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

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General discussion and summary

Pulmonary embolism (PE) is a serious and potentially life-threatening disease in the acute phase, and may also have a major impact on a patient's daily life in the long run. The overall aim of this thesis was evaluating important aspects of the post-PE syndrome with an emphasis on early diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) and the associated consequence for patients' prognosis. **Chapter 1** provides a general introduction to the post-PE syndrome and CTEPH in particular, and gives an overview of the presented studies.

Chapter 2 visually summarizes all essential aspects of optimal care following an acute PE, including its natural course with possibly unresolved thrombi and the impact of impaired recovery. Current evidence suggests that there is little awareness for persistent dyspnea and impaired functional status after acute PE. This has been illustrated by large international practice variation with regard to follow-up of PE patients with insufficient use of healthcare resources, and a considerable diagnostic delay of CTEPH of up to 14 months that contributes to loss of quality-adjusted life years and excess mortality. Since reducing this delay is crucial in improving patient outcomes, we argue that the following issues need to be addressed: 1) increasing physicians' and patients' awareness regarding long-term consequences of acute PE; 2) validating and implementing follow-up algorithms aimed at early CTEPH diagnosis; and 3) formulating clear guideline recommendations for optimal follow-up after acute PE. Physiological determinants of exercise intolerance months to years after an acute PE have been evaluated in many studies, which have been reviewed in **chapter 3.** Echocardiographic signs of right ventricular dysfunction or pulmonary hypertension (PH) are common (~25-50% of PE survivors), and have been associated with a shorter '6-minute walk distance' many years after the acute PE diagnosis. In PE patients with persistent dyspnea, studies focusing on cardiopulmonary responses to exercise proved to be able to detect reduced exercise capacity, impaired stroke volume, increased dead-space ventilation and poor ventilatory efficiency. This reinforces the hypothesis that incomplete thrombus resolution may result in poor adaptation of the vascular bed to the increase in stroke volume during exercise, even in the absence of PH. The exercise tests, however, were not abnormal in all these patients. Importantly, these studies were all performed using heterogenous diagnostic testing, largely caused by a lack of uniform definitions. Hence, more thorough research is needed to determine the exact pathophysiological mechanism of the post-PE syndrome.

In **chapter 4**, we have elaborated on the usefulness of screening for CTEPH based on the recently updated principles of population-based screening by Wilson and Jungner published in 1968. Considering increased operational and implementation challenges over the last decades, a refined and more comprehensive list of screening principles was developed. Guided by this modern perspective, we conclude that CTEPH is a suitable condition for implementing a screening program because the diagnostic

criteria and target population are well-defined, the current diagnostic delay has a major impact on patients' quality of life, and available treatment options have been shown to considerably improve their prognosis.

Until recently, there were no simple tools available for monitoring the course of symptoms after a venous thromboembolism (VTE) and its impact on patients' daily activities. **Chapter 5** describes optimization of the recently proposed Post-VTE Functional Status (PVFS) Scale through a Delphi analysis and patient focus groups. This scale does not only quantify the full spectrum of physical and psychological long-term complications of VTE and its treatment, it also focuses on both limitations in usual duties/activities and changes in lifestyle. It is a patient-reported outcome measure that allows ranking patients into meaningful categories, beyond binary outcomes such as mortality. The PVFS Scale may be used by health care providers to identify patients with suboptimal recovery after VTE in clinical practice and help explaining the implications of persistent symptoms to both physicians and relatives. Moreover, the scale may be especially useful in future clinical trials since it captures the impact of anticoagulant treatment and potential complications as well as the impact of recurrent PE and the post-PE syndrome. Based on input received by a large panel of international VTE specialists and by VTE patients, we have refined the scale and its assessment methods. The subsequent achieved broad consensus resulted in a good-to-excellent interrater agreement, underlining its validity in research settings.

While pursuing a reduced diagnostic delay of CTEPH, health-economic implications need to be taken into account. Hence, in **chapter 6**, we constructed a Markov model to estimate lifelong outcomes depending on the degree of diagnostic delay, i.e. quality of life, life expectancy and healthcare costs. Through modelling based on the Dutch healthcare setting, we found a substantial health gain when CTEPH is diagnosed earlier. Associated additional costs comprise a maximum amount of €31,000 per quality-adjusted life year, which compares favorably to the willingness-to-pay threshold of €50,000 according to Dutch health-economic standards. These beneficial lifelong patient-relevant outcomes against acceptable additional costs endorse implementing strategies aimed at diagnosing CTEPH earlier. Our model is the first major effort for evaluating such diagnostic approaches and can be used in future cost-effectiveness studies that will ultimately guide policy makers in economic decisions.

