Pulmonary embolism: clinical features and management

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Pulmonary embolism (PE) often presents diagnostic difficulties, as its presentation is varied and non-specific. This article attempts a logical approach to the management of a patient with suspected PE, starting with how it may occur, the assessment of clinical probability of PE and subsequent investigations and treatment.

Pulmonary embolism (PE) is common but can be difficult to diagnose. It remains in general under-diagnosed, often occurring as a terminal event with comorbid disease (post-mortem studies show under-diagnosis as a contributing cause of death in up to 70% of patients coming to autopsy; Modan et al, 1972). In the UK, 20 000 patients die of PE each year in hospital, often associated with comorbid disease, and 40 000 have non-fatal episodes.

Pathology is caused by the occlusion of a pulmonary artery by venous thrombus, almost always originating in the upper leg and pelvic veins. Air, amniotic fluid and fat emboli are rarer causes, beyond the remit of this article. Combining clinical suspicion based on presenting features, appropriate risk factors and appropriate investigations usually allows the diagnosis to be reached.

PRESENTATION

Presentation is diverse, depending on the size of vessel occluded and the patient's cardiorespiratory reserve. A small PE in a young fit adult may cause little or no symptoms, but could cause significant cardiac compromise in an elderly patient with underlying lung disease. Most PE are small, with a considerable differential diagnosis to eliminate. There are many risk factors, the presence of which provides important circumstantial evidence.

A small embolism will reach the periphery of the lung, sometimes producing a wedge-shaped shadow on the chest X-ray, and may cause lung infarction. The precise mechanism of infarction is not clear. It may present with dyspnoea, pleuritic chest pain, and occasionally haemoptysis, without significant circulatory impairment.

A large embolism suddenly obstructing a major pulmonary vessel has marked effects on cardiac function, often associated with anterior chest pain and collapse, and is less likely to cause pleuritic pain.

Chronic (recurrent) pulmonary embolic disease can develop over years and may manifest as pulmonary hypertension and right ventricular failure. Dyspnoea is incremental, often with small, clearly elicitable episodes of deterioration.

In assessing the patient with an acute presentation one must distinguish between small and large PE, as the latter are life-threatening and must be diagnosed and treated swiftly.

SYMPTOMS

The common symptoms and their frequencies are:

- Dyspnoea (84%)
- Pleuritic pain (74%)
- Anterior chest pain (68%)
- Cough (53%)
- Haemoptysis (30%)
- Asymptomatic (10%) (based on Bell et al, 1977).

Symptoms of cardiac compromise are important and indicate a large PE. These include collapse or dizziness on standing, severe dyspnoea and often severe anterior chest pain.

SIGNS

The signs of PE are non-specific and may be absent. The presence of a clinical deep vein thrombosis (DVT) must be looked for, as it provides further evidence of venous thromboembolic disease. *Table 1* lists the most common signs and their association with a large or small PE. Signs of right heart strain should prompt early, rapid action. The highlighted signs suggest a rise in pulmonary vascular pressure as a result of a large PE.

As symptoms and signs vary between presentations, the presence of a risk factor will add to the suspicion of PE and helps decide if further investigation is warranted.

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RISK FACTORS

These include recent surgery or trauma, immobility, malignancy and increasing age (*Table 2*). If a patient has no apparent risk factors and is young, then a family history of venous thromboembolic disease is very important as it may represent an inherited clotting disorder.

A combination of risk factors is synergistic, so a patient with a clotting disorder who acquires a further risk factor has a greater chance of venous thrombosis. Resistance to activated protein C is found in Caucasians with prevalence between 2400–7000/100 000 population and occurs in 21% of patients with venous thromboembolic events. It is caused by a factor V Leiden defect, the result of a single point mutation in the factor V gene.

DIFFERENTIAL DIAGNOSIS

As the symptoms and signs of PE are often non-specific there is a wide differential diagnosis (*Table 3*), with large and small PE having different differential lists.

