Journal of Cardiovascular Emergencies 2026;12(2):52-60
DOI: 10.2478/jce-2026-0001

REVIEW

Biomechanical Characterization and Remodeling of Pulmonary Arteries in Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct and potentially curable form of pulmonary hypertension that develops following incomplete resolution of acute pulmonary embolism, leading to persistent fibrotic obstruction of the pulmonary arteries and progressive microvascular disease. Although CTEPH has traditionally been assessed using steady-flow hemodynamic parameters such as mean pulmonary arterial pressure and pulmonary vascular resistance, growing evidence suggests that pulmonary artery stiffness and altered vascular biomechanics are critical contributors to disease severity, right ventricular dysfunction, and patient outcomes. This narrative review summarizes current knowledge on the structural remodeling and biomechanical behavior of pulmonary arteries in CTEPH, with emphasis on changes affecting arterial compliance, impedance, and right ventricle–pulmonary artery coupling. Key mechanisms include thrombus organization, endothelial dysfunction, smooth muscle cell proliferation, extracellular matrix deposition, and mechanobiological feedback loops that reinforce vascular stiffening. The review further discusses available experimental and computational approaches used to characterize pulmonary vascular mechanics and highlights the clinical relevance of biomechanical markers in improving prognostic stratification and therapeutic decision-making. Finally, it outlines gaps in current evidence regarding reversibility of vascular stiffness and the long-term impact of surgical, interventional, and medical therapies, supporting the need for integrated biomechanical assessment in future CTEPH research and management.

Keywords: chronic thromboembolic pulmonary hypertension, biomechanical characterization, vascular remodeling, pulmonary artery, acute pulmonary embolism

ARTICLE HISTORY

Received: January 2, 2026
Accepted: February 19, 2026

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INTRODUCTION

Pulmonary artery hypertension (PAH) is a hemodynamic condition marked by a persistent and abnormal rise in mean pulmonary arterial pressure (mPAP > 20 mmHg).[1] This occurs as a result of increased pulmonary resistance and higher pulmonary venous pressure, caused by vasoconstriction, endothelial dysfunction, vascular remodeling, and vessel obstruction, ultimately leading to right ventricular hypertrophy.[1] Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct form of pulmonary hypertension (PH) resulting from repetitive and unresolved episodes of pulmonary embolism (PE). It is characterized by persistent intravascular fibrotic clots of the pulmonary arteries, leading to increased pulmonary vascular pressure and, if left untreated, to right heart failure.[2,3] According to ESC/ERS guidelines, CTEPH is classified as group 4 PH associated with pulmonary artery obstructions.[4] In patients with PH, the presence of mismatched perfusion defects on ventilation–perfusion (V′/Q′) scintigraphy after at least 3 months of effective anticoagulation is suggestive of CTEPH, with definitive diagnosis confirmed by right heart catheterization, computed tomography pulmonary angiography, and digital subtraction angiography.[1]

The most common risk factors for CTEPH include a history of PE1[1,5–7] and underlying thrombophilic conditions. Thrombophilias, such as antiphospholipid antibody syndrome, factor V Leiden mutation, and deficiencies of protein C, protein S, or antithrombin III, further increase susceptibility.[1,5–7] Additional risk factors include prior splenectomy, which alters platelet function and promotes hypercoagulability, as well as malignancy, hypothyroidism, and chronic inflammatory disorders, all of which can contribute to a prothrombotic state.[1,5–7] Moreover, the COVID-19 pandemic has recently had a detrimental impact on healthcare services[8,9] and the management of chronic diseases, while also increasing the risk of overall complications,[10–13] as well as coagulation disorders, acute limb ischemia,[14] deep vein thrombosis,[15] and acute pulmonary embolism (APE).[15] In contrast, studies have not found an increased incidence of CTEPH associated with PE in patients with COVID-19 compared with patients without COVID-19. Despite a notable rise in APE, the long-term development of CTPEH remained similar between the two groups.[16–18]

This narrative review summarizes current evidence on structural and mechanical changes of the pulmonary arteries in CTEPH, highlighting available experimental and computational approaches used to characterize these phenomena. It also discusses the clinical relevance of these findings and outlines key knowledge gaps to guide future research and therapeutic strategies.

