A more granular view on pulmonary embolism

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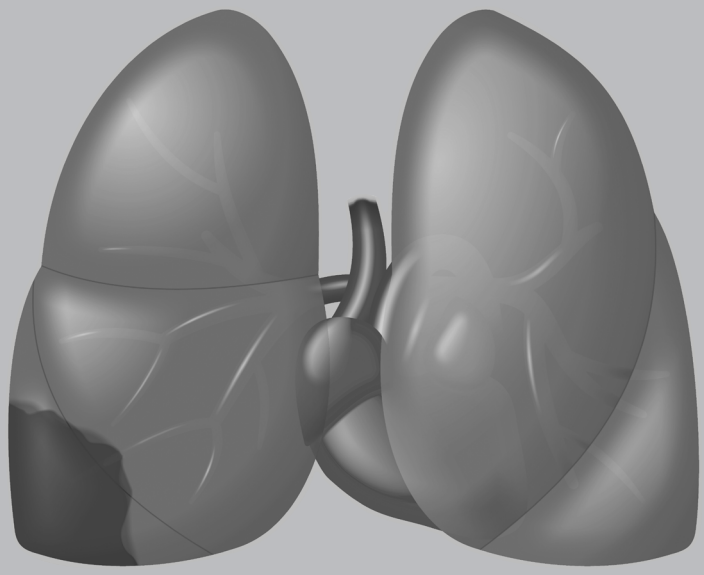
PART I

Diagnostic Management of Acute Pulmonary Embolism



CHAPTER 2

Update on diagnostic techniques for the diagnosis of pulmonary embolism

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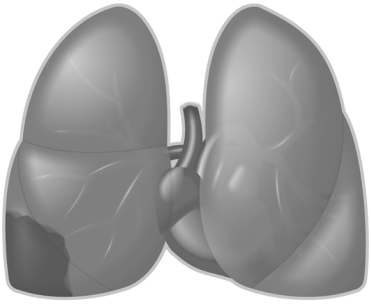

ABSTRACT

Importance of the field

The clinical suspicion of acute pulmonary embolism (PE) is frequently raised. However, the diagnosis PE is confirmed in only 20-30% of these patients. The high incidence in addition to the potential harm from false positive or negative diagnostic decisions, underlines the importance of a standardized diagnostic algorithm with high sensitivity as well as specificity.

Areas covered in this review

This article reviews the diagnostic tests for the diagnosis of PE.

What the reader will gain

This review provides an overview of the different clinical decision rules (CDRs), D-dimer tests and imaging techniques in patients suspected of PE. Furthermore, the diagnostic process in patients with clinically suspected recurrent PE, suspicion during pregnancy and new research areas will be discussed.

Take home message

Various diagnostic tests are available to detect or exclude PE with good accuracy. CDRs and D-dimer tests play an important role in the exclusion of PE. Neither is sufficient as single test, but the combination of an "unlikely" clinical prediction and a normal D-dimer test result safely excludes PE. In case of a high CDR score and/or an elevated D-dimer concentration, additional imaging is necessary with multi-slice computed tomography as first choice modality.

INTRODUCTION

Venous thromboembolism (VTE), including both pulmonary embolism (PE) and deep venous thrombosis (DVT), is the third most common cardiovascular disorder in industrialized countries and in addition, a potentially fatal one.[1] The incidence of PE is 0.6-1.2 per 1000 inhabitants per year.[2] The diagnosis of PE can only be confirmed in 20-30% of the patients with a clinical suspicion of PE.[3,4] The signs and symptoms of PE are diverse and non-specific. Clinical suspicion of PE arises in approximately 80% of patients with eventually proven PE with presentation of sudden onset of dyspea without an apparent cause. Other symptoms are acute (pleuritic) chest pain worsening with breathing (present in 52%), or less frequent syncope, cough or hemoptysis.[5] Common signs are tachypnea, tachycardia or the presence of a swollen and red leg. Objective diagnostics are very important, because of the increased risk on morbidity and mortality when the diagnosis is missed, and because of the risk of bleeding in case of anticoagulant use. Mortality due to PE if left untreated is not precisely known. One small study in 1960 reported an outcome of 26% fatal PE in these patients.[6] The 3-month mortality ranges from 6-11% in patients with hemodynamically stable PE on anticoagulant treatment, to approximately 30% in hemodynamically unstable patients receiving treatment for PE.[7]

Various diagnostic tests are available to confirm or exclude PE. Nowadays, diverse tests have been integrated in diagnostic algorithms. The combination of a clinical decision rule (CDR), which provides a standardized determination of the clinical probability of the disease based on medical history and physical examination, and a D-dimer test comprise the initial diagnostic steps in patients with suspected PE. Depending on the results of these tests, additional imaging testing should be performed, including conventional angiography, computed tomography pulmonary angiography (CTPA), ventilation perfusion (V/Q) scintigraphy or magnetic resonance angiography (MRA).

In this review, the role of the CDR, D-dimer test and different imaging modalities in the diagnostic management of patients with suspected PE is discussed. Finally, new areas of research are explored.

