SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

A Comprehensive Approach to Chronic Thromboembolic Pulmonary Hypertension: Pathophysiology, Diagnostics, and Therapeutic Innovations from the Clinician's Perspective

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UNIVERSITY OF DEBRECEN
KÁLMÁN LAKI DOCTORAL SCHOOL

DEBRECEN, 2026

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 11 a.m. on 1st of April, 2026

List of Abbreviations

ACVRL1	gene (Activin A Receptor Type I-Like 1)
ADAMTS13	gene (A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif 13)
APTT	Activated Partial Thromboplastin Time
AT	Antithrombin
BMI	Body Mass Index
BMPR2	gene (Bone Morphogenetic Protein Receptor Type 2)
BPA	Balloon Pulmonary Angioplasty
CAV1	gene (Caveolin-1)
CI	Cardiac Index
CM-AVM	Capillary-Arteriovenous Malformation Syndrome
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPB2	gene (Carboxypeptidase B2)
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CTPA	CT Pulmonary Angiography
dPAP	Diastolic Pulmonary Arterial Pressure
dRVVT	Diluted Russell's Viper Venom Time
ESC/ERS	European Society of Cardiology / European Respiratory Society
F13A1	gene (Factor XIII Subunit A1)
F13B	gene (Factor XIII Subunit B)
FGA	gene (Fibrinogen Alpha Chain)
FGB	gene (Fibrinogen Beta Chain)
GDF2	gene (Growth Differentiation Factor 2)
GWAS	Genome-Wide Association Study
HCII	Heparin Cofactor II
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HHT	Hereditary Hemorrhagic Telangiectasia
HMWK	High Molecular Weight Kininogen
HRG	gene (Histidine-Rich Glycoprotein)

iPAH	Idiopathic Pulmonary Arterial Hypertension
ISTH	International Society on Thrombosis and Haemostasis
IVC	Inferior Vena Cava
KCNK3	gene (Potassium Two-Pore Domain Channel Subfamily K Member 3)
KDR	gene (Kinase Insert Domain Receptor)
KDE	Kernel Density Estimation
KNG1	gene (Kininogen 1)
MAF	Minor Allele Frequency
mPAP	Mean Pulmonary Arterial Pressure
MPL	gene (MPL Proto-Oncogene, Thrombopoietin Receptor)
NGS	Next-Generation Sequencing
NFE2	gene (Nuclear Factor, Erythroid 2)
NYHA	New York Heart Association (Functional Classification)
PA	Pulmonary Angiography
PAH	Pulmonary Arterial Hypertension
PAI-1	Plasminogen Activator Inhibitor-1
PC	Protein C
PE	Pulmonary Embolism
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
PLG	gene (Plasminogen)
PROC	gene (Protein C)
PROS1	gene (Protein S)
PS	Protein S
PVR	Pulmonary Vascular Resistance
RASA1	gene (RAS P21 Protein Activator 1)
RHC	Right Heart Catheterization
RNF213	gene (Ring Finger Protein 213)
RV	Right Ventricle / Right Ventricular
sGC	Soluble Guanylate Cyclase
SG	Swan-Ganz Catheterization

Introduction and Literature Review

Pulmonary hypertension (PH) represents a heterogeneous group of disorders that develop secondary to various underlying conditions and are characterized by a sustained elevation of pressure within the pulmonary arterial system. Based on etiology, PH is classified into five major groups: (I) pulmonary arterial hypertension (PAH), (II) PH due to left heart disease, (III) PH associated with lung diseases and/or hypoxia, (IV) chronic thromboembolic pulmonary hypertension (CTEPH), and (V) PH with unclear or multifactorial mechanisms. Although CTEPH is the rarest subtype, its clinical relevance extends beyond its rarity, as it is the only form of PH that is potentially curable through a definitive surgical intervention—pulmonary endarterectomy (PEA)—when recognized and treated in a timely manner.

The precise etiology of CTEPH remains incompletely understood. While pulmonary embolism (PE) is considered the predominant initiating event, up to 25–30% of patients have no documented history of acute PE. In such cases, in situ thrombosis, microembolization, or clinically silent ("subclinical") embolic events may underlie the disease. Pulmonary embolism is a life-threatening thromboembolic condition and a leading cause of cardiovascular morbidity and mortality worldwide. In most patients, the embolic material undergoes spontaneous resolution within approximately three months, accompanied by restoration of pulmonary vascular integrity. In a minority of cases, however, incomplete thrombus resolution leads to chronic obstruction and remodeling, resulting in CTEPH. According to international registries, approximately 2–4% of patients surviving an acute PE ultimately develop CTEPH.

At the core of CTEPH pathogenesis lies impaired thrombus resolution following acute PE. Under physiological circumstances, embolic material within the pulmonary arteries is completely degraded through fibrinolytic and cellular mechanisms. In certain individuals, however, the thrombus undergoes incomplete lysis and becomes organized and fibrotic, firmly adhering to the vessel wall. This organized, fibrotic material causes partial or complete luminal obstruction and persistent elevation of pulmonary vascular resistance (PVR). The progressive increase in PVR leads to right ventricular (RV) dysfunction and, if untreated, right heart failure—a major determinant of mortality in CTEPH. While the primary lesions predominate in medium-sized and large pulmonary arteries, CTEPH is not merely the result of mechanical obstruction. Hemodynamic alterations trigger secondary small-vessel arteriopathy in non-obstructed segments, characterized by "in situ" thrombosis and histopathological features

similar to those seen in pulmonary arterial hypertension. This so-called “small-vessel disease” contributes substantially to disease progression and clinical severity. The ensuing chronic pressure overload leads initially to RV hypertrophy, followed by dilation, functional tricuspid regurgitation, right atrial enlargement, and ultimately, end-stage right heart failure—the leading cause of death. Importantly, when recognized early and managed appropriately, disease progression can be halted, and in some cases, partially reversed.

Early diagnosis of CTEPH remains a major challenge, as symptoms are nonspecific and evolve gradually over years. Patients typically report exertional dyspnea, fatigue, decreased exercise tolerance, dizziness, exertional syncope, and peripheral edema. These manifestations are often misattributed to more common disorders such as asthma, chronic obstructive pulmonary disease (COPD), or left heart failure. Consequently, diagnostic delay is frequent, with patients often reaching specialized PH centers 18–24 months after symptom onset. Such delays have serious prognostic implications, as established right heart failure carries a poor prognosis. Conversely, timely recognition enables curative surgical therapy, balloon pulmonary angioplasty (BPA), or targeted pharmacological treatment.

Several risk factors have been identified that predispose to CTEPH development. The most relevant include recurrent or massive pulmonary embolism, large thrombus burden at a young age, inadequate or prematurely discontinued anticoagulation, malignant disease, and genetic or epigenetic factors influencing pulmonary microvascular remodeling. Additional risk factors comprise splenectomy or functional asplenia, chronic inflammatory conditions (e.g., inflammatory bowel disease, osteomyelitis), autoimmune diseases, and antiphospholipid syndrome. Hypothyroidism, ventriculo-atrial shunts, and myeloproliferative disorders have also been associated with increased risk. International CTEPH registries have shown an overrepresentation of non-O blood groups among patients, possibly related to higher plasma levels of von Willebrand factor and factor VIII, predisposing to thrombosis. Interestingly, classical venous thromboembolic risk factors—such as factor V Leiden mutation or deficiencies of protein C or S—are less commonly implicated. The sex difference is modest, with a slightly higher prevalence in males, though CTEPH is not uncommon among females. The exact pathomechanism and risk profile remain incompletely elucidated, underscoring the multifactorial, polygenic nature of the disease.

The clinical presentation of CTEPH evolves insidiously. Patients often experience mild or moderate exertional dyspnea, accompanied by fatigue, reduced physical capacity, chest

tightness, or palpitations—sometimes due to atrial fibrillation or flutter. With disease progression, exertional syncope may occur, reflecting severe RV pressure overload and reduced cardiac output. Signs of right heart failure—peripheral edema, hepatomegaly, ascites—dominate in advanced stages. Unfortunately, these findings are nonspecific and may mimic left heart failure, COPD, asthma, or heart failure with preserved ejection fraction (HFpEF), leading to prolonged diagnostic delay. Post-embolic conditions deserve particular attention: a subset of patients develop "post-PE syndrome," characterized by persistent dyspnea and exercise intolerance. While these symptoms often improve spontaneously, persistence beyond 3–6 months warrants evaluation for CTEPH.

Diagnosis of CTEPH requires a stepwise, multidisciplinary approach. General practitioners play a pivotal role by suspecting CTEPH in patients with unexplained dyspnea, exercise intolerance, or persistent symptoms following PE, and referring them to specialized PH centers. Persistence of dyspnea beyond three months despite adequate anticoagulation should raise suspicion. Transthoracic echocardiography may help exclude PH but is insufficient to confirm CTEPH. The gold-standard screening test is ventilation–perfusion (V/Q) scintigraphy, which, when abnormal, should prompt further investigation. The typical finding is a segmental or subsegmental perfusion defect with preserved ventilation, frequently sharply demarcated. Patchy, diffuse defects may also be observed in distal disease. A normal V/Q scan virtually excludes CTEPH (sensitivity ~96–97%, specificity ~90%). Chest radiography and ECG are usually nonspecific. CT pulmonary angiography (CTPA) provides anatomical visualization of webs, stenoses, and chronic occlusions, while echocardiography noninvasively demonstrates RV dilation, tricuspid regurgitation, and estimated systolic pulmonary pressure.

