Diagnosis and initial treatment of patients with suspected pulmonary thromboembolism

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Pulmonary thromboembolism (PTE) remains a frequently occurring diagnostic problem, with an incidence of approximately one to two cases per thousand of population per year. Only 15–25% of patients undergoing radiological investigation will have the diagnosis confirmed and the remaining patients should not be subjected to the risks of anticoagulant therapy, unless they are too unwell to move to the radiology department.

Many risk factors have been identified, including genetic predisposition, pregnancy, oral contraceptive use, malignancy, immobilization, and prior surgery. The risks increase, particularly if multiple factors are present.

Classification

PTE is part of the spectrum of venous thromboembolism, which also includes deep vein thrombosis of lower and upper extremities. This concept is based on the finding that patients with proven PTE may have a co-existing deep venous thrombosis in ~30% of cases, whereas those with deep vein thrombosis had (often silent) pulmonary emboli in 50% of cases.

The classification of pulmonary embolism can be based on physiological grounds, which have a direct impact on treatment decisions. Thus, a differentiation between massive, submassive, and non-massive pulmonary embolism has been proposed. Massive pulmonary embolism (5%) is characterized by haemodynamic instability, marked hypotension, or frank cardiopulmonary arrest. The emboli in this situation tend to be larger (including saddle emboli) and there is demonstrable right ventricular dysfunction. Submassive pulmonary embolism (25%) is more difficult to ascertain, as patients are haemodynamically stable. However, systematic investigation using echocardiography will demonstrate right heart strain and abnormalities of function. Increasing interest has also focused on the use of biomarkers such as troponin and brain natriuretic peptide and their role in risk stratification in this patient group. Non-massive pulmonary embolism (70%) is any other event, in which the circulation and right heart function remain stable.

Treatment and prognosis

Pulmonary embolism that remains untreated carries a high mortality. The exact figures are not really known, as they are based on a single study in a very limited number of patients. However, up to 30% mortality and 30% recurrent rate should be expected in patients who are not diagnosed. Hence, a low threshold of suspicion is warranted in order to limit the number of patients with pulmonary embolism which go unnoticed and untreated.

With adequate anticoagulation, and where appropriate thrombolytic therapy, the mortality rate decreases to 5–10% at 1 month (Table 1). It is also important to recognize that many patients with a diagnosis of acute PTE will die of other problems such as malignant disease.

Low-molecular-weight heparin

Up to 10% of patients suffering acute pulmonary embolism will never reach the physician, as the patient dies acutely within the first hour of the event. However, the vast majority of patients with pulmonary embolism will fall into the non-
massive category. These patients should be treated with low-molecular-weight heparin (LMWH), as these newer agents have a more favourable spectrum of safety. After the first injection of LMWH, the patient can start with oral anticoagulant therapy using vitamin K antagonists. Patients should continue with LMWH for a minimum of 5 days and until the INR > 2.0 on two consecutive days. The optimal duration of anticoagulation is not clear. Studies have established that 3 months anticoagulation is superior to 6 weeks anticoagulation, although traditionally a period of 6 months has been advocated. The benefits of prolonged periods of anticoagulation are dependent on the risk of recurrence. Interestingly, acute PTE occurring within 6 weeks of surgery has a negligible recurrence rate. These patients do not require prolonged anticoagulation. In contrast, patients with idiopathic PTE have a recurrence rate of ~30% in the 5 yr after anticoagulation. More prolonged periods of anticoagulation should be considered for such patients, and particularly, if they present with an unheralded life-threatening event, they may be considered for long-term anticoagulation.

**Thrombolysis**

Patients with massive pulmonary embolism and circulatory insufficiency should be considered for thrombolytic therapy. These unstable patients should not be sent for radiological investigations, rather they should undergo (bedside) echocardiography. In patients who require cardiopulmonary resuscitation, thrombolytic therapy should be administered and prolonged resuscitation efforts should take place to allow the agent to act. Several agents have been used, including urokinase, streptokinase, and recombinant tissue plasminogen activator (rt-PA). Streptokinase is now rarely used due to associated hypotension and the availability of alternative agents such as rt-PA which are not associated with this problem.

