Pulmonary embolism: update on diagnosis and management

Paul C Kruger[1,2,3], John W Eikelboom[3,4], James D Douketis[4,5], Graeme J Hankey[6]

Summary

- Pulmonary embolism (PE) is a potentially life-threatening condition, mandating urgent diagnosis and treatment.
- The symptoms of PE may be non-specific; diagnosis therefore relies on a clinical assessment and objective diagnostic testing.
- A clinical decision rule can determine the pre-test probability of PE. If PE is "unlikely", refer for a D-dimer test. If the D-dimer result is normal, PE can be excluded. If D-dimer levels are increased, refer for chest imaging. If PE is "likely", refer for chest imaging.
- Imaging with computed tomography pulmonary angiogram is accurate and preferred for diagnosing PE, but may detect asymptomatic PE of uncertain clinical significance.
- Imaging with ventilation–perfusion (VQ) scan is associated with lower radiation exposure than computed tomography pulmonary angiogram, and may be preferred in younger patients and pregnancy. A low probability or high probability VQ scan is helpful for ruling out or confirming PE, respectively; however, an intermediate probability VQ scan requires further investigation.
- The direct oral anticoagulants have expanded the anticoagulation options for PE. These are the preferred anticoagulant for most patients with PE because they are associated with a lower risk of bleeding, and have the practical advantages of fixed dosage, no need for routine monitoring, and fewer drug interactions compared with vitamin K antagonists. Initial parenteral treatment is required before dabigatran and edoxaban.

Pulmonary embolism (PE) is characterised by embolic occlusion of one or more pulmonary arteries. The incidence of symptomatic PE is estimated to be about 0.5–1 per 1000 people per year, and is increasing as the population ages. PE may also be asymptomatic and undetected.[1] It has different clinical manifestations from deep vein thrombosis (DVT), and may result in chronic thromboembolic pulmonary hypertension (CTEPH) and mortality.[2] This article focuses on the diagnosis and management of PE, and refers to an accompanying *MJA* article on DVT regarding evidence that is common to both DVT and PE.[3]

We have used clinical guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) to formulate evidenced-based recommendations.[4] Evidence supporting the treatment recommendations has been graded according to National Health and Medical Research Council criteria (Box 1).[5]

Diagnosis

Symptoms and signs of PE

The clinical manifestations of PE range from no symptoms to sudden death, depending on the degree of obstruction of the pulmonary vasculature, and the cardiovascular reserve of the patient. Symptoms include dyspnoea (82% of patients), central or pleuritic chest pain (49%), cough (20%), syncope (14%) and haemoptysis (7%).[1] Clinical examination may reveal tachycardia, cyanosis, tachypnoea, low grade fever, and signs of right ventricular dysfunction that include distended jugular veins, tricuspid regurgitation and accentuated pulmonary component of the second heart sound. Up to 50% of PEs are asymptomatic.[2]

Pre-test clinical decision rule: the simplified Wells rule to exclude PE

In patients with suspected PE, clinical decision rules are helpful to determine the pre-test probability of PE and guide further investigation.[6] For example, the simplified Wells rule assigns one point to various clinical factors to determine an "unlikely" (≤ 1 point) or "likely" (≥ 2 points) clinical pre-test probability, as shown in Box 5 of the THANZ guidelines.[4]

Laboratory testing

The utility of the D-dimer test for diagnosis of PE is similar to DVT,[3] with a median sensitivity of 95–97% and median specificity of 39–43%.[7]

Medical imaging

In patients with suspected PE, a chest x-ray may help identify alternative diagnoses such as pneumonia, heart failure or pneumothorax. Two objective non-invasive imaging modalities — multidetector row computed tomography pulmonary angiogram (CTPA) and ventilation–perfusion (VQ) scan — are used to assess patients with suspected PE.[8,9] Deciding which modality is most suitable depends on availability of the imaging equipment, chest x-ray findings (if normal, VQ scan is reasonable, but if abnormal, CTPA is superior to VQ for finding alternative diagnoses), contraindications to iodinated contrast media used in CTPA, and concerns about radiation exposure (which are higher for CTPA than VQ scan), especially in women of childbearing age.

