INTERNATIONAL JOURNAL OF ALTERNATIVE AND CONTEMPORARY THERAPY

Chronic Thromboembolic Pulmonary Hypertension: From Pathogenesis to the Choice of Treatment Strategy

G. I. Sunnatova[1], L. Kh. Tashinova[1], G. T. Madjidova[2]
[1]Department of Therapeutic Disciplines, Samarkand Zarmed University
[2]Department of Internal Diseases and Cardiology No. 2, Samarkand State Medical University
Corresponding author: gulbaxor1965@icloud.com

Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive form of pulmonary hypertension caused by persistent organized thromboembolic obstruction and secondary remodeling of the pulmonary microcirculation. This narrative review summarizes the mechanisms that link unresolved thrombi to increased pulmonary vascular resistance and evaluates their implications for contemporary treatment selection. Evidence from clinical guidelines, expert statements, randomized trials, registries, and major observational studies was organized around pathobiology, diagnostic assessment, pulmonary endarterectomy, balloon pulmonary angioplasty, targeted pharmacotherapy, and multimodal care. The synthesis shows that operability assessment by an experienced multidisciplinary CTEPH team remains central because pulmonary endarterectomy can be curative in anatomically accessible disease. Balloon pulmonary angioplasty and riociguat provide effective options for technically inoperable or persistent/recurrent disease, while other pulmonary hypertension therapies have more limited evidence. Treatment should be individualized according to lesion distribution, hemodynamic severity, comorbidity, and local expertise. Early referral and planned multimodal management offer the best opportunity to improve symptoms, hemodynamics, and long-term outcomes.

Keywords: chronic thromboembolic pulmonary hypertension; pulmonary endarterectomy; balloon pulmonary angioplasty; riociguat; pulmonary vascular resistance; multimodal treatment

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is classified as group 4 pulmonary hypertension and is defined by precapillary pulmonary hypertension associated with chronic organized thromboembolic obstruction after an adequate period of anticoagulation [1]. Persistent obstruction increases pulmonary vascular resistance (PVR), while redistribution of blood flow and progressive small-vessel remodeling place additional load on the right ventricle. The disorder is uncommon but clinically important because it is potentially curable by pulmonary endarterectomy (PEA). Its true incidence after acute pulmonary embolism varies across populations and study designs, and delayed recognition remains common [2]. Registry data demonstrate marked heterogeneity in presentation, operability, and treatment pathways, reinforcing the need for assessment in specialized centers [3].

This review examines the pathobiological basis of CTEPH and connects that evidence to selection among PEA, balloon pulmonary angioplasty (BPA), targeted pharmacotherapy, and combined strategies. Particular attention is given to the distinction between surgically accessible mechanical obstruction and distal microvasculopathy, because this distinction influences both procedural eligibility and residual pulmonary hypertension after intervention [4].

2. Methodology

This article was prepared as a structured narrative review [5]. The evidence base was organized around six prespecified domains: disease definition and epidemiology, thrombus non-resolution, pulmonary microvasculopathy, diagnostic and operability assessment, interventional treatment, and pharmacological treatment. Priority was given to international clinical guidelines, expert consensus or

scientific statements, randomized controlled trials, prospective registries, and large surgical or interventional cohorts published in English. Seminal mechanistic studies were retained when they explained clinically relevant features not addressed by later trials [6].

Evidence was synthesized qualitatively because the included sources differed substantially in design, population, intervention, and outcome definitions [7]. Treatment findings were compared using exercise capacity, hemodynamics, functional class, procedural complications, clinical worsening, and survival where available. No new patient data were collected, and no meta-analysis was performed. Consequently, the results below represent a structured synthesis of published evidence rather than outcomes from an original clinical cohort [8].

3. Results and Discussion

3.1 Pathogenesis and pulmonary microvasculopathy

The evidence supports a two-compartment model of CTEPH. The proximal component consists of fibrotic, organized material adherent to elastic pulmonary arteries, producing complete occlusions, eccentric stenoses, webs, and bands [9]. The distal component consists of remodeling in resistance vessels that resembles pulmonary arterial hypertension and can develop in both obstructed and non-obstructed territories [10]. This model explains why anatomical obstruction alone does not fully predict PVR or symptom severity [11]. Pulmonary venous and capillary remodeling may further contribute to postoperative or post-interventional pulmonary hypertension [12].

Failure of thrombus resolution is likely multifactorial. Abnormal fibrin architecture can make thrombi resistant to physiological fibrinolysis, while endothelial dysfunction, inflammation, impaired angiogenesis, infection-related mechanisms, and disordered cellular signaling may promote persistence and organization of thrombotic material [13]. Endothelial imbalance involving nitric oxide, prostacyclin, and endothelin pathways provides a biological rationale for pulmonary vasodilator therapy in selected patients. Nevertheless, vasodilator treatment does not remove proximal obstruction and must not delay evaluation for PEA.

