Investigation of pulmonary embolism

It all depends on the risk

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The presentation of pulmonary embolism is variable, which can lead to delays in diagnosis and treatment. A high level of clinical suspicion and the ability to stratify patients according to their level of risk are therefore needed to prevent potentially fatal outcomes. This article provides a framework for the investigative approach to patients with suspected pulmonary embolism.

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Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most frequent cardiovascular disease after myocardial infarction and stroke, with an overall annual incidence of 100 to 200 per 100,000 people.

The symptoms of PE are variable, which can lead to delays in diagnosis and treatment. A high index of clinical suspicion and the ability to stratify patients according to their level of risk of VTE are therefore required to enable appropriate and timely investigation.

In contemporary practice, especially with the advent of novel oral anticoagulant drugs, the diagnosis and treatment of PE in a stable patient may be achievable in the primary care setting.

Key points

- **In most patients, pulmonary embolism is suspected based on the presence of dyspnoea, chest pain, presyncope or syncope, and/or haemoptysis.**
- **A negative D-dimer assay in a nonhigh-risk outpatient can safely exclude pulmonary embolism.**
- **If a pregnant woman is suspected of having a pulmonary embolism and the chest x-ray is normal, ventilation perfusion scintigraphy scan may be preferable to computed tomographic pulmonary angiography because of lower maternal radiation exposure.**
- **The finding of a proximal lower limb deep vein thrombosis on compression ultrasonography in a patient suspected of having a pulmonary embolism is sufficient to diagnose pulmonary embolism when further imaging modalities are not readily available or their use is prohibited.**
- **Use of the simplified Pulmonary Embolism Severity Index may help select patients with pulmonary embolism who may be suitable for outpatient care or early hospital discharge.**

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This article provides a framework for the investigation of suspected PE based on the clinical assessment of a patient's pretest probability. Factors that may affect the use of each investigation, as well as the potential risks, adverse effects and contraindications, are outlined. Finally, a tool that may be useful in selecting suitable candidates for outpatient management is described.

Clinical assessment

In most patients, PE is suspected based on the presence of dyspnoea, chest pain, presyncope or syncope, and/or haemoptysis. Dyspnoea is a common symptom, with up to 73% of patients with PE experiencing it. Dyspnoea may be acute and severe in patients with central PE, whereas it is often mild and may be transient in patients with small peripheral PE. In patients with pre-existing heart failure or pulmonary disease, worsening dyspnoea may be the only symptom indicative of PE. Chest pain, classically pleuritic in nature, is also a frequent symptom in patients with PE reported to occur in up to 66% of patients, and is usually caused by pleural irritation due to distal emboli. In central PE, chest pain may have a typical angina character, possibly reflecting right ventricle ischaemia and requiring differential diagnosis with acute coronary syndrome or aortic dissection. Arterial hypotension and shock are rare but important clinical presentations because they indicate significant PE and/or a severely reduced haemodynamic reserve. Syncope is infrequent, but may occur regardless of the presence of haemodynamic instability. Finally, PE may be completely asymptomatic and be found incidentally during the work up for another disease.

Clinical judgement lacks standardisation; therefore, several explicit clinical prediction rules for PE have been developed. The most widely used and validated of these rules is the Wells criteria (Table), which is simple and based on information that is easy to obtain. Using the Wells criteria, 10% of patients with a confirmed PE after imaging can be expected to be in the low-probability category, 30% in the moderate-probability category and 65% in the high-probability category.[1]

Table. Wells criteria for pulmonary embolism

Symptoms	Score
Clinical symptoms of DVT (leg swelling, pain with palpation)	3
Alternative diagnosis less likely than PE	3
Heart rate >100 beats per minute	1.5
Immobilisation (≥3 days) or surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1.0
Malignancy	1.0
Clinical pretest probability	**Total score**
Low	<2
Moderate	2 to 6
High	>6

Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolism.

Investigations

ECG

Sinus tachycardia may be the only change seen in 40% of cases of PE, especially in milder cases.[1] Atrial arrhythmias, most frequently atrial fibrillation, are also seen in patients with PE. Electrocardiographic changes indicative of right ventricle strain, such as inversion of T waves in leads V1 to V4, S1Q3T3 pattern and incomplete or complete right bundle branch block, are helpful but usually found only in more severe cases.

D-dimer testing

Levels of D-dimer, a fibrin degradation product, are elevated in the plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The use of D-dimer testing in this setting is primarily to rule out PE in patients who have a low or intermediate risk of VTE (see flowchart).

D-dimer testing has a high negative predictive value. This has been demonstrated in various studies, including a meta-analysis which concluded that a negative D-dimer automated assay combined with a nonhigh pretest probability can safely and effectively exclude PE in outpatients.[2] On the other hand, a positive D-dimer test generally prompts further diagnostic testing. Fibrin is also generated in a wide variety of conditions, such as cancer, inflammation, bleeding, trauma, surgery and necrosis; D-dimer testing is therefore best avoided in these settings.

