Acute Venous Thromboembolism

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ABSTRACT

Objective: To review the recent advances in management of acute venous thromboembolism.

Data sources: Articles and published reviews on venous thromboembolism, pulmonary embolism and deep vein thrombosis.

Summary of review: Acute venous thromboembolism describes a group of disorders that includes venous thrombosis (usually deep vein thrombosis) and pulmonary thromboembolism. Ultrasound supplemented by Doppler flow detection imaging has become the investigation of choice in the diagnosis of deep vein thrombosis and spiral volumetric computed tomography or ventilation perfusion scan (if the patient is haemodynamically stable) or bedside echocardiography (if the patient is hypotensive) are often the initial investigations in a patient who has a suspected pulmonary thromboembolism. Magnetic resonance venography has only recently been evaluated and may prove in future to be a valuable diagnostic test for both deep vein thrombosis and pulmonary thromboembolism.

Treatment requires immediate anticoagulation using either subcutaneous low molecular weight heparin (e.g. enoxaparin 1 mg/kg 12-hourly or dalteparin 100 IU anti Xa/kg twice daily) or intravenous unfractionated heparin (80 U/kg as a bolus then 18 U/kg/hr and adjusted to keep the APTT 1.5 – 2 x the control value). Oral anticoagulation using warfarin is started simultaneously with heparin. Fibrinolytic therapy is considered in all patients with pulmonary thromboembolism in whom there are no contraindications, as the improvement in right ventricular function is greater and the pulmonary artery perfusion defect is less compared with patients treated by anticoagulation alone. Fibrinolytic therapy is usually only considered in patients with deep vein thrombosis if severe limb oedema is present.

While streptokinase, urokinase and alteplase have been recommended, alteplase (100 mg over two hours with heparinisation) may be the treatment of choice as alteplase has a shorter half life, has a more rapid effect and may be more effective in lysing older clots, when compared with streptokinase or urokinase. Reteplase (10 U over 2 minutes followed by 10 U 30 minutes later) may be as effective as alteplase.

Conclusions: Acute venous thromboembolism is a disorder that carries a high morbidity and mortality. Anticoagulation with or without fibrinolysis is the treatment of choice. (Critical Care and Resuscitation 2000; 2: 290-303)

Key words: Venous thromboembolism, deep vein thrombosis, pulmonary embolism, fibrinolytic therapy, anticoagulation,
left untreated). Two-thirds of leg thromboses cause no symptoms and in one-half of these patients, the diagnosis will be missed on clinical examination. Complete spontaneous lysis of a large proximal venous thrombus (i.e. one that produces pulmonary emboli) is uncommon, even if treated with heparin, and occurs in less than 10% of cases. In contrast, complete dissolution of small asymptomatic calf vein thrombi occurs frequently.

Cause

A number of protective mechanisms operate to prevent formation of intravascular thrombi, including the nonthrombogenic nature of the intact endothelial lining of blood vessels, circulating inhibitors, reticulo-endothelial system clearance of activated coagulation factors and the fibrinolytic system. A breakdown in one or more of these protective mechanisms may lead to a hypercoagulable state which may be either a primary or secondary disorder (Table 1) and predispose the patient to thrombosis and thromboembolism.

<table>
<thead>
<tr>
<th>Primary</th>
</tr>
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<tbody>
<tr>
<td>Congenital antithrombin III and heparin cofactor II deficiency</td>
</tr>
<tr>
<td>Protein C and protein S deficiencies and factor V Leiden mutation</td>
</tr>
<tr>
<td>Fibrinolytic abnormalities</td>
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<tr>
<td>Factor XII deficiency</td>
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<td>Factor VIII and XI elevation</td>
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<table>
<thead>
<tr>
<th>Secondary</th>
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<tbody>
<tr>
<td>Major trauma or abdominal, thoracic, pelvic or orthopaedic surgery</td>
</tr>
<tr>
<td>Neoplasia (pancreatic, ovary, liver and brain)</td>
</tr>
<tr>
<td>Cardiac failure, acute myocardial infarction</td>
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<tr>
<td>Pregnancy, oestrogen therapy</td>
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<tr>
<td>Immobility (antipsychotic drugs)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Dehydration, hyperviscosity</td>
</tr>
<tr>
<td>Myelofibrosis, polycythaemia</td>
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<tr>
<td>Homocystinuria</td>
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<tr>
<td>Heparin-induced platelet antibodies</td>
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<tr>
<td>Antiphospholipid antibody (e.g. anticardiolipin antibody, lupus anticoagulant)</td>
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<tr>
<td>Behcet’s syndrome</td>
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<td>Paroxysmal nocturnal haemoglobinuria</td>
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</table>

Virchow’s triad of venous stasis, hypercoagulation and venous endothelial damage still remains fundamental to the understanding of the aetiology of intravascular thrombosis. The greater the number of these factors present, then the higher the risk of developing venous thrombosis.