3.2 Diagnosis and operability assessment

Ventilation–perfusion scintigraphy remains a sensitive screening test for chronic thromboembolic disease, whereas computed-tomography pulmonary angiography, digital-subtraction angiography, and right-heart catheterization define anatomy and hemodynamic severity. Diagnosis should integrate symptoms, perfusion defects, chronic vascular lesions, and precapillary hemodynamics rather than rely on a single test. Operability is not determined by a fixed PVR threshold alone; it depends on whether the obstructive burden is surgically accessible and proportionate to the hemodynamic impairment, together with age, comorbidity, right-ventricular function, and institutional expertise. A multidisciplinary team should include PEA surgeons, BPA interventionists, pulmonary hypertension physicians, radiologists, and anesthetic or critical-care specialists [14].

3.3 Pulmonary endarterectomy

PEA is the treatment of choice for operable CTEPH because it directly removes organized material and can normalize or substantially improve hemodynamics. Large expert-center experience demonstrates durable benefit with acceptable perioperative mortality when patients are appropriately selected. Modern surgery can reach segmental and selected subsegmental disease, so distal appearance on routine imaging should not automatically be interpreted as inoperability. Persistent or recurrent pulmonary hypertension after PEA remains clinically important and is associated with worse long-term outcomes, particularly when postoperative hemodynamic abnormalities are substantial. These observations support lifelong follow-up and reassessment for medical therapy or BPA when clinically indicated.

3.4 Balloon pulmonary angioplasty

BPA has evolved from an early high-risk procedure into a staged intervention for selected patients with technically inoperable disease or persistent/recurrent pulmonary hypertension after PEA. Refined imaging, smaller balloon sizing, limited treatment per session, and staged procedures have improved safety. Multicenter registry data show clinically meaningful improvements in PVR, functional class,

exercise capacity, and symptoms, although complications such as pulmonary-artery injury, hemoptysis, and lung injury remain relevant.

In the randomized RACE trial, BPA produced a larger reduction in PVR than riociguat at the primary assessment, but treatment-related serious adverse events were more frequent during the initial BPA strategy. Sequential treatment suggested that pretreatment with riociguat may reduce BPA-related complications in patients subsequently undergoing intervention. The findings favor individualized sequencing rather than a universal competition between the two treatments. Lesion accessibility, hemodynamic severity, bleeding risk, patient preference, and center experience should guide the initial choice [15].

3.5 Pharmacological treatment

Lifelong therapeutic anticoagulation is a foundation of CTEPH management unless contraindicated. Riociguat has the strongest randomized evidence for symptomatic inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA. In CHEST-1, riociguat improved the 6-min walk distance and reduced PVR over 16 weeks; improvements were generally maintained during the CHEST-2 extension. Riociguat must not be combined with phosphodiesterase type 5 inhibitors because of the risk of clinically significant hypotension [16].

Evidence for other pulmonary hypertension drugs is less definitive. Bosentan improved hemodynamic measures in BENEFIT but did not improve the primary exercise-capacity endpoint. Macitentan improved PVR and exercise capacity in the phase 2 MERIT-1 trial in patients with inoperable disease, including some receiving background therapy [17]. Subcutaneous treprostinil improved exercise capacity in severe inoperable CTEPH in CTREPH. These findings may support carefully selected off-label or jurisdiction-specific use, but they do not replace referral for PEA or BPA evaluation [18].

3.6 Integrating treatment in a multimodal strategy

The central result of the evidence synthesis is that contemporary CTEPH care is multimodal. PEA should be offered when lesions are surgically accessible and the anticipated benefit outweighs risk. BPA is appropriate for selected technically inaccessible lesions and may complement surgery when residual segmental obstruction remains. Riociguat is evidence based for inoperable or persistent/recurrent disease and can be used before BPA in selected patients with high PVR. Hybrid strategies may therefore address different anatomical and biological components of the same disease [19].

The principal limitation of the evidence is its concentration in expert centers. Surgical and BPA outcomes are strongly influenced by operator experience, patient selection, procedural technique, and local definitions of operability. Drug trials also differ in background therapy and eligibility criteria. Accordingly, reported outcomes may not transfer directly to low-volume settings. A second limitation is the incomplete ability of current imaging and hemodynamics to quantify microvasculopathy. Future studies should standardize outcome definitions, evaluate treatment sequencing, and identify markers that predict response to PEA, BPA, or combination therapy [20].

4. Conclusion

CTEPH results from persistent organized thromboembolic obstruction combined with variable small-vessel remodeling. This dual pathology explains the heterogeneity of hemodynamic severity and the need for individualized treatment. PEA remains the preferred potentially curative option for operable disease, while BPA and riociguat are established treatments for selected inoperable or persistent/recurrent cases. Other targeted therapies have supportive but less conclusive evidence. Early diagnosis, lifelong anticoagulation, expert multidisciplinary assessment, and structured follow-up are essential. The most rational strategy is not a single universal therapy but a planned multimodal pathway matched to vascular anatomy, hemodynamics, comorbidity, treatment response, and local expertise.

