REVIEW

The post-PE syndrome: a new concept for chronic complications of pulmonary embolism

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ABSTRACT

Long-term follow-up studies have consistently demonstrated that after an episode of acute pulmonary embolism (PE), half of patients report functional limitations and/or decreased quality of life up to many years after the acute event. Incomplete thrombus resolution occurs in one-fourth to one-third of patients. Further, pulmonary artery pressure and right ventricular function remain abnormal despite adequate anticoagulant treatment in 10–30% of patients, and 0.5–4% is diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) which represents the most severe long term complication of acute PE. From these numbers, it seems that CTEPH itself is the extreme manifestation of a much more common phenomenon of permanent changes in pulmonary artery physiology of CTEPH. In this clinically oriented review, we discuss the established associations and hypotheses between the process of thrombus resolution or persistence, lasting hemodynamic changes following acute PE as well as the consequences of a PE diagnosis on long-term physical performance and quality of life.

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1. Introduction

The post-thrombotic syndrome (PTS) of the leg is a common and chronic complication of deep vein thrombosis (DVT) of the leg that develops in up to one third of patients despite optimal anticoagulant treatment [1,2]. PTS symptoms may vary, ranging from pain, swelling or skin changes to ill controlled edema and chronic leg ulcers [3]. In essence, venous valve damage, local inflammation and residual thrombosis result in raised deep vein pressure causing tissue edema, subcutaneous fibrosis and ultimately chronic ulceration [4]. As a result, patients with PTS report significant disability and impaired quality of life [5].

Although a previous diagnosis of acute pulmonary embolism (PE) has been found to frequently have a negative impact on both physical performance and quality of life [6,7], and chronic thromboembolic pulmonary hypertension (CTEPH) is a well-known long-lasting complication of acute PE associated with poor thrombus resolution and altered pulmonary artery hemodynamics [8,9], a comprehensive definition of a “post-PE syndrome” has not been proposed yet, let alone a pathophysiological explanation for such a syndrome.

This clinically oriented review covers the process of thrombus resolution or persistence, the long term hemodynamic changes following acute PE and the consequences of a PE diagnosis on long term physical performance and quality of life; this, in analogy to the PTS. Further, we take a step in closing the gap between the frequent observation of persisting dyspnea and decreased quality of life after PE on one hand, and the rare cases of manifest CTEPH on the other. For the purpose of this review, we performed an extensive Medline literature search to identify all relevant papers.

2. Thrombus resolution after DVT

Acute DVT is the formation of a blood clot in a deep vein that causes partial or complete obstruction of venous outflow. After the initiation of heparin treatment the spontaneous process of thrombus resolution and recanalization allows the venous lumen to be re-established. This process starts when the initial loose thrombus becomes adherent to the vessel wall, after which a local inflammatory response initiates thrombus organization starting with spontaneous lysis of areas within the thrombus, that ultimately leads to recanalization [10]. Angiogenesis within the thrombus plays an essential role for this latter process. Within 6 weeks after DVT diagnosis and treatment initiation, most blood clots show evidence of recanalization [10]. Nonetheless, thrombus extension in the first days despite optimal anticoagulant treatment is not
uncommon, and ultrasound abnormalities persist in up to 60% of patients after 3 months and up to 40% of patients one year after DVT diagnosis [10–12].

The inflammatory response to acute thrombosis, the process of recanalization and residual thrombi, all bring damage to the venous valves, resulting in valvular reflux. Valvular reflux can be found as soon as one week after DVT diagnosis, and is present in about 70% of patients after one year [13]. Both the presence and severity of reflux closely correlates with the extent of initial vein occlusion and the rate as well as the degree of thrombus resolution [4,13–15]. Reflux and valvular dys-function eventually lead to the development of venous microangiopathy with increased permeability of the capillaries. Fluid accumulation, high venous pressure and—in advanced stages—skin fibrosis are responsible for the clinical signs and symptoms of PTS [4,16].

3. Thrombus resolution after acute PE

As in DVT, organization of pulmonary blood clots begins after adherence of the clot to the vessel wall, with formation of a thin lining of endothelial cells over its surface, followed by ingrowth of cells from the intima media and capillary buds into the thrombus [17]. Even so, thrombus organization and recanalization after acute PE is in some aspects different from that process after DVT, partly because of the higher blood flow in pulmonary arteries that exposes thrombi to more plasminogen, and possibly a greater thrombolytic capacity of pulmonary artery endothelium than that of peripheral veins [17,18].

