Pulmonary embolism

Assessment and management

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BACKGROUND Pulmonary embolism (PE) is a potentially life threatening disorder most commonly seen in debilitated patients with other common medical problems.

OBJECTIVE This article aims to increase the reader's understanding of the aetiology and pathophysiology of PE so as to identify particular at risk patients. An approach to investigation and management will also be explored.

DISCUSSION Pulmonary embolism has an incidence of approximately two per 1000 per year, generally as a consequence of deep venous thrombosis (DVT), in the setting of immobility. Deep venous thrombosis and PE during a prolonged airline flight in an otherwise fit person is a rare event. Clinical assessment and simple investigations form the basis of initial evaluation. The confirmatory test is generally a ventilation/perfusion lung scan or a computerised tomography pulmonary angiogram. There is still considerable discussion as to which is the better test – both are valid if performed to acceptable standards – thus local factors often determine which is performed. Further tests may be needed in those with intermediate probability of PE after a confirmatory test. These patients, and those presenting with massive PE, may require pulmonary angiography (still regarded as the gold standard test). Treatment is anticoagulation, typically with low molecular weight heparin followed by 6 months of warfarin. Thrombolytic therapy is reserved for the acute massive presentation. Appropriate treatment reduces mortality substantially, however, rarely the clot remains unresolved and thromboembolic pulmonary hypertension (requiring expert evaluation) develops.

Pulmonary embolism (PE) is an uncommon but important cause of sudden onset breathlessness that needs to be diagnosed early to prevent a subsequent fatal embolus.

Pathophysiology

Pulmonary embolism occurs as a complication of deep venous thrombosis (DVT). Virchow's triad identifies abnormalities of blood flow, blood constituent and vein wall singularly or in combination as the key mechanisms in thrombosis. Reduction in the flow may be due to:

- immobilisation
- local pressure
- reduced perfusion (eg. low cardiac output or hypovolaemia), or
- venous obstruction (eg. congestive cardiac failure).

Abnormalities of the blood itself predisposing to DVT include:

- defined hypercoaguable states, or
- increased blood viscosity (eg. polycythaemia or sickle cell disease), and
- other conditions where the precise mechanism is unclear (eg. malignancy, pregnancy, oral contraceptive pill use, recent trauma).

The vessel wall may be damaged by local trauma or inflammation and this may trigger formation of thrombosis.

The ileo-femoral system is the commonest site of significant PEs, but smaller veins (eg. axillary) may still produce clinically and haemodynamically significant PE.

Aetiology

Pulmonary embolism is most commonly seen in patients with reduced mobility and underlying medical illness.[1] Immobilisation, surgery in the past 3 months, stroke, previous history of venous thromboembolism,

and malignancy are the most important risk factors. The incidence increases exponentially with age, with many patients manifesting multiple risk factors and a consequent very high DVT/PE risk.

In patients with extensive or recurrent DVT/PE (especially age <50 years), genetic prothrombotic disorders (factor V Leiden mutation, excess factor VIII, antithrombin 3 deficiency, protein C and S deficiencies) are often present. Other important risk factors include the oral contraceptive pill, smoking, obesity and hypertension.

'Economy class syndrome' (or traveller's thrombosis) is a rare but recently much publicised condition. The incidence through various studies appears to be in the range of 0.25 per 100 000 passengers in flights longer than 8 hours, but an increased risk of thrombosis has not yet been confirmed in flights of less than 4 hours. Thromboembolism has been described with other forms of travel where immobilisation has exceeded 4 hours. Simple advice given by airlines such as keeping mobile and well hydrated in flight would be adequate prevention for most patients. In those with multiple risk factors, in particular previous thromboembolic disease, compressive stocking and/or prophylaxis with warfarin or low molecular weight heparins may be considered (*Table 1*).

Clinical features

Clinical features vary depending on the size of the embolus (thus the degree of pulmonary vascular bed obstruction) and the ability of the right ventricle to respond to increased afterload. The presentation may be 'acute massive', or 'classic'; approximately half are asymptomatic.