CTPA involves peripheral intravenous injection of iodinated contrast followed by a multidetector row computed tomography scan of the chest. A filling defect within a pulmonary artery indicates a PE. CTPA can visualise the pulmonary arteries down to the subsegmental level. The sensitivity of CTPA is 83% (95% CI, 76–92%) and the specificity is 96% (95% CI, 93–97%) in the largest trial to date.[10] In patients with a "likely" PE, the positive predictive value of CTPA is 96%.[10] In patients with an "unlikely" PE, the negative predictive value is 96% (92–98%); a negative CTPA can therefore accurately rule out PE (evidence level A).[9,10]

CTPA is the preferred imaging modality for most patients with suspected PE as it is highly accurate and can detect alternative diagnoses. Potential disadvantages of CTPA include radiation exposure and allergic reactions to iodinated contrast (anaphylaxis in about 1 in 100 000 patients), and acute kidney injury. Severe renal impairment is not an absolute contraindication to establishing the diagnosis by CTPA because the potential

[1] Fiona Stanley Hospital, Perth, WA. [2] PathWest Laboratory Medicine, Perth, WA. [3] Population Health Research Institute, Hamilton, Canada. [4] Hamilton Health Sciences, Hamilton, Canada. [5] St. Joseph's Healthcare Hamilton, McMaster University, Hamilton, Canada. [6] University of Western Australia, Perth, WA. graeme.hankey@uwa.edu.au • doi: 10.5694/mja2.50233

1 National Health and Medical Research Council levels of evidence[5]

Level	Evidence base	
A	Excellent	One or more level I studies with a low risk of bias, or several level II studies with a low risk of bias
B	Good	One or two level II studies with a low risk of bias, or a systematic review or several level III studies with a low risk of bias
C	Satisfactory	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias
D	Poor	Level IV studies, or level I–III studies/systematic reviews with a high risk of bias

mortality associated with undiagnosed, untreated PE exceeds the treatable risk of acute kidney injury.[11]

A VQ scan involves administering aerosolised radiolabelled xenon to visualise bronchial ventilation and radiolabelled intravenous albumin to visualise the pulmonary circulation. The scan result is classified as low, intermediate or high probability for a diagnosis of PE.[8] A low probability VQ scan reliably excludes PE because it has a high negative predictive value (evidence level A).[12] An intermediate probability VQ scan neither confirms nor excludes PE, and indicates the need for bilateral lower limb compression ultrasound to identify an embolic source, or consideration of a CTPA. A high probability VQ scan, which is characterised by absent perfusion in well ventilated lung segments, has a positive predictive value for PE of > 90%.[13] An advantage of a VQ scan is that the exposure to ionising radiation is lower than in CTPA, which makes it safer for younger patients and women of childbearing age or who are pregnant (see below). VQ scan limitations include a non-diagnostic or "intermediate probability" result, which is as high as 50% in some studies, and inability to identify alternative diagnoses.[12]

Diagnosing first PE using integrated information from clinical presentation, clinical decision rule and investigations

Symptoms and signs of PE are neither sensitive nor specific. An integrated diagnostic approach using a clinical decision rule and confirmatory investigations assists in diagnosis (Box 2).

If PE is "unlikely" (simplified Wells rule ≤ 1) a D-dimer test is indicated. In patients with "unlikely" PE, a negative D-dimer result has a negative predictive value of 99.7% and effectively rules out PE without chest imaging (evidence level A).[14] A positive D-dimer result should prompt a CTPA or VQ scan.