CLINICAL DECISION RULES

The diagnostic management of acute PE represents a challenge, since the signs and symptoms of PE are various and largely nonspecific (e.g. dyspnea, pleuritic chest pain and palpitations). Clinical probability by implicit evaluation of an experienced clinician has a reasonably good accuracy but decreases with less experienced physicians and is subject of interobserver variability.[8-10] To simplify and standardize the diagnostic process, several CDRs have been developed to evaluate the pretest probability of patients

suspected of having PE. The best validated and widely integrated decision rules are the original Wells rule, the Geneva score and the revised Geneva score.[11-13] The original Wells rule is composed of seven items, obtained from medical history and physical examination and one subjective variable, by which the physician must consider the possibility of an alternative diagnosis for the patient's complaints (Table 1).[11] This latter variable carries a major weight in the score and is often debated because of its subjective nature.[14] On the other hand, it permits the clinician to use other test results and symptoms that are not considered in the score.[9] The Geneva score consist of 13 objective items. The major

Table 1. Clinical decision rules.

The Geneva score [12]		**Revised Geneva score[13]**			**Wells rule[11]**		
Items	**Score**	**Items**	**Original score**	**Simplified score**	**Items**	**Original score**	**Simplified score**
Previous PE or DVT	2	Previous DVT or PE	3	1	Previous PE or DVT	1.5	1
Heart rate > 100/min	1	Heart rate - 75 – 94/min - ≥95/min	 3 5	 1 2	Heart rate >100/ min	1.5	1
Recent surgery	3	Surgery or fracture within 1 month	2	1	Surgery or immobilization < 4 weeks	1.5	1
Atelectasis	1	Hemoptysis	2	1	Hemoptysis	1	1
Elevated hemidiaphragm	1	Active malignancy	2	1	Active malignancy	1	1
PaCO2* - < 4.8 kPa - 4.8-5.19 kPa	 2 1	Unilateral lower limb pain	3	1	Clinical signs of DVT	3	1
PaO2* - < 6.5 kPa - 6.5-7.99 kPa - 8-9.49 kPa - 9.5-10.99 kPa	 4 3 2 1	Pain on lower limb deep vein palpation and unilateral edema	4	1	Alternative diagnosis less likely than PE	3	1
Age - 60-79 years - ≥ 80 years	 1 2	Age > 65 years	1	1			
Clinical probability		**Clinical probability**			**Clinical probability**		
Low	0-4	Low	0-3		Low	< 2	
Intermediate	5-8	Intermediate	4-10		Intermediate	2-6	
High	≥ 9	High	≥ 11		High	> 6	
		Dichotomized			**Dichotomized**		
		PE unlikely		≤ 2	PE unlikely	≤ 4	≤ 1
		PE likely		> 2	PE likely	> 4	> 1

PE: pulmonary embolism; DVT: deep vein thrombosis; *breathing room air.

limitation of this score is the need of a blood gas analysis while breathing room air.[12] The revised Geneva rule contains only objective variables but does not require blood gas analysis (Table 1).[13]

The clinical probability can be categorized in low, intermediate or high clinical probability, corresponding to a prevalence of PE of 4-10% in the low, 21-38% in the intermediate, and 67-81% in the high clinical probability cohort for the three rules mentioned above.[11-13]

To facilitate more practical clinical use, the Wells rule and the revised Geneva score have been dichotomized (unlikely or likely clinical probability). The Wells rule has a higher interobserver agreement using the dichotomized rule than using a three level scheme.[15] Since these CDRs have never been directly compared in a prospective outcome study, there is no evidence to prefer one above another and a recent meta-analysis showed similar accuracy for the available CDRs.[16] The revised Geneva score and Wells rules have also been simplified recently, to facilitate computation and memorization, by assigning one point to all items, with the exception of the heart rate in the simplified revised Geneva score (Table 1). The prevalence of PE was 12% for both rules in the "unlikely" cohort and 47% and 42% in the "likely" cohort for the Wells rule and revised Geneva score respectively.[17,18] However, at present, these simplified rules have only been studied retrospectively.

Of note, the CDRs mentioned above have been validated for outpatients and only the combination of the Wells rule and D-dimer testing has been studied in (a small number of) inpatients which appeared to be safe.[19]

Importantly, a CDR alone is not reliable enough to exclude or confirm the diagnosis of PE, and additional testing is always necessary. For instance, the negative predictive value (NPV) of a Wells rule indicating low probability is only 90-94%. Also, the positive predictive value of high Wells rule is in the order of 70-85%. In conclusion, several CDRs exist to aid the physician in estimating the probability of the presence of acute PE, however, treatment decisions cannot be taken on the basis of a CDR alone.

D-DIMER TESTS

The formation of a thrombus is associated with elevated fibrinolytic activity leading to the production of fibrin degradation products including D-dimers.[20] Therefore, the presence of an elevated D-dimer concentration is an indication for the presence of thrombosis. D-dimer concentration also increases in several other conditions, including malignancy, inflammation, postoperative state, pregnancy, reduced creatinine clearance and increasing age which leads to a low specificity.[21] Hence, the diagnostic strength of D-dimer tests in patients with suspected acute PE lies therefore in ruling out this disease.