An acute massive PE may present as circulatory collapse or even cardiac arrest. It should also be considered in those presenting with severe dyspnoea and type 1 respiratory failure (hypoxia without hypercapnia). Key physical findings are that of clinical shock: the patient is cold, clammy, hypotensive and the jugular venous pressure is elevated.

The 'classic' presentation of PE is of sudden onset dyspnoea, chest pain and haemoptysis, the latter two being less common and due to pulmonary infarction. Cough and wheeze are occasionally described. Examination reveals tachypnoea, tachycardia, and an elevated jugular venous pressure. The chest is usually clear to auscultation, however a pleural rub may be heard if pulmonary infarction is present.

Investigation of suspected PE

History, examination and basic tests are used to determine the clinical probability of PE (*Table 2*). Initial investigations should include:

- chest X-ray (typically normal, occasionally showing regional hypo-perfusion but useful to exclude other differential diagnoses)
- electrocardiogram (the classic S1Q3T3 – an S wave in standard lead I, Q wave and T wave inversion in standard lead III is infrequently seen), and
- arterial blood gases, where a widened A-a gradient should mandate further investigation.

At present no test has 100% sensitivity and specificity for PE. Therefore, many approaches to further evaluation have been advanced, an example is shown in *Figure 1*. Generally once the pretest probability is determined a confirmatory test is performed.[2–4] The optimal confirmatory investigation is much debated and is usually a choice of a:

- nuclear medicine ventilation perfusion (V/Q) scan, or
- spiral computerised tomography pulmonary angiogram (CTPA).

Each have their merits and limitations, and performed well, each test is valid. A V/Q scan uses less radiation and contrast, however it is more ambiguous in those with underlying lung disease. The results of V/Q scanning are most often given as high, intermediate or low probability and should increase, not change or decrease the pretest

Table 1. Prevention of pulmonary emboli

Who to investigate for procoagulant disorders

Patients <50 years of age with recurrent PE or strong family history of proven venous thromboembolism

What to investigate

- prothrombotic panel usually includes lupus anticoagulant, protein C and S level, activated protein C level, homocystine level, factor V Leiden, (excess) factor VIII, and antithrombin 3 deficiency
- testing for occult malignancy is only warranted in those with clinical suspicion or abnormal chest X-ray or routine blood results

Who warrants prophylaxis/what type is given

- persisting risk factors: indefinite anticoagulation, eg. warfarin international normalisation ratio (INR) 2.0–3.0
- in hospitalised patients undergoing routine surgery, eg. 20 mg enoxaparin SC daily
- in patients admitted for acute medical conditions, eg. 40 mg enoxaparin SC
- in pregnancy warfarin is teratogenic but safer in breastfeeding, low molecular weight heparin is recommended
- consider calf stimulators, compressive stockings and IVC filters if appropriate

probability respectively. A CTPA is usually reported as a dichotomous PE seen/not seen but often an alternative diagnosis such as pneumonia can be made.

The V/Q scan or CTPA are pivotal to decision making in PE (*Figure 1*).[5,6] Patients with a high post-test probability will be treated. Those with a low post-test probability with normal, or near normal, V/Q scan or CTPA will not be treated for PE and an alternative diagnosis is sought; the remainder are intermediate probability and require further investigation. In these patients further corroborative evidence of thrombosis (eg. lower limb duplex ultrasound, CT or magnetic resonance imaging [MRI] venography, impedance plethysmography or contrast venography to confirm the presence of DVT) is sought. A new approach utilising a fibrin breakdown product (the D-dimer) has great attraction and if performed appropriately, a negative result excludes DVT/PE.[4] Unfortunately the D-dimer is exquisitely sensitive for inflammatory and thrombotic conditions (eg. recent operations and procedures) so has a high false-positive rate in the typical 'at risk' patient. The widespread use of the D-dimer test as a screening test may result in many patients being unnecessarily and extensively investigated.

The gold standard test for diagnosis of PE remains pulmonary angiography. However, this is a more invasive procedure and should be performed as near as practical to the time of embolus in an experienced centre. In patients with acute massive PE, the need for rapid diagnosis may dictate a need for early pulmonary angiography.

