Chronic thromboembolic pulmonary hypertension: a review

Cheryl Zhiya <u>*Chong*</u>[1], MBBS, *Edgar Lik Wui* <u>*Tay*</u>[1], MBBS, MRCP, *Ching Hui* <u>*Sia*</u>[1], MBBS, *Kian Keong* <u>*Poh*</u>[1], MBBChir, MA

ABSTRACT Chronic thromboembolic pulmonary hypertension (CTEPH) is a unique form of pulmonary hypertension resulting from obstruction of the pulmonary artery by fibrotic thromboembolic material, usually initiated by recurrent or incomplete resolution of pulmonary embolism. This distinct form of pulmonary hypertension is classified under Group 4 of the World Health Organization classification. Further investigations are usually initiated, with transthoracic echocardiography followed by right heart catheterisation and pulmonary angiography as the gold standard. Definitive treatment is usually in the form of surgical pulmonary endarterectomy. Inoperable CTEPH is medically treated with pharmacological agents such as phosphodiesterase Type 5 inhibitors, endothelin receptor antagonists, soluble guanylate cyclase stimulators and prostacyclin. Recent developments have made balloon pulmonary angioplasty a viable option as well.

Keywords: chronic thromboembolic pulmonary hypertension, pulmonary embolism, pulmonary endarterectomy, pulmonary hypertension, thromboemboli

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) usually manifests in patients due to recurrent or incomplete resolution of pulmonary embolism (PE). It is caused by the fibrotic transformation of pulmonary artery thromboemboli, resulting in chronic obstruction in the macroscopic pulmonary arteries, as well as vascular remodelling in the microvasculature of the pulmonary system.[1] The true incidence of CTEPH is likely to be underestimated by studies that only follow patients after a PE,[2] but is estimated to be 1%–5% among survivors of acute PE.[3,4]

CTEPH could represent the progression of long-standing and unresolved PE. In the early stages of the disease, patients may not have resting pulmonary hypertension (known as chronic thromboembolic disease [CTED]), but often have exercise intolerance. Exercise intolerance associated with exertional chest pain could be attributed to increased dead space ventilation. This is also often related to pulmonary vascular obstruction and hence limitation of maximal cardiac output upon exertion. Thus, in patients with a past medical history of PE, symptoms such as exercise intolerance and exertional chest pain should be evaluated.[5,6]

RISK FACTORS

Risk factors for CTEPH are often related to those of PE (Box 1). In particular, prior deep vein thrombosis (DVT) and PE have been established to be risk factors for CTEPH.[7-9] This is especially important, as CTEPH could be an alternative natural history of a condition in cases where there is limited resolution of thromboemboli and pulmonary artery obstruction leading to pulmonary hypertension (Fig. 1).[7,10]

While CTEPH is more likely to develop in patients with a past medical history of PE or DVT, up to 25% of patients diagnosed with CTEPH do not have a documented history of PE and up to 45% do not have a history of DVT.[11]

PATHOPHYSIOLOGY

Clinical features

Patients who develop CTEPH generally have an asymptomatic or latent phase. They may present with shortness of breath, chest discomfort and increased fatigability. Some patients present late, only when there are signs or symptoms suggestive of right ventricular failure such as peripheral oedema, ascites or syncope.[12]

Physical examination findings are those of pulmonary hypertension. These include discernible right ventricular impulse, a split second heart sound with accentuation of the pulmonic component, varying degrees of tricuspid regurgitation and a right ventricular S4 gallop. In advanced stages, there may be signs of right heart failure, including jugular venous distension, peripheral oedema, hepatomegaly, ascites and a right-sided S3 (third heart sound).[13] However, it must also be noted that most physical examination findings may not be unique to CTEPH and are also found in other forms of pulmonary hypertension. Fig. 1 shows the pathophysiology of CTEPH.

