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Late outcomes of pulmonary embolism: The post-PE syndrome

Akhilesh K. Sista [a], Frederikus A. Klok [b,*]

[a] New York University Langone School of Medicine, New York, NY, USA
[b] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

The post-Pulmonary Embolism (post-PE) syndrome is being increasingly recognized as a long-term consequence of PE. Its most severe manifestation, chronic thromboembolic pulmonary hypertension (CTEPH), affects a small proportion of PE survivors. However, many more with less severe post-PE syndrome have reduced quality of life and functional capacity. The pathophysiology is incompletely understood, but involves unresolved pulmonary artery thrombi, right ventricular damage, and abnormal gas exchange. Treatment has only been established for CTEPH, and further studies are required to determine how less severe forms of the post-PE syndrome should be treated and if preventive strategies can reduce its incidence.

1. Introduction

Patients diagnosed with acute pulmonary embolism (PE) are at risk for recurrent VTE, major bleeding from anticoagulant therapy, mortality, arterial cardiovascular diseases, and chronic thromboembolic pulmonary hypertension (CTEPH) [1–7]. In recent years, chronic functional limitations and decreased quality of life have also been increasingly recognized as long-term complications of acute PE [8]. This "post-PE syndrome" is defined by suboptimal cardiac function, pulmonary artery flow dynamics, or pulmonary gas exchange at rest or during exercise, in combination with dyspnea, exercise intolerance, or diminished functional status or quality of life, without an alternative explanation. Here we discuss the epidemiology, pathophysiology, disease burden, treatment, and prevention of the post-PE syndrome.

2. Epidemiology

The incidence of chronic thromboembolic pulmonary hypertension (CTEPH), the most severe manifestation of the post-PE syndrome, is reported to range from 0.1% to 11.8% [3,5,9,10]. This wide range in reported incidences is a result of major differences in selection and diagnostic criteria between available studies. A recent meta-analysis that studied specific subgroups of PE patients, i.e. "all comers", "survivors" or "survivors without major comorbidities", and excluded studies in which the diagnosis was based on echocardiographic data alone, found that the pooled incidence of CTEPH in the all comer group was 0.56% (95%CI 0.1–1.0) versus 3.2% (95%CI 2.0–4.4) and 2.8% (95%CI 1.5–4.1) in both survivor cohorts respectively [11]. "All comers" was defined as all consecutive patients with symptomatic PE with no exclusion criteria, "survivors" as all consecutive patients with symptomatic PE who were alive after an initial treatment period of 6 months and "survivors without major comorbidity" as all consecutive patients with symptomatic PE who were alive after an initial treatment period of 6 months and did not have predefined significant cardiopulmonary, oncologic or rheumatologic comorbidities. The 0.56% incidence in the all-comer group probably provides the best reflection of the incidence of CTEPH after PE at a population level while the ~3% incidences in the survivor categories are most relevant for daily clinical practice. Given that a minority of PE survivors undergoes right heart catheterization in the years following the index PE, and that those who have severe symptoms are most likely to seek medical attention, the prevalence of CTEPH is probably underestimated.

The incidences of less severe manifestations of the post-PE syndrome appear to be higher than those of CTEPH. Several cohort studies have evaluated functional impairment following acute PE. In a prospective study of 109 previously healthy patients with acute PE who were alive at 6-months and completed cardiopulmonary exercise testing, 53 had a New York Heart Association (NYHA) heart failure score of II or higher (48%) [12]. A second study of 421 patients with a history of acute PE indicated that 189 (45%) were NYHA Class II or higher, even after a follow-up period of over 3 years [13]. In a third study of 162 PE survivors who underwent cardiopulmonary function tests at 6 months, 84 (52%) had an NYHA score of II or more [14]. The incidence of more serious functional limitations such as NYHA class III/IV and/or impaired 6-minute walking test in these studies was 41% and 42% respectively [12,14]. Interestingly, it was suggested that functional limitations as measured by the 6-minute walking test seem to improve during the first year following a PE diagnosis, although most improvement occurs

* Corresponding author at: Department of Thrombosis and Hemostasis, LUMC, Albinusdreef 2, 2300 RC Leiden, The Netherlands.
E-mail address: f.a.klok@LUMC.nl (F.A. Klok).