A variety of potential tests or examinations have been explored in order to detect CTEPH earlier. In this setting, a stand-alone routine screening test seems inaccurate because of several reasons, including suboptimal diagnostic accuracy, lack of cost-effectiveness and radiation exposure. Algorithms of sequential diagnostic tests have been proposed and are promising, but prospective management studies are currently lacking, hindering implementation in clinical practice. In **chapter 7**, we performed a prospective, international, multicentre management study evaluating the safety of a

simple strategy for excluding CTEPH early after a diagnosis of acute PE. This InShape II algorithm is based on consecutive tests to determine whether echocardiographic evaluation of PH is indicated, with subsequent confirmatory testing if appropriate. It starts with pre-test probability assessment based on the 'CTEPH prediction score', combined with evaluation of the presence of symptoms suggestive of CTEPH and the application of the 'CTEPH rule-out criteria'. These criteria, determined by ECG reading and an NT-proBNP assay, are applied if patients either have a prediction score of more than 6 points or in case of matching symptoms. Only if these results cannot rule out the presence of right ventricular pressure overload, patients are referred for echocardiography. In our study, a total of 424 consecutive patients were managed according to this algorithm three months after a diagnosis of acute PE. We found that this non-invasive algorithm accurately ruled out CTEPH early after acute PE without the need for echocardiography in 81% of patients. The overall CTEPH incidence was 3.1% (13/424), of whom 10 patients were diagnosed within 4 months after the PE presentation. This was the first study validating a dedicated CTEPH screening tool after PE. The InShape II algorithm provides optimal use of healthcare resources and leads to timely detection of CTEPH, which is associated with improved prognosis. Moreover, it is applicable to a wide range of healthcare settings including primary care. Therefore, it may serve as a relevant alternative to the follow-up program proposed by the 2019 Guidelines on PE from the European Society of Cardiology and European Respiratory Society. Importantly, even if our algorithm indicates absence of CTEPH, in some cases, echocardiography may still be necessary for evaluation of other heart diseases. While exploring ways to further accelerate diagnosing CTEPH, previous studies have shown that expert chest radiologists often retrospectively reveal radiological signs of CTEPH or chronic thrombi on computed tomography pulmonary angiography (CTPA) performed at the time of suspected acute PE. To study the potential value of closer CTPA reading, such index CTPA images have been assessed by two CTEPH-non-expert readers in a case-control study that is described in **chapter 8**. After simple instruction, the readers correctly distinguished the majority of CTEPH patients from those with acute PE. Interestingly, in the original CTPA reports, most concomitant signs suggestive of CTEPH had not been reported spontaneously. Our findings emphasize that radiological characteristics of CTEPH are often underrecognized. In **chapter 9**, these results were confirmed in an unselected practice-based PE cohort as a predefined endpoint within the aforementioned InShape II study. Based on index scans, overall judgment by expert chest radiologists was highly specific for a future CTEPH diagnosis, as was a previously proposed set of 6 objective radiological signs that are most predictive of a future CTEPH diagnosis. This further underlines that vigilance on prevalent signs of chronic thrombi and PH could play an important role in identifying patients with chronic thromboembolic obstructions clinically presenting as acute PE, even outside of CTEPH

expert centres. Of note, since refined CTPA assessment had not identified each CTEPH case, it might not be a sufficient to use as stand-alone assessment.

Persistent thromboembolic obstructions are observed in up to 20-30% of patients after a first episode of acute PE, whereas it remains unclear how these lesions evolve after initiation of anticoagulant treatment. To gain a better understanding of its clinical relevance, thrombus morphology on CTPA images was analysed in a case-cohort study in **chapter 10**. To do so, two CTPAs at the moment of acute PE diagnosis and after at least 3 months of anticoagulant treatment were compared in both PE and CTEPH patients: all lesions in central and segmental pulmonary arteries were classified by expert chest radiologists. Webs and tapered pulmonary arteries at index CTPA persisted on repeat CTPA, and were also strongly associated with an ultimate CTEPH diagnosis. These unique data demonstrate that this specific morphology presumed to be suggestive of CTEPH actually does denote a chronic disease state. Therefore, such types of unresolved thrombi on CTPAs performed for suspected acute PE should prompt a high suspicion of CTEPH, especially in case of persistent dyspnoea. The question whether poor-quality initial anticoagulation may contribute to a higher CTEPH risk was assessed in **chapter 11**. In this case-control study using rare data on vitamin-K antagonists therapies, we demonstrated that subtherapeutic anticoagulant treatment was not more prevalent among PE patients diagnosed with CTEPH than in those who did not develop CTEPH over the course of 2 years. Both studies fuel the concept a chronic disease state at the time of acute PE diagnosis indicating the possibility of concurrent (pre-existing) CTEPH that had not been recognized yet. This has been argued previously, largely based on the presence of long-lasting symptoms at the time of CTEPH diagnosis and chronic thrombi on index CTPA scans.