Diagnosis

It should be noted that all patients with pulmonary hypertension should be assessed for CTEPH even in the absence of prior PE. Echocardiography is often the first modality to detect pulmonary hypertension in the evaluation of a breathless patient. Based on the European Society of Cardiology/European Respiratory Society (ESC/ERS) 2015 guidelines for the diagnosis and treatment of pulmonary hypertension, peak tricuspid regurgitation velocity and the presence of other echocardiographic pulmonary hypertension signs (Box 2) help to suggest the probability of

[1]Department of Cardiology, National University Heart Centre Singapore, Singapore

Correspondence: Dr Cheryl Chong Zhiya, House Officer, Department of Cardiology, National University Heart Centre Singapore, National University Health System, Tower Block Level 9, 1E Kent Ridge Road, Singapore 119228. cherylchong@u.nus.edu
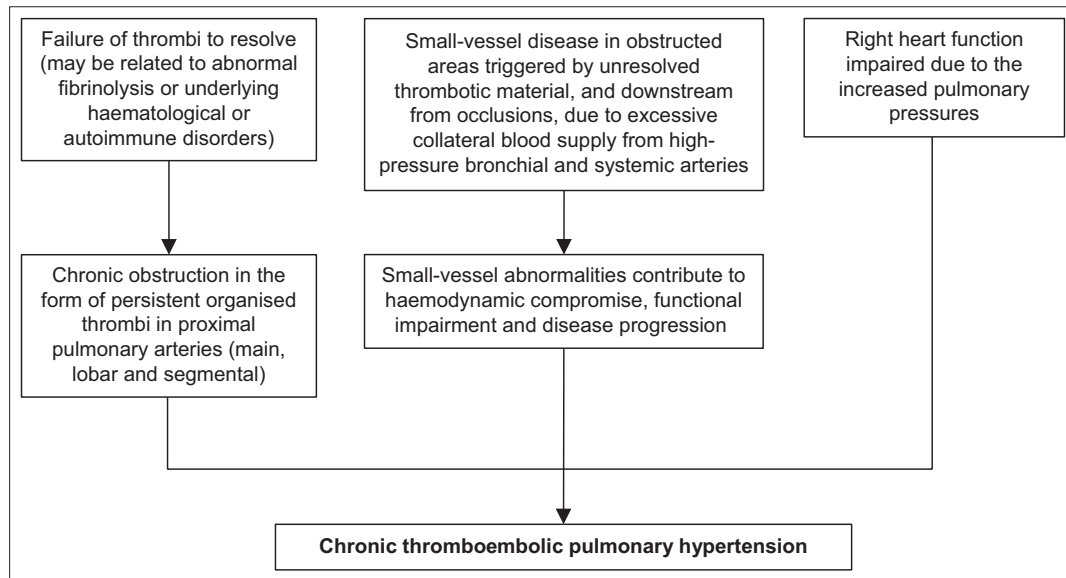
Fig. 1 Diagram shows the pathophysiology of chronic thromboembolic pulmonary hypertension.

Box 1. Risk factors for development of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism (PE):

Haemostatic factors
- Elevated levels of factor VIII
- Elevated levels of phospholipid antibodies
- Intrinsic abnormalities in fibrinogen

Medical conditions
- Splenectomy
- Cancer
- Ventriculoatrial shunt
- Chronic inflammatory disease
- Antiphospholipid antibodies
- Hypothyroidism
- Higher pulmonary artery pressures at time of diagnosis of acute PE

Factors related to PE
- Large PE
- Idiopathic aetiology of PE
- Recurrent PE

Box 2. The European Society of Cardiology/European Respiratory Society 2015 guidelines for the diagnosis and treatment of pulmonary hypertension:

Ventricles
- Right ventricle/left ventricle basal diameter ratio > 1.0
- Flattening of interventricular septum

Pulmonary artery
- Right ventricular outflow Doppler acceleration time < 105 ms
- Mid-systolic notching
- Early diastolic pulmonary regurgitation velocity > 2.2 m/s
- Pulmonary artery diameter > 25 mm

Inferior vena cava and right atrium
- Inferior cava diameter > 21 mm with decreased inspiratory collapse
- Right atrial area (end-systole) >18 cm^2

pulmonary hypertension. Right ventricular function can also be assessed, and the presence of pericardial effusion or an abnormal right atrial size would suggest a poorer prognosis.[14]

A ventilation/perfusion (V/Q) lung scan, which has higher sensitivity than conventional computed tomography pulmonary angiography (CTPA),[15] should be performed to diagnose CTED. There are several different published criteria for the diagnosis of pulmonary hypertension based on the degree and extent of mismatch between ventilation and perfusion imaging. However, V/Q scans are not available in most centres. CTPA is commonly used in acute PE, but may be less sensitive in detecting distal disease compared to V/Q scans. Signs of CTEPH seen on CTPA include the presence of dilated pulmonary arteries and right heart chambers. Newer technologies, such as dual-energy CTPA, are increasingly shown to have high sensitivity in the detection of CTEPH. These newer technologies may hence become more commonly used.