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between month 1 and 3 [15]. The same study showed that after year, 46.5% of patients had percent-predicted VO2peak <80%, which was associated with poorer performance on the 6-minute walking test and quality of life. Based on a recent meta-analysis that included smaller cohort studies, the pooled prevalence of mild or greater functional impairment (NYHA II–IV) is 33.2% (95%CI 21.3-46.4) after a median follow-up duration of 40 months.

Persistent perfusion defects, one of the main determinants of the Post-PE syndrome, are also common despite adequate anticoagulant therapy. Studies with serial pulmonary angiograms have indicated that resolution of thrombi is negligible 2 h after treatment initiation, 10% after 24 h, 40% after 7 days, and 50% after 2 to 4 weeks [16]. In the long term, complete resolution may be achieved in only 70–85% of all patients [17–20]. Interestingly, ventilation/perfusion lung scintigraphy seems to detect residual thrombi more frequently than computed tomography (CT) [20,21]. The condition of persistent perfusion defects without resting pulmonary hypertension (mean pulmonary systolic pressure > 25 mm Hg) has been referred to as chronic thromboembolic disease (CTED). When associated with functional impairment, CTED falls under the umbrella of the post PE syndrome.

The second most relevant determinant of the Post-PE syndrome is persistent right ventricle dysfunction, also relatively common in PE survivors. In three small cohort studies, right ventricular dysfunction 6 to 12 months post PE was present in 10–44%; persistent perfusion defects, severe right ventricular dysfunction at baseline, known cardiovascular comorbidities, and older age were associated with a higher risk of persistent right ventricular dysfunction. On the other hand, up front thrombolytic therapy was associated with a lower risk in three studies, but not in a fourth study [12,14,22,23].

The overall incidence of PE in the Western world has been reported to range between 0.52 and 0.69 per thousand per year, indicating ~ 200.000 incident cases in the United States alone, of whom 40.000 die within the first 6 months after diagnosis [24,25]. Applying above mentioned incidences to these patients results in the following notable numbers: of the ~160.000 survivors, a projected 90.000 will have functional limitations after 6 months and ~64.000 after 3 years. About 35.000 will have CTED and ~1250 will develop CTEPH [26]. These numbers unequivocally underline the high frequency and relevance of the post-PE syndrome.

3. Pathophysiology

A central unanswered question regarding the post-PE syndrome is why some PE survivors completely recover while others do not. Research thus far has mainly focused on CTEPH, since it is the most severe manifestation of the post-PE syndrome. Pathophysiologically, it is unknown why some develop mild symptoms and others develop CTEPH. The text below discusses risk factors for CTEPH development, vascular pathobiology, and right ventricular pathology.

Approximately 75% of those with a CTEPH diagnosis will have had a prior PE [27]. Large clot burden, large perfusion defects, and elevated pulmonary pressures (>50 mm Hg) at baseline and at 1 month confer a higher risk of CTEPH development [5,22,28,29]. Right heart strain and ventricular damage during the acute event have been linked to CTEPH. Recurrent VTE also has an association [30]. Other demographic risk factors include a younger age; a history of splenectomy, inflammatory bowel disease, or chronic osteomyelitis; and non-O type blood groups [31]. Although inflammation has been implicated in CTEPH development, it is unclear why these specific demographic traits are risk factors. There is no clear association between hypercoagulable states and CTEPH, although there is some data to suggest an increased risk with elevated Factor VIII and lupus anticoagulant and anti-cardiolipin antibodies [30–33].

