

# Venous thromboembolism

## — manifestations and diagnosis

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Deep vein thrombosis and pulmonary embolism are responsible for a large number of preventable deaths in hospital, yet prompt diagnosis can dramatically reduce mortality and morbidity. This article describes the causes of these conditions and the techniques used for diagnosis



Deep vein thrombosis commonly occurs in the veins of the calf

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**V**enous thromboembolism is defined as any thromboembolic event occurring within the venous system, including deep vein thrombosis (DVT) and its sequela, pulmonary embolism (PE). DVT is a blood clot (thrombus) in a deep vein within the muscle, typically the calf or thigh. If part of the thrombus breaks off, it becomes an embolus which can travel through the heart and block the arteries to the lungs, known as a PE. DVT and PE are currently the leading causes of preventable in-hospital mortality. This article will cover the causes, clinical manifestations and diagnosis of DVT and PE. The pharmacological management of these conditions is described in a second article (p205).

### — Epidemiology

Many DVTs are clinically silent and resolve spontaneously without complication. This fact, coupled with the fact that the clinical diagnosis is often inaccurate, makes it difficult to determine a true incidence of DVT but it is thought that around 80 cases per 100,000 population occur per year. The incidence of DVT in patients in hospital is much higher and can vary from 20 to 70 per cent. DVT primarily affects patients over the

age of 40 years and is slightly more common in males.

The long-term complication of DVT is chronic venous insufficiency resulting in limb oedema, pain and venous ulceration, which pose significant morbidity for the patient. Mortality from DVT is secondary to pulmonary embolism.

Pulmonary embolism is an extremely common condition and a leading cause of death in all age groups. Prompt diagnosis and treatment can dramatically reduce the mortality rate and morbidity of the disease but this is often difficult because patients may only present with non-specific symptoms. In fact, in an estimated 80 per cent of cases diagnosis is not made until autopsy.

PE affects one in every 1,000 of the UK population per year and is the second most common cause of unexpected death after ischaemic heart disease. It accounts for 10 per cent of all deaths in hospital and is a major contributing factor in a further 10 per cent. It is estimated that the cost to the NHS of post-operative DVT/PE is £200m per year. Of patients presenting with acute PE, 10 per cent will die within an hour, but if prompt diagnosis and treatment is initiated the mortality rates are significantly reduced.

If patients survive the initial PE they are at risk of further embolic events with an 8 per cent one-year recurrence rate. If left untreated, a third of patients who survive the initial event will die of future embolic events, regardless of the size of the initial thrombus.

The frequency of PE increases with age due to an accumulation of risk factors but it is not an independent risk factor. Risk factors for developing PE are the same as for DVT and it can be caused by venous stasis, hypercoagulability and damage to the venous intima. The most important risk factor is a prior history of DVT or PE, recent surgery or pregnancy, immobilisation, or underlying malignancy. PE is common throughout pregnancy and in women taking oestrogen-based contraceptives or hormone replacement therapy.<sup>1,2</sup>

### — Aetiology

Endothelial injury can expose collagen, resulting in platelet aggregation that, in the presence of venous stasis or hypercoagulability, triggers the coagulation cascade. The combination of vessel wall injury, venous stasis and hypercoagulability is known as the Virchow triad.

Under normal conditions, microthrombi (tiny aggregates of red cells, platelets, and fibrin) are formed and lysed continually within the venous system. This dynamic equilibrium ensures local haemostasis in response to injury without permitting uncontrolled propagation of a clot. Under pathological conditions, microthrombi may escape the normal fibrinolytic system to grow and propagate.

DVT of the lower extremity usually begins around the valve cusps of the deep veins of the calf, although a small number can arise directly in the iliofemoral system

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(around the thigh and pelvis). Exposure of tissue thromboplastin during cell injury allows the formation of a complex with blood clotting factor VIIa, and subsequent activation of the extrinsic pathway of coagulation. This results in the formation of thrombin and fibrin, which trap red blood cells, forming a red thrombus. Most calf DVTs will resolve spontaneously but 20 per cent will spread proximally and are prone to embolisation.

The propagation and organisation of the thrombus usually results in destruction of the venous valves and produces varying degrees of venous outflow obstruction. This results in chronic venous insufficiency. Spontaneous lysis of an established proximal DVT and complete restoration of blood flow through the vein occurs in less than 10 per cent of patients.

Venous thrombosis mostly involves the lower extremities and nearly always begins in the calf veins. Over 80 per cent of DVTs will have propagated above the knee before the diagnosis is made. However, DVT may arise at any point in the venous system, especially following pelvic surgery or major trauma.