The diagnosis of CTEPH is confirmed with invasive right heart catheterisation and catheter pulmonary angiography.[14] Catheter pulmonary angiography is the current gold standard for assessment of pulmonary vessels. Angiography findings include pulmonary arterial pouching, webs or bands, intimal irregularities, vascular narrowing and obstruction.[16]

The diagnosis of CTEPH is based on the following findings obtained after at least three months of effective anticoagulation: (a) mean pulmonary artery pressure (PAP) ≥ 25 mmHg, (b) pulmonary artery wedge pressure ≤ 15 mmHg and (c) elevated pulmonary vascular resistance (PVR) > 3 wood units, confirmed by right heart catheterisation.[17] The diagnostic algorithm for CTEPH is shown in Fig. 2.

Management
CTEPH is the only type of pulmonary hypertension that is amenable to surgical treatment and potentially curable. Pulmonary endarterectomy (PEA) is the procedure of choice for CTEPH,[18] offering the best chance of symptomatic and prognostic improvement in eligible patients with excellent long-
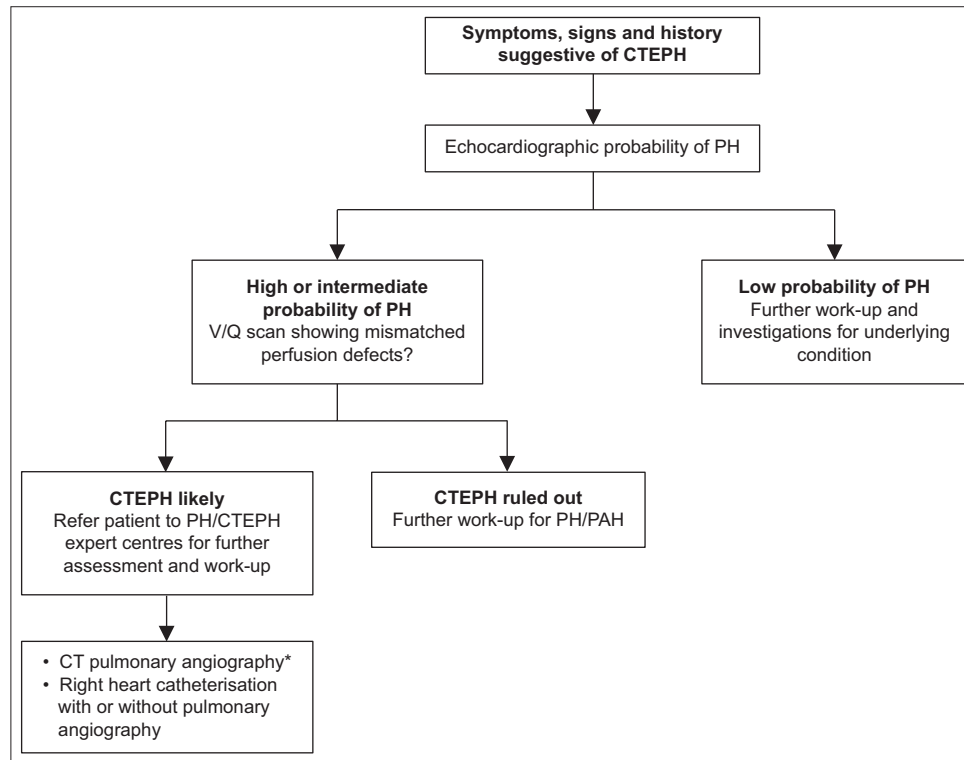
Fig. 2 Flowchart shows the diagnostic algorithm of chronic thromboembolic pulmonary hypertension (CTEPH). *CT pulmonary angiography alone may miss the diagnosis of chronic thromboembolic pulmonary hypertension. CT: computed tomography; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; V/Q: ventilation/perfusion (Adapted from 2015 ESC/ERS Guidelines, Fig. 3).

