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Chronic Thromboembolic Pulmonary Hypertension in Hospitalized Patients: An Interprofessional Approach to Diagnosis, Pharmacologic Management, and Nursing Care

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Abstract

Background: Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a rare but life-threatening condition classified as Group 4 pulmonary hypertension. It arises from persistent obstruction of the pulmonary arteries by organized thromboembolic material, leading to increased pulmonary vascular resistance, progressive pulmonary hypertension, and right heart failure. CTEPH is a potential sequela of acute pulmonary embolism, though a significant number of patients have no prior embolic history.

Aim: This article synthesizes the essential knowledge for the diagnosis and management of CTEPH, emphasizing the critical need for a systematic, interprofessional approach to improve patient outcomes. It aims to outline the pathophysiological mechanisms, diagnostic pathway, and comprehensive treatment strategies.

Methods: A stepwise diagnostic evaluation is recommended for at-risk patients, beginning with transthoracic echocardiography and utilizing ventilation-perfusion (V/Q) scanning as a highly sensitive screening tool. Confirmation requires right heart catheterization for hemodynamic assessment and imaging via computed tomography pulmonary angiography (CTPA) or pulmonary angiography to define the extent and accessibility of thromboembolic obstructions.

Results: Pulmonary endarterectomy (PEA) is the cornerstone curative treatment for operable patients, significantly improving survival and hemodynamics. For inoperable cases or those with residual hypertension, balloon pulmonary angioplasty (BPA) and targeted medical therapy (notably the soluble guanylate cyclase stimulator riociguat) are effective alternatives. Lifelong anticoagulation is mandatory for all patients to prevent disease recurrence and progression.

Conclusion: CTEPH is a complex disorder whose management hinges on early diagnosis within a specialized multidisciplinary team to determine the optimal treatment pathway among surgical, interventional, and medical options.

Keywords: Chronic Thromboembolic Pulmonary Hypertension (CTEPH), Pulmonary Endarterectomy (PEA), Balloon Pulmonary Angioplasty (BPA), Riociguat, Anticoagulation, Multidisciplinary Team.

Introduction

Chronic Thromboembolic Pulmonary Hypertension Overview

Chronic thromboembolic pulmonary hypertension (CTEPH) represents a severe and potentially fatal cardiovascular condition characterized by persistent obstruction of the pulmonary arteries due to organized thromboembolic material. This disorder is associated with significant morbidity and mortality, yet advancements in both pharmacologic interventions and surgical procedures have substantially improved patient prognosis and survival rates [1][2][3]. CTEPH is classified as a form of precapillary pulmonary hypertension and is specifically recognized under group 4 in the World Health Organization's classification of pulmonary hypertension [4]. The condition frequently develops as a sequela of acute pulmonary embolism, particularly in individuals with predisposing risk factors such as prothrombotic states, recurrent thromboembolic events, genetic susceptibility, and concomitant comorbidities. Over time, unresolved thromboembolic obstructions can transform into chronic lesions, contributing to elevated pulmonary arterial pressures

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and progressive right ventricular dysfunction. Left untreated, this pathological progression can culminate in overt right heart failure, severely limiting functional capacity and leading to premature mortality [5][6]. Consequently, clinicians must maintain a low threshold for screening and longitudinal monitoring in populations at heightened risk, ensuring timely diagnosis and intervention.

Pulmonary Circulation

A comprehensive understanding of the pulmonary circulatory anatomy and physiology is essential to elucidate the pathophysiological mechanisms underlying CTEPH. The pulmonary circulation functions as a specialized low-pressure vascular network, facilitating the transport of deoxygenated blood from the right side of the heart to the pulmonary parenchyma and returning oxygenated blood to the left atrium. Blood is pumped from the right ventricle into the main pulmonary arteries, which progressively branch into smaller arterioles and capillaries that permeate the alveolar tissue. Within the pulmonary capillary bed, gas exchange occurs as carbon dioxide diffuses from the blood into the alveoli for exhalation, while oxygen from inhaled air diffuses into the blood to replenish systemic oxygen delivery [1][2][3]. The pulmonary vascular system is highly compliant and optimized for efficient gas exchange, accommodating variations in blood flow while maintaining low resistance. This compliance allows the right ventricle to generate adequate cardiac output without substantial increases in ventricular workload under normal conditions. Furthermore, pulmonary vessels demonstrate dynamic responsiveness to local oxygen tension, enabling redistribution of blood flow to regions with optimal ventilation and maintaining ventilation-perfusion matching critical for systemic oxygenation. Disruption of this finely tuned system, as occurs in CTEPH due to persistent thromboembolic obstruction, results in increased pulmonary vascular resistance, impaired right ventricular function, and compromised gas exchange, forming the pathophysiological basis for the clinical manifestations and progression of the disease. By integrating knowledge of thromboembolic pathophysiology with the anatomy and dynamics of pulmonary circulation, clinicians can better anticipate hemodynamic consequences, optimize diagnostic evaluation, and implement timely therapeutic strategies to mitigate the progression of CTEPH [3][4].

Etiology

Chronic thromboembolic pulmonary hypertension (CTEPH) arises from a complex interplay of thromboembolic, hemodynamic, and vascular remodeling processes. Its pathogenesis bears resemblance to that of deep vein thrombosis and acute pulmonary embolism, wherein organized thrombotic material embolizes into the pulmonary vasculature, obstructing blood flow and triggering maladaptive vascular remodeling that culminates in sustained pulmonary arterial hypertension. This chronic obstruction increases pulmonary vascular resistance, leading to progressive right ventricular strain and eventual right heart dysfunction. The precise molecular and hemostatic mechanisms underlying the persistence of thrombi in CTEPH remain incompletely elucidated; however, several risk factors and predisposing conditions have been identified, emphasizing a multifactorial etiology [7]. Hypercoagulability has emerged as a central factor in the development of CTEPH. Elevated levels of phospholipid antibodies, lupus anticoagulant, and prothrombotic factor VIII have been frequently observed in affected patients. In particular, increased factor VIII levels are present in approximately 41% of CTEPH cases, highlighting the importance of coagulation dysregulation in the disease's pathogenesis [8]. These findings suggest that an underlying prothrombotic state contributes to the failure of thrombus resolution and the persistence of vascular obstruction, establishing a substrate for chronic pulmonary hypertension.

