CTEPH is shown in ►**Fig. 1**. Echocardiography is often used as first modality to detect PH for screening symptomatic patients at

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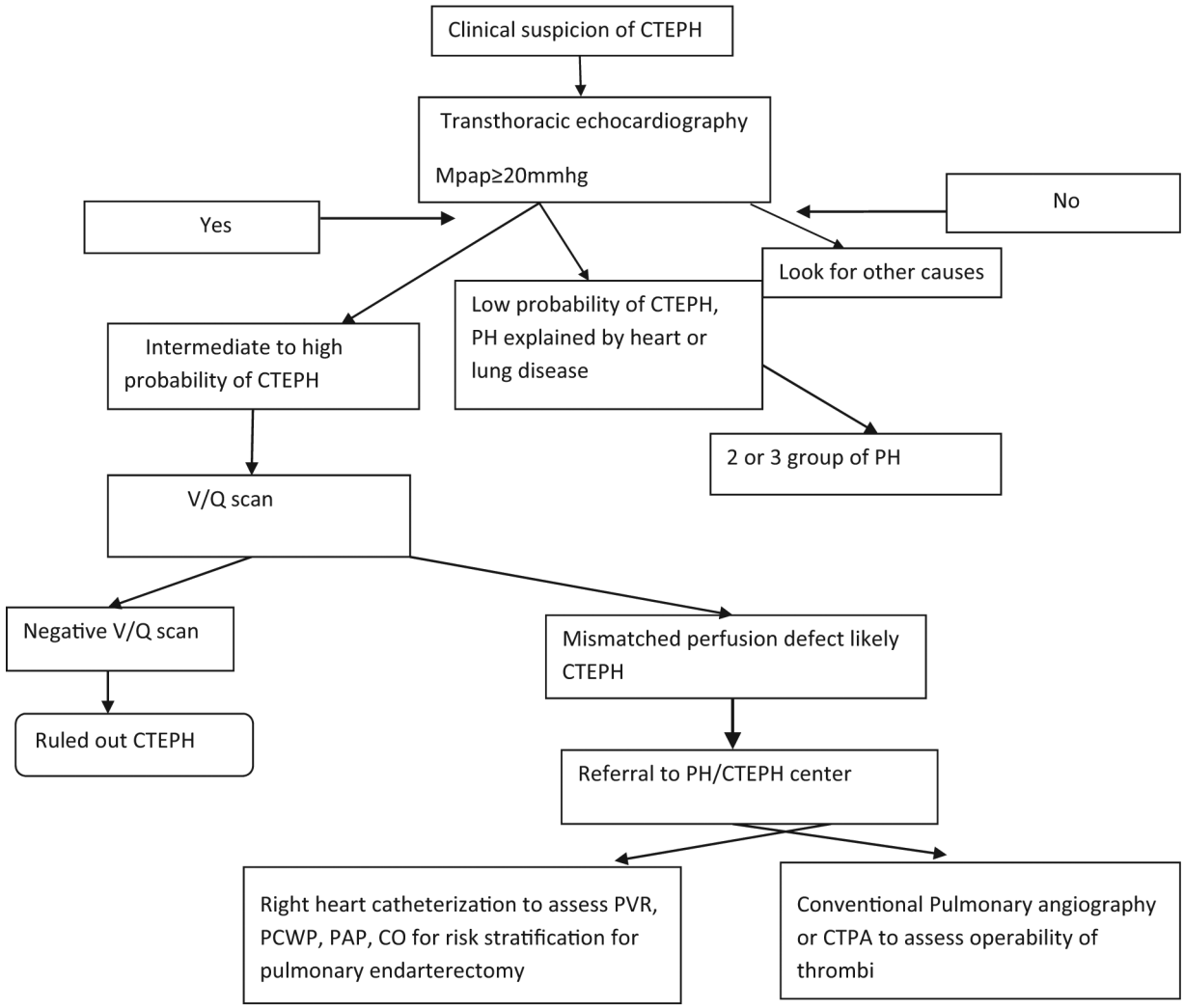

Fig. 1 Diagnostic algorithm of CTEPH. CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; mPAP, mean pulmonary artery pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; V/Q scan, ventilation and perfusion scan.