Patients in whom right ventricular dysfunction is demonstrated by echocardiography, but who are otherwise haemodynamically stable, are at the centre of debate at the moment. Some studies have now suggested that these patients have a better prognosis after thrombolytic therapy, but several issues still need to be resolved, including identification of such patients and the risk–benefit ratio of bleeding complications vs improved outcome.

**Chronic thromboembolism**

The true prevalence of chronic thromboembolic pulmonary hypertension (CTEPH) after acute PTE is not known, but studies have estimated this at between 0.5% and 4%. Recent studies have identified patients with idiopathic PTE, larger embolic load, previous history of PTE, and systolic pulmonary artery pressure at echocardiography > 50 mm Hg on presentation as increasing the risk of CTEPH. Patients breathless after PTE or who have an estimated systolic pulmonary artery pressure above 40 mm Hg more than 6 weeks after PTE are also at increased risk of having CTEPH.

It should also be recognized that the right ventricle is only capable of generating a systolic pulmonary artery pressure of ~50 mm Hg acutely. Therefore, patients presenting with breathlessness and systolic pulmonary artery pressure above this level, for example, 80 mm Hg, should be considered as having pre-existing pulmonary vascular disease. Although the thrombotic load of these patients may be large, their arterial pressure is usually well maintained and they are unlikely to benefit from thrombolysis.

**Bleeding complications**

Most bleeding complications are relatively minor, but they are lethal in up to 1 per 100 treatment years (Fig. 1). The bleeding risks are obviously higher in thrombolytic therapy, with more major bleeding reported. However, the risks are far outweighed by the benefits of aggressive therapy.

**Vena cava filters**

Cava filter insertion varies widely according to country and even hospital. In the USA, many cava filters are inserted based on prevention of pulmonary embolism in patients whom anticoagulant prevention is (relatively) contraindicated: major trauma or after major orthopaedic or neurosurgical procedures. However, investigators in France have demonstrated that patients with cava filters only have a benefit during the initial period. During a 2 yr follow-up, post-thrombotic syndrome and recurrent venous thromboembolism occurred much more frequently in patients in whom cava filters had been inserted. A few essential indications remain, such as patients with uncontrollable thromboembolic disease (recurrence in spite of adequate treatment), those who undergo pulmonary endarterectomy for chronic thromboembolic disease, those in whom an absolute contraindication for anticoagulants exists (e.g. post-major neurosurgery thrombosis), and those with limited life expectancy. In patients in whom cava filters are deemed necessary as an interim prophylaxis method, preference should be given to retrievable filters, which may stay in place for increasingly prolonged periods of several months.

**Diagnostic tests**

The clinical assessment of patients with suspected PTE is absolutely crucial and a number of scoring systems such as the Wells and Geneva scores have been validated in patients with PTE. Although the diagnosis of suspected PTE cannot be excluded on clinical assessment alone, it is helpful in combination with other diagnostic tests such as the d-dimer to reduce the need for...
radiological investigation. Other investigations such as chest X-ray (CXR), arterial blood gas analysis, and ECG may suggest an alternative diagnosis but have insufficient sensitivity even when used in association with clinical assessment to exclude a diagnosis of PTE. Electrocardiography may demonstrate atrial fibrillation, right ventricular overload, and right axis shift. The S1Q3T3 pattern is a non-specific sign of acute right heart strain and occurs in <20% of patients with PTE. Chest radiography in pulmonary embolism can demonstrate hypovascularity (Westermark’s sign) or an area of peripherally placed usually wedge-shaped consolidation with the base against the pleural surface suggesting infarction (Hampton’s hump). However, none of these tests is either sensitive or specific for the diagnosis of pulmonary embolism, and additional objective tests are required, if a clinical suspicion arises.