INITIAL INVESTIGATIONS

Chest X-rays are useful in excluding other diagnoses. In PE the chest X-ray is more likely to appear normal than show a wedge-shaped defect (see article by Howling and Hansell on p. 41). Occasionally there may be other features such as small pleural effusions, and large emboli may cause dilatation of a proximal pulmonary artery with oligaemia in the distal lung field.

Laboratory tests are helpful in providing markers of other disease, such as raised cardiac enzymes in heart disease and raised white cell count in infection (although this may be raised when there has been lung infarction). D-dimer levels are more specific (see below).

Arterial blood gas tensions (ABGs) should only be taken if pulse oximetry reveals hypoxia with the patient breathing room air or if the patient is tachypnoeic. ABGs may show a respiratory alkalosis and may confirm hypoxaemia. This may not be present with a small PE and so its absence does not exclude emboli.

Electrocardiography helps exclude other diagnoses, specifically acute myocardial infarction and tachyarrhythmias. In PE it is more likely to show a non-specific tachycardia or atrial fibrillation than classical S1, Q3, T3 changes (seen in only 25% of large PE; Stein et al, 1975). Signs of right ventricular strain with right bundle–branch block, P pulmonale, right axis deviation and T wave inversion in leads V1–V3 are more common than S1, Q3, T3 changes, but still only occur after obstruction of over 50% of pulmonary vasculature in a previously healthy patient (McIntyre et al, 1972).

The decision to investigate further should be based on clinical suspicion as to whether a PE has occurred. The commonest scenario is a patient with a risk factor who becomes breathless suddenly, with a normal chest X-ray and perhaps mild hypoxia, and no obvious cause. Assessment of the patient allows a clinical probability to be arrived at, either high, intermediate or low, which has a valuable predictive effect (Hyers, 1995).

High clinical probability
(80–100% chance of PE)

- Presence of a risk factor
- Radiographical or ABG consistent finding, lack of evidence for another explanation.

TABLE 1.
Signs of pulmonary embolism (PE)

Sign	Small PE	Large PE
Tachypnoea	Usually present	Marked
Tachycardia	Usually present	Marked
Pleural rub	May be present	Unlikely
Crackles	May be present	If resultant heart failure
Fever	May be present	Uncommon
Jugular venous pressure	Normal	**Raised**
Blood pressure	Normal	**Low**
Gallop rhythm	No	**Common**
Cyanosis	No	**Common**

TABLE 2.
Risk factors for pulmonary embolism

Acquired risk factors	**Surgery or trauma**
	Immobility including transitory causes such as air flight and long coach journeys
	Age over 40 years
	Malignancy
	Pregnancy
	Stroke
	Lupus anticoagulant
	Nephrotic syndrome
	Congestive cardiac failure
	Hyperviscosity states, e.g. myeloproliferative disorders
	Oral contraceptives (oestrogen-containing)
Inherited risk factors	**Activated protein C resistance**
	Protein C deficiency
	Protein S deficiency
	Antithrombin III deficiency
	Elevated factor VIII levels
	Prothrombin G20210
	Hyperhomocystinaemia (rare)

The most important factors are highlighted

Intermediate clinical probability (20–80% chance of PE)

- Neither high nor low probability.

Low clinical probability (1–19% chance of PE)

- No risk factor
- Clinical symptoms or signs explainable by other causes
- ABG and/or chest X-ray explainable by other causes.

Further investigation should be undertaken in intermediate and high probability cases.

SPECIFIC INVESTIGATIONS

Radiology of PE is discussed in the article in this issue by Howling and Hansell (p. 41).

