

Diagnosis of acute Pulmonary Embolism

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Keywords

Pulmonary embolism, pre-test clinical probability, D-dimer, age-adjusted D-dimer cutoff, computed tomography pulmonary angiography

Summary

During the last three decades, considerable advances in the management of patients with suspected pulmonary embolism (PE) have improved diagnostic accuracy and made management algorithms safer, easier to use and well standardized. These diagnostic algorithms are mainly based on the assessment of clinical pretest probability, D-Dimer measurement and imaging tests, mainly computed tomography pulmonary angiography (CTPA). These diagnostic algorithms allow a safe and cost-effective diagnosis for most patients with suspected PE. In this review, we discuss current existing evidence for PE diagnosis, the challenge of diagnosing PE in special patient populations, as well as novel imaging tests for PE diagnosis.

Schlüsselwörter

Lungenembolie, klinische Prä-Test-Wahrscheinlichkeit, D-Dimer, altersadjustierter D-Dimer-Schwellenwert, Computertomografie-Pulmonalangiografie

Zusammenfassung

In den vergangenen drei Jahrzehnten haben erhebliche Fortschritte bei der Diagnostik von Patienten mit Verdacht auf Lungenembolie (LE) zu einer Verbesserung der Diagnosesicherheit geführt. Dadurch wurden die diagnostischen Algorithmen sicherer und einfacher in der Anwendung und sind mittlerweile zuverlässig standardisiert. Diese diagnostischen Algorithmen beruhen vor allem auf der Beurteilung der klinischen Prä-Test-Wahrscheinlichkeit, der D-Dimer-Messung und bildgebenden Untersuchungen, insbesondere der Computertomografie-Pulmonalangiografie (CTPA). Diese diagnostischen Algorithmen erlauben bei den meisten Patienten mit Verdacht auf LE eine sichere und wirtschaftliche Diagnose. In dieser Übersicht diskutieren wir die aktuell vorliegende Evidenz für die LE Diagnostik, die Herausforderung einer LE-Diagnose in speziellen Patientenkollektiven sowie neuartige bildgebende Verfahren für die LE-Diagnose.

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Introduction and General Considerations

Venous thromboembolism (VTE), which comprises of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease after acute coronary syndrome and stroke. Due to its non-specific clinical presentation, the diagnosis of PE remains difficult. One of the main challenges in everyday clinical practice is actually to determine when to suspect PE. There remains a gap between management outcome studies and real life in one sense: in most clinical trials studying diagnostic strategies for PE, patients were included if they had acute or worsening shortness of breath and/or chest pain without any obvious explanation. In real life, this definition of “suspected PE” does not sufficiently help clinicians to determine if they should suspect PE in their patient.

The ever-increasing availability of non-invasive imaging tests, mainly computed tomography pulmonary angiography (CTPA), has led to a tendency to suspect PE much more frequently than previously in outpatients, with a shift towards aiming to exclude PE in any patient presenting with chest symptoms rather than to confirm PE in a patient with high suspicion. This overall tendency is well illustrated by the decreasing prevalence of PE in clinical studies, i.e. the decreasing percentage of patients among all suspected patients in whom the diagnosis of PE is confirmed. Prevalences as low as 5% have been reported in some recent North American studies, a figure that contrasts with the ~50% prevalence reported in the early 1980's (1).

This major change in the population of patients tested for suspected PE in clinical practice explains why current diagnostic management studies are designed to assess how to *exclude* PE in a population of pa-

tients with a rather low prevalence of the disease. This is nowadays performed through the use of a test with high sensitivity, namely D-dimer measurement, at the beginning of the diagnostic management, before imaging. The gold standard reference for the diagnosis of PE remains pulmonary angiography, although the invasiveness, costs and risks of this test have rendered it obsolete in routine clinical practice.

In light of all these elements, the performance of modern diagnostic strategies for PE is most often presented as their ability to safely exclude PE. Because the gold standard test is no longer performed, the reference standard to confirm the safety of any strategy has nowadays become a clinical standard: an uneventful follow-up in patients left without anticoagulant treatment after a “negative” strategy, expressed as a low three-month VTE rate. As the three-month VTE rate after a normal pulmonary angiography is known to be ~2%, it is now well accepted that modern diagnostic strategies should be associated with a similar three-month thromboembolic risk in a patient considered as not having PE based on a negative strategy.

