Pulmonary embolism

More than 150 years after the first Virchow description of his triad of risk factors for venous thromboembolism (VTE), pulmonary embolism (PE) remains an important preventable cause of morbidity and mortality. It was estimated that in 2008 there were approximately 15,000 episodes of VTE in Australia, a substantial proportion of which were PE. Both the diagnosis and initial management of PE still largely take place within the hospital setting. However, an understanding and awareness of PE by the primary care clinician remains important, due to the need for a high diagnostic suspicion of PE to enable prompt recognition of a potentially fatal disease and also the increasing tendency for early discharge of patients being treated for PE.

Epidemiology

Venous thromboembolism, consisting of both deep vein thrombosis (DVT) and PE, has an annual incidence in caucasian populations of approximately 1.5 per 1000, with the incidence increasing with age. Approximately 30-40% of patients with VTE will present with symptomatic PE. Pulmonary embolism will be fatal in up to 25% of patients in whom the diagnosis has been made if left untreated, with anticoagulation substantially reducing the risk of fatal PE during the initial treatment period to less than 2%. However, in up to 25% of individuals with PE the initial presentation will be sudden death before therapy can be initiated. The risk of death in patients with confirmed PE who have been treated with anticoagulation at 3 months postdiagnosis is approximately 10-15%, with the majority being due to comorbid conditions.

Risk factors for pulmonary embolism

There are a number of well defined risk factors for PE (Table 1), the presence of which will raise the level of diagnostic suspicion in patients with suggestive symptoms.

Recent hospitalisation

Venous thrombosis occurring after recent hospitalisation accounts for approximately 50% of cases, with recent surgical and medical admissions accounting for an equal proportion of events. There is an approximate seventyfold increase in risk of VTE following inpatient surgery, and a tenfold increase in risk following day surgery, despite modern surgical practice. The risk is maximal at...
Table 1. Risk factors for venous thrombosis

**Recent surgery**
- Joint replacement, cancer surgery, fracture, major gastrointestinal surgery, gynaecological surgery

**Inpatient day surgery**

**Acute medical illness**
- Congestive cardiac failure, acute respiratory failure
- Inflammatory conditions (eg. inflammatory bowel disease, rheumatological disease)

**Malignancy**
- Increased by chemotherapy, hormone therapy, surgery

**Hormonal risk factors**
- Oral contraceptive use, hormone replacement therapy
- Pregnancy

**Miscellaneous**
- Increased body mass index
- Prolonged travel
- Heparin induced thrombocytopenia
- Antiphospholipid antibody syndrome

**Inherited risk factors**
- ‘Strong’ – antithrombin, protein C + S deficiency
- ‘Moderate’ – factor V leiden and prothrombin gene mutations

3 weeks following surgery and remains elevated for up to 12 weeks. Therefore the majority of cases of PE related to surgery will occur following hospital discharge.

**Cancer**

Patients with cancer make up 15–20% of patients with VTE. The risk of venous thrombosis in patients with cancer is increased with the administration of chemotherapy, hormone therapy and surgical procedures. Malignancies with a high risk of venous thrombosis include brain, ovarian and pancreatic cancer.

**Oral contraceptive pill use and pregnancy**

The use of currently available combined oral contraceptive preparations is associated with a 2–7 fold increase in the risk of VTE. The magnitude of the increase in risk varies according to the type of progestosterone, being lowest with second generation preparations (2–4 fold increase in risk), and higher with either third generation pills or preparations containing cyproterone or drospirenone (4–7 fold increase in risk). Due to the low background annual incidence of VTE in women of reproductive age (~1 in 10 000), the absolute risk in oral contraceptive users is still low, being less than 0.1% per year.

The incidence of VTE during pregnancy and the postpartum period is approximately 1 in 1000, ie. approximately tenfold of that in nonpregnant women of similar age. The risk of PE is highest during the 4–6 weeks postpartum, with more than 50% of episodes of pregnancy related PE occurring during this time period.

**Extended travel**

Much publicity has been given to air travel as a risk factor for VTE. However in a recent large cohort study less than 2% of individuals with venous thrombosis had undertaken a prolonged flight within the 8 weeks before diagnosis. Flights shorter than 4 hours do not appear to be associated with any increase in risk of venous thrombosis, with flights between four and 8 hours in duration associated with a twofold increase in the risk of VTE, and flights more than 12 hours a fivefold risk increase. The magnitude of the increase in risk is therefore substantially less than that associated with recent surgery. While there is less data, the risk of venous thrombosis with travel of the same duration by other modes of transport, including car and rail, appears similar to that associated with flying.

