Follow-up after acute Pulmonary Embolism

Predicting chronic thromboembolic pulmonary hypertension and post-pulmonary embolism syndrome

Frederikus A. Klok¹,²; Stefano Barco¹

¹Center for Thrombosis and Hemostasis, University Hospital of the Johannes Gutenberg University Mainz, Mainz, Germany; ²Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

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Summary
In addition to among others major bleeding from anticoagulant therapy and recurrent venous thromboembolism (VTE), patients who survived acute pulmonary embolism (PE) face an increased risk of chronic functional limitations and decreased quality of life. In recent years, this latter complications have been better framed within the evolving definition of “post-PE syndrome” of which chronic thromboembolic pulmonary hypertension (CTEPH) represents the most extreme presentation. The post-PE syndrome in all its aspects is a frequent and clinically relevant long-term complication of PE but except for CTEPH has been largely understudied. There is great need to better define and understand the natural course of acute PE, to predict the development of the post-PE syndrome and to evaluate the potential benefits evolving treatments such as cardiopulmonary rehabilitation.

Introduction
After surviving acute pulmonary embolism (PE), patients face an increased risk of developing major bleeding from anticoagulant therapy, recurrent venous thromboembolism (VTE), arterial cardiovascular diseases, or chronic functional limitations (1-8). In recent years, this latter complication has been better framed within the evolving definition of “post-PE syndrome”, which accounts for suboptimal cardiac function, pulmonary artery flow dynamics, or pulmonary gas exchange at rest or during exercise, in combination with symptoms of exercise intolerance, dyspnea, impaired functional status, or worsened quality of life (8, 9). Chronic thromboembolic pulmonary hypertension (CTEPH) is the most extreme form of this syndrome, characterized by a chronic thromboembolic obstruction of the pulmonary arteries. Despite recent advances in the understanding of the pathophysiology and treatment of CTEPH, the natural course of the disease is still poorly understood, and patients often experience significant morbidity and mortality. The aims of this review are to summarize the current knowledge on the natural course of acute PE, the development of the post-PE syndrome, and the potential benefits of evolving treatments for CTEPH.
bolic pulmonary hypertension (CTEPH) represents the most severe manifestation of the post-PE syndrome (10–12). In the present review, we discuss the pathophysiology and frequency of CTEPH and post-PE syndrome, as well as the strategies under development to predict, prevent, and treat long-term sequelae of acute PE.

**Chronic thromboembolic pulmonary hypertension**

**Pathophysiology of CTEPH**

A commonly accepted mechanistic hypothesis is that CTEPH results from an incident episode of ‘unresolved’ PE characterized by the persistence of residual thrombi despite anticoagulant therapy, which contributes to increase pulmonary vascular resistance and ultimately results in progressive right ventricular overload (13–15). The exact pathophysiological mechanism that may prevent from complete resolution of acute thrombus is however not fully clarified yet, although pro-inflammatory state, abnormal fibrinogen variants, aberrations in angiogenesis, and mesenchymal cell activation have been implicated in poorer pulmonary thrombus resolution (Table 1) (13–21). Notably, whereas radiological signs of unresolved thrombotic material are necessary criteria for confirming a CTEPH diagnosis, these do not always match with the severity of the clinical presentation of individual patients and therefore cannot be accounted as an indicator for prognosis. In addition to chronic blood clots, CTEPH patients usually exhibit widespread pulmonary microvasculopathy, which resembles that of other pulmonary arterial hypertension subtypes (13, 22–24). Diffuse areas of the lung-affected or not by chronic thrombotic occlusions- similarly manifest microvasculopathy, indicating that higher share stress caused by chronic thrombi is not solely responsible for arterial remodeling. One of the explanations that has been hypothesized is that microvascular changes may be caused by altered blood flow from multiple anastomoses between systemic and pulmonary circulation through hypertrophic bronchial arteries that are opened by the high pressure gradient which develops between bronchial and pulmonary arteries affected by chronic blood clots (22).