Treatment

Treatment of a PE, as with any medical problem, involves general measures (eg. resuscitation), as well as specific treatments (eg. anticoagulation and/or thrombolytics). Resuscitation includes reversing hypoxia with supplemental oxygen, and restoring the circulating blood volume with intravenous fluids and ionotropes. In the setting of massive PE, with evidence of right heart strain on echocardiogram, thrombolysis or occasionally thrombectomy may be indicated (*Table 3*).[9] Thrombolysis has little effect on a clot that is more than a few hours old, however it may reduce further propagation of the clot and probably more rapidly reduce clot burden. There have not been studies large enough to show a clear effect of thrombolysis on survival. Therefore, thrombolytic agents are generally reserved for when extensive pulmonary vascular bed obstruction has led to demonstrable right heart strain or failure.

Table 2. Three commonly used scoring systems to determine the clinical probability of PE

Wells scoring system

Clinical feature	Score
Symptoms of DVT	3
PE most likely diagnosis	3
Heart rate >100	1.5
Immobilised in past 4 weeks	1.5
Previous PE or DVT	1.5
Haemoptysis	1
Malignancy	1

Clinical 'pretest' probability of PE
High if score >6
Intermediate if score 2–6
Low if score <2

Modified British Thoracic Society

1. Are other diagnoses unlikely?
   - on clinical grounds
   - after basic investigations: white cell count, chest X-ray, ECG, spirometry, peak flow and ABGs

   If yes, score +1
2. Is a major risk factor present
   - recent immobilisation or major surgery
   - recent lower limb trauma and/or surgery
   - clinical DVT
   - previous proven DVT or PE
   - pregnancy or postpartum
   - major medical illness

   If yes, score +1

Clinical 'pretest' probability of PE
High if score 2
Intermediate if score 1
Low if score 0

Geneva scoring system

Clinical variable	Points
Age 60–79 years	1
Age >80 years	2
Previous PE/DVT	2
Recent surgery	3
Pulse rate>100	1
PaCO2 <4.8 kPa	2
PaCO2 4.8–5.16 kPa	1
PaO2 <6.5 kPa	4
PaO2 6.5–7.99 kPa	3
PaO2 8–9.49 kPa	2
PaO2 9.5–10.99 kPa	1
Chest X-ray plate atelectasis	1
Chest X-ray raised hemidiaphragm	1

Clinical 'pretest' probability of PE
High if >9 points
Intermediate if 5–8 points
Low if <4 points