The diagnostic management of pulmonary embolism has increasingly moved into non-invasive modalities. For outpatients, one can consider performing a plasma d-dimer assay in patients with a low or intermediate clinical probability of PTE (a normal assay result virtually excludes the presence of pulmonary embolism). Importantly in patients with a high clinical probability of PTE, d-dimer should not be performed and the investigator should go straight to radiological investigation. In hospitalized patients, d-dimer has little value as most will have underlying diseases or postoperative states that cause increased plasma d-dimer levels, especially in patients with sepsis. In addition, d-dimer has not been validated in pregnant patients. d-dimer levels may increase in pregnancy, but there are insufficient data to suggest that a normal d-dimer level excludes the diagnosis.

**Ultrasonography**

Ultrasonography of the leg veins is a good alternative in patients with leg symptoms, as this technique has high sensitivity and specificity in such situations. However, in asymptomatic legs, the sensitivity of ultrasonography decreases to <30%. Nevertheless, one can consider ultrasonography in pregnancy to avoid ionizing radiation. Thus, an abnormal test result can result in anticoagulant therapy, whereas a normal test result should lead to additional investigations.

**Lung scintigraphy**

This technique has historically dominated the diagnostic management. A normal perfusion lung scan result rules out pulmonary embolism (with the exception of very high clinical likelihood cases, where a non-obstructive proximal pulmonary embolus could go unnoticed). Follow-up studies have shown that it is safe to withhold treatment in patients with a normal perfusion lung scan. Pulmonary embolism is more than 90% likely, if a high probability perfusion–ventilation lung scintigram is obtained. Thus, this should lead to anticoagulant therapy unless contra-indications exist and absolute certainty is essential (such as in the immediate post-operative course of major surgery). Unfortunately, >50% of patients will have inconclusive lung scan results. The diagnostic value of the test can be improved by combining the clinical and scan probability, but the advent of new radiological investigations such as CT limits the role of this investigation in the assessment of suspected PTE. Some clinicians have suggested that in pregnant women with suspected PTE and a normal CXR and leg Doppler scans that perfusion lung scanning may be preferable to computerized tomographic pulmonary angiography (CTPA) due to concerns regarding radiation exposure to the breast in these patients. However, lung scintigraphy is generally not available 24 hr or in every hospital.

**Computerized tomographic pulmonary angiography**

The introduction of CTPA first with single and now with multiple detector rows has changed the diagnostic approach completely.
First, CT is available in every hospital, with most hospitals offering multiple detector row scanners. Secondly, CT is available 24 h per day, 7 days a week. Finally, CTPA offers the additional diagnostic capability of chest CT, thus allowing one to obtain information on aortic disease (such as dissection), lung parenchymal disease, and pulmonary embolism in a single setting and examination. The technique is probably equally efficient in diagnosis and exclusion of pulmonary embolism compared with conventional pulmonary angiography, which should now be reserved for those cases where either discordance exists between clinical and CT findings or where CT is inconclusive. In practice, pulmonary angiography is rarely performed. In addition, CT can be used in assessment of disease severity and features of right heart strain such as dilated right-sided chambers and a flat interventricular septum or a septum bowing into the left ventricle may be helpful in judging risk and severity (Fig. 2). Features may also give information regarding the chronicity of the clot (Fig. 3).

CTPA is safe in pregnant patients and ionizing radiation has been shown to be within acceptable range even during the first trimester. Concerns have arisen regarding the pregnant mothers breast which have been alluded to above. Caution should be exercised in patients with impaired renal function, and in those situations lung scintigraphy or MR angiography may be a preferred method of investigation.

Since the introduction of CTPA, the number of investigations with a presumptive diagnosis of pulmonary embolism has almost doubled in most hospitals.

**MR angiography**

This has been developed and has the advantage of absence of ionizing radiation, reduced nephrotoxicity of Gadolinium contrast, and is useful in follow-up of patients after treatment and in the assessment of PTE disease. It is now possible to obtain a full MR pulmonary angiogram during a single breath-hold of <10 s. Thus far, the diagnostic accuracy for MR angiography is not as good as for CT angiography, and therefore, the technique cannot be advised as a routine. Furthermore, accessibility to MR scanners remains a significant barrier.