DEFINITION AND EPIDEMIOLOGY OF CTEPH

Estimating the true incidence of CTEPH is challenging, mainly because the condition is often underdiagnosed and reported rates following APE may be overestimated.[19] Only a limited number of studies have evaluated the epidemiology of CTEPH, with reported incidence rates ranging from 0.9 per million inhabitants in the Spanish registry[20] to 5.7 per million inhabitants in the CTEPH European registry.[21] Moreover, a systematic review by Leber *et al.*,[22] encompassing 33 studies, reported the following estimated ranges in adults (per million inhabitants): PAH incidence of approximately 5.8; PAH prevalence of 47.6–54.7; CTEPH incidence of 3.1–6.0; and CTEPH prevalence of 25.8–38.4.

PATHOPHYSIOLOGY OF CTEPH

The pathophysiological process of CTEPH is believed to begin with incomplete resolution of APE, with thrombi transforming into fibrotic, wall-adherent tissue that is incorporated into the intima of proximal and segmental pulmonary arteries, resulting in fixed mechanical obstruction and luminal narrowing.[23–28] This leads to various hemodynamic consequences confirmed by right heart catheterization: increased pulmonary vascular resistance (PVR ≥ 2 Wood units), increased mean pulmonary arterial pressure (mPAP ≥ 20 mmHg) at rest, and normal or low pulmonary artery wedge pressure (PAWP ≤ 15 mmHg).[23–28]

Most cases of CTEPH start with APE, predominantly from deep vein thrombosis. Normally, thrombi are resolved through fibrinolysis, but some fail to fully dissolve and organize into fibrotic clots, becoming permanent intravascular obstructions that increase vascular resistance in the pulmonary circulation. Furthermore, a secondary small-vessel microvasculopathy affecting vessels <500 μm in diameter is also present.[29] Non-obstructed arterioles undergo remodeling, including intimal proliferation, as part of the microvasculopathy.[23–28] These alterations are similar to those observed in PAH. Both the proximal fibrotic obstructions and distal microvascular remodeling contribute to elevated PVR, increased mPAP, and progressive right ventricular overload and failure.[23–28]

The hallmark symptom is dyspnea on progressively less exertion. Other common symptoms include fatigue and reduced exercise tolerance, as well as palpitations,

hemoptysis, syncope or pre-syncope.[25–28] The principal clinical signs are tachycardia and tachypnoea, a loud pulmonary component of the second heart sound (P2), and a right ventricular heave or parasternal lift.[25–28] As the disease advances to right heart failure, additional findings may include hepatomegaly, peripheral edema, ascites, and prominent pulsatile jugular veins.[26–28] CTEPH is further characterized by an insidious onset and progressive decline in functional capacity. Early in the course, patients may be asymptomatic but gradually develop persistent exercise limitation as PVR increases, leading to PH and eventual right ventricular failure.[29,30] This gradual progression and the non-specific nature of symptoms frequently result in delayed diagnosis, with most patients presenting in NYHA functional class III/IV at the time of diagnosis.[30]

ANATOMY AND ROLE OF PULMONARY ARTERIES

The pulmonary artery arises from the right ventricle and serves as the main vessel carrying blood into the pulmonary circulation. The pulmonary trunk lies superior to the heart and slightly to the left of the ascending aorta.[31] After a short course, it bifurcates into the right and left pulmonary arteries at approximately the level of the T5–T6 vertebrae. The left pulmonary artery typically continues in line with the pulmonary trunk, whereas the right pulmonary artery branches off at a near right angle.[32] The pulmonary trunk is approximately 5 cm long and 3 cm in diameter, allowing it to accommodate the large volume of blood ejected from the heart with each contraction.[33] Like other major arteries, the pulmonary arteries are composed of three distinct layers: the tunica intima, a smooth inner lining; the tunica media, a muscular middle layer responsible for maintaining blood flow; and the tunica adventitia, a supportive and protective outer layer.[34]

Functionally, the pulmonary arteries transport deoxygenated blood from the right side of the heart to the lungs for oxygenation, forming the essential link between the heart and the pulmonary system.[35] Blood flows from the right atrium into the right ventricle, which pumps it through the pulmonary trunk and into its branches. This blood is low in oxygen and relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries, after which oxygen-rich, carbon dioxide-poor blood returns to the left atrium via the pulmonary veins. It then passes into the left ventricle, which pumps it into the systemic circulation.[34,35]

