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Imaging Tests in the Diagnosis of Pulmonary Embolism

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Abstract and Introduction

Abstract

Imaging modalities play an essential role in diagnosing pulmonary embolism (PE). Clinical outcome studies demonstrated that PE can be safely ruled out in patients with unlikely clinical probability in combination with a normal D-dimer test result; in all other patients additional imaging is needed. The aim is to accurately confirm or rule out the diagnosis of PE, after which, if indicated, anticoagulant treatment can be initiated. Various diagnostic tests are available, and this article reviews the different imaging techniques in patients with suspected PE. Computed tomographic pulmonary angiography (CTPA) is the imaging test of choice because of its high sensitivity and specificity. Compression ultrasonography and ventilation perfusion scintigraphy are reserved for patients with concomitant suspicion of deep vein thrombosis or contraindication for CTPA. Furthermore the diagnostic process in patients with clinically suspected recurrent PE, PE during pregnancy, and PE in the elderly and in patients with malignancy are discussed.

Introduction

Suspicion of pulmonary embolism (PE) is a common condition in daily clinical practice. PE and deep venous thrombosis (DVT) together with venous thromboembolism (VTE) are common cardiovascular disorders and potentially fatal. The signs and symptoms of PE are diverse and may include dyspnea or (pleuritic) chest pain. In ~20% of patients presenting with suspicion of acute PE, the diagnosis can be confirmed.[1] An incidence of 0.6 to 1.2 per 1000 persons per year has been reported.[2]

Objective diagnostic testing is important because of the potential morbidity and mortality if the diagnosis is missed, and because of the bleeding risk associated with anticoagulant treatment. The 3-month mortality ranges from 6 to 11% in patients with hemodynamically stable PE to 30% in unstable patients.[3] Several tests are available for the diagnosis of PE. Formerly, the reference standard for the diagnosis of PE was pulmonary angiography. This invasive technique, however, is cumbersome to the patient and is also expensive. It has thus been replaced by computed tomographic pulmonary angiography (CTPA). The diagnostic strategy at present starts with the combination of a clinical decision rule (CDR) and a D-dimer test, followed, if needed, by imaging tests including CTPA or ventilation perfusion (V/Q) scintigraphy ([Fig. 1]). Imaging is required in the case of a CDR indicating that PE is likely or an elevated D-dimer test. This review discusses the different imaging modalities in diagnostic management of acute PE. Also discussed are the diagnostic possibilities in patients with clinically suspected recurrent VTE, suspected PE during pregnancy, or malignancy and in the elderly patient.