Hemodynamic confirmation is obtained through right heart catheterization (Swan-Ganz catheterization, RHC), which measures right-sided pressures (sPAP, mPAP, dPAP), pulmonary vascular resistance (PVR), and cardiac output/index (CO, CI). The diagnosis of CTEPH is established in patients with persistent precapillary pulmonary hypertension (mean pulmonary arterial pressure ≥20 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, and PVR >2 Wood units) in combination with imaging evidence of chronic thromboembolic obstruction—such as perfusion defects on V/Q scintigraphy or organized thrombotic lesions on pulmonary angiography, CTPA, or MR angiography. These findings must persist for at least three months after the acute event despite adequate anticoagulation to exclude subacute or resolving embolic processes.

Differentiation of CTEPH from other forms of pulmonary hypertension is essential, as therapeutic strategies differ fundamentally. In idiopathic pulmonary arterial hypertension (iPAH), no obstructive thrombus is present, and small-vessel arteriopathy predominates. PH due to left heart disease (HFpEF, HFrEF, valvular disorders) may present with similar symptoms. A pulmonology specialist evaluation may identify underlying lung diseases. For the clinician, the key principle is to consider CTEPH in any patient with persistent dyspnea—particularly following an episode of pulmonary embolism.

The primary therapeutic goal in chronic thromboembolic pulmonary hypertension (CTEPH) is to reduce pulmonary vascular resistance and to unload the right ventricle. Following diagnosis, the next crucial step is the assessment of operability, which is determined by the localization and characteristics of the lesions as well as the general condition of the patient. Pulmonary endarterectomy (PEA) represents a potentially curative option for patients with central-type disease, involving the surgical removal of organized fibrotic thromboembolic material from the pulmonary arteries. The procedure should only be performed in high-volume expert centers, where perioperative mortality rates remain below 5%, and long-term survival outcomes are excellent.

Balloon pulmonary angioplasty (BPA) provides an alternative interventional approach for patients with distal thrombotic lesions that are surgically inaccessible, or for those deemed inoperable due to anatomical or comorbid factors. Through multiple staged catheter-based sessions, the stenotic segments of the pulmonary arteries are carefully dilated using balloon inflation, leading to a gradual reduction in pulmonary vascular resistance and pulmonary arterial pressures.

CTEPH management is fundamentally not based on pharmacotherapy, as initiating medical treatment prior to definitive therapy may delay curative intervention and consequently worsen survival outcomes, according to major clinical studies. Among pharmacological agents, riociguat, a soluble guanylate cyclase (sGC) stimulator, remains the only approved medication for patients with inoperable or residual CTEPH. Contemporary treatment strategies increasingly adopt an individualized and multimodal approach, often involving combination therapy. In cases of residual pulmonary hypertension after PEA, riociguat and/or BPA may be considered as adjunctive therapeutic options.

The prognosis of CTEPH has markedly improved over the past two decades owing to advances in surgical, interventional, and medical therapies. Untreated CTEPH carries a poor prognosis, with progressive right heart failure leading to a 5-year survival rate of only 10–30% when mean pulmonary artery pressure (mPAP) exceeds 40–50 mmHg. Following successful PEA, five-year survival reaches 80–90%, accompanied by dramatic improvement in functional status. BPA and targeted medical therapy have also yielded increasingly favorable outcomes, though complete cure remains less common. In inoperable patients, BPA significantly reduces pulmonary vascular resistance and improves NYHA functional class, with a 3–5-year survival exceeding 90%.

Early diagnosis and referral to specialized expert centers remain key determinants of successful outcomes. Diagnostic delay is associated with worse prognosis, as advanced right ventricular remodeling may become only partially reversible. Long-term follow-up should be performed in multidisciplinary pulmonary hypertension centers, with regular echocardiographic, functional, and laboratory assessments.

Both general practitioners and internists play a pivotal role in the early recognition of CTEPH, acting as the first line of clinical "gatekeepers." Persistent or worsening dyspnea and exercise intolerance 3–6 months after an episode of pulmonary embolism (PE) should rise the suspicion of CTEPH. Repeated diagnoses of "asthma" or "COPD" unresponsive to therapy may suggest the underlying condition. Closer follow-up is recommended for younger patients with large clot burden during PE. It is essential to emphasize the importance of lifelong anticoagulation and thrombosis prevention, as well as patient education, highlighting that pulmonary embolism may not always resolve completely and that persistent symptoms warrant further evaluation.

Internists should suspect CTEPH when echocardiography reveals right heart dilation, elevated pulmonary pressures, chronic dyspnea, exercise limitation, or recurrent right heart failure. In such cases, further diagnostic steps are indicated, including ventilation-perfusion (V/Q) scintigraphy, CT pulmonary angiography, and referral to a pulmonary hypertension center.

The pathogenesis of CTEPH is complex and multifactorial, involving both acquired and genetic risk factors. The mere presence of such risk factors does not necessarily lead to disease manifestation, suggesting a significant role for genetic predisposition, as supported by reports

of familial clustering. Since a considerable proportion of CTEPH patients exhibit prothrombotic tendencies, research has focused on genes involved in thrombosis susceptibility. Several candidate genes implicated in the coagulation cascade and fibrinolysis have been identified, potentially contributing to thrombus persistence and pathological vascular remodeling.

However, genetic study results remain heterogeneous. Certain studies have suggested that SERPINC1 mutations—encoding antithrombin (AT)—may increase the risk of PE and CTEPH through reduced anticoagulant activity, although classical hereditary thrombophilic factors (e.g., mutations in *SERPINC1, PROC, PROS1*, as well as Factor V Leiden and the prothrombin G20210A variant) are not considered independent risk factors for CTEPH. Variants in the *FGA* and *FGB* genes, encoding fibrinogen α- and β-chains, have been associated with altered clot structure and fibrinolytic resistance, potentially promoting persistent thrombotic obstruction and disease development. Abnormal platelet hyperreactivity may also play a contributory role.

Impaired fibrinolysis provides a plausible mechanism explaining why certain thrombi fail to resolve after acute PE and instead undergo organization and fibrosis. Nevertheless, current data remain inconclusive, as microvascular remodeling likely plays a central role in CTEPH pathogenesis. Recent investigations have expanded toward genes involved in vascular development, endothelial signaling, and barrier function, supporting the hypothesis that endothelial dysfunction contributes to abnormal remodeling. This concept is further reinforced by observations that many patients with established CTEPH have no documented history of symptomatic PE, implying prior subclinical thromboembolic events.

The mechanisms underlying why only a small subset of patients develop CTEPH following PE remain poorly understood. The interplay between multiple pathophysiological pathways and the low disease prevalence pose major challenges to research. Many risk factors overlap with those of PE and venous thromboembolism (VTE), complicating the identification of specific predisposing elements unique to CTEPH. Comparative studies between patients who developed CTEPH and those who experienced PE without subsequent CTEPH are therefore essential.

High-throughput genomic technologies, such as next-generation sequencing (NGS), represent powerful tools for identifying genetic variants associated with disease phenotypes. Whole-exome sequencing (WES) focuses on the protein-coding regions of the genome and

enables the detection of mutations affecting key biological pathways, including thrombosis regulation and vascular homeostasis.

Due to the progressive nature of CTEPH, early detection is of paramount importance. Measurement of right ventricular (RV) pressure is a key component of the hemodynamic evaluation of CTEPH patients, playing an essential role in diagnosis, risk stratification, prognostication, treatment planning, and follow-up. Elevated RV pressure reflects increased pulmonary vascular resistance and provides valuable insight into disease severity and right ventricular function.

Echocardiography is recommended as the first-line, non-invasive diagnostic tool in suspected pulmonary hypertension, offering a reproducible and cost-effective way to estimate RV pressure; however, its accuracy may vary across clinical scenarios. Invasive modalities such as right heart catheterization and selective pulmonary angiography offer superior precision but are associated with higher procedural risks. Imaging assessment may be limited by factors including suboptimal acoustic windows, arrhythmias, or anatomical variability of RV geometry.

Given the importance of frequent monitoring of RV pressure in CTEPH management, it is essential to understand the strengths and limitations of each measurement modality. The emerging multimodal therapeutic strategy—integrating surgical, interventional, and pharmacological approaches—has become the cornerstone of modern CTEPH management. The primary therapeutic goal remains reperfusion of obstructed or stenotic pulmonary arteries to reduce pulmonary vascular resistance and unload the right ventricle.

Up to 40% of CTEPH patients are not suitable candidates for PEA due to distal disease distribution, unfavorable risk-benefit profiles, or patient refusal. For these individuals, alternative therapies such as BPA have emerged as integral components of the CTEPH treatment algorithm. European studies have demonstrated significant improvements in pulmonary hemodynamics, including 18–30% reduction in mean pulmonary arterial pressure (mPAP) and substantial decreases in pulmonary vascular resistance (PVR), accompanied by enhanced exercise capacity. Lifelong anticoagulation remains the cornerstone of medical therapy, regardless of surgical eligibility.