Indeed, both the small vessel disease and the chronic proximal obstruction of the pulmonary arteries contribute to the progression of right ventricular overload. Initially, this outflow burden leads to right ventricular hypertrophy as a mechanism of the heart in order to increase the effectiveness of its pumping function, a process also referred to as ‘adaptive remodeling’. (25) However, adaptive remodeling is associated with a maintained right ventricular function for a limited period of time, after which inevitably ‘uncoupling’ occurs, causing right ventricular dilatation and especially during exercise- insufficiency, which ultimately lead to terminal right ventricular failure and death (25, 26).

How often is CTEPH diagnosed after acute PE?

The incidence of CTEPH after symptomatic acute PE has been reported to range from 0.1% to 11.8%, with most studies showing a frequency of 2–4% (10, 27–36). Beyond geographic or historical variations, such wide range can be explained by differences in patient selection and diagnostic criteria adopted by the investigators of published studies. For instance, most studies focused on specific subgroups of PE patients characterized by the absence of cardiopulmonary comorbidities and some did not apply right heart catheterization to confirm CTEPH.

To provide more clarity, a systematic review and meta-analysis of relevant studies and meeting abstracts has been recently published (37). Studies adopting invasive measurements to confirm the diagnosis of CTEPH were included in the main analysis and three patient subgroups were predefined to limit heterogeneity, namely i) ‘all comers’ (unselected consecutive PE patients), ii) survivors’ (PE patients who survived the first three to six months), and iii) ‘survivors without comorbidities’ (survivors further selected by excluding patients with cardiopulmonary, malignant and/or other severe comorbidities). A total of 4,047 PE patients were evaluated in the meta-analysis for pooled incidences in the predefined cohorts of 0.56% (95%CI 0.1–1.0), 3.2% (95%CI 2.0–4.4), and 2.8% (95%CI 1.5–4.1), respectively (Figure 1) (37).

Notably, the comparable incidences of both ‘survivor’ cohorts indicated that the presence of other conditions that may explain symptoms of functional impairment and dyspnea, such as COPD, do not appear to rule out the diagnosis of CTEPH, and adequate diagnostic tests for CTEPH should not be withheld in such patients. A final important observation of the meta-analysis regards the clear overdiagnosis of

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Tab. 1 Summary of the pathophysiological mechanisms implicated for the transition of acute PE to CTEPH and clinical conditions which may ‘predispose’ to CTEPH
CTEPH in studies that did not apply right heart catheterization but echocardiography as the diagnostic standard for CTEPH with a 3-fold higher CTEPH incidence (9.1%, 95%CI 4.1–14), indicating that echocardiography is not an accurate standalone test to confirm this diagnosis.

It must be noted however that the cases of CTEPH reported in the aforementioned follow-up studies likely represent a mix of incident and prevalent cases, therefore overestimating the actual figures of CTEPH incidence, since the diagnosis of CTEPH was often made within a few months after the index PE. In particular, a highly cited French study reported detailed reevaluation of the clinical PE presentation of the 7 (of 146) PE patients who were diagnosed with CTEPH (33). In five of seven patients, the authors described a notable elevated (assessed via echocardiography) systolic pulmonary arterial pressure of 70 mmHg, while historical data suggested that acute PE can be associated with an increase in mean pulmonary arterial pressure of up to 40 mmHg only with an extensive 70% of the pulmonary artery tree occluded by blood clots (38). This observation would suggest that these five patients may have developed pulmonary hypertension before the PE diagnosis was confirmed. Indeed, after review of the initial CTPA images by an expert radiologist, all seven patients had at least two signs of the condition at initial acute PE presentation, as did 20% of patients who did not develop CTEPH during the median follow-up of 26 months. Based on the latter observation, it could be hypothesized that preexisting (prevalent) CTEPH would have been misclassified as acute PE in some or even all the patients eventually diagnosed with CTEPH over follow-up. Nevertheless, as long as it remains impossible to distinguish ‘true’ acute PE from CTEPH at a (sub)acute clinical presentation, the difference between prevalent and incident cases of CTEPH after acute PE does not appear of clinical relevance for the initial treatment of these patients since all are candidate to extended anticoagulation, nor for determining the proper level of awareness for CTEPH of PE caretakers.