risk for developing CTEPH. Tricuspid Regurgitation (TR) Velocity max > 3.4 m/s is considered high probability of PH. A significant number of patients with severe PH may not have an accurate TR signal on Doppler; other parameters like right atrial enlargement, right ventricular systolic function, and leftward displacement of the interventricular septum can be used in patients with CTEPH.[6] Chest radiography may show differential areas of hypoperfusion and hyperperfusion, enlargement of main pulmonary arteries and enlargement of the right atrium or right ventricle.[7] Pulmonary function test is used to rule out obstructive and restrictive defects, and an isolated out-of-proportion decrease in diffusing capacity for carbon monoxide hints toward probable underlying pulmonary vascular defect. Arterial blood gas may show an increased A-a gradient with the low partial pressure of oxygen, especially with exertion.[7]

V/Q scan is preferred over CTPA as the initial imaging of choice because of its greater sensitivity and ability to differentiate CTEPH from more distal small vessel involvement in Group 1 PH.[8] Single or multiple larger mismatches found on the V/Q scan indicate CTEPH as opposed to smaller subsegmental defects seen in Group 1 PH. In disease of distal pulmonary vascular bed, perfusion scans either are normal or exhibit a "mottled" appearance characterized by nonsegmental defect. A normal V/Q scan effectively excludes CTEPH with a sensitivity of 90 to 100% and a specificity of 94 to 100%.[7] A study done in confirmed cases of CTEPH by Tunariu et al found V/Q scan was superior to CTPA with a sensitivity of 97.4 versus 51%.[9] This difference has narrowed as computed tomography (CT) technology and interpretation have advanced. Indeed, a more recent study has shown that both V/Q scan and CTPA are accurate methods for the detection of CTEPH with excellent diagnostic efficacy

(100% sensitivity, 93.7% specificity, and 96.5% accuracy for V/Q scan; 96.1% sensitivity, 95.2% specificity, and 95.6% accuracy for CTPA).[10] Although V/Q scan is not available in majority of centers, where CTPA is currently available.

Magnetic resonance angiography with lung perfusion magnetic resonance imaging (MRI) is an emerging tool in the diagnostic evaluation of CTEPH. MRI also assess right ventricular disease and pulmonary hemodynamics. Lung perfusion MRI had sensitivity of 96% compared with 96% of V/Q scan and 94% of CTPA in a study done by Rajaram et al in the United Kingdom. Future research is needed to demonstrate role of MRI in CTEPH.[11,12]

Pulmonary Angiography and Right Heart Catheterization

Pulmonary angiography with RHC is gold standard imaging in patients of CTEPH. It is used for the confirmation of diagnosis as well as to assess whether the thrombotic occlusions are surgically amenable.[13] Furthermore, it also confirms that the increased pulmonary vascular resistance (PVR) is not secondary to distal vessel disease, arteriopathy, or pulmonary venous hypertension.[7] With advances with distal endarterectomy and the advent of balloon pulmonary angioplasty (BPA), and general focus on more distal vascular assessment, conventional pulmonary angiography may not always be suitable for providing fine details. Advanced CT technologies, including dual-energy CT, electrocardiogram-gated area detector CT, cone-beam CT, and contrast-enhanced magnetic resonance pulmonary angiography, are emerging as valuable modalities for detailing the pulmonary vasculature by providing greater resolution than conventional digital subtraction angiography, particularly in the more distal vessels.[14] These imaging techniques are not widely available and require expertise. Biplane subtraction angiography is done for right pulmonary artery; the frontal and lateral flat detectors are kept in anterior posterior and left lateral views, respectively. Left pulmonary angiograms are performed in anterior posterior and left lateral views to avoid the overlap of lung fields and mediastinum. Angiograms are acquired at 4 frames/s during contrast injection and reduced to 1 frame/s during the levophase. Imaging during levophase is necessary to rule out pulmonary vein stenosis and other venous anomalies. Angiographic findings suggestive of CTEPH are webs or bands, intimal irregularities, pouch defects, abrupt vascular narrowing, and complete obstruction (►**Fig. 2**).[15]

Management of Chronic Thromboembolic Pulmonary Hypertension

The management depends on whether the disease is operable or inoperable, which can be decided by the level of obstruction, functional status, and comorbidities (►**Fig. 3**). CTEPH is the only type of PH that is potentially curable and amenable to the surgical treatment but almost half of the patients are technically inoperable. Pulmonary endarterectomy (PEA) is the surgical treatment of choice. All eligible patients with CTEPH should be offered for PEA, regardless of