Venous stasis. Venous stasis is often associated with lower limb immobilisation or cardiac failure. Evidence of intravenous fibrin deposition has been noted in 30 - 40% of patients with acute myocardial infarction and 30 - 60% in patients with acute stroke or postoperative gynaecological, thoracic, abdominal and orthopaedic surgery. In general, it is believed that the postoperative incidence of deep vein thrombosis (DVT) without prophylaxis is approximately 20%.

Hypercoagulation. Hypercoagulable states that are secondary to an underlying disorder often have a common effect of increasing coagulation factor levels (particularly factors I and VIII), decreasing AT III levels and reducing plasminogen activation activity.

Abnormalities in the venous endothelium. The endothelium normally protects against the development of intravascular thrombosis by its negative charge and production of an alpha-2-macroglobulin protease inhibitor, protein C, prostacyclin and plasminogen activator. Damage to the endothelium and venous thrombosis often occurs with lower limb trauma, predisposing these patients to venous thrombosis.

Clinical features

Clinical features of venous thrombosis include symptoms and signs of venous obstruction and mild inflammation, in particular, pain, tenderness, warmth, erythema and swelling. However, patients with a DVT are often asymptomatic and symptoms and signs have inconsistent sensitivities and specificities. For example, when diagnosing a DVT, calf pain has a sensitivity between 66 - 91% and specificity between 3 - 87%. Homan’s sign (calf pain with passive dorsiflexion of the foot) has a sensitivity between 13 - 48% and specificity between 39 - 84% and swelling of the calf or leg has a sensitivity between 35-97% and specificity between 8 - 88%. Nevertheless, when they are present, particularly in the presence of risk factors, they warrant further investigation.

Thrombosis with clinical sequelae may occur in any venous system. For example, back pain and nephrotic syndrome with renal vein thrombosis, ascites with hepatic vein thrombosis (i.e. Budd-Chiari syndrome), drowsiness, coma and seizures with cerebral vein thrombosis, and small and large bowel infarction or ulceration with mesenteric vein thrombosis.

Investigation

The investigations performed in a patient with a suspected DVT include:

Venography. To diagnose a DVT, venography of the legs has been the gold standard against which all other
diagnostic methods are judged. However, as it is invasive, time-consuming, frequently painful and, paradoxically, has an associated risk of causing DVT, it is now no longer the initial diagnostic test for the evaluation of symptoms and signs suggestive of an acute DVT. Compression ultrasound has now become the investigation of choice.

**Ultrasound.** Real-time B-mode ultrasound scanning using a 7.5 MHz transducer has been found to be associated with a specificity of 90% and sensitivity of 100% for venous thrombi in the femoropopliteal segment, when a radiologists skilled in ultrasonic scanning performs the test. The most sensitive finding is failure of the vein to collapse under gentle pressure. An added advantage is that ultrasound may show conditions that mimic DVT (e.g. haematoma, abscess and ruptured Baker’s cyst). Calf veins (which are unlikely to give rise to embolism and which often resolve within 72 hr), iliac veins and the femoropopliteal segment are blind spots for ultrasound.

In duplex scanning, real time B-mode ultrasonography is supplemented by Doppler flow-detection ultrasonic imaging. Doppler flow studies have a sensitivity of 88% and specificity of 88% in diagnosing occlusive DVT in the iliac and femoral veins, but like impedance plethysmography are much less sensitive in detecting thrombosis in the lower leg as well as the potentially dangerous proximal nonocclusive thrombosis.

**Impedance plethysmography.** Impedance plethysmography (measuring an electrical impedance between two electrodes wrapped around the leg) has a sensitivity of 92% and specificity of 95% in diagnosing occlusive DVT in the iliac and femoral veins, but is much less sensitive in detecting thrombosis in the lower leg as well as the potentially dangerous proximal nonocclusive thrombosis. The technique does not distinguish between venous obstruction due to DVT and non thrombotic obstruction (e.g. haematoma, tumor) and potential false positive results may occur with increased intrathoracic or intraabdominal pressure and even in low cardiac output states. Impedance plethysmography is best suited for the identification and repeated monitoring of proximal thrombi in symptomatic patients.