If PE is "likely" (simplified Wells rule ≥ 2), rapid CTPA or VQ imaging is indicated. In this risk group, an abnormality in a segmental or larger vessel on CTPA has a high positive predictive value for PE.[10] VQ scan has similar diagnostic accuracy to CTPA, provided that the chest x-ray is normal; however, VQ scans have a higher risk of being non-diagnostic in patients with an abnormal chest x-ray. In a high clinical risk patient with a negative CTPA or VQ scan showing a low probability of PE, anticoagulation is not indicated because the negative predictive value of objective testing is high.

Investigations to exclude other diagnoses

Electrocardiogram and chest x-ray can help identify some differential diagnoses of PE, including myocardial infarction, pericarditis, congestive heart failure, pneumothorax and pneumonia. The most common but non-specific electrocardiogram manifestation of PE is sinus tachycardia, whereas other electrocardiogram features such as right ventricular strain (deep S wave in lead I, Q wave in lead III, T wave inversion in leads III and aVF) are less common.[15] Similarly, chest x-ray features of PE, which include pleural effusion, atelectasis and consolidation related to pulmonary infarction, are non-specific for PE.[3]

Right ventricular systolic dysfunction, as suggested by increased blood concentrations of troponin T or I, or brain natriuretic peptide or echocardiographic features of right ventricular hypokinesis, typically correlates with the extent of pulmonary vascular obstruction and is a predictor of all-cause mortality.[16–18] However, acute right ventricular dysfunction is common after PE and typically resolves within a few weeks in most patients. If right ventricular dysfunction is identified when PE is diagnosed, a repeat echocardiogram after 3 months of anticoagulation is warranted whether the patient has cardiorespiratory symptoms or not, because CTEPH can be asymptomatic. Persistent right ventricular dysfunction may indicate lung imaging and right heart catheterisation to further investigate for CTEPH.[19]

Prognosis

Survival

PE is associated with a mortality risk of about 15% at 3 months.[2] The simplified Pulmonary Embolism Severity Index (PESI) tool estimates survival and can help guide the decision for hospitalisation (Box 3). A simplified PESI score of 0 denotes low risk (30-day mortality about 1%), whereas a score of 1 or more denotes high risk (30-day mortality about 10.9%).[20] Survival risk is also influenced by the pulmonary artery pressure. At the time of diagnosis of PE, mean pulmonary artery pressure ≥ 30 mmHg is associated with an increased risk of progressive pulmonary hypertension, and mean pulmonary artery pressure ≥ 50 mmHg is associated with < 20% survival at 2 years.[21]

Chronic thromboembolic pulmonary hypertension

CTEPH should be considered in patients who have been diagnosed with PE and have ongoing dyspnoea, fatigue and/or chest pain 3–6 months after diagnosis. Patients with suspected CTEPH should undergo echocardiography to identify right ventricular dysfunction and if this is present, a VQ scan is indicated. The presence of persistent VQ mismatches warrants further assessment in a specialised pulmonary hypertension clinic to consider right heart catheterisation and pulmonary thromboendarterectomy.[22]

