

Clinical problems in acute thromboembolism

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This joint meeting with the British Thoracic Society was held at the Royal College of Physicians on 7 April 2005

Clin Med 2005;5:402-5

Acute venous thromboembolism (VTE) has been topical within the British press for some time. Dramatic headlines seem to imply that physicians frequently misdiagnose VTE with disastrous consequences.

This conference explored different aspects of the difficult diagnoses of deep vein thromboses (DVT) and pulmonary emboli (PE) and how to avoid common pitfalls. The main message remains that while diagnostic tools and sensitive blood tests exist to aid junior doctors and nurse specialists, the need for assessment by a senior clinician remains crucial. The panel case discussions at the end of the day, a first for an RCP conference, were invaluable. There was no uniformity of opinion amongst experts in certain situations, illustrating the difficulties and problematic nature of VTE.

Acute assessment of venous thromboembolism

Junior doctors, who tend to be the initial point of contact for the majority of patients presenting to the emergency department, can have a rather low

threshold for diagnosing VTE in anyone presenting with acute breathlessness and chest pain. They do not want to misdiagnose a VTE as the consequences could be fatal. A typical situation could be that of a young female patient who might complain of breathlessness and chest pain, and with a moderately positive d-dimer test, being diagnosed as PE and started treatment with low-molecular-weight heparin (LMWH). The fact that she also had pyrexia, productive cough and consolidation on chest X-ray (CXR) may be completely ignored. The patient is then exposed to unnecessary radiation from a computed tomography pulmonary angiogram (CTPA) as the CXR is abnormal. Such a situation needs to be avoided and it is crucial that the entire clinical picture is taken into account. A normal CXR is helpful in excluding other diagnoses in a patient with symptoms and signs consistent with a PE. The more abnormal a CXR the less likely it is that PE will be the diagnosis. All doctors must be trained to consider other diagnoses before they diagnose a PE.

Pre-test probability scores and d-dimer tests in the diagnosis of venous thromboembolism

Pre-test probability scores

A number of pre-test probability scores have been devised and validated for the diagnosis of PE, eg the Canadian (Wells) score and Geneva method. They combine the clinical assessment of the patient and the likelihood of another non-PE diagnosis. However, these scores are complicated and difficult to remember. The British Thoracic Society has proposed a simpler assessment tool, which has been validated (awaiting publication).¹ In patients with clinical features of a PE, the tool asks only two questions and gives a low, intermediate or high pre-test probability depending on the score (Table 1). This has the potential for routine use in emergency departments.

D-dimer tests

A negative d-dimer test can help in the acute assessment of a VTE and has a particular role in reducing the need for imaging. A positive d-dimer test cannot be used alone to make a diagnosis. The optimum timing of a d-dimer test after onset of symptoms is

Conference programme

Differential diagnosis

Dr Andrew Miller, Mayday Hospital, Croydon (Conference Organiser)

Assessing pre-test clinical probability

Dr Chris Davies, Royal Berkshire and Battle Hospitals, Reading

d-dimer: help or hindrance?

Dr Trevor Baglin, Addenbrooke's Hospital, Cambridge

Imaging of pulmonary embolism

Dr John Reid, Borders General Hospital, Melrose

Pulmonary embolism and the heart

Dr Simon Gibbs, Imperial College London, Hammersmith Hospital

Anticoagulation: how long?

Dr Ian Campbell, Llandough Hospital, Cardiff

Thromboembolism and cancer

Dr Tony Fennerty, Harrogate District Hospital

Thrombophilia testing: if and when

Professor Mike Greaves, University of Aberdeen

Deep vein thrombosis

Mr John Scurr, Lister Hospital, London

Clinical dilemmas: what do I do now?

Real-life clinical scenarios submitted in advance by delegates

not known and there is no evidence that repeating a d-dimer test after an interval aids diagnosis.

A VTE can, however, be excluded in a patient with a low pre-test probability and negative d-dimer result² and in such a situation an alternative cause for the patient's symptoms should be sought. On the other hand, a patient with a history suggestive of a VTE with an intermediate or high probability score should proceed straight to an investigation, missing out a d-dimer test, as the result would not change management. Similarly, a man with a clear history of trauma followed by calf pain should not have a d-dimer test, as a positive result due to the trauma might lead a doctor to prescribe a treatment dose of LMWH, exposing him to side-effects. It is reasonable not to investigate a patient with a positive d-dimer test for a VTE if another diagnosis is made.

