The aftermath of acute pulmonary embolism: approach to persistent functional limitations

Boon, G.J.A.M.

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Introduction

Pulmonary embolism (PE) encompasses more than just an acute health risk. Persistent dyspnea and/or functional limitations occur in up to half of PE patients despite adequate anticoagulant treatment, and negatively affect patients' quality of life.[1] Underlying causes of these long-term sequelae are captured by the 'post-PE syndrome', of which chronic thromboembolic pulmonary hypertension (CTEPH) is the most severe presentation.[2,3] In this rare condition, driven by endothelial dysfunction, persistent thrombi evolve into fibrotic masses that obstruct proximal pulmonary arteries, leading to flow redistribution and small-vessel disease.[4] Further disease progression results in a gradual increase of pulmonary vascular resistance, abnormal pulmonary artery pressures (PAP) and - ultimately –irreversible right ventricular dysfunction.[5,6] Traditionally, a CTEPH diagnosis can be established if the following strict diagnostic criteria are met after at least three months of adequate therapeutic anticoagulation: 1) ≥ 1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scintigraphy with specific vascular lesions suggestive of CTEPH on other imaging tests; 2) mean PAP of ≥ 25 mm Hg at rest measured by invasive right heart catheterization; and 3) pulmonary artery wedge pressure ≤ 15 mm Hg.[7] Whether the recently adjusted definition of pulmonary hypertension – a threshold for mean PAP of 21 instead of 25 mm Hg – should also be applied to CTEPH is a matter of debate.[8-10]

Other entities of the post-PE syndrome include chronic thromboembolic pulmonary disease *without* pulmonary hypertension at rest (CTEPD), chronic right ventricular impairment and functional impairment.[11] In recent years, CTEPD is gaining ground and has been suggested to represent an early stage of CTEPH, although the exact pathophysiological mechanisms and prognostic implications are still to be further elucidated.[12,13] Of note, functional impairment after PE is explained by other etiologies in a large proportion of patients, including deconditioning, pain or anxiety, or alternatively (pre-existing) comorbidities such as chronic obstructive pulmonary disease, diastolic dysfunction and/or obesity.

In the first chapters of this thesis, an overview of available literature on important aspects of the course after an acute PE is provided. **Chapter 2** is an illustrated review in which infographics are used to visualize the epidemiology of the post-PE syndrome and its impact on patients' daily lives, as well as on the clinical presentation and therapeutic options of CTEPH. **Chapter 3** is an extensive summary of available data on physiological determinants that might help understand why adequately treated PE patients often do not completely recover. All currently published studies showcasing results of transthoracic echocardiography and functional outcome measures after PE, such as cardiopulmonary exercise testing, pulmonary function testing and/or 6-minute walk distance, were captured and put in perspective.

CTEPH may be treated by pulmonary endarterectomy, balloon pulmonary angioplasty and/or pulmonary hypertension drugs. The sooner CTEPH treatment is

initiated, the better the prognosis of patients usually is. However, diagnosing CTEPH remains a major challenge given its non-specific presentation and since characteristics of CTEPH are often underrecognized. Currently, the time between symptom onset and diagnosis exceeds 1 year.[14] Since the longest delays have been reported to be associated with higher PAP and higher risk of all-cause mortality, early diagnosis is crucial.[15] Considerations regarding screening for CTEPH are thoroughly discussed in **chapter 4**, on the basis of contemporary principles of early disease detection.

Obtaining a clear insight into the degree of functional impairment in patients' daily activities is useful for both clinical and research purposes. Recently, an objective ordinal outcome measure has been developed to quantify patient-relevant functional outcomes, the so-called Post-VTE Functional Status Scale (PVFS Scale). The refinement of this scale guided by the input of VTE experts and patients is addressed in **chapter 5**.

Elaborating on a reduced diagnostic delay of CTEPH, its implications on health economic outcomes should be taken into account. Therefore, a cost-effectiveness model concerning early CTEPH detection has been developed, which is described in **chapter 6**. In order to actually establish CTEPH at an earlier stage, a simple screening strategy was evaluated in the InShape II study, of which details are provided in **chapter 7.** This international multicenter management study was performed to prospectively validate the InShape II algorithm for timely exclusion of CTEPH in patients recently diagnosed with acute PE, with optimal use of healthcare resources. This is in line with the 2019 ESC/ERS Guidelines on PE suggesting an active screening algorithm for the first time.[16]

Some studies have demonstrated that a high suspicion of CTEPH should also be triggered by specific findings on echocardiography and computed tomography pulmonary angiography (CTPA). For instance, in a recent case-control study from our research group, expert chest radiologist have identified radiological characteristics predictive of a future CTEPH diagnosis on CTPA scans performed for suspected PE: the InShape III study.[17] To further study the potential diagnostic value of closer reading of such index CTPA images, an identical assessment has been applied by CTEPH-non-expert radiologists in **chapter 8**. Besides, in **chapter 9**, dedicated CTPA reading was performed by expert chest radiologists in a larger unselected cohort as a predefined endpoint within the InShape II study.

In the last chapters of this thesis, the role of persistent thromboembolic obstructions has been studied, aiming for a better understanding of the association between PE and the post-PE syndrome. Firstly, the influence of anticoagulant treatment on the development of CTEPH is uncertain. Radiological abnormalities on two consecutive CTPAs within both PE and CTEPH patients have been assessed in **chapter 10** to gain insight into the evolution of acute and chronic vascular lesions after 6 months of anticoagulants. Also, the influence of the quality of anticoagulant treatment in PE patients treated with vitamin-K antagonist was assessed in **chapter 11** among those

with versus without an ultimate diagnosis of CTEPH. **Chapter 12** describes a cohort study among PE patients with persistent functional impairment whom are all subjected to extensive diagnostic work-up. Moreover, results of a PE-specific rehabilitation program are evaluated in patients without CTEPH or other treatable conditions.

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