VASCULAR REMODELING IN PULMONARY ARTERIAL HYPERTENSION

REMODELING MECHANISMS ACROSS PAH TYPES

PAH is primarily driven by pulmonary vascular remodeling, a process marked by structural alterations affecting all three layers of the vessel wall.[36] This progressive remodeling converts the normally high-compliance, low-resistance pulmonary circulation into a rigid, narrowed, and obstructive vascular system, ultimately increasing PVR. At the cellular level, these changes arise through multiple interrelated mechanisms. Endothelial dysfunction is often an early event, in which vascular injury promotes a ‘cancer-like’ endothelial phenotype that is pro-proliferative and resistant to apoptosis, leading to intimal thickening and the development of plexiform lesions, both of which significantly reduce the diameter of the arterial lumen.[36,37] In parallel, pulmonary artery smooth muscle cells undergo hypertrophy and hyperplasia, shifting from a contractile to a synthetic, proliferative phenotype, thereby contributing to medial thickening of previously non-muscular distal arterioles.[38] Additionally, the activation of adventitial fibroblasts increases the production and deposition of extracellular matrix (ECM) components such as collagen and elastin, promoting perivascular fibrosis and further stiffening of the vessel wall.[38,39]

REMODELING DRIVERS

Structural remodeling in PH is driven by three major biological and physical stimuli. Mechanical forces, including increased circumferential stretch and shear stress, trigger mechanobiological feedback mechanisms that promote a self-perpetuating cycle of vascular stiffening by activating signaling pathways that enhance cellular proliferation and ECM deposition.[39] Inflammation and immune dysregulation also play a central role, as perivascular infiltration by macrophages, T cells, and B cells increases the release of pro-inflammatory cytokines such as IL-6, thereby accelerating vascular remodeling.[40] This contributes to the so-called ‘angioproliferative’ phenotype, which is now thought to arise largely from a loss of coordination between innate and adaptive immune responses in PH.[41] Finally, hypoxia-related mechanisms, particularly prominent in group 3 PH, promote the upregulation of hypoxia-inducible factors, leading to sustained vasoconstriction and increased proliferation of pulmonary artery smooth muscle cells, processes that can contribute to disease progression across several PH subtypes.[36]

CONSEQUENCES OF REMODELING

The progressive accumulation of these structural alterations ultimately results in marked hemodynamic compromise.[42,43] Narrowing of the vascular lumen, combined with ECM deposition and medial thickening, increases PVR while simultaneously reducing vascular compliance, producing a 'stiffened' pulmonary circulation and a greater pulsatile load on the heart.[44] Over time, this chronically elevated afterload drives the development of right ventricular (RV) dysfunction, initially provoking compensatory RV hypertrophy to maintain cardiac output.[45] However, with sustained pressure overload and ongoing remodeling, the right ventricle eventually decompensates, leading to RV dilation, impaired contractility, and systemic congestion, which represent major contributors to morbidity and mortality in patients with PH.[46–50]

CLINICAL IMPLICATIONS OF PULMONARY ARTERY STIFFENING IN CTEPH

RIGHT VENTRICULAR AFTERLOAD BEYOND RESISTANCE

CTEPH is traditionally characterized and assessed using steady-flow hemodynamic parameters, most notably PVR. However, growing evidence indicates that pulmonary artery stiffening and altered vascular biomechanics play a critical role in disease expression, RV dysfunction, and treatment response.[23] In CTEPH, unresolved organized thrombi within the pulmonary arteries undergo fibrotic transformation and are frequently accompanied by distal pulmonary vasculopathy, including small-vessel remodeling and post-capillary changes.[51] Together, these processes lead to reduced pulmonary arterial compliance and increased vascular stiffness, thereby imposing a complex RV afterload that extends beyond resistance alone.[23,51]

The importance of arterial compliance, pulsatile load, and pulmonary vascular impedance in CTEPH is underscored by the well-documented dissociation between the anatomical extent of vascular obstruction and measured hemodynamic severity.[52] Patients with similar degrees of mechanical obstruction may exhibit markedly different pulmonary pressures, RV function, and exercise capacity, suggesting that pulsatile components of RV afterload substantially influence clinical presentation.[23] Increased pulmonary artery stiffness augments systolic RV workload and impairs efficient energy transfer from the RV to the pulmonary circulation, thereby contributing to RV–pulmonary artery (PA) uncoupling.[23,53] This maladaptive interaction promotes RV hypertrophy, dilation, and eventual failure, even in patients with only moderate elevations in mPAP. Conventional echocardiographic indices of RV function correlate imperfectly with invasive afterload measurements and may lose prognostic accuracy following therapeutic interventions, highlighting the need for metrics that better capture RV–PA coupling and pulsatile load.[54]

PROGNOSTIC VALUE OF BIOMECHANICAL MARKERS

Beyond their pathophysiological relevance, biomechanical alterations of the pulmonary circulation may hold important prognostic value in CTEPH. Persistent symptoms, impaired exercise capacity, and adverse long-term outcomes observed in a subset of patients despite anatomically successful pulmonary endarterectomy (PEA) suggest that residual vascular remodeling and arterial stiffening, particularly within the distal pulmonary circulation, have clinically meaningful consequences.[51,52] Reduced pulmonary arterial compliance and impaired RV–PA coupling likely contribute to ongoing RV dysfunction and exercise limitation, independent of resting pulmonary pressures or PVR.[23] These observations support the potential role of biomechanical markers, such as pulmonary arterial stiffness, compliance, and impedance, as complementary prognostic indicators that may improve risk stratification beyond conventional hemodynamic parameters.