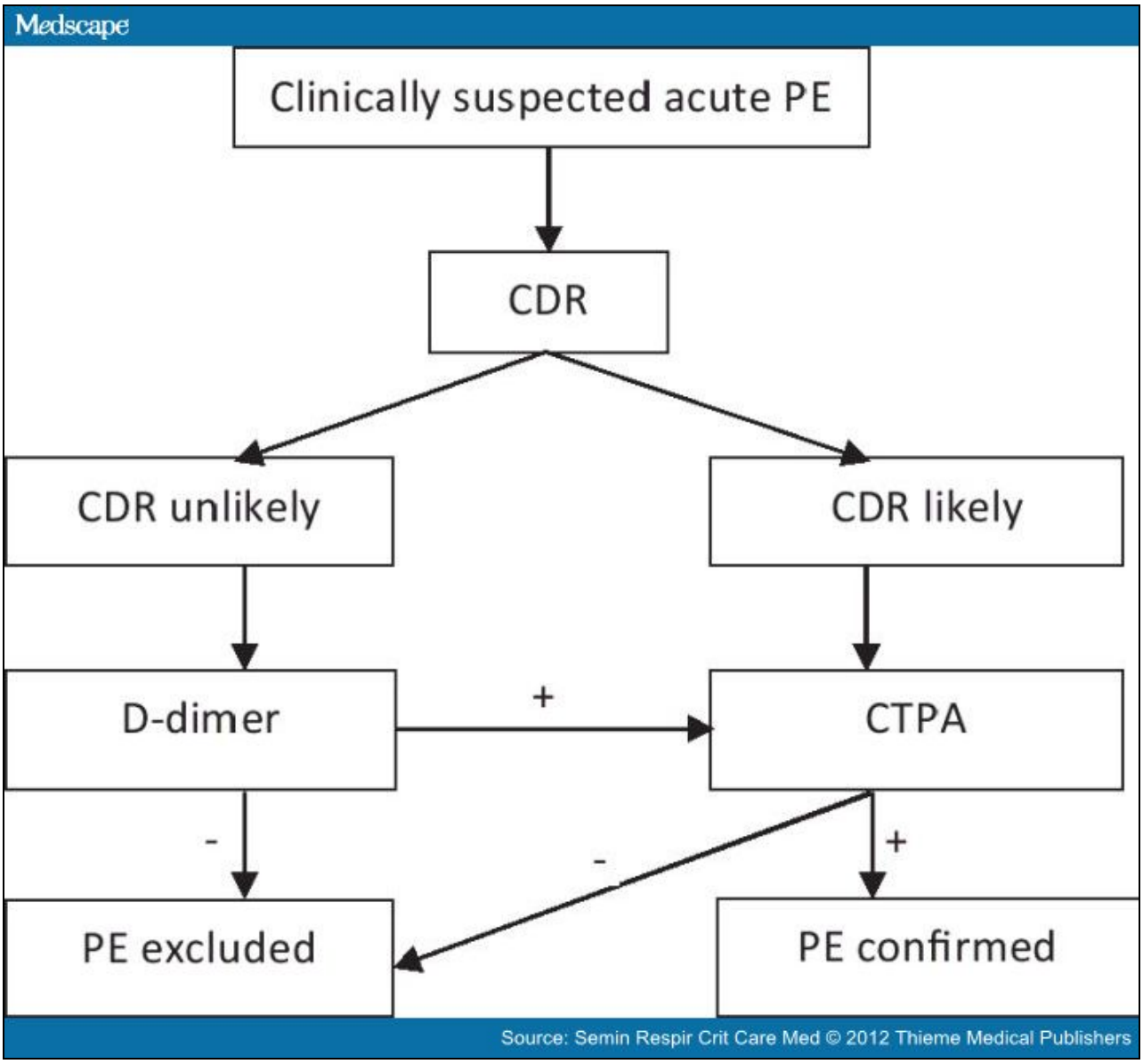

Figure 1. Flowchart of the diagnostic strategy in patients suspected of having pulmonary embolism. PE, pulmonary embolism; CDR, clinical decision rule; D-dimer (+), elevated D-dimer concentration; D-dimer (−), normal D-dimer concentration; CTPA, computed tomographic pulmonary angiography.

Computed Tomography Pulmonary Angiography

Multirow CTPA is the first-line imaging test in patients suspected for acute PE. After applying intravenous contrast material, CTPA can be performed within 4 to 6 seconds, and PE can be diagnosed in the case of interruptions of the contrast material in the pulmonary veins. With the first single-slice computed tomographic (CT) scanners, sensitivity was not optimal, especially in patients with a high pretest probability. A significant increase in sensitivity was seen with the introduction of multi-detector row CT scanners. CTPA studies using the multislice technique showed a high sensitivity (96 to 100%) and specificity (97 to 98%), and they have replaced invasive pulmonary angiography as the reference test for acute PE.[4] Sensitivity and specificity, depending on the location of the emboli, vary from 20 to 30% for small subsegmental emboli using single-row CT up to 95% for segmental, lobar, and central emboli using multislice CTPA.[5–7]

Several follow-up studies have demonstrated that it is safe to withhold anticoagulant treatment if CTPA has excluded acute PE. In only 1.3% of the patients with a high pretest probability of PE but a negative CTPA, a VTE was diagnosed during 3-month follow-up.[8] In a meta-analysis these results were confirmed and showed a high negative predictive value of a normal CTPA result (98.8%; 95% CI 98.2 to 99.2).[9]