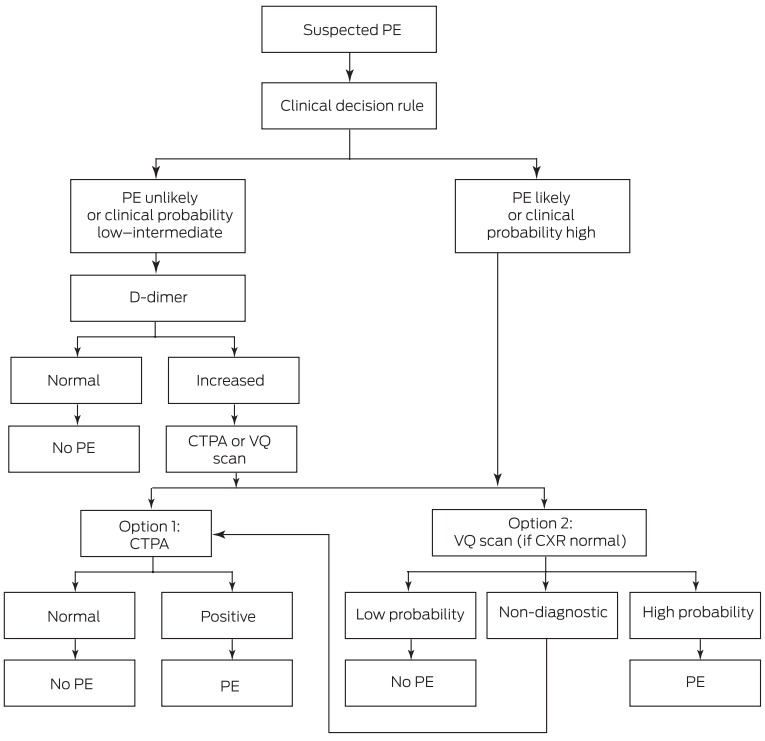
Management

Treatment of PE aims to prevent thrombus progression and recurrent embolisation, and decrease the risk of mortality and CTEPH. Patients with a simplified PESI score of 0 (and selected patients with a simplified PESI score ≥ 1; for example, a patient with cancer but no other risk factors) may be considered for outpatient management or early hospital discharge with therapeutic anticoagulation, provided they have adequate post-discharge follow-up.[23] Hospitalisation is considered in patients with a simplified PESI score ≥ 1 or with either haemodynamic instability, need for oxygen or parenteral analgesics, or comorbidities.[24]

Anticoagulation

The anticoagulant management for acute PE is generally the same as for DVT (see Box 4 of the accompanying *MJA* article),[3] although thrombolytic therapy is considered more frequently. In patients being considered for thrombolytic therapy, treatment may be initiated with intravenous unfractionated heparin or low

2 Diagnosing first pulmonary embolism (PE) using integrated information from clinical presentation, clinical decision rule and investigations



CTPA = computed tomography pulmonary angiogram; CXR = chest x-ray; VQ = ventilation–perfusion. ◆

molecular weight heparin instead of a direct oral anticoagulant, because heparins have a shorter half-life.[25]

When PE is suspected and there is a delay in objective testing, empirical anticoagulation is recommended if there is a moderate to high clinical suspicion of PE. When clinical suspicion of PE is low, it is reasonable to wait up to 24 hours for the results.[26]

Duration of anticoagulation

As with DVT, the duration of anticoagulation for PE is determined by the underlying cause (eg, risk factors) and the estimated risk of recurrence after stopping anticoagulation. Three months of anticoagulation is recommended for treatment of provoked PE associated with surgery (evidence level A), PE associated with non-surgical transient risk factors (eg, oestrogen therapy, pregnancy and puerperium, being confined to bed with an acute illness, leg injury with associated reduced mobility for at least 3 days), and unprovoked PE in patients at high risk of bleeding. At least 6 months of anticoagulation is recommended for PE that is associated with active cancer (evidence level A). Extended anticoagulation therapy is recommended for unprovoked PE if the long term risk of bleeding is acceptable (low or moderate), and for patients with PE and active cancer.[27] All patients receiving extended therapy should have anticoagulation reassessed at least annually to re-evaluate their individual risk of thrombosis and bleeding, monitor for anticoagulant-related adverse effects, and assess renal and hepatic function, which can affect anticoagulant safety.