Tremendous advances have been made in the field of PE diagnosis over the last 30 years with the introduction of sequential diagnostic strategies including clinical probability assessment and D-dimer measurement, allowing ruling out PE in 1 out of 3 outpatients in a completely non-invasive and cost-effective way. The remaining two thirds will need imaging tests, and CTPA is at present the imaging modality of choice. Unfortunately, the widespread use of multidetector CTPA without selecting patients has brought in new issues, such as overdiagnosis and radiation (2, 3). An effort to implement the robust validated strategies in clinical practice could overcome some of these problems.

Finally, two conflicting issues confront clinicians when faced with suspected VTE: not missing a VTE because of the risk of death in untreated patients, and not unnecessarily treating patients because of the bleeding risk of anticoagulants. Therefore, all patients with suspected VTE should be investigated until reaching a definitive diagnosis. Not meeting this goal exposes pa-

tients to a significantly higher risk of recurrent VTE and death. In this review, we will discuss the challenges of diagnosing PE, recent major improvements made in diagnostic strategies, as well as some unresolved issues.

The Challenge of Suspecting PE

Over the last two decades, there has been a trend towards testing more patients for PE, resulting in a decrease in the proportion of confirmed cases. Indeed, in some recent studies, as few as 5% of patients with suspected PE are actually diagnosed with this condition (1). This raises the question of when and in whom patient, a clinician should suspect PE. In most studies on PE diagnosis, patients were included if they presented with sudden onset or worsening of dyspnea or chest pain without another obvious cause (4, 5). This definition is admittedly difficult to standardize and there is probably a trade-off between over-suspecting and over-testing for PE versus missing PE diagnosis. Searching for PE in all patients with dyspnea or chest pain likely would lead to increases in cost and test complications without improvements in health.

Therefore, a new challenge is to better select who should be suspected of having PE. A clinical prediction rule (the PERC rule) was built in emergency department patients to identify those at such low risk of PE on clinical grounds that they would not need any other investigation (6). Overall prevalence of PE was 11% in their derivation set. The final model comprised of eight variables significantly associated with absence of PE: age < 50 years, pulse < 100 bpm, SaO₂ > 94%, no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no history of VTE, no estrogen use. If all these criteria are absent, then PE should not be further investigated. In a validation set of 1427 patients with a prevalence of PE of 8%, the rule was negative (all criteria met) in 25%. Among these, PE was found in only 1.4% (5/362, 95% CI 0.4 to 3.2) suggesting that such patients would not need to be tested for PE. The same figure was obtained in a prospective vali-

dation study of 8138 emergency room patients in the US who were included if the physician in charge ordered any objective diagnostic test for PE. Twenty-four percent of those patients were classified into the low risk group, and 1.3% of them had PE at the initial workup or during the 45 days follow-up (7). However, attempts of retrospective validation of this rule in European cohorts of patients (with a higher prevalence of the disease) suggested that the rule could not be used safely in populations of patients different from the initial studies as it was associated with a higher three-month thromboembolic risk of 6.7% (95% CI: 3 to 14) (8) in patients with a negative PERC rule. Further ongoing studies aim at prospectively validating the rule alone or in combination with a low pre-test clinical probability (NCT02360540).

Overview of Current Diagnostic Strategies

Confirmatory imaging tests such as CTPA or V/Q scan are associated with a non-negligible radiation dose and are expensive. Given the low prevalence of confirmed PE among tested patients, systematic imaging is not cost-effective and likely harmful. Therefore, current diagnostic strategies aim at identifying, among patients with suspected PE, a group of low-risk patients in whom no imaging test is required.