References

1. M. Humbert et al., "2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension," Eur. Heart J., vol. 43, no. 38, pp. 3618–3731, 2022, doi: 10.1093/eurheartj/ehac237.
2. N. H. Kim et al., "Chronic thromboembolic pulmonary hypertension," Eur. Respir. J., vol. 53, no. 1, Art. no. 1801915, 2019, doi: 10.1183/13993003.01915-2018.
3. E. M. Ende-Verhaar et al., "Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: A contemporary view of the published literature," Eur. Respir. J., vol. 49, no. 2, Art. no. 1601792, 2017, doi: 10.1183/13993003.01792-2016.
4. J. Pepke-Zaba et al., "Chronic thromboembolic pulmonary hypertension: Results from an international prospective registry," Circulation, vol. 124, no. 18, pp. 1973–1981, 2011, doi: 10.1161/CIRCULATIONAHA.110.015008.
5. I. M. Lang, M. Dorfmüller, and A. Vonk Noordegraaf, "The pathobiology of chronic thromboembolic pulmonary hypertension," Ann. Am. Thorac. Soc., vol. 13, suppl. 3, pp. S215–S221, 2016, doi: 10.1513/AnnalsATS.201509-620AS.
6. M. Dorfmüller et al., "Microvascular disease in chronic thromboembolic pulmonary hypertension: A role for pulmonary veins and systemic vasculature," Eur. Respir. J., vol. 44, no. 5, pp. 1275–1288, 2014, doi: 10.1183/09031936.00169113.
7. T. A. Morris et al., "High prevalence of dysfibrinogenemia among patients with chronic thromboembolic pulmonary hypertension," Blood, vol. 107, no. 3, pp. 944–948, 2006, doi: 10.1182/blood-2005-08-3158.
8. R. Quarck et al., "Characterization of proximal pulmonary arterial cells from chronic thromboembolic pulmonary hypertension patients," Respir. Res., vol. 13, Art. no. 27, 2012, doi: 10.1186/1465-9921-13-27.
9. N. Tunariu et al., "Ventilation–perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension," J. Nucl. Med., vol. 48, no. 5, pp. 680–684, 2007, doi: 10.2967/jnumed.106.039438.
10. M. M. Madani et al., "Pulmonary endarterectomy: Recent changes in a single institution's experience of more than 2,700 patients," Ann. Thorac. Surg., vol. 94, no. 1, pp. 97–103, 2012, doi: 10.1016/j.athoracsur.2012.04.004.
11. D. Jenkins et al., "Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension," Eur. Respir. Rev., vol. 26, no. 143, Art. no. 160111, 2017, doi: 10.1183/16000617.0111-2016.
12. J. E. Cannon et al., "Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: Results from the United Kingdom national cohort," Circulation, vol. 133, no. 18, pp. 1761–1771, 2016, doi: 10.1161/CIRCULATIONAHA.115.019470.
13. J. A. Feinstein et al., "Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension," Circulation, vol. 103, no. 1, pp. 10–13, 2001, doi: 10.1161/01.CIR.103.1.10.
14. A. Ogawa et al., "Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: Results of a multicenter registry," Circ. Cardiovasc. Qual. Outcomes, vol. 10, no. 11, Art. no. e004029, 2017, doi: 10.1161/CIRCOUTCOMES.117.004029.
15. X. Jaïs et al., "Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): A multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study," Lancet Respir. Med., vol. 10, no. 10, pp. 961–971, 2022, doi: 10.1016/S2213-2600(22)00214-4.
16. H.-A. Ghofrani et al., "Riociguat for the treatment of chronic thromboembolic pulmonary hypertension," N. Engl. J. Med., vol. 369, no. 4, pp. 319–329, 2013, doi: 10.1056/NEJMoa1209657.
17. G. Simonneau et al., "Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: Data from the CHEST-2 open-label, randomised, long-term extension trial," Lancet Respir. Med., vol. 4, no. 5, pp. 372–380, 2016, doi: 10.1016/S2213-2600(16)30022-4.

18. X. Jaïs et al., “Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT, a randomized, placebo-controlled trial,” J. Am. Coll. Cardiol., vol. 52, no. 25, pp. 2127–2134, 2008, doi: 10.1016/j.jacc.2008.08.059.
19. H.-A. Ghofrani et al., “Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): Results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study,” Lancet Respir. Med., vol. 5, no. 10, pp. 785–794, 2017, doi: 10.1016/S2213-2600(17)30305-3.
20. S. Sadushi-Kolici et al., “Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): A double-blind, phase 3, randomised controlled trial,” Lancet Respir. Med., vol. 7, no. 3, pp. 239–248, 2019, doi: 10.1016/S2213-2600(18)30367-9.