Thrombolysis

Systemic thrombolysis involves intravenous administration of a thrombolytic agent which accelerates the resolution of PE compared with anticoagulation but increases the bleeding risk. There are two situations where thrombolytic therapy should be considered. The first is patients with clinically massive PE, manifest by systemic hypotension (systolic blood pressure < 90 mmHg or cardiogenic shock) or impending respiratory failure and acceptable bleeding risk (evidence level C). The second is clinically apparent haemodynamic deterioration after starting anticoagulation in conjunction with a bleeding risk that is not unacceptably high.[27] However, there are relative contraindications to thrombolysis in selected patients; for example, those with recent (within 2 weeks) bleeding, an intracranial mass or vascular malformation, or recent (within 2 weeks) surgery.[28] Hence, the potential benefits of thrombolysis should be weighed against the bleeding risks on a case-by-case basis (eg, type of recent surgery and post-surgical haemostasis, clinical severity of PE).[29,30] Moreover, thrombolytic therapy can be adjusted according to bleeding risk; for example, using a lower dose parenterally or direct administration by pulmonary catheter.

Catheter-directed thrombolysis involves inserting a catheter into the pulmonary artery and infusing a thrombolytic directly into the PE. The treatment appears to be as effective as systemic thrombolysis for thrombus removal but is more difficult to undertake.[27] In an observational study of 2060 patients with PE, the risk of in-hospital mortality and major bleeding was lower with catheter-directed thrombolysis compared with systemic thrombolysis (7.9% *v* 15.5%; $P < 0.001$), and the risk of intracranial haemorrhage was not significantly different (1.0% *v* 0.9%; $P = 0.849$).[31] Limited evidence suggests that, if available, catheter-directed thrombolysis is preferred to systemic thrombolysis in patients with risk factors for bleeding.[27,32]

Thrombus removal strategies

Evidence for catheter-based thrombus removal for acute PE is limited because it has not been evaluated without thrombolytic therapy. However, it may be an option when a patient is hypotensive and has a high bleeding risk, failed systemic thrombolysis, or shock that is likely to cause death before systemic thrombolysis can take effect.[28] Surgical pulmonary embolectomy may be considered in patients with a massive PE that is surgically accessible and who have absolute contraindications to thrombolysis.

3 Simplified Pulmonary Embolism Severity Index[20]

Variable	Score
Age > 80 years	1
History of cancer	1
Chronic cardiopulmonary disease*	1
Pulse ≥ 110 beats/min	1
Systolic blood pressure < 100 mmHg	1
Arterial oxyhaemoglobin saturation < 90%	1

The simplified Pulmonary Embolism Severity Index assigns one point to each of the above variables. A total score of 0 denotes low risk and a total score ≥ 1 denotes high risk of mortality. * Combination of history of heart failure and history of chronic lung disease. ◆

4 Pulmonary embolism rule-out criteria (PERC) rule[57]

- Arterial oxygen saturation ≤ 94%
- Pulse rate ≥ 100 beats/min
- Age ≥ 50 years
- Unilateral leg swelling
- Haemoptysis
- Recent trauma or surgery
- Prior pulmonary embolism or deep vein thrombosis
- Exogenous oestrogen use

The PERC rule has a pooled sensitivity of 97% in patients with unlikely pulmonary embolism.

Special circumstances that may influence diagnosis and management

Pregnancy may normally cause dyspnoea and increase D-dimer levels, which can obscure the diagnosis of PE.[33] Clinical judgement and a high index of suspicion for diagnosing PE is therefore required.[34] Ionising radiation from CTPA and VQ scan carries risks for mother and fetus. For the mother, the average whole body dose of radiation associated with CTPA ranges from 2 to 10 mSv, and with VQ scan from 0.6 to 1.5 mSv.[35] The lifetime risk of breast cancer may be increased after exposure to radiation from CTPA.[35,36] For the developing fetus, exposure to ionising radiation has teratogenic and carcinogenic risks which are dependent on the stage of fetal development (highest risk during first trimester) and fetal absorbed dose.[37,38] The risk of miscarriage or major fetal malformations is negligible when the fetus is exposed to < 50 mGy of ionising radiation.[38] The estimated fetal doses of radiation from CTPA and VQ scan are within acceptable limits at about 0.66 mGy and 0.6 mGy, respectively.[39,40] The carcinogenic risk for the fetus is controversial. The International Commission on Radiological Protection estimates that exposure to 30 mGy is associated with one cancer per 500 fetuses.[41] Despite these risks, it is important for pregnant or post partum women with suspected PE to undergo prompt diagnostic work-up, including imaging, because the risk of ionising radiation from imaging is lower than the risks of undetected PE.[42] VQ scan is considered the chest imaging investigation of first choice for a young woman, and radiation dose reduction technologies should be used if available.[42] CTPA should be used in pregnant women with an abnormal chest x-ray, or when compression ultrasound or VQ are non-diagnostic.[43] As for DVT, treatment for PE during pregnancy typically involves low molecular weight heparin, which does not cross the placenta.[44]