3.1. Radiological changes after treatment initiation

Serial pulmonary angiograms and perfusion lung scans (VQ-scan) in patients diagnosed with acute PE and treated with heparin indicate that, while resolution of thrombi is negligible 2 hours after treatment initiation, it is 10% after 24 hours, 40% after 7 days, and 50% after 2 to 4 weeks [19]. The long term rate of PE resolution remains a matter of debate. Based on the largest studies, complete resolution may be achieved in 70–85% of all patients 6 to 12 months after initial PE diagnosis with partial resolution in the vast majority of the remaining patients [20–26], although smaller observational studies have reported complete resolution rates as low as 30% or as high as 98% after 12 months [27–29]. Notably, the resolution of thrombi appears to reach a plateau phase after 3 months of adequate treatment since only very small improvements are seen after that time, suggesting that remaining clots then have been remodeled into permanent fibrous scars [22,26,27,30]. Also, ventilation/perfusion lung scintigraphy seems to detect residual thrombi more frequently than computed tomography (CT) since complete normalization is more often observed with CT-scan in direct comparisons [21,31]. Larger, more centrally located blood clots, older age, a longer duration of symptoms before PE is diagnosed, and a history of VTE are associated with a lower degree of thrombus resolution as well [22,25,27].

3.2. Unresolved thrombi

The mechanisms, by which some of the pulmonary emboli fail to completely resolve, and instead organize into occluding fibrotic material, are currently unknown [8,32]. Pathological studies report that material removed during pulmonary artery endarterectomy in patients with CTEPH shows different stages of thrombus remodeling associated with variable degrees of inflammation within the specimen, and either consist of fibrous plaques with signs of angiogenesis, or atherosclerosis-like lesions with cholesterol clefts, macrophages, T-lymphocytes and calcification [33,34]. The clinical or biological relevance of these findings is still to be established.

Several mechanisms for poor thrombus clearance have been suggested: abnormal genetic variants of fibrinogen, predisposing pulmonary endothelial cell abnormalities, impairments in the angiogenesis process, and bacterial infection of fresh thrombi. Abnormalities of circulating fibrinolytic factors, i.e. plasma levels of plasminogen, antiplasmin, tissue-type plasminogen activator or plasminogen activator inhibitor 1, have not been associated with chronic pulmonary thrombi [35]. In contrast, in some patients with unresolved thrombi, differences in the molecular structure of fibrin associated with a relative resistance of fibrin to plasmin-mediated lysis have been demonstrated [36–38]. Further, differences in fibrinogen genotype and allele frequencies between CTEPH subjects, patients with acute PE, and healthy controls have been reported [39,40]. Notably, classical ‘thrombophilias’ are not typically encountered in patients with unresolved thrombi [41].

Failure to resolve pulmonary vascular obstructions may also be interconnected with a deficiency in angiogenesis and endothelial function. For instance, organized CTEPH thrombi were shown to be largely devoid of vascular structures indicative of active angiogenesis, and several vessel-specific genes associated with angiogenesis were expressed at lower levels in CTEPH thrombi than in organizing deep vein thrombi or organizing thrombi from aortic aneurysm [42]. Also, impaired plasmin-mediated removal of specific fibrin fragments negatively affects a variety of physiological processes including angiogenesis [43]. In addition, a recent study in surgical pulmonary artery endarterectomy material described significantly different calcium homeostasis in endothelial cells as compared to pulmonary artery endothelial cells from normal controls [44]. This was explained by the presence of high levels of angiostatic factors in the same surgical material which affect cell proliferation, migration and vessel formation in the thrombus, as an ultimate sign of inadequate endothelial response to local thrombotic material.

Finally, infection with staphylococci has been shown to enhance fibrotic vascular remodeling after thrombosis, causing misguided thrombus resolution [45]. This observation is an argument for the role of thrombus infection as trigger for non-resolution of PE. Importantly, the above discussed pathophysiological mechanisms for thrombus resolution are all derived from studies in patients with established CTEPH. It is unknown whether the delayed and/or incomplete resolution of perfusion defects after acute PE occurs by the same mechanism as that by which CTEPH develops.

4. Hemodynamic response to PE

Historical angiographic studies have shown that at least 25% of the pulmonary arteries needs to be obstructed by acute PE before the pulmonary arterial pressure ultimately starts to rise [46]. After treatment initiation, this pressure returns to normal in the majority of patients within one month [47]. This pressure normalization is probably caused by reversal of pulmonary arterial vasoconstriction induced by the inflammatory response to the acute PE, and restoration of blood flow after thrombus recanalization and resolution [46].

