The diagnosis and treatment of acute pulmonary thromboembolism

INTRODUCTION

There are certain conditions that prompt urgent investigation as soon as they enter the differential diagnosis. Pulmonary thromboembolism (PE) is among the most important, with an in-hospital mortality rate of 6–15% and a high proportion of early deaths.1,2 Indeed, this mortality rate is higher than the inpatient mortality for myocardial infarction. Yet PE is often missed, and frequently poorly managed. If PE is suspected in primary care then the patient should be rapidly sent to the nearest appropriate secondary care service for diagnosis and appropriate treatment.3

The annual incidence of PE is 23–69 cases per 100,000, and increases with age.4,5 In half of these cases it is the primary complaint; the remainder occur while the patient is under hospital care for another reason. Overall, three-quarters of patients will have a recognised predisposing factor (Table 1).

This article focuses on suspected PE and only deals with deep venous thrombosis (DVT) where relevant, although they are both part of the spectrum of venous thromboembolism (VTE). The European Society of Cardiology (ESC) published its new PE guidelines in September 2008.3 Much of the present article takes cognisance of this highly detailed contemporary statement from the ESC. There has been considerable progress since the publication of the existing UK guideline, the British Thoracic Society (BTS) guidance of 2003. The BTS has begun a complete revision of this guideline and plans to publish it in late 2009 or 2010. The Scottish Intercollegiate Guidelines Network (SIGN) has begun work on its first specific guideline for this critical condition.

DIAGNOSTIC APPROACH

There has been a lack of precision in terminology regarding the diagnosis and management of PE in general hospital practice. The BTS 2003 guideline was produced to clarify this and the 2008 ESC guidance attempts to further refine these issues. There are two principal areas of confusion. The first is the definition of the likelihood, or probability, of the clinical features and baseline tests being those of a pulmonary embolus. The second is the

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<th>Major risk factors (relative risk 5–20)</th>
<th>Minor risk factors (relative risk 2–4)</th>
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<td>Surgery</td>
<td>Cardiovascular</td>
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<td>Obstetrics</td>
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<td>Lower limb problems</td>
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<td>Reduced mobility</td>
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<td>Past history of proven VTE</td>
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Confusion exists when ‘risk’ and ‘probability’ are used interchangeably. In this review we hope to make clear the appropriate terminology.

There are many ways in which a PE may present, ranging from dyspnoea and/or pleuritic chest pain to haemodynamic collapse. History and examination are unreliable, particularly in excluding the diagnosis of PE.

Defining individual clinical probability of PE is fundamental. Patients have high probability if they have clinical features of PE, a major risk factor and an absence of a reasonable alternative explanation. Tables to define individual probability are well established but poorly used and should be referred to much more often.

The most frequently used and therefore best validated are the Wells score and the Revised Geneva score.6–9 The Wells score includes a clinical judgement on whether an alternative diagnosis is more likely than a PE and carries significant weight, but is necessarily subjective (Table 2). The original Geneva score required an arterial blood gas analysis on air but has since been revised (with comparable predictive value) and is entirely based on clinical variables (Table 3). The two scores have been shown to have equivalent performance in ruling out PE when combined with D-dimer measurement.10 The prevalence of PE in patients with low or intermediate probability Geneva scores is 20% as opposed to 83% when the probability is high.11

**INVESTIGATION**

The initial presentation of the individual with suspected PE defines the management strategy. The stratification is determined by clinical status, as shown in Figure 1. The patient with shock has a high mortality risk and appropriate investigations and treatment must be initiated without delay. The patient who is clinically stable should also receive treatment immediately, but imaging tests need not necessarily be performed as an emergency procedure. Figure 1 also shows the diagnostic algorithms for patients presenting with and without clinical features of shock.