Unresolved issues

Incidental, asymptomatic PE has been disclosed by multidetector CT, performed increasingly for other indications, with prevalence of about 2.6% overall and 3.1% in patients with malignancy.[45] Up to 50% of incidental PEs may be found in the main and lobar pulmonary arteries.[46] Management is uncertain due to a lack of high quality evidence. Anticoagulation is recommended if the patient has symptoms that could be attributable to the PE; the PE is located in the main, lobar and/or segmental pulmonary arteries; concurrent DVT is present; or the patient has active cancer.[26,47–49] Anticoagulation may not be necessary if the patient has a single subsegmental PE and no additional VTE risk factors.[49,50]

Isolated symptomatic subsegmental pulmonary embolism (SSPE) also poses a management challenge and has become more frequently detected following the introduction of CTPA.[51] While it has been suggested that SSPE represents an overdiagnosis of PE in which the risks of anticoagulation outweigh the benefits,[52,53] two studies report that patients with SSPE have a higher risk of recurrence and mortality than patients without PE,[54] thus supporting anticoagulation for SSPE.[51] Factors that support anticoagulation for SSPE include concurrent DVT, which increases the risk of recurrent VTE, and persistent risk factors for VTE, which are common in patients with SSPE. In patients with SSPE and a contraindication to anticoagulation or risk factors for bleeding, an alternative to anticoagulation is to perform serial compression ultrasound to investigate for new proximal DVT before it leads to recurrent PE, provided that the patient has adequate cardiopulmonary reserve and does not have risk factors for recurrent VTE.[51,55] A study of the safety of withholding anticoagulation in patients with negative serial compression ultrasound is currently recruiting patients (NCT01455818).

The increasing availability of CTPA has created a tendency for clinicians to test more patients for suspected PE.[53] Due to an increase in the use of diagnostic imaging for suspected PE, the proportion of patients undergoing testing who are diagnosed with PE has decreased from ~ 20% in the 1990s to ~ 5% in the 2010s.[56] This potential overutilisation of CTPA may be decreased by restricting testing to patients with low clinical suspicion who have a positive D-dimer result and those with a moderate to high clinical suspicion for PE.[53] The PE rule-out criteria (PERC) rule along with the Wells and Geneva clinical decision rules identify patients in the emergency department setting whose probability of PE is so low as to justify not measuring D-dimer levels (Box 4).[29] Patients are suitable for assessment by the PERC rule if PE is "unlikely" and they are aged < 50 years. If all eight PERC variables are negative, PE can be excluded without D-dimer testing or imaging (evidence level C).[57] The PROPER trial showed that the use of a PERC-based strategy was non-inferior to the usual diagnostic strategy using D-dimer and CTPA for the rate of subsequent thromboembolic events among low risk emergency department patients.[58]

Conclusion

PE is a potentially fatal condition that requires prompt diagnosis and treatment. With the increasing availability of rapid and accurate medical imaging which can detect asymptomatic PEs, the incidence of PE appears to be increasing. Direct oral anticoagulants have expanded the available treatment options and are now recommended as a first line anticoagulant treatment for most patients. Further information on the diagnosis and treatment of PE is available from the THANZ guidelines.[4]

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