D-dimer

This is a sensitive but not specific test of venous thromboembolic disease. Proteolysis of fibrin by plasminogen at the site of thrombus formation releases D-dimer, which can be measured in the serum. Values of <500 μg/litre reliably exclude PE in patients with intermediate and low probability lung scans (see later) (Perrier et al, 1994; Jeffrey et al, 1998). It does not exclude PE in high probability scans. It has no positive predictive value as there are many causes for it to be raised, e.g. recent surgery, trauma, myocardial infarction and sepsis.

Ventilation/perfusion lung scanning

This remains the first-line investigation of possible PE. Following the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study the interpretation and use of ventilation/perfusion (V/Q) scans seems most effective in conjunction with clinical probability (Worsley and Alavi, 1995). V/Q results should be interpreted as normal or showing low, intermediate or high probability for PE. A normal scan excludes PE with 96% accuracy and a high probability scan with a risk factor is diagnostic of PE with 86–92% accuracy (Kipper et al, 1982). A low probability scan with no risk factors requires no further investigation for PE. Patients with intermediate scans and those where there is discordance between the V/Q result and clinical suspicion require further investigation.

TABLE 3.
Differential diagnosis of pulmonary embolism (PE)

Differential diagnosis of any PE	Acute myocardial infarction
	Pneumonia
	Asthma
	Pneumothorax
	Congestive cardiac failure and acute pulmonary oedema
	Tachyarrhythmia
	Pleurisy/pericarditis
	Musculoskeletal/rib fracture
	Lobar collapse, e.g. secondary to tumour
Differential diagnosis of large PE	Acute myocardial infarct
	Acute pulmonary oedema
	Pericardial tamponade
	Hypovolaemia
	Sepsis
	Aortic dissection

Spiral computed tomography of the lungs

V/Q scans are often not performed until the day after presentation or after a weekend. This delay has prompted many clinicians to use spiral computed tomography (CT) as the first-line investigation and it is often the first-line investigation when a large PE is suspected and early diagnosis is needed. The speed of spiral CT scanning allows the pulmonary vasculature to be examined with the use of peripherally administered contrast during a single breathold. It is sensitive and specific for central and segmental vessels, but is less good at detecting peripheral emboli, which may account for up to 30% of PE (see previous article).

Echocardiography and pulmonary angiography

Echocardiography may be useful after a large PE in a compromised patient, as it can show right heart dilatation, occasionally thrombus and increased pulmonary artery pressure readings if tricuspid regurgitation has developed. Pulmonary angiography remains the gold standard investigation for PE but is invasive, time consuming, needs experienced radiologists and is only available in 15% of British hospitals. For practical purposes it is hardly ever done.

Doppler ultrasound scans of the legs

If this is positive, with an intermediate probability lung scan, this is strong evidence of PE, as over 90% of PE are secondary to DVT. Doppler ultrasound is a powerful adjunct to lung scanning, and can be performed with minimal delay. An algorithm for investigation of PE is shown in *Figure 1*.

TREATMENT

The aims of treatment are to prevent death and morbidity acutely and to reduce the incidence of recurrence. It can be divided into prevention, primary treatment and secondary treatment.

Prevention

Identifying patients in hospital with risk factors is essential, as prophylaxis with low molecular

weight heparin (LMWH) by once-daily subcutaneous injection is simple. It does not need monitoring, as its effects are predictable and weight dependent. Perioperative use of subcutaneous heparin can prevent about half of PE and about two-thirds of DVTs, with a significant reduction in fatal episodes (Gray and Firoozan, 1992).

Primary treatment

If the PE is small and the patient reasonably well, then the supportive care required may be just analgesia and oxygen. Specific treatment is with intravenous heparin infusion following an initial bolus dose of 5000 units. The activated partial thromboplastin time (APTT) should be monitored 4–6 hours after initiation, 6–10 hours after any dosage change, then daily with a target of 1.5–2.5 times normal. This is usually achieved with a continuous infusion of between 25 000 and 35 000 units per 24 hours (400–600 units/kg). If clinical suspicion of a PE is low, treatment need not be commenced until after the V/Q scan if the result is positive. Heparin does not reduce acute mortality but significantly reduces further events.