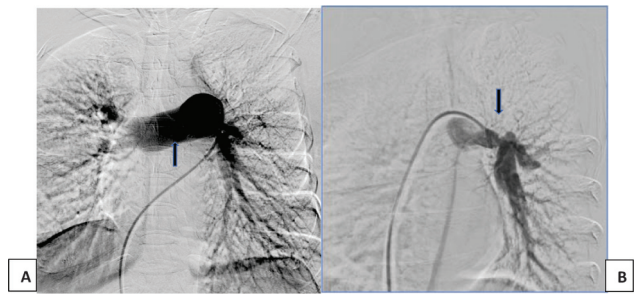

Fig. 2 (**A**) Digital subtraction pulmonary angiogram (DSPA) in posterior anterior view shows dilated main pulmonary artery, occlusion of right lower lobe pulmonary artery (up arrow), narrowing of left pulmonary artery with complete occlusion of left upper lobe pulmonary artery (down arrow). (**B**) Selective DSPA of left pulmonary artery shows narrowing of left pulmonary artery with complete occlusion of left upper lobe pulmonary artery.

hemodynamic parameters and clinical symptoms.[16,17] BPA that has been there for decades has been recently refined to give therapeutic options to patients deemed inoperable. Medical management is an integral part in treatment of CTEPH whether patient is treated by surgery or by percutaneous angioplasty. Other than anticoagulation, only two PH-specific pharmacological treatments riociguat and subcutaneous treprostinil are currently approved for CTEPH.

Pulmonary Thromboendarterectomy

Bilateral pulmonary thromboendarterectomy offers the best survival advantage in patients of CTEPH. The technique was introduced in University of California (UC) San Diego in 1970. The perioperative mortality has come down drastically from 20 to 2% over the last five decades.

The decision to choose PEA depends on comorbidities complicating peri- and postoperative outcomes, surgical accessibility of thrombotic occlusions, imbalance between peripheral vascular resistance and the accessibility of occlusions, and patient's preference.[18] Thrombotic occlusions located in the proximal pulmonary vasculature including

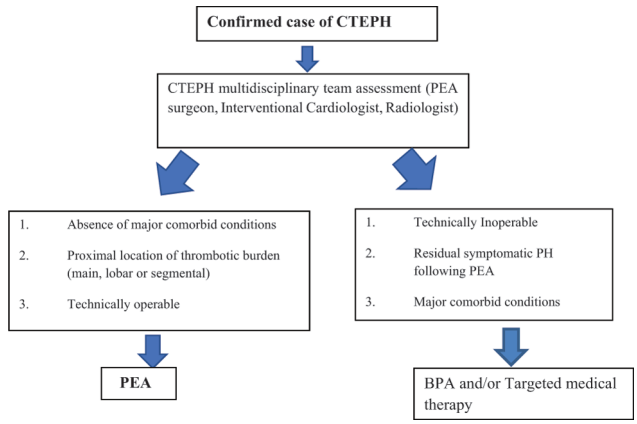

Fig. 3 Treatment algorithm for CTEPH. BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension.

Table 1 Factors determining noneligibility for pulmonary endarterectomy

Comorbidities
Advanced age
Coronary artery disease
Left ventricular dysfunction
Severe lung disease
Diabetes
Chronic kidney disease
Disease involvement
Distal vessel thrombus
Inaccessible thrombus
Small vessel disease
Hemodynamic factor
Imbalance between pulmonary capillary wedge pressure and volume of accessible occlusions

main, lobar, and segmental arteries are more easily amenable to PEA and can be expected lower PVR postsurgery.[16,17]

Nevertheless, around 50% of the patients are ineligible for PEA (►**Table 1**), either because of associated comorbidity or involvement of distal (subsegmental) vessels, which are not surgically accessible.[19] Furthermore, almost one-third of patients who undergo PEA may have persistent or residual pulmonary hypertension despite having undergone a successful procedure, and this complication was associated with higher early mortality. Complications of PEA are summarized in ►**Table 2**. Persistent pulmonary hypertension can result from incomplete removal of more distal thrombi by inexperienced surgeons or from concomitant small vessel disease in patients with operable proximal disease.[19–21]

Table 2 Complications of pulmonary endarterectomy

Complication	Mechanism
Neurological complications	Brain ischemia due to deep hypothermic circulatory arrest
Persistent pulmonary artery hypertension	Inadequate or incomplete endarterectomy
Pulmonary hemorrhage	Pulmonary vessels injury
Reperfusion lung injury	Abrupt normalization of extracellular osmotic pressure in endarterectomized parts of lungs (up to 10% of cases)
Arrhythmias, atelectasis, wound infection, and delirium are the other complications	

