Pulmonary embolism : diagnostic management and prognosis

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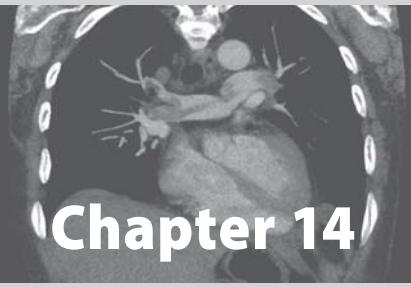

Chapter 14

General discussion and summary

The main objectives of this thesis are to validate and simplify current diagnostic strategies for clinically suspected acute pulmonary embolism (PE) and to predict the short and long term prognosis of patients diagnosed with and treated for acute PE. Therefore, several studies were performed focusing on the safety of different diagnostic algorithms and several aspects of the patients' prognosis. **Chapter 1** provides a general introduction to the pathophysiology of acute PE and its associated clinical course. Furthermore, it evaluates current clinical insights regarding diagnostic and treatment strategies and addresses scientific gaps yet to be bridged.

PART I: DIAGNOSTIC MANAGAMENT OF ACUTE PE

Many clinical decision rules to estimate the pretest probability of the individual patient for having PE have been proposed. The most widely used one, the Wells rule, includes the subjective judgment of the clinician and as a result, this rule has average reproducibility. **Chapter 2** describes a study on the clinical validity and performance of the recently developed and more objective revised Geneva score in a patient cohort in whom the Wells rule was initially utilized for clinical practice. In 300 consecutive patients with suspected PE, the predictive accuracy of both scores was compared by the area under the receiver operating characteristic curves (AUC of ROC). These AUCs were not different for both rules: 0.72 (95% confidence interval [CI] 0.65–0.80) and 0.67 (95% CI 0.59–0.76) respectively. Furthermore, after three months of follow-up, no patient classified into the low or intermediate clinical probability category by the revised Geneva score and a normal D-dimer result was subsequently diagnosed with acute venous thromboembolism (VTE). In **chapter 3**, we simplified the revised Geneva score by attributing 1 point to each item of the original clinical decision rule, as an alternative for the original different weights of the individual items. These different weights might be more difficult to remember and could lead to miscalculations in an acute setting. This simplification of the revised Geneva rule did not result in decreased AUC of the ROC analyses in 1049 patients with suspected PE: 0.75 (95% CI 0.71-0.78) for the original and 0.74 (95% CI 0.70-0.77) for the simplified rule. Further analysis indicated that during a three months follow-up period, no patient with a combination of either a low or intermediate clinical probability, or a "PE unlikely" assessment with the simplified score and a normal D-dimer test result was diagnosed with symptomatic VTE. These study results suggest that the performances of the simplified and original revised Geneva score are equivalent to that of the Wells rule. Furthermore, it was safe to rule out acute PE by a combination of a "low", "intermediate" or "unlikely" probability assessment by the simplified or original revised Geneva score, in combination with a normal highly sensitive D-dimer test result.

A negative computed tomography pulmonary angiography (CTPA) result alone is considered to be a controversial criterion for the safe exclusion of PE in a high risk population, since the negative predictive value (NPV) of this imaging modality might be reduced in case of high pretest

probability for having PE. **Chapter 4** is a meta-analysis to determine the safety of ruling out PE by a normal CTPA in a specific group of patients with a strict indication for CTPA, i.e. likely or high clinical probability for PE, an elevated D-dimer concentration, or both. The pooled NPV after three months was 98.8% (95% CI 98.2-99.2) based on a normal CTPA as a sole test and 98.9% (95% CI 98.0-99.4) based on normal CTPA followed by negative compression ultrasonography of the legs. In addition, risk of fatal PE did not differ between both diagnostic strategies (0.6% vs. 0.5%). Since these test characteristics compare favorably with those of normal conventional pulmonary angiography, we conclude that a normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out this disease.