Patients suffering from functional impairment after acute PE whom are not suitable to undergo surgical or interventional treatment might benefit from pulmonary rehabilitation, especially those without any treatable pulmonary, cardiovascular, and/or mental health conditions. **Chapter 12** describes a cohort study evaluating cardiopulmonary responses to exercise aimed at a better understanding of (impaired) physical recovery after PE. Abnormal cardiopulmonary responses to exercise appeared not to be limited to those with chronic thrombi, indicating a multifactorial etiology underlying post-PE dyspnea rather than just pulmonary vascular disease as single explanation. Additionally, we studied changes in physical condition and patient-reported outcome measures after completing a 12-week outpatient pulmonary rehabilitation program in patients not otherwise treated. In line with previous studies, our data support offering a PE-specific pulmonary rehabilitation program to patients with the post-PE syndrome.

FUTURE PERSPECTIVE

Current evidence shows that a targeted follow-up program after acute PE results in earlier detection of CTEPH. Since the InShape II study was the first study to validate a follow-up strategy, the optimal strategy still needs to be determined. In 2019, the European Society of Cardiology suggested an alternative approach consisting of performing echocardiography in each patients with risk factors, predisposing conditions and/or symptoms of CTEPH. Actively seeking for radiological clues of CTEPH on the index CTPA results in high case finding and, thus, will likely result in improved diagnostic accuracy of the InShape II algorithm or alternative strategies. Therefore, future prospective studies should evaluate the additional value of enriching pre-test probability testing of CTEPH with comprehensive assessment of CTPA images. The optimal combination of parameters needs to be explored, ideally in a randomized fashion. Interestingly, artificial intelligence-based software for quantifying vascular morphology and perfusion are being developed and validated in ongoing studies. Integrating the set of radiological characteristics that are most predictive of a future CTEPH diagnosis in such software will further improve the diagnostic accuracy of CTPA reading. Subsequently, it would be interesting to thoroughly compare the cost-effectiveness of several methods, for which the Markov model presented in chapter 7 can be used. Altogether, such studies are required to provide sufficient evidence to allow for an internationally uniform diagnostic approach in future guidelines, which is the ultimate road towards decreasing the current diagnostic delay of CTEPH.

Randomized trials are needed in determining the exact benefit of management interventions on long-term outcomes after PE. Therefore, functional status as determined by the PVFS Scale would be a highly relevant outcome measure to integrate in future clinical trials aimed at determining and standardizing functional outcomes over time after a VTE. The International Consortium for Health Outcomes Measurement (ICHOM) is currently discussing about a "Standard Set" of standardized outcomes and measurement tools for CTEPH for which the PVFS Scale is being considered. This scale may help to determine optimal treatment strategies in various settings, such as the optimal duration of anticoagulant treatment in unprovoked VTE by weighing functional impairment in patients' daily lives of recurrence risks versus bleeding complications. In several ongoing trials, the PVFS Scale has already been implemented. For example, in the "PEITHO-3 study" (NCT04430569), patients with intermediate-high risk acute PE are randomized between low-dose thrombolytic therapy and placebo (in addition to low molecular weight heparin at therapeutic doses). Another example is the "HI-PEITHO study" (NCT04790370) comprising a similar patient population, aimed at comparing local (ultrasound-facilitated and catheter-directed) delivery of low-dose thrombolytic therapy and anticoagulation with anticoagulation alone. The "SAFE-SSPE study" (NCT04263038)

is a third example where the use of this scale addresses an ongoing debate. In low-risk patients with isolated subsegmental PE, the efficacy and safety of clinical surveillance without anticoagulation is compared to anticoagulation treatment. Consequently, such trials will also result in more data on the value of the PVFS Scale when correlating its scale grades with health-related quality of life, pain, dyspnea, etcetera.

Lastly, a PE-specific pulmonary rehabilitation program is promising and safe based on our study and previous literature. Still, a large randomized controlled trial is required among PE patients with persistent dyspnea and/or functional impairment. A first and major step in that direction is the "PE@home" study. This randomized trial will evaluate the impact of a home-based exercise program early in the course of PE on the incidence and severity of the post-PE syndrome. This will provide further evidence on optimal follow-up of patients with acute PE.