D-dimers are raised in a number of other conditions, including infection, inflammatory disorders, malignancy and pregnancy; following surgery, bleeding and thrombophilia; and in patients at risk of atherosclerosis: therefore, positive tests have little value in the assessment of inpatients.

Imaging in venous thromboembolism

If a patient with a high clinical probability of a DVT has a negative leg ultrasound, this should be repeated after a week. If it is still negative and clinical probability remains high then the patient may need to proceed to a venogram, which remains the gold standard test for DVT.

CTPA is the investigation of choice for PE. V/Q scans are appropriate tests if:

- the patient has no underlying symptomatic cardiorespiratory disease
- it is the first episode of presumed PE
- the good quality CXR is normal and available
- the pre-test probability has been assessed
- further imaging will be available on the same day should the result be non-diagnostic.

CTPA is not yet a routine investigation for PE in all district general hospitals, but where available CTPAs can also identify a wide variety of other diagnoses, including type A aortic dissections, pericarditis, anterior myocardial infarctions and

pneumonia. Again, there is no substitute for a thorough clinical assessment prior to investigations. The presence of sub-segmental thrombus within an area of acute lung pathology, such as pneumonia, is not an indication for anticoagulation. This is *in situ* thrombus and not an embolus.

In pregnancy the radiation dose to the fetus from a CTPA is approximately one-third of the V/Q scan dose, unless only a perfusion scan is performed. Conversely, the mother is subjected to four times the radiation dose from a CTPA than from a V/Q scan.

Acute treatment of venous thromboembolism

Symptomatic calf DVTs should not be left untreated as they may propagate. One option is to treat such patients with anticoagulation. However, an acceptable alternative is to repeat the ultrasound in one week and to stop treatment if there is no evidence of propagation.

A theme arose from a number of the cases discussed: that echocardiography may have an important role in managing patients with PE. For example, if a patient with a confirmed PE, being treated with LMWH, deteriorates with increasing dyspnoea, exertional syncope, hypotension, or cardiogenic shock, an urgent echocardiogram would be invaluable in assessing right ventricular size and function. In massive PE, the right ventricle dilates due to increased pulmonary artery pressure, resulting in ventricular septal displacement and reduced left ventricular filling, and therefore reduced cardiac output and hypotension. Right ventricular clot might also be visible on echocardiogram. In such circumstances the panel felt thrombolysis with recombinant tissue Plasminogen Activator (rtPA) should be considered; however, the role of thrombolysis in a stable patient with right ventricular dysfunction is uncertain.³ A patient with a positive troponin test is more likely to have a massive PE, and therefore this test may have a place in the acute assessment of patients. Another factor to consider in a deteriorating patient is whether the dose of LMWH is correct for the patient's weight.

Asymptomatic PEs may be discovered during CTPAs. The question of whether to treat depends on when the clinician believes the PE occurred and whether there is evidence of right heart strain. If there is no clear history of onset and no evidence of right heart dysfunction, the panel agreed that there was no indication for anticoagulation. Filling defects can still be seen within pulmonary arteries on CTPA at 6 months after presentation, but this would not prompt a clinician to extend anticoagulation. Presence of right heart strain, however, would be an indication for prolonged anticoagulation as it would either indicate an acute PE or the development of pulmonary hypertension requiring long-term anticoagulation.

The panel was divided on whether a cardiovascularly stable 66-year-old man should be thrombolysed for a proximal DVT with reduced pedal pulses suggesting venous gangrene.

Anticoagulation in haemorrhage

A particularly difficult clinical scenario arises when VTE occurs in inpatients following intracerebral haemorrhage and gastro-

Table 1. Pre-test probability score for use in suspected acute pulmonary embolism. Adapted from the British Thoracic Society pre-test probability score for pulmonary embolism.¹

<i>In a patient with breathlessness ± tachypnoea ± pleuritic chest pain ± haemoptysis how likely is the diagnosis of PE?</i>	Is another diagnosis unlikely?	
	No	Yes
Is there a major risk factor?	No	Low risk Intermediate risk
	Yes	Intermediate risk High risk

intestinal haemorrhage. While inferior vena cava filters can be used to prevent a PE in a patient with a proven DVT, there is no evidence that they are beneficial in the long term and the debate over their removal continues. As far as the risk of further bleeding after anticoagulation for VTE is concerned, it is extremely low in a patient with an intracerebral haemorrhage compared to the significantly increased risk of bleeding in an anticoagulated patient with a gastrointestinal haemorrhage.

