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Pulmonary embolism : diagnostic management and prognosis

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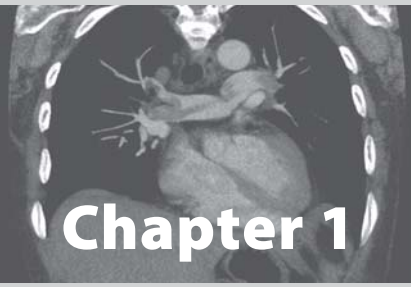
Citation
Klok, F. A. (2010, March 2). *Pulmonary embolism : diagnostic management and prognosis*. Retrieved from https://hdl.handle.net/1887/15031

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/15031

Note: To cite this publication please use the final published version (if applicable).



Chapter 1

Introduction

Even though the first reports on venous thromboembolism date back to the 13th century and the mechanism of acute pulmonary embolism (PE) was unraveled almost 150 years ago by Rudolf Virchow, PE still keeps medical researchers occupied around the globe.[1,2] PE is a disease characterized by obstruction of the pulmonary arteries with thrombotic emboli originating predominantly from pathological thrombi in the deep venous system of the lower extremities.[2] This obstruction of the pulmonary arteries causes an increase in right ventricular afterload that, in combination with the release of several neurohumoral factors, might induce right ventricle enlargement and decreased stroke volume.[3] When the compensatory mechanisms to maintain right ventricular systolic function, i.e. catecholamine-driven tachycardia and the Frank-Starling preload reserve, are utilized, right ventricular cardiac output decreases resulting in decreased left ventricular filling. In turn, this causes left ventricular systolic function impairment and thus decreased coronary perfusion pressure.[3] In the right ventricle, when exposed to increased oxygen demand, decreased coronary perfusion pressure contributes to the relative oxygen deficit and might therefore cause myocardial ischemia and further loss of systolic performance.[3] Depending on comorbid conditions as well as the extent of the embolus load, this vicious circle may have fatal outcome within minutes, or after several hours or days, especially when the patient is left untreated. Hence, accurate and rapid identification and treatment of patients with acute PE is of great clinical importance.

The diagnostic process of acute PE however, represents several challenges. In essence, the physician has to distinguish patients with this disease - and treat them - from patients that are suspected of PE but do not have the disease. Because the signs and symptoms of PE are largely non-specific, many patients presenting with respiratory or chest symptoms are further investigated but do not have PE. As a result of limitations of individual diagnostic tests, mis-management of PE on the basis of the results of single diagnostic tools has been a frequent problem. In addition, invasive diagnostic procedures and exposure to ionizing radiation or nephrotoxic contrast dye should be prevented when possible. The use of well validated diagnostic algorithms combining different non-invasive tests, i.e. clinical decision rules, D-dimer blood tests and radiological imaging, are the solution for these issues.[4] Clinical decision rules predict the probability of having PE for individual patients and aid the clinician in determining the preferred diagnostic approach. D-dimer blood tests should be performed in patients with an unlikely probability since a normal test result safely excludes PE under this condition.[4,5] Because this is not true for patients with a likely probability, D-dimer tests are not useful for these patients and radiological imaging should follow.[4,6] Chapter 2 and 3 of this thesis focus on the clinical validation, simplification and performance of a recently developed clinical decision rule, the revised Geneva score.[7]

Currently, the radiological imaging test of choice for suspected PE is computed tomography pulmonary angiography (CTPA). It has been shown that this test has excellent sensitivity and specificity for diagnosing acute PE.[8] Nonetheless, experts have raised concern for false negative CT results, especially in patients with high clinical probability for PE.[9] For this reason, we have

studied the safety of withholding anticoagulant treatment in patients with suspected PE and a strict indication for CTPA, in whom the CT scan revealed no pulmonary emboli. Furthermore, we have evaluated the additional clinical value of performing compression ultrasonography of the legs subsequent to a normal CTPA to exclude deep venous thrombosis before deciding to withhold treatment. The results of this study are described in chapter 4.

After establishing the diagnosis of acute PE, patients should be treated with at least 5 days of either weight based therapeutic doses of low molecular weight heparin or unfractionated heparin aiming at a 1.5 to 2.5 prolongation of the activated partial thromboplastin time, followed by vitamin K antagonists for a period of at least three to six months with a target international normalized ratio (INR) of 2.0 to 3.0.[10] For patients presenting with hemodynamic instability, more aggressive treatment is warranted which may include administration of thrombolytic drugs, thrombosuction or surgical thrombectomy.[10] These latter two are reserved for those patients in whom thrombolysis is contraindicated. Importantly, the clinical condition of apparently stable patients may deteriorate rapidly and unexpectedly to cardiogenic shock of even death in the first hours or days after establishing the diagnosis of acute PE. In most cases, this phenomenon is caused by silent and unnoticed worsening of right ventricular function impairment by the viscous circle described above. It is a challenge to distinguish patients at risk for clinical deterioration from those with relatively mild disease since these first patients might benefit from more intensive clinical surveillance and treatment regimes whereas home treatment may be considered for the latter patient category. It seems pathophysiologically plausible to include specific markers of ventricular function in risk stratification models for patients with acute PE. In chapters 5 to 7 of this thesis, we explore the predictive value for adverse clinical events of several biomarkers of ventricular overload as well as easy obtainable CT-measured indicators of right ventricular function in patients with acute PE.

One other important objective of clinical research in the field of acute PE concerns the patients' prognosis. Patients who survive the acute embolic event face the risk of recurrent venous thromboembolism, bleeding complications from anticoagulant therapy, chronic emboli leading to pulmonary hypertension and in addition arterial cardiovascular events and detection of previously unknown cancer.[11-14] However, despite the increased risk for these serious clinical complications compared to population controls, patients with a first episode of acute PE stop their anticoagulant therapy after three to six months and are from then on referred to their general practitioner. This is mainly due to the absence of evidence-based, well validated guidelines for specific screening programs, intensified clinical surveillance or prolonged treatment regimens. The development of such guidelines is complicated by the lack of knowledge of underlying pathophysiological mechanisms and accurate risk estimates regarding these complications. To further study the long term prognosis of patients with acute PE, we have performed a large cohort study of patients with acute PE, the so called INSHAPE study (INcidence

of Symptomatic chronic thromboembolic pulmonary Hypertension after Acute Pulmonary Embolism). The primary goal of this study was the determination of the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after acute PE in an unselected patient cohort, which is described in chapter 8. In the subsequent chapter, we have compared various clinical algorithms for managing dyspnoeic patients with previous PE who are suspected of having CTEPH. Analyses regarding the prevalence and causes of exertional dyspnea in the clinical course of acute PE, further evaluation of the risk of cardiovascular events after acute PE and the overall prognosis of patients with acute PE including a pooled survival analysis of different adverse events, are presented in chapters 10, 11 and 12 respectively. Finally, in chapter 13 we describe a newly derived disease specific quality of life instrument for patients with acute PE.

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