Nowadays, several techniques exist to measure the D-dimer concentration. Most commonly used are the enzyme-linked immunosorbent assays (ELISA), with high sensitivity of 95% (95% CI 84-99) and a moderate specificity of 50% (95% CI 29-71).[22] Quantitative latex agglutination assays are frequently used, with a sensitivity and specificity of 95% (95%CI 88-98) and 50% (95%CI 36-64) respectively. Finally, the whole-blood erythrocyte agglutination tests have a sensitivity of 87% (95%CI 64-96) and a specificity of 69% (95%CI 48-84) to detect PE.[22] The basic principle of all tests is the use of D-dimer specific antibodies, but the tests differ on several aspects. First, in general, a test has a moderate sensitivity and specificity or a high sensitivity at the cost of a lower specificity. In daily practice, especially the high-sensitive D-dimer tests are recommended because of the associated high NPV of a normal test result. Of note, the sensitivity of the D-dimer test is dependent of the location of the thrombus. While in segmental, lobar and central pulmonary emboli the sensitivity is 93%, sensitivity decreases to 50% in case of sub-segmental emboli.[23] Second, quantitative as well as qualitative tests are available. A major disadvantage of the qualitative D-dimer tests is the moderate inter-observer variability (kappa=0.65), especially in case of an intermediate test result (kappa=0.04).[24] For this reason, the use of these tests is discouraged. Third, the time to get a test result differs; varying from 35 minutes (ELISA) to less than 5 minutes (full-blood agglutination tests).

Beside the regular D-dimer assays, so-called point-of-care D-dimer tests have been evaluated. Despite the advantage of an immediate test result, most of these tests are qualitative. The SimpliRed point-of-care D-dimer test, a type of whole-blood agglutination assay, has a sensitivity of 82-86% and a specificity of 70-72%.[22] A second quantitative point–of-care D-dimer test, the CARDIAC D-dimer test, had a promising sensitivity of 96.6% with a specificity of 60.8% in a study evaluating patients with suspected DVT.[25] The potential role of point-of-care D-dimer tests in the diagnostic management of suspected PE should be further evaluated in future prospective management studies.

Although the diagnostic strength of the D-dimer tests is not sufficient to confirm or exclude the presence of PE in every patient, it can be used to safely rule out PE in certain patient categories with non-high pretest probability, assessed by a formal CDR. A recent meta-analysis demonstrated an incidence of VTE of 0.3% (95%CI 0.04-1.0%), resulting in a NPV of 99.7% (95%CI 99.0-100%) during 3-month follow-up in patients with clinically suspected PE and an "unlikely" CDR and a normal D-dimer concentration.[26]

IMAGING TECHNIQUES

Conventional pulmonary angiography

Catheter pulmonary angiography is traditionally regarded as the reference imaging test in patients suspected of having PE.[27] However, the 3-month incidence of recurrent

VTE after a normal pulmonary angiography has been reported to be 1.7% (95%CI 1.0%-2.7%).[28] An important disadvantage is the invasive character of this investigation, with right heart catheterization and injection of contrast material. With the availability of the V/Q-scan and CTPA, the role for invasive pulmonary angiography nowadays is negligible.

Ventilation-perfusion scintigraphy

Before the introduction of CTPA, V/Q scintigraphy has replaced invasive pulmonary angiography for several years. This non-invasive technique entails scintigraphic imaging of pulmonary perfusion by intravenous albumin aggregates labeled with technetium 99 m and a ventilation scan imaging (Figure 1). The scintigrams can be classified in three categories: normal, high probability and non-high probability. A normal perfusion scan excludes the diagnosis of PE (3-month VTE failure rate of 0.9%; upper 95%CI 2.3%).[29] A high probability lung scan (i.e. at least one segmental defect on the perfusion scan, combined with a normal ventilation scan) has a positive predictive value of 85-90% and a specificity of 97% (95% CI: 96-98) for PE.[8,30] The major problem of the V/Q imaging technique is that the scintigram is non-diagnostic (non-high probability) in up to 30%-70% of the patients requiring further investigation.[8,31] The non-diagnostic number may decrease if the V/Q technique is used in patients with a normal chest X-ray result. Furthermore, the nucleated gas needed to perform a ventilation scan may not always available. Several studies explored the replacement of the ventilation scan by chest X-ray.[32-34] Perfusion scintigraphy combined with chest radiography had a sensitivity of 84.9% and a specificity of 92.7% which was similar to the diagnostic accuracy to V/Q scintigraphy in the PIOPED II study and 20.6% of the patients had a non-diagnostic result.[33] This strategy