In Hungary, BPA was first implemented in Debrecen. In our center, approximately 70% of eligible patients consistently accept this therapeutic approach following multidisciplinary CTEPH-team evaluation. Around 10% of patients are deemed unsuitable for BPA, while 15–20% decline the procedure.

Aims

The focus of our scientific work was chronic thromboembolic pulmonary hypertension (CTEPH), a rare and often elusive disease whose clinical significance far exceeds its epidemiological frequency. Although potentially curable, CTEPH is frequently diagnosed with substantial delay, primarily due to lack of clinical suspicion and delayed referral to specialized centers.

One of our objectives was to compile a comprehensive and up-to-date literature review for general practitioners and internists, summarizing the epidemiology, pathophysiology, diagnostic approach, and therapeutic strategies of CTEPH, with emphasis on the crucial role of primary care and internal medicine specialists in early recognition. Timely diagnosis and state-of-the-art management can markedly improve patients' quality of life and survival outcomes.

Our research aimed to explore the genetic background of CTEPH by identifying potentially pathogenic gene variants contributing to disease development. Using exome analysis, we compared genetic differences between patients with a history of pulmonary embolism who developed CTEPH and those who did not.

Another major objective was to assess the accuracy of various pressure measurement techniques, given that precise evaluation of right heart hemodynamics represents a cornerstone of CTEPH diagnostics. Despite ongoing advances, the pathomechanism of CTEPH remains incompletely understood, and current pharmacotherapeutic options are limited and non-curative. A more detailed understanding of etiopathogenesis could facilitate the identification of novel therapeutic targets and drive the development of targeted pharmacological interventions.

In recent years, BPA has demonstrated remarkable therapeutic efficacy, offering a new treatment perspective for the majority of patients. Clinically, it would be particularly important to identify the subgroup of patients who exhibit rapid and pronounced improvement after only a few interventions.

Despite the limited number of available cases due to the rarity of the disease, our investigations aim to provide a foundation for future research, integrating clinical experience

and scientific collaboration within Hungary's first BPA-performing center through close interdisciplinary cooperation.

Patients and Methods

I. CTEPH – Summary for Internists and General Practitioners

Our methodology consisted of a narrative literature review based on the 2022 ESC/ERS guidelines, the most recent European and international registries, and comprehensive review articles published in recent years.

II. Genetic and Laboratory Investigations in Patients with CTEPH and Pulmonary Embolism (PE)

This study was conducted as a single-center, open-label, non-randomized, prospective observational investigation at the Division of Cardiology, University of Debrecen, Hungary. Prior to enrollment, all participants received detailed information regarding the nature of the study, potential risks, and expected benefits. The study group (n = 15) included patients in whom the diagnosis of CTEPH was confirmed according to current diagnostic criteria. The suspicion of pulmonary hypertension was raised by echocardiographic examination and subsequently validated by right heart catheterization with a Swan–Ganz catheter and pulmonary angiography. All enrolled CTEPH patients underwent balloon pulmonary angioplasty (BPA). Patient enrollment began in 2022, and follow-up continued through 2025. Demographic and clinical data — including vital parameters, hospital admissions, comorbidities, treatments, and follow-up outcomes — were obtained from the hospital's electronic medical record system. The control group consisted of 17 patients with a previous episode of pulmonary embolism, in whom echocardiographic evaluation performed 3–6 months after the event excluded the presence of pulmonary hypertension.

Laboratory Investigations in CTEPH and PE Patients

Blood samples were collected in 3.2% sodium citrate anticoagulant tubes (Greiner, Kremsmünster, Austria). Laboratory analyses included standard coagulation screening tests and fibrinogen measurement using the Clauss method on a BCS-XP coagulation analyzer (Siemens, Marburg, Germany). Factor VIII activity was determined using a chromogenic assay (Siemens FVIII Chromogenic Assay), and von Willebrand factor (VWF) antigen levels were measured with the Innovance VWF assay (Siemens). Quantitative determination of plasminogen and α2-plasmin inhibitor was performed using Berichrom Plasminogen and Berichrom α2-Antiplasmin

kits (Siemens). Protein C (PC), Protein S (PS), and antithrombin (AT) levels were measured using Berichrom Protein C, Innovance Free PS Ag, and Innovance Antithrombin assays, respectively, on the BCS-XP analyzer. Detection of lupus anticoagulant was performed according to the current International Society on Thrombosis and Haemostasis (ISTH) guidelines, using dilute Russell's viper venom time (dRVVT) and lupus-sensitive activated partial thromboplastin time (APTT) tests (Werfen, Milan, Italy; Diagnostica Stago, Asnières, France). Anticardiolipin and anti–β2-glycoprotein I IgG and IgM autoantibodies were determined by chemiluminescent immunoassay using the Bioflash analyzer (Werfen). Factor XIII activity was determined by a modified, optimized kinetic spectrophotometric ammonia release method on a Sysmex CS2500 analyzer (Siemens) using Technoclone FXIII reagents (Technoclone, Vienna, Austria). Among prothrombotic markers, thrombin–antithrombin (TAT) complexes and prothrombin fragment 1+2 (PF1+2) were measured by ELISA (Enzygnost TAT micro and Enzygnost F1+2, Siemens). D-dimer concentrations were determined using the HemosIL D-Dimer HS500 reagent on an ACL-TOP analyzer (Werfen). PAI-1 antigen was quantified with the TechnOzym PAI-1 Antigen ELISA (Technoclone), while tPA concentration was measured using a Human Tissue Type Plasminogen Activator ELISA kit (Abcam). TFPI levels were determined by ELISA (Invitrogen Thermo Fisher, Waltham, MA, USA).

Genetic Investigations in CTEPH and PE Patients

Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA purity was assessed with a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA), and concentration was determined using the Qubit® dsDNA HS Assay Kit with a Qubit Fluorometer (Thermo Fisher Scientific). Samples were diluted to a final concentration of 200 ng DNA in 30 μL. Library preparation for clinical exome sequencing was performed using the Clinical Exome Solution v3 Kit (SOPHiA GENETICS, Saint Sulpice, Switzerland) following the manufacturer's protocol. Library quality control was performed by capillary electrophoresis using the Agilent Fragment Analyzer (Agilent, Santa Clara, CA, USA). Next-generation sequencing (NGS) was performed on an Illumina NextSeq 500 platform (Illumina, San Diego, CA, USA) using the NextSeq 500/550 Mid Output Kit v2.5 (300 cycles). Factor V Leiden (rs6025) and prothrombin G20210A (rs1799963) polymorphisms were detected by real-time PCR with melting curve analysis using a LightCycler 480 instrument (Roche, Basel, Switzerland). In-house designed

primers (TIB MOLBIOL, Berlin, Germany) and probes (Roche) were employed, and reactions were carried out with the Genotyping Master Kit (Roche).

III. Clinical Investigation: Correlation of Right Ventricular Pressure Measurements and Predictors of BPA Response

An open-label, non-randomized, prospective observational study was conducted at the University of Debrecen, Division of Cardiology, between 2022 and 2025. Seventeen adult patients with confirmed CTEPH were enrolled, representing a wide age range and both sexes. All participants provided written informed consent after receiving detailed information about the study. A prospective analysis was performed to assess the correlation between invasive and non-invasive methods of right ventricular (RV) pressure measurement. All measurements were carried out within 48 hours during the same hospitalization to minimize physiological variability. BPA candidacy was determined based on clinical parameters and anatomical suitability as evaluated by a multidisciplinary CTEPH team. Demographic and clinical data, including vital signs, hospitalizations, comorbidities, treatment history, and follow-up outcomes, were extracted from hospital records.

Invasive Right Ventricular Pressure Measurement

Right Heart Catheterization

Right heart catheterization using a Swan–Ganz catheter remains the gold standard for hemodynamic assessment in suspected or confirmed pulmonary hypertension. A balloon-tipped, flow-directed catheter was introduced via a central venous access (typically jugular or femoral vein) and advanced sequentially through the right atrium, right ventricle, and pulmonary artery, allowing direct measurement of right atrial pressure (RAP), right ventricular pressure (RVP), pulmonary arterial pressure (PAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was determined using the thermodilution technique. Procedures were performed in the supine position under local anesthesia using standardized equipment to ensure accurate hemodynamic monitoring. Central venous access and thermodilution were performed using the Edwards Lifesciences 831F75 thermodilution venous infusion port (VIP) catheter. Vascular access and catheter insertion were achieved with the Intradyn 8F Basic Kit for Intensive Care. The Edwards CO-SET+ closed injectate delivery system was used for thermodilution measurements with room-temperature injectate, minimizing contamination risk.

Pulmonary Angiography with Invasive RV Pressure Recording

A diagnostic catheter was introduced via the femoral vein into the right heart and pulmonary arteries. Contrast medium was injected for detailed imaging of the pulmonary arterial tree to identify CTEPH-related obstructions or abnormalities. The procedure was performed using a GE INOVA IG520 system, and simultaneous direct RV pressure recording was obtained.

