Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism

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Introduction and outline of the thesis

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Pulmonary embolism (PE) is a potentially fatal condition, in which an embolism, usually a thrombus originating from one of the deep veins of the legs, blocks one or more pulmonary arteries, causing impaired blood flow and increased pressure of the right cardiac ventricle. PE and deep vein thrombosis (DVT) are considered two entities of the same disease: venous thromboembolism. The clinical presentation of patients with suspected acute PE is nonspecific and varies widely, from only limited symptoms, to severe shortness of breath, pain on exertion, syncope, cardiogenic shock and death. As PE is a frequently occurring disease, with an incidence of 1-2 per 1000 to nearly 8 per 1000 in older-aged patients per year, it is the third most common cardiovascular disorder in Western society (1;2).

The first step in the diagnostic work-up of suspected PE consists of clinical history taking and physical examination, in order to determine the clinical probability of PE. Information regarding clinical signs and symptoms can be used to classify patients in probability categories, by either using implicit judgement or validated clinical decision rules. Although four clinical decision rules have been proven to perform equally (3), the most commonly used clinical decision rule is the Wells score (4). This score consists of items obtained from clinical history such as risk factors for PE, physical examination such as increased heart rate and signs of DVT, and a subjective item, where the physician judges whether an alternative diagnosis is more likely than PE (5). When the low clinical probability (Wells score ≤ 4 points) is combined with a normal D-dimer test result, PE is safely excluded in 20 to 40% of the patients with suspected PE, without the need for imaging techniques (6). Fibrin D-dimer is the final product of the plasmin-mediated degradation of cross-linked fibrin and D-dimer levels are typically elevated in patients with acute venous thromboembolism. The sensitivity of the D-dimer, using a cut-off value of 500 µg/L, is nearly 100% (7). In contrast, since D-dimer levels can be elevated in other clinical conditions, e.g. malignancy, increased age, infection, postoperative states and pregnancy, the specificity for acute venous thromboembolism is only between 30% and 40% (7-9), and further decreases with advancing age. As aging increases the risk of PE, it is likely that a higher D-dimer cut-off results in higher specificity without a relevant fall in sensitivity in older patients (10;11). Indeed, in a retrospective analysis the use of an age-adjusted cut-off of the D-dimer (patient’s age x 10 µg/L) in combination with an unlikely clinical decision rule greatly increased the number of patients above 50 years in whom PE could safely be excluded (12). These results need to be confirmed in a
prospective study where patients are managed according to their age-adjusted D-dimer level.

If the clinical probability of PE is likely or the D-dimer test is abnormal, further imaging is necessary to confirm or exclude the diagnosis. Next to the clinical decision rule-D-dimer strategy, computed tomography (CT-) scan has increasingly become the most preferred imaging test to either confirm or exclude PE (13). With the introduction of multi-detector row CT-scan, the sensitivity of the CT-scan has greatly improved, ranging from 83% to 100% with specificity ranging from 96% to 100% (14;15), and even small subsegmental emboli can now be visualized (16). Besides, compared to the previous reference standard, i.e. ventilation perfusion scintigraphy (if necessary followed by pulmonary angiography), advantages of CT-scan are that the CT-scan is easily accessible, quickly performed and non-invasive. Another potential advantage of the CT-scan is the capability of detecting other findings supporting an explanation for the patient's complaints or symptoms when PE is excluded (17). On the other hand, the newer generation of CT-scans increases the rate of subsegmental filling defects and the clinical relevance of these subsegmental emboli is a topic of debate (18).

Besides, despite the improvement of diagnostic yield with the clinical decision rule-D-dimer strategy, of the patients with an indication for CT-scan only 20% to 30% indeed has a diagnosis of PE (19). This proportion is even lower in the United States, where it is approximately 10% (20). Additionally, CT-scan can also cause adverse effects, such as an increased lifetime risk of (breast) cancer from radiation exposure, especially in young women, and the risk of contrast nephropathy (21;22). These concerns force physicians to use a diagnostic strategy, which results in fewer CT-scans and the lowest possible false negative rates.

Regarding the treatment and prognosis of PE, important questions have surfaced. Although most hemodynamically stable patients with PE benefit from standard anticoagulant treatment, the rates of residual thrombosis at the end of anticoagulant therapy and the short-term clot resolution with anticoagulant treatment is not well known. Nowadays, although without solid evidence for clinical relevance, physicians often perform repeat CT-scans after six months of anticoagulant treatment, as the presence of residual thrombotic obstruction appears to have two important implications. First, repeat scans after discontinuation of anticoagulant therapy may aid in the differentiation between residual and recurrent thrombi in the diagnostic work-up of patients with suspected recurrent PE. This is of importance given the therapeutic consequences of prolonged or even lifelong anticoagulant treatment after a recurrence of PE.
Chapters 1

(23). Second, patients with residual thrombotic occlusion may be at increased risk of recurrent PE or chronic thromboembolic pulmonary hypertension (24). Finally, little attention has been paid to the quality of life in patients after PE.

**Outline of the Thesis**

This thesis consists of two parts. The first part focuses on the diagnosis of PE. In chapter 2, an age-adjusted cut-off point (patient’s age x 10 µg/L) of D-dimer levels was validated in four recently introduced and widely used clinical decision rules, which all four showed to perform equally well. In chapter 3, the performance of these four clinical decision rules was investigated in patients with cancer and suspected PE.

An alternative diagnostic strategy, in which women younger than 50 years of age with a high risk of PE are investigated with the combination of a chest X-ray and perfusion scintigraphy, in order to avoid CT-scanning and thereby radiation exposure to the breasts, is prospectively evaluated in chapter 4. In chapter 5, the accuracy of the D-dimer test is tested in patients with zero, one or two items of the Wells score, and additionally, in chapter 6 we designed a new clinical decision rule that includes the D-dimer as a first step, with the aim to further lower the number of unnecessary CT-scans.

Next, in chapter 7 we studied whether alternative diagnoses observed on CT-scans, ordered for PE, have diagnostic or therapeutic consequences. In chapter 8, we investigated whether the level of prothrombin fragments in serum and urine in patients with venous thromboembolism and myocardial infarction is elevated compared to healthy volunteers.

**Part II** of this thesis focuses on the treatment and the prognosis of PE. An overview of the current treatment and the potential of the new oral anticoagulants in PE patients is presented, as well as the treatment in ‘special’ populations, such as patients with obesity or severe renal failure, in chapters 9 and 10.

Chapter 11 focuses on the resolution of the pulmonary clots in patients with acute PE, diagnosed with either a CT-scan or a perfusion-scan, and followed up by a similar scan after three weeks of anti-coagulant treatment. Furthermore, in chapter 12, residual pulmonary thrombi are investigated with a CT-scan after six months of anticoagulant treatment, by two independent radiologists. Chapter 13 investigated the clinical outcome of patients with subsegmental PE versus more proximal PE (segmental
and central PE). The influence of the duration of complaints before CT-scanning on the D-dimer level and the prognosis of patients is described in chapter 14. The quality of life in patients with a history of PE is described and compared to patients with other (cardio-) pulmonary diseases in chapter 15.

Reference List