**Radionuclide imaging.** Radionuclide imaging using radiolabelled fibrinogen (radiolabelled platelets or red blood cells have also been used) relies on the incorporation of the radiolabel into the thrombus. It detects thrombi in only 60 - 80% of cases of DVT and for technical reasons is less accurate for thrombi above the knee. It also requires 24 hr for the background readings to be obtained before one can assess whether there is an abnormality. Cellulitis and haematomas may also produce false-positive results.

**Cross-linked fibrin degradation products (XDP’s or D-dimer).** Concentrations of plasma XDP’s (or D-dimer, which is a product of plasmin proteolysis of mature cross-linked fibrin) are increased in patients with venous thrombosis. The sensitivity of XDP’s when measured by enzyme-linked immunosorbent assay (ELISA) is 97%. However, the specificity of the test is low, so while venous thrombosis may be unlikely in a patient with normal plasma D-dimer concentrations, a positive result requires confirmation by more specific imaging tests.

**Magnetic resonance (MR) venography.** Magnetic resonance venography has only recently been evaluated and appears to have at least a 90% sensitivity and a specificity approaching 100%, not only for thigh venous thrombosis but also for pelvic vein thrombosis. It is also useful for upper extremity venous thrombosis. Currently, however its use is restricted to a few centers and metallic devices from injury or surgery preclude its use.

**Lung scan.** A lung scan should be performed when a DVT is diagnosed (see later), as one study revealed a 40% incidence of pulmonary embolism in patients with DVT who had no symptoms of pulmonary embolism, highlighting the fact that venous thrombosis and pulmonary embolism are one disorder.

**Treatment**

Treatment for venous thrombosis usually includes:

**Anticoagulation.** Anticoagulation reduces the risk of recurrent thromboses from 25% to less than 4%. While management for DVT involves either subcutaneous low-molecular weight (LMW) heparin (e.g. enoxaparin 1 mg /kg twice daily or dalteparin 100 IU anti Xa/kg twice daily) or intravenous unfractionated (UF) heparin (80 U/kg as an intravenous bolus dose, followed by 18 U/kg/hr as an intravenous infusion or 5500 U stat then 18 U/kg/hr and adjusted to keep the APTT 1.5 - 2.5 x the control value), currently it is believed that LMW heparin is superior to UF heparin in terms of safety and efficacy. Heparin is continued for a minimum of five days and oral anticoagulation (e.g. warfarin 5 mg daily, which is started simultaneously with heparin, and adjusted to keep the INR between 2.0 - 3.0) is continued for six weeks thereafter in low risk patients (i.e. patients with reversible risk factors, for example following surgery or trauma) and for six months in intermediate risk patients (i.e. patients with idiopathic venous thrombosis). In high-risk patients (i.e. patients who have two or more spontaneous thromboembolic events, or those who have irreversible primary or secondary hypercoagulable states) a lifetime of anticoagulant therapy is required which will reduce
the risk of recurrent thromboses from 21% to less than 3%.20,26,27

In the absence of pulmonary embolism (or other reasons for hospitalisation), patients may be treated at home with warfarin and subcutaneous LMW heparin for five days or longer if the INR has not reached the desired range.28,29

Thrombolytic therapy. Thrombolytic therapy (see later) may be used in a patient who has a DVT with severe limb oedema and who has no contraindications to thrombolytic therapy.30

Prophylaxis

Asymptomatic patients who have primary or secondary hypercoagulable states should have antithrombotic prophylaxis before surgical procedures. The methods used for venous thrombosis prophylaxis include the following.31

Mechanical therapy

Routine leg exercises, intermittent pneumatic leg or calf compression (even intermittent compression of the arms has been shown to reduce the incidence of DVT in the legs32), elastic (graded compression) stockings, physiotherapy and early mobilisation decrease the incidence of postoperative DVT.33

Low dose heparin

This reduces the incidence of DVT in general surgical patients by 60%, which is associated with a 50% reduction in pulmonary embolism, with a reduction in fatal pulmonary embolism from 0.7 to 0.2%.34,35 In a review of results of 70 randomised trials involving gastrointestinal, orthopaedic, thoracic and urologic surgical patients, the overall incidence of deep venous thrombosis of 20% was reduced by two-thirds, and the incidence of pulmonary embolism of 2% was reduced by about 50%, by the use of prophylactic low-dose heparin.36