Box 3. Reasons for non-eligibility for surgery:
Patient factor
- Age

Comorbidities
- Severe lung disease
- Conditions affecting the left ventricle of the heart
- Diabetes mellitus
- Hypertension
- Hyperlipidaemia
- Coronary heart disease
- Asthma
- Atrial fibrillation

Anatomical reasons
- Distal thromboembolism
- Inaccessible thromboembolism

Disease factor
- Imbalance between peripheral vascular resistance and amount of accessible occlusions

term results in expert centres.[19] The ESC/ERS guidelines[20] also recommend PEA as the treatment of choice for CTEPH patients. The guidelines recognise that operability is multifactorial, and not all patients will be eligible for PEA (Box 3). When assessing the patient's operability, factors such as advanced age, comorbidities, imbalances between increased PVR and the number of accessible occlusions, and poor general condition need to be considered.[21] Operability is dependent on the severity of the symptoms, the anatomy of the disease (how distal lesions are) and pre-existing comorbidities. This is assessed by the CTEPH team, which comprises cardiologists, surgeons, respiratory physicians and anaesthetists.[12] Until recently, PEA remained the only available treatment. However, significant progress has been made in medical treatment and balloon pulmonary angioplasty.

SURGICAL MANAGEMENT: PULMONARY ENDARTERECTOMY
Goals
The main haemodynamic goal is to alleviate right ventricular compromise caused by high PVR. Key respiratory objectives include improving V/Q matching and treating dyspnoea. Treatment is also meant to prevent progressive right ventricular dysfunction and secondary arteriopathy in the remaining patent vessels.[22]

Procedure
PEA involves the removal of organised and incorporated fibrous obstructive tissue from the pulmonary arteries during circulatory arrest under deep hypothermia. After proximal intrapericardial pulmonary artery incision, the correct endarterectomy plane is established and circumferentially followed down to the lobar, segmental, and sometimes subsegmental pulmonary artery branches in each lobe. Completion of the endarterectomy procedure in one lung is usually possible within a 15–20-minute period of deep hypothermic circulatory arrest (providing a bloodless field for visualisation and surgery). This is followed by reperfusion and another period of circulatory arrest for the endarterectomy on the contralateral side. During the rewarming

Table I. Postoperative complications of PEA.

Complication	Cause
Pulmonary haemorrhage	Injury to pulmonary vessels
Neurological complications	Brain ischaemia
Persistent pulmonary artery hypertension	• Inadequate endarterectomy • Significant secondary vasculopathy
Reperfusion oedema	Abrupt normalisation of extracellular osmotic pressure in endarterectomised parts of lung

Box 4. Complications of balloon pulmonary angioplasty:[38-40]

During procedure:
- Vessel dissection
- Vessel rupture
- Contrast extravasation and leakage into bronchi
- Wire injury

After procedure:
- Reperfusion oedema
- Pulmonary artery perforation
- Haemorrhagic pleural effusions
- Haemoptysis

period, additional cardiac procedures can be performed after arteriotomy closure if required, depending on the patient's clinical status.

The outcomes with regard to functional status, quality of life, haemodynamics, right ventricular function, and gas exchange make PEA the ideal treatment. After surgery, significant and durable decreases in PAP and PVR are observed in the majority of patients. Cardiac output is increased and right heart function is improved.[23] PEA was also shown to reduce mortality compared to medical management.[24]

Preoperative and postoperative concerns

Preoperative haemodynamic severity and the site of anatomic obstruction are believed to be key predictors of the postoperative outcome of PEA. Patients who benefit from PEA are typically those with fewer distal thrombi, mean PAPs below 38 mmHg and PVR below 425 dynes/s/cm^5. Mean PAP of $\geq$ 38 mmHg and PVR $\geq$ 425 dynes/s/cm^5 at reassessment was correlated with worse long-term survival.[25] Outcomes are also worse in patients with distal thrombi.[26]