Clinical probability of pulmonary embolism

As previously discussed, sensitivity and specificity of clinical symptoms and signs are low when considered alone in patients with suspected PE. Nevertheless, these findings can be combined, either implicitly (9, 10) or by prediction rules (11, 12), in order to estimate the likelihood of a patient with suspected PE to actually have confirmed PE. Both means of assessing clinical likelihood of PE allow a fairly accurate stratification of patients into two (PE unlikely or PE likely) or three (low, intermediate or high clinical probability) categories corresponding to an increasing prevalence of PE (4, 5). The two most widely used prediction rules for PE are the Wells rule and

the Geneva rule. Two meta-analyses confirmed the validity of the original and simplified versions of the Wells and the revised Geneva rules (13, 14). A direct prospective comparison of these rules has also confirmed similar diagnostic performances (15). Of note, these rules should not be used as “PE suspicion rules” applied as a screening test to all patients with chest symptoms in the ER, but should only be used after a suspicion of PE has been raised after clinical assessment of the patient. Moreover, they are not intended to be used as a stand-alone test and are only useful within established diagnostic strategies applied to patients in whom PE is suspected. ► Table 1 summarizes the validated versions of the Wells and Geneva prediction rules for PE.

D-dimer measurement

Plasma D-dimer, a degradation product of cross-linked fibrin, has been extensively investigated in VTE diagnosis (16). D-dimer levels rise in presence of an acute clot. A normal D-dimer level renders acute VTE unlikely. There are numerous available assays with different characteristics (16). As D-dimers are used as an exclusion test, the sensitivity of the test used in a patient is a crucial issue. The quantitative ELISA or ELISA-derived assays have the highest sensitivity (over 95%) and a specificity around 40% (16, 17). In the emergency department, a negative ELISA D-dimer can exclude PE without further testing in combination with a non-high or an unlikely clinical probability. A systematic review of outcome studies using the VIDAS® D-dimer assay to exclude PE showed a three-month thromboembolic risk well below 1% in patients left untreated after a negative test result (18). Therefore, clinical probability and D-dimer are used in most diagnostic strategies as a first filter, in order to avoid thoracic imaging. It allows to safely rule out the diagnosis of PE in approximately 1 out of 3 outpatients with suspected PE without any further testing (4, 5, 19–21).

On the other hand, the specificity of D-dimer for VTE is poor. Therefore, D-dimer is not useful for confirming PE. Another important message is that a positive D-dimer test should not be considered

Tab. 1
Most validated clinical prediction rules for PE

Items	Points	
	Original version (11)	Simplified version (67)
Revised Geneva score		
Age > 65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within one month	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate		
75 to 94 beats per minute	3	1
≥ 95 beats per minute	5	2
Pain on lower limb deep vein palpation and unilateral edema	4	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥ 11	≥ 5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥ 6	≥ 3
Wells score	Original version (12)	Simplified version (68)
Previous PE or DVT	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Cancer	1	1
Hemoptysis	1	1
Heart rate > 100 bpm	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	NA
Intermediate	2–6	NA
High	≥ 7	NA
Two-level score		
PE unlikely	0–4	0–1
PE likely	>4	≥ 2

DVT: deep vein thrombosis; PE: pulmonary embolism

as a reason to raise the suspicion of PE and begin a diagnostic work-up. Physicians are sometimes frustrated when a D-dimer test comes back positive and feel obliged to order a thoracic imaging test. It is important to remember that D-dimer measurement should be performed only after a clinical suspicion of PE is raised, and in patients in whom thoracic imaging would otherwise be performed (22). A positive D-dimer test in a patient without a prior suspicion of PE is not a clinically relevant finding. Therefore, D-dimer test should not be performed as a triage test before a medical assessment.

How to increase diagnostic usefulness of D-dimer test ?

D-dimer test is not specific, as D-dimer levels increase in a wide variety of conditions, such as cancer, inflammation, infection, chronic kidney failure, pregnancy, previous venous thromboembolism, and advancing age (23–25). As a result, the clinical usefulness of the test in elderly patients, that is the proportion of the patients with a negative D-Dimer (i.e. below the predetermined cut-off, < 500 µg/L for most available commercial assays) in whom PE may be ruled out is reduced (26). Recently, the value of a progressive D-Dimer cut-off adjusted to age was derived and retrospectively validated in a sample of 1,712 patients (26). The optimal age-adjusted cut-off was defined as patient's age multiplied by 10 in patients aged 50 years or more with the usual 500 µg/L cut-off value being used for patient younger than 50 years. This approach has been formally evaluated in a recent large multicentre prospective outcome study, in which all non-high or PE unlikely pretest probability patients with D-Dimer levels below their age-adjusted cut-off were left untreated without further diagnostic testing, confirmed the safety of using the age-adjusted cutoff (27). The D-dimer tests used in this study were highly sensitive assays (ELISA or immunoturbidimetric). Among 3,346 included patients, 817 (28%) had a D-dimer level below the conventional 500 µg/L cut-off, and an additional 337 (12%) had a D-dimer above 500 µg/L but below their age-adjusted cutoff. The three-month