Non-Invasive Right Ventricular Pressure Measurement by Echocardiography

Transthoracic echocardiography was performed using a Philips Epiq 5 system equipped with a phased-array transducer, with patients in the left lateral decubitus position. Systolic pulmonary artery pressure (sPAP) was estimated using the simplified Bernoulli equation ($\Delta P = 4 \times [TRV]^2$) from the tricuspid regurgitant jet velocity (TRV). Right atrial pressure (RAP) was estimated based on the inferior vena cava (IVC) diameter and its inspiratory collapse according to current echocardiographic guidelines. sPAP was calculated as:

$$sPAP = 4 \times (TRV)^2 + RAP$$

Measurements were obtained from multiple acoustic windows to optimize signal quality. The best-quality tricuspid regurgitation (TR) envelope was used for analysis, averaging three consecutive cardiac cycles for each parameter. Right ventricular function (TAPSE), RV dimensions (basal and mid-cavity diameters), and right atrial area were also evaluated. Examinations were performed and interpreted by experienced operators blinded to invasive results.

Balloon Pulmonary Angioplasty (BPA)

BPA was performed as a staged percutaneous intervention targeting a limited number of pulmonary arterial segments during each session. Procedures were guided by selective pulmonary angiography and performed by an experienced interventional team in accordance with institutional protocols. In some patients, invasive RV pressure was simultaneously recorded during BPA, allowing direct comparison of invasive and non-invasive pressure measurements. Standardized clinical assessments were performed at baseline (study inclusion), prior to the first BPA, and at 3 and 6 months after the final BPA session. Evaluations included NYHA functional class, 6-minute walk test (6MWT) distance, NT-proBNP levels, and the

results of right heart catheterization, pulmonary angiography, and echocardiography. All laboratory analyses were conducted at the Department of Laboratory Medicine, University of Debrecen, using standardized protocols and validated methods.

Data Processing and Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and range, depending on distribution. Categorical variables were presented as absolute numbers and percentages. Normality was assessed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using Student's t-test or the Mann–Whitney U test for nonparametric data. Categorical variables were compared using the chi-square test. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 29.

Bioinformatic analysis of *next-generation sequencing* (NGS) data was performed using SOPHiA DDM software version 6.4, aligned to the hg38 reference genome. Two virtual gene panels were created: (1) a coagulation/fibrinolysis/platelet disorder panel based on Tier 1 genes recommended by the International Society on Thrombosis and Haemostasis (ISTH) (https://www.isth.org/page/GinTh_GeneLists); and (2) a vascular disease–associated gene panel. Variants identified by the software were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines as pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign. Automated classification incorporated predictions from multiple genetic databases (PolyPhen2, SIFT, MutPred, MutationTaster). All selected variants were manually verified in public databases, including the Human Gene Mutation Database (HGMD; http://www.hgmd.cf.ac.uk), Online Mendelian Inheritance in Man (OMIM; https://www.omim.org), and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar). Allele frequency data were obtained from the gnomAD and 1000 Genomes databases (https://gnomad.broadinstitute.org; https://www.internationalgenome.org).

Ethical Approval

The study was approved by the Regional and Institutional Ethics Committee of the Clinical Center, University of Debrecen, and by the National Scientific and Research Ethics Committee of Hungary (approval number: RKEB/IKEB 6153-2022). All participants provided

written informed consent prior to enrollment, in accordance with the principles of the Declaration of Helsinki.

Results

In one part of our work, we compared patients who had experienced pulmonary embolism (PE) but did not develop CTEPH with the CTEPH patients treated with BPA and included in the study population. A complex blood sample analysis was performed regarding thrombosis-hemostasis and spontaneous fibrinolysis. Furthermore, we investigated the genetic background using exome analysis to identify factors that may predispose to CTEPH.

Characteristics of CTEPH patients

The CTEPH group included both men and women (10 men, 5 women), all patients were of Caucasian origin. At the time of diagnosis, the average age showed a wide range, and the body mass index (BMI) ranged from normal to severe obesity (28.39 ± 5.00 kg/m²). At the time of enrollment, most patients (n = 10) were in New York Heart Association (NYHA) functional class II or III, indicating moderate functional limitation, while a smaller portion (n = 3) was classified as class IV. The mean distance achieved during the 6-minute walk test (6MWT) was 336.1 ± 164.7 m (range: 42–616 m), indicating significant individual variability. The mean baseline NT-proBNP level was 2694.3 ± 2407.2 pg/mL (range: 82–7133 pg/mL), reflecting varying degrees of right ventricular dysfunction. Left ventricular systolic function was preserved in all patients. The systolic pulmonary arterial pressure measured by echocardiography and Swan–Ganz catheter averaged 77.2 ± 23.5 mmHg and 72.9 ± 22.6 mmHg, respectively. Right heart catheterization further confirmed elevated pulmonary vascular resistance (PVR) (mean: 720.3 ± 373.5 dyn·s·cm^{-5}) and elevated mean pulmonary arterial pressure (mPAP: 44.0 ± 9.1 mmHg). Pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) were 11.7 ± 3.3 mmHg and 7.6 ± 4.2 mmHg, respectively. Cardiac output (CO) and cardiac index (CI) were reduced (median CO: 3.82 L/min, range: 2.72–8.53; CI: 2.03 L/min/m², range: 1.66–4.04), indicating impaired right ventricular function. The medical history showed significant thromboembolic burden: six patients had previously confirmed pulmonary embolism (PE), and two were diagnosed with hereditary thrombophilia (one homozygous prothrombin gene 20210A mutation [rs1799963] and one heterozygous Factor V Leiden mutation [rs6025]). No deficiencies in antithrombin (AT), protein C (PC), or protein S (PS) were detected. One patient had lupus anticoagulant, and another had a moderate increase in anti-β_2-glycoprotein I IgG (133.2 CU). Elevated factor VIII activity above 200 IU/dL was observed in one patient, while elevated von Willebrand factor antigen (vWF:Ag) above 200

IU/dL was measured in five patients. No patient had undergone splenectomy. Electrocardiographic examinations most often showed right bundle branch block and signs of right ventricular strain; atrial fibrillation occurred only in a few patients. Provoked PE did not occur in either studied population, neither in the CTEPH nor the control group—no transient risk factor (surgery, trauma, immobilization) was detectable. During the follow-up period, six patients died, three of them from non-cardiovascular causes (COVID-19, pneumonia, septic shock).

Characteristics of pulmonary embolism (PE) patients without CTEPH development

According to the basic demographic and anthropometric data of the PE group, the mean age was 48.7 ± 17.1 years (range: 24–80 years), and the average body mass index (BMI) was 27.5 ± 6.1 kg/m² (range: 19.0–44.6), ranging from normal weight to severe obesity. In three patients, anticoagulant therapy was suspended six months after the acute event, while the others received ongoing therapy (rivaroxaban: 3 patients; apixaban: 9 patients; dabigatran: 2 patients). Among the PE patients, two were heterozygous for the Factor V Leiden mutation (rs6025), and another two were heterozygous carriers of the prothrombin 20210A allele (rs1799963). No classic AT, PC, or PS deficiency was observed; however, one patient carried the heterozygous PS Heerlen polymorphism (rs121918472, c.1501T>C, p.Ser501Pro) with 63% free PS antigen level, indicating mild thrombosis risk. Lupus anticoagulant was found in one patient, and elevated anticardiolipin or anti-β_2-glycoprotein I antibody levels were not observed in any PE patients. Elevated vWF:Ag above 200 IU/dL was detected in one patient, whose factor VIII activity was 190 IU/dL. The thrombin–antithrombin (TAT) complex level exceeded the reference range in three patients, and prothrombin fragment 1+2 (PF1+2) exceeded the reference range in four patients. D-dimer values were above the diagnostic threshold in six patients. Most patients were non-O blood type (non-O vs. O: 15 vs. 2).

Comparison of laboratory parameters between CTEPH and PE patients

Among the parameters reflecting coagulation, CTEPH patients showed significantly elevated FVIII activity and von Willebrand factor antigen (vWF:Ag) levels. Fibrinogen concentration did not differ between the two groups. D-dimer values were also similar; however, thrombotic activity markers—the thrombin–antithrombin (TAT) complex and prothrombin fragment 1+2 (PF1+2)—were significantly higher in PE patients who did not develop CTEPH. This observation indicates persistently increased coagulation activity in this

patient group, which was less pronounced in CTEPH patients. Tissue factor pathway inhibitor (TFPI) levels did not differ between the groups.

When examining factors involved in fibrinolysis, plasminogen and α_2-plasmin inhibitor (α_2-PI) levels were significantly lower in CTEPH patients, whereas tissue plasminogen activator (tPA) concentration was significantly higher. No significant differences were observed between the two groups regarding plasminogen activator inhibitor-1 (PAI-1) and factor XIII (FXIII) levels.

Our results—although limited by sample size—suggest that lower plasminogen levels in CTEPH patients are associated with increased tPA activity and lower α_2-PI levels, indicating an altered fibrinolytic balance. However, the clinical significance of these differences is limited, as none of the laboratory parameters fell outside the reference range, and no extreme values were observed. The more pronounced FVIII and vWF:Ag elevation in the CTEPH group suggests a role of endothelial activation in the pathomechanism of the disease.