Due to the complications of PEA, mortality rates reported for this procedure range from 4% to 24%.[23] However, in recent years, in-hospital mortality rates have been less than 5% for experienced centres with high volumes of PEA cases.[1] Adequate postoperative care is therefore essential. Table I shows the postoperative complications of PEA.[27-29]

Persistent pulmonary hypertension after pulmonary endarterectomy

Almost one-third of patients who undergo PEA may have persistent or residual pulmonary hypertension despite having undergone a successful procedure.[2,30] 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.[21] The precise incidence is unclear, as right heart catheterisation is not routinely performed in all patients after PEA. There is also no agreed definition of persistent pulmonary hypertension. This remains the most important cause of early postoperative morbidity and mortality. In the international CTEPH registry, 16.7% of patients had persistent pulmonary hypertension, and this complication was associated with higher early mortality.[31] Furthermore, persistent/recurrent CTEPH following surgery

occurs in up to 35% of patients. There is hence a strong rationale for consideration of targeted therapies, which is supported by the current guidelines.[32] Therapeutic anticoagulation is also important in preventing repeat embolic episodes and recurrence of pulmonary hypertension or CTEPH.

BALLOON PULMONARY ANGIOPLASTY: AN ALTERNATIVE TREATMENT

Balloon pulmonary angioplasty (BPA) has also emerged recently as a promising treatment modality.[33] It is interventional, involving the insertion of a balloon catheter into pulmonary vessels to dilate pulmonary stenoses. Since 1988, BPA has been performed for patients with CTEPH who are ineligible for surgical management of PEA.[34]

Initial studies showed that BPA could potentially improve haemodynamics and symptoms. BPA, however, was initially associated with high complication rates (Box 4).[35-40] In recent years, Japanese colleges have revolutionised procedural techniques and demonstrated that BPA can be performed with improved safety while preserving good outcomes.[26] One study of 424 BPA sessions in 84 consecutive patients had a five-year survival rate of 98.4% with no periprocedural death. In 92% of patients, BPA treatment significantly improved mean PAP, PVR and six-minute walk distance, and improvements persisted throughout the follow-up period.[38]

Recent studies done with regard to BPA showed consistently beneficial effects on haemodynamics, symptoms, six-minute walk distance, exercise capacity and right ventricular function. Hence, BPA should be an option for patients with inoperable CTEPH or perhaps hybrid treatment (in combination with PEA) for patients with both proximal and distal vessel disease.[35-37]

MEDICAL MANAGEMENT

An estimated 20%–40% of all CTEPH patients are deemed inoperable.[41] Inoperable patients or those with post-intervention pulmonary hypertension are treated with pulmonary hypertension-targeted medical therapy.[35] Medical therapy should be considered in patients with inoperable disease, but should not be a substitute for PEA in appropriate surgical candidates. Standard medical treatment of CTEPH consists of diuretics, oxygen therapy and lifelong anticoagulant therapy.

Long-term anticoagulation therapy

Currently, anticoagulation is considered part of standard management for CTEPH. Warfarin is used most frequently. Direct oral anticoagulants (DOACs) such as rivaroxaban, dabigatran and apixaban have been approved for their viability and efficacy in venous thromboembolic disease. The main advantages of DOACs over traditional anticoagulants such as warfarin include a lower overall mortality rate, mainly due to fewer episodes of fatal intracranial bleeding;[36] and the lack of the need for blood monitoring. However, DOACs are not a panacea due to the contraindication in patients with significant renal impairment or obesity.[37]

The ideal anticoagulant remains elusive. A study on rivaroxaban proved that it was superior to the combination of unfractionated or low-molecular-weight heparins with warfarin.[42] Other non-randomised studies comparing warfarin to DOACs in patients with CTEPH showed heterogeneous results.[43-46]

Specific medical treatment options for CTEPH include phosphodiesterase Type 5 inhibitors, endothelin receptor antagonists, soluble guanylate cyclase stimulators and prostacyclin.[47] Pulmonary hypertension-targeted therapy should only be prescribed by tertiary centres with CTEPH expertise. Choice of medication depends on cost, availability, safety and the functional class of the patient. At present, medical treatment is recommended for patients who are deemed inoperable, such as patients with PEA, or have persistent pulmonary hypertension after PEA surgery.