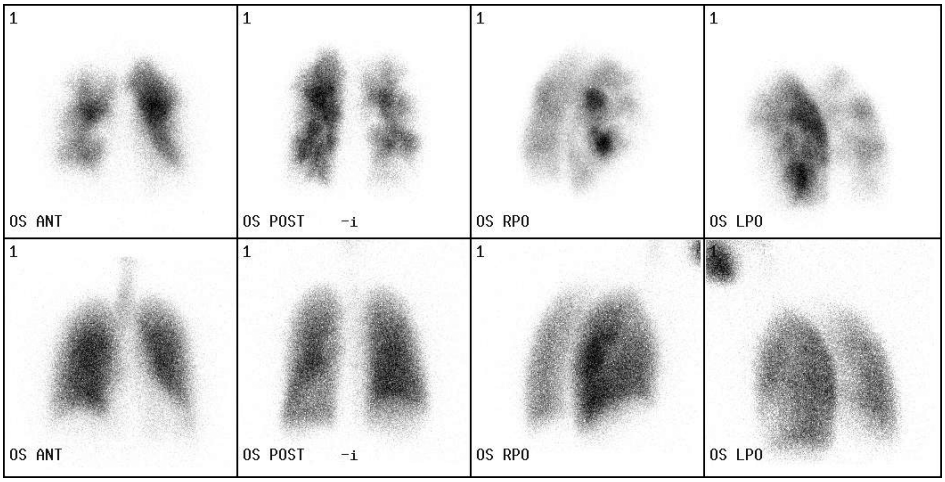

Figure 1. Ventilation perfusion scintigraphy showing multiple perfusion defects (upper panels) and homogenous ventilation (lower panels) diagnostic for pulmonary embolism.

has the advantage of lower costs and radiation dose. Using the PISAPED criteria for interpretation of the lung scan, the number of non-diagnostic results decreased compared to V/Q scanning.[33,34]

Young women might benefit from a strategy including chest X-ray and perfusion scintigraphy as alternative for CTPA because of the concern of radiation exposure to the breasts in this particular patient cohort.[35,36] The positive predictive value of a strategy including clinical probability, D-dimer, chest X-ray and perfusion-scintigraphy in woman younger than 50 years, has been shown 82% and 100% in two retrospective cohorts.[37] Patients with an intermediate probability result still require CTPA. However, the proportion of intermediate results in this particular group of patients is expected to be lower due to less co-morbidity in comparison with the average population suspected of PE.[32] Nevertheless, this strategy needs a prospective validation before it can be generally applied.

Computed tomography

Currently, multi-slice CTPA is the first-line imaging test for acute suspected PE. CTPA is very accurate in excluding or demonstrating pulmonary emboli (Figure 2,3). With the current scanners, CTPA can be performed within 4-6 seconds during breath-holding, acquiring thin 0.5-1 mm slices that can be reconstructed to 2-4 mm slices for evaluation on the post-processing workstation. Single or two-row detector contrast CTPA has a sensitivity of 86% (95%CI 80-92) with a specificity of 94% (95%CI 91-96).[38] The sensitivity of CTPA is depending on the location of the embolus; 89% for main, lobar or segmental PE and only 21% for distal subsegmental PE.[39] The PIOPED II study, using multi-slice CTPA showed a sensitivity of 83% with a specificity of 96%.[40] Other studies showed higher sensitivity using multi-detector row CTPA varying from 96 to 100%.[41,42] Since the introduction of multi-slice CTPA, the sensitivity has increased and according to expert panels, the multi-detector row CTPA technique fulfilled the conditions to replace pulmonary angiography as the reference test for acute PE.[43] CTPA, compared to V/Q scintigraphy, showed a similar prevalence of PE (19 vs 14%) and a similar incidence of recurrent VTE during a 3-month follow-up (0.6 vs. 1.0%).[31] Important advantages of CTPA over V/Q scintigraphy are the low number of inconclusive investigations (0.9-3.0% vs. 30-70% for V/Q scintigraphy)[3,31] and the possibility of finding an alternative diagnosis such as aortic dissection, pneumonia or pneumothorax.[39,43] With the evolvement of this technique, new challenges arise like the increased accuracy for smaller, subsegmental emboli with uncertain clinical relevance.[44] Multi-slice CTPA seem to increase the proportion of patients diagnosed with subsegmental PE without lowering the 3-month risk of thromboembolism in patients without PE, suggesting that treatment of subsegmental PE might be redundant.[45] Disadvantages of this technique include the relatively contra-indication in patients with renal insufficiency or allergy to iodinated contrast material, allergic contrast reactions occur in about 0.7% of patients.[46] Two studies have reported

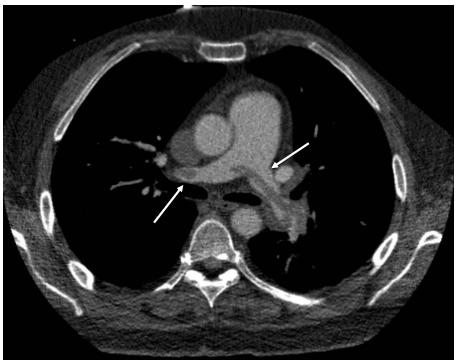

Figure 2. Computed tomography pulmonary angiography (CTPA) of patient with saddle embolus. Large central pulmonary emboli are well recognizable by CTPA.