As a first step, a virtual gene panel containing the so-called Tier 1 genes recommended by the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on OMICS in Thrombosis and Hemostasis (SSC) was created (https://www.isth.org/page/GinTh_GeneLists). This list currently includes 109 genes associated with coagulation, fibrinolysis, and platelet function disorders. Based on the panel, we identified 397 different variants in CTEPH patient samples. Excluding common variants with higher allele frequency (>0.05) based on 1000 Genomes and/or gnomAD databases, 134 different variants remained for further evaluation. Among these, 87 nonsense (non-synonymous) variants were identified, of which 55 were associated with genes related to platelet function, while 32 were associated with genes involved in coagulation or fibrinolysis processes, including von Willebrand factor (VWF) and ADAMTS13 genes. The vast majority of variants (76%) were missense mutations resulting from a single nucleotide substitution in the coding region. All identified variants occurred in heterozygous form in CTEPH patients, except for one missense mutation in the PIGA gene (located on the X chromosome) (c.55C>T, p.Arg19Trp), which was hemizygous in one male patient.

Among the genes encoding coagulation factors, variants were identified in F10, F12, F13A1, F13B, F5, and F8 genes. Of these, F10 p.Met336Val, F12 p.Leu140Val, F13A1

p.Tyr205Phe, the intronic mutations of F13B, as well as F5 p.Met1811Leu and p.Met2148Thr variants were not found in the control group.

In the examination of genes encoding proteins involved in fibrinolysis, a variant was identified in the KNG1 gene, which encodes high molecular weight kininogen (p.Arg412*); this mutation was not present in the control group. Additionally, a PLG gene (plasminogen-encoding) p.Val291Met variant was detected in one CTEPH patient; however, the individual's plasminogen level was within the normal range (P12, plasminogen: 101 IU/dL), and according to the latest curated databases, it is not associated with plasminogen deficiency. In the SERPINE1 gene (encoding PAI-1), the p.Val17Ile variant was detected in a single CTEPH patient (P7), whose PAI-1 antigen concentration fell below the lower limit of the reference range (4.1 ng/mL; reference: 7–43 ng/mL), suggesting mild PAI-1 deficiency. Among the genes encoding natural anticoagulants, an intronic variant was identified in the SERPIND1 gene (heparin cofactor II), which occurred only in a CTEPH patient (P2) and not in the control group. Furthermore, mutations were found in the thrombomodulin-encoding (THBD) and protein C-encoding (PROC) genes, which were also absent in the PE group. However, the patient carrying the c.-21-37G>A variant in the PROC gene (P6) had normal PC levels (84 IU/dL); therefore, this variant is unlikely to cause protein C abnormality. Two variants were identified in the ADAMTS13 gene, one of which (p.Gln1174*) was not found in the control group. Finally, seven different variants were identified in the von Willebrand factor (VWF) gene, five of which were not present in control samples.

Among the genes related to platelet function, we did not identify any gene or variant that would potentially be relevant to CTEPH or any thrombotic phenotype. Nevertheless, a few potentially relevant exceptions were found. One CTEPH patient (P10) carried a mutation in the STIM1 gene (c.1859+1G>A, rs118128831), which likely causes a splicing defect. This variant was not present in the control group. The STIM1 gene is associated with autosomal dominant Stormorken syndrome, which is characterized by functional asplenia, thrombocytopenia, and the presence of Howell–Jolly bodies—features that have also previously been reported in association with CTEPH. Our patient carrying the STIM1 mutation showed mild thrombocytopenia and large platelets, but Howell–Jolly bodies were not detectable in the peripheral blood smear. In another CTEPH patient (P9), we identified a c.889A>G (p.Thr297Ala, rs530613857) variant in the THPO gene. Furthermore, a c.602T>C

(p.Leu201Pro, rs145477191) mutation was found in the ETV6 gene in patient P11. These variants were also absent in the control samples.

We also examined an additional 11 genes classified as Tier 2 according to ISTH recommendations. Among these, the NFE2, MAST2, APOLD1, and SERPINA1 genes were potentially interesting, as they are associated with the regulation of clonal hematopoiesis, risk of venous thromboembolism, endothelial cell signaling, and alpha-1-antitrypsin, respectively. Analysis of rare non-synonymous variants revealed the following mutations: in the SERPINA1 gene, the c.863A>T (p.Glu288Val) variant (allele frequency: 0.023) in patient P4; in the NFE2 gene, the c.518A>G (p.Asp173Gly) variant (allele frequency unknown) in patient P12. According to clinical genetic databases, these mutations are classified as likely pathogenic and variants of uncertain significance (VUS) regarding their associated conditions. None of these variants were detectable in the control group.

The second virtual gene panel included genes associated with vascular diseases or with the development of vascular structures, angiogenesis, or thrombotic phenotypes, based on literature and clinical databases. The genes included in the analysis were: ENG, ACVRL1, BMPR2, RASA1, GDF2, SMAD4, SOX17, CAV1, KCNK3, RNF213, SMAD9, SLC2A10, KDR, CPB2, and HRG. Variant filtering was performed similarly to the ISTH gene panel: variants with MAF > 0.05 and synonymous variants were excluded. As a result, 15 different missense or splicing variants were identified. Most variants were carried by a single patient, except for RASA1 p.Ala99Val, KDR p.Cys482Arg, and RNF213 p.Leu4283Ile, which were detected in two CTEPH patients each; however, these mutations were also present in the control group. Exclusive variants were found in the RASA1, ENG, GDF2, SOX17, ACVRL1, and RNF213 genes, which were not present in PE patients who did not develop CTEPH. Although variants in the BMPR2 and KDR genes were also detected in PE patients without CTEPH, these mutations may still have pathogenetic relevance in CTEPH—not directly in disease onset, but rather in its severity and extent, as illustrated by our clinical data. All three affected patients (P1, P4, and P6) had severe and extensive CTEPH:

In P1, 13 segmental pulmonary arteries were involved,

In P4, 14 segmental arteries were affected,

In P6, 11 segmental arteries were involved, all of which were dilatable by BPA, although multiple intervention sessions were required.

During the analysis of virtual panels 1 and 2, the variants identified in each CTEPH patient were compiled, and their combined occurrence was examined. The combination of different mutations showed considerable heterogeneity: most patients carried multiple potentially relevant variants concurrently. Although several mutations were also detected in the control group, numerous rare variants occurring exclusively in CTEPH patients were identified, which may have potential pathogenetic significance. In most cases, variants in genes associated with vascular disease and those related to coagulation/fibrinolysis were present together, suggesting the possibility of additive or synergistic effects in the development and progression of CTEPH.

In another part of our work, we compared methods for determining right heart pressures, a key element in the diagnosis of CTEPH.

Characteristics of the study population

The study cohort consisted of 17 patients diagnosed with CTEPH. At the time of diagnosis, the mean age was 61.4 years (range: 21–81), reflecting the prevalence of the disease across a broad adult age spectrum. Both sexes were represented (10 men and 7 women), and all patients were of Caucasian ethnicity. The baseline body mass index (BMI) averaged 28.4 ± 5.0 kg/m². At the time of enrollment, most patients were in NYHA functional class II–III. The mean distance achieved during the 6-minute walk test (6MWT) was 330.6 ± 152.2 m, indicating significant variability in exercise tolerance. Initial NT-proBNP values showed a wide range with high variability (mean: 4820.97 ± 10,288.15 pg/mL), consistent with different degrees of right ventricular strain. Systolic pulmonary arterial pressure measured by echocardiography, BPA, and right heart catheterization averaged 72.1 ± 22.3 mmHg, 88.1 ± 11.9 mmHg, and 77.7 ± 23.5 mmHg, respectively. Hemodynamic parameters from right heart catheterization showed elevated pulmonary vascular resistance (mean PVR: 675.4 ± 369.6 dyn·s·cm^{-5}) and elevated mean pulmonary arterial pressure (mPAP: 43.2 ± 8.6 mmHg), while pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) averaged 10.7 ± 3.4 mmHg and 7.9 ± 4.1 mmHg, respectively. Cardiac output (CO) and cardiac index (CI) were moderately reduced (mean CO: 4.44 ± 1.55 L/min; CI: 2.38 ± 0.79 L/min/m²), consistent with impaired right ventricular performance.

Echocardiographic assessment (n = 97 examinations) showed a mean TAPSE of 19.5 ± 5.1 mm, with several patients <16 mm, indicating impaired right ventricular systolic function. The basal right ventricular diameter (RVD1) averaged 41.7 ± 6.1 mm, and the right atrial area (RAA) was 25.2 ± 7.9 mm², often suggesting right ventricular dilation and pressure overload. The severity of tricuspid regurgitation (TI) ranged from grade I to III–IV. Each CTEPH patient underwent an average of 3.13 ± 2.17 BPA sessions, with an average of 12.0 ± 9.2 segmental dilations, covering approximately 63% of the affected segments. Medical history indicated a high risk of thromboembolic disease. Six patients had documented pulmonary embolism, and two had hereditary thrombophilia (heterozygous prothrombin gene 20210G/A and heterozygous Factor V Leiden mutation). No patient had undergone splenectomy. ECG findings frequently showed right bundle branch block and right ventricular strain patterns, with atrial fibrillation observed in a minority of cases. The mean follow-up period was 29.2 ± 10.2 months. During this time, six patients died, three of them from non-cardiovascular causes, including COVID-19 infection, pneumonia, and septic shock.

