How I diagnose acute pulmonary embolism

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Abstract

The clinical diagnosis of acute pulmonary embolism is frequently considered in patients presenting to the Emergency Department or when hospitalised. Since this diagnosis is a-specific and the consequences of anticoagulant treatment are considerable, objective tests to either establish or refute the diagnosis have become standard of care. Traditionally, pulmonary angiography has been the gold standard, but over the years computed tomography pulmonary angiography (CTPA) has replaced it and is now the first line imaging test. In view of the large increase in use of CTPA, with resulting diminishing prevalence of PE, it is critical to review the diagnostic algorithm of PE. This should always include a clinical decision rule to assess the likelihood of PE being present, a D-dimer blood test and CTPA. Using a standardised algorithm, CTPA can be avoided in 20-30% of patients presenting with a first or recurrent episode of clinically suspected acute PE. The aim of this review is to provide clinicians a practical diagnostic management approach of acute PE with evidence from the literature.
Introduction

Clinically suspected acute pulmonary embolism (PE) is frequently encountered in general practice as well as in hospitalized patients. Together with acute deep-vein thrombosis (DVT) PE has been recognized the third most common cardiovascular disorder in industrialized countries. The diagnostic pathway of acute PE is guided by two principles. First, accurate and fast identification of patients who have PE is of critical importance as PE is a potentially fatal condition, while anticoagulation is associated with risk of major bleeding. A false diagnosis thus exposes patients to unnecessary risk of either death from PE or bleeding which can also be fatal. Second, the use of individual diagnostic tests in isolation may lead to mismanagement of suspected PE. For that reason, integrated diagnostic approaches with a combination of different diagnostic tests are to be preferred. This article will focus on hemodynamically stable patients, who represent over 95% of all patients with symptomatic acute PE. Based on the clinical cases of three patients who recently presented to our hospital, we will review the literature and discuss the latest evidence as well as the currently most optimal treatment strategies.

Case 1

A 69-year old male patient with a history of mild COPD presents to the emergency department with acute-onset dyspnea. He does not report coughing, fever or symptoms of deep vein thrombosis. On physical examination, he is hemodynamically stable and no abnormalities are observed at auscultation of the heart and lungs. His ECG reveals a sinus rhythm of 60 beats/min, with a S1Q3T3 pattern. A chest X-ray is normal. The attending physician considers acute PE as a possible explanation for his symptoms. What would be the next diagnostic step?

Clinical probability assessment and D-dimer tests

The clinical presentation of acute PE varies widely between patients. While the majority of patients present with rapid onset dyspnea or pleuritic chest pain, in some patients wheezing or a non-
productive cough are the only symptoms.\textsuperscript{2} The initial clinical evaluation includes risk factor consideration, physical examination, results from blood tests, ECG monitoring or a chest X-ray. Although nonspecific for PE diagnosis, these items are of considerable value in the selection of patients in whom acute PE might be present. If after initial evaluation acute PE is still considered, further diagnostic work-up should start with a standardized estimation of the likelihood of PE being present, i.e. by using a validated clinical decision rule. The importance of this estimation lies in the fact that, in accordance with Bayes Theorum, when combined with knowledge of the accuracy of the chosen diagnostic test this enables estimates of probability that the patient has PE. Since no test with 100\% sensitivity and or specificity is available, only knowledge of the pretest probability of PE and the accuracy (sensitivity/specificity) of the available diagnostic test can enable the most optimal (i.e. safe and effective) diagnostic workup for each individual patient can be determined.

Two widely validated clinical decision rules to establish the clinical probability of acute PE are available. The Wells rule consists of 7 variables (table 1) including a judgement of whether PE is the most likely diagnosis.\textsuperscript{3} Using this rule, patients are classified as PE unlikely (\leq 4 points, 2.3-9.4\% PE risk) or PE likely (>4 points, 28-52\% PE risk).\textsuperscript{3} The revised Geneva score contains nearly the same items (table 1) except for a clinical subjective judgement of the likelihood of PE.\textsuperscript{4,5} Patients with an unlikely clinical probability according to this rule (\leq 2 points) have a 13-19\% PE risk, patients with a likely probability (>2 points) 28-35\% PE risk.\textsuperscript{4,6} For practical purposes, both rules have been simplified by assigning only one point to each item (table 1), without a resulting decrease in diagnostic accuracy.\textsuperscript{6-8}