There was also a significant reduction in deaths related to pulmonary embolism37 as well as a significant reduction in overall mortality.36 As both the 8-hourly and 12-hourly regimens of 5000 U of subcutaneous heparin seem to be equally effective, it is recommended that the more convenient twice daily dosage should be used. Because peak plasma concentrations of heparin following subcutaneous injections occur 4 hr after the injection with only small amounts being detected after 8 hr,38 and as a circadian change in the anticoagulant effect of heparin has been described,39 a twice daily dose of 5000 U 8 hr apart (e.g. 6 am and 2 pm for 5 - 7 days or until the patient is ambulant) may be more effective than a strict 12-hourly dose.6

However, in one study of a high-risk group of intensive care unit (ICU) patients (i.e. patients who had an ICU stay of > 4 days) receiving prophylactic low-dose heparin (5000 U 12-hourly, s.c.) the incidence of deep venous thrombosis was found to be up to 12%,40 and in another study of medical patients admitted to hospital with infectious diseases (upper respiratory tract infections, pneumonia, meningitis, skin and soft-tissue infections, urinary tract infections, gastroenteritis), heparin prophylaxis (5000 U s.c. 12-hourly) did not reduce the incidence of pulmonary embolism.31,42

Currently, because of a longer half-life and no requirement for anticoagulation monitoring (apart from determining the base values for APTT, INR and platelet count), LMW heparin is often used for DVT prophylaxis.43 A single subcutaneous daily dose of 30 - 45 anti Xa IU/kg for moderate risk patients (e.g. 2500 IU dalteparin or 40 mg enoxaparin per 70kg adult) or twice daily dose of 30 - 45 anti Xa IU/kg for high risk patients is usually all that is required.43,44 As the dosages used depend on the patient’s lean body weight they are usually administered without plasma anti-Xa activity monitoring. However, as the LMW heparins are excreted predominantly by the kidneys, their use is required to be carefully monitored in the patient with acute or chronic renal failure (and in obese patients), otherwise the haemorrhagic side-effects will be greater than those observed using UF heparin preparations (which are cleared predominantly by the endothelium).35,46

While there is no convincing evidence that in general surgery patients LMW heparin is associated with a lower incidence of deep vein thrombosis when compared with UF heparin,46 in orthopaedic patients,45 and patients with major trauma,48 there is a larger absolute risk reduction for venous thrombosis with LMW heparin when compared with UF heparin. In addition, in patients with total hip replacement, prophylaxis for one month is more effective in reducing thromboembolic complications when compared with prophylaxis given for the period of hospitalisation only.45

Although some believe that there appeared to be no increase risk of spinal haematoma using LMW heparin prophylaxis in patients who have spinal or epidural analgesia,50 recent calculations place the frequency of spinal haematoma between 1:1000 to 1:10,000.51 For patients requiring spinal or epidural analgesia, it is now believed that the lowest dose of LMW heparin should be used (e.g. 40 mg enoxaparin s.c. daily - remembering that antiplatelet or oral anticoagulants increase the risk of bleeding), the first dose should be delayed for a minimum of 12 hr and ideally 24 hr after the procedure.
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and catheter removal should occur 12 - 24 hr after the last dose of LMW heparin. Throughout the patient’s spinal analgesia the neurological state should also be reviewed carefully.52

Fibrinolytic activation

Exercise and intermittent venous occlusion activates the natural fibrinolytic system and may be the mechanism responsible for the success of intermittent pneumatic compression prevention of postoperative DVT.53

Antiplatelet agents

Antiplatelet agents (e.g. aspirin, dipyridamole or sulphinpyrazone) alone are ineffective in reducing the incidence of DVT.33 However, one study of patients undergoing hip-fracture surgery reported a reduction in symptomatic pulmonary embolism or DVT by 36% (preventing 4 fatal pulmonary embolisms per 1000 patients treated) with aspirin (160 mg daily) in addition to other thrombophrophylactic treatment (e.g. LMW or UF heparin).34

Inferior Vena Cava interruption

Methods used to interrupt the inferior vena cava include:

1) Vena caval ligation. This is not effective in reducing the incidence of pulmonary embolism as it causes large collaterals to form, through which thromboemboli travel causing pulmonary emboli in 30 - 50% of patients. It also may cause severe lower limb oedema.55

2) Vena caval filters. The Greenfield vena caval filter captures thromboemboli without occluding the inferior vena cava,55,56 although if is tilted it may not capture small thrombi. Other filters (e.g. Bird’s nest, Simon nitinol and Vena-Tech) have added advantages, including rapid percutaneous insertion through a small calibre catheter, high efficiency in filtering small emboli, and (particularly the Bird’s nest filter) an ability to accommodate a large inferior vena cava size. Unfortunately MRI is contraindicated when these filters are used.57 These filters may be indicated when pulmonary embolic episodes continue despite adequate anticoagulation or when anticoagulants are contraindicated.