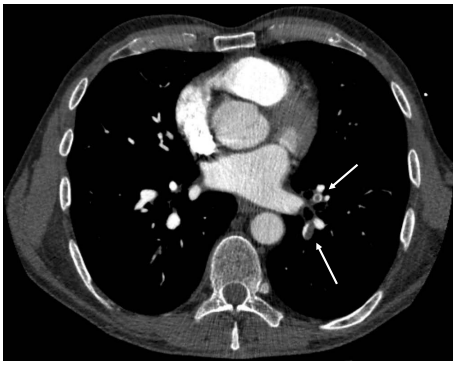

Figure 3. Computed tomography pulmonary angiography of patient with segmental pulmonary emboli in the left pulmonary artery.

the incidence of contrast induced nephropathy after CTPA in patients with suspected acute PE to be between 8.9% and 12%.[47,48] Finally, there is rising concern for long term radiation complications. The radiation dose of a single CTPA is in the range of 3-5 mSv and the cancer risk has been estimated at approximately 150 excess cancer deaths per million when exposed to a single CT examination for PE.[43]

Overuse of CTPA as first imaging test in patients suspected of PE may lead to a very high rate (>90%) of negative CT results,[49-51] which underlines the need of assessing pretest probability before performing CTPA.

Magnetic resonance angiography

Magnetic resonance angiography has potential to be an alternative to CTPA. The less nephrotoxic gadolinium contrast-enhanced acquisitions can be used for thrombus imaging with the advantage of avoiding ionizing radiation and iodinated contrast material. Some early studies using MRA reported a sensitivity of 75-100% and a specificity of

95-100% for detecting PE.[52,53] However, in the recently published PIOPED III study that included 371 patients, a 25% rate of technically inadequate images was observed. Diagnostic MRA images had a sensitivity of only 78% with a specificity of 99%. Sensitivity was 79% for detecting PE in a main or lobar pulmonary artery and decreased to 50% in segmental and even 0% in subsegmental arteries.[54] Hence, MRA is not an optimal alternative for CTPA.

Compression ultrasonography

A proximal DVT can be found in 18% of patients with suspected PE and 36-45% in patients with proven PE.[55] DVT can be found around four times more often in patients with clinical signs and symptoms of DVT compared to patients without DVT complaints.[4] Because patients with DVT receive the same treatment as patients with proven PE, further imaging tests to detect PE can be avoided.[56] Compression ultrasonography could also be interesting as an alternative in patients with contra-indications to CTPA (e.g. renal failure or allergy to iodine contrast agents). Nevertheless, the sensitivity of compression ultrasonography for patients suspected of PE is limited to 23-29% and false positive compression ultrasonography will result in anticoagulation treatment in 2-3% of patients.[57,58] Furthermore, it is not cost effective to apply compression ultrasonography as first imaging test in all patients.[4] Therefore, compression ultrasonography should be reserved for patients suspected of PE who display clinical signs of DVT and for patients with contra-indications for CTPA.

Combination of clinical decision rules, D-dimer testing and imaging

Diagnostic management of suspected acute PE that does not adhere to guidelines is common and unsafe. In one study, 7.7% of patients who received inappropriate management experienced a VTE during follow-up in contrast to 1.2% patients after appropriate management.[59]

The use of standardized diagnostic algorithms combining different diagnostic test has reduced the number of radiological imaging tests without losing safety. PE could be ruled out safely without the need for imaging testing in patients with a low, low or intermediate or unlikely clinical probability with a normal D-dimer test result.[60,61] Notably, the combination of some CDRs with non-highly sensitive D-dimer tests could not rule out PE with enough safety.[16] Currently, in patients with suspected PE, a diagnostic strategy is used in which a highly sensitive quantitative D-dimer test is combined with a CDR, followed by a CTPA (Figure 4). This diagnostic strategy has been evaluated in outpatients as well as inpatients.[3] In case of a CDR result indicating PE unlikely in combination with a normal D-dimer test result, further imaging can safely be withheld. The 3-month failure rate in patients who were not treated with anticoagulants after applying such a strategy was found to be only 0.3% (95%CI 0.04-1.0%), resulting in a NPV of 99.7% (95%CI: 99.0-

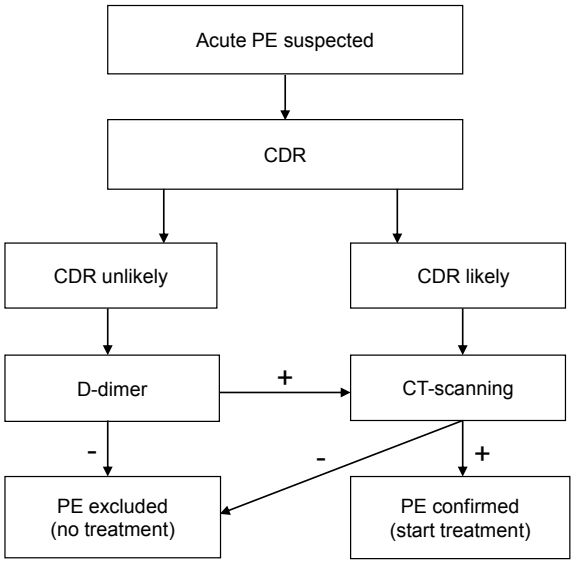

Figure 4. Flow chart diagnostics in patients suspected of having pulmonary embolism. PE: pulmonary embolism; CDR: clinical decision rule; D-dimer (+): elevated D-dimer concentration; D-dimer (-): normal D-dimer concentration.