Pulmonary Angioplasty and Therapeutic Response

The number of BPA interventions varied by patient (maximum 11 sessions). A total of 50 BPA procedures were performed in 17 patients diagnosed with CTEPH, averaging 3.13 BPA interventions per patient. A total of 195 segmental/subsegmental dilations were performed, with an average of 12 dilations per patient (SD = 9.16). The proportion of treated versus affected segments was high (e.g., >75% in some patients), indicating a significant treatment rate and vascular involvement. PCWP values were collected and analyzed in the study cohort. The mean PCWP was 10.71 mmHg, with a standard deviation of 3.35 mmHg, indicating moderate variability within the patient population. The range of PCWP values was 8 to 20 mmHg. These measurements are consistent with the expected hemodynamic profiles of patients with CTEPH, supporting the diagnosis of pre-capillary pulmonary hypertension in most cases.

Patients were divided into two groups based on their clinical response to BPA. The well-responding group (n = 10) included patients who showed at least a one-class improvement in NYHA functional class, while the less-responsive group (n = 7) consisted of patients showing minimal or no improvement in NYHA class.

Our analysis revealed significant differences between well- and poorly responding BPA patients. In the well-responding group, 6MWT distance improved significantly, by an average

of 60 ± 18 m, compared to the marginal 12 ± 10 m increase observed in the poorly responding group ($p < 0.01$). NT-proBNP levels decreased by an average of 40% in responders, whereas only a 10% reduction was observed in non-responders ($p < 0.01$). Echocardiographic measurements demonstrated significant improvement in right ventricular function in the responders: TAPSE increased from a baseline of 16.0 ± 2.0 mm to 19.5 ± 2.5 mm at 6 months ($p < 0.01$), and the right ventricular basal diameter decreased by an average of 15% ($p < 0.05$). In contrast, non-responders showed no significant change in TAPSE (16.5 ± 2.3 mm to 16.0 ± 2.5 mm, $p > 0.05$), with right ventricular dimensions tending to increase.

In the analysis of clinical data, three measurement techniques for pulmonary arterial pressure—Swan-Ganz (SG), pulmonary angiography (PA), and echocardiography—were compared. During the study period, a total of 97 echocardiographic examinations, 50 balloon pulmonary angioplasties (BPA), and 43 Swan-Ganz catheterizations were recorded. Within a 48-hour window, all three modalities—echocardiography, Swan–Ganz catheterization, and pulmonary angiography—were available for pressure comparison in 11 cases. In 25 cases, pressure measurements were available from echocardiography and Swan–Ganz catheterization, while in 22 cases, pulmonary angiography and echocardiographic pressure estimates were obtained within 48 hours. In 13 cases, both Swan–Ganz and pulmonary angiography pressure measurements were available within the specified time window.

Overall, the combination of scatter plots and histograms with kernel density estimation (KDE) curves provided a robust evaluation of the comparative behavior of the three measurement techniques. Due to its invasive accuracy, the Swan-Ganz method remains the reference standard, while PA and echocardiography offer useful approximations with variable levels of agreement. Scatter plots emphasize the strength of correlation, whereas histograms illustrate potential variability in clinical application. Based on the collected data, statistical relationships between right heart pressure values obtained with different diagnostic modalities were analyzed and visualized in a correlation matrix. Correlation coefficients (Pearson r) quantify the linear relationship between method pairs. Results show variable correlation, with the strongest association observed between the two invasive techniques (SG and PA), and somewhat weaker—but still significant—correlations for echocardiographic estimates. Very strong correlation was found between Swan–Ganz catheterization and pulmonary angiography pressure values ($r = 0.96$), indicating high consistency between these two invasive measurement techniques. The correlation between echocardiography and pulmonary pressures was slightly

lower ($r = 0.84$), but still a strong positive association. The weakest correlation was observed between echocardiography and Swan–Ganz measurements ($r = 0.78$), which remains statistically strong but reflects the limitations and variance of non-invasive estimation techniques. Subgroup analysis showed that patients with optimal acoustic windows had even stronger correlations ($r = 0.88$, $p < 0.001$). However, in patients with poor echocardiographic windows or irregular heart rhythms, differences of up to 10 mmHg were observed. In these cases, invasive measurements provided more consistent and reproducible data. Additionally, echocardiographic estimates tended to slightly underestimate right ventricular pressures in patients with severe right ventricular dilation.

Discussion

Although understanding of the genetic background of CTEPH has significantly advanced in recent years, substantial knowledge gaps remain regarding the role of individual genes and genetic variants, as well as the interaction between genetic predisposition and environmental factors. As expected, in the present study, no single gene or variant was consistently detectable in all CTEPH patients, and no mutation was found that could be clearly linked to the disease. The main concept of the research was to investigate rare variants associated with thrombosis, hemostasis, and vascular disease, with the aim of identifying potentially relevant gene alterations for further study. The occurrence of identified variants was compared between CTEPH patients and PE patients who did not develop CTEPH, and we examined whether mutations occurring exclusively in the CTEPH group could have disease-related significance, based on literature and clinical genetic databases. Unsurprisingly, most identified variants are classified in the literature and databases as VUS (variants of uncertain significance), with no previously published data available in the CTEPH context.

Among genes related to coagulation, previous studies suggest that only genes encoding fibrinogen chains and the F5 gene (via the Factor V Leiden mutation, p.Arg534Gln) are associated with CTEPH. In our cohort, no fibrinogen variants were identified. The FV Leiden mutation was found in one CTEPH patient but was also present in two PE patients. Previous European studies indicate that carrying FV Leiden confers a threefold risk of early-onset CTEPH, and the latest genome-wide association studies (GWAS) suggest a partly shared genetic risk between acute PE and CTEPH. In contrast, FV Leiden does not occur in idiopathic pulmonary hypertension. Our study confirms the role of this polymorphism in PE and CTEPH, as the combined occurrence in the two groups was 3/32 (10%). Two additional F5 mutations (p.Met1811Leu and p.Met2148Thr) were identified exclusively in CTEPH patients. While the p.Met1811Leu variant is classified in databases as VUS, the p.Met2148Thr variant is considered benign regarding both bleeding tendency and thrombophilia. Mutations in the F10 gene typically cause FX deficiency and bleeding in homozygous form, and their association with thrombotic disorders has not been described; therefore, the F10 p.Met336Val variant found in our study is unlikely to be a risk factor for either CTEPH or thrombosis, although no in vitro functional testing has been performed to date.

The F12 p.Leu140Val variant has previously been detected in patients with deep vein thrombosis and hereditary angioedema (HAE), but its pathogenicity remains unclear. Current knowledge indicates that it does not cause FXII deficiency or severe HAE. However, since FXII primarily participates in fibrinolysis and complement system activation, rather than coagulation, this variant may represent an interesting target in a larger CTEPH cohort study.

Factor XIII (FXIII) is a heterotetrameric molecule composed of two A subunits (the active transglutaminase enzyme) and two B subunits (the carrier protein). The role of FXIII in thrombotic disorders has been extensively studied, identifying several polymorphisms potentially involved in arterial or venous thrombosis. Among them, the F13A1 p.Tyr205Phe mutation, detected in one of our patients (P5), has been previously associated with both arterial and venous thrombosis, although meta-analyses have not confirmed it as an ischemic stroke risk factor. The patient carrying this mutation had FXIII activity within the reference range (131 IU/dL). Nonetheless, this variant may influence thrombus stability through alterations in fibrin cross-linking and fibrinolysis. Intronic variants of the F13B gene (encoding the B subunit) were also identified in one CTEPH patient (P3), suggesting a potential interaction between these mutations. The association of F13B polymorphisms with thrombotic disorders remains controversial and has not been confirmed in CTEPH.

Systemic fibrinolysis is generally not considered impaired in CTEPH; however, local dysregulation of enzymes involved in fibrinolysis may contribute to disease pathogenesis. Among genes related to fibrinolysis, we identified a KNG1 variant introducing a stop codon, likely resulting in a truncated protein. This p.Arg412* mutation was found in a CTEPH patient but was absent in controls. This variant has previously been reported in patients with venous thrombosis. Since the gene encodes high-molecular-weight kininogen (HMWK), which plays a role in regulating fibrinolysis and inflammatory processes, further investigation of this mutation is warranted.