PART II: SHORT TERM CLINICAL OUTCOME AFTER PE

The ability of accurately predicting adverse clinical outcome in hemodynamic stable patients with acute PE is of great importance for the therapeutic management of these patients. In **chapter 5**, the potential role of brain-type natriuretic peptides (BNP) in the differentiation of patients suffering from acute PE at risk for adverse clinical outcome is evaluated. A meta-analysis of all previous studies on this subject revealed that patients with elevated levels of BNP or NT-pro-BNP were at higher risk of complicated in-hospital course (odds ratio [OR] 6.8, 95% CI 4.4-10) and 30-day mortality (OR 7.6, 95% CI 3.4-17).

In a prospective study, the clinical utility of NT-pro-BNP for predicting adverse outcome after PE was further studied by comparing that to the utility of other biomarkers and right ventricular enlargement assessed on static CTPA images (**chapter 6**). We included 113 consecutive normotensive patients with CT pulmonary angiography (CTPA) proven PE. All predictors under study were associated with adverse outcome in patients with PE, with ORs of 3.7 (95% CI 0.74-19) for right/left ventricular ratio >1 on axial CTPA view, 9.0 (95% CI 1.1-79) for right/left ventricular ratio >1 on 4-chamber CTPA view, 3.5 (95% CI 0.86-15) for D-dimer >3000 pg/mL FEU, 6.3 (95% CI 1.3-31) for Troponin-T >0.09 ng/mL and 31 (95% CI 3.6-257) for NT-pro-BNP >600 pg/mL. The NPV of NT-pro-BNP was highest (99%). Importantly, 72% of patients had a NT-pro-BNP ≤600 pg/mL; 4-chamber RV/LV-ratio <1 had equally excellent NPV (98%), but less patients were categorized as having low risk for complications (43%). We concluded that NT-pro-BNP had the highest discriminative power and clinical utility as predictor of adverse events after PE in our study population. This conclusion could point towards using NT-pro-BNP as stratification tool for identifying patients for outpatient treatment.

The positive predictive value (PPV) of NT-pro-BNP or the other predictors was not sufficient to justify more invasive treatment measures in normotensive patients with PE. We hypothesized that CT-measured right ventricular ejection fraction would be a more specific predictor for adverse outcome, and therefore involve a higher PPV. In the identical patients who are described in chapter 6, the right ventricular ejection fraction was assessed by electrocardiography

(ECG)-synchronized multi-detector row CTPA (**chapter 7**). RV dysfunction was defined as RV ejection fraction below 47%, which was present in 45% of the patients. In addition, the AUC of its ROC analysis proved to be higher than simple, right/left ventricular ratio assessment. RV dysfunction was identified in 90% of the patients with adverse events (OR 36, 95% CI 2.2-590). In spite of this OR and high NPV (98%), this technique was not able to identify patients with such high risk for adverse events, that patients with RV ejection fraction below 47% are likely to benefit from more invasive treatment measures (positive predictive value 18%). Furthermore, the NPV of the ECG-synchronized ventricular measurements was comparable to those of the simple CTPA measurements. Importantly, ECG-synchronized cardiac CT involves increased radiation and contrast dose which should be considered before this technique is considered for integration in routine clinical care.

PART III: LONG TERM CLINICAL COURSE AFTER PE

In **chapter 8**, we discuss the results of a cohort screening study for chronic thromboembolic pulmonary hypertension (CTEPH) in an unselected series of 866 consecutive patients diagnosed with acute PE. All patients who were not previously diagnosed with pulmonary hypertension (PH) and had survived until study inclusion, were invited for transthoracic echocardiography. Patients with echocardiographic suspicion of PH underwent complete work-up for CTEPH, including ventilation-perfusion lung scan and right heart catheterization. For the patients who had died, the cause of death was extracted from autopsy reports or verified with the general practitioner. The presence of CTEPH in patients who were unable to visit our hospital for echocardiography was assumed not present in case of absence of unexplained clinical symptoms of this disease. After an average follow-up of 34 months, PH was diagnosed in 19 patients by routine clinical care and in 10 by our screening program; 4 patients had CTEPH, who were all diagnosed by routine clinical care. The cumulative incidence of CTEPH after all cause acute PE was 0.57% (95% CI 0.02-1.2%) and after unprovoked PE 1.5% (95% CI 0.08-3.1%). Because of this low incidence and the very low yield of the echocardiography based screening program, wide scale implementation of prolonged follow-up including echocardiography of all patients with PE to detect CTEPH seems not warranted.