A study from 2007 compared diagnostic test results of CTPA with V/Q scintigraphy and revealed comparable results with a

prevalence of PE of 14 to 19% and a 0.6 to 1.0 incidence of recurrent VTE after normal V/Q scan during 3-month follow-up[10] The most important advantage of CTPA over V/Q scintigraphy is the low number of inconclusive test results (0.9 to 3.0 vs 28 to 46%) and the possibility to achieve an alternative diagnosis that can explain the complaints of the patients, including pneumonia, malignancy, or aortic dissection.[10] With the development of the CTPA technique, more and smaller, subsegmental emboli may become visualized. The clinical relevance of these emboli is yet uncertain.[11] Although observational research suggests that treated as well as untreated patients have a good prognosis, the clinical relevance is not clear at this moment given the lack of good randomized outcome studies.[11–13] Disadvantages of CTPA are the relative contraindications in patients with allergy to iodinated contrast material, occurring in 0.7% of patients, and in patients with impaired renal function. Contrast-induced nephropathy after CTPA is estimated to occur in 8.9 to 12% of patients.[14–16] Overuse of CTPA, without assessment of the pretest probability, may lead to a high rate of more than 90% of negative results.[17] Finally, the radiation dose of a single CTPA range from 3 to 5 mSv, with an estimated cancer risk of 150 excess cancer deaths per million resulting from exposure to a single CT scan for suspected PE.[4] The cancer risk is more of interest on the younger, female patient during reproductive age.

Ventilation Perfusion Scintigraphy

V/Q lung scan for many years was the first-line imaging test instead of classical pulmonary angiography, before the introduction of CTPA. Scintigrams of pulmonary perfusion (vascularization) and ventilation are performed after application of intravenous radioactive isotopes labeled with technetium 99 m. Test results can be classified in three categories: normal, high probability, and non-high probability. A normal perfusion-scintigraphy result excludes PE with a 0.9% failure rate (upper 95% CI 2.3%).[18] A high-probability test result, defined as at least one segmental defect on perfusion scintigraphy in combination with a normal ventilation scintigraphy, is diagnostic for PE with an 85 to 90% predictive value and specificity of 97%.[19,20] All other test results, which may be 28 to 46% of all patients presenting with suspected acute PE, are inconclusive, and further imaging is required in these patients. The latter is the major problem of ventilation-perfusion scintigraphy.[10]

The amount of nondiagnostic scintigrams may decrease if this test is used in patients with a normal x-ray result. Recent studies investigated the combination of perfusion scintigraphy and chest x-ray, without adding ventilation scintigraphy.[21–23] This combination seems reliable in detecting or excluding PE with a sensitivity of 80 to 85% and a specificity of 93 to 97%, depending on the kind of criteria used, and this was comparable to the diagnostic accuracy of V/Q scintigraphy in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study. This combination also has lower costs and a lower radiation dose compared with CTPA.[22] This technique could be an alternative to the current imaging modalities, especially in young women, due to the increased risk of breast cancer by radiation and because of the low amount of comorbidity in this specific group of patients.[24] The positive predictive value including clinical probability, D-dimer, chest x-ray, and perfusion scintigraphy in women below 50 years of age was 82 to 100%.[25] Additional prospective studies are necessary before implementation of this diagnostic strategy in routine care is endorsed.

Pulmonary Angiography

Catheter pulmonary angiography was traditionally regarded as the reference test for PE. Nevertheless, the 3-month VTE incidence after a normal pulmonary angiography result has been reported to be 1.7% (95% CI 1.0 to 2.7) with 0.3% fatal PE (95% CI 0.02 to 0.7).[7] Due to the invasive character, including right heart catheterization and injection of contrast material, and the current availability of noninvasive diagnostic imaging modalities like CTPA and V/Q scintigraphy, catheter pulmonary angiography now has an insignificant role.[26]

Compression Ultrasonography of the Lower Extremities

In ~13 to 15% of patients with suspected PE, a proximal DVT can be found.[27] This figure may increase fourfold in patients with clinical signs and symptoms of DVT.[28] Because treatment with anticoagulants is the same in patients with proven DVT as in proven PE, further imaging by V/Q scintigraphy or CTPA could be avoided in patients with proven DVT.[29] However, the sensitivity of compression ultrasonography in patients with suspicion of acute PE is limited to 23 to 29%, and false-positive compression ultrasonography will result in unnecessary treatment in 2 to 3% of patients.[30,31] Moreover, ultrasonography as the first-line imaging test in all patients with suspected PE is not cost effective.[28] It has been suggested that negative CTPA is not enough for safe exclusion of PE in a high-risk population, and additional ultrasonography of the legs should be performed in patients with negative CT results. Recent studies have shown that in the case of a suspected PE and a negative CTPA, compression ultrasonography of the lower extremities for identifying DVT has no additional value. The negative predictive value after normal CTPA as sole test was 98.8% versus 98.9% after normal CTPA followed by negative compression ultrasonography.[9]

In conclusion, compression ultrasonography is only indicated in patients with clinical signs of DVT or in patients with suspicion

of PE and a contraindication for CTPA.