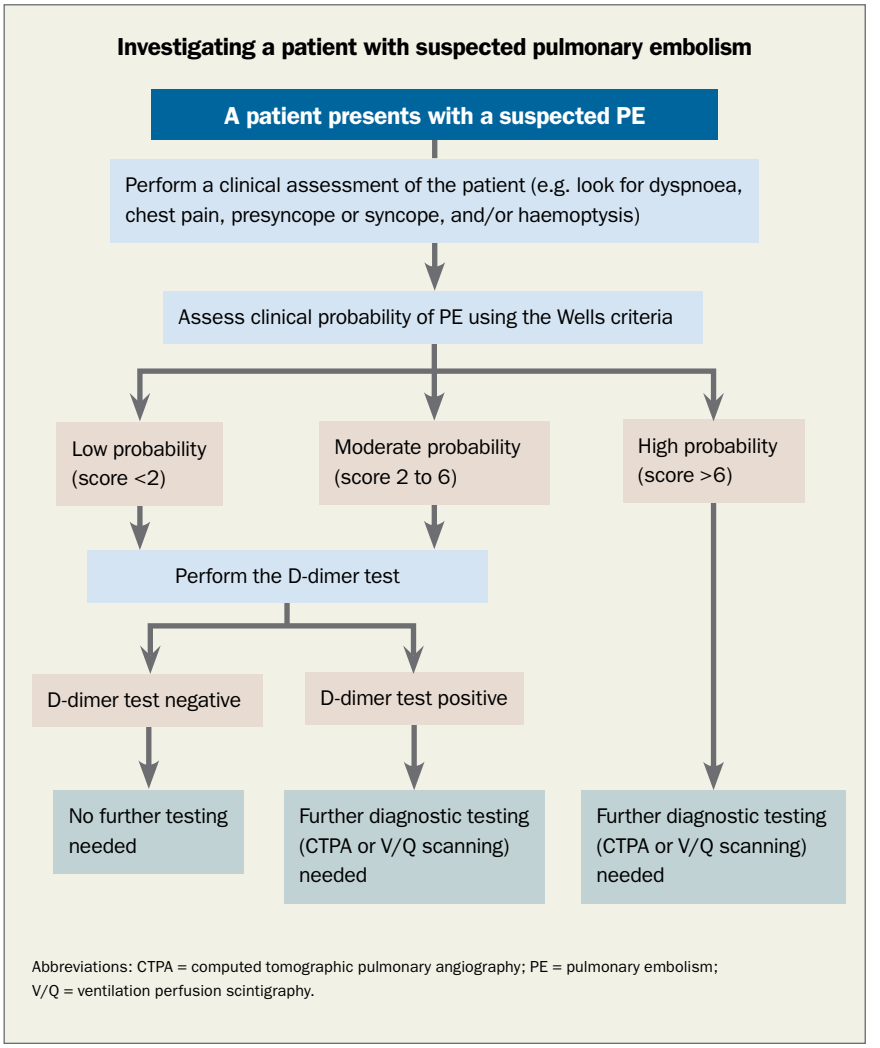
Imaging

Chest radiograph

The chest x-ray findings in PE often consist of nonspecific changes. The main use of a chest x-ray in the evaluation of PE is excluding alternative diagnoses for dyspnoea or chest pain, such as pneumonia or pneumothorax. Westermark's sign, a focus of oligaemia seen distal to a PE, and Hampton's hump, a pleurally-based wedge-shaped opacity representing an area of pulmonary infarction, are present in a minority of cases but interoperator reliability is low. An ipsilateral pleural effusion can be noted in some cases of PE but is nonspecific.

Computed tomographic pulmonary angiography and ventilation perfusion scintigraphy scan

The two imaging modalities that have become the mainstay of PE diagnosis are computed tomographic pulmonary angiography (CTPA) and ventilation perfusion scintigraphy (V/Q) scan.



CTPA has become the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualisation of the pulmonary arteries down to at least the segmental level. V/Q scanning involves the intravenous injection of technetium (Tc)-99m-labelled macroaggregated albumin particles, which block a small fraction of the pulmonary capillaries and thereby enable scintigraphic assessment of lung perfusion. Perfusion scans are combined with ventilation studies in which radioisotope-labelled aerosols or carbon microparticles are inhaled. The purpose of the ventilation scan is to increase specificity: in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatch).

The clinical probability of PE has a significant impact on the predictive value of CTPA and this was demonstrated well in the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) II trial.[3] CTPA was shown to have a much higher negative predictive value in patients with a low pretest probability of PE than in those with a high pretest probability. Conversely, the positive predictive value of CTPA is much higher in patients with a high pretest probability of PE than in those with a low pretest probability. Therefore, clinicians should be particularly cautious in cases of discordancy between clinical judgement and the CTPA result.

