Diagnosis of pulmonary embolism

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Summary

Pulmonary embolism is the third cause of mortality by cardiovascular disease after coronary artery disease and stroke, and its incidence is around 1/1000 per year. During the last two decades, many different non-invasive diagnostic tests have been developed and validated. For hemodynamically stable outpatients, the diagnosis of acute pulmonary embolism mainly rests on the sequential use of clinical assessment, D-dimer measurement and multidetector CT. In patients with a contraindication to CT, lower limb venous ultrasonography and ventilation-perfusion scintigraphy remain valid options. Massive pulmonary embolism is a distinct clinical entity with a specific diagnostic approach. In unstable patients with suspected pulmonary embolism, echocardiography should be the initial test.

Introduction

Pulmonary embolism (PE) is the third cause of mortality by cardiovascular disease after coronary artery disease and stroke. It has been estimated that over one million venous thromboembolic (VTE) events or deaths occur each year in six large European countries. Three quarters of VTE-related deaths are due to hospital-acquired VTE, which therefore represents a major health concern [1]. PE is difficult to diagnose because of variable clinical manifestations and poor sensitivity and specificity of symptoms and signs. However, considerable progress has been made in the workup of patients with clinically suspected PE with the advent of diagnostic instruments such as plasma D-dimer measurement, lower limb venous compression ultrasonography and computed tomography pulmonary angiography (CTPA). Moreover, well-validated, rational and cost-effective diagnostic strategies are now available [2].

Clinical presentation

None of the various presenting symptoms of PE is specific to this disease. In 65% of patients, PE is evoked because of pleuritic chest pain. Isolated shortness of breath, usually acute but sometimes
slowly progressive and without an obvious alternative cause, is reported in about 20% of patients [3]. Syncope or shock are a rare clinical presentation of PE (less than 10%). Finally, PE may be discovered in the absence of a clinical suspicion on CT scans performed for other reasons, mostly cancer staging and follow-up.

**Diagnostic strategies**

**Clinical probability of pulmonary embolism**

Sensitivity and specificity of clinical symptoms, signs and abnormalities of blood gases, chest X-ray and electrocardiogram in suspected PE are low when considered singly. Nevertheless, these findings can be combined effectively by clinicians to estimate the patient’s probability of having PE, either implicitly or by prediction rules [4,5]. Both ways of assessing clinical likelihood of PE allow a fairly accurate stratification of patients into two (PE unlikely or PE likely) or three categories (low, intermediate or high clinical probability) corresponding to an increasing prevalence of the disease [6,7]. The vast majority of patients have a low or intermediate clinical probability of PE (around 90%) or belong to the PE unlikely category (around 70%). Table 1 shows the two most widely used prediction rules for PE in their original and simplified versions. The Wells rule [5] has been widely validated and can be applied to both in- and outpatient settings, but it requires a subjective judgment on the probability of an alternative diagnosis, which reduces its interobserver reliability. The revised Geneva score [4] has only been validated in outpatients, but is entirely based on objective criteria. Two recent meta-analyses confirmed the validity of the original and simplified versions of both the Wells and the revised Geneva rules [8,9]. These rules have also been formally evaluated by a direct prospective comparison that showed similar diagnostic performances [10].