Many risk factors for venous thrombosis have been identified. The most important are increasing age, immobility, major surgery in the previous four weeks, pregnancy and the post-partum period and underlying malignancy. Other conditions that predispose to the development of DVT include congestive heart failure, sepsis, nephrotic syndrome, trauma, vasculitis, high dose oestrogen therapy and haematological conditions affecting the coagulation cascade.<sup>3</sup>

Pulmonary embolism is a complication of underlying venous thrombosis and occurs when propagating clots from the deep venous system break free and embolise to the lungs where they obstruct the pulmonary arterial system. Occlusion of the pulmonary arteries results in increased pulmonary arterial pressure, right heart failure and infarction of lung tissue.

DVT of the calf is a significant source of PE and autopsy studies have shown that the frequency of PE from isolated calf DVTs is 33–46 per cent. Although calf veins have a small calibre they can form long, sinuous clots that can result in haemodynamic collapse when they obstruct the pulmonary arteries.

Thromboemboli distribute to both lungs in 65 per cent of cases, the right lung alone in 25 per cent and the left lung in 10 per cent. The majority lodge in large or intermediate sized pulmonary arteries, but 35 per cent will reach the smaller arteries. The lower lobes of the lungs are affected four times more frequently than other areas of the lung.

The pathological consequence of PE is proportional to the degree of obstruction of the pulmonary arterial tree. Obstruction of the pulmonary arterial system results in pulmonary hypertension and right heart failure in up to 70 per cent of cases. Pulmonary hypertension results from increased pulmonary vascular resistance where the right ventricle has to generate higher pulmonary arterial pressures to maintain cardiac output. Significant pulmonary hypertension occurs when 30–50 per cent of the pulmonary arterial tree is obstructed. It can occur with a smaller thrombotic load if there is co-existent cardio-respiratory disease. If pulmonary vascular resistance increases acutely and by more than 50 per cent, the right ventricle may not be able to compensate, leading to a fall in cardiac output and cardiogenic shock.

Pulmonary infarction (localised necrosis of lung tissue) is only seen in 10 per cent cases because the collateral circulation from the bronchial arteries keeps the lung tissue viable despite pulmonary arterial obstruction.

### — Clinical manifestations

The clinical manifestations of DVT are related to the degree of venous outflow obstruction and inflammation of the vessel wall. Patients may be asymptomatic but may

present with unilateral leg swelling associated with tenderness, warmth and redness and prominent superficial veins. There is no correlation between symptoms and the size, location or extent of the DVT. As there are three main veins draining the lower limb, a DVT in one vein may not obstruct venous return and swelling may not always be present. Pulmonary embolism may be the primary clinical presentation in 10 per cent of patients without clinical evidence of DVT.

Only 50 per cent of patients with DVT describe calf pain. This is non-specific and may only be present on forced upwards flexing of the foot (Homan's sign), which is regarded as an unreliable sign. Superficial thrombophlebitis (inflammation of superficial veins) may also be seen and a low-grade fever is not uncommon. Complete occlusion of the iliofemoral vessels can lead to severe unilateral limb oedema with cyanotic discoloration (called phlegmasia cerulea dolens) and if the femoral artery is compressed the limb may become ischaemic (phlegmasia alba dolens). It must be remembered that alternative diagnoses are found in 70 per cent patients with clinically suspected DVT.

The clinical manifestations of PE are often non-specific and vary in frequency and intensity, depending on the extent of vascular occlusion and the degree of underlying cardio-respiratory disease. Patients classically present with acute onset chest pain (80–90 per cent), dyspnoea (75–85 per cent) and haemoptysis (13–20 per cent) but all three of these symptoms are only seen in 20 per cent of patients. Other symptoms include cough, wheeze, abdominal pain, anxiety, cardiac arrhythmias and syncope. Due to the difficulty in diagnosing PE it should be considered in any patient presenting with unexplained respiratory symptoms. Patients may have signs of underlying DVT. If the emboli are small and occur over a longer period of time, these may not be noticed until the insidious onset of cor pulmonale (alteration in the structure and function of the right ventricle).

Massive, ie, life-threatening, PE may present with cardio-respiratory arrest due to acute occlusion of the pulmonary arteries or with syncope and hypotension and cyanosis.

