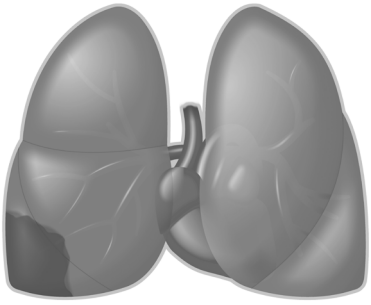
CHAPTER 1

General introduction



INTRODUCTION

Pulmonary embolism (PE) is characterized by an obstruction of the pulmonary arteries with a thrombotic embolus. These pulmonary emboli commonly originate from thrombi of the deep venous system of the lower extremities. The phenomenon venous thrombo-embolism (VTE) consisting of both deep vein thrombosis (DVT) and PE, was first described by Laennec, whereas Virchow was the first to coin the term pulmonary embolus in 1846.[1] PE is a potentially fatal condition which requires a rapid and correct diagnosis and treatment with anticoagulants that could prevent morbidity and mortality. It is important to treat patients with PE, but also to withheld treatment with concomitant bleeding risks to patients without PE. However, with varying and non-specific symptoms, clinical recognition is challenging, making objective testing a necessity in patients with clinical suspicion of PE. The diagnosis of PE can only be confirmed in 20 to 30% of the patients with a clinical suspicion of PE, and has an incidence of 0.6-1.2 per 1000 inhabitants per year.[2]

Clinical suspicion of PE arises in the majority of patients with presentation of sudden onset of dyspnea without an apparent cause (approximately 80%), acute (pleuritic) chest pain which worsens with breathing (52%), or less commonly occurring symptoms such as syncope, cough or hemoptysis.[3] Common indicators are tachypnea, tachycardia or the presence of a swollen, red leg.

Diagnostics in patients with suspected PE has been a subject of research for many years and the first objective diagnostic method became available in the 60s with the introduction of pulmonary angiography[4,5], followed by the ventilation-perfusion scintigraphy (1968) and helical computed tomography (CT).[6,7] CT-scanning is applicable since 1992, and widely applied for diagnosis nowadays. The diagnosis derived from CT imaging is often more conclusive since it also has the possibility to reveal an alternative diagnosis than PE. This is in contrast to ventilation perfusion scintigraphy, which has a high percentage of non-conclusive results. However, CT-scanning has drawbacks, including exposure to radiation, the possibility of allergic reactions to venous contrast as well as nephrotoxicity.

The development of clinical decision rules (CDRs) and D-dimer tests has made it possible to limit the use of CT-scanning. A CDR stratifies patients with suspected PE to a low or a high pretest probability of having PE according to a predefined algorithm using information from clinical history and physical examination. The first and one of the best validated and widely integrated CDRs is the Wells rule.[8] In addition to CDRs, a D-dimer blood test can be used. D-dimer is a degradation product of fibrin and indirectly indicates activation of blood coagulation. An elevated D-dimer concentration is an indication of the presence of thrombosis. However, this test is nonspecific; elevation

can also be found in patients with other conditions like malignancy, pregnancy or an infection. A low clinical probability according to a CDR combined with a normal D-dimer test result safely excludes PE without the need for further imaging. In case of high clinical probability according to the CDR or abnormal D-dimer test, further imaging is necessary to confirm or rule out the diagnosis of PE. Several algorithms integrating CDRs, D-dimer testing and imaging modalities have been developed and focus on excluding PE in a safe and efficient way. The Christopher study for instance revealed that CT-scanning can be avoided in approximately one third of the patients by combining an unlikely clinical probability and a normal D-dimer test.[9]

According to current guidelines, patients with proven PE should be admitted to the hospital and start treatment with anticoagulants. Standard treatment consists of at least five days of weight based therapeutic dose low molecular weight heparin along with vitamin K antagonists. After approximately one week, the low molecular weight heparin is discontinued while the vitamin K antagonist is continued for a period of three to six months with a target international normalized ratio (INR) in the therapeutic range (2.0-3.0).[10] For hemodynamically instable patients more aggressive treatment could be necessary, like thrombolytic treatment or thrombectomy. Risk-stratification could help to identify patients who could benefit from more intensive treatment, and on the other hand, some patients might be treated less aggressively at home.