Technique of Pulmonary Endarterectomy

This procedure is done via median sternotomy and requires cardiopulmonary bypass and deep hypothermia (core temperature 18–20°C). Pulmonary artery is exposed, and the plane of dissection is identified. The plane of dissection is between the intimal and medial layer, but it is usually distorted. The endarterectomy is continued into the lobar, segmental, and subsegmental branches, which requires a bloodless field. The circulatory arrest time is usually 20 minutes but the cooling and rewarming each may take 30 to 75 minutes.[22,23] Operating for distal disease is more challenging than the proximal disease. Surgery also has the theoretical advantage of halting the progression of disease and irreversible changes in small vessels. There is also improvement in functional class, right ventricular remodeling during the follow-up.[24] There is no cutoff for PVR, which is contraindication for surgery, although very high values (above 1,000 dynes/s/cm^{-5}) are associated with higher perioperative mortality. Two important exceptions are advanced pulmonary emphysema and severe left ventricular systolic dysfunction.[25] The 5- and 10-year survival rates are 82 and 75%, respectively, as reported by the UC San Diego group.[26,27]

Balloon Pulmonary Angioplasty

BPA method for treatment of CTEPH has been redefined technically over the last decade. The first case of BPA was reported in 1988 and the first series of 18 patients was published by Feinstein et al[28] in 2001. In 2015, European Society of Cardiology recommended BPA for inoperable patients of CTEPH with a Class 2b recommendation.[29]

Procedural Details

The procedure is done under mild sedation. Venous access is taken through either femoral vein (preferred) or internal jugular vein. A long sheath is used for support and minimizing the catheter movement with respiration. There is no dedicated hardware for this procedure and most of the hardware is taken from coronary field. The baseline hemodynamics are measured with a Swan–Ganz catheter. Coronary guide catheters like Judkins right, multipurpose, or hockey stick are used depending on location of lesion. Workhorse coronary guide wires are used for crossing the lesion, whereas the polymer jacketed wires are generally avoided to reduce the risk of wire-induced injury. Rapid exchange semicompliant balloons with diameter typically ranging from 2 to 5 mm are used to dilate the lesions, although balloons of diameter of up to 14 mm have been used in main pulmonary artery. Noncompliant and cutting balloons are generally avoided and used only for recalcitrant lesions.[30–32] BPA mainly targets distal lesions in segmental and subsegmental vasculature down to distal pulmonary arteries of 3 to 5 mm diameter. Navvus microcatheter or pressure wire scan be used for pressure measurement distal to lesion to achieve a distal pressure of 0.75 to 0.80 of proximal pressure where mean pulmonary artery pressure (mPAP) is <35 mmHg. Anticoagulation is done with heparin

to achieve the activated clotting time around 200 to 250 s. Angiography is done with diluted saline (50:50) and the lesions are identified.

Ventilation perfusion scan assessment will guide to prioritize the underperfused areas. The lower lobe vessels (right lung > left lung) are prioritized as this will have greater physiological impact. On an average, two to six sessions are required for each patient, with two to five segments are treated per session (one BPA procedure each lung as per UC San Diego protocol). Procedure is also concluded if the total contrast volume exceeds 400 mL or radiation dose of 2 Gy is reached. Patients are monitored for 24 hours after the procedure and started on heparin to provide the bridge for oral anticoagulation. The interval between two sessions can vary from 1 week to a month. In severe PAH, during the initial sessions simpler nonocclusive lesions are targeted to optimize the hemodynamics and reduce the risk of complications.[30,31]

Patient Selection for Balloon Pulmonary Angioplasty

There have not been any fix criteria for patient selection undergoing BPA and the selection for this procedure is complex and multifactorial. Most of the patients who underwent BPA had severe vascular disease, comorbidities, and rejection for PEA. Anatomically subsegmental disease (Level 4) is more amenable to BPA. Assessment is made on degree and level of vascular obstruction, hemodynamics, and symptoms. A new ongoing registry is comparing BPA versus PEA in proximal disease. Another role of BPA will be for bridging sick patients for PEA in whom initial surgical risk is very high. BPA is also effective in post-PEA patients who have recurrence of disease. The subset of patients with distal diffuse disease will have only option of medical therapy.[32–35] BPA contraindications include history of iodinated contrast allergy, although gadolinium contrast media may be considered as an alternative and in patients who are unable to undergo RHC. Relative contraindications for BPA include active infectious diseases, severe hepatic or renal dysfunction, severe chronic obstructive pulmonary disease, bleeding or clotting tendency, poorly controlled or uncontrolled diabetes, and hypertension.[35–37]