4.1. Echocardiographic follow-up after acute PE

Three studies have followed patients with acute PE with serial echocardiograms to evaluate the long term pulmonary artery and cardiac hemodynamic responses in treated PE. The first study included 78 patients with acute PE who were repeatedly evaluated by echocardiography during the first year following PE diagnosis [47]. The patterns of the restoration of pulmonary artery pressure and recovery of right ventricular function with time was characterized by an initial dynamic phase followed by a stable phase, which was achieved within 30 days in >90% of patients. Older patients (age >70 years, corrected odds ratio 4.1) and patients with a baseline pulmonary artery pressure >50 mmHg (corrected odds ratio 3.3) were at higher risk for persistent pulmonary hypertension or right ventricular dysfunction. None of the patients with normalized pulmonary artery pressure was later on diagnosed with CTEPH, because they were not (all) subjected to a dedicated CTEPH diagnostic work-up after the 1-year follow-up period ended.
The second study involved 127 hemodynamically stable PE patients without relevant comorbidity [48]. All patients had transthoracic echocardiography at the time of diagnosis and after six months of follow-up. Half the patient population had right ventricular dysfunction at baseline. The latter patients had higher pulmonary artery occlusion (56% vs. 40%) and more diagnostic delay (time between symptom onset and diagnosis), i.e. 54 hours versus 36 hours respectively. After 6 months, 25% of patients still had echocardiographic signs of right ventricular dysfunction. Unfortunately, the number of patients with normal baseline and abnormal follow-up echocardiography was not provided by the authors.

The third study included 144 normotensive patients with CT angiography-proven PE and a baseline echocardiogram, who were all subjected to a second echocardiograph after a 6-month period [49]. About 10% of patients were treated with thrombolytic drugs in addition to heparin and vitamin-K antagonists. At baseline, 38% of the patients were diagnosed with (estimated) right ventricular systolic pressure >40 mmHg (definition of pulmonary hypertension in that study), whereas only 7.4% of patients had a right ventricular systolic pressure above that threshold six months after the initial diagnosis. Noteworthy, right ventricular systolic pressures assessed during the follow-up visit were at the same level or even higher than the baseline measurements in 24% of patients. Baseline administration of thrombolytic agents seemed to protect against a worsening hemodynamic profile, although small numbers and confounding by indication make hard conclusions from this observation impossible.

Other studies have largely confirmed the above findings. For instance, in a study of 300 PE patients, none of those with a normal echocardiogram at baseline developed pulmonary hypertension during the in-hospital course, whereas 50% of patients with evidence of right ventricular dysfunction on admission failed to show complete echocardiographic normalization at discharge [50]. In a historical study, baseline pulmonary hypertension as assessed by right heart catheterization progressed further over time in patients with initial mean pulmonary artery pressure >30 mm Hg. None of the patients with normal or borderline pulmonary artery pressure developed severe pulmonary hypertension during follow-up [51].

From these studies we can conclude that right ventricular function and pulmonary artery pressure normalize in the majority of patients in the first months following PE diagnosis, although lack of improvement or even worsening of pulmonary artery and right ventricular hemodynamics can be demonstrated in a considerable number of cases. Further, a worse baseline hemodynamic profile seems associated with persistent pulmonary hypertension and the later occurrence of CTEPH.

4.2. CTEPH

CTEPH is considered to be the ultimate consequence of hemodynamic compromise and persistent pulmonary perfusion defects. CTEPH is defined by the following two criteria after 3 months of effective anticoagulation for acute PE: 1) invasively measured mean pulmonary arterial pressure >25 mmHg with a pulmonary capillary wedge pressure <15 mmHg; and 2) at least one (segmental) perfusion defect detected by lung scanning, multi-detector computed tomographic angiography or pulmonary angiography [8]. In addition to intraluminal thrombus organization resulting in fibrous stenosis or complete obliteration of the pulmonary arteries, CTEPH is characterized by intense remodeling of the small pulmonary arteries in areas that are affected, but also in those that are spared by thromboembolic occlusion. Remarkably, this pulmonary arteriopathy in CTEPH closely resembles the histopathology of patients with idiopathic PAH [52]. In the latter patients, in situ thrombosis is a common finding, caused by a dysfunctional endothelium that loses the anticoagulant properties which usually prevent intravascular clotting of blood material [53].