Dyspnea is one of the key clinical symptoms of CTEPH. Although we found CTEPH to be a rare complication after acute PE, persistent dyspnea is reported by one third of patients at 3.6 ±1.7 years after the PE. This subjectively reported dyspnea is significantly correlated to decreased exercise performance. Therefore, the possibility of CTEPH is frequently considered. In **chapter 9**, we study several non-invasive clinical tests for ruling out CTEPH in symptomatic patients with a history of PE. ECG criteria of right ventricular overload were more frequent in patients with CTEPH (77%) than in symptomatic patients without pulmonary hypertension (11%; $p<0.01$).

Also, clotting factor FVIII activity and levels of NT-pro-BNP, growth differentiation factor-15, C-reactive protein and urate were higher in the patients with CTEPH, in contrast to D-dimer levels. A diagnostic model including ECG criteria and NT-pro-BNP levels had a sensitivity of 94% (95% CI 86-98), a specificity of 65% (95% CI 56-72) and an AUC of the ROC analysis of 0.80 (0.74-0.85) for the presence of CTEPH in dyspnoeic patients. Adding other or additional biomarkers to ECG and NT-pro-BNP assessment resulted in a decrease of predictive value of the model. Even with unrealistically high disease prevalences up to 10%, the negative predictive value of our final model proved very high (>99%). We concluded that additional diagnostic tests to rule out CTEPH in dyspnoeic patients after acute PE are not necessary in absence of ECG criteria of right ventricular overload and a normal NT-pro-BNP level.

Chapter 10 extends the findings presented in chapters 8 and 9 by evaluating determinants and alternative causes of chronic dyspnea after acute PE. After multivariate analysis, cardiopulmonary comorbidity (OR 12; 95% CI 6.5-20), advanced age (OR 1.02 per year; 95% CI 1.01-1.03), higher BMI (OR 1.06 per kg/m^2; 95% CI 1.01-1.1) and a smoking history (OR 1.6; 95% CI 1.02-2.6) were identified as independent predictors of chronic dyspnea after PE. An alternative diagnosis reasonably explaining the dyspnea could be established in all patients. The clinical consequence of our study is that chronic dyspnea in the clinical course of acute PE is mainly caused by pre-existing comorbid conditions and alarming direct complications of PE such as CTEPH are very rare.

In **chapter 11**, the association between venous thromboembolism and arterial cardiovascular disease is assessed by comparing the cumulative incidence of serious cardiovascular events (defined as clinically adjudicated acute myocardial infarction, stroke or transient ischemic attack, claudication, unstable angina, carotid endarterectomy, coronary artery bypass graft, peripheral arterial bypass or angioplasty) in patients with unprovoked PE to that of patients with provoked PE and a control population of patients in whom PE was suspected but ruled out. After a median follow-up period of 4.2 years, the adjusted hazard ratio (HR) for arterial cardiovascular events was not different between patients with all cause PE and control patients (1.4, 95% CI 0.83-2.3), but increased for patients with unprovoked PE versus patients with provoked PE as well as control patients without PE (HR 2.2; 95% CI 1.1-4.5 and 2.6; 95% CI 1.4-4.9 respectively). This observation underlines the hypothesis of a shared but yet unidentified mechanism causing events in both venous and arterial systems.