thromboembolic risk after excluding PE based on a negative D-dimer was low and similar in both groups 1/817 (0.1%, 95% CI 0.0 to 0.7%) and 1/331 (0.3%, 95% CI 0.1 to 1.7%). The increase in the diagnostic yield of D-dimer was more pronounced in patients \geq 75 years of age: using the age-adjusted cut-off resulted in a five-fold increase in the proportion of patients in whom PE could be safely ruled as compared with the conventional cutoff, from 6% to 30% (27). This corresponds to a number of patients needed to test to obtain one negative test of 3, meaning that PE can be ruled out by negative D-dimers in 1 out of 3 patients even in the elderly by the use of age-adjusted cutoff. Because of this major increase in the diagnostic usefulness of D-dimer, the age-adjusted D-dimer cut-off has been implemented in diagnostic algorithms in many ER around the world, and also as part of the American College of Physicians Best Practice Advice for the evaluation of patients with suspected acute PE (28).

Other approaches to increase the yield of the D-dimer test are being developed, using a higher cut-off value in patients with a low pre-test clinical probability, or using cut-off values adjusted on pregnancy trimester (29, 30). "Other approaches to increase the yield of the D-dimer test are being developed, using a higher cut-off value in patients with a low pre-test clinical probability, or using cut-off values adjusted on pregnancy trimester (29, 30). Recently, a prospective trial managing patients by the simultaneous use of the YEARS clinical decision rule and D-dimer concentrations was published (31). YEARS rule consists of three items: clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis. In patients with no YEARS item and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL, PE was considered excluded. All other patients underwent CTPA. Of the 3465 included patients, 456 (13%) were diagnosed with PE at baseline. Of the 2946 patients (85%) in whom PE was ruled out at baseline and who remained untreated, 18 patients were diagnosed with symptomatic VTE during 3-month follow-up (0.61%, 95% CI

0.36–0.96) of whom six had fatal PE (0.20%, 0.07–0.44). CTPA was not indicated in 1651 (48%) patients with the YEARS algorithm compared with 1174 (34%) patients, if Wells' rule and fixed D-dimer threshold of less than 500 ng/mL would have been applied, a difference of 14% (95% CI 12–16). Therefore, this study suggests that using a D-dimer adapted to clinical probability might be an interesting option and is associated with an absolute 14% decrease of CTPA examinations.

A limitation of the YEARS study is that all patients had D-dimer performed before clinical probability assessment. As physicians were not blinded to D-dimer results, this could have hampered the validity of the YEARS score. Indeed, one of the items of the YEARS score is "PE is the most likely diagnosis", and it is unlikely that physicians in charge would have reported this item as positive knowing the D-dimer result was negative. In view of this limitation and the limited level of overall validation of the YEARS score compared to the Geneva and the Wells scores, the strategy presented in the YEARS study might presently not be the first choice when assessing a patient with suspected PE."

Computed tomography pulmonary angiography (CTPA)

CTPA was introduced in the early 1990s. It allows direct visualisation of pulmonary arteries after intravenous injection of iodinated contrast medium. The value of CTPA for decision making in suspected PE has evolved with improvements in technology. The older single-detector CTPA had a high specificity but a low sensitivity (around 70%) for PE (32, 33), precluding its use as a standalone test to rule out PE. Additional lower limb venous CUS was required, and 10 to 15% of patients had a proximal DVT despite a negative single-detector CTPA. Using a strategy that included CUS and single-detector CTPA proved safe to exclude PE in two large-scale outcome studies (20, 34). Since the introduction of higher resolution multidetector-row computed tomography (MDCT), CTPA has become the method of choice when imaging is needed for suspected PE (35). It allows an direct visualization of the pulmonary ar-