Lesion Selection for Balloon Pulmonary Angioplasty

Compared with the left, the right lung is given priority owing to easier manipulation, and more blood flow and lesion distribution. Due to the effect of gravity, the blood flow in the inferior lobe is physiologically larger than in the superior and middle lungs; therefore, targeting lesions in the lower lobes may enable more prevalent improvements in pulmonary hemodynamics.[30,38] Chronic subtotal/total occlusion and tortuous lesions have high complication rates (nearly 2% for webs or bands; 15.5% for subtotal occlusion, 6% for total occlusion, and 43.2% for tortuous lesions) and low success rates (nearly 100% for webs or bands, 86.5% for subtotal occlusion, and 52.2% for total occlusion, and 63.6% for tortuous lesions). Moreover, high mPAP before BPA is an independent predictor of the need for mechanical ventilation once lung injury occurs after BPA. Thus, priority selection of target lesions is as follows: right lung > left lung, inferior lobe > superior or middle lobes, webs or bands > subtotal occlusion > chronic total occlusion > tortuous lesions.[38,39]

Imaging in Balloon Pulmonary Angioplasty

Optical coherence tomography (OCT) is a promising diagnostic method, which can help characterize lesion morphology enabling better lesion selection and treatment. OCT characterizes lesions into lesion with septum, multihole with thin wall, multihole with thick wall, and monohole types, which can help identify lesions more amenable to BPA, although dye, radiation, and cost constraint limit their use. Studies have shown that patient with thin wall responds better to BPA.[40]

Intravascular ultrasound (IVUS) can provide useful information regarding vessel diameter for selection of appropriate balloon sizing, whereas virtual histology IVUS can characterize lesion composition in stenotic lesions amenable to BPA.[41]

Complications of Balloon Pulmonary Angioplasty

Two major complications of BPA leading to periprocedural mortality are reperfusion pulmonary edema and vascular injury rarely perforation/rupture.[30] Complications of BPA can be either vascular access related, contrast or radiation related, or procedure related. Procedural complications like wire perforations, rupture, dissection, or reperfusion injury. Ogo et al proposed methods to avoid vascular injury, which include proper wire positioning, knuckle wire technique, avoiding pouch lesions without distal runoff, and under or proportionate balloon sizing.[14]

Outcomes

Inoperable CTEPH patients can benefit from BPA. Optimal CTEPH treatment requires a multidisciplinary team approach considering PEA, medical therapy, and BPA. Experienced canters from have shown 50 to 60% reduction in PVR after BPA, which are maintained at 1 year. Long-term survival is reported up to 7 years after mean follow-up of 51 months. Despite the procedure, up to one-fourth of patients had persistent symptoms. There are no end points or universal definition of procedural success after BPA.[42,43] Riociguat versus balloon pulmonary angioplasty in nonoperable CTEPH (RACE) trial included 124 patients randomized 1:1 to BPA versus riociguat. After 6-month PVR fell in 60% in BPA patients and 32% in medical therapy group ($p < 0.001$), although the adverse events were significantly more common in BPA group (50 vs. 26%).[44] Long-term results after BPA are available 8 years after the procedure. Safety and efficacy of BPA correlate with center experience. Vascular injury rather than reperfusion pulmonary edema is the likely cause of any severity of lung injury after BPA. Similar to PEA, proper training in a high-volume center is critical for BPA.

Medical Management

CTEPH represents the later stage consequence of at least one or more unresolved episodes of acute PE. Early initiation of

Table 3 Randomized clinical trials of pharmacotherapy in patients with chronic thromboembolic pulmonary hypertension