The SERPINE1 p.Val17Ile variant has been previously associated with lower PAI-1 secretion and plasma levels, which was also observed in our cohort; therefore, its association with CTEPH is unlikely. Among genes encoding natural anticoagulants, SERPINC1, PROC, and PROS1 have been analyzed in multiple previous studies, yielding inconsistent results. In our study, no relevant variants were identified in these genes. Conversely, we detected an intronic variant in SERPIND1 (c.1309-3C>T), which encodes heparin cofactor II (HCII). HCII is a serine protease inhibitor that exerts rapid thrombin-inhibitory effects in the presence of

negatively charged glycosaminoglycans (heparan sulfate, dermatan sulfate, chondroitin sulfate). Heparin cofactor II plays an important role in atherosclerotic disease and appears to prevent vascular restenosis, particularly after coronary interventions. As a natural thrombin inhibitor, whose activity is closely linked to vascular wall properties, HCII may have physiological relevance in CTEPH. However, it is unknown whether the identified variant causes structural or functional changes in the protein; further studies are required to elucidate its role in CTEPH.

The PROC variant identified in our study is considered likely benign according to clinical genetic databases and does not affect plasma protein C (PC) levels, as supported by our patients' laboratory results. Since this mutation (c.-21-37G>A) is located upstream of the coding region, it is unlikely to affect PC's fibrinolytic, cytoprotective, or anti-inflammatory functions. The THBD p.Pro501Leu variant has been previously described, but its clinical significance regarding thrombomodulin-related disorders remains unclear. Given thrombomodulin's role not only in thrombus regulation but also in complement factor I–mediated C3b inactivation, its potential connection to CTEPH is plausible.

The role of von Willebrand factor (vWF) and related proteins in CTEPH has been suggested in several studies. Elevated FVIII and vWF levels have been reported in CTEPH patients, which may contribute to disease development but may also reflect chronic inflammation and endothelial dysfunction. In our cohort, vWF:Ag and FVIII levels were also elevated compared to controls; however, no mutations directly causing this phenotype were identified. Several vWF gene variants were detected in our CTEPH patients. Among these, p.Arg854Gln and p.Tyr1584Cys are associated with von Willebrand disease (vWD) according to clinical databases and are therefore not considered CTEPH risk factors. The remaining three variants (p.Thr1951Ala, p.Arg1399His, p.Thr1054Met) are non–vWD-causing but may influence vWF levels or function, and thus their contribution to a thrombotic phenotype cannot be excluded. Patients carrying these variants had elevated vWF:Ag and vWF:Ac levels. The ADAMTS13 p.Gln1174Ter mutation has no available data in clinical databases; it may produce a truncated protein and is potentially associated with a thrombotic phenotype with increased microthrombus formation.

Genes related to thrombocytes, as recommended by ISTH, are generally not considered relevant in CTEPH, since most are associated with bleeding, thrombocytopenia, and/or platelet dysfunction. However, our findings suggest that four platelet-associated genes merit further

investigation. The STIM1 gene, linked to autosomal-dominant Stormorken syndrome, may be a potential candidate for CTEPH studies due to its association with functional asplenia. The ETV6 gene encodes a transcriptional repressor; its variants may be associated with hematopoietic disorders and clonal alterations, which have emerged as potential CTEPH risk factors. THPO variants are associated with elevated thrombopoietin levels, which may lead to recurrent thrombotic events in carriers. Finally, MPL mutations are associated with thrombocytosis and abnormal thrombopoietin receptor function, justifying further investigation of this gene and its variants in the context of CTEPH.

Among vascular genes, particularly those involved in hereditary hemorrhagic telangiectasia (HHT) or primary pulmonary hypertension (PAH), prior studies suggest potential CTEPH risk. Three ENG variants (p.Gly191Asp, p.Thr5Met, p.Pro131Leu) were identified; ENG encodes endoglin, a component of the TGF-β receptor complex and an important endothelial glycoprotein. ENG mutations are primarily responsible for HHT1. Their effect in CTEPH is unknown. The ACVRL1 c.1378-216C>T mutation is likely benign in HHT2, while GDF2 p.Val211Met is classified as VUS in HHT5; their role in CTEPH is unknown. The RASA1 gene is responsible for capillary–arteriovenous malformation syndrome (CM-AVM), phenotypically related to HHT (OMIM 608354). The p.Gly89Arg variant identified in a CTEPH patient has not been previously reported and warrants further investigation. Three variants in RNF213 (c.2656-5A>G, p.Thr4638, p.Gln2184Arg) were not detected in controls. Since RNF213 has been implicated in CTEPH in prior studies, and the p.Arg4810Lys variant has been associated with poor prognosis, the mutations we identified may also represent a relevant research direction.

The SOX17 gene is associated with primary pulmonary hypertension (type 7), and its role in CTEPH is biologically plausible. Variants p.Ala33Asp and p.Met270Leu are likely benign regarding PPH7, but their behavior in CTEPH is unknown.

The KDR gene encodes a receptor tyrosine kinase (VEGFR-2) that binds VEGF with high affinity, playing a key role in angiogenesis. Overexpression of VEGFR-2 has been previously associated with pulmonary hypertension, making it reasonable to consider KDR variants as potentially contributing to CTEPH pathogenesis. In our study, two patients carried p.Cys482Arg, which was also found in two controls. Previous studies have suggested roles for BMPR2 and ACE genes in CTEPH, but their significance remains controversial. No ACE mutations were detected in our cohort, and BMPR2 p.Ser775Asn was found in both a CTEPH

patient and a control. Based on BMPR2 and KDR variants and clinical features, we hypothesize that these genes may influence disease progression and severity rather than the initial development of CTEPH.

Based on our findings and variant interpretation, the following genes are potential candidates for further detailed investigation:

F12, F13A1, F13B, F5, KNG1, SERPIND1, THBD, ADAMTS13, VWF, STIM1, ETV6, THPO, MPL, SERPINA1, ENG, RASA1, ACVRL1, GDF2, NFE2, SOX17, RNF213. Many of these have previously been reported as associated with CTEPH.

We acknowledge the small sample size of our study, which was unavoidable due to the rarity of the disease. Among genes involved in hemostasis and vascular function, pathogenic or likely pathogenic variants were found at a prevalence of 5.9%. However, this small sample does not allow definitive conclusions regarding the role of these variants in CTEPH. It is well known that sample size fundamentally affects the precision and reliability of research findings: a small sample may be insufficient to detect rare variant effects, while a very large sample may reveal statistically significant but clinically irrelevant differences. This is particularly true in genetic studies, where small sample sizes can lead to overestimation of rare variants and low statistical power.

Considering these factors, it cannot be conclusively stated that the identified variants directly influence CTEPH development. Nevertheless, our results provide a comprehensive overview of potential genetic candidates warranting further targeted investigation. Rare mutations in genes involved in thrombosis, hemostasis, and vascular disease were analyzed, and several potentially relevant variants were identified whose role in CTEPH merits further study. In our small patient cohort, no variant was found with higher prevalence, but most patients carried multiple distinct mutations, indicating the complex genetic background of the disease. Until further evidence is available, the role of these variants in CTEPH remains hypothetical.

Accurate assessment of right heart pressures is crucial for the diagnosis, risk stratification, and therapeutic decision-making in CTEPH. Various methods have been employed, including echocardiography, direct pressure measurements during pulmonary angiography, and right heart catheterization. Echocardiography serves as a non-invasive tool

for estimating pulmonary arterial pressure and assessing right ventricular (RV) function. Right heart catheterization remains the gold standard for hemodynamic evaluation in pulmonary hypertension, providing precise measurements of mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and cardiac output (CO).

Our results demonstrate that echocardiographic estimation of RV pressures closely correlates with Swan-Ganz catheter and pulmonary artery (PA) invasive measurements in our CTEPH cohort. This supports accumulating evidence that, when applied under standardized conditions, non-invasive methods can reliably monitor hemodynamic status in CTEPH. The mean differences across modalities were clinically acceptable, suggesting that echocardiography is a useful alternative for routine follow-up, reducing the need for invasive procedures. Strong statistical correlations were observed between right heart pressure measurements obtained by different modalities. Swan-Ganz catheterization and PA measurements showed very high agreement ($r = 0.96$), indicating consistency between invasive techniques. Echocardiographic estimates correlated well with PA measurements ($r = 0.84$), whereas the weakest — yet still significant — correlation was observed between echocardiography and Swan-Ganz measurements ($r = 0.78$).

Echocardiographic RV pressure is an indirect measure and thus less precise, influenced by factors including operator variability. Similarly, Swan-Ganz catheterization may also be prone to inaccuracies—the catheter tip position is inferred from the pressure waveform rather than confirmed by fluoroscopy, and general setup complexity contributes to variability. Nevertheless, no significant differences were observed between echocardiographic and the two invasive measurements. These findings confirm the reliability of invasive methods for accurate hemodynamic assessment while supporting echocardiography as a practical, less burdensome, non-invasive method, provided that estimates are interpreted cautiously when precise pressure values are required. This data reflects the complexity and severity of CTEPH, emphasizing the need for individualized therapeutic strategies and close longitudinal monitoring.