**D-dimer**

Plasma D-dimer, a degradation product of cross-linked fibrin, has been extensively investigated in the last 25 years in the setting of VTE diagnosis [11]. Plasma D-dimer levels increase in presence of an acute clot. Hence, a D-dimer level below a certain prespecified cut-off, referred to as "negative" D-dimer, renders acute PE unlikely. However, D-dimer has a low specificity and is not useful for confirming PE. There are numerous available D-dimer assays with different characteristics [11]. The quantitative ELISA or ELISA-derived assays have a sensitivity above 95% at the usual cut-off level of 500 μg/L. They can therefore be used to rule out PE in patients with either low or moderate probability of PE (using three-level scores) or patients classified as PE unlikely (using two-level scores). In the emergency department or in the outpatient setting, a negative ELISA D-dimer can exclude PE without further testing in approximately 30% of patients [6,7]. Outcome studies have shown that the three-month thromboembolic risk was very low (< 1%) in patients left untreated based on a negative ELISA D-dimer test result [12]. Quantitative latex-derived assays and a whole-blood agglutination assay have lower sensitivity in the range of 85 to 90% [11]. Using the two-level Wells rule, moderately sensitive assays are still safe to exclude PE in patients categorized as PE unlikely [7]. However, if a three-level clinical prediction rule is used, the lower sensitivity D-dimer tests only allow to safely rule out PE in patients with a low clinical probability. The diagnostic yield of D-dimer is linked with the false-positive rate that varies according to patient characteristics, for example patient age [13]. As a result, the clinical usefulness of the test, that is the proportion of patients with a D-dimer level below the predetermined cut-off value in whom the diagnosis of PE may be ruled out by the test, is reduced [14]. Recently, the value of a progressive D-dimer cut-off adjusted to age was derived and retrospectively validated (age-adjusted cut-off, in μg/L, equals patient’s age multiplied by 10 in patients aged 50 years or more; usual 500 μg/L cut-off value in younger patients) [14]. Using the age-adjusted D-dimer cut-off would have increased the diagnostic yield by about 20% without increasing the false negative rate. This approach has been formally evaluated in a large prospective outcome study [15] in which all patients with a non-high clinical probability (three-level rule) or belonging to the PE unlikely category (two-level rule) with D-dimer levels below the age-adjusted cut-off were left untreated without further diagnostic testing. In this multicenter European study including 3346 patients, 817 patients (28%) had a D-dimer level below the conventional 500 μg/L cut-off, and an additional 337 patients (12%) had a D-dimer level above 500 μg/L but below their age-adjusted cut-off. The three-month thromboembolic risk was below 1% and similar in both groups. In patients aged 75 years and more, the age-adjusted cut-off increased the proportion of patients in whom PE could be safely ruled out by D-dimer five-fold [15]. Using the age-adjusted D-dimer cut-off thus significantly increases the diagnostic yield of D-dimer in elderly patients.

D-dimer is also more often elevated in patients with cancer, in hospitalized patients and during pregnancy. Deciding whether measuring D-dimer is still worthwhile in these situations remains a matter of clinical judgment. In summary, a "negative" D-dimer result by a highly sensitive assay safely excludes PE in patients with a low or moderate clinical probability, while a moderately sensitive assay excludes PE in patients with a low clinical probability or classified as PE unlikely. The use of an easily remembered age-adjusted D-dimer cut-off value has great potential to further reduce the number of unnecessary imaging tests in older patients with suspected PE.

**Lower limb venous compression ultrasonography**

Lower limb venous compression ultrasonography has become the standard test for diagnosing deep venous thrombosis (DVT)
Finding a proximal DVT by ultrasonography in a patient with clinically suspected PE represents sufficient evidence to warrant anticoagulant treatment without further testing [17]. However, the diagnostic yield of compression ultrasonography is quite limited, as it detects a DVT in only approximately 30–50% of patients with proven PE. In a randomized trial comparing two strategies for diagnosing PE, with and without venous compression ultrasonography, performing systematic ultrasound in patients with an elevated D-dimer allowed avoiding a CT pulmonary angiography (CTPA) in only 9% of patients [6].

Ventilation-perfusion lung scintigraphy

Perfusion lung scintigraphy is a non-invasive technique allowing the visualization of pulmonary perfusion through intravenous injection of albumin macroaggregates labeled by Technetium 99m. Localised pulmonary hypoperfusion is not highly specific for an embolus, since any disease that narrows the airways or fills the alveoli with fluid will result in hypoxic pulmonary arterial vasoconstriction and reduced flow in that pulmonary region. The addition of ventilation scintigraphy (by Xenon 133, Krypton 81m or aerosolized Technetium 99m) further increases specificity, a so-called matched defect (perfusion defect with normal ventilation) usually indicating pulmonary embolism. The high negative predictive value of a normal ventilation-perfusion lung scintigraphy has been confirmed by several studies, including a large outcome study [18] and is a perfectly valid criterion for excluding PE. The positive predictive value of a high probability scan is approximately 90% and most clinicians consider such a result to rule in PE at least in patients with an intermediate or high clinical probability [19]. The main weakness of ventilation-perfusion scintigraphy is the high proportion of non-diagnostic results, particularly in elderly patients. However, in combination with clinical probability assessment, D-dimer and compression ultrasonography, diagnostic algorithms based on the ventilation-perfusion scan allow to safely assess patients with suspected PE [18, 20]. Recent small series suggest that SPECT imaging might increase the diagnostic yield of

<table>
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<th>TABLE I (Continued).</th>
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<tbody>
<tr>
<td>Items</td>
</tr>
<tr>
<td>PE unlikely</td>
</tr>
<tr>
<td>PE likely</td>
</tr>
<tr>
<td>DVT: deep vein thrombosis; PE: pulmonary embolism.</td>
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ventilation-perfusion lung scanning, alone or in combination with low-dose native chest CT, but the results are too preliminary to guide clinical practice [21].