In patients with an unlikely probability, D-dimer tests can be applied to rule out PE. Fibrin D-dimer is a marker of fibrinolysis and D-dimer levels are typically elevated in patients with acute thrombotic disease. Other clinical conditions associated with enhanced fibrin formation as malignancy, trauma, disseminated intravascular coagulation, infection and postoperative states also can give rise to elevated D-dimer levels. Hence, sensitivity of Dimer tests for acute PE is very high at cost of a rather poor specificity.\textsuperscript{9} In general, the D-dimer threshold for a normal test result is 500 µg/L, although three
recent post-hoc analyses have suggested that an age dependent cut-off defined as patient's age \( \times 10 \) microgram/l (only for patients >50 years old) is safe and more efficient for use in clinical practice.\(^{10-12}\) A prospective management study to confirm the safety of this age dependent cut-off is currently well under way, of which the results are expected in the end of 2013. The combination of a normal high sensitivity quantitative D-dimer test result and an unlikely clinical probability has enough negative predictive value to rule out acute PE without further imaging. For the original Wells rule, a meta-analysis including all high-quality prospective management studies confirmed the very low 3-month VTE risk in 1660 consecutive patients with an unlikely probability and a normal D-dimer with a pooled negative predictive value of 99.7\% (95%CI 99.0–99.9).\(^{13}\) The PE related 3-month mortality risk in these patients was very low as well (0.06\%; 95%CI 0.0017–0.46).\(^{13}\) In the recently published Prometheus study, both the original and the simplified Wells rule and revised Geneva score were for the first time directly compared in 807 consecutive patients.\(^6\) The four decision rules showed similar performance for exclusion of acute PE in combination with D-dimer testing with 3-month venous thromboembolic recurrence rates of all four scores ranging between 0.5\% and 0.6\%. Since none of the 4 rules has been proven to be superior, the choice for a specific rule is dependent on local preference. Notably, D-dimer tests lack the sensitivity to safely rule out PE in patients with a likely probability. Therefore, all patients with an elevated D-dimer or a clinical decision rule indicating ‘likely probability’ should be referred for radiological evaluation. Finally, the indiscriminate use of clinical probability scores or D-dimer assays as screening test for PE in the workup of unselected patients with respiratory or chest symptoms will lead to a large amount of falsely positive test results and therefore result in excessive and unneeded diagnostic testing.

**Computed tomography pulmonary angiography**

Computed tomography pulmonary angiography (CTPA) has become the first-line imaging method for assessment of patients with clinically suspected acute PE. CTPA is readily available in most hospitals and has been shown to have high sensitivity and specificity for PE, comparable with the traditionally
golden standard invasive pulmonary angiography. The sensitivity is dependent on thrombus location and clot burden as well as on the number of CT detector rows, and ranges from 20 to 30% for small distal subsegmental emboli with single-row CTPA to well over 95% for segmental, lobar and centrally located pulmonary emboli using multi-detector-row CTPA. It has been widely shown by numerous management studies that CTPA can be used as single diagnostic test to rule out or establish acute PE. A meta-analysis of 23 studies with a total of 4657 patients found a 3-month venous thromboembolic event rate after negative CTPA of 1.4% (95% CI 1.1–1.8%), and a 3-month fatal PE rate of 0.51% (95% CI 0.33–0.76%). The safety of using CTPA as a single imaging test has been further established by a randomized non-inferiority trial in which performing compression ultrasonography (CUS) of the leg veins in addition to MD-CTPA did not lead to better results in excluding PE. This evidence has strongly supported the widespread implementation of CTPA. Several concerns however can be raised regarding the lowering threshold and increased frequency of CTPA use. First, overuse of CTPA as the first and only diagnostic test in patients suspected of PE leads to a very low prevalence (< 10%) of PE diagnosed. This low diagnostic yield seems consistent with a trend to overdiagnosis, because of an observed rising PE incidence with minimal change in mortality and lower case fatality since the introduction of CTPA. Second, there is increasing fear for long-term radiation complications, allergic reactions to iodinated contrast material and contrast-induced nephropathy. Finally, smaller subsegmental emboli are more frequently detected. Although observational research suggests that treated as well as untreated patients with subsegmental PE have a good prognosis, the true clinical relevance of these emboli is yet uncertain. Taken together, it is imperative that the use of CTPA should be limited to those patients with a strict indication for CTPA, i.e. patients with a high clinical probability or an elevated D-dimer level in whom PE cannot be ruled out without performing radiological imaging. The diagnostic safety for excluding PE in these selected patients has been confirmed in several outcome studies where only patients with either an elevated D-dimer level or a likely clinical probability were subjected to CTPA, with a pooled 1.2% (95% CI 0.8–1.8%) risk for recurrent venous thromboembolism (VTE) during three months following a negative CTPA. The risk for fatal pulmonary embolism was consistently low (0.6%; 95% CI 0.4–1.1%).
Integrated approach