**Echocardiography**

Echo is a very useful bedside test for assessment of right heart function and for demonstration of central pulmonary embolism. Very occasionally, the thrombus can be seen proximally in the main pulmonary artery. More usually, it is the effect on the right side of the heart that can be seen, that is, dilated right atrium and right ventricle and impaired right ventricular function. Hence, it can be used for patients with massive (and submassive) emboli. However, routine use of echocardiography is not advised for diagnosis or exclusion of pulmonary embolism at present. The technique should be reserved for the subgroup of patients who cannot be transported to the radiology department and for those with haemodynamic instability or in whom right ventricular dysfunction is suspected.

**Pulmonary angiography**

An invasive technique that is increasingly being abandoned. It still retains a role in difficult patients, in the work-up for PTE hypertension for endarterectomy, and in cases of diagnostic uncertainty. The latest techniques have dramatically improved the safety of the technique, but access and experience are required and not always available.

**Diagnostic management according to classification**

**Massive pulmonary embolism**

These patients require urgent and aggressive treatment, if they are to survive. There is generally no time to perform radiodiagnostic procedures, and the best option is bedside echocardiography. This can be followed by thrombolytic treatment regimen according to local practice.

Follow-up after successful therapy should consist of CTPA after ~1 week of therapy to determine residual clot burden. The risks of developing chronic pulmonary hypertension are highest in this patient group, particularly if incomplete clot lysis is demonstrated.

**Submassive pulmonary embolism**

These patients will likely remain unnoticed unless a proactive approach with routine echocardiography is taken, although recent work has supported the role of biomarkers such as brain natriuretic peptide and troponin in identification of patients with right heart strain and increased risk of mortality. Patients who demonstrate
right heart strain on ECG should undergo echocardiography (Fig. 4).

A recent RCT study in the USA in patients with submassive PTE demonstrated no mortality benefit in patients receiving thrombolysis, although the need for rescue thrombolysis in the placebo group was significantly increased. It is not known whether the symptomatic limitation that is being increasingly recognized post-PTE would be reduced after thrombolysis. In future studies examining the role of thrombolysis, post-PTE exercise capacity at follow-up should be considered as an important endpoint. It is likely that the use of biomarkers in combination with CT/ECHO and clinical parameters may help in the more accurate risk stratification of patients. Clearly targeting thrombolysis to the highest risk group provides the most effective benefit:risk ratio.

Currently, the choice to thrombolyse or not rests with the clinician in patients with submassive PTE. It should be noted that patients with PTE who deteriorate while on LMWH or those who have progressive ECG changes, the mortality is high and in such patients with submassive PTE, the authors would certainly have a low threshold for thrombolysis.

Non-massive pulmonary embolism

Adequate diagnosis is essential in order to avoid unnecessary use of anticoagulant therapy. This diagnosis should be obtained with 24–36 h, and current diagnostic centres are well capable of reaching this target.

In outpatients, a combination of clinical assessment and D-dimer test can be used to try and rule out the disease. However, this is not an option for hospitalized patients and will only lead to unnecessary delay of diagnosis.
In patients with leg symptoms, ultrasonography should be considered as a first-line test. The same is true for pregnant patients. However, without leg symptoms, ultrasonography is unlikely to demonstrate deep vein thrombosis.

Whether one starts with lung scintigraphy is a contentious point. The advantage is that it is non-invasive and well-founded over years, but a diagnostic result is obtained in only 50%. Thus, CTPA has largely replaced the lung scan, as it is capable of accurately diagnosing or excluding pulmonary embolism, while it has the additional benefit of giving vital information on other chest diseases that can mimic as pulmonary embolism.

Pulmonary angiography should no longer be necessary, unless there is a vital contraindication to anticoagulant therapy or a persistent (repeated) inconclusive CT result (usually, CT can be repeated after 6–8 h).

Conclusion

Pulmonary embolism remains a common diagnostic problem. The prognosis is greatly aided by adequate diagnosis and appropriate treatment. A low threshold for suspicion should be used, as good diagnostic tests exist that can aid the clinician in his/her diagnosis.

References

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Please see multiple choice questions 15–16