**Computed tomography pulmonary angiography (CTPA)**

Since the introduction of multidetector-row computed tomography (MDCT) with high spatial and temporal resolution and quality of arterial opacification, CT angiography has become the test of choice to diagnose PE. It allows an adequate visualization of the pulmonary arteries up to at least the segmental level [22]. The large PIOPED II series observed a sensitivity of 83% and a specificity of 96% of multidetector (mainly 4-detector) CT [23]. That sensitivity, although higher than that of single-detector CT, may appear disappointing. However, most false negative CT results occurred in patients with a high clinical probability, highlighting the importance of clinical assessment. Five recent outcome studies in which MDCT was used for clinical decision-making, among which two randomized studies, provide evidence in favor of CT as a stand-alone test to exclude PE [6,7,15,18,24]. Table II summarizes the findings of those studies. Whether patients with a negative CT and a high clinical probability should be further investigated by venous compression ultrasonography and/or ventilation-perfusion scintigraphy or pulmonary angiography is controversial [25].

During the development of CTPA as a diagnostic tool for PE, the main focus has been its ability to exclude PE. Management outcome studies have been reassuring in this regard, demonstrating a very low risk of VTE in the three months following a negative CTPA [6,7]. However, 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 a 30% minimal change in mortality, and lower case-fatality [26]. More recently, the improved technology enables visualization of smaller thrombi in peripheral arteries, but their clinical relevance and management is controversial. Patients with SSPE appear to mimic those with more proximal PE regarding VTE risk factors, and outcomes on anticoagulant therapy [28]. On the other hand, in a statement from the Fleischner Society, it is suggested that in patients with small PE and no DVT, the risks associated with anticoagulant treatment might outweigh the benefits [29]. An ongoing study, in which patients with symptomatic SSPE, no DVT and no cancer are left untreated and carefully followed for a three-month period, will add useful data to this complex topic (NCT01455818).

**Magnetic resonance angiography**

Magnetic resonance angiography (MRA) could have been an attractive option for imaging PE due to absence of irradiation and reduced renal toxicity of gadolinium. However, two recent studies shed light on the relatively poor performance of MRA in suspected PE [30,31]. The PIOPED-III study included 371 patients and showed a high 99% specificity with good interobserver agreement. Sensitivity was however rather low at only 78%. Moreover, 25% of MRAs were inconclusive [31]. The French IRM-EP study yielded very similar results in a series of 274 patients. Specificity was also 99 or 100% according to readers with a high interreader concordance (kappa value of 0.93) [30]. Sensitivity varied among readers from 79 to 85%, and 28 to 30% of MRA scans were inconclusive. Therefore, a negative MRA does not allow safely ruling out PE while a positive result is probably indicative of PE.

**Table II**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients, n</th>
<th>PE, %</th>
<th>Negative CT, not treated, n</th>
<th>Clinical probability</th>
<th>3-month thromboembolic risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTEP3 study</td>
<td>Outpatient</td>
<td>756</td>
<td>26</td>
<td>318</td>
<td>Non-high</td>
</tr>
<tr>
<td>Christopher study</td>
<td>Out- and inpatient</td>
<td>3306</td>
<td>21</td>
<td>1505</td>
<td>Any</td>
</tr>
<tr>
<td>PEDS study</td>
<td>Out- and inpatient</td>
<td>694</td>
<td>19</td>
<td>561</td>
<td>Any</td>
</tr>
<tr>
<td>CTEP4 study</td>
<td>Outpatient</td>
<td>1693</td>
<td>22</td>
<td>1359</td>
<td>Non-high</td>
</tr>
<tr>
<td>ADJUST-PE study</td>
<td>Outpatient</td>
<td>3346</td>
<td>19</td>
<td>1481</td>
<td>Any</td>
</tr>
</tbody>
</table>
Pulmonary angiography

Although formerly considered the criterion standard for diagnosing PE, pulmonary angiography is difficult to interpret, frequent disagreement occurring even between expert readers. It is also costly and invasive. The mortality due to pulmonary angiography is around 0.2% [32]. The rare deaths attributable to pulmonary angiography occur in very sick patients with hemodynamic compromise or acute respiratory failure.