The main purpose of using an integrated diagnostic algorithm for the diagnostic work-up of suspected PE is to reduce the number of necessary radiological imaging tests as well as keeping the 3-month VTE failure rate below 2%, as these are the rates of VTE detected during follow-up after the gold standard of invasive pulmonary angiography or CTPA. We recommend a strategy starting with clinical probability assessment by means of a validated clinical decision rule. In case of unlikely clinical probability, a D-dimer test should be ordered. Only with a normal test result, PE is ruled out and the patient can be safely left untreated. If the decision rules indicates ‘PE likely’ or D-dimer levels are elevated over the threshold, patients should be referred for CT-scanning and further managed according to the CTPA result. Using this algorithm (figure 1), CTPA can be avoided in 30% of patients with suspected acute PE and an effective management decision can be made in 98% of patients.27,30

As for our patient, both the Wells rule and the revised Geneva score indicated an ‘unlikely probability’ (Wells score: 3 points for PE as the most likely diagnosis; revised Geneva score: 1 point for age >65 years). Subsequent laboratory testing revealed an elevated D-dimer concentration of 2200 µg/L. Even when applying an age dependent cut-off (age 69, adjusted D-dimer cut-off 69*10=690 µg/L), this concentration is well over the normal threshold. Consequently, he was subjected to CTPA that confirmed a fresh embolus in the segmental artery to the right lower lobe (Figure 2a).

Case 2

A 22-year old previously healthy although obese woman is admitted to the emergency ward because of acute onset right sided chest pain. She remembers coughing up a small amount of blood earlier that morning but denies a fever or mucus production. She was recently prescribed an oral contraceptive because of menorrhagia. On examination the attending clinician notices a tachycardia of 130
beats/min. The chest X-ray is of poor quality because of her obesity and since the chest pain prohibited her from holding her breath, and shows signs of a subtle right-side paracardial consolidation. Because acute PE is high in the differential diagnosis, the Wells score is calculated (5.5 points; revised Geneva score 7 points) and it is concluded that she can be categorized as ‘PE likely’. Being concerned of radiation exposure in this young woman, the physician questions herself whether there are alternative radiological options other than CTPA.

Ventilation-perfusion scintigraphy

In the past three decades, the total number of CT-scans performed for any indication has grown exponentially. For instance, over 70 million CT-scans were performed in the United States in 2007.\textsuperscript{31} It has been postulated that CT scan-associated radiation may increase an individual’s lifetime risk of developing cancer. The organs in the field of view, i.e. breasts, esophagus, heart en lungs, are exposed to the overall highest absorbed doses and hence at highest risk. The radiation dose of a single CTPA ranges from 3 to 5 mSv, with an estimated risk of 150 excess cancer deaths per million exposures to a single CTPA.\textsuperscript{15,32,33} The risk of CT-associated cancer is especially of interest to the younger female patient, because the lifetime attributable risk -especially for breast cancer- rises exponentially with exposure at younger age.\textsuperscript{31,33}