Clinical and epidemiological studies have further delineated risk factors associated with CTEPH development. A prior history of pulmonary embolism markedly increases the likelihood of subsequent CTEPH, with an odds ratio reported as high as 19.0. Younger age appears to confer elevated risk, increasing approximately 1.79 times per decade, while larger perfusion defects identified on lung imaging also correlate with heightened susceptibility, with odds ratios increasing 2.22 times per decile decrement in perfusion [9]. Acute pulmonary embolism precedes nearly 90% of CTEPH cases, and recurrent thromboembolic events are observed in nearly half of all patients [10]. Despite the high prevalence of acute pulmonary embolism, most thrombi resolve spontaneously, restoring pulmonary circulation. The factors contributing to incomplete thrombus resolution remain uncertain, though hypotheses include the presence of large, fibrin-rich emboli with red blood cells resistant to lysis, or intrinsic deficiencies in endogenous fibrinolytic activity. Additional risk factors implicated in the pathogenesis of CTEPH encompass a broad spectrum of conditions, including thrombophilias, immunologic disorders, ventriculoatrial shunts, pacemaker leads, peripherally inserted central catheters, malignancy, chronic inflammatory diseases such as inflammatory bowel disease or osteomyelitis, splenectomy, and endocrine disorders such as diabetes and hypothyroidism [11][12]. Hemodynamic perturbations, such as right ventricular dysfunction or the presence of large arterial thrombi, may further exacerbate disease progression. Determining whether patients develop CTEPH de novo following pulmonary embolism or harbor pre-existing pulmonary hypertension that mimics acute embolic presentations presents a diagnostic challenge, complicating both epidemiologic assessment and early intervention strategies [13]. Overall, the etiology of

CTEPH reflects a multifactorial process involving thromboembolic events, underlying hypercoagulable states, immune-mediated mechanisms, and vascular remodeling. Understanding these contributing factors is essential for identifying at-risk populations, guiding early diagnostic evaluation, and implementing timely therapeutic interventions aimed at mitigating progression and improving long-term outcomes.

Epidemiology

Chronic thromboembolic pulmonary hypertension (CTEPH) remains a relatively rare condition, and its epidemiology has not been extensively characterized, partly due to underdiagnosis and misclassification [14]. Current estimates suggest that the incidence of CTEPH ranges between 2% and 6% among individuals who experience a pulmonary embolism, with prevalence figures reported at approximately 26 to 38 cases per million in the general population [15]. The risk of developing CTEPH after an acute pulmonary embolism is temporally dependent, with an estimated 1% incidence at six months and rising to 3% at one year post-event [9]. Beyond two years following an embolic episode, the development of CTEPH is considered exceedingly uncommon, indicating a relatively narrow window for disease emergence [16]. In the United States, post-pulmonary embolism incidence estimates vary widely, ranging from 0.1% to 9.1%, reflecting heterogeneity in study design, patient populations, and diagnostic approaches [17]. Meta-analytic data suggest that fewer than 1% of all patients with a prior pulmonary embolism are subsequently diagnosed with CTEPH at the population level. This low figure underscores the challenge of accurate epidemiologic assessment, as the condition is often overlooked or misattributed to other cardiopulmonary disorders. Contributing factors include limited awareness among clinicians and the so-called "honeymoon period," which describes the asymptomatic interval between the initial thromboembolic event and the gradual onset of clinical manifestations of CTEPH [18]. This latency complicates early recognition and contributes to underestimation of disease prevalence.

In recent years, the European Society of Cardiology and the European Respiratory Society have introduced the concept of "chronic thromboembolic pulmonary disease" (CTEPD), a classification that encompasses patients with persistent pulmonary vascular obstructions and perfusion defects regardless of resting pulmonary hypertension [19]. CTEPD highlights the spectrum of thromboembolic pulmonary disease, identifying individuals who may present with comparable symptomatology and functional limitations yet do not fulfill hemodynamic criteria for CTEPH at rest. Epidemiologic data indicate that approximately 20% of patients evaluated for suspected CTEPH meet criteria for CTEPD. Notably, these patients tend to be younger and exhibit better functional status, as evidenced by longer distances achieved in the six-minute walk test, suggesting that early identification and intervention could potentially improve long-term outcomes and prevent progression to overt pulmonary hypertension. Overall, epidemiologic evidence demonstrates that while CTEPH is uncommon, it is frequently underrecognized, and the broader spectrum of chronic thromboembolic disease warrants increased clinical vigilance to ensure timely diagnosis and management.

Pathophysiology

The underlying pathophysiological mechanisms of chronic thromboembolic pulmonary hypertension (CTEPH) remain incompletely defined, reflecting the complex interplay between thromboembolic events and pulmonary vascular remodeling [20]. The prevailing model posits that CTEPH typically develops following one or more episodes of pulmonary embolism, most often originating from deep vein thrombosis. In these cases, thrombotic material fails to undergo complete lysis, leading to persistent vascular obstruction, which subsequently promotes progressive pulmonary arterial hypertension. The organized thrombi induce structural remodeling of the pulmonary arteries, including intimal fibrosis and medial hypertrophy, which increase pulmonary vascular resistance and impose a chronic afterload on the right ventricle. Over time, this hemodynamic burden can precipitate right ventricular dilation, hypertrophy, and eventual right heart failure if untreated. An alternative, increasingly recognized mechanism involves the formation of in situ thrombosis within the pulmonary vasculature, independent of prior embolic events. This process may be driven by primary arteriopathy, endothelial dysfunction, and abnormal local coagulation, resembling the vascular pathology observed in pulmonary arterial hypertension (PAH) [21]. This model provides a plausible explanation for the significant proportion of CTEPH cases—reported as high as 63%—in which patients do not have a documented history of acute pulmonary embolism. In such instances, local vascular factors, including impaired fibrinolysis, endothelial injury, and prothrombotic states, may predispose to persistent obstruction and vascular remodeling. Overall, the pathophysiology of CTEPH represents a convergence of embolic persistence, abnormal thrombus organization, and intrinsic pulmonary vascular pathology. The resulting vascular obstruction and remodeling elevate pulmonary pressures and compromise right ventricular function, establishing the hemodynamic and clinical sequelae characteristic of this serious condition. Understanding these mechanisms is essential for targeted therapeutic strategies, including surgical and medical interventions, aimed at restoring pulmonary perfusion and mitigating right heart strain.