The overarching hypothesis is that unresolved pulmonary artery thrombus increases pulmonary vascular resistance and is either directly or indirectly involved in small vessel remodeling into plexogenic lesions seen in other pulmonary arterial hypertension subtypes. Small vessel arteriopathy (plexogenic lesions) may occur in both occluded and non-occluded arterioles through poorly understood mechanisms. Factors released from the endothelium and/or platelets, or as a result of altered pulmonary blood flow, may contribute to this pathology seen in other forms of pulmonary hypertension [34].

Since residual thrombus is necessary (though not sufficient) for development of CTEPH, research has focused on abnormal fibrinolysis and thrombus remodeling (Fig. 1). In a dog model of acute PE, inhibition of fibrinolysis resulted in chronic, organized pulmonary thrombus, persistent perfusion defects, and elevated pulmonary vascular resistance [35]. Impaired fibrinolysis in humans may be due to fibrinolytic enzyme under-expression/under-activity, or overexpression/over-activity of fibrinolysis inhibitors. However, CTEPH patients have not exhibited abnormalities in plasminogen or plasminogen activator inhibitor 1 (PAI-1) [36]. An alternative hypothesis is that fibrin itself is resistant to degradation, and its persistence signals exuberant remodeling and scar formation. In particular, the N-terminus of fibrin (termed the “B-knob”) may be resistant to degradation in CTEPH patients. The B-knob binds to endothelial cells and fibroblasts and may induce cell signaling that leads to scar formation [37–40]. Abnormal variants of fibrinogen have been found in some CTEPH patients [41–43].

In parallel, acute PE induces a vigorous inflammatory response, consisting of neutrophil infiltration followed by monocytes and accompanying cytokines and chemokines [44]. This response is consistent and, in most individuals, appears to facilitate thrombus resolution. While not proven, an altered inflammatory response may inhibit thrombus resolution or promote remodeling and scar formation. The subacute phase of thrombus resolution involves neovascularization and angiogenesis, which recanalize the vessel, albeit with residual webs that are characteristics of post-thrombotic pulmonary arteries [45,46]. If this process is altered or inhibited, potentially due to differentiation of progenitor cells into a fibroblast sub-type instead of an angiogenic one, the balance may tip towards scar formation rather than recanalization. Adding to these factors, a global hypercoagulable state, activated platelets, blunted nitric oxide production or response, and smooth muscle hypertrophy and extracellular matrix deposition potentially influence large and small vessel disease [44,47–49].

Right ventricular pathophysiology has not been as extensively studied as vascular pathobiology in the development of CTEPH, but likely influences the severity of clinical manifestations in patients with the post-PE syndrome. As described above, patients with evidence of acute and/or persistent RV strain are at greater risk for CTEPH development. Animal and human studies demonstrate an intense inflammatory reaction in the right ventricular wall following acute PE [50–57]. This inflammatory response is likely triggered by myocyte stretch, shear forces, decreased perfusion, and increased metabolic demand in the setting of increased afterload. The chronic result is myocyte necrosis, apoptosis, enzymatic release, and ultimately, thinning and fibrosis of the right ventricle [55]. Attenuating inflammation in an animal model of pulmonary embolism actually preserved myocardial architecture and function, supporting the idea that excess inflammation is maladaptive [58]. If there is chronic elevation in pulmonary vascular resistance, a compensatory myocyte hypertrophy may ensue, though this compensation in an already damaged ventricle may be incomplete or mechanically inefficient.

In summary, a combination of impaired fibrinolysis, over-exuberant thrombus remodeling into scar tissue, impairment in pulmonary vasodilation, and small vessel occlusion lead to elevated pulmonary vascular resistance and chronically elevated afterload. If the right ventricle sustained enough damage during the initial embolism, its ability to function, especially during exercise, may be impaired, especially if there is pathological elevation in pulmonary vascular resistance during exercise [59]. Increased alveolar dead space and ventilation-perfusion mismatch may contribute to subjective dyspnea and exercise intolerance [17,60]. Varying penetrance of these factors may explain the spectrum of presentation from mild post-PE syndrome to CTEPH.