The diagnostic management of suspected pulmonary embolism
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Summary and Conclusions

Overview of Bologna, Italy
Pulmonary embolism is a potentially fatal disease in which early recognition and institution of anticoagulant treatment can prevent mortality. The diagnostic tools available to establish whether a patient has a pulmonary embolism were limited to pulmonary angiography and ventilation-perfusion scintigraphy. Both tests have considerable limitations. Helical CT evolved as a new technique in diagnosing PE and gained widespread interest but has been implemented rapidly, without appropriate assessment in clinical practice. Two accuracy studies, comparing helical CT to the golden standard pulmonary angiography, showed a disappointing sensitivity of only 70%, but management studies showed a 3-month thromboembolic failure rate (the risk of developing DVT or PE despite negative tests) of less than 2% after a negative helical CT combined with other techniques. These diagnostic algorithms were usually complicated and therefore not easily implemented in clinical practice.

The Christopher-study was performed to investigate whether a dichotomization of the Wells clinical decision rule, classifying patients into ‘PE unlikely’ and ‘PE likely’ in combination with a D-dimer test is safe to rule out pulmonary embolism in patients with a clinical suspicion. Furthermore, the study was designed to investigate whether helical CT is safe to rule out PE without performing any additional diagnostic tests.

In Chapter 3, the results of this prospective management-study are described in 3306 consecutive patients suspected of PE. The Wells clinical decision rule classified patients as ‘PE unlikely’ in 2206 (66.7%) of patients. These patients underwent D-dimer testing and 1057 (32.0%) had a negative D-dimer result ($\leq 500$ ng/ml). PE was considered excluded in these patients. All other patients, i.e. those classified as ‘PE likely’ or those classified as ‘PE unlikely’ but with an abnormal D-dimer test, underwent helical CT. PE was diagnosed in 674 (20.4%) patients and these were consequently treated with anticoagulants. In 1505 patients (45.5%), CT excluded PE. In 50 patients (1.5%) the protocol was violated and CT was not performed and in 20 (0.9%) patients the CT was inconclusive. Hence, the diagnostic algorithm could be completed according to the protocol in 3256 (98.5%) patients and allowed a management decision in 3236 patients (97.9%). In patients in whom PE was excluded by a clinical decision rule indicating ‘PE unlikely’ combined with a negative D-dimer and were not treated with anticoagulants, during three months of follow-up venous thrombo-embolism was diagnosed in 5 out of 1028 untreated patients (0.5%, 95%CI: 0.2-1.1). In patients in whom PE was excluded by a clinical decision rule indicating ‘PE unlikely’ combined with a negative D-dimer and were not treated with anticoagulants, during three months of follow-up venous thrombo-embolism was diagnosed in 5 out of 1028 untreated patients (0.5%, 95%CI: 0.2-1.1). In patients in whom PE was excluded by a clinical decision rule indicating ‘PE unlikely’ combined with a negative D-dimer and were not treated with anticoagulants, during three months of follow-up venous thrombo-embolism was diagnosed in 5 out of 1028 untreated patients (0.5%, 95%CI: 0.2-1.1). In conclusion, the Christopher-study demonstrates that a simple diagnostic algorithm consisting of a dichotomised clinical decision rule, D-dimer and helical CT can guide treatment decisions with a low risk of subsequent venous thrombo-embolism.

Chapter 4 discusses whether varying the cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test could lead to an increase in clinical utility (i.e. the proportion of patients in whom the diagnosis of PE can be safely excluded without additional imaging tests) without jeopardizing safety. For each increment of clinical decision rule and D-dimer...
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cut-off point, the number of patients with PE at baseline or during follow-up, the clinical utility and the 3-month thrombo-embolic failure rate were recalculated. By increasing the cut-off level of the clinical decision rule from 4 to 5 points, pulmonary embolism could be ruled out in an additional 4% of the study population (from 29.3 to 33.3%) at an expense of an increased three-month thrombo-embolic failure rate of 1.5% (95%CI: 0.6-3.0%) in comparison to 0.9% (95%CI: 0.3-2.4) for patients who had a clinical decision rule cut off at 4 points. By increasing the D-dimer cut-off level from 500 to 600 ng/ml, PE could be ruled out in an additional 3% (from 29.3% to 32.3%) of the study population but the three-month thrombo-embolic failure rate increased 0.9 (95%CI: 0.3-2.4) to 2.2% (95%CI: 1.1-4.0). This sub-study concluded that at the prevalence of 29.3%, the cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be kept at the original 4 points and 500 ng/ml respectively, in order to prevent exposure of patients to a 3-month thrombo-embolic failure rate exceeding that of a normal pulmonary angiography.