**Other risk factors**

Comorbid medical conditions that have been demonstrated to be risk factors for pulmonary embolism include cardiac failure, acute or chronic respiratory failure, acute rheumatological disease, acute infection, inflammatory bowel disease, and increased body mass index. Recent data suggests that smoking is associated with a 1.5 fold increase in the risk of venous thrombosis.

**Clinical presentation of pulmonary embolism**

Pulmonary embolism is usually suspected due to acute onset new, or worsening, shortness of breath or chest pain. Dyspnoea is present in 70–80% of patients with confirmed PE, with chest pain present in 60–70% of cases. Between 10–20% of patients with confirmed PE report haemoptyisis. Symptoms at presentation vary according to thrombus location, with patients with larger pulmonary emboli more likely to present with isolated dyspnoea (25% of cases), and those with more peripheral emboli causing pulmonary infarction with pleuritic chest pain +/– haemoptysis (60% of cases). Five to 8% of patients with PE who survive long enough to have a diagnostic evaluation, will present with circulatory collapse, as defined by a systolic blood pressure of <90 mmHg. A proportion of these patients will not have symptoms of chest pain nor dyspnoea.

Clinical features shown to be predictive for the presence of PE include concurrent symptoms of DVT, a history of syncope, presence of pleuritic chest pain, tachypnoea and tachycardia. However the presence or absence of any single symptom or sign cannot be used to confirm or refute the diagnosis. This fact, along with the consequences of a missed diagnosis, mean that the threshold for initiating further investigation in patients presenting with symptoms known to be associated with PE, particularly in the absence of an alternative explanation, should be low.

**Diagnostic algorithms for pulmonary embolism**

The incidence of confirmed PE in patients undergoing investigation has fallen over time to a current figure of approximately 20%.
Given that the majority of patients will not have confirmed PE, diagnostic algorithms have been developed to safely exclude PE while limiting the need for diagnostic imaging.

Clinical prediction rules for pulmonary embolism

Experienced clinicians are able to accurately stratify the probability of PE using unstructured clinical assessment. Clinical prediction rules have been developed to formalise this process, with the assessment of pretest probability being used to guide further diagnostic testing (Figure 1). The most widely used prediction rule for PE is the Wells score, in which points are given according to the presence or absence of risk factors for, and symptoms and signs of, PE (Table 2). A simplified version classifying patients as either PE unlikely (prevalence of PE 12%) or PE likely (prevalence of PE 47%) is optimal for helping to exclude PE without diagnostic imaging.

D-dimer testing

D-dimer, a degradation product of cross-linked fibrin, is a highly sensitive test for recent VTE. A negative D-dimer test can be used to help exclude PE in patients with a low pretest probability. In patients classified as PE unlikely with a negative highly sensitive D-dimer test, the probability of PE is sufficiently low (<1%) to exclude the diagnosis without further testing. In patients classified as PE likely, the prevalence of PE in patients with a negative D-dimer is still ~10%. Therefore patients in the latter category should proceed directly to diagnostic imaging without D-dimer testing being performed (Figure 1).

Diagnostic imaging for pulmonary embolism

Computerised tomographic pulmonary angiography (CTPA) has become the most widely used radiological investigation for suspected PE. Modern multidetector CTPA is highly sensitive for PE, with a single negative study having been shown to safely exclude PE. A filling defect within a segmental or more proximal vessel confirms PE and justifies commencing therapy. An additional benefit of CTPA is that alternative diagnoses will also be detected. Downsides include the detection of small subsegmental emboli, for which the need for anticoagulation remains unclear, contrast complications, and concerns regarding the degree of radiation exposure and the subsequent increase in the risk of breast cancer, particularly in women of reproductive age.

Ventilation perfusion (VQ) scanning remains an alternative method of imaging for PE, particularly in individuals without pre-existing lung disease in whom the incidence of nondiagnostic results is decreased. It has the advantage over CTPA of not requiring contrast exposure, and therefore is the investigation of choice in patients with renal impairment. Breast radiation exposure is also substantially reduced with VQ scanning in comparison to CTPA, and therefore it should be considered as a first line investigation for PE in women of reproductive age. A normal VQ scan can be used to exclude PE, while a high probability scan justifies anticoagulation. All other results are associated with an intermediate probability of PE (10–40%) and further imaging, normally CTPA, is therefore required.

Ultrasound of the lower limbs can be used as an initial investigation, particularly where there are concurrent symptoms suggestive of DVT. The finding of DVT justifies commencement of anticoagulation, although further investigation is still required if no evidence of DVT is found. This strategy is useful where there are concerns regarding radiation exposure, such as during pregnancy.