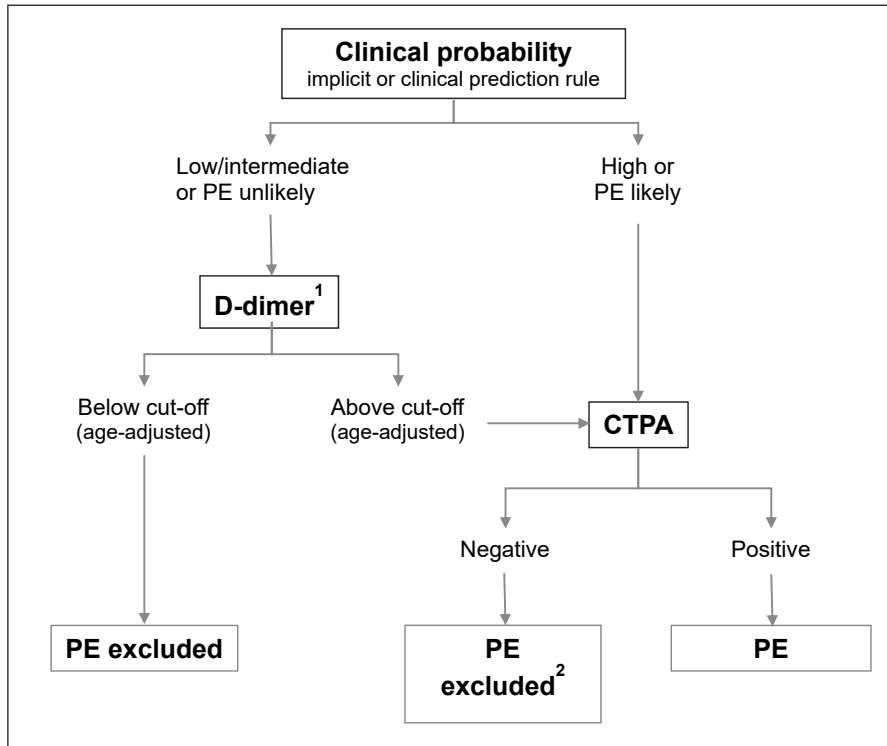


Fig. 1 Diagnostic strategy of pulmonary embolism (adapted from references [69] and [27]). ¹ If using a highly sensitive D-dimer assay; If a less sensitive assay is used, a negative test result rules out PE only in patients with low (or unlikely) clinical probability; ² In case of negative CTPA in high clinical probability patients, additional imaging, e.g. lung ventilation/perfusion scintigraphy or pulmonary angiography (suspected PE) might be considered. Abbreviations: CTPA: Computed Tomography Pulmonary Angiography

teries down to at least the segmental level (36). Many recent prospective outcome studies provide evidence that it is safe to rule out PE after a negative CTPA (4, 5, 21, 37). An example of validated diagnostic algorithm for PE is displayed in ►Figure 1.

Whether patients with a negative CTPA and a high clinical probability should be further investigated by venous CUS and/or ventilation-perfusion scintigraphy or pulmonary angiography is still controversial (5, 38, 39). Another controversial area is the clinical significance of isolated subsegmental PE, i.e. the presence of a single subsegmental intraluminal defect on MDCT, which is found in 1% to 5% in patients with suspected PE. Indeed, the positive predictive value of such a findings is low, and limited data suggest that such patients left untreated by anticoagulants may have an uneventful course (40). Recent ACCP guidelines suggest that some patients with isolated subsegmental PE without associated deep vein thrombosis, might not

require anticoagulant treatment. An international prospective cohort study will provide further data on the safety of this approach (NCT01455818).

Recently, the introduction of dual-energy CT (DECT) has been studied in the setting of acute PE. By using two X-ray tubes at low and high peak kilovolt levels, DECT can produce a thorough iodine distribution image, providing a good representation of lung parenchymal perfusion (41). Although the extent of perfusion defects seems to be correlated with right ventricular dysfunction and might thus be used as a prognostic marker, this issue has only been studied in small sample retrospective studies (42).