The anatomic distribution of pulmonary embolism in central, segmental and sub-segmental arteries is understudied and an often-debated issue is the possible limitation of computed tomography to accurately detect peripheral emboli. Multi-detector row CT is thought to increase the detection rate of sub-segmental emboli compared to single-detector row CT. In Chapter 5, we evaluate the prevalence and anatomic distribution of PE in consecutive patients with proven PE diagnosed by MDCT or SDCT. The location of PE was classified into three groups (central, segmental and sub-segmental PE) with emphasis on the largest pulmonary arterial branch involved. A total of 3306 consecutive patients were included in the diagnostic study, of whom 674 (20%) were diagnosed with PE. Data regarding the localisation of PE were missing in 41 patients. Localisation of PE in MDCT was central in 160 patients (29%, 95%CI: 25-33), segmental in 293 patients (53%, 95%CI: 49-57) and sub-segmental in 98 patients (18%, 95%CI: 15-21). In patients diagnosed with SDCT, PE was central in 31 patients (38%, 95%CI: 27-49), segmental in 39 patients (48%, 95%CI: 36-59) and sub-segmental in 12 patients (15%, 95%CI: 8-24). The percentage of detected PE did not differ significantly between MDCT and SDCT (31% vs. 32%, p=0.65), neither the percentage of sub-segmental PE (18% vs. 15%, p=0.48) detected by MDCT or SDCT. In conclusion, based on these data there seems to be no danger of over-diagnosis of small subsegmental PE using multi-detector row systems.

In Chapter 6, the natural course of patients diagnosed with PE is described in terms of incidence of recurrent venous thrombo-embolism, bleeding and mortality. Moreover, risk factors for these events were identified as well as the time course of these events. Of 673 patients with complete follow-up, 20 patients (3.0%, 95%CI: 1.8-4.6) had recurrent VTE. Eleven of 14 patients with recurrent PE had a fatal PE (79%, 95%CI: 49-95%), occurring mostly in the first week after diagnosis of initial PE. In 23 patients (3.4%, 95%CI: 2.2-5.1) a hemorrhagic complication occurred of whom 10 were major bleeds (1.5%, 95%CI: 0.7-2.7) and two were fatal (0.3%, 95%CI: 0.04-1.1). During the three-month follow-up, 55 patients died (8.2%, 95%CI: 6.2-10.5). Risk factors for recurrent VTE were immobilisation for more
than 3 days, while being an inpatient, having COPD or malignancies were risk factors for bleeding. Age, immobilisation, malignancy and being an inpatient were risk factors for mortality. In conclusion, recurrent VTE occurred despite anticoagulant therapy in 3% of patients with PE and the majority of recurrent PE’s (79%) were fatal. Also, patients with PE have a high mortality rate, 8.2% during three months of follow-up. Immobilization, hospitalization, age, COPD and malignancies were risk factors for complications of PE. Close monitoring may be indicated in these patients, precluding them from out of hospital start of treatment.