Venous thromboembolism and cancer

A recent study revealed that 4% of patients with a proven VTE were diagnosed with cancer following a clinical assessment.⁴ The risk of an associated malignancy is particularly high if the VTE is idiopathic. Most occult malignancies will be discovered after a full history, examination and screening investigations, including tumour markers, abdominal and pelvic imaging and endoscopies where indicated. Interestingly, prognosis is not changed by screening. Such intensive screening may not be possible in some district general hospitals, but clinicians must ensure that all patients are fully examined and have a CXR. Patients in particular who have new unexplained weight loss and gastrointestinal symptoms should be thoroughly investigated.

Cancer patients with metastases, those on chemotherapy with or without a semi-permanent central venous catheter (CVP) and those undergoing surgery are at an increased risk of developing a VTE. It might seem sensible to prescribe prophylactic low-dose anticoagulation (warfarin 1 mg/day) to these patients, but the concern is that patients who are formally anticoagulated for a proven VTE are at an increased risk of haemorrhage compared to anticoagulated patients without cancer. Patients with a known malignancy and proven VTE should continue their anticoagulation long term until their malignancy is thought to be inactive. It is unclear if low-dose anticoagulation should be used as prophylaxis against VTE in higher risk cancer patients, although low-dose warfarin is being used in some centres as prophylaxis in patients with CVP lines.

Controversies surrounding thrombophilia testing

The risk of a VTE is 1 in 10,000 in a young person and 1 in 1,000 in the general population, rising to 1 in 100 in the elderly. Factor V Leiden is a late-onset polygenetic disorder of incomplete penetrance. The presence of factor V Leiden or taking the combined oral contraceptive pill (OCP) both independently increase the risk of VTE five-fold, but the presence of both these factors in the same female increases the risk of VTE 40-fold. A factor V Leiden-positive woman should be advised against taking the OCP if she has a family history of idiopathic VTE in a first-degree relative with factor V Leiden. This also applies to other heritable thrombophilias if diagnosed.

There are numerous other genes, some unmapped, that cause heritable thrombophilias. Therefore, a negative screen does not exclude the possibility of thrombophilia. The panel agreed that the OCP is contraindicated in a woman with a family history of maternal death from an idiopathic PE under 50 years of age.

Thrombophilia screening in such individuals will not be helpful. Similarly, screening the asymptomatic daughter of a woman who had a postoperative DVT aged 50 years will not be helpful, even though the mother may be a factor V Leiden carrier. The surgery is more likely to be the precipitant in this situation rather than her factor V Leiden status.

A heritable thrombophilia is not a disease, so before screening patients with recurrent idiopathic VTEs one must consider how a positive result will alter management, bearing in mind that a negative result does not fully exclude such an abnormality. The panel could not agree on whether asymptomatic family members should be screened. The British Thoracic Society guidelines¹ suggest thrombophilia screening for patients with recurrent idiopathic VTE under the age of 50 or a history of proven idiopathic VTE in several family members of more than one generation.

Prevention of deep vein thrombosis

Preventing a DVT is always preferable to treating one. Medical inpatients have a 20-30% risk of developing a DVT and a 1% risk of a PE, similar to the risks associated with general surgery. Medical inpatients over the age of 40 with significant pathology, like myocardial infarction, stroke or diabetic coma, have a high risk of VTE and should wear compression stockings. Prophylactic doses of LMWH should also be considered. The risk of VTE remains after discharge but prophylaxis is not routinely continued.

The benefits of compression stockings during economy flights have been confirmed.⁵ Patients who are elderly, have a history of VTE or have a co-existing illness are at increased risk of a VTE during a flight and are advised to consult their general practitioner before flying. Evidence is accumulating that specific conditions within the plane – low partial pressure of oxygen and reduced space – do not contribute to the risk of VTE. Passenger health and the duration and frequency of flights appear to be more important.

Conclusion

The conference was a thorough and topical review of the more challenging aspects of VTE. A recurring theme was that there is no substitution for a full history and examination by a senior clinician prior to further expensive tests and investigations. Time constraints on senior staff do mean that pre-test probability scores and d-dimer tests have an important role for junior doctors and nurse specialists, but only after appropriate education. The VTE management debate will surely continue as further research is published.

References

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