Ventilation-perfusion lung scintigraphy (V/Q scan)

Ventilation-perfusion lung scintigraphy is a non invasive technique allowing an indirect diagnosis of PE, a so-called mis-

matched defect (perfusion defect with normal ventilation) usually representing PE. The interpretation of V/Q scan has long been based on criteria validated in the landmark Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) study (10), and their subsequent revision (43). More recently, it has been greatly simplified and V/Q scan results are now classified into three categories: normal, high probability and non diagnostic (37). The high negative predictive value of a normal V/Q scan has been confirmed by several studies, including a large outcome study (37) and is recognized as a valid criterion for excluding PE. The positive predictive value of a high probability V/Q scan is approximately 90% (10) and most clinicians consider such a result enough to rule in PE. The main weaknesses of V/Q scan are the high proportion of non diagnostic results (around 50% in recent series) and the inability to provide alternative diagnosis, as opposed to CTPA (37). However, diagnostic strategies based on V/Q scan have been prospectively validated in many outcome studies and were associated with a very low three-month thromboembolic risk. Also, a randomized trial comparing V/Q scan and CTPA, suggested that both test were associated with a similar safety (37). Overall, V/Q scan has been widely replaced by CTPA and remains mainly used in patients with a contra-indication to CTPA, most often patients with renal failure. It is also important to point out that V/Q scan is the initial diagnostic test of choice to exclude Chronic Thromboembolic Pulmonary Hypertension (CTEPH) in a patient with persisting symptoms and a suspicious heart ultrasound after an initial PE.

Compression ultrasonography

Compression ultrasonography of lower limb veins is the main diagnostic tool for DVT. It may be used in patients with suspected PE. Indeed, the presence of a proximal DVT is highly predictive of PE, allowing to rule in the diagnosis of PE without further thoracic imaging (44): a recent systematic review of the performances of CUS for diagnosing PE reported a sensitivity of 41% (95% confidence interval [CI],

36–46%), and a specificity of 96% (95% CI, 94–98%) (45).

Compression ultrasonography was highly used in diagnostic algorithms based on single detector CTPA. Thanks to the improved accuracy of multidetector CT, it is no longer necessary to ensure absence of DVT in patient with a negative CTPA (4). However, it might have some interest in patients in whom CTPA is contra-indicated or not desirable, as in patients with renal failure, allergy to iodine contrast media or pregnant women. However, even if a positive CUS allows to confirm PE diagnosis, and thus the need for anticoagulation, the risk stratification of PE with clinical scores, echo and/or biomarkers is still necessary.

An unfortunately often-encountered reasoning mistake is to stop investigations after a normal CUS. This is of course not acceptable as the absence of proximal DVT does not rule out PE, and further thoracic imaging is necessary in this setting, unless an alternative diagnosis has become obvious or PE is no longer suspected.

Other imaging tests for PE

Other imaging tests are being developed to overcome some limitations of previously described diagnostic tools.

Magnetic resonance angiography (MRA)

The accuracy of gadolinium-enhanced MRA was compared to a composite reference standard (D-dimer, V/Q scan, CTPA) in the PIOPEP III trial (46). In this study, MRA was technically inadequate in a large proportion (25%) of patients. Among technically adequate tests, sensitivity was 78% and specificity 99% (46). Similar results were found in a prospective study including 300 patients referred for CTPA in whom MRA was also performed (47). Once again, 30% of MRA resulted to be inconclusive. For patients with conclusive MRA results, sensitivity and specificity were around 85% and 97% respectively compared to the standard diagnostic workup including CTPA (47). A recent systematic review and patient-based meta-analysis reported similar results with an overall sensitivity of 75% (95% CI 70–79%) and an

overall specificity of 80% (95% CI 77–83%) (48).

Despite the fact that use of MRA could overcome some of the inconveniences of CTPA, especially the exposure to radiation and iodine contrast media, the above-mentioned data on the high proportion of inconclusive results and lack of sensitivity obviously preclude the use of MRA as a routine test to rule out PE in everyday clinical practice. Moreover, MRA is not as widely available as CTPA and acquisition times are much longer. An ongoing study is assessing whether the combination of leg vein CUS and MRA would increase the diagnostic performances of MRA in suspected PE (NCT02059551).