It is unknown whether strategies validated for diagnosing pulmonary embolism are valid in patients with a history of PE. Chapter 7 describes whether the Christopher-algorithm, consisting of sequential application of a clinical decision rule (CDR), a quantitative D-dimer test and helical computed tomography, could safely rule out a clinical suspicion of recurrent PE. All patients of the Christopher-study who had a history of PE were included in this sub-study. Recurrent PE was ruled out by an unlikely probability of PE (CDR score ≤ 4 points) combined with a normal D-dimer test (≤500 ng/ml) or by a normal CT in all other patients. The primary outcome was the incidence of recurrent venous thrombo-embolism during three months of follow-up in patients with normal tests and not treated with anticoagulants. Of 3306 patients suspected of PE, 259 patients (7.8%) had a history of PE. Of these, 25 (9.7%) were treated with anticoagulants and excluded. The probability of PE was unlikely in 82 of 234 patients (35%) and 42 had a normal D-dimer test (18%), excluding recurrent PE. None of these patients had a venous thrombotic event during follow-up (0%, 95%CI: 0–6.9). A CT was indicated in all other patients (n=192) and ruled out recurrent PE in 127 patients (54%). One patient had a fatal recurrent PE during follow-up (0.8%; 95%CI: 0.02–4.3). This is the first prospective study that demonstrated the safety of ruling out a clinical suspicion of recurrent PE by a simple diagnostic algorithm in patients with a history of PE.

Much attention has been paid in recent years to optimizing the diagnosis of acute pulmonary embolism. However, little is known about the changes in clot burden that occur at the level of the pulmonary arteries after documented PE. It is often problematic to distinguish between a new or residual defect on lung scintigraphy or helical computed tomography. This may lead to falsely labeling patients with residual PE as having recurrent PE and consequent unnecessary treatment changes.

In Chapter 8 a systematic analysis is shown of studies of imaging tests (radionuclide and computerized tomography) evaluating resolution rate of PE with independent assessment of predefined methodological criteria by two investigators. We identified 29 clinical studies. Of these, 25 were excluded and 4 studies were included in our review. The percentage of patients with residual pulmonary thrombi was 87% at eight days after diagnosis, 68% after six weeks, 65% after three months, 57% after six months and 52% after 11 months. No definite conclusions can be made on the resolution of PE beyond 11 months after diagnosis.
Summary and Conclusions

This review shows that complete resolution of PE is not routinely achieved between 8 days and 11 months after diagnosis. More than 50% of patients with PE still have defects six months after diagnosis, after which resolution of thrombi appears to reach a plateau phase.

In pregnancy, the diagnosis of pulmonary embolism is problematic. There is doubt as to whether objective diagnostic tests are needed and confusion as to what objective test is the safest with respect to fetal radiation exposure. However, pulmonary embolism is still one of the leading causes of maternal mortality and it is critically important to objectively diagnose pulmonary embolism since a clinical diagnosis is notoriously inaccurate. However, physicians are reluctant to perform helical CT in pregnant women because it is assumed that helical CT exposes the fetus to a higher radiation dose than VQ scintigraphy. In Chapter 9 we describe the results of a calculation of fetal radiation dose by helical CT and compare these to VQ scintigraphy. Our calculation of fetal radiation dose in helical CT was based on the assumption that radiation dose to the uterus is a good approximation of the radiation dose to the fetus in early pregnancy. This early period is the most important period since the fetus is considered to be most vulnerable to radiation exposure. The calculated dose of radiation absorbed by the fetus for a single-detector row helical CT was 0.026 mSv. An even lower dose (0.013 mSv) was calculated for the multi-detector row helical CT. In comparison, the calculated dose of fetal radiation with perfusion scintigraphy was 0.11-0.20 mSv.

Diagnosing deep vein thrombosis and pulmonary embolism in pregnancy is challenging. Many of the common diagnostic tests, including compression ultrasonography (CUS), ventilation-perfusion scintigraphy and helical computed tomography that have been extensively investigated in non-pregnant patients, have not been appropriately validated in pregnancy. Extrapolating results of diagnostic studies of DVT and PE in non-pregnant patients to those who are pregnant may not be correct because of differences in pathophysiology and presentation of DVT and PE in pregnancy. In Chapter 10 a systematic analysis is shown of published studies addressing diagnostic testing for DVT and PE in pregnancy to determine the accuracy of these tests in pregnancy. According to our predefined inclusion criteria, only four studies remained for inclusion, three studies investigating diagnostic testing in patients with a clinical suspicion of DVT and one study in patients with a clinical suspicion of PE. From our systematic analysis of published studies investigating diagnostic testing for a clinical suspicion of DVT or PE in pregnancy we conclude that; 1) two studies support withholding anticoagulant therapy in pregnant women with a clinical suspicion of DVT and normal results on serial IPG (impedance plethysmography), however, IPG is no longer used; 2) only one study demonstrated that a normal CUS at presentation combined with a normal D-dimer test or an abnormal D-dimer test combined with normal serial CUS appears promising for safely excluding DVT in pregnant patients, but too few patients were included in this pilot-study to draw firm conclusions; 3) only one study investigated pregnant patients with a clinical suspicion of PE and this study concluded that in case of normal or non-diagnostic VQ scans, withholding anticoagulant therapy might be safe, but this needs confirmation in larger studies.
Conclusions