To further reinforce this concept, several observations demonstrated that CTEPH is not preceded by symptomatic VTE in 19–63% of patients (39, 40). It remains purely speculative the hypothesis of these patients suffering from episodes of ‘silent PE’, or, alternatively, if they represent a different clinical scenario of CTEPH developing from in situ thrombosis as a thrombogenic phenotype of class 1 pulmonary hypertension.

Can we predict CTEPH?

The ability to predict which PE patients will develop CTEPH will likely improve their prognosis by allowing physicians to better apply valuable resources to a specific high-risk group, while preventing unnecessary imaging tests to patients with a negligible risk of developing or having CTEPH. Unfortunately, evidence for strategies of risk prediction are scarce and this is largely due to the absolute low incidence of the disease and the unavailability of large databases of consecutive patients at risk of developing CTEPH (41, 42).

One possible strategy to overcome these limitations would be to focus on cohorts of PE patients with identified risk factors for CTEPH such as splenectomy, prior infected pacemaker leads, chronic inflammatory disease, antiphospholipid syndrome, known hypothyroidism, and ventriculo-atrial shunt (Table 1) (43–46). The first issue that may raise by adopting this approach is represented by the fact that these variables have been identified as risk factors associated with CTEPH, but not validated as predictors of the disease and therefore cannot be used (yet) for a first risk stratification in order to increase the expected rate of CTEPH in the study cohort. Moreover, the absolute risk of CTEPH for patients presenting with these risk factors is unknown as they were often identified in case-control studies comparing subjects diagnosed with CTEPH and population controls or patients with class I PH, and not in cohorts of PE survivors (47). Finally, since their prevalence in PE cohorts is low (e.g. for splenectomy about 2%), this approach appears unlikely to be sufficiently accurate.

A second strategy would be to study the added value of reassessing CTPA scans for detecting signs of chronic PE or pulmonary hypertension such as right ventricular hypertrophy, webs and bands, tortuous bronchial arteries or mosaic perfusion (33). As discussed above, these signs may be very sensitive for prevalent CTEPH. Even so, the aforementioned French study included only seven patients with CTEPH and does not provide sufficient evidence for strong recommendations for clinical practice.

Clinical decision rules and risk assessment models are widely used in clinical practice for diagnostic or prognostic purposes. A collaborative study between German, Polish and Dutch PE expert centers aimed at developing a score for prediction of CTEPH after PE (47). They performed a patient-level analysis of a total of 772 PE-survivors without major cardiopulmonary or oncological comorbidities at baseline, and fit multivariate regression models to identify clinical variables easily assessable at the time of index PE event that would independently predict CTEPH. A score con-
sisting of six variables was derived (Table 2), the so-called ‘CTEPH prediction score’. Approximately, 75% of patients was classified as ‘low-risk’ with a PE incidence during follow-up of <0.5%, and one quarter as ‘high-risk with’ a CTEPH incidence of 10%. The overall predictive value of the score was good with an area under the receiver operator characteristic curve (ROC) in both the primary as well as the sensitivity analysis of >0.85 (47). External validation of the CTEPH prediction score is not yet available. Interestingly, the score provides two striking variables that seemed to ‘protect’ against CTEPH, namely thrombolyis and diabetes, which must be confirmed for their pathophysiological role in future studies.

**Can we prevent CTEPH?**

Thrombolysis was recently been shown not to protect against CTEPH development in a follow-up study including a large proportion of patients with acute PE associated with right ventricular dysfunction on echocardiography or computed tomography, as well as positive laboratory markers for myocardial injury, previously enrolled in the Pulmonary Embolism Thrombolysis (PEITHO) trial (5). Additionally, the European CTEPH registry, which also includes patients treated with thrombolysis, indicated that reperfusion therapy does not prevent the development of CTEPH (39, 48). The main ‘methodological’ reason for which thrombolytic treatment was included in the score is the fact that, although only 22 patients who developed the outcome (CTEPH) were included in this study, none received thrombolysis, which may have been due to chance or to the presence of biases for selection, indication, or reporting intrinsic to the observational study design of the derivation cohorts. Whether lysed (high-risk) patients are less likely to suffer from more chronic thromboembolic disease remains to be proven.