Supportive therapy is important as well. Oxygen therapy has been shown to reduce PVR in patients with pulmonary arterial hypertension, but no data suggests any benefits of long-term oxygen therapy in CTEPH. Current guidelines recommend oxygen therapy if arterial oxygen partial pressure is consistently less than 60 mmHg.[45]

COMPARISON OF PHARMACOLOGICAL THERAPIES

The various types of pharmacological therapy for the management of CTEPH are shown and compared in Table II.[27,28,32,36,41,48-56]

Riociguat

Currently, riociguat has the strongest evidence of effective medical management specific to CTEPH.[28] Riociguat is a member of a class of drugs known as soluble guanylate cyclase stimulators, which cause vasodilation and other disease-modifying effects such as anti-fibrotic, anti-proliferative and anti-inflammatory activity.[29]

Phosphodiesterase Type 5 inhibitor: sildenafil

Sildenafil is still a preferred option for medical therapy. Sildenafil inhibits phosphodiesterase Type 5, an enzyme that metabolises cyclic guanosine monophosphate, thereby enhancing the cyclic guanosine monophosphate-mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lungs.[57]

Endothelin receptor antagonists

The endothelin pathway is involved in the pathology of chronic thrombus reorganisation leading to CTEPH, hence supporting the use of endothelin receptor antagonists in the treatment of CTEPH.[46,58] In the MERIT-1 (Macitentan for the Treatment of Inoperable CTEPH) study, macitentan was shown to significantly improve PVR in patients with inoperable CTEPH and was well tolerated.

Prostacyclin

CTEPH results from non-resolving pulmonary thromboemboli that are resistant to plasmatic anticoagulation. One possibility is that secondary pulmonary arteriopathy is accompanying major vessel obstruction, making CTEPH a potential target for prostacyclin vasodilator therapy.[48]

Sildenafil versus riociguat

A retrospective study (Table II) supports the benefits of riociguat over sildenafil in treating CTEPH. The replacement of sildenafil with riociguat in patients with inoperable or persistent CTEPH may improve pulmonary haemodynamics and functional capacity.[59] However, riociguat is still not well established to demonstrate improvement in patients who are deteriorating and have inoperable CTEPH.[57]

ASIAN PERSPECTIVE AND MANAGEMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION IN SINGAPORE

In most Asian countries, CTEPH remains underdiagnosed due to a lack of trained CTEPH physicians/teams and minimal patient awareness of this condition.[60] Limited access to radioisotope V/Q imaging may also contribute to the difficulty in diagnosing CTEPH.[61] There are few publications relating to CTEPH in Asia. The rate of CTEPH in patients with a history of previous PE was estimated to be 14% in Japan. This is higher than in other published registries.[58] A study in 2017 showed that the crude annual incidence of diagnosed PE and crude annual full (i.e. including both diagnosed and undiagnosed) incidence of CTEPH were 6.7 and 1.9 per 100,000 population in Japan, respectively.[29] There is currently no Asian registry of CTEPH, and we feel that a multicentre registry should be initiated to study this condition in detail and understand if there are inter-ethnic differences in the clinical presentation and response to treatment.

CTEPH patients in Singapore are currently privileged to have access to surgical management (i.e. PEA), BPA and medical management. In terms of medical treatment, riociguat, bosentan, ambrisentan and sildenafil are available to our patients. There is currently a collaboration between the two national heart centres to study patients with pulmonary arterial hypertension, including those with CTEPH, and we hope that this will shed light on this disease and provide better future care for these patients.

Table II. Comparison of pharmacological therapy for chronic thromboembolic pulmonary hypertension (CTEPH).