Histopathology

Histopathological examination of lung tissue from patients diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) who have undergone pulmonary thromboendarterectomy reveals distinctive vascular alterations that contribute to the disease's pathophysiology [22]. The most consistent finding is the presence of small vessel arteriopathy, characterized by structural changes in the distal pulmonary arteries and arterioles. These changes include intimal thickening, proliferation of smooth muscle cells, and fibrosis, which collectively narrow the vascular lumen and increase pulmonary vascular resistance. The progressive luminal narrowing contributes to elevated pulmonary arterial pressures, further burdening right ventricular function. Microvascular thrombosis is another critical histopathological feature observed in CTEPH. This involves the presence of organized thrombotic material within small pulmonary vessels that fails to undergo complete lysis, perpetuating chronic obstruction. These microthrombi often contain fibrin-rich elements and entrapped red blood cells, rendering them resistant to natural fibrinolytic processes. This persistent vascular obstruction promotes localized ischemia and contributes to ongoing endothelial dysfunction, which exacerbates vascular remodeling and the pathogenesis of pulmonary hypertension. Intimal proliferation, frequently observed in these histological specimens, is a hallmark of the remodeling process. Endothelial cells and subendothelial fibroblasts undergo hyperplasia, leading to thickened vessel walls and reduced cross-sectional area of the pulmonary arteries. The combination of organized thrombotic material, microvascular changes, and intimal proliferation results in a heterogeneous pattern of obstruction, affecting both proximal and distal pulmonary vessels. These histopathological insights not only corroborate the hemodynamic abnormalities seen in CTEPH but also inform surgical and medical strategies aimed at restoring pulmonary perfusion and mitigating right ventricular strain.

History and Physical

Chronic thromboembolic pulmonary hypertension (CTEPH) frequently presents with nonspecific symptoms that evolve insidiously, complicating early diagnosis. Patients often report exertional dyspnea as the initial manifestation, which progressively limits physical activity and exercise tolerance. Over time, this symptom may escalate to breathlessness at rest, reflecting the increasing pulmonary vascular resistance and impaired right ventricular function [23]. Fatigue, generalized weakness, and exercise intolerance are common complaints, while chest discomfort or atypical chest pain may occur, reflecting strain on the right ventricle or episodic pulmonary ischemia. Dizziness, syncope, or presyncope can also be present, particularly during exertion, indicating advanced right heart compromise. Less frequent symptoms include cough, episodic hemoptysis, and palpitations, which may mimic other cardiopulmonary conditions, thereby delaying clinical recognition [23].

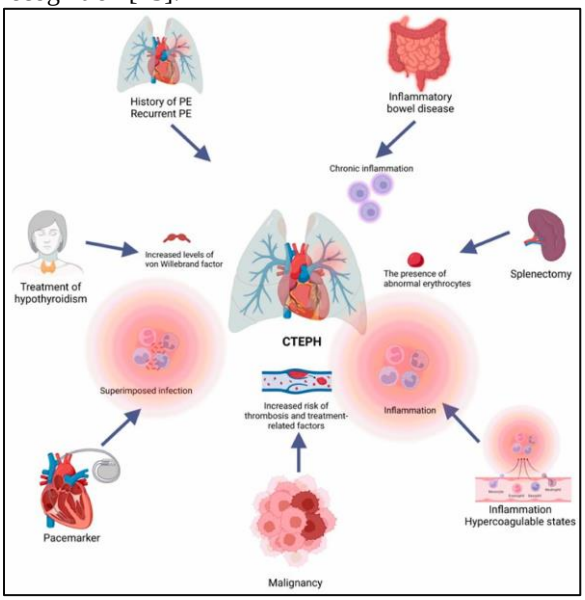

Fig. 1: Pathophysiology of chronic thromboembolic pulmonary hypertension.

During the early stages of CTEPH, physical examination may be largely unremarkable, as many characteristic findings develop only after prolonged pulmonary vascular obstruction and right ventricular overload. In later stages, signs of right heart dysfunction become prominent. Peripheral edema, hepatomegaly, ascites, and jugular venous distension are indicative of systemic venous congestion secondary to right ventricular failure. Fatigue and dyspnea during activities of daily living signal the progression of pulmonary hypertension and declining cardiac output [23].

Cardiac auscultation may reveal an accentuated second heart sound (P2), reflecting increased pulmonary artery pressures. An S4 gallop may be present due to right ventricular hypertrophy, and systolic ejection clicks over the pulmonary artery can occasionally be detected. More specific to CTEPH are pulmonary flow murmurs, which present as subtle, high-pitched, blowing bruits over the lung fields, often accentuated on inspiration and heard best with breath-holding. These murmurs arise from turbulent blood flow through partially obstructed medium-to-large pulmonary arteries [24]. As pulmonary hypertension advances, tricuspid regurgitation murmurs may develop, correlating with right ventricular dilation and valvular incompetence. Peripheral edema, ascites, and hepatomegaly progress in severity. Hypoxemia is common due to ventilation-perfusion mismatch, with arterial oxygen levels inversely proportional to pulmonary vascular resistance and the extent of vascular obstruction. The degree of hypoxia also reflects the mean pulmonary artery pressure and

overall hemodynamic burden [25]. Collectively, these historical and physical findings underscore the importance of vigilant evaluation in patients with unexplained exertional symptoms, particularly in individuals with a prior history of pulmonary embolism or known thromboembolic risk factors, to facilitate timely recognition and intervention in CTEPH.

Evaluation

The evaluation of chronic thromboembolic pulmonary hypertension (CTEPH) requires a methodical and stepwise approach, particularly because early clinical manifestations are frequently nonspecific and overlap with other cardiopulmonary conditions. Diagnostic assessment is generally recommended for patients presenting with persistent or new-onset dyspnea, exercise intolerance, or other suggestive symptoms, particularly after a minimum of three months of anticoagulation following an acute pulmonary embolism [26]. This timeframe ensures that residual thromboembolic material is chronic and excludes transient hemodynamic alterations associated with acute embolic events. Early recognition is challenging, as initial physical and radiographic findings may not reveal the full spectrum of pathophysiologic changes, necessitating a combination of imaging modalities and hemodynamic assessments. The initial evaluation typically begins with a chest radiograph, which can be unremarkable in early CTEPH. In contrast, advanced disease often demonstrates indirect signs of pulmonary hypertension, including right heart chamber enlargement, prominent pulmonary arteries, and segmental oligemia. Secondary changes such as pleuroparenchymal scarring or atelectasis may also be observed in areas of prior thromboembolic obstruction [27]. However, chest radiography lacks sensitivity for detecting smaller or subsegmental chronic thrombi, necessitating adjunctive imaging modalities for definitive assessment.

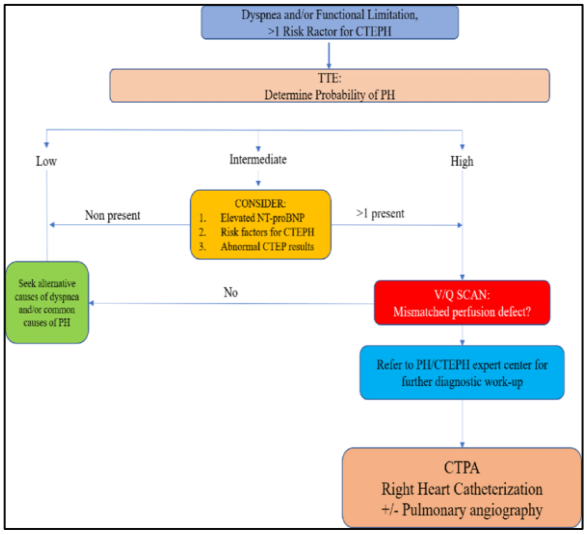

Fig. 2: Diagnosis of Chronic thromboembolic pulmonary hypertension.