In one prospective randomised study of 400 patients with proximal DVT who were anticoagulated for three months, vena caval filters did not alter the morbidity or mortality (due to the late recurrence of DVT), indicating that when a vena caval filter is inserted, the patient should also be anticoagulated for life.59

PULMONARY THROMBOEMBOLISM

Pulmonary embolism is the partial or complete obstruction of pulmonary arterial blood flow by an intravascular embolus. Pulmonary thromboembolism is considered as the pulmonary embolic manifestation of venous thrombosis. Massive pulmonary embolus is defined as an embolus which obstructs greater than 50% of the pulmonary vasculature.

Cause

Pulmonary thromboembolism occurs in 1 - 2% of hospital patients,60 and in 95% of cases originates from the lower limb veins (two thirds of which have no signs or symptoms). An upper limb thrombus is almost never responsible for a pulmonary thromboembolism.61

Clinical features

Virtually all patients who have a pulmonary embolism have dyspnoea that is sudden in onset. The dyspnoea may be transient, although with severe embolism it is usually persistent and often out of proportion to the degree and extent of the objective abnormal findings. The common clinical features of a minor pulmonary thromboembolism (i.e. associated with normal systemic blood pressure and right ventricular function) include dyspnoea, pleuritic chest pain, tachycardia, pyrexia and tachypnoea.62

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Table 2. The incidence of symptoms and signs of pulmonary thromboembolism

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence %</th>
<th>Signs</th>
<th>Incidence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>80</td>
<td>Tachypnoea (rate &gt; 16)</td>
<td>90</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>Auscultation:</td>
<td></td>
</tr>
<tr>
<td>Pleuritic</td>
<td>70</td>
<td>Crepitations, wheezing</td>
<td>60</td>
</tr>
<tr>
<td>Non pleuritic</td>
<td>10</td>
<td>Accentuation of P2</td>
<td>50</td>
</tr>
<tr>
<td>Apprehension</td>
<td>60</td>
<td>S3 or S4</td>
<td>30</td>
</tr>
<tr>
<td>Cough</td>
<td>50</td>
<td>Pleural friction rub</td>
<td>10</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>30</td>
<td>Elevated JVP</td>
<td>50</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>30</td>
<td>Tachycardia (&gt; 100)</td>
<td>40</td>
</tr>
<tr>
<td>Syncope</td>
<td>10</td>
<td>Pyrexia (&gt; 37.8°C)</td>
<td>40</td>
</tr>
<tr>
<td>Need to evacuate</td>
<td>10</td>
<td>Diaphoresis</td>
<td>40</td>
</tr>
<tr>
<td>bowels</td>
<td></td>
<td>Thrombophlebitis</td>
<td>30</td>
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<tr>
<td></td>
<td></td>
<td>Cyanosis</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension (systolic &lt; 80)</td>
<td>5</td>
</tr>
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**Investigations**

The investigations performed in a patient with a suspected pulmonary thromboembolism often include:

*Plasma biochemistry.* Liver function tests may reveal an increase in plasma lactic acid dehydrogenase and an increase in bilirubin.

*Plasma XDPs (D-dimer).* Plasma XDP’s are increased in patients with pulmonary thromboembolism. The sensitivity of this test is 96% (when measured by enzyme linked immunosorbent assay). However, the specificity of the test is low (e.g. 20%), so while venous thrombosis and pulmonary embolism may be unlikely in a patient with normal plasma D-dimer concentrations (i.e. it is useful in ruling out pulmonary embolism), a positive result requires confirmation by more specific imaging techniques. While more specific D-dimer tests are available, they are less sensitive and therefore have less predictive value in excluding venous thromboembolism.