The Christopher-study demonstrates that a simple diagnostic algorithm consisting of a dichotomised clinical decision rule according to Wells, D-dimer test and helical CT is safe in excluding pulmonary embolism with a low risk of subsequent venous thromboembolism. In one-third of the study population, PE could be ruled out without using imaging tests. In all other patients, a helical CT demonstrating no PE turned out to be safe in excluding PE without performing additional tests. Furthermore, the algorithm of the Christopher-study is easily implemented in daily clinical practice since 98% of the patients could be managed according to our protocol. In order to prevent exposure of patients to a 3-month thrombo-embolic failure rate exceeding that of a normal pulmonary angiography, the cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be strictly adhered to at the original 4 points and 500 ng/ml respectively. As regards to the type of CT-scanner, i.e. multi- or single-detector row CT, we did not find a significant difference in the percentage of detected PE between MDCT and SDCT, neither in the percentage of sub-segmental PE. Based on these data, there seems to be no danger of over-diagnosis of small subsegmental PE using multi-detector row systems.

In patients diagnosed with PE and treated with anticoagulants, recurrent VTE occurred despite anticoagulant therapy in a small percentage of patients and the majority of recurrent PE’s were fatal, occurring mostly in the first week after diagnosis of PE. Also, patients with PE have a high mortality rate during three months of follow-up. Immobilization, hospitalization, age, COPD and malignancies were risk factors for complications of PE, i.e. recurrent venous thrombo-embolic events, bleeding or mortality. Close monitoring may be indicated in these patients, precluding them from out of hospital start of treatment.

In patients with a clinical suspicion of recurrent PE, the Christopher-design appeared to rule out recurrent PE safely, although confidence limits of the three-month thromboembolic risk were rather wide and do not permit to conclude that our approach is as safe as pulmonary angiography. The proportion of patients with a clinical suspicion of recurrent PE that could be ruled out without using imaging tests was one-fifth compared to one-third in patients without a history of PE. The less discriminative power of the clinical decision rule in patients with a history of PE is due to the item “history of VTE” on which all patients score 1.5 points.

A complicating factor in diagnosing recurrent PE, is that it is currently unknown whether pulmonary emboli resolve completely. There seems to be a wide variation in resolution of thrombi in individual patients and the pathophysiologic mechanisms and clinical consequences remain largely unknown. Physicians should be aware that complete resolution of pulmonary thrombi may not be achieved and it may complicate the objective and accurate diagnosis of recurrent PE.

Another group of patients that need major concern in diagnosing pulmonary embolism are pregnant patients. Despite the fact that pulmonary embolism is still one of the leading causes of maternal mortality, there’s a major lack of evidence concerning the accuracy
of diagnostic tests in pregnant women. One complicating factor is fear of radiation exposure. Based on our calculation with a computerized model, taking into account certain assumptions, we conclude that helical CT exposes the fetus to less radiation than perfusion scintigraphy. The main issue following in-utero exposure at typical diagnostic levels of radiation is induction of malignancies with a number of excess malignancies cases up to age 15 years following in-utero exposure is considered to be 1 in 16,000 per mSv. Fear of radiation exposure is therefore not an argument to withhold objective tests in pregnant patients with a clinical suspicion of PE and to expose them to a potential fatal disease.