Medication	Approval for CTEPH	Medication class	Study	Participants	Outcome
Riociguat	Yes (FDA)	Soluble guanylate cyclase stimulator	CHEST-1[45]CHEST-2 (open label extension of CHEST-1)	261	Significant improvement in PVR and 6-MWD at 16 weeks
Bosentan	No	Dual endothelin receptor antagonist	BENEFiT[48]	157	Significant improvement in PVR, no significant improvement in 6-MWD at 16 weeks
Macitentan	No	Dual endothelin receptor antagonist	MERIT-1[47]	80	Significant improvement in PVR and 6-MWD at 16 weeks
Ambrisentan	No	Selective endothelin receptor antagonist	Amber-1[51]	33	Trend toward improvement in 6-MWD and PVR at 16 weeks
Sildenafil	No	Phosphodiesterase-5 inhibitor	Suntharalingam et al[52]	19	Significant improvement in PVR, no significant improvement in 6-MWD at 12 weeks
Treprostinil (subcutaneous)	Yes (EMA)	Prostacyclin analog	CTREPH[46]	105	Significant improvement in PVR and 6-MWD at 24 weeks
Inhaled iloprost	No	Prostacyclin analog	AIR Trial[53]	203	Significant improvement in PVR and 6-MWD at 12 weeks
Selexipag	No	Oral selective IP prostacyclin-receptor agonist	Kinoshita et al[49]	39	Significant improvement in PVR and hemodynamics

Abbreviations: 6-MWD, 6-minute walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; EMA, European Medicines Agency; FDA, Food and Drug Administration; PVR, pulmonary vascular resistance.

anticoagulation is strongly recommended. Historically, vitamin K antagonists have been widely used in these patients. However, recent data indicate a shift toward direct oral anticoagulants, due to lower bleeding risk with these drugs as seen in patients of venous thrombosis, despite lack of data on the safety and efficacy in this patient population. Therapeutic anticoagulation must be continued for long term, regardless of whether patients are treated surgically or medically.

Most of the PAH-targeted therapies have been tried in CTEPH, but till now riociguat, a soluble guanylate cyclase stimulator, was only approved. Recently, subcutaneous treprostinil has been approved by the European Medical Agency. CHEST-1 trial was a multicenter double-blind randomized trial of 261 patients either inoperable CTEPH or persistent symptoms following thromboembolism. There was significant improvement in 6-minute walk distance of 39 m in riociguat group, reduction in PVR, NT-Pro BNP levels, and improvement in functional class.[45] Subcutaneous treprostinil was found useful in CTREPH trial, which showed significant improvement in 6-minute walk test and functional class.[46]

Recently, endothelin receptor antagonist macitentan was also studied in Phase 2 trial (MERIT trial) in 80 patients with inoperable CTEPH. There was reduction of PVR in the macitentan-treated group and increase in 6-minute walk distance. However, this trial was smaller in size and many patients were on background PDE-5 inhibitors or prostanoids.[47] Bosentan was used in BENEFIT trial (bosentan effects in inoperable forms of CTEPH), which also showed slight decrease in PVR but no improvement in 6-minute walk distance. The subgroups of patients treated with PAH therapies had no advantage but a significant delay in referral for surgery.[48]

Selexipag, an oral selective IP prostacyclin-receptor agonist approved for pulmonary arterial hypertension, is a potential treatment option for CTEPH. In a recent study selexipag significantly improved PVR and other hemodynamic variables in patients with CTEPH, although exercise capacity remained unchanged (►**Table 3**).[49]

Intervention versus Medical Management in Inoperable Treatment

BPA and riociguat both have been used in inoperable CTEPH. Multicenter randomized controlled BPA is an open randomized trial comparing BPA and riociguat in inoperable CTEPH patients in the World Health Organization functional Class 2 and 3. A total of 61 patients were enrolled out of which 32 were randomized to BPA group. Patients in BPA group underwent a total of 147 procedures (4.7 procedures per patient) over a period of 4 months.[50] Patients in riociguat group were started on dose of 1 mg thrice daily and increment of dose was done by 0.5 mg every 2 weeks to a maximum of 2.5 mg thrice daily in 4 months. Over the next 1 year, mean PAP improved by 16.3 mmHg in BPA group versus 7 mmHg in riociguat group, although there were some procedure-related complications in the intervention group.

Conclusion

CTEPH is the only curable form of PH with PEA, although all the patients of CTEPH are not amenable for PEA. A hybrid or a

bridging approach might be beneficial for patients who are not amenable for PEA. One-third of the patients who have persistent symptoms after PEA can be benefitted by BPA or medical management. Few patients who not amenable to PEA initially can be bridged with BPA or medical therapy to undergo pulmonary endarterectomy. Most of the patients who have undergone BPA were surgical reject for PEA so there is a need for larger data comparing these two treatment modalities. In future, we need to characterize patients who can be benefitted either with BPA or medical therapy or a hybrid approach for the best of outcome.

Conflict of Interest
None declared.

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