Drug	Author, yr	Study	Results
ERA – macitentan	Ghofrani et al, 2017[50]	Macitentan for the treatment of inoperable CTEPH (MERIT-1): multicentre, Phase 2, randomised, double-blind, placebo-controlled study	Wk 16: geometric mean PVR decreased to 73.0% of baseline in the macitentan group and to 87.2% in the placebo group.
ERA – bosentan	Jais et al, 2008[56]	Bosentan for treatment of inoperable CTEPH: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension): randomised, placebo-controlled trial	Significant treatment effect of bosentan over placebo on PVR was demonstrated: −24.1% of baseline. Total pulmonary resistance (TE: −193 dynes/s/cm^5 to −104 dynes/s/cm^5) and cardiac index (TE: 0.3 L/min/m^2 to 0.46 L/min/m^2). Mean treatment effect on 6MWD was +2.2 m.
ERA – bosentan	Mitsakis et al, 2017[27]	Effects of ERA bosentan on myocardial glucose metabolism in PAH and CTEPH	2 NYHA class III patients clinically responded by 6MWD, NT-proBNP and cardiac echocardiography. RV/LV uptake ratio decreased after therapy initiation towards normalisation with a NT-proBNP decrease and tricuspid annular plane systolic excursion normalisation.
ERA – ambrisentan	Escribano-Subias et al, 2019[55]	Ambrisentan for treatment of inoperable CTEPH	Wk 16: mean change from baseline in 6MWD was 28.3 ± 41.7 m with ambrisentan and 6.8 ±67.5 m in the placebo group. Geometric mean NT-proBNP concentration (% baseline) = −29.4% vs. +14.1%; and mean PVR = −212.5 ± 392.8 dynes/s/cm^5 vs. −108.5 ± 51.3 dynes/s/cm^5.
Phosphodiesterase Type 5 inhibitor	Suntharalingam et al, 2008[41]	Long-term use of sildenafil in inoperable CTEPH: double-blind, placebo-controlled pilot study	17 patients demonstrated significant improvements in 6MWD, activity and symptom components of QOL, cardiac index, PVR and NT-proBNP.
Soluble guanylate cyclase stimulators – riociguat	Ghofrani et al, 2010[49]	Riociguat for CTEPH and PAH: a Phase 2 study: 12-week, multicentre, open-label, uncontrolled Phase 2 study	Median 6MWD increased in patients with CTEPH and PAH. PVR was significantly reduced.
Soluble guanylate cyclase stimulators – riociguat	Ghofrani et al and CHEST-1 Study Group, 2013[53]	Riociguat for the treatment of CTEPH	Riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with CTEPH. 6MWD distance increased by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group. Riociguat was also associated with significant improvements in NT-proBNP level (p < 0.001) and WHO functional class (p = 0.003).
Soluble guanylate cyclase stimulators – riociguat	Simonneau et al, 2015[54]	Riociguat for the treatment of CTEPH: a long-term extension study (CHEST-2)	Long-term riociguat had a favourable benefit-risk profile and apparently showed sustained benefits in exercise and functional capacity for up to one year. Improvements in 6MWD and WHO functional class observed in CHEST-1 persisted for up to one year in CHEST-2. In the observed population at one year, mean ± SD 6MWD changed by +51 ± 62 m (n = 172) vs. CHEST-1 baseline (n = 237), and WHO functional class improved, stabilised and worsened in 47, 50 and 3% of patients (n = 176), respectively, versus CHEST-1 baseline (n = 236).
Soluble guanylate cyclase stimulators – riociguat	Halank et al, 2017[51]	Riociguat for PAH and CTEPH: results from a Phase 2 long-term extension study	68 patients (inoperable CTEPH, n = 41; PAH, n = 27) Month 48: 6MWD increased from baseline by 69 ± 105 m, WHO functional class improved vs. baseline in 50% of patients. Starting new PAH treatment was the most frequent clinical worsening event.
Prostacyclins	Skoro-Sajer et al, 2007[48]	Treprostinil for severe inoperable CTEPH	Significant improvement in 6MWD (P ¼ 0.01), WHO functional class (P ¼ 0.001), NT-proBNP plasma levels, cardiac outputs and PVR after 19.0 ± 6.3 mth. Long-term survival was significantly better than in controls.
Prostacyclin	2021	Study to find out if selexipag is effective and safe in patients with CTEPH when the disease is inoperable or persistent/recurrent after surgery (SELECT)	Trial was terminated early due to futility.

6MWD: six-minute walk distance; ERA: endothelin receptor antagonist; LV: left ventricle; NT-proBNP: N-terminal-pro hormone B-type natriuretic peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; QOL: quality of life; RV: right ventricle; SD: standard deviation; WHO: World Health Organization

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