Computed tomography (CT) of the chest is frequently employed to identify obstructive thrombus, evaluate pulmonary vasculature, and detect anatomical anomalies consistent with CTEPH. Suspicion for the disease is heightened in patients with a history of venous thromboembolism or characteristic auscultatory findings such as pulmonary flow bruits. However, while CT can identify central or segmental thromboembolic obstruction, it may not reliably detect microvascular disease or distal vessel involvement, emphasizing the need for additional confirmatory studies. Ventilation/perfusion (V/Q) scanning remains a highly sensitive and specific first-line screening tool for CTEPH, with reported sensitivity and specificity rates ranging from 90% to 100% and 94% to 100%, respectively [29][30]. A normal V/Q scan effectively excludes chronic thromboembolic disease, although central obstructions may be underestimated, and alternative causes of V/Q mismatch should be considered. Transthoracic echocardiography is instrumental in estimating pulmonary artery pressures and evaluating right ventricular function. Although it is a key noninvasive tool, echocardiography is nonspecific for CTEPH and cannot distinguish chronic from acute pulmonary embolism [28]. Pulmonary function tests may provide supportive evidence by revealing restrictive or obstructive patterns, though their primary role lies in baseline assessment rather than definitive diagnosis.

Definitive diagnostic criteria for CTEPH include a mean pulmonary artery pressure exceeding 20 mmHg, a pulmonary arterial wedge pressure below 15 mmHg, pulmonary vascular resistance greater than 3 Wood units (>240 dynes·s·cm^{-5}), and objective evidence of chronic thromboembolic material on CT or V/Q imaging. Right heart catheterization remains the gold standard for diagnosis, allowing direct hemodynamic measurement and confirmation of pulmonary hypertension. Conventional pulmonary angiography performed concurrently provides anatomical delineation critical for determining surgical candidacy [31]. Negative CT findings do not exclude CTEPH, highlighting the necessity of invasive evaluation in suspicious cases. Advanced imaging techniques have increasingly complemented traditional modalities. Dual-energy CT allows improved visualization of perfusion defects and assessment of thrombus composition, whereas dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) facilitates the evaluation of both central and distal pulmonary vasculature. Optical coherence tomography and digital subtraction pulmonary angiography further enhance the precision of vessel imaging and thrombus characterization. The combination of these modalities enables comprehensive assessment, informs therapeutic decision-making, aids in surgical planning, and allows monitoring of post-intervention outcomes. Integration of multiple diagnostic tools is essential not only to

confirm the presence of CTEPH but also to optimize individualized patient management, stratify surgical risk, and identify candidates for pulmonary thromboendarterectomy or alternative interventions. Overall, the evaluation of CTEPH requires a multidimensional strategy, leveraging clinical assessment, noninvasive imaging, functional studies, and invasive hemodynamic measurements. Early and accurate diagnosis is critical to prevent progression of pulmonary hypertension, minimize right ventricular compromise, and improve patient prognosis. Employing a structured diagnostic pathway ensures timely identification, appropriate intervention, and optimal outcomes for patients at risk of this complex and potentially life-threatening condition.

Treatment / Management

Chronic thromboembolic pulmonary hypertension (CTEPH) represents a complex cardiovascular disorder that requires management within specialized centers equipped with the appropriate expertise, multidisciplinary teams, and advanced diagnostic and therapeutic tools. Initial management universally involves anticoagulation therapy, administered for a minimum duration of three months for all patients with suspected CTEPH. This initial period serves a dual purpose: it may induce regression of thromboembolic material, facilitating partial or complete resolution of pulmonary hypertension, and simultaneously functions diagnostically by differentiating CTEPH from subacute pulmonary embolism, which typically involves smaller pulmonary vessels and often resolves spontaneously. Persistent symptoms despite anticoagulation confirm the chronicity of the thromboembolic obstruction, thereby directing clinicians toward definitive intervention [32]. Surgical management, particularly pulmonary endarterectomy (PEA), remains the cornerstone of treatment in appropriately selected patients. PEA is a technically demanding procedure, necessitating significant surgical expertise and careful patient selection. Ideal candidates include individuals with proximal thromboembolic lesions, significant hemodynamic compromise, minimal comorbid conditions, and sufficient physiological reserve to tolerate cardiopulmonary bypass and deep hypothermic circulatory arrest [33]. To standardize the assessment of operative feasibility, the University of California–San Diego developed a classification system that stratifies the anatomical complexity of CTEPH lesions. This system ranges from Level 0, indicating no surgically identifiable disease, to Level 4, which denotes subsegmental pulmonary artery obstruction. The classification serves as a guide for determining the complexity of surgical intervention and anticipated postoperative outcomes [34].

PEA directly removes organized thromboembolic material from the pulmonary arteries, restoring patency and significantly improving hemodynamic parameters, including mean pulmonary artery pressure (PAP), pulmonary vascular resistance, and cardiac output. The procedure can also reverse right ventricular remodeling by alleviating pressure overload, resulting in improved right ventricular function. Despite the efficacy of PEA, residual CTEPH persists in 5% to 35% of cases, highlighting the importance of careful postoperative follow-up and ongoing anticoagulation to prevent recurrent thromboembolism. Vitamin K antagonists have demonstrated superior efficacy in reducing the recurrence of thromboembolic events compared to direct-acting oral anticoagulants, underscoring their role in long-term management [35][36][37][38]. Postoperative outcomes frequently include normalization of gas exchange, enhanced exercise capacity, and substantial improvements in quality of life, further emphasizing the transformative impact of surgical intervention [33]. For patients deemed inoperable due to distal thromboembolic burden, comorbidities, or other contraindications to PEA, balloon pulmonary angioplasty (BPA) has emerged as a viable therapeutic alternative. BPA involves percutaneous dilation of obstructed pulmonary arteries and has demonstrated significant improvements in hemodynamics, exercise tolerance, and functional capacity. Recent meta-analyses suggest that BPA may surpass medical therapy with riociguat in ameliorating exercise intolerance and pulmonary vascular resistance [39][40][41]. However, BPA is not without risk. Complications include procedural issues such as wire perforation, vessel dissection, or rupture, as well as reperfusion pulmonary edema, pulmonary parenchymal bleeding, and hemothorax. The procedural risks necessitate careful patient selection, operator expertise, and postprocedural monitoring. Targeted pulmonary vasodilators may be reserved for individuals exhibiting severe pulmonary hypertension or right ventricular failure to optimize hemodynamics prior to or following BPA.