The extent to which adverse vascular remodeling is reversible following treatment appears to be variable and therapy-dependent. PEA often results in dramatic reductions in mPAP and PVR, with substantial improvements in RV function.[52] Nevertheless, normalization of pulmonary vascular mechanics is not universal, particularly in patients with long-standing disease or advanced microvascular involvement. Persistent arterial stiffening after surgery may explain incomplete functional recovery and residual PH in some patients.[53] In contrast, balloon pulmonary angioplasty (BPA), which targets segmental and subsegmental vascular lesions, has been shown to improve pulmonary arterial compliance, RV function, and cardiac strain biomarkers. These findings suggest that distal pulmonary vascular remodeling retains at least partial reversibility and that improvements in pulsatile afterload may translate into meaningful clinical benefit.[51–53]

THE IMPACT OF TREATMENT STRATEGY

The recognition of pulmonary artery stiffening also has important implications for treatment strategy in CTEPH. PEA remains the treatment of choice for operable dis-

ease, as it directly removes proximal obstructive material and immediately reduces RV afterload.[52,54] However, appreciation of the role of vascular stiffness reinforces the importance of early referral for surgical evaluation, before irreversible distal remodeling and RV–PA uncoupling develop.[52] BPA has emerged as an effective alternative or adjunctive therapy in inoperable CTEPH and in patients with persistent or recurrent PH after PEA, with favorable effects on vascular compliance and RV performance. These biomechanical improvements highlight that the benefits of BPA extend beyond resistance reduction alone.[53–55]

Pharmacologic therapy further underscores the relevance of vascular stiffness in CTEPH. The presence of pulmonary microvascular disease and endothelial dysfunction provides the rationale for targeted medical treatment, particularly in inoperable patients or those with residual PH.[53] Riociguat, a soluble guanylate cyclase stimulator, has demonstrated improvements in exercise capacity and pulmonary hemodynamics in this population, likely through effects on vascular tone and compliance.[53,55] Although medical therapy does not address fixed proximal obstruction, its impact on the dynamic components of RV afterload supports the concept that modulation of pulmonary vascular biomechanics is a clinically meaningful therapeutic goal.[55]

KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

Despite the substantial improvement in prognosis achieved with PEA and BPA, the pathogenesis of CTEPH remains only partially understood. The disease cannot be attributed solely to the mechanical persistence of thrombotic material; rather, accumulating evidence supports an active biological process characterized by thrombus organization and progressive vascular remodeling. In a landmark prospective study, Pengo *et al*.[56] reported a cumulative CTEPH incidence of 3.8% at 2 years after APE. Similarly, a meta-analysis by Ende-Verhaar *et al*.[57] estimated an incidence ranging from 0.5% to 4%, underscoring that thrombus resolution is the predominant outcome, whereas progression to CTEPH represents a biological exception. Further mechanistic insights were provided by Morris *et al*.,[58] who demonstrated that fibrin derived from patients with CTEPH displays distinct structural properties, including thicker fibers, reduced porosity, and increased resistance to fibrinolysis, alongside elevated levels of plasminogen activator inhibitor-1 (PAI-1), which suppresses plasminogen activation. Moreover, Bonderman *et al*.[59] showed that increased factor VIII levels, independent of inflammation, promote a denser fibrin network and reduce susceptibility to plasma-mediated fibrinolysis in patients with CTEPH.

Quarck *et al*.[60] identified macrophage infiltration and increased expression of monocyte chemoattractant protein-1 (MCP-1) within endarterectomized material obtained during surgery, highlighting a prominent inflammatory component in CTEPH lesions. Consistently, Magoń *et al*.[61] reported elevated circulating levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in patients with CTEPH. In PAH, IL-6 blockade has been shown to attenuate experimental vascular remodeling, suggesting a potential pathogenic role for IL-6 in CTEPH as well. Mechanistically, IL-6 promotes vascular remodeling by driving smooth muscle cell proliferation through STAT3 activation.[62–64] Moreover, Giaid *et al*.65 demonstrated endothelin-1 overexpression in severe PH, including CTEPH, and reported endothelial features consistent with dysfunction, namely reduced nitric oxide bioavailability and increased expression of adhesion molecules such as VCAM-1 and ICAM-1. Together, these findings support a central role for endothelial dysfunction in CTEPH, contributing to impaired fibrinolysis, enhanced leukocyte adhesion, and pathological vascular proliferation.