In addition to arterial cardiovascular events and CTEPH, further adverse clinical events which are associated with acute PE and have a major impact on the long term prognosis of patients with PE include mortality, newly diagnosed malignancies and recurrent VTE. In **chapter 12**, we explore the risk of suffering from any of these conditions in the first years after the diagnosis of PE. Patients with unprovoked PE had lower overall risks for mortality than patients with provoked PE (adjusted HR 0.59, 95% CI 0.43-0.82), but higher risk for non-malignancy related

mortality (adjusted HR 1.8, 95% CI 1.3-2.5), recurrent VTE (adjusted HR 2.1, 95% CI 1.3-3.1), cancer (adjusted HR 4.4, 95% CI 2.0-10), cardiovascular events (adjusted HR 2.6, 95% CI 1.5-3.8) and CTEPH (cumulative incidence 1.5% vs 0%). The risk for the combined endpoint did not differ between both groups (adjusted HR 0.98, 95% CI 0.82-1.1). A control cohort consisting of patients without PE had similar risks for malignancy and cardiovascular events compared to patients with provoked PE, but significantly lower risks for the remaining outcomes and the combined outcome in patients with provoked as well as with unprovoked PE. Importantly, the fraction of both patients with provoked as well as with unprovoked PE without events after 1 year was only 70%, and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients without PE.

In **chapter 13**, we validate a disease specific quality of life instrument for patients after acute PE. The recently developed Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire and the Short-Form 36 were distributed twice among 90 PE survivors, with a mean period of 38 months after diagnosis. Internal consistency of the questionnaire was adequate with a Cronbach's α statistic ranging from 0.62 to 0.94. The test-retest reliability was good as well (intra-class correlation coefficients 0.78-0.94). Furthermore, good correlations between the PEmb-QoL questionnaire and the SF-36 questionnaire supported convergent validity between the 2 instruments. Multivariate analysis identified age, obesity, cardiopulmonary comorbidity, centrally located PE and a family history of venous thromboembolism to be independent determinants for disease-specific QoL. The PEmb-QoL questionnaire was shown to be a reliable instrument to specifically assess QoL following PE, which is helpful in the identification of patients with decreased QoL after surviving PE.

FUTURE PERSPECTIVES

Although the diagnostic management of suspected PE remains a challenge in clinical practice, physicians can fall back on a simple, non-invasive and well validated diagnostic algorithm consisting of a clinical decision rule, D-dimer tests and CTPA. This algorithm has been shown to be widely available and safe. Nonetheless, further studies are necessary to validate this -or an alternative- algorithm for recurrent PE, determine which of many clinical decision rules has the highest clinical efficacy and to address the increasing concern of radiation exposure by CTPA, especially in women of child bearing potential.

Risk stratification of normotensive patients with established PE can be based on high levels of biomarkers or measurements of right ventricular volume or function. Current evidence suggests that patients with a very low risk on adverse events can be treated on an outpatient basis, thereby saving costs and increasing patient satisfaction. However, the safety of home treatment, preferably based on a reproducible risk stratification scoring system, is yet to be

determined. On the other hand, with respect to identifying patients with very high risk who might benefit from thrombolytic therapy, evidence is scarce and inconsistent. Up till now, no stratification tool that can be easily integrated in routine clinical care and identifies a small patient group with particular high risk for complications, has been validated. Such a tool should be sought for in future trials.

Finally, although we have demonstrated that the risk of CTEPH after acute PE is very low, other very serious conditions occur frequent in the clinical course of acute PE. Especially those conditions that might be prevented, i.e. arterial cardiovascular events and recurrent PE, deserve a great deal of attention in the coming years. More accurate individualized assessment of the risk for recurrent PE followed by prolonged anticoagulant treatment for those patients with high recurrence risk, and individualized or population based proper preventive treatment measures to prevent arterial cardiovascular disease are likely to improve the patients' prognosis after acute PE. In addition, it would be very interesting to use the PEmb-QoL to measure the QoL in a larger cohort of patients and moreover, establish the effect of cardiopulmonary rehabilitation programs or other interventions on life style or coping mechanisms on QoL after PE.