LMWHs are now first-line treatment for DVT and are as effective as intravenous heparin in PE (Simonneau et al, 1997), but not all LMWHs are licensed for this use.

With a large PE, presentation may be more dramatic and supportive care is very important, consisting of manoeuvres to increase venous return and maintain filling pressures within the heart, maintaining cardiac output. This can be achieved by lying the patient flat, giving intravenous fluids or colloid, and giving intravenous vasopressor agents if fluids are not producing adequate filling pressures and cardiac output. Once the patient is stabilized spiral CT should be performed.

Specific therapy will consist of anticoagulation using the heparin regimen as above. Thrombolysis is used when there is significant cardiac compromise, which is not responding to intravenous fluid and vasopressor resuscitation.

Thrombolysis: Thrombolysis achieves faster resolution of thrombus and more rapid recovery of normal vascular flow than simple anticoagulation, but the long-term outcomes are similar. However, it has potentially devastating side-effects, so its use is restricted to life-threatening cardiac compromise. Cerebral haemorrhage can occur in up to 1% of cases. Thrombolysis has been used successfully and safely in pregnancy and this is not a contraindication unless immediately postpartum.

Regimens for thrombolysis are varied. Accelerated protocols can be used, although they have not been shown to be better or worse than the recommended regimens summarized in *Table 4*.

Pulmonary embolectomy: This is reserved for severe cardiac compromise where thrombolysis has either failed or is contraindicated. It requires an experienced team to be successful and, although used infrequently, small studies (Doerge et al, 1999) have shown favourable outcomes.

Secondary prevention

These consist of oral anticoagulants (and LMWH subcutaneously), and vena caval filters.

Anticoagulants: Coumarins, warfarin in the UK, are commenced in hospital and heparin continued until the prothrombin time is therapeutically elevated. This is measured using the international normalized ratio (INR), which should reach levels of 2–3 times normal and must be maintained at this level for 24 hours before heparin is stopped (usually within 4–5 days). Warfarin can be started at the same time as heparin, as there is no advantage in prolonging heparin therapy beyond the few days needed to establish a desired INR

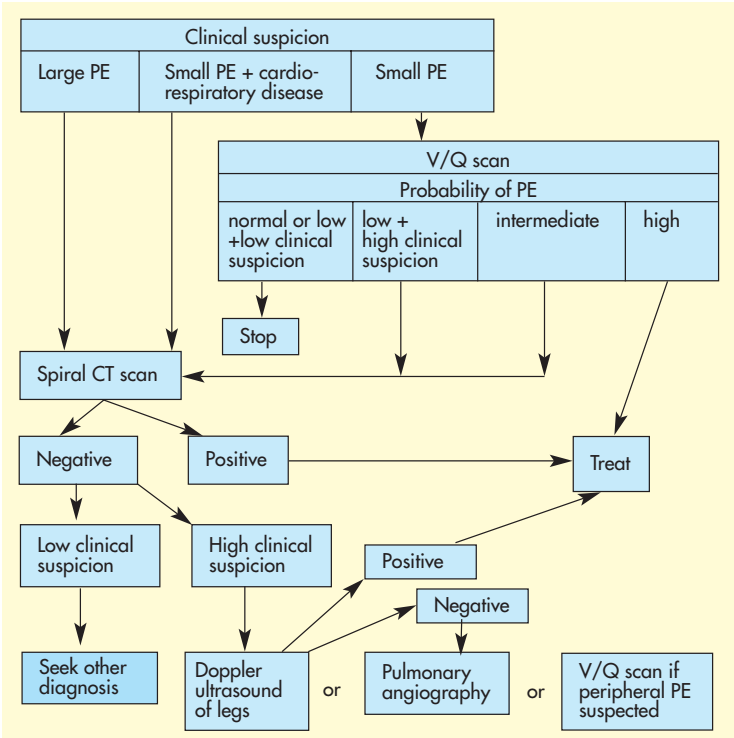

Figure 1. Algorithm for investigation of pulmonary embolism (PE). CT = computed tomography; V/Q = ventilation/perfusion.