Endarterectomized specimens from patients with CTEPH reveal disorganized neoangiogenesis and evidence of activation of the platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) pathways within lung tissue.[27,66] Enhanced PDGF signaling promotes smooth muscle cell migration, partly through fibroblast activation, whereas increased TGF-β drives extracellular matrix accumulation via endothelial-to-mesenchymal transition.[67–69] Several mechanisms may account for the persistence of residual PAH after PEA, including irreversible microvasculopathy, progressive postoperative vascular remodeling, and recurrent thrombosis. In experienced centers, perioperative mortality is now reported to be below 5%, as shown by Jamieson *et al*.[70] However, Cannon *et al*.[71] demonstrated that residual PH remains a key determinant of adverse outcomes and poorer long-term prognosis. Therapeutic response is highly heterogeneous, likely reflecting the lack of molecular phenotyping and validated predictors of treatment response.

Additional studies are needed to better characterize the biomechanical properties of the pulmonary artery in patients with and without CTEPH. Only a limited number of studies have performed ex vivo planar equibiaxial tensile testing of pulmonary arteries,[72–76] mainly because ex vivo assessment of biomechanical properties can be affected by several sources of bias. These include the protocol used to measure specimen thickness,[77,78] variations in testing

procedures and the biotesting equipment used,[79,80] as well as differences in specimen storage conditions.[81]

In the context of interventional advances, the next stage of CTEPH research must move beyond the purely mechanical paradigm and integrate molecular biology, advanced phenotyping, and personalized medicine. Future directions should be multidisciplinary, combining translational research, prospective clinical studies, and multi-omics technologies. Dedicated genomic studies are needed to address several hypotheses, including whether CTEPH results from a gene–environment interaction in which pulmonary embolism acts as a trigger on a biologically predisposed background.

A central challenge will be establishing large, multicenter cohorts capable of supporting robust genomic, transcriptomic, proteomic, and metabolomic profiling to identify reproducible molecular signatures. The multi-omics network analysis approach successfully applied in PAH could be adapted to CTEPH to define molecular subtypes, uncover dominant pathogenic pathways (whether primarily inflammatory, fibrotic, or mixed), and identify biomarkers predictive of therapeutic response. Histopathological studies already demonstrate marked heterogeneity within CTEPH lesions, reinforcing the need for more granular biological characterization. Single-cell RNA sequencing is a powerful tool for resolving distinct cellular subpopulations, mapping pathway activity within specific cell types, and interrogating cell–cell interactions that drive disease progression. Notably, studies in PAH have identified hyperproliferative endothelial subpopulations, providing a compelling model for similar discoveries in CTEPH.

CONCLUSIONS

CTEPH remains a complex and frequently underdiagnosed condition in which persistent thromboembolic obstruction and secondary microvascular disease jointly drive progressive pulmonary vascular remodeling and RV dysfunction. While PVR has traditionally represented the main hemodynamic marker used to evaluate disease severity, increasing evidence highlights that pulmonary artery stiffening and impaired vascular compliance are equally important determinants of RV afterload, clinical deterioration, and functional limitation. This review emphasizes that biomechanical changes of the pulmonary circulation, including altered elasticity, reduced compliance, and increased impedance, contribute substantially to RV–PA uncoupling and may explain the dissociation often observed between anatomical obstruction and hemodynamic severity in CTEPH. In this context, BPA and targeted pharmacologic therapies, such as riociguat, appear to offer meaningful improvement not only by reducing resistance but also by modulating the pulsatile components of RV afterload. Overall, understanding pulmonary artery remodeling through mechanobiological perspectives may enhance risk stratification and support more personalized treatment strategies in CTEPH. Future studies integrating experimental vascular characterization with computational modelling and clinically accessible stiffness metrics are essential to clarify reversibility, identify novel therapeutic targets, and ultimately improve long-term outcomes in this challenging disease.

CONFLICT OF INTEREST

Nothing to declare.

FUNDING

This work was supported by the George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania (research grant no. 837/3/23.01.2025).

AUTHOR CONTRIBUTIONS

Both authors have contributed equally to this work, reviewed, and approved the final manuscript prior to publication.

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