Breathlessness is the most consistent physical sign, seen in 80–90 per cent of patients. Other signs include tachycardia, gallop rhythm (extra heart sound), low-grade fever and detection of a rubbing sound on breathing caused by inflamed pleural membranes (a pleural rub). It must be remembered that the results of a physical examination may be completely normal, especially in the early stages after PE.<sup>4</sup>

### — Diagnosis of DVT

A diagnosis of DVT is confirmed in only 20–30 per cent of patients with clinically suspected DVT. Risk factors are helpful in

#### Panel 1: Wells clinical score for deep vein thrombosis

Clinical parameter	Score
Active cancer (treatment ongoing, or within six months or palliative)	+1
Paralysis or recent plaster immobilisation of the lower extremities	+1
Recently bedridden for more than three days/major surgery in the last four weeks	+1
Localised tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling of >3 cm compared to the asymptomatic leg	+1
Pitting oedema (greater in the symptomatic leg)	+1
Previous DVT documented	+1
Collateral superficial veins (nonvaricose)	+1
Alternative diagnosis (as likely or greater than that of DVT)	-2
<b>Total of above score</b>	
High probability	≥ 3
Moderate probability	1 or 2
Low probability	≤ 0

deciding who needs further investigation to improve diagnostic accuracy. Only 11 per cent of patients with clinically suspected DVT have a confirmed diagnosis if no risk factors are present but this rises to 50 per cent if three risk factors are present. The Wells Clinical Score for DVT is a useful tool to help with the clinical diagnosis. It stratifies patients into high, moderate, or low-risk groups (see Panel 1, p200).<sup>5,6</sup>

**D-dimer** D-dimer fibrin fragments are present in fresh fibrin clots and in fibrin degradation products. D-dimer levels may be elevated in any condition where clots form, such as trauma, recent surgery, haemorrhage, cancer, and sepsis, which in turn are associated with an increased risk for DVT. D-dimer assays have a low specificity for DVT and therefore they should only be used to rule out and not to confirm the diagnosis of DVT.<sup>7</sup> A negative D-dimer assay excludes DVT in patients with a low to moderate risk and a Wells score of <2. Patients with a positive D-dimer assay and a moderate to high risk of DVT (Wells DVT score >2) require additional investigation.

**Imaging studies** Contrast venography was formerly considered as the investigation of choice for patients with suspected DVT. However, it is either contraindicated or non-diagnostic in up to 25 per cent of patients, and other non-invasive imaging studies have now replaced venography as the initial diagnostic test. Duplex ultrasonography is a non-invasive technique that combines ultrasonographic imaging with Doppler flow studies. Venous thrombosis is confirmed when the vascular lumen cannot be compressed due to the presence of an occluding thrombus. The absence of normal Doppler signals arising from venous flow provides further evidence of venous occlusion. It may also verify an alternative diagnosis such as a haematoma or abscess. The main disadvantage of the technique is its inaccuracy in the diagnosis of calf vein thrombosis and thrombi proximal to the inguinal ligament (ie, above the deep veins of the lower limb). Despite this it remains the initial diagnostic test of choice in patients with suspected DVT.<sup>8</sup> Furthermore, magnetic resonance imaging is increasingly being used to evaluate suspected DVT, particularly for suspected iliac vein or inferior vena cava thrombosis and during the second and third trimester of pregnancy.

A diagnostic plan for patients with suspected DVT appears in Panel 2.

## — Diagnosis of PE

Unlike with DVT, scoring algorithms have little impact on PE risk stratification. If PE is suspected, diagnostic tests must be performed, bearing in mind the seriousness of missing the diagnosis.

## Panel 2: Diagnostic plan for patients with suspected DVT

The Wells DVT score is used to stratify patients into two risk groups where DVT is unlikely (a DVT score of <2) or likely (DVT score >2). A D-dimer assay (a test for levels of fibrin fragments) can then be used to determine who requires further investigation. A negative D-dimer assay excludes DVT in the unlikely group. Patients with a positive D-dimer assay and those in the likely group require duplex ultrasonography to determine who requires treatment.

If the duplex scan is positive and DVT is likely then the patient is treated. If the duplex scan is negative and DVT is unlikely, then DVT is excluded even if the D-dimer assay is positive. However, there may be discrepancy between the clinical probability of DVT and the duplex scan. If DVT is likely but the duplex scan is negative then there is a significant probability of DVT and repeat ultrasonography is recommended in one week. An alternative approach is to perform a venogram to exclude a calf vein DVT not detected by the duplex scan but the majority of doctors would use D-dimer levels to guide management at this point. A negative D-dimer assay excludes DVT but a positive result warrants a repeat duplex scan in one week.

If the duplex scan is positive but DVT is unlikely, most doctors would treat the patient, although some would recommend a venogram to confirm the diagnosis. If DVT is likely, and the D-dimer assay is positive but the duplex scan is negative, ultrasonography is advised.

**Laboratory tests** Arterial oxygen saturation (PaO<sub>2</sub>) may be reduced in patients with PE but this is non-specific and seen in other respiratory conditions so does not help to differentiate PE. A normal PaO<sub>2</sub> is seen in at least 15 per cent of cases of proven PE. The white blood cell count may be normal or elevated and elevated erythrocyte sedimentation rate and lactate dehydrogenase levels are not uncommon, particularly if pulmonary infarction has occurred. D-dimer levels may be elevated but this is not sensitive or specific enough to diagnose PE and, unlike in patients with DVT, does not help stratification.