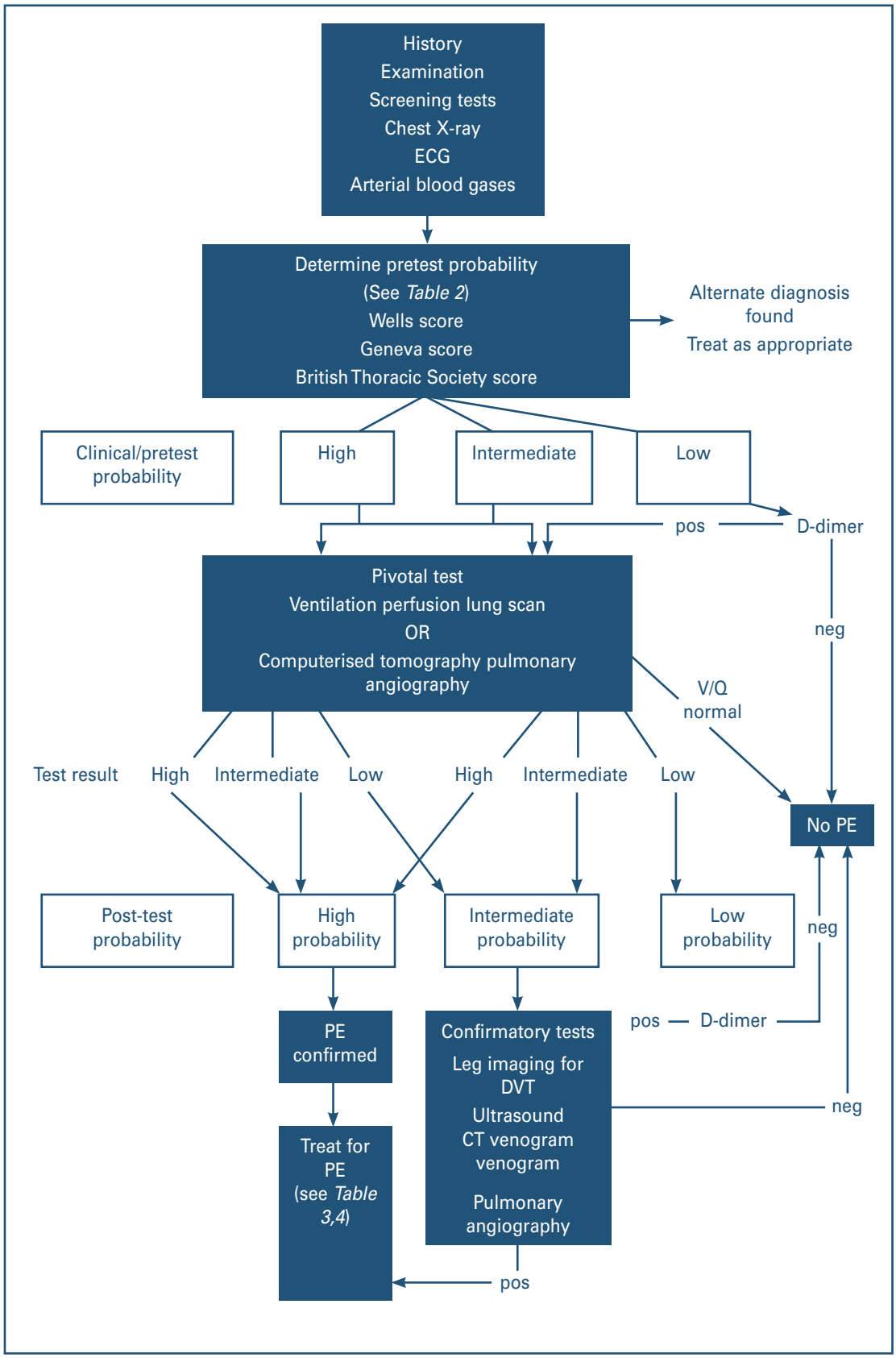

Figure 1. Algorithm for investigation and diagnosis of PE. The determined clinical (pretest) probability of PE is modified by the confirmatory test (V/Q scan or CTPA). Those with intermediate probability after confirmatory test will require further investigation[2,3,7,8,10]

Heparin

Systemic anticoagulation is the mainstay of treatment (*Table 4*). Heparin is usually administered first as it has a short onset of action. Fractionated low molecular weight heparins are commonly used in both inpatient and 'hospital in the home' settings.[11] Dosing is convenient – it is given subcutaneously once or twice per day and blood monitoring is not usually required. Efficacy can be measured by monitoring levels of factor Xa, however this is generally only required for prolonged courses or in those with obesity or renal impairment (particularly in the elderly). If a rapidly reversible agent is required, then unfractionated heparin is available in the in patient setting, however it requires regular titration to the activated partial thromboplastin time (APTT).

Prevention of venous thromboembolism by low dose heparin is almost routine in the setting of acute hospitalised patients and those undergoing surgery. This has resulted in a substantial decrease in DVT/PE incidence in these patient groups. Indications for prevention are outlined in *Table 1*.

Table 3. Definition and approach to treatment of acute massive PE

Defined as

- Cardiovascular instability with:
  - hypotension and/or shock
  - echocardiogram/CT/MRI demonstrating RV strain
  - V/Q scan demonstrating extensive multi-segment involvement

General measures

Airway oxygen
Breathing intubation and ventilation
Circulation fluids and inotropes

Specific treatment

Thrombolysis

- Unfractionated heparin (*Table 4*)
  - loading dose
  - infusion adjust to APTT

And

- Alteplase (rtPA-actilyse)
  - 10 mg bolus followed by
  - 90 mg over 3 hours

Or

- Streptokinase (or urokinase)
  - 250 000 units over 30 minutes followed by
  - 100 000 units per hour for 24–48 hours

Consider

- Thrombectomy/thrombus fragmentation
  - if thrombolysis contraindicated

Warfarin

Warfarin is the most widely available oral anticoagulant. It is recommended to commence warfarin several days into the treatment course, overlapping with heparin as both protein C and S are vitamin K dependent; therefore warfarin may be transiently procoagulant. Alternatives to warfarin are available for those who have allergies or specific side effects; involvement of a haematologist is recommended. The recommended duration of anticoagulation has been extrapolated from natural history studies of recurrent thromboses. Most guidelines recommend 6 months for a first episode without an identifiable reversible risk factor.