**Laboratory tests**

For patients with a low or moderate pre-test probability of PE, D-dimer levels should be assessed using a highly sensitive enzyme-linked immunosorbent assay (e.g. Vidas ELISA). A negative plasma D-dimer result (<500 μg/l) in these patients does not require further investigation, with a three-month thromboembolic risk in patients left untreated below 1%.12–14 If there is a high pre-test clinical probability then there is no need to do the test. The D-dimer test also does not need to be used in patients that are post surgery, aged over 80 years, pregnant or have cancer. The D-dimer concentrations in these groups of patients are frequently non-specifically elevated.

The widespread availability of biochemical markers of myocardial injury, most frequently troponin I or T (19) (or brain natriuretic peptide),20 has revolutionised our understanding of risk in PE. Patients with an undetectable troponin have a very low mortality from PE; individuals with a raised troponin have a much higher mortality, especially if there is right ventricular dysfunction. This is summarised in Table 4 below.
Imaging

A chest X-ray is often taken but may be normal in PE, unless there is other pathology present. For example, later in the natural history of PE, if pulmonary infarction has occurred there may be atelectasis in subpleural areas, but this is of little value in the acute presentation. In most centres, ventilation-perfusion scintigraphy (V/Q) isotope scanning and computed tomography pulmonary angiography (CTPA) are used to make the diagnosis of PE. Computed tomography pulmonary angiography is gradually replacing isotope scanning as the investigation of choice and the combination of clinical probability, D-dimer testing and CTPA to guide management of suspected PE has been validated in prospective trials. An isolated subsegmental thrombus is the exception where the exclusion of DVT will help plan management.

Isotope scanning (the V/Q scan) for the detection of segmental lung ventilation perfusion mismatches (strictly ≥2) has been in use for many years. However, it only reliably diagnoses or excludes PE in patients who do not have underlying cardiac or pulmonary diseases. Further imaging is required if the probability of the V/Q scan is in the face of intermediate or high probability, or high with a low clinical probability. If the suspicion of PE is high, an urgent V/Q scan or CTPA should be performed. Out of office hours it may be easier to obtain a CTPA than a V/Q scan.

Venous compression Doppler ultrasonography to identify thrombus in lower limb veins has its advocates and should be reserved for patients with suspected PE in whom a CTPA is impossible (allergy to iodine contrast dye is only a relative contraindication in the emergency situation), or if there are concerns about radiation. Pulmonary angiography was the gold standard from the
1960s and allows direct haemodynamic measurements to be made, but because it is invasive and because modern CTPA techniques are so good it tends to be reserved for select situations where intravascular fragmentation of massive thrombus is being considered.

**ACUTE TREATMENT**

All patients usually require supplemental oxygen. Immediate definitive treatment is determined by cardiovascular stability. Table 4 shows the major risk markers in the stratification of patients with a PE and serves as a guide to potential treatment implications.

**Haemodynamically unstable**

These patients have a PE-related mortality risk of more than 15%, it is an emergency situation and the clinical probability is usually high. Shocked patients need haemodynamic support with fluids and inotropes (noradrenaline, dobutamine or dopamine) and specific treatment strategies which include thrombolysis, surgical embolectomy or catheter disruption. Simply administering subcutaneous heparin and hoping for the best is poor medicine, and this practice must be abandoned.

Thrombolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on haemodynamic parameters with more than 90% of patients classified as responders within the first 36 hours.21 The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for six to 14 days. A meta-analysis of thrombolytic therapy versus heparin in haemodynamically unstable patients showed a significant reduction in recurrent PE or death (9.4% vs 19.0%; OR 0.45, 95% CI 0.22–0.92; number needed to treat = 10).22 Therefore, thrombolysis should be administered to patients with PE who have a high mortality risk, unless there are absolute contraindications to its use such as active internal bleeding or recent spontaneous intracranial bleeding.

Currently, the best agent is recombinant tissue plasminogen activator (rtPA). Urokinase or streptokinase can be used if rtPA is unavailable. Tenecteplase (TNK) is not yet licensed for PE but is the thrombolytic of choice for acute myocardial infarction and the drug being studied in the ongoing major European trial (see below).