Ventilation/perfusion single photon emission tomography (V/Q SPECT)

Along with the dramatic progress in CT technology, important advances have taken place in nuclear medicine imaging over the twenty-five years that have passed since the PIOPEP study was conducted with planar V/Q scans. As its name indicates, V/Q SPECT provides tomographic (transverse, coronal and sagittal) rather than planar images. It is performed with patient in the supine position. After the ventilation study with inhalation nowadays most often of 25–30 MBq of Technegas, 100–120 MBq of radio-labelled macro-aggregated albumin (^{99m}Tc -MAA) is given intravenously for perfusion imaging. Total acquisition time is around 20 minutes (49). Three-dimensional imaging allows better contrast resolution and limits the overlapping of small perfusion defects by normal tissue. These advantages should render V/Q SPECT superior to planar V/Q for the diagnosis of PE.

In a systematic review and meta-analysis recently published, the authors performed a summary receiver operating characteristics (SROC) analysis, a statistical technique applied to meta-analysis of imaging tests in order to overcome the limitations of simple pooling of sensitivities and specificities. In this study, the area under the SROC curve for V/Q SPECT was 0.99 (95% CI 0.96–1.00) as compared to 0.85 (95% CI 0.75–0.95) for planar V/Q and 0.98 (95% CI 0.94–1.00) for CTPA

(50). The patient population consisted of 2435, 3028 and 1904 patients for each of the imaging modalities respectively. The conclusion of this analysis in terms of performance of V/Q SPECT was that V/Q SPECT is as accurate as CTPA, and that both these modalities are more accurate than planar V/Q (50).

Just as radiology societies recommend CTPA as the imaging test of choice in the diagnosis of PE, the European Association of Nuclear Medicine broadly recommends V/Q SPECT over CTPA wherever available (51). Nevertheless, robust clinical evidence of the clear superiority of SPECT remains scarce. Moreover, before the SPECT V/Q could be used in everyday clinical practice, a management study in which clinical decisions would be made on the basis of this test remains to be conducted. If the safety of such a strategy is confirmed in a prospective outcome study, V/Q SPECT could become a very interesting alternative to CTPA, especially in patients in whom radiation is particularly a concern (young female patients, or in patients with contra-indication to CTPA as renal failure or allergy to iodine contrast media).

CT venography

When using CTPA, it is possible to also image the deep veins of the legs during the same acquisition (52). However, this approach has not been widely implemented given that CTPA alone is able to safely rule out PE and that the added value is likely very limited (4). Moreover, using CT venography is associated with an increased irradiation doses (53, 54).

Unresolved Issues in VTE

Patients with prior VTE

Patients with prior VTE often have persistently elevated D-Dimer levels. As a result, in case of suspected recurrent VTE, a lower proportion of them will benefit from non-invasive testing: the proportion of patients in whom PE was ruled out on the basis of a negative D-dimer were 16% and 33% in patients with and without a history of previous VTE, respectively (55). Patients with prior VTE have modified symptoms and

signs because of residual manifestations of previous episodes (chronic leg pain and swelling after DVT, persistent shortness of breath after PE) (56, 57). Finally, the interpretation of imaging tests is difficult because of the frequent presence of residual thrombi that are sometimes difficult to distinguish from an acute recurrent thrombus, thereby resulting in overdiagnosis (58). A small study, including patients with a first unprovoked VTE, suggested that baseline imaging at completion of anticoagulant therapy helped in interpreting diagnostic tests performed in cases of suspected recurrent VTE (59). Some diagnostic criteria for recurrent PE have been proposed based on the comparison of imaging result with previous imaging. However, this strategy requires the completion of a complete baseline imaging and is only useful if 1) standardized measurements are reported and 2) these images are available at the time and place of the suspected recurrent event and 3) if we dismiss possible interim asymptomatic events.

Another important issue when faced with residual emboli or thrombi in the pulmonary arteries, is not to miss the diagnosis of Chronic ThromboEmbolic Pulmonary Hypertension (CTEPH).