Medical management serves as an adjunct or primary therapy in patients ineligible for surgical intervention. Standard medical therapy encompasses anticoagulation, diuretics, supplemental oxygen when indicated, and targeted pulmonary hypertension therapies. Lifelong anticoagulation is mandated for confirmed CTEPH patients to prevent recurrent thromboembolism and in situ thrombosis. Direct oral anticoagulants—including dabigatran, rivaroxaban, apixaban, and edoxaban—represent the first-line therapy, with vitamin K antagonists and low-molecular-weight heparins reserved for second- and third-line therapy, respectively. Placement of an inferior vena cava filter may be considered in patients with elevated bleeding risk, with initiation of anticoagulation deferred until hemostatic stability is achieved [42].

Pharmacologic agents traditionally used in pulmonary arterial hypertension (PAH) have demonstrated efficacy in CTEPH. Endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoids

such as treprostinil and macitentan have shown hemodynamic and functional benefits in both operable and inoperable patients. Among these, riociguat, a soluble guanylate cyclase stimulator, has emerged as the treatment of choice for patients who are either ineligible for surgery or who continue to exhibit residual pulmonary hypertension following PEA. Clinical trials have consistently demonstrated that riociguat reduces pulmonary vascular resistance, improves exercise capacity, and enhances quality-of-life metrics, solidifying its position as the preferred targeted medical therapy in CTEPH management [43]. Bilateral lung transplantation is considered the ultimate therapeutic option for patients with severe, refractory disease who have either failed surgical or medical therapy or possess contraindications to both. While transplantation carries inherent perioperative risks, it offers a potential definitive resolution of pulmonary hypertension and right heart dysfunction in carefully selected individuals.

In conclusion, optimal management of CTEPH necessitates a multidisciplinary approach that integrates anticoagulation, surgical intervention, percutaneous therapies, and targeted medical treatment. Pulmonary endarterectomy remains the standard of care for operable patients, providing substantial hemodynamic improvement, reversal of right ventricular remodeling, and enhanced functional capacity. For inoperable cases, BPA offers a minimally invasive option with proven efficacy in improving exercise tolerance and pulmonary hemodynamics, although procedural risks must be carefully managed. Lifelong anticoagulation remains a fundamental component of therapy across all patient subgroups to prevent recurrence and further thromboembolic events. Targeted PAH therapies, particularly riociguat, provide significant hemodynamic and functional benefits for patients with persistent disease, while lung transplantation serves as a salvage therapy in refractory cases. The integration of these therapeutic modalities within a specialized, multidisciplinary framework ensures individualized patient care, maximizes treatment efficacy, and optimizes long-term outcomes in this complex and potentially life-threatening condition.

Differential Diagnosis

Chronic thromboembolic pulmonary hypertension (CTEPH) requires careful differentiation from other disorders that affect the pulmonary vasculature and may present with thrombotic or fibrotic changes. Accurate distinction is critical because CTEPH is potentially curable, unlike many other causes of pulmonary hypertension. A primary condition requiring differentiation is idiopathic pulmonary arterial hypertension (IPAH).

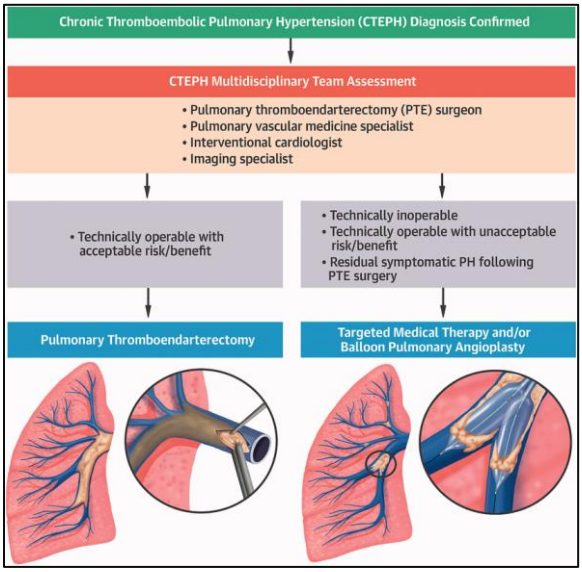

Fig. 3: Treatment guidelines for chronic thromboembolic pulmonary hypertension.

IPAH is characterized by precapillary pulmonary hypertension without thromboembolic or fibrotic obstructions in the pulmonary arteries. Imaging studies, particularly computed tomography (CT), demonstrate markedly decreased diameters in segmental and subsegmental pulmonary arteries in IPAH. Additionally, a hallmark feature of IPAH is the presence of corkscrew-like pulmonary arteries, reflecting plexogenic arteriopathy, which is absent in CTEPH [44][45]. Doppler echocardiography may provide noninvasive insight into distinguishing these conditions by assessing pulmonary artery pressure waveforms, as pulse pressure is typically more pronounced in CTEPH than in IPAH. Primary pulmonary arterial sarcoma is another rare but significant differential diagnosis. This malignant tumor arises in the central pulmonary arteries and is often difficult to distinguish from CTEPH due to overlapping nonspecific symptoms such as dyspnea, fatigue, and chest discomfort. Imaging plays a crucial role in differentiation: sarcomas appear as solid, lobulated masses on CT or magnetic resonance imaging (MRI) and do not respond to anticoagulation therapy, which contrasts with the thrombotic nature of CTEPH. Positron-emission tomography (PET) with F-fludeoxyglucose may help differentiate sarcomas from CTEPH by highlighting metabolic activity unique to malignancy [46].

Acute pulmonary thromboembolism with associated right heart failure can sometimes mimic CTEPH clinically. However, anatomical distinctions on imaging can differentiate these conditions. In acute pulmonary embolism, thrombi typically form at acute angles with the pulmonary arterial wall, whereas chronic thromboembolic material in CTEPH forms obtuse angles due to organization and fibrosis. Additionally, right ventricular hypertrophy is a chronic adaptive response seen in CTEPH, but it is less

prominent or absent in acute embolic events [47]. Several other conditions must be considered in the differential diagnosis of CTEPH. These include in situ thrombosis, which may occur in hypercoagulable states, Takayasu arteritis, congenital proximal pulmonary artery interruption, and congenital pulmonary artery stenosis. Malignant and benign pulmonary artery tumors may also mimic the vascular obstruction seen in CTEPH, while fibrosing mediastinitis can lead to secondary pulmonary arterial compression and perfusion defects. Rare genetic or systemic diseases such as Von Recklinghausen disease and Osler-Weber-Rendu syndrome may produce vascular anomalies that mimic chronic thromboembolic obstruction [48][49][50][51]. Differentiating CTEPH from these diverse entities requires an integrated approach involving clinical assessment, advanced imaging modalities, hemodynamic studies, and, in selected cases, invasive diagnostic techniques. Correctly identifying CTEPH is crucial not only for timely surgical intervention but also to avoid inappropriate therapies that may not address the underlying pathophysiology, ultimately affecting morbidity and mortality. The clinician must remain vigilant for these mimics to ensure that patients receive accurate diagnosis and optimal, potentially curative management.