The other notable factor that was negatively associated with the presence of CTEPH was diabetes mellitus. It was nonetheless previously shown that patients with class I pulmonary hypertension more often have Diabetes than patients with CTEPH (43, 44, 49). One possible explanation for these independent observations would be that metformin, which is the first line treatment of type 2 diabetes mellitus, has pro-fibrinolytic properties by reducing the activity of plasminogen activator inhibitor-1 (50, 51). Indeed, use of metformin has been reported to be associated with a lower risk of venous thromboembolism in cohort study of moderate quality (52).

**Post-PE syndrome**

**Does a “Post-PE syndrome” exist?**

The frequency of functional impairment after acute PE was evaluated in several cohort studies. In a prospective study of 109 previously healthy patients experiencing incident acute PE, more than half (53%) reported symptoms of exercise intolerance corresponding to a New York Heart Association (NYHA) heart failure score of ≥II after a 6-month follow-up period (53). A second study in 162 PE survivors showed similar figure (52%) of persisting symptoms (NYHA score of II or more) six months after PE diagnosis and anticoagulant treatment initiation (54). Similarly, a third study found a 3-year NYHA incidence rate of class II (or higher classification) of 45% among 189 PE survivors (55). If one focuses on severe functional limitations only (i.e. NYHA class III/IV and/or impaired 6-minute walking test), the resulting percentages are of 41% and 42%, respectively (53, 54). Initial follow-up data suggest that 6-minute walking test may improve up to one year after PE diagnosis, although most improvement occurs in the first three months (8). Based on a recent meta-analysis that included the aforementioned studies as well as smaller cohort studies, the pooled prevalence of mild or greater functional impairment (NYHA II–IV) in PE survivors is 33.2% (95%CI 21.3–46.4) after a median follow-up duration of 40 months (56). While CTEPH is a rare condition, this phenomenon must be explained by another pathophysiological mechanism (Figure 2) (9).

The condition of persistent perfusion defects without resting pulmonary hypertension (mean pulmonary systolic pressure >25 mmHg) has been previously referred to as chronic thromboembolic vascular disease (CTED) when associated with functional impairment: CTED falls under the umbrella of the post-PE syndrome (9, 57). In one study, patients with CTED were found to have gas exchange disturbances and ineffective ventilation to a similar degree as can be found in patients with CTEPH (57). The mechanism for functional impairment in CTED may be heterogeneous and includes exercise-induced pulmonary hypertension, ventilatory dead space, right ventricular dysfunction (e.g. decreased contractile reserve), and abnormal pulmonary flow dynamics (e.g. running pressure wave reflection). The most frequent cause of the post-PE syndrome may however very well be deconditioning after an acute cardiovascular disease with associated hospitalization and correlated burden (8, 59).

**Impact of CTEPH and the post-PE syndrome**

CTEPH, but not the less severe presentations of the post-PE syndrome, has been
associated with increased risk of death. Historical data indicate that 5-year survival after CTEPH diagnosis is as poor as 20% in patients with pulmonary artery pressures >50 mmHg if adequate treatment is not provided (60). More recent data in all-severity pulmonary hypertension patients showed a 5-year survival rate of 70%, with marked better prognosis in those who underwent pulmonary endarterectomy (PEA), which is still indicated as the first-line treatment of CTEPH (39).

In general, patients with post-PE syndrome have lower score measured by quality of life questionnaires compared with population controls or with PE patients who report full recovery (7, 61, 62). Poorer quality of life has been demonstrated to be greatly dependent on functional impairment and correlates with poor physical performance on exercise testing. Other factors being possibly associated with worse quality of life include higher clot burden at index PE event, abnormal NT-proBNP at index PE event, persistent right ventricular dysfunction, as well as non-VTE comorbidities such as COPD, obesity and cancer (8, 55, 59, 63–70). As it may be expected, the association between CTEPH and poor quality of life has been unequivocally established (71–74).