TABLE 4.
Regimens for thrombolysis in pulmonary embolus

Drug	Regimen
Streptokinase	250 000 units in 20–30 minutes followed by 100 000 units/hour for up to 24 hours
Tissue plasminogen activator (t-PA)	10 mg intravenously over 1–2 minutes followed by an infusion of 90 mg over 2 hours

with warfarin. Heparin is continued for a 24-hour overlap with warfarin, which can be thrombogenic when started alone during active thrombosis.

Subcutaneous LMWH can be given when warfarin is contraindicated, e.g. in pregnancy. Long-term side-effects of heparin should be considered, particularly osteopenia with prolonged use. A dose of 20 000IU per day for 6 months can be given before osteopenia is significant; it is usually reversible (Ginsberg and Hirsch, 1995).

There is some controversy as to how long anticoagulation should be continued. After the first episode of PE, treatment is recommended for 3–6 months. Studies suggest that 3 months' treatment is adequate (British Thoracic Society, 1992) and that for first events treating for longer than this is not effective when assessing risk:benefit ratio of anticoagulation. With repeated PE, unless there is an obvious reversible cause, permanent anticoagulation is recommended. Repeat Doppler ultrasound scans of the legs or repeat V/Q scans have been used to confirm complete resolution of thrombus before stopping anticoagulation.

Vena caval filters: These have been used in patients with recurrent venous thromboembolic disease where anticoagulation is contraindicated or has been ineffective. They are inserted under radiological guidance via the femoral or jugular veins and are lodged between the renal veins. They can be permanent, or temporary and retrievable. Complications of insertion are low but can be extremely serious, including life- and limb-threatening events, so use is very conservative.

CHRONIC THROMBOEMBOLIC PULMONARY DISEASE

Recurrent pulmonary microemboli, often occurring over many years, eventually lead to irreversible pulmonary hypertension with resultant right heart failure and cor pulmonale. In these patients dyspnoea is chronic with insidious and often stepwise progression. Cyanosis and peripheral oedema is common; the jugular venous pressure is raised and there are third and fourth heart sounds. The pulmonary component of the second heart sound is loud. The systolic pulmonary artery pressure is often greater than 70 mmHg.

Treatment is aimed at preventing further progression but is unlikely to reverse symptoms. It consists of anticoagulation, domicilary oxygen and some offloading of peripheral oedema, although filling pressures must be maintained. Heart–lung transplantation is a final alternative.

KEY POINTS

- Pulmonary embolism (PE) is common with a diverse presentation. It may be asymptomatic or present through a wide spectrum of symptoms.
- A history of risk factors is important, recent surgery and immobility being common.
- There is often a wide differential diagnosis to exclude with initial investigations.
- A clinical probability of PE can be determined based on the presence of a risk factor, chest X-ray or arterial blood gas findings, and lack of evidence for another cause of the symptoms.
- Subsequent investigation combines clinical probability with a number of different possible investigations of which ventilation/perfusion scans are still first line. A low or intermediate probability lung scan requires further investigation, as 60% of PE will give this result.
- Treatment is anticoagulation, unless it is a life-threatening episode in which case thrombolysis should be given.

CONCLUSIONS

PE has a wide spectrum of clinical presentations, ranging from isolated dyspnoea without an obvious cause to an extremely ill, shocked patient, and can have a high mortality. It often presents diagnostic difficulties that should be approached logically, with criteria for investigation based on local facilities. Treatment should consist of anticoagulation, with thrombolysis reserved for life-threatening events. The British Thoracic Society (1997) recommends that each acute hospital adopt a local strategy, which is clearly defined and dependent on local expertise and equipment available. **HM**

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