Magnetic Resonance Angiography

There is growing evidence that magnetic resonance angiography (MRA) may be an alternative diagnostic tool in cases of suspected acute PE.[32] MRA is a modality without ionizing radiation and potentially provides an alternative for patients with contraindications, including allergy to iodinated contrast material, because of the use of less nephrotoxic gadolinium contrast. Some studies with a limited number of patients showed sensitivity of 77 to 100% with 95 to 98% sensitivity.[32–34] However, in the recent published PIOPED III study in which MRA was performed in 371 patients with suspected acute PE, a 25% rate of technically inadequate images was observed. The sensitivity of MRA was only 78% with a specificity of 99%.[35] Moreover, sensitivity decreased from 79% for main or lobar PE to 50% for segmental and 0% for subsegmental PE.[35] Furthermore, a large proportion of patients were not eligible or declined to participate. Sanchez et al studied MRI performance for acute PE diagnosis by reference to 64-detector CTPA in 300 patients and demonstrated a high specificity (99 to 100%) with a sensitivity of 79 to 85% for conclusive MRI results. However, 28 to 30% of the included patients had an inconclusive MRI result. Sensitivity was higher in proximal (98 to 100%) than in segmental (68 to 91%) and subsegmental PE (21 to 33%).[36]

In conclusion, MRA is not yet an optimal alternative in the diagnostic process of suspected PE.

Further Alternative Imaging Tests

Dual-energy CTPA distinguishes different absorption characteristics of different tissue types. It visualizes blood clots in the pulmonary arteries and will also give information of perfusion defects without additional radiation exposure compared with CTPA. Sensitivity of CTPA might improve using dual energy CTPA but needs further validation in outcome trials.[37,38]

Electrocardiographically gated CTPA can differentiate between cardiac events and PE and may be of use in patients presenting with thoracic pain and suspected PE, cardiac events, or aorta dissection. However, more contrast material is needed, and the radiation dose is higher compared with CTPA.[39]

Three-dimensional images acquired by single-photon emission computed tomography (SPECT) using a gamma-emitting radioisotope may improve V/Q scintigraphy and has a lower radiation dose.[40] A few accuracy studies are published. Miles et al reported a 95% agreement between SPECT V/Q scintigraphy and CTPA data for the diagnosis of PE and a sensitivity of 83% with specificity of 98% for SPECT V/Q.[41] Another study showed a superior diagnostic performance of V/Q SPECT to planar V/Q scintigraphy with a sensitivity of 100% and specificity of 87% for SPECT V/Q.[42] But formal outcome studies in acute PE are lacking.

Imaging in Specific Patient Groups

Recurrent PE

The consequences of identifying a recurrent PE are major, due to the indication of usually lifelong treatment with anticoagulants with the attendant risk of bleeding.

It has been estimated that in more than 50% of the patients with prior PE, residual emboli are visible on V/Q scintigraphy or CT-PA 6 months after initial diagnosis.[43] The diagnosis of suspected recurrent PE can be challenging because it may be difficult to differentiate between the former (residual) thrombus and new emboli. VTE failure at 3-month follow-up after negative CTPA in patients suspected of recurrent PE was 0.8% (95% CI 0.02 to 4.3).[44] CTPA is the first-choice imaging test, and it could be considered for repetition after 6 months of treatment in patients with high risk of recurrence to provide new baseline imaging.[45] However, the patient will receive additional radiation due to extra imaging.