It is necessary to consider the risk of radiation exposure when using these imaging modalities, especially in younger patients and pregnant women. In the setting of pregnancy, current studies estimating radiation exposure to the mother and fetus have shown that maternal exposure to radiation, particularly in the context of the radiosensitive glandular breast in pregnancy, is significantly greater with CTPA than with V/Q scanning, resulting in a higher life attributable risk of cancer. On the other hand, the radiation dose to the fetus is marginally greater with V/Q scanning than with CTPA. However, the risk appears to be low with both techniques. CTPA and V/Q scanning have been shown to have equivalent negative predictive values in pregnant women when the radiographic findings are normal and there is no clinical suspicion of an alternative diagnosis. Therefore, it is suggested that chest radiography should be performed as an initial step in deciding on imaging choice. If the chest x-ray is normal, reducing the amount of radiation to the maternal breast favours the use of V/Q scanning over CTPA.[4,5]

There are a few other important precautions to consider regarding contrast use in CTPA, each of which should prompt review of the risks and benefits, and may favour the use of V/Q scanning. One is contrast-induced nephropathy, which is a particular concern in patients with pre-existing renal impairment, especially those with concurrent diabetes and/or heart failure. Intravenous fluid volume loading with isotonic saline (normal saline) is the single most important measure comprehensively proven to reduce the risk of contrast-induced nephropathy. Uncertainty marks regarding the role of sodium bicarbonate for intravenous hydration or the use of agents such as N-acetylcysteine exists due to variable outcomes reported in the literature. Precaution should also be applied to patients who have a contrast reaction history, the most common being a nonallergic anaphylactoid reaction, and to those taking the oral hypoglycaemic agent metformin. The rare risk of lactic acidosis in patients taking metformin increases in the presence of renal insufficiency, and is therefore relevant because of the perceived risk of contrast-induced nephrotoxicity.[6]

Compression venous ultrasonography

Compression venous ultrasonography identifies the presence of DVT in 30 to 50% of patients with PE. In particular, the presence of a proximal DVT on compression venous ultrasonography has been shown to be highly specific (specificity 99%) for PE on CTPA in patients with suspected PE. Therefore, finding a proximal DVT in patients suspected of having a PE is considered sufficiently diagnostic, and anticoagulant treatment can be commenced without further testing. This is especially so when CTPA or V/Q scanning is not readily available or prohibited due to contraindications, or the patient is concerned about radiation exposure.

Echocardiography

Echocardiography is not routinely indicated in the evaluation of the haemodynamically stable patient with suspected PE. However, in the unstable patient, obtaining an echocardiogram is useful in assessing for signs of right ventricular overload or dysfunction seen in patients with a large PE, as well as to help exclude other causes of haemodynamic instability, including pericardial tamponade, acute valvular dysfunction, severe global or regional left ventricular dysfunction, aortic dissection and hypovolaemia. In the long term, echocardiography may be used in assessing patients with PE for chronic thromboembolic pulmonary hypertension.

Prognosis and implications for management

Several prognostic scores have been developed in an attempt to predict which patients may be suitable for complete outpatient care or early hospital discharge, and there is a growing body of evidence regarding the safety of this approach in low-risk patients.[7] One such system is the simplified Pulmonary Embolism Severity Index (sPESI), which uses six easy to obtain variables and a very simple low- or high-risk stratification that has been externally validated retrospectively in a large multinational cohort study (Box).[8] With a negative predictive value of 98.9% for all-cause 30-day mortality in the validation cohort, the sPESI has very sound prognostic accuracy and is simple enough to be used to aid decision making in the primary care or emergency department settings.[8] Using this tool, it is patients in the low-risk group, scoring an sPESI score of 0, who could be considered for outpatient management. Outpatient care should lead to a substantial reduction in healthcare costs and resource utilisation, as well as an increase in patient satisfaction.

Conclusion

Pulmonary embolism is the most serious form of VTE and the presentation is variable. A high level of clinical suspicion is therefore needed to prevent potentially fatal outcomes.

Clinical prediction tools, such as the Wells criteria, have been developed to predict the risk of VTE and the next step in the investigative pathway can be chosen based on the pretest probability of PE. For an otherwise well outpatient who is at low risk of PE, a D-dimer test may be appropriate to exclude PE without the need for further testing. A high-risk score may prompt imaging studies as the first investigation, with the decision between CTPA and V/Q scan depending on several factors (see flowchart). The combination of clinical assessment and the appropriate use of diagnostic tests therefore assists the clinician in identifying patients with venous thromboembolic disease.

The sPESI prognostic tool may be helpful in selecting a small low-risk group of patients who may be appropriate for outpatient care or early hospital discharge. **CT**

Simplified Pulmonary Embolism Severity Index[8]

- Age >80 years
- History of cancer
- History of chronic cardiopulmonary disease
- Pulse rate ≥110 beats/minute
- Systolic blood pressure <100 mmHg
- Arterial oxyhaemoglobin saturation <90%

Each variable scores 1 point, with a total score of 0 points indicating low risk of 30-day mortality and a total score of ≥1 point indicating high risk.

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