Concerning acute PE, one of the alternative imaging methods to CTPA is ventilation-perfusion (V-Q) lung scintigraphy, which involves the simultaneous scintigraphic imaging of the pulmonary arteries and airways, at cost of an exposure to a radiation dose of 1.2 mSv.\textsuperscript{34,35} A normal V-Q scintigraphy, i.e. with no perfusion defects, virtually rules out PE with a 3-month failure rate of 0.9% (upper 95\%CI 2.3\%).\textsuperscript{35,36} A V-Q scintigraphy showing at least one segmental perfusion defect combined with a normal ventilation scan -the so called 'high-probability' lung scan- has a 85–90\% predictive value for PE.\textsuperscript{35,36} The main drawback of V-Q scintigraphy is the large proportion of non-diagnostic scan results when both perfusion as well as ventilation defects are present in the same anatomic area, being reported to occur in 28\% to 46\% patients.\textsuperscript{37} Since the PE prevalence in that specific cohort is still 10-
30%, further imaging with CTPA is warranted. Several potential solutions have been proposed to deal with this issue. For instance, by applying adjusted ruling criteria, the so called PISAPED criteria, the number of non-diagnostic V-Q scintigraphy results is likely to decrease. Limiting the number of non-diagnostic lung scans can also be achieved by performing V-Q scintigraphy only in patients with normal chest X-rays. The sensitivity and specificity of the combination of perfusion scintigraphy and chest x-ray only, i.e. without adding ventilation lung scanning, was found to be 80% to 85% and 93% to 97% respectively. Notably, only post-hoc analyses regarding both the PISAPED criteria and the Q-X combination are available, and formal outcome studies are lacking. The same is applicable for three-dimensional images acquired by single-photon emission computed tomography (SPECT), a technique that may improve V-Q scintigraphy by applying a gamma-emitting radioisotope.

Magnetic resonance pulmonary angiography

Magnetic resonance-pulmonary angiography (MRPA) is a potentially attractive method for PE imaging since it avoids the use of ionizing radiation. In addition, nephrotoxicity and contrast allergies caused by gadolinium-based contrast agents are less of a concern, especially not in young patients with normal renal function. In preliminary studies with limited sample sizes, sensitivities of 77% to 100% and specificities of 95% to 98% were observed after comparison with conventional pulmonary angiography. More recently, two larger cohort studies were performed, in which MRPA was directly compared to either CTPA or V-Q scintigraphy. Both studies confirmed the high diagnostic accuracy of MRPA for acute PE, although limitations of MRPA were exposed as well: a disturbing 25% to 30% of scans remained none-diagnostic. MRPA requires prolonged breath-holding from patients with respiratory distress. Breathing or motion artefacts and poor arterial opacification of segmental and subsegmental branches are the most prevalent reasons for a non-interpretable MRPA. Moreover, MRI may not be tolerated by patients with claustrophobia, and is contraindicated during pregnancy or in the presence of intracranial vascular clips, metal implants, and cardiac pacemakers. Taken these contraindications together, the majority of potentially eligible patients had to be excluded.
on forehand from the two studies\textsuperscript{43,44}. Finally, since there are no reports of patients being managed based on MRPA result alone, MRPA cannot yet be recommended as an alternative imaging method to CTPA in the diagnostic work-up of suspected PE.

In conclusion, CTPA is associated with an actual health risk, although the absolute risk of cancer is probably small. Nevertheless, V-Q scintigraphy as well as MRPA is associated with a considerable chance of a non-diagnostic test, resulting in the need for repeated radiological examinations with associated costs, further radiation exposure and other complications. The safety of promising alternative techniques including MRPA, X-Q scanning or SPECT is yet to be confirmed in management studies. From an individual standpoint, if a CT is justified by a strong medical indication, the associated cancer risk is small, relative to the value of the diagnostic information that can be obtained. From a population standpoint, use of CT examinations and the resultant cancer risk could be reduced by adhering closely to appropriate-use criteria. With this in mind, the patient was informed of the suspected PE and the potential risks of radiation exposure. She agreed to CTPA, which showed a large embolus in a right segmental pulmonary artery (Figure 2b). A wedge-shaped, pleural-based opacity in the right lower lobe indicated the presence of pulmonary infarction (figure 2c).

**Case 3**

The third patient is a 52-year old man with a prior history of an unprovoked acute bilateral PE 4 years ago. He had noticed a progressive sharp pain on the left side of his back with every deep breath. Initially, he thought that he had teared a muscle while painting his garden house. Since his symptoms persisted for two days and he recognized this particular pain from his first thromboembolic episode, he decided to visit his general practitioner who referred him to our outpatient clinic to rule out recurrent PE. Physical examination revealed no abnormalities. Chest-X-ray and ECG were normal as well. His pain could be provoked by firm pressure on the 7\textsuperscript{th} and 8\textsuperscript{th} left rib. Consequently, a musculoskeletal cause of the pain was judged most likely, although recurrent PE could not be ruled out yet. Both the Wells rule (1.5 points for previous PE) as well as the revised Geneva score (3 points for previous PE)
indicated ‘PE unlikely’. Because the subsequently assessed D-dimer level was 910 µg/L, the patient was referred for CTPA, which only showed one small organizing mural thrombus in a right basal segmental pulmonary artery. No intrapulmonary or ossal irregularities were observed. Since his first acute PE was confirmed in a different hospital, we had no earlier CTPA for comparison. Nonetheless, the radiologist’s final conclusion was ‘no signs of an acute pulmonary thrombus, only evidence of residual emboli’. Can we at this point safely discharge this patient without anticoagulant treatment?