**Treatment and prevention of CTEPH and the post-PE syndrome**

The gold standard treatment for CTEPH is PEA, which has been shown to reduce mortality and improves right circulation hemodynamics as well as exercise tolerance in prospective studies. During this surgical procedure, thromboembolic material is removed from the pulmonary artery tree after median sternotomy and during deep hypothermic circulatory arrest (75, 76). Postoperative hemodynamics become normal or near normal in most patients after PEA with an average 65% decrease in pulmonary artery resistance and a sharp decrease in mean pulmonary artery pressure. In high-volume centers, the in-hospital mortality currently is lower than 5% (75, 76). PEA is not an established therapeutic option for CTED since such death risk overcome possible benefits: despite that, surgery is sometimes performed for this indication. In fact, a small cohort study including 42 patients undergoing PEA for CTED demonstrated a significant improvement in NYHA functional status, mean pulmonary artery pressure, pulmonary vascular resistance, 6-minute walk distance, and quality of life at cost of major complications such as supra-ventricular tachycardia’s, re-surgery or re-intubation occurring in up to 40% of patients (77). Hence, on a risk-benefit balance, PEA should not be routinely performed in CTED patients, but may be considered in individual cases based on the extend of the thrombotic lesions, gas exchange abnormalities, severity of symptoms, and patient’s preferences.

Due to extensive distal CTEPH or severe comorbidities, a not-negligible subset of patients is considered inoperable and must be considered for the sole medical and support therapy. A trial of Riociguat, a soluble oral stimulator of guanylate cyclise, showed to improve 6-minute walk distances and reduce pulmonary vascular resistance in inoperable CTEPH patients (78). Based on a growing number of observation of its effectiveness, Riociguat is currently the only approved medical therapy for inoperable CTEPH (78–81). Off-label use of other pulmonary hypertension drugs (e.g. bosentan, iloprost, and prostacyclin), or the use of riociguat as a therapeutic bridge to PEA, is currently not recommended mostly based on unavailable data (81). Similarly, its benefit in patients with post-PE syndrome have never been studied and therefore Riociguat remains contra-indicated, despite some rationale for its use in this setting.

A catheter-based approached, balloon pulmonary angioplasty (BPA), is being explored at several centers for patients who do not match surgical suitability with PEA. In this procedure, small angioplasty balloons are introduced into segmental pulmonary artery branches and used to dilate webs and strictures (82–86). This procedure was firstly performed in a Dutch patient in 1988, who developed non-lethal pulmonary edema after two procedures (87). In the past decades, the technique of BPA has been much improved in Japan and re-introduced in Europa and North-America in recent years. While preliminary results indeed are promising, solid randomized studies are needed to define BPA’s efficacy and the place of BPA in the treatment algorithm of CTEPH. As with medical treatment, although patients with CTED may also benefit from BPA, BPA has never been systematically evaluated in this specific patient group.

Unlike patients with myocardial infarction or other severe cardiopulmonary conditions, cardiopulmonary rehabilitation is not routinely offered to patients with a PE diagnosis, nor to patients with post-PE syndrome. However, available data -although scarce- suggest the effectiveness of such intervention in patients with PE (88, 89) or with an established CTEPH diagnosis (90–92) in terms of exercise parameters and quality of life. Although these preventable death.
liminary data suggest a benefit of cardiopulmonary rehabilitation for patients with the post-PE syndrome, future larger randomized outcome studies will establish the relevance and cost-effectiveness of such approach. Importantly, for patients with CTEPH, cardiopulmonary rehabilitation programs should not delay PEA if patients are operable.

How should patients be followed after acute PE?