Patients with established CTEPH have marked impairment of their exercise capacity and frequently report dyspnea matching NYHA class III or IV heart failure symptoms [8,54–56]. Right heart failure and death result from CTEPH if patients are not surgically treated. The occurrence of established CTEPH after acute PE has been associated with several ‘PE-related’ parameters: diagnostic delay, high thrombus load, recurrent symptomatic PE, pulmonary hypertension or right ventricular compromise at baseline, failure to achieve complete thrombus resolution and failure to achieve normalization of pulmonary artery pressure or right ventricular function despite adequate anticoagulant treatment [8,25,26,46,49,51,57–59]. The exact incidence of CTEPH after PE is debated: most studies on the subject report incidence rates of 0.5% to 4% within the first 2 years after diagnosis, depending on patient selection as well as CTEPH diagnostic criteria [8,23,57,60–62].

The distal pulmonary vascular remodeling specific for CTEPH plays a major part in the rise of pulmonary artery pressure in addition to the effect of unresolved thrombi. This is supported by the lack of correlation between pulmonary artery pressure and the degree of angiographic pulmonary vascular bed obstruction, by the frequently observed progress of pulmonary hypertension in the absence of demonstrable recurrent embolism, and by the fact that pulmonary vascular resistance is significantly higher in CTEPH patients than in patients with acute PE and a similar obstruction index [63–65]. Whether the “final hit” for CTEPH development, i.e. the progress to pulmonary arteriopathy and in situ thrombosis in addition to unresolved acute PE, requires factors identical to those that cause impaired thrombus resolution, or whether the presence of a different pathophysiological trigger is necessary for this extensive small vessel remodeling, remains unknown. The rather unpredictable rate of distal pulmonary arteriopathy is poorly understood as well [8].

5. Functional outcomes

5.1. Functional limitation and severity

Few studies have focused on the long-term effects of diagnosed PE on the physical performance of patients without ‘formal’ CTEPH. Even so, all studies that we retrieved from our literature search appear to convey a consistent message: self-reported dyspnea and measured poor physical performance are present in more than half of the patients 6 months to 3 years after adequate treated acute PE [6,25,48,49,66,67]. In these studies, it was demonstrated that self-reported dyspnea, as translated into the NYHA classification, was closely correlated with physical performance by the 6-minute-walking test [25,48,49,66]. Notably, 20% to 75% of the patients reported that their health status was worse at 6-month follow-up than it had been at the time of PE diagnosis [6,49,62,66]. Higher baseline pulmonary artery pressures and right ventricular dysfunction predicted decreased exercise tolerance [25,48,49,59]. In contrast, a small study of only 23 patients could not link persistent pulmonary perfusion defects on ventilation/perfusion SPECT scan with dyspnea [30]. Cardiopulmonary comorbidity, advanced age, higher BMI and a smoking history were identified as independent predictors of exertional dyspnea over the long term following acute PE, more so than clot location or cause of PE [66]. In summary, we acknowledge that evidence supporting the hypothesis that non-resolution of PE is associated with impaired physical performance even in the absence of persistently raised pulmonary artery pressures is still rather weak.

Altered gas exchange might also play a role in compromised exercise performance after acute PE, although this has not been extensively studied. Acute PE causes increased ventilation/perfusion ratios in embolized lung areas and decreased ventilation/perfusion ratios in remaining non-embolized lung areas. Both physiologic dead space and physiologic shunting increase accordingly, resulting in hypoxemia and hypocapnia. In the acute phase of PE, the extent of the thrombus has been reported to closely correlate to severity of impairment of the alveolar to arterial gradient and the derived indexes [68,68,69]. Moreover, gas exchange parameter improvements were found to be related to pulmonary artery perfusion recovery [70]. Notably, a recently published study reported...
that gas exchange parameters during exercise were worse in patients suffering from CTEPH than in patients with persistent thrombi but normal pulmonary artery pressure after acute PE, and worse in the latter patients than in sedentary controls without a VTE history [71]. From this observation one could hypothesize that chronic thrombi do affect gas exchange, just as acute thrombi.