Vena caval filters

In those whom anticoagulation is absolutely contraindicated, vena caval filters may provide some protection against embolism. These are usually inserted by an interventional radiologist and placed below the renal veins. Filters can also be positioned in the superior vena cava for rarer upper limb DVT. Both temporary and long term filters are available (the temporary filter usually requiring removal at 12 weeks). The filter may become obstructed with thrombus, particularly in the setting of an inferior vena cava filter, but collateral veins can usually accommodate the additional blood flow.

Outcome

A 3 month mortality of up to 15% has been reported, however much of this relates to the predisposing medical disease. Further complicating estimates of outcome is the realisation that many PEs are not diagnosed or are found postmortem. Most patients with acute PEs have complete clinical and radiological resolution. Rarely patients have persistent thrombus as evidenced by a persistent perfusion defect on VQ scan beyond 6 weeks from the acute PE.[12] Unresolved thrombosis can lead to the development of pulmonary hypertension, the so-called chronic thromboembolic pulmonary hypertension (CTEPH).[13] Patients with CTEPH may be suitable for surgical correction by pulmonary thrombo-endarterectomy. Patients with symptoms not fully resolved within 6–8 weeks should be referred to a specialised centre for further evaluation. A post-DVT phlebitic syndrome can occur, often without

documented previous DVT. This appears as a chronic venous insufficiency. There is no role for anticoagulation unless recent DVT is documented; treatment with compression stockings is recommended.

Conclusion

Pulmonary embolism (and DVT) are most commonly seen in those with reduced mobility and underlying medical conditions. An initial clinical assessment forms a pivotal part of the pathway to investigate PE. Both V/Q scans and CTPAs are useful tests for the confirmation of a diagnosis as long as their limitations are understood. Anticoagulation therapy substantially reduces mortality, and with the availability of low molecular heparins treatment regimens are simpler allowing 'hospital in the home', or outpatient management. An uncommon complication of PE is CTEPH. Recognition of this complication is important as many patients may be suitable for corrective surgery.

Summary of important points

- Pulmonary embolism is an important cause of sudden onset breathlessness.
- Typically patients are immobile with underlying medical illnesses.
- A clinical assessment with simple tests is pivotal for determining the likelihood of PE.
- Both V/Q scans or CTPAs are valid confirmatory tests.
- Treatment with low molecular weight heparins is simple and effective.
- Duration of anticoagulation is usually 6 months unless underlying risk factors are identified.
- Chronic pulmonary emboli rarely complicates PE, but is a potentially treatable cause of pulmonary hypertension.

Conflict of interest: none declared.

Table 4. Treatment of pulmonary embolism

Immediate anticoagulation

- Low molecular weight heparins (SC)
  - enoxaparin 1.5 mg/kg per day, or
  - dalteparin 100 units/kg twice per day
- in elderly or renal impairment
  - reduce dose (eg. enoxaparin 1 mg/kg per day)
  - monitor anti-Xa levels

Or

- Unfractionated heparin (IV)
  - bolus 5000 units
  - infusion initially 1000 units/hr targeting APTT 1.5–2.5 X control

Other measures

- Caval filter
  - if anticoagulation contraindicated, can be removed

Chronic anticoagulation

- Warfarin
- loading dose
  - start after >24 hours on heparin and run in conjunction with heparin
- continuing dose
  - target INR 2.0–3.0
  - stop heparin (at least 2 day overlap and 5 day duration) when target INR achieved
- duration
  - 6 months standard
  - 3 months if risk factors removed
  - indefinite if: risk factors persist, recurrent emboli, or chronic thromboembolic pulmonary hypertension flow on

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