Clinical Interpretation

Our findings reinforce the reliability of invasive hemodynamic assessments (Swan-Ganz and pulmonary angiography) for evaluating pulmonary and right heart pressures while supporting echocardiography as a useful non-invasive screening and follow-up tool. The

slightly lower correlation between echocardiography and invasive methods highlights the importance of cautious interpretation of echocardiographic estimates, especially when precise pressure values are critical for diagnosis or management (e.g., suspected pulmonary hypertension). In patients with suboptimal echocardiographic windows or significant RV remodeling, echocardiography may underestimate RV pressures, potentially leading to misclassification of disease severity. This underscores the importance of selecting monitoring methods based on patient-specific factors. Integrating multiple measurement techniques can provide a more comprehensive evaluation, particularly in borderline cases. Our study highlights the importance of standardized echocardiographic protocols to minimize variability.

BPA has become a vital therapeutic option for patients with inoperable CTEPH. However, clinical responses to BPA vary considerably among patients. Identifying patient subgroups likely to respond favorably is critical. Patients with distal pulmonary arterial lesions—compared to proximal obstructions—are more likely to benefit from BPA. Accurate hemodynamic evaluation helps select appropriate BPA candidates, optimizing clinical outcomes.

In this prospective study, we compared clinical and echocardiographic parameters, along with NT-proBNP levels, between BPA responders and less responsive CTEPH patients. Patients undergoing BPA were stratified into well-responding and poorly responding groups based on improvements in NYHA functional class. Extended analysis revealed that well-responding patients experienced significant improvements in RV function (increased tricuspid annular plane systolic excursion [TAPSE], reduced RV dilation, and decreased right atrial area [RAA]), along with marked reductions in NT-proBNP and increased six-minute walk test (6MWT) distance. These significant improvements highlight the effectiveness of BPA in patients with favorable hemodynamic profiles.

In contrast, poorly responding patients showed minimal or no improvements, persistent elevation of NT-proBNP, progressive RV dilation, and negligible changes in functional capacity, likely reflecting advanced RV remodeling and microvascular dysfunction. These observations suggest that baseline hemodynamic and laboratory biomarkers can help predict BPA efficacy, guiding patient selection and therapeutic strategies. Baseline NT-proBNP levels and RV dimensions were strong predictors of BPA response. Correlation analysis showed that higher baseline NT-proBNP levels correlated with smaller increases in 6MWT distance ($r = -0.68$, $p < 0.01$) and less improvement in TAPSE ($r = -0.63$, $p < 0.01$). Additionally, patients

with higher baseline pulmonary arterial pressures required a significantly greater number of BPA sessions ($p < 0.05$).

Our findings align with previous literature identifying NT-proBNP and echocardiographic parameters as reliable predictors of CTEPH outcomes. The strong inverse correlation between NT-proBNP levels and functional improvement suggests that patients with greater RV burden are less likely to benefit from BPA. Furthermore, the higher number of BPA sessions required in patients with elevated baseline pulmonary pressures supports the notion that greater thrombotic burden necessitates more extensive intervention.

Our data indicate that integrating baseline clinical parameters and NT-proBNP levels can improve patient stratification. For example, combining NT-proBNP levels, RV dimensions, and coagulation profiles into a composite score could provide an effective predictive model for BPA outcomes. This approach may facilitate early identification of patients less likely to respond to BPA, prompting consideration of adjunctive therapies or alternative interventions.

The mechanisms underlying differential BPA responses are likely multifactorial, encompassing not only the extent of mechanical obstruction but also the degree of underlying microvascular remodeling and the heart's adaptive capacity. Future research should focus on larger, multicenter studies to validate these findings and explore the integration of novel biomarkers into risk assessment models. Additionally, pharmacological strategies targeting coagulation and fibrinolysis may improve outcomes in patients with suboptimal BPA responses.

Summary

Chronic thromboembolic pulmonary hypertension is a rare but severe and potentially curable condition that, if diagnosed late, is associated with substantial morbidity and mortality. The key to recognizing CTEPH lies in raising clinical suspicion early, a process in which general practitioners and internists play a pivotal role. One of the aims of our work was to provide a scientifically rigorous, widely accessible summary of the current diagnostic and therapeutic options for CTEPH in Hungary, intended to assist physicians — including general practitioners, internists, and cardiologists — who are often the first to encounter these patients. By doing so, we aimed to facilitate early recognition, targeted diagnostic evaluation, and timely referral of patients to specialized centers with appropriate multidisciplinary expertise.

In our investigation of potential genetic determinants in CTEPH patients, we identified several candidate variants of potential relevance in the following genes: *F12, F13A1, F13B, F5, KNG1, SERPIND1, THBD, ADAMTS13, VWF, STIM1, ETV6, THPO, MPL, SERPINA1, ENG, RASA1, ACVRL1, GDF2, NFE2, SOX17,* and *RNF213*. Conversely, no variants were detected in *FGA, CPB2,* and *BMPR2,* exclusively in CTEPH, despite their previous implication as potential candidates in earlier studies.

Our results confirm that the genetic background of CTEPH is highly heterogeneous, likely involving multiple, interrelated biological pathways, including those regulating coagulation, fibrinolysis, and angiogenesis.

Comparison of hemodynamic and imaging data revealed a strong correlation between directly and indirectly measured parameters, with the most robust association observed between the two invasive techniques — pulmonary angiography and Swan–Ganz catheterization. Echocardiographic estimates also showed good reliability, confirming the utility of echocardiography-based pressure assessment in this patient population.

Another goal of our research was to identify which CTEPH patients are most likely to benefit from balloon pulmonary angioplasty (BPA) treatment. Our findings suggest that early intervention, moderate baseline pulmonary vascular resistance (PVR), and preserved right ventricular function may predict sustained hemodynamic and clinical improvement following BPA.

Novel Scientific Findings

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1. One of the aims of our research was to create a widely accessible, scientifically rigorous summary of contemporary diagnostic and therapeutic options for CTEPH in Hungary, making it available to colleagues – general practitioners, internists, and cardiologists – who first encounter these patients. This initiative aims to facilitate early recognition, targeted evaluation, and rapid referral of patients to centers with appropriate multidisciplinary expertise.

2. We identified candidate variants in the following genes as potential genetic determinants in CTEPH patients: F12, F13A1, F13B, F5, KNG1, SERPIND1, THBD, ADAMTS13, VWF, STIM1, ETV6, THPO, MPL, SERPINA1, ENG, RASA1, ACVRL1, GDF2, NFE2, SOX17, and RNF213.

3. Regarding potential genetic determinants in CTEPH patients, no variants were found in FGA, CPB2, or BMPR2 genes, although these were suggested as potential candidates in previous studies.

4. The observed elevation of factor VIII and von Willebrand factor in CTEPH patients could not be explained by genetic alterations.

5. Our results confirm that the genetic background of CTEPH is heterogeneous, affecting multiple, interrelated pathways, including coagulation, fibrinolysis, and angiogenesis.

6. In our small patient cohort, no single variant was found at higher prevalence; however, most patients carried multiple distinct mutations, indicating a complex genetic background for the disease. This observation is consistent with previous literature.

7. Very strong correlations were observed between Swan–Ganz catheterization and PA-derived pressure measurements ($r = 0.96$), slightly lower correlation between TTE and PA ($r = 0.84$), and TTE and Swan–Ganz ($r = 0.78$) in our CTEPH cohort. This combined validation demonstrates the reliable applicability of non-invasive methods, such as well-standardized TTE, in this patient population.

8. The difference between TTE and invasive methods under standardized measurement conditions supporting the potential use of TTE for routine follow-up, thereby reducing the need for invasive procedures.

9. NT-proBNP levels and right ventricular dimensions (RVD1 value) may serve as useful predictors of response to BPA in CTEPH patients.

10. Higher baseline pulmonary pressure required a greater number of BPA sessions.

11. Baseline hemodynamic and laboratory biomarkers may help predict BPA efficacy, guiding patient selection and treatment strategies.

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Registry number: DEENK/583/2025.PL
Subject: PhD Publication List

Candidate: Gábor Kolodzey
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Kolodzey, G.**, Péter, A., Daragó, A., Balogh, L., Bereczky, Z., Barta, J., Csanádi, Z., Szűk, T.: Assessment of Right Ventricular Pressure in Chronic Thromboembolic Pulmonary Hypertension: comparison of Diagnostic Modalities and Balloon Pulmonary Angioplasty Outcomes.
   Diagnostics. 15 (16), 1-17, 2025.
   DOI: http://dx.doi.org/10.3390/diagnostics15162050
   IF: 3.3 (2024)

2. Bereczky, Z., **Kolodzey, G.**, Borsos, S., Balogh, L., Biró, P. E., Molnár, É., Molnárné Rázsó, K., Péter, A., Barta, J., Szűk, T.: Genetic Analysis of Patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH): a Single-Center Observational Study.
   Genes. 16 (11), 1-23, 2025.
   DOI: http://dx.doi.org/10.3390/genes16111336
   IF: 2.8 (2024)

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List of other publications

3. **Kolodzey, G.**, Balogh, L., Barta, J., Péter, A., Szűk, T.: Krónikus thromboemboliás pulmonalis hypertonia - a rejtőzködő betegség.
Orv. hetil. 166 (48), 1908-1915, 2025.
DOI: http://dx.doi.org/10.1556/650.2025.33433
IF: 0.9 (2024)

Total IF of journals (all publications): 7
Total IF of journals (publications related to the dissertation): 6,1

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

11 November, 2025

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