5.2. Quality of life

In recent years, several papers have consistently reported a decreased quality of life after acute PE compared to population controls [7,48,72–75]. In a population of 392 patients who completed the Short Form-36 (SF-36) 3.5 years after PE diagnosis, patients had substantially lower QoL than population norms on all subscales except for the health change subscale. Multivariate analysis indicated that recurrent PE, the time interval between the last thromboembolic episode and study inclusion, age, obesity, active malignancy, and cardiopulmonary comorbid conditions were significant determinants of poor QoL [7]. A second study in 109 consecutive patients in an outpatient clinic two years after PE diagnosis confirmed the worse scores measured by the SF-36 in PE patients as compared to the general Dutch population [72]. A hypothesis-generating finding is the lower quality of life in patients after acute PE than after DVT, especially on the subscales physical quality of life and mental fatigue [73,76]. Interestingly, in a study that randomized patients with submassive PE in a double-blinded fashion to receive fibrinolytic treatment or placebo, the primary benefit of fibrinolytic treatment was a significantly improved self-perception of their quality of physical health, which was correlated with a better exercise capacity [75].

Patients with established CTEPH experience severely impaired health-related quality of life that may improve after adequate treatment [56,77–79]. Especially exercise capacity seems to be an important determinant of quality of life in these patients [54–56].

6. The post-PE syndrome

Considering all the above, it seems that CTEPH is the extreme (and perhaps ultimate) manifestation of a much more common phenomenon of abnormalities in pulmonary artery flow, pulmonary ventilation and/or cardiac function after acute PE, which—in analogy to PTS—might be referred to as the post-PE syndrome, although its underlying pathophysiology is not as clearly described or understood as that of PTS. In Fig. 1, the hypothesized pathophysiological mechanism of the post-PE syndrome is shown. To validate this hypothesis, future studies should specifically focus on 1) the association between the extent of residual thrombosis after PE and the patients’ cardiac functional reserve as well as long-term functional status, 2) tools for quantification of the severity of the post-PE syndrome, 3) the molecular and cellular processes which determine thrombus resolution and the conversion of unresolved thrombi to CTEPH and 4) the possible benefits of thrombolysis on long-term functional outcomes after PE and on the prevention of CTEPH and post-PE syndrome development.

The clinical relevance of acknowledging the existence of the post-PE syndrome, if this entity is confirmed, is the possibility to explain and target the functional complaints after acute PE so often heard in clinical practice. In addition, it may provide a concept that aids in further understanding of the pathophysiology of developing CTEPH. At present, no clear diagnostic criteria for the post-PE syndrome are available; moreover, poor quality of life, functional impairment and cardiopulmonary dysfunction in patients with a history of PE may be the result of comorbidity such as malignancies or non-thrombotic cardiopulmonary disease. We propose to consider the post-PE syndrome in the presence of persistent or worsening parameters of cardiac or pulmonary function (on echocardiography or cardiopulmonary exercise testing) after an index PE event, in combination with deterioration of the clinical symptoms, functional status or quality of life of the patient, in the absence of an obvious alternative explanation (Fig. 2). These worsening parameters

Fig. 1. Proposed pathophysiological cascade of the post-PE syndrome; whether the “final hit” for CTEPH development constitutes the same factors that cause hampered thrombus resolution or persistent elevated PAP and/or RV dysfunction after acute PE, or is a different pathophysiological trigger remains unknown. PE = pulmonary embolism, PAP = pulmonary artery pressure, RV = right ventricular, QoL = quality of life, CTEPH = chronic thromboembolic pulmonary hypertension.
of cardiac or pulmonary function should be determined objectively by echocardiography and/or cardiopulmonary exercise testing, but do not have to meet the criteria for established CTEPH. By applying these criteria, our focus will shift to more subtle changes or abnormalities that may be crucial in the pathophysiology of the post-PE syndrome. Notably, although our focus is on patients who have suffered symptomatic PE and their follow-up and course, there may still be cases of post-PE syndrome and CTEPH that develop without a history of symptomatic PE. A large German, prospective, multicenter, observational study which will systematically follow all-comers with PE over a 2-year period, as well as the prevalence of predefined criteria for worsening parameters of cardiac and pulmonary function. With this study, we will hopefully cast more light into the post-PE syndrome. The results are expected in 2018.

Conflicts of interest

FAK, TvdH and PdE have nothing to disclose. MVH reports receiving grant support from Boehringer Ingelheim and GlaxoSmithKline. SK declares that he has received lecture fees and advisory board honoraria from Astra Zeneca, Bayer Health Care, Boehringer Ingelheim, Pfizer-Bristol-Myers Squibb and Daichi Sankyo. ML reports receiving lecture fees and advisory board honoraria from Bristol-Myers Squibb, Bayer Vital GmbH, Bristol-Myers Squibb and Bayer Pharma AG.

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