Indeed, most acute pulmonary emboli resolve on anticoagulation without remaining sequelae; however, some emboli fail to fully resolve becoming endothelialised with the development of chronic thromboembolic disease (CTED). Increased pulmonary vascular resistance arising from CTED may lead to CTEPH, a debilitating disease affecting up to 3 to 4% of survivors of acute PE. Diagnostic evaluation is more complex in CTEPH/CTED than acute PE with subtle imaging features often being overlooked or misinterpreted. Therefore, the finding of residual emboli in an anticoagulated patient with persisting respiratory symptoms may require further imaging tests that are beyond the scope of the present paper.

Isolated symptomatic subsegmental PE

Attention to subsegmental pulmonary embolism (SSPE) has increased with the ability of CTPA to show such small PE, not to

mention ongoing debate on unsuspected PE, which won't be discussed herein. The exact prevalence of SSPE in patients with suspected PE varies between 0.4 and 18% according to literature (60). The prevalence is probably dependent on the number of detector. A systematic review of diagnostic studies in patients with suspected PE found isolated subsegmental PE in 4.7% of patients with PE diagnosed by single-detector CT and in 9.4% of patients with PE diagnosed by multi-detector CTPA (61).

One of the main problems is that the reading of modern multi-row CTPA is complicated and time-consuming. Radiologists are often faced with small images which interpretation remains difficult. Of note, in the PIOPED II trial, the positive predictive value of CTPA (when compared to a composite standard reference) was of 98% for central PE but was only of 25% for subsegmental PE (52). Therefore, the most puzzling question might well be: is this image truly a subsegmental PE?

In a time-trend analysis of the incidence and mortality of PE in the United States, authors concluded that the introduction of CTPA was associated with changes consistent with overdiagnosis: rising incidence but minimal change in mortality and lower case-fatality (3). Even when images with thin-collimation multidetector CT are compelling, the clinical relevance and management of patients with symptomatic SSPE is controversial (62, 63). In a recent systematic review and meta-analysis, the 3-month thromboembolic risk in patients with suspected PE who were left untreated based on a diagnostic algorithm including a negative single-detector CTPA was 0.9% (95% CI: 0.4–1.4). It was of 1.1% (95% CI: 0.7–1.4) in patients left untreated after a multi-detector CTPA. Thus, the use of multi-detector CT increases the rate of SSPE detection, but without resulting in a decreased 3-month thromboembolic risk (61), suggesting that these additional SSPE may not be clinically relevant. However, only few investigations have evaluated the outcome of untreated patients with symptomatic isolated subsegmental PE. A recent review of the literature including 4 diagnostic studies reported a favorable outcome in 60 patients left untreated after the diag-

nosis of SSPE without associated DVT (64).

In a statement from the Fleischner Society on the management of suspected acute pulmonary embolism, it is suggested that the clinical relevance of small peripheral PE and the need to give anticoagulant treatment in such patients is matter to debate (63, 65). They also suggested that in patients with small PE and no DVT, the risks associated with anticoagulant treatment might outweigh the benefits. More recently, the last release of the ACCP guidelines suggested that some patients with subsegmental PE and no proximal DVT could be left untreated (66). An ongoing study, in which patients with symptomatic SSPE are left untreated, will add useful data to this complicated topic (NCT01455818).

Conclusion

During the last two decades, the improvement of diagnostic strategies almost completely eliminated the need for invasive diagnostic testing (i.e. pulmonary angiography). Current algorithms are based on the sequential use of pre-test probability assessment, D-dimer measurement, and if required chest imaging test. These strategies are fairly simple, easy to use and cost-effective. Despite these diagnostic strategies have been very well validated, some efforts still should be done to increase their use and implementation in everyday clinical practice. Initiatives such as Choosing Wisely campaign, which for example suggest not to perform imaging in case of negative D-dimer test and a non-high or unlikely clinical probability, could also reduce the gap between knowledge and practice.

The diagnosis of VTE in special patient populations such as pregnant women and such as suspected VTE recurrence remains challenging. There are also some additional challenges raising that might require adjustments to current diagnostic strategies such as the reduced clinical suspicion threshold resulting in a lower proportion of VTE in suspected patients, as well as the issue of overdiagnosis and overtreatment especially regarding subsegmental PE.

Conflict of Interests

All authors declare that they have no conflicts of interest.

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