100%).[26] In a large prospective multicenter study, this percentage was 0.5% (95% CI 0.2-1.1). In this particular study, PE was excluded safely in 32% without using additional imaging tests and the algorithm allowed a management decision in 98% of patients.[3] Only 1.3% (95% CI 0.7-2.0%) of patients with CTPA indicated because of either a high CDR or an abnormal D-dimer test, and with PE excluded by CTPA, were eventually diagnosed with VTE during follow-up. The strategy using a negative CTPA to exclude PE was demonstrated to be as safe as a negative CTPA followed by a compression ultrasonography negative for DVT, both with a 3-month VTE recurrence of 0.3%.[62,63] Consequently, additional compression ultrasonography (CUS) to rule out VTE is unnecessary.

V/Q scintigraphy can be used as an alternative initial imaging technique to CTPA in patients suspected of PE, but is more complicated. The results of the V/Q scintigraphy should be interpreted in combination with the pretest probability.[64] If the CDR indicates low probability or unlikely and the V/Q scintigraphy is normal, anticoagulant treatment can be safely withheld.[29] The diagnosis is confirmed by a clinical decision rule indicating "likely" in combination with high probability for PE. However, in case of a high probability V/Q scintigraphy with an unlikely pretest probability, further imaging (CTPA or compression ultrasonography) should be considered.[65] With a non-diagnostic V/Q scintigraphy (neither normal nor high probability V/Q scintigraphy), compression ultrasonography is recommended.[8,66] With a normal compression ultrasonography in combination with an unlikely clinical pretest probability, PE can be excluded. Combined with a likely pretest

probability, a D-dimer test should be performed. With a normal D-dimer test, PE could be excluded and in case of an elevated D-dimer concentration, a repeated compression ultrasonography should be performed before PE could be excluded safely and treatment can be withheld. In the meantime, until the repeated compression ultrasonography, treatment can be withheld (Figure 5).[64]

In conclusion, in patients with clinically suspected PE, the first diagnostic step is to determine the clinical probability by performing a CDR. In case of a non high clinical probability (PE 'unlikely'), a normal D-dimer test result can safely exclude PE. When the CDR indicates a high clinical probability or if the D-dimer test reveals a concentration above the predefined cut-off level, additional imaging is necessary and CTPA is the first choice imaging modality. If PE is proven by CTPA, the patient must be treated with anti-coagulants. If CTPA excludes PE, an alternative diagnosis should be considered (Figure 4).