Prognosis

Pulmonary endarterectomy (PEA) remains the cornerstone intervention for improving survival among operable patients with chronic thromboembolic pulmonary hypertension (CTEPH). Evidence from longitudinal studies highlights that patients undergoing PEA demonstrate substantial improvements in both functional capacity and hemodynamic parameters. A notable study conducted in 2017 reported five-year survival rates ranging from 70% to 80% following PEA, underscoring the procedure's life-extending potential [52]. Beyond survival, PEA provides significant reductions in pulmonary artery pressures and pulmonary vascular resistance, contributing to improved right ventricular function and overall cardiac output [53]. The timing of surgical intervention also plays a critical role in outcomes; extended intervals between the last pulmonary embolism episode and PEA have been associated with increased in-hospital mortality. This relationship emphasizes the necessity for early recognition and timely diagnosis of CTEPH to maximize patient survival and long-term prognosis. Long-term outcomes after PEA are generally favorable, particularly when combined with comprehensive postoperative care, including anticoagulation and management of comorbidities. The procedure not only restores pulmonary circulation but also alleviates right ventricular remodeling induced by chronic pressure overload, improving functional status and exercise tolerance. Even in patients with residual pulmonary hypertension postoperatively, hemodynamic parameters often improve sufficiently to enhance quality of life. Importantly, lifelong anticoagulation post-PEA is recommended to mitigate the risk of recurrent thromboembolic events. Collectively, these findings underscore that with timely and appropriate intervention, the prognosis for patients with CTEPH has improved substantially, transforming what was once considered a uniformly fatal condition into a potentially curable disease.

Complications

Chronic thromboembolic pulmonary hypertension represents a significant complication of unresolved thromboembolic events. In the absence of appropriate intervention, the disease exerts progressive hemodynamic stress on the right ventricle, ultimately leading to severe right heart failure. Clinically, patients experience progressive dyspnea, marked reduction in exercise tolerance, fatigue, syncope, and eventual circulatory collapse. Mortality in untreated cases remains high, with a three-year death rate estimated at 90% [51]. The pathophysiological burden arises from persistent obstruction of pulmonary arteries, leading to increased pulmonary vascular resistance, right ventricular hypertrophy, and impaired cardiac output. Secondary complications, including hypoxemia and multiorgan dysfunction, may emerge as the disease progresses. In addition, patients often experience recurrent thromboembolic events, which further compromise pulmonary circulation and accelerate clinical deterioration. Early recognition and intervention are essential to preventing these devastating sequelae [51].

Patient Education

Preventive strategies play a pivotal role in reducing the incidence of CTEPH in at-risk populations. Measures aimed at preventing acute pulmonary embolism can indirectly mitigate the risk of subsequent chronic thromboembolic disease. In hospitalized patients, pharmacologic prophylaxis with anticoagulants and mechanical interventions, such as inflatable compression devices or graduated compression stockings, can reduce thrombus formation. For individuals engaged in long-duration travel, particularly air travel, frequent ambulation or positional changes every one to two hours is recommended to maintain venous flow and minimize stasis. For patients diagnosed with CTEPH, structured education is critical to optimize adherence to anticoagulation therapy and other prescribed treatments. Patients should be counseled on the importance of regular follow-up visits to monitor disease progression, manage comorbid conditions, and assess functional capacity. Education regarding the potential need for supplemental oxygen during air travel is essential, particularly for those with advanced disease. By emphasizing lifestyle modifications, medication adherence, and timely clinical evaluations, healthcare providers can significantly improve both short-term and long-term outcomes for individuals with CTEPH [51].

Other Issues

CTEPH is rare but represents the only potentially curable form of pulmonary arterial hypertension, highlighting the necessity for high clinical suspicion in all patients presenting with unexplained pulmonary hypertension or progressive exercise intolerance. Diagnostic evaluation relies heavily on imaging modalities, with ventilation-perfusion (V/Q) scanning serving as a first-line screening tool. Criteria for diagnosing CTEPH include a mean pulmonary artery pressure exceeding 20 mm Hg, pulmonary arterial wedge pressure below 15 mm Hg, pulmonary vascular resistance greater than 3 Woods units, and objective evidence of chronic thromboembolism on CT, MRI, or V/Q scanning. Medical management typically involves PAH-targeted pharmacotherapy and lifelong anticoagulation, while surgical intervention via PEA remains the definitive treatment for operable patients [51].

Enhancing Healthcare Team Outcomes

Management of CTEPH necessitates a coordinated, interprofessional approach to optimize patient outcomes. Delays in diagnosis or treatment correlate with significantly higher mortality, emphasizing the importance of timely evaluation for surgical candidacy. In patients who are not surgical candidates, alternatives include balloon pulmonary angioplasty (BPA), targeted medical therapy, and lifelong anticoagulation. Primary care clinicians, nurses, and specialty pharmacists play a critical role in patient education, medication management, and follow-up. Nurses and pharmacists can advise on prophylaxis for hospitalized patients and support adherence to complex anticoagulation regimens. Clinicians must ensure that comorbid conditions are actively managed to maintain functional capacity, while considerations for in-flight oxygen supplementation may be necessary for patients undertaking air travel. Communication and collaboration among interprofessional team members—including physicians, surgeons, nurses, and pharmacists—are essential to implement evidence-based strategies effectively and improve both clinical and quality-of-life outcomes for patients with CTEPH. This multidisciplinary strategy, emphasizing early recognition, surgical intervention when feasible, and targeted medical management for inoperable cases, represents the standard of care and offers the best prognosis for this otherwise life-threatening condition [52].

Conclusion:

In conclusion, Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a complex and progressive vascular disorder, yet it remains the only potentially curable form of pulmonary hypertension. Its management demands a high index of clinical suspicion, particularly in patients with unexplained dyspnea or a history of pulmonary embolism, to ensure timely diagnosis. The cornerstone of treatment is pulmonary endarterectomy (PEA), a specialized surgical procedure that offers a curative potential for patients with proximal obstructive disease, leading to dramatically improved hemodynamics, functional capacity, and long-term survival. For patients who are inoperable due to distal disease or comorbidities, or who have persistent symptoms post-surgery, two primary modalities have proven effective: balloon pulmonary angioplasty (BPA) to mechanically dilate obstructed vessels and targeted medical therapy, most effectively with riociguat. Lifelong anticoagulation is a fundamental component of care for all patients to prevent recurrent thromboembolic events. Ultimately, optimal outcomes are achieved through a coordinated, interprofessional approach within specialized centers. This model ensures accurate diagnosis, careful selection of the most appropriate intervention—be it surgical, interventional, or medical—and comprehensive long-term follow-up, thereby transforming a once uniformly fatal condition into one with a significantly improved prognosis.