Echocardiography

Doppler echocardiography has several uses in suspected pulmonary embolism and it may play a role in risk stratification. In a small subset of patients with PE, transthoracic echocardiography allows a direct visualization of the clot in the right heart chambers or in the right main pulmonary artery. However, the most frequent echocardiographic manifestations of PE are indirect and reflect the hemodynamic changes caused by an acute increase in pulmonary arterial resistance and pulmonary hypertension, usually observed in rather extensive PE. Several echocardiographic measurements have been proposed to quantify right ventricular dilation, of which the most standardized is the right ventricle over left ventricle diameter ratio. Right ventricular hypertrophy and pulmonary artery pressures above 60 mmHg usually suggest chronic pulmonary hypertension. The sensitivity of these signs which are often combined, lies between 40 and 70% in clinically suspected PE, and their specificity is approximately 90%, provided the patient does not have another disease causing chronic pulmonary hypertension [33]. Echocardiography is the first-line test in suspected high-risk or massive PE. Indeed, in patients with shock, it is extremely effective for differential diagnosis with tamponade and cardiogenic shock.

Diagnostic strategies

Suspected non-massive pulmonary embolism

Computed tomography pulmonary angiography (CTPA) has become the thoracic imaging test for investigating suspected PE [2]. Ventilation-perfusion scintigraphy is a valid option but is less often used because of its limited availability in many centers, and the high proportion of inconclusive results. However, since most patients with suspected pulmonary embolism do not have the disease, CTPA should not be the first-line test. In patients admitted to the emergency department, plasma D-dimer measurement combined with clinical probability assessment is the logical initial step and allows ruling out PE in around 30% of patients, with a 3-month thromboembolic risk in patients left untreated below 1%. As previously discussed in the D-dimer section, the use of an age-adjusted D-dimer cut-off seems an interesting option to increase the diagnostic yield in elderly patients [15]. D-dimer should not be measured in patients with a high clinical probability because of a low negative predictive value in that population, nor in hospitalized patients due to a high number needed to test to obtain a negative result. In most centers, CTPA is the second-line test in patients with an elevated D-dimer level and the first-line test in patients with a high clinical probability. CTPA is considered diagnostic of PE when it shows a clot at least at the segmental level or the pulmonary arterial tree. A possible algorithm for PE diagnosis is displayed in figure 1.

Suspected massive pulmonary embolism

Patients with suspected massive pulmonary embolism have a very high mortality rate and require emergent thrombolytic treatment. The clinical presentation evokes a differential diagnosis with other causes of shock such as pericardial tamponade or myocardial infarction and cardiogenic shock. Therefore, the logical initial test in such patients is transthoracic echocardiography. In a patient with hemodynamic shock, an echocardiogram showing signs of acute pulmonary hypertension and right ventricular strain, and normal left ventricular contractility is a very strong argument in favor of massive PE. In fact, most clinicians would readily begin thrombolytic treatment in such a patient without awaiting further diagnostic information. On the other hand, in a patient temporarily stabilized by vasopressive drugs (dopamine or noradrenaline), confirmation may be sought by CTPA.

Conclusions

During the last two decades, the improvement of diagnostic strategies of PE almost completely eliminated the need for...
invasive diagnostic testing (pulmonary angiography). Current algorithms are fairly simple, easy to use and cost-effective. Remaining challenges include the diagnosis of PE in elderly patients as well as the issue of overdiagnosis and overtreatment of subsegmental pulmonary embolism.

**Key-points**

- The incidence of pulmonary embolism is around 1/1000 per year. It is the third cardiovascular cause of death in Western countries.
- Clinical assessment either implicit or by a prediction rule allows an accurate stratification of patients in categories of increasing prevalence of pulmonary embolism (low, intermediate and high clinical probability, or pulmonary embolism unlikely or likely).

**References**


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