**Electrocardiogram** The electrocardiogram is usually normal apart from tachycardia. In severe cases, dilation of the right side of the heart results in an abnormal ECG, seen as P pulmonale (tall, peaked P waves), right axis deviation and right bundle branch block. Classic ECG patterns reflecting right ventricular strain are rarely seen. Only 20 per cent of patients with proven PE have any of these classic ECG abnormalities.

**Chest X-ray** The initial chest X-ray is often normal in patients with PE. After 24 hours, loss of pulmonary surfactant leads to alveolar collapse, which may be indistinguishable from pneumonia on the X-ray. A pleural effusion and elevation of the hemidiaphragm may be present. The pulmonary vessels proximal to the PE may dilate with abrupt collapse of the distal vessels (Westermark sign). Pulmonary infarction may be seen as a wedge-shaped opacity adjacent to the pleural edge (Hampton hump).

**V/Q scanning** Nuclear scintigraphic ventilation-perfusion (V/Q) scanning is a technique widely used in the detection of pulmonary emboli. Technetium-99m labelled human albumin is injected intravenously and lodges in the pre-capillary arterioles of both lungs for several hours. A

gamma camera is used to detect the position of the particles and gives an image of pulmonary blood flow distribution. If blood flow is interrupted as in PE, "cold spots" are seen where there is absent blood flow. Single or multiple wedge-shaped marginal cold spots in a segmental or lobar distribution are highly suggestive of vascular occlusion. However, this technique alone cannot detect when blood flow has been reduced due to poor ventilation of adjacent lung. The perfusion scan is therefore often combined with the inhalation of xenon-133 gas, which is detected at the same time as the labelled human albumin. PE causes a marked reduction in perfusion relative to ventilation (mis-matched defect), whereas other lung diseases impair both ventilation and perfusion (matched defect). V/Q scanning may not produce a clear distinction if there are obvious radiological abnormalities and in such cases other imaging techniques may be more useful. A V/Q scan is, however, useful to determine the probability of PE. It has a high sensitivity so a negative scan almost excludes PE, but since specificity is low a positive scan does not confirm PE. Therefore, V/Q patterns can be used to guide diagnosis by classifying patients as having a high probability of PE, or no PE. The results of the scan must be combined with the clinical suspicion of PE. If there is a discrepancy between clinical suspicion and the results of a V/Q scan, further imaging by computed tomographic pulmonary angiography or pulmonary angiography is warranted to clarify the diagnosis.

**CTPA** The single most important finding of PE on computed tomographic pulmonary angiography (CTPA) is an intraluminal filling defect surrounded by contrast. Other findings suggestive of PE include an expanded, unopacified vessel; eccentric filling defects; peripheral, wedge-shaped consolidations; and pleural effusion. CTPA is essentially 100 per

cent sensitive and specific for large central emboli. Numerous studies evaluating the accuracy of CTPA have been performed which suggest an overall sensitivity of CTPA for acute PE of approximately 90 per cent when compared with pulmonary angiography. However, there is controversy as to whether CTPA can accurately detect smaller clots. In the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) study, approximately 6 per cent of all patients were diagnosed with isolated sub-segmental clot. In studies where angiography is performed after V/Q scan, the frequency of isolated sub-segmental emboli may be as high as 30 per cent. This supports the idea that strategies directing patients to CTPA after negative V/Q scan tend to select patients that are more likely to have smaller clots.<sup>9-10</sup>

**Pulmonary angiography** Pulmonary angiography is performed by injecting contrast media through a catheter introduced into the main pulmonary artery under X-ray guidance. Intra-arterial filling defects and complete obstruction of pulmonary arterial branches may be seen. A positive pulmonary angiogram confirms obstruction to pulmonary arterial blood flow. A negative pulmonary angiogram provides greater than 90 per cent certainty that PE is not present. It is the gold standard for diagnosing PE but

it is an invasive investigation and carries significant procedural risks in inexperienced hands with a mortality rate of up to 0.5 per cent. It has now been superseded by V/Q scan and CTPA in the majority of cases.

### — Conclusion

Deep vein thrombosis and pulmonary emboli are common clinical conditions that are responsible for significant preventable in-hospital mortality. These conditions may present with insidious symptoms and may demonstrate very little in the way of clinical signs. Careful investigation is required to confirm the diagnosis so that treatment can be initiated promptly with subsequent reduction in morbidity and mortality. Prophylaxis against thromboembolic disease must be considered in high risk patients.

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