References:

1. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, Ageno W. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006 Jul:130(1):172-5
2. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares K, Tsui SS, Armstrong IJ, Torpy C, Crackett R, Carlin CM, Das C, Coghlan JG, Pepke-Zaba J. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. American journal of respiratory and critical care medicine. 2008 May 15:177(10):1122-7. doi: 10.1164/rccm.200712-1841OC.
3. Ng C, Jenkins DP. Surgical management of chronic thromboembolic pulmonary hypertension. British journal of hospital medicine (London, England : 2005). 2013 Jan:74(1):31-5
4. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European heart journal. 2022 Oct 11:43(38):3618-3731. doi: 10.1093/eurheartj/ehac237.
5. Oldroyd SH, Manek G, Sankari A, Bhardwaj A. Pulmonary Hypertension. StatPearls. 2024
6. Farishta M, Sankari A. Pulmonary Hypertension Due to Lung Disease or Hypoxia. StatPearls. 2024

7. Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. The European respiratory journal. 2013 Feb:41(2):462-8. doi: 10.1183/09031936.00049312.
8. Bonderman D, Turecek PL, Jakowitsch J, Weltermann A, Adlbrecht C, Schneider B, Kneussl M, Rubin LJ, Kyrle PA, Klepetko W, Maurer G, Lang IM. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thrombosis and haemostasis. 2003 Sep:90(3):372-6
9. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P, Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. The New England journal of medicine. 2004 May 27:350(22):2257-64
10. Kerr KM, Elliott CG, Chin K, Benza RL, Channick RN, Davis RD, He F, LaCroix A, Madani MM, McLaughlin VV, Park M, Robbins IM, Tapson VF, Terry JR, Test VJ, Jain S, Auger WR. Results From the United States Chronic Thromboembolic Pulmonary Hypertension Registry: Enrollment Characteristics and 1-Year Follow-up. Chest. 2021 Nov:160(5):1822-1831. doi: 10.1016/j.chest.2021.05.052.
11. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuß G, Huisman MV, Konstantinides S, Lankeit M. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Journal of thrombosis and haemostasis : JTH. 2016 Jan:14(1):121-8. doi: 10.1111/jth.13175.
12. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011 Nov 1:124(18):1973-81. doi: 10.1161/CIRCULATIONAHA.110.015008.
13. Guérin L, Couturaud F, Parent F, Revel MP, Gillaizeau F, Planquette B, Pontal D, Guégan M, Simonneau G, Meyer G, Sanchez O. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thrombosis and haemostasis. 2014 Sep 2:112(3):598-605. doi: 10.1160/TH13-07-0538.
14. Catella-Chatron J, Merah A, De Magalhaes E, Moulin N, Accassat S, Duvillard C, Mismetti P, Bertoletti L. Chronic thromboembolic pulmonary hypertension suspicion after pulmonary embolism in cancer patients. Respiratory medicine and research. 2019 Nov:76():34-37. doi: 10.1016/j.resmer.2019.08.002.
15. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. Pulmonary circulation. 2021 Jan-Mar:11(1):2045894020977300. doi: 10.1177/2045894020977300.
16. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu AT, Huisman MV, Klok FA. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. The European respiratory journal. 2017 Feb:49(2):. pii: 1601792. doi: 10.1183/13993003.01792-2016.
17. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. European respiratory review : an official journal of the European Respiratory Society. 2017 Mar 31:26(143):. doi: 10.1183/16000617.0121-2016.
18. Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, Keogh A. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. Pulmonary circulation. 2013 Jan:3(1):89-94. doi: 10.4103/2045-8932.109919.
19. Swietlik EM, Ruggiero A, Fletcher AJ, Taboada D, Knightbridge E, Harlow L, Harvey I, Screaton N, Cannon JE, Sheares KKK, Ng C, Jenkins DP, Pepke-Zaba J, Toshner MR. Limitations of resting haemodynamics in chronic thromboembolic disease without pulmonary hypertension. The European respiratory journal. 2019 Jan:53(1):. pii: 1801787. doi: 10.1183/13993003.01787-2018.
20. Peacock A, Simonneau G, Rubin L. Controversies, uncertainties and future research on the treatment of chronic thromboembolic pulmonary hypertension. Proceedings of the American Thoracic Society. 2006 Sep:3(7):608-14
21. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation. 2006 Apr 25:113(16):2011-20
22. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. The New England journal of medicine. 2011 Jan 27:364(4):351-60. doi: 10.1056/NEJMra0910203.
23. Gopalan D, Blanchard D, Auger WR. Diagnostic Evaluation of Chronic Thromboembolic

Pulmonary Hypertension. Annals of the American Thoracic Society. 2016 Jul:13 Suppl 3():S222-39. doi: 10.1513/AnnalsATS.201509-623AS.