Limitations of diagnostic algorithms in the primary care setting

The majority of studies evaluating diagnostic algorithms for PE have been performed in the emergency department setting. The Wells score requires the clinician to make a judgment regarding the likelihood of PE in comparison to alternative explanations, which in most studies was guided not only by clinical symptoms and signs but also initial investigations such as chest X-ray and electrocardiogram. Caution should therefore be applied in applying diagnostic algorithms for PE when the patient is assessed solely in the primary care setting, and prompt evaluation of such patients in an emergency department, particularly in those with a high pretest probability, is recommended. If there is likely to be a substantial delay in definitive investigation, an initial therapeutic dose of low molecular weight heparin (LMWH) is warranted in the absence of contraindications.
Inpatient versus outpatient therapy

The ability to give LMWH subcutaneously has meant that outpatient therapy of PE is now theoretically possible. There is limited observational data supporting the safety of this approach in low risk patients with PE. Tools have been developed to identify a low risk subgroup of patients with PE potentially best suited for outpatient therapy. However, the safety of inpatient versus complete outpatient therapy has not yet been examined in randomised trials, and therefore at least a short period of initial inpatient evaluation is still recommended for patients with PE until such trials are performed.

The role of thrombolytic therapy

Thrombolysis is accepted as being indicated in patients with PE who present with haemodynamic instability (systolic BP <90 mmHg), due to a high fatality rate with standard anticoagulant therapy. It has been proposed that patients without haemodynamic compromise with markers of poor prognosis present, such as right ventricular dilatation or elevated troponin, should also be considered for thrombolytic therapy. There are however, no randomised studies that clearly demonstrate that early thrombolysis improves survival in this subgroup of PE patients, provided that rescue thrombolysis can be administered in the event of clinical deterioration.

Duration of anticoagulation

After the initial treatment period with LMWH, warfarin is usually used for continued anticoagulation, with a recommended target International Normalised Ratio (INR) of 2.0–3.0. A minimum of 3 months anticoagulation is recommended in patients with symptomatic PE, as the risk of recurrent thrombosis is increased in patients receiving a shorter duration of therapy. The strongest predictor of the risk of recurrent events is the circumstances at the time of the initial event. In patients with PE associated with a definite provoking risk factor, such as recent major surgery, the risk of recurrence is generally low, and 3–6 months of anticoagulant treatment is sufficient. In patients with unprovoked PE the recurrence risk is higher, and long term anticoagulation may be indicated. This particularly applies if additional prognostic factors known to be associated with an increased recurrence risk including male gender, antithrombin, protein C and protein S deficiency or antiphospholipid antibody syndrome are present. The decision regarding the duration of anticoagulation in such patients should be made in conjunction with a specialist with an interest in venous thrombosis.

Conclusion

Pulmonary embolism remains a potentially fatal disease for which a high diagnostic suspicion must be maintained. The future is likely to see improved strategies for risk stratification of patients with PE, identifying low risk patients able to be managed as outpatients and high risk patients likely to benefit from more aggressive intervention. The emergence of new oral anticoagulants, such as the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban, that have the potential to be used for both initial and long term anticoagulation without the need for therapeutic monitoring, is likely to simplify management of patients with venous thrombosis. The exact role of these agents is however, still to be determined, and will be influenced by drug cost, which in turn will influence any restrictions that are placed on drug availability.

Table 2. Simplified Wells pulmonary embolism score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
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<tbody>
<tr>
<td>Clinical signs and symptoms of deep vein thrombosis</td>
<td>3.0</td>
</tr>
<tr>
<td>(minimum of leg swelling and pain on palpation of the deep veins)</td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilisation (&gt;3 days) or surgery within the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous pulmonary embolism or deep vein thrombosis</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (receiving treatment, treated in last 6 months or palliative)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clinical probability of PE unlikely: score ≤4 points</td>
<td></td>
</tr>
<tr>
<td>Clinical probability of PE likely: score &gt;4 points</td>
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Treatment

Anticoagulation has been the mainstay of treatment for PE since the study of Barritt and Jordan, in which 25% of patients receiving placebo died of recurrent PE, with all patients treated with anticoagulant therapy surviving.

Choice of initial anticoagulant

Due to the delay in therapeutic effect of warfarin, initial treatment with a parenteral anticoagulant is necessary in patients with acute PE. Subcutaneous weight based LMWH has been found to be at least as effective and safe as intravenous unfractionated heparin in the treatment of PE, and has the additional benefit of not requiring therapeutic monitoring, therefore it can be administered at a fixed weight based dose. Low molecular weight heparin is therefore usually the agent of choice for initial treatment of PE. Unfractionated heparin is still preferred in patients with significant renal impairment, due to the renal clearance of LMWH, and is also recommended in unstable patients in whom thrombolytic therapy may still be considered.

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Conflict of interest: none declared.
References