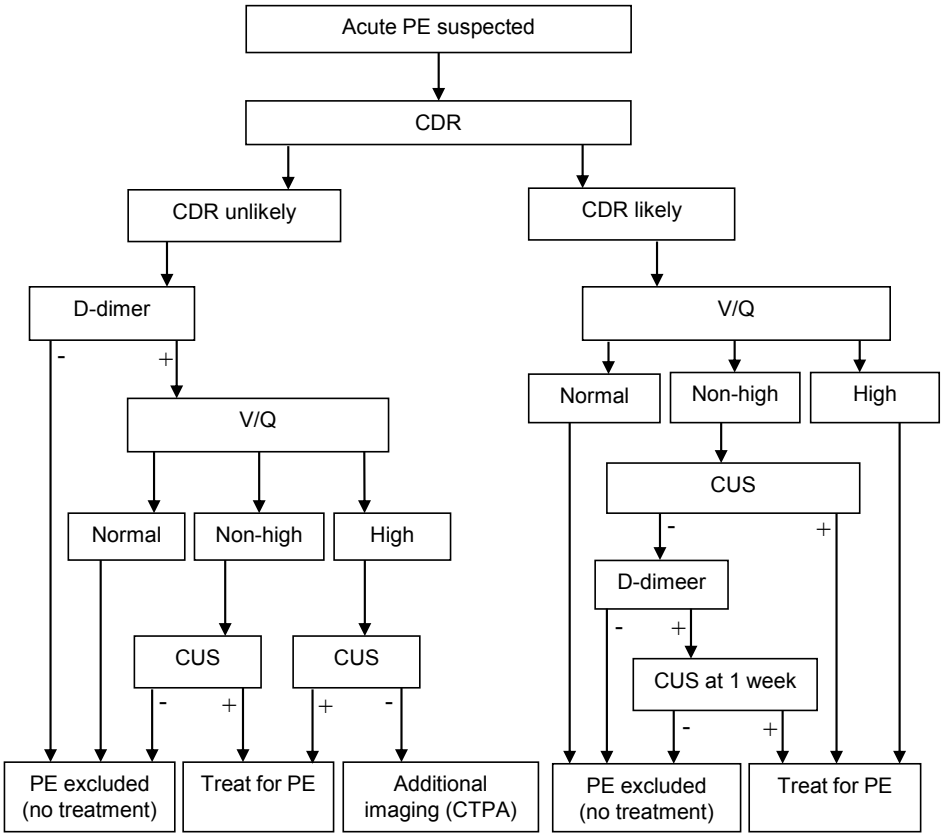

Figure 5. Flowchart in patients suspected of having pulmonary embolism (PE) using ventilation perfusion (V/Q) scintigraphy; CDR: clinical decision rule; D-dimer ventilation perfusion (+): elevated D-dimer concentration; D-dimer (-): normal D-dimer concentration; non high: non high probability (nondiagnostic); high: high probability; CUS: compression ultrasonography; CUS (-): CUS negative for deep venous thrombosis; CUS (+): CUS positive for deep vein thrombosis.

Suspected recurrent pulmonary embolism

The management of patients with suspected recurrent PE is challenging as it is unclear whether the above-mentioned diagnostic strategies are valid in patients with a prior history of proven PE. Nevertheless, the diagnosis of recurrent PE is associated with major therapeutic consequences since lifelong treatment with anticoagulants is usually required.

A diagnostic strategy consisting of a D-dimer test and a CDR could be useful in patients suspected of recurrent PE without anticoagulant treatment.[67] In a post-hoc analysis of the Christopher study, none of the 124 patients with suspected recurrent PE who were not treated based on a low clinical probability according to the Wells rule and a normal D-dimer test result, developed a VTE during a 3-month follow-up period (0%; 95%- CI 0-6.9).[67] Further research is warranted to provide definitive evidence regarding the use of CDRs and the diagnostic value of the D-dimer test in patients suspected of recurrent PE. Of note, it has been suggested that (especially initiation of) anticoagulant treatment is associated with a decrease in D-dimer concentration and therefore with decreased sensitivity[68-70] and CDRs are not validated in patients using anticoagulants. Hence, direct imaging tests are recommended in patients on anticoagulant treatment.

In patients with a history of PE, it may be difficult to differentiate between a residual thrombus or new thrombus on CTPA. It has been estimated that up to 50% of patients have residual thrombus, 6 months after diagnosis of PE.[71] In patients with high risk of recurrence, studies are required to determine whether repeating CTPA six months after anticoagulant treatment may be valuable, as to provide a baseline-imaging test in case patients return with new complaints suspected for recurrent PE. A strategy of CRD and D-dimer testing can be used in patients suspected of recurrent PE without receiving anticoagulant treatment and direct imaging tests are needed in patients on treatment In these latter patients, CTPA is the first choice imaging test.

Diagnostic management during pregnancy

During pregnancy and puerperium the risk of thrombosis is increased due to immobilization, venous stasis, hormonal changes or after caesarian section. During pregnancy, the inappropriateness in diagnostic management increases.[59] Dyspnea and swelling of legs frequently occurs during normal pregnancy, but may also be an indicator of PE. Because pregnancy has been a strict exclusion criterion in most diagnostic studies, the possible diagnostic value of a CDR is not known in this specific population.

The value of the D-dimer test during pregnancy and post partum is also limited. During pregnancy, a physiological elevation of the D-dimer concentration occurs decreasing the specificity of the test: from 35 weeks pregnancy through the post partum period, the values are almost always elevated above the commonly used threshold of 500 ng/ml.[72] In conclusion, further studies in pregnant patients are needed and the use of a CDR

and D-dimer test is discouraged during pregnancy and puerperium and imaging tests are always required.

Prospective studies about the safety of ruling out PE by V/Q scintigraphy or CTPA are lacking. Most experience in patients suspected of PE during pregnancy is with V/Q scintigraphy and this technique is considered as first line imaging test in pregnant women.[73,74] The percentage of patients with a high probability V/Q scan is very low (1.8% versus ~10% without pregnancy), the percentage of normal perfusion scans is high (73.5% versus 33% without pregnancy) whereas 25% of the V/Q scans are inconclusive.[75] Additional imaging is needed in these latter patients, potentially exposing them to further radiation.

Although pregnant patients have been excluded from participation in most clinical outcome studies using CTPA, the calculated radiation dose received by the fetus as a result of CTPA has always been lower compared to V/Q scintigraphy.[76-78] Furthermore, CTPA shows fewer non diagnostic tests compared to V/Q scintigraphy and has the ability to show alternative diagnosis. Disadvantage of CTPA compared to V/Q scintigraphy is the 150 times higher amount of radiation exposure to the breasts.[79] It is also possible to start with compression ultrasonography of the lower extremities. If a DVT is identified, treatment with anticoagulants is indicated and CTPA or V/Q scintigraphy can be avoided.

CONCLUSIONS

Various diagnostic tests are available to accurately confirm or exclude PE. The CDR and D-dimer test play an important role in the diagnostic algorithm. The CDR as well as the D-dimer test can not be used as single tests, but the combination of a low clinical probability and a normal D-dimer test result can exclude PE safely without the need of additional testing. In case of a likely clinical probability and/or an elevated D-dimer value, additional testing is required. Multi-slice CTPA is the first choice imaging test and can safely exclude PE. V/Q scintigraphy may be used if CTPA is contra-indicated.