Practice patterns of patient follow-up after acute PE differ greatly and solid evidence to provide guidance is lacking. The only strong guideline recommendations from different international guidelines is that all patients with acute PE need to be treated with a 3-month minimum course of anticoagulant therapy, after which the net clinical benefit of secondary anticoagulant prevention accounting for bleeding risk should be reassessed (81). This routine 3-month follow-up visit would be the ideal time-frame for the assessment risk factors for post-PE syndrome and specifically CTEPH. We propose that in all patients at an estimated high risk of CTEPH, based on i) clinical and radiological characteristics of index PE and persistent RV dysfunction at discharge, ii) CTEPH prediction score (as described above), or iii) clear functional impairment, the presence of CTEPH should be evaluated. Importantly, subjecting all PE survivors routinely to echocardiography or ventilation perfusion scintigraphy has a low diagnostic yield, leads to gross overdiagnosis and is not cost-effective. Hence, such practices need to be abandoned. Since it may take much longer than three months for CTEPH to develop, patients as well as PE caretakers should be educated to be aware of this long term complication: CTEPH should be included in the deferential diagnosis of patients who develop chronic dyspnea or functional impairment in the longer-term follow-up after PE, regardless of the presence of other cardiopulmonary comorbidities.

Future landscape

Four key clinical studies that will definitely change the landscape of post-PE care include the FOCUS study, the InShape II study, a Danish rehabilitation study and the RACE study. The FOCUS study is a large prospective observational German cohort study of PE patients (German Clinical Trials registry: DRKS00005939). In FOCUS, a total of 1000 PE patients are systematically followed over a 2-year period with a standardized comprehensive program of clinical, echocardiographic, functional and laboratory testing. This study will provide definite answers to relevant remaining questions such as the occurrence of CTEPH and temporal patterns of and risk factors for post-PE abnormalities. Moreover, it will contribute to better standardize the concept of post-PE syndrome by adopting predefined diagnostic definition including clinical symptoms and advanced imaging criteria (93).

The InShape II study is an international, multicenter intervention study that will prospectively validate a PE follow-up algorithm aimed at early diagnosis of CTEPH (ClinicalTrials.gov: NCT02555137). The algorithm consists of sequential application of the CTEPH prediction score, followed by the so called ‘rule-out criteria’ for patients with either a high clinical probability for CTEPH or with specific symptoms of CTEPH (47, 94, 95). The ‘rule-out criteria’ consist of NT-proBNP measurement and ECG assessment for 3 specific signs of pulmonary hypertension. Only patients with either elevated NT-proBNP or those with 1 of the 3 ECG signs present will be referred for CTEPH diagnostic tests, limiting the number of necessary imaging tests and false-positive test results. The main endpoints of the InShape II study are the sensitivity of the algorithm, i.e. the number of missed CTEPH diagnoses after 2-year follow-up, and the cost-effectiveness of the algorithm.

The first large randomized controlled trial to assess the benefit of pulmonary rehabilitation in PE patients is being performed in Denmark (ClinicalTrials.gov: NCT02684721). The aim of this study is to examine whether an 8-week home-based exercise intervention may improve physical capacity, quality of life, sick leave, and use of psychotropic drugs in patients with a history of acute PE (96). This important study will provide sufficient evidence on the question whether cardiopulmonary rehabilitation may be a relevant treatment for the post-PE syndrome, allowing for many further clinical trials to determine the optimal rehabilitation program.

The RACE study (ClinicalTrials.gov: NCT02634203) is a randomized open-label clinical trial, in which patients with CTEPH who are not eligible for PEA will be randomised to riociguat or BPA as first-line treatment. The primary aim of the study is to establish the difference in change in pulmonary vascular resistance from baseline to the end of the 26-week follow-up period. This study will show us whether medical treatment or BPA may be the better first-line treatment option in non-operable CTEPH patients.

Conclusion

The post-PE syndrome in all its aspects is a frequent and clinically relevant long-term complication of acute PE. Except for CTEPH, its most severe manifestation, the post-PE syndrome remains largely understudied. In addition to the optimal treatment approach for non-operative CTEPH, there is great need to better define and understand the natural course of acute PE and to predict its development, as well as to extensively evaluate the potential benefits of BPA, medical treatment, and cardiopulmonary rehabilitation for patients with the post-PE syndrome.

Disclosures

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