24. Auger WR, Kerr KM, Kim NH, Fedullo PF. Evaluation of patients with chronic thromboembolic pulmonary hypertension for pulmonary endarterectomy. Pulmonary circulation. 2012 Apr-Jun:2(2):155-62. doi: 10.4103/2045-8932.97594.
25. Kapitan KS, Buchbinder M, Wagner PD, Moser KM. Mechanisms of hypoxemia in chronic thromboembolic pulmonary hypertension. The American review of respiratory disease. 1989 May:139(5):1149-54
26. Tapson VF, Platt DM, Xia F, Teal SA, de la Orden M, Divers CH, Satler CA, Joish VN, Channick RN. Monitoring for Pulmonary Hypertension Following Pulmonary Embolism: The INFORM Study. The American journal of medicine. 2016 Sep:129(9):978-985.e2. doi: 10.1016/j.amjmed.2016.03.006.
27. Woodruff WW 3rd, Hoeck BE, Chitwood WR Jr, Lyerly HK, Sabiston DC Jr, Chen JT. Radiographic findings in pulmonary hypertension from unresolved embolism. AJR. American journal of roentgenology. 1985 Apr:144(4):681-6
28. Ghio S, Raineri C, Scelsi L, Recusani F, D'armini AM, Piovella F, Klersy C, Campana C, Viganò M, Tavazzi L. Usefulness and limits of transthoracic echocardiography in the evaluation of patients with primary and chronic thromboembolic pulmonary hypertension. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2002 Nov:15(11):1374-80
29. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. Revista espanola de cardiologia (English ed.). 2016 Feb:69(2):177. doi: 10.1016/j.rec.2016.01.002.
30. Expert Panel on Thoracic Imaging:, Sirajuddin A, Donnelly EF, Crabtree TP, Henry TS, Iannettoni MD, Johnson GB, Kazerooni EA, Maldonado F, Olsen KM, Wu CC, Mohammed TL, Kanne JP. ACR Appropriateness Criteria(®) Suspected Pulmonary Hypertension. Journal of the American College of Radiology : JACR. 2017 May:14(5S):S350-S361. doi: 10.1016/j.jacr.2017.01.040.
31. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. The European respiratory journal. 2019 Jan:53(1):. doi: 10.1183/13993003.01915-2018.
32. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. European respiratory review : an official journal of the European Respiratory Society. 2017 Jan:26(143):. doi: 10.1183/16000617.0111-2016.
33. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. American journal of respiratory and critical care medicine. 2011 Jun 15:183(12):1605-13. doi: 10.1164/rccm.201011-1854CI.
34. Madani MM. Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension: Pulmonary Thromboendarterectomy. Methodist DeBakey cardiovascular journal. 2016 Oct-Dec:12(4):213-218. doi: 10.14797/mdcj-12-4-213.
35. Corsico AG, D'Armini AM, Cerveri I, Klersy C, Ansaldo E, Niniano R, Gatto E, Monterosso C, Morsolini M, Nicolardi S, Tramontin C, Pozzi E, Viganò M. Long-term outcome after pulmonary endarterectomy. American journal of respiratory and critical care medicine. 2008 Aug 15:178(4):419-24. doi: 10.1164/rccm.200801-101OC.
36. Reesink HJ, Marcus JT, Tulevski II, Jamieson S, Kloek JJ, Vonk Noordegraaf A, Bresser P. Reverse right ventricular remodeling after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. The Journal of thoracic and cardiovascular surgery. 2007 Jan:133(1):58-64
37. Freed DH, Thomson BM, Berman M, Tsui SS, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. The Journal of thoracic and cardiovascular surgery. 2011 Feb:141(2):383-7. doi: 10.1016/j.jtcvs.2009.12.056.
38. Bunclark K, Newnham M, Chiu YD, Ruggiero A, Villar SS, Cannon JE, Coghlan G, Corris PA, Howard L, Jenkins D, Johnson M, Kiely DG, Ng C, Screaton N, Sheares K, Taboada D, Tsui S, Wort SJ, Pepke-Zaba J, Toshner M. A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. Journal of thrombosis and haemostasis : JTH. 2020 Jan:18(1):114-122. doi: 10.1111/jth.14649.
39. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circulation. Cardiovascular

interventions. 2012 Dec:5(6):748-55. doi: 10.1161/CIRCINTERVENTIONS.112.971077.
40. Fukui S, Ogo T, Goto Y, Ueda J, Tsuji A, Sanda Y, Kumasaka R, Arakawa T, Nakanishi M, Fukuda T, Takaki H, Yasuda S, Ogawa H, Nakanishi N. Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. International journal of cardiology. 2015 Feb 1:180():66-8. doi: 10.1016/j.ijcard.2014.11.187.
41. Wang W, Wen L, Song Z, Shi W, Wang K, Huang W. Balloon pulmonary angioplasty vs riociguat in patients with inoperable chronic thromboembolic pulmonary hypertension: A systematic review and meta-analysis. Clinical cardiology. 2019 Aug:42(8):741-752. doi: 10.1002/clc.23212.
42. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb:149(2):315-352. doi: 10.1016/j.chest.2015.11.026.
43. Zhang Y, Yu X, Jin Q, Luo Q, Zhao Z, Zhao Q, Yan L, Liu Z. Advances in targeted therapy for chronic thromboembolic pulmonary hypertension. Heart failure reviews. 2019 Nov:24(6):949-965. doi: 10.1007/s10741-019-09798-x.
44. Scheidl SJ, Englisch C, Kovacs G, Reichenberger F, Schulz R, Breithecker A, Ghofrani HA, Seeger W, Olschewski H. Diagnosis of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. The European respiratory journal. 2012 Jan:39(1):119-24. doi: 10.1183/09031936.00109710.
45. Grosse C, Grosse A. CT findings in diseases associated with pulmonary hypertension: a current review. Radiographics : a review publication of the Radiological Society of North America, Inc. 2010 Nov:30(7):1753-77. doi: 10.1148/rg.307105710.
46. Bendel EC, Maleszewski JJ, Araoz PA. Imaging sarcomas of the great vessels and heart. Seminars in ultrasound, CT, and MR. 2011 Oct:32(5):377-404. doi: 10.1053/j.sult.2011.06.001.
47. Wijesuriya S, Chandratreya L, Medford AR. Chronic pulmonary emboli and radiologic mimics on CT pulmonary angiography: a diagnostic challenge. Chest. 2013 May:143(5):1460-1471. doi: 10.1378/chest.12-1384.
48. Nishiyama KH, Saboo SS, Tanabe Y, Jasinowodolinski D, Landay MJ, Kay FU. Chronic pulmonary embolism: diagnosis. Cardiovascular diagnosis and therapy. 2018 Jun:8(3):253-271. doi: 10.21037/cdt.2018.01.09.
49. Njei B, Sanchez H. Neurofibromatosis type 1, recurrent pulmonary embolism, and a periampullary carcinoid tumor: is there a link? Connecticut medicine. 2013 Feb:77(2):77-80
50. Guzman S, Khan MS, Chodakiewitz Y, Khan M, Chodakiewitz MS, Julien P, Luthringer DJ. Pulmonary capillary hemangiomatosis: a lesson learned. Autopsy & case reports. 2019 Jul-Sep:9(3):e2019111. doi: 10.4322/acr.2019.111.
51. Hartopo AB, Dinarti LK, Wahab AS. The Challenge in Diagnosis and Current Treatment of Chronic Thromboembolic Pulmonary Hypertension. Acta medica Indonesiana. 2017 Apr:49(2):183-191
52. Korsholm K, Andersen A, Mellemkjær S, Nielsen DV, Klaaborg KE, Ilkjær LB, Nielsen-Kudsk JE. Results from more than 20 years of surgical pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Denmark. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2017 Oct 1:52(4):704-709. doi: 10.1093/ejcts/ezx182.
53. Segel MJ, Kogan A, Preissman S, Agmon-Levin N, Lubetsky A, Fefer P, Schaefers HJ, Raanani E. Pulmonary Endarterectomy Surgery for Chronic Thromboembolic Pulmonary Hypertension: A Small-Volume National Referral Center Experience. The Israel Medical Association journal : IMAJ. 2019 Aug:21(8):528-531