Recurrent pulmonary embolism

Large trials on the diagnostic management of acute PE have not or only very sparsely included patients with suspected recurrent PE. For several reasons, diagnosing recurrent PE can be challenging. First, it has been suggested that both sensitivity and specificity of D-dimer assays for recurrent PE are decreased. Second, recurrent emboli may be difficult to differentiate from residual chronic emboli, which may persist in 20–40% of patients after an initial PE episode. In two post-hoc analyses, the safety of ruling out recurrent PE based on an unlikely clinical probability and a normal D-dimer test was evaluated. Both studies had a 0% failure rate during 3-month follow-up, but with very high upper 95% confidence limits (6.9% and 7.9% respectively) due to a relatively small sample size. A recently finished prospective trial included 516 consecutive patients with suspected recurrent PE. From these, 182 were classified ‘PE unlikely’. Based on a normal D-dimer result, 88 were left untreated. None of those 88 patients was diagnosed with recurrent DVT or PE in the subsequent three months (0%; 95% CI 0.0–3.4%). On the other hand, recurrent VTE was diagnosed during three months of follow-up in 3.2% (95% CI 1.5–5.9%) of the patients with a negative CTPA result, which is more than twice as high than the 1.2% (95% CI 0.8–1.8%) in a population with mostly first PE. Whether this discrepancy should be explained by failure of the CTPA or an intrinsic higher thrombotic risk is a matter of debate. In case of a normal CTPA but still a high clinical suspicion of recurrent PE, either ultrasonography of the legs or conventional angiography can be considered, although there is no evidence available to validate such a strategy. Perhaps the most pragmatic approach would be to
closely monitor those patients in an in- or outpatient setting, dependent on their condition. The latter strategy was also applied to our patient: based on the discrepancy between the location of the pain and the location of the chronic embolus, we judged the presence of acute recurrent PE to be very unlikely and prescribed him an NSAID to ease to pain which we considered to be of musculoskeletal origin. We advised his general practitioner to monitor the course of the symptoms in the following days and arranged a follow-up visit at our outpatient clinical two weeks later. At that time, the pain had completely resolved and he had stopped taking NSAIDs. Six months after initial presentation, the patient was doing well and did not report any new symptoms of recurrent DVT or PE in the intervening period.

**Conclusion**

A diagnostic strategy starting with the assessment of clinical probability and followed by either D-dimer testing or CTPA is a safe and effective management strategy for patients with a suspected first or recurrent acute PE. Strictly adhering to this algorithm that has been validated in many high quality trials totalling well over 5,000 consecutive patients will limit the number of necessary imaging tests by at least 30% with an associated reduction in healthcare costs and complications.

**Authorship**

M.V.H. and F.A.K. wrote and reviewed the manuscript and reviewed and approved each other’s sections.

**Conflict-of-interest disclosure**

The authors have no relevant conflict of interest to disclose.
References


Table 1: Clinical decision rules for suspected acute pulmonary embolism

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<td>Heart rate ≥95/min</td>
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<td>Active malignancy</td>
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<td>Unilateral lower limb pain</td>
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**Figure legends**

Figure 1: Preferred diagnostic algorithm for clinically suspected acute pulmonary embolism.

PE=pulmonary embolism, CDR= clinical decision rule, HS=highly sensitive, MD-CTPA= multi-row detector computed tomography pulmonary angiography

Figure 2: CTPA of patients from case 1 (figure 2a, arrow indicates acute thrombus in segmental artery to the right lower lobe), case 2 (figure 2b, despite breathing artefacts clear visualisation of acute PE in right segmental artery; figure 2c, arrow shows a wedge-shaped peripheral consolidation indicative of pulmonary infarction) and case 3 (figure 2d, arrow points out an organizing mural thrombus in a right basal segmental pulmonary artery).
Figure 1

Suspected acute PE

- CDR likely
  - MD-CTPA
    - Positive → PE confirmed
    - > 500 µg/L → Negative
  - CDR unlikely
    - HS D-dimer
      - ≤ 500µg/L → PE ruled out
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