OUTLINE OF THIS THESIS

The first part of this thesis focuses on the diagnosis of PE. An overview of the current diagnostic tools available in patients with clinically suspected acute PE to exclude or confirm the diagnosis is presented in **chapter 2**. **Chapter 3** of this thesis describes the simplification of a recently developed CDR, the revised Geneva score, and its validation for safety and clinical utility for the exclusion of PE. Simplification by awarding one point for all variables was performed because the individual weights of the CDR variables from the revised Geneva score are difficult to memorize and could lead to miscalculations in an acute setting. Four recently introduced and widely used CDRs are prospectively compared for the exclusion of PE in combination with D-dimer testing in **chapter 4**. The use of CDRs decreases the need for imaging techniques involving intravenous contrast and radiation. Several CDRs are available of which the Wells rule and revised Geneva score are well established. Both scores have been simplified, facilitating an easy computation of the CDR score. The four scores have never been directly compared for safety and clinical utility of excluding PE in combination with a D-dimer test. Therefore, we performed a prospective multi-center study in patients suspected of PE to directly compare the performance of

the four CDRs in excluding PE in combination with D-dimer testing. Currently, CT pulmonary angiography (CTPA) is the radiological imaging test of choice for suspected PE. It has an excellent sensitivity and specificity for diagnosing acute PE. However, concern for false negative results have raised, especially in patients with a high clinical pretest probability for PE[3]. Therefore, we have studied the safety of withholding anticoagulant treatment in patients with suspected acute PE and a strict indication for CTPA, i.e. likely or high clinical probability or an elevated D-dimer concentration, in whom CTPA revealed no PE. In addition, we have evaluated the additional value of performing compression ultrasonography of the legs, subsequent to normal CTPA to exclude DVT before deciding to withhold treatment. The results of this study are described in **chapter 5**.

Part two of this thesis focuses on recurrent acute PE. Patients being treated for PE are at increased risk for developing a recurrent PE. Although studies have reported on the cumulative incidence of recurrent VTE, no study has assessed the incidence of recurrent VTE in a well defined population. The epidemiology in this group of patients is of particular interest because of implications for prevention of morbidity and mortality, and consequences of management with the indication for prolonged anticoagulant treatment with associated bleeding risks and costs. The aim of **chapter 6** was to determine the incidence of acute recurrent VTE in a defined general population and to assess this incidence according to age and gender. Diagnostic strategies in patients with clinically suspected acute PE are well defined. However, the value in patients presenting with recurrent symptoms has not been established. In **chapter 7** the safety of withholding anticoagulant treatment in patients, in whom recurrent acute PE was excluded on the basis of a of a simple diagnostic algorithm using the Wells CDR, quantitative D-dimer test and CTPA, was evaluated.

In **chapter 8**, we investigate the predictive value for adverse clinical events of the biomarker (N-terminal-pro-) brain-type natriuretic peptide, which is a marker of ventricular overload, in patients with acute PE. Obstruction of the pulmonary arteries causes an increase in right ventricular afterload and might induce right ventricle enlargement and dysfunction, depending on the extent of the embolus load and comorbid conditions.

Finally, according to current guidelines, patients with proven PE will be admitted to the hospital and start with anticoagulant treatment. It may be possible to identify patients with a low risk for complications who may be treated safely at home, like the current standard for patients with DVT of the lower extremities. We conducted a cohort study in patients with objectively proven acute PE. Patients who met predefined criteria were considered as low risk patients and were treated at home. These results are presented in **chapter 9**. The findings of this thesis including the limitations and implications are discussed in **chapter 10**. This final chapter also offers a perspective for future research.

REFERENCES

1. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest. 2002;122:1440-56.
2. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000;83:657–60
3. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008;29:2276-315.
4. Williams JR, Wilcox C, Andrews GJ, Burns RR. Angiography in pulmonary embolism. JAMA. 1963; 184:473-6.
5. Sasahara AA, Stein M, Simon M, Littmann D. Pulmonary angiography in the diagnosis of thromboembolic disease. N Engl J Med. 1964;270:1075-81.
6. Wagner HN Jr, Sabiston DC Jr, Mcafee JG, Tow D, Stern HS. Diagnosis of massive pulmonary embolism in man by radioisotope scanning. N Engl J Med. 1964;271:377-84.
7. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique--comparison with pulmonary angiography. Radiology. 1992;185:381-7.
8. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-20.
9. van Belle A, Büller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006;11;295:172-9.
10. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):454S-545S.