EXPERT OPINION

Our recommended diagnostic strategy in patients with suspected PE starts with a standardized CDR to assess the pretest probability. If this rule indicates PE "unlikely", a quantitative, highly sensitive D-dimer test should be performed. A normal D-dimer test result excludes PE safely. With a CDR indicating "likely" pretest probability or an elevated D-dimer test result, additional diagnostic testing is needed, with multi-slice CTPA as imaging test of first choice. When the CTPA is negative, the diagnosis PE is ex-

cluded without the need for additional testing (e.g. compression ultrasonography). All patients with a CTPA demonstrating PE should be treated with anticoagulants. In case of inconclusive CTPA, we recommend repeating CTPA within 24 hours and patients with high clinical probability should be treated by anticoagulants while awaiting diagnostic confirmation.[80] V/Q scintigraphy may be used as an alternative to CTPA in case of contraindications, MRA may be used as an alternative when CTPA is contra-indicated, but accuracy is currently insufficient for implementation in routine clinical care.

The main goal in diagnostic management of PE is to achieve a standardized, accurate and relative simple diagnostic strategy that can be easily applied to the majority of patients suspected of acute PE. This should be a strategy with a minimum of false positive or false negative test results, and with acceptable use of radiation and contrast material. We recommend the use of the Wells rule for inpatients. Because there is no evidence to prefer one CDR above another for outpatients, the preference may depend on the familiarity with a score or the type of D-dimer assay. The type of D-dimer assay has consequences on the proportion of the population on which D-dimer testing can be applied; highly sensitive D-dimer assays can be used in patients with low and intermediate probabilities in a three level scheme and patients categorized as 'unlikely' to rule out PE. In case of a less sensitive D-dimer, PE could be ruled out in patients with a normal D-dimer test and a low clinical probability of a trichotomized score.[16]

One topic of interest is the prospective validation and implementation of the simplified CDRs (mentioned before) in clinical practice. The potential role of quantitative point-of-care D-dimer tests should be further evaluated in prospective management studies.

On the other hand, risk estimation of specific subgroups become of more interest. Using specific diagnostic strategies and cut-off points may help in predicting the individual chance for having PE. Implementation in daily clinical practice seems more difficult, but using electronic assistance may help in improved individual based risk estimation and diagnostic decision-making.[81]

Concerning subgroup analysis, standard strategies may not be applicable to all patients. For example, in the elderly patients, with increasing age, D-dimer testing becomes less accurate. Also, in patients with impaired renal function, avoiding or limiting the use of iodinated contrast material is desirable. In patients suspected of having a recurrent PE, it is difficult to differ between old and new emboli on CTPA. In young women, radiation dose, especially to the breasts, is of concern. Finally, data for woman with a suspicion of PE during pregnancy are limited at the moment and it is a challenge to avoid radiation to the fetus. Diagnostic management strategies in pregnant women have to be validated in future research. Studies concerning CDR and D-dimer testing already exists in pregnant patients suspected of DVT and seems promising with a high NPV (100%; 95%CI 95-100) of the D-dimer test and also the use of the "LEFt" prediction rule excludes DVT during pregnancy but prospective validation is still needed.[82,83]

In the future, development of existing imaging modalities will also be subject of research. With the development of faster CT scanners with high spatial resolution, more (subsegmental) emboli can be detected. However, the clinical relevance of isolated subsegmental emboli is not exactly known and must be subject of research. Using ECG-gated CTPA, it is possible to obtain information about pulmonary arteries, thoracic aorta, heart and even the coronary arteries within a single examination. This is of interest because the clinical differentiation between cardiac events and PE is not always clear and this information can be helpful to predict clinical outcome in patients diagnosed with PE. However, ECG-gated protocols may result in a higher radiation dose and more contrast is needed compared to non-gated CTPA.[84] Therefore, these protocols are not recommended for routine use; only patients suspected of either PE, aorta dissection or cardiac events may benefit from these techniques.[85]

The development of single photon emission computed tomography (SPECT), acquiring 3D images, may be of growing interest and may further improve V/Q imaging, which may be used as an alternative when CTPA is contraindicated.[86,87] New experimental MRA-techniques show potential for improved PE imaging. MR-direct thrombus imaging by methemoglobin, a transformation product of hemoglobin in a thrombus, may be used as endogenous contrast to depict subacute thrombosis.[88] Further, new MRI contrast agents such as fibrin or alpha(2)-antiplasmin (activated factor XIII covalently cross-links alpha(2)-antiplasmin to fibrin) will be evaluated to visualize PE. Labeling using bimodal contrast agents consisting of gadolinium and a peptide that binds to alpha(2)-antiplasmin or to fibrin in the thrombus seems to be a promising technique. These latter methods are under investigation in experimental in-vivo models for arterial thrombosis and should be evaluated further.[89,90]

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