In patients with absolute contraindications to thrombolysis or in those in whom thrombolysis has failed to improve haemodynamic status, surgical embolectomy is the preferred therapy. If not immediately available, percutaneous catheter embolectomy or thrombus fragmentation may be considered.23 Although no controlled trials are available of catheter embolectomy for acute PE, there are cohort studies that suggest outcomes are similar to surgery.24

Pending the decision to thrombolise or perform embolectomy by thoracotomy or percutaneously, full dose, weight-adjusted intravenous heparin should be administered immediately upon clinical diagnosis while the decision for specific therapy is being considered. Subcutaneous low molecular weight heparin (LMWH) is poorly absorbed from underperfused skin in shocked patients and should not be used.

Chronic pulmonary hypertension is a recognised long-term complication of pulmonary embolism and is associated with considerable morbidity and mortality.25 The cumulative incidence of chronic thromboembolic hypertension (CTPH) post PE has been shown prospectively to be about 4% at two years, with no new cases occurring after this time point.26 Potential risk factors include multiple episodes of pulmonary embolism, a larger perfusion defect, a younger age and idiopathic presentation of pulmonary embolism. The use of thrombolytic treatment was related in the univariate model to an increased risk of CTPH but not after adjustment for other risk factors and was likely due to extensive PE at presentation.

**Haemodynamically stable**

Most patients fall into this category. There is the greatest body of evidence for these individuals, and patients who are non-high risk usually have a favourable prognosis. There is currently no evidence to support the use of thrombolysis in unselected patients with PE.27 Patients at intermediate risk of death (normotensive but with evidence of right ventricular strain or damage) may have a risk–benefit ratio that favours thrombolysis, particularly without an elevated bleeding risk. A large multinational European trial has been initiated and will attempt to resolve the controversy still surrounding the appropriate treatment of this group of patients (ClinicalTrials.gov number NCT00639743).

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**TABLE 4 New risk stratification table from the European Society of Cardiology’s 2008 guideline**

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<th>PE-related early mortality risk</th>
<th>Risk markers</th>
<th>Potential treatment implications</th>
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<tbody>
<tr>
<td>High &gt;15%</td>
<td>+ (+) (+)</td>
<td>Thrombolysis or embolectomy</td>
</tr>
<tr>
<td>Intermediate 3–15%</td>
<td>– + –</td>
<td>Hospital admission</td>
</tr>
<tr>
<td>Low &lt;1%</td>
<td>– – –</td>
<td>Early discharge or home treatment</td>
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Until the results of this trial are available, standard management is anticoagulation with weight-adjusted LMWH using either enoxaparin 1 mg/kg twice daily or tinzaparin 175 IU/kg once daily while awaiting results of diagnostic work-up. Low molecular weight heparin should be given with care in patients with renal failure and the dose adjusted according to anti-Xa level.

Warfarin should be given as soon as possible and preferably on the same day as the initial anticoagulant. Heparin should be stopped when the international normalised ratio (INR) lies between 2.0 and 3.0 for at least two consecutive days. Patients with proximal deep vein thrombosis should be fitted with compression stockings as these have been shown to reduce the cumulative incidence of post-thrombotic syndrome in such patients at two years after the index event.

**LONG-TERM TREATMENT**

The aim of long-term anticoagulant treatment of patients with PE is to prevent fatal and non-fatal recurrent VTE events. Warfarin is used in the vast majority of the patients, while LMWH may be an effective and safe alternative in cancer patients.25-27 For patients with PE secondary to a transient (reversible) risk factor such as surgery, trauma, medical illness, oestrogen therapy or pregnancy, treatment with warfarin for three months is usually enough.10,21

For patients with unprovoked PE, treatment with warfarin is recommended for at least three months.21 If patients are at low bleeding risk and stable anticoagulation can be achieved, long-term oral anticoagulation may be considered. For patients with a second episode of unprovoked PE, longer treatment is recommended, but as yet there have been no trials exploring the optimum duration in such patients. Those receiving long-term anticoagulant treatment should be reassessed at regular intervals regarding the risk–benefit ratio of continuing such treatment.

**REFERENCES**

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