Pregnancy

The risk for VTE is increased during pregnancy and puerperium due to immobilization, venous stasis or cesarean section. The diagnostic value of CDRs and D-dimer testing has not been validated well in pregnant patients, and in these patients imaging is required as a first-line test. In case of a suspected acute PE during pregnancy, the risk of inadequate diagnostics and withholding treatment if necessary is greater than the risk of radiation to the fetus. Diagnostic imaging has to be done and has to be finished. Most experience in pregnant patients exists with V/Q scintigraphy. The number of high-probability scans in pregnant women with suspicion of acute PE was low with 1.8% in a retrospective study, compared with 10% without pregnancy; the percentage of normal perfusion scans was high, 74%, whereas 25% of the patients had an inconclusive test result. Additional imaging is necessary in this latter patient group, exposing them to further radiation.[46] Although pregnant women are frequently excluded from clinical trials using CTPA, the calculated radiation dose of a CTPA scan is lower for a fetus compared with V/Q scintigraphy,[47] and levels are below those thought to induce neurological harm to the fetus.[48]

Furthermore, CTPA will give fewer inconclusive test results.[49] In cases of clinical signs of DVT, it is possible to start with compression ultrasonography; if DVT is identified, anticoagulant treatment is indicated and CTPA or V/Q scanning can be withheld.

Elderly

The prevalence of PE increases markedly with age to ~1% per year in the elderly.[50] The diagnosis in the elderly is difficult because of higher amounts of comorbidity. Cardiopulmonary conditions may mimic clinical presentation of PE. Furthermore, impaired renal function and age may unfavorably influence the characteristics of diagnostic tests for PE. Age reduces the clinical usefulness of D-dimer and V/Q lung scan. D-dimer allows excluding PE in only 5% of patients aged 80 and older, compared with 60% younger than 40. Similarly, the rate of inconclusive V/Q lung scans is almost twice as high (58%) in patients older than 70 compared with patients younger than 40 (32%).[51]

Douma et al studied an age-adjusted D-dimer cutoff value defined as age × 10 in patients above 50 years of age. Of 5132 included patients, a 5 to 6% increase was found in D-dimer levels below the cutoff value, and in patients above 70 years of age, the increase was even 13 to 16%. The failure rates during 3-month follow-up were low (0.2 to 0.6%). It seems safe to exclude PE in a larger group of patients without the need for CTPA.[52]

Malignancy

Patients with malignancy and particularly with metastatic disease have a four- to sevenfold higher risk of thrombosis compared with patients without cancer, caused by prothrombotic effects of the tumor and also because of treatment, particularly with surgery, use of a central venous catheter, and chemotherapy. Otherwise, ~20% of patients presenting with VTE have active cancer, associated with reduced survival.[53] Patients with active cancer often have a high clinical suspicion of PE, and the value (specificity) of D-dimer testing is reduced, leading to an increased need for imaging. In an elegant subanalysis of the Christopher Study[8] the proportion of patients presenting with suspicion of PE and with active malignancy with indication for CTPA was 90% compared with 68% in the overall population, and in 31% of these patients PE could be confirmed.[54]

Beside patients presenting with suspicion of PE, incidental VTE is found on staging scans, up to 6.3% of all oncological patients at reevaluation of the scans versus 1.5% PE in a population without malignancy.[55] The routine use of modern CT scanners has led to an increased detection of incidental PE, in particular in patients with cancer. Patients diagnosed with and treated for incidental PE have similar high rates of recurrent VTE, bleeding complications, and mortality, as compared with oncology patients who develop symptomatic PE.[56]

Conclusion

Imaging modalities play an important role in detecting or excluding PE and diagnosing PE is complicated. In patients with clinically suspected acute (recurrent) PE, CTPA is the first-choice imaging modality with a high positive and negative predicting value. V/Q scintigraphy can be used as an alternative technique, for example, in patients with a contraindication for CTPA such as allergy to intravenous contrast material or impaired kidney function. This latter technique yields a substantial amount of inconclusive test results. Compression ultrasonography can be used in the presence of suspicion of deep vein thrombosis. Tests such as MRA, dual energy CTPA, and perfusion scintigraphy combined with chest x-ray need further validation before implementation in clinical care. In patients with a suspicion of PE during pregnancy, CTPA as well as V/Q scintigraphy could be used, but radiation to the mother and fetus is a concern.

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