*Arterial gas analysis.* In 90% of patients with pulmonary thromboembolism blood gas analysis reveals a low PaCO₂ due to overventilation (or hyper-ventilation) and a low PaO₂ due to ventilation perfusion mismatch. A low cardiac output may also decrease the PaO₂ by decreasing pulmonary perfusion as well as by decreasing mixed venous oxygen tension (thereby increasing the effect of a pulmonary shunt). The increase in right atrial pressure may also cause a right-to-left shunt through a patent foramen ovale producing profound hypoxia during pulmonary embolism. The end-expired CO₂ is reduced due to a reduction in cardiac output and increase in dead space ventilation.

*Electrocardiograph (ECG).* A transient rSR pattern in the anterior chest leads (i.e. new RBBB), S₃, Q₃ - T₃, clockwise rotation and right axis deviation are the classical ECG findings of an acute pulmonary embolism, although these signs have low sensitivity and specificity as they are found in only 5 - 10% of cases (Fig. 1).

Commonly, there is sinus tachycardia and T wave inversion in the right precordial leads (i.e. V₁ - V₄). One study found that new T wave inversion in the right precordial leads in patients with a diagnosis of pulmon-

**Figure 1.** A 12 lead ECG in a patient with massive pulmonary thromboembolism, demonstrating sinus tachycardia (rate 160/min), an rSR pattern in V₁, and a Q₃-T₃ pattern.
ary embolism was indicative of the severity of the pulmonary obstructive defect with 81% of patients having a mean pulmonary artery pressure (MPAP) > 30 mmHg, and that normalisation of the T wave (before day 6) with thrombolysis was indicative of the MPAP returning to < 25 mmHg. Atrial flutter or fibrillation may also occur.

While the ECG may contribute very little to the diagnosis of pulmonary embolism, it often contributes by excluding other disorders (e.g. myocardial infarction, pericarditis).

Chest X-ray. The chest X-ray may reveal oligaemic areas (i.e. reduced vascular markings) within the lung fields, pulmonary artery hilar attenuation, and an elevated hemidiaphragm on the side of the embolism. Atelectasis and pleural effusion are usually only seen with pulmonary infarction. A normal chest X-ray, however, is the commonest finding in a patient with pulmonary thromboembolism, but like the ECG, often contributes by excluding other disorders (e.g. pneumothorax).

Echocardiography. Echocardiography should be performed in all patients to detect the presence of acute right ventricular dysfunction and the need for thrombolytic therapy. Echocardiographic findings of dilated chambers of the right side of the heart (i.e. right atrium and right ventricle), mild to moderate tricuspid regurgitation and small and often actively contracting chambers of the left side of the heart (i.e. left atrium and left ventricle) are characteristic of pulmonary embolism, particularly when associated with shock. Pulmonary arterial pressures can also be estimated (which are characteristically elevated), septal position assessed (which is often flattened or displaced to the left) and in some cases intracardiac thrombi may be identified. A transoesophageal echocardiogram may also be used to demonstrate thrombus in the pulmonary artery (and a thrombus in the chambers of the right side of the heart). Ventilation perfusion scan. This was often the investigation of choice which when described as normal, does not exclude the diagnosis of pulmonary emboli (i.e. there is a 9% chance of pulmonary embolism), low probability (16% chance of pulmonary embolism), intermediate probability (33% chance of pulmonary embolism) or high probability (greater than 88% chance of a pulmonary embolism). However, echocardiography, spiral volumetric computed tomography and magnetic resonance angiography of the lung are now often the initial investigations of choice depending on the severity of the haemodynamic effect of the pulmonary embolus.

Angiography. This has been used as the only precise method of diagnosing pulmonary thromboembolism and should be performed in patients who have a high clinical suspicion for pulmonary embolism associated with an intermediate, or low probability ventilation perfusion scan. It is also mandatory if pulmonary embolectomy is to be performed. Pulmonary angiography demonstrates pulmonary artery intravascular filling defects or ‘cut-off’ in the presence of pulmonary thromboembolism.

Computed tomography (CT) and magnetic resonance (MR) imaging. Spiral volumetric CT and pulmonary MR angiography (gadolinium-enhanced) are recent techniques that have been used to detect pulmonary emboli in second to fourth division pulmonary vessels. Both have specificities ranging between 92 - 97% and sensitivities ranging between 63 - 100%.

However, helical CT cannot safely exclude pulmonary embolism in a clinically stable patient who has a non-diagnostic ventilation perfusion scan, as it is insensitive to embolism in subsegmental branches (although these are also difficult to diagnose with pulmonary angiography). One study using a noninvasive strategy of combining spiral volumetric CT, ventilation perfusion scan and plasma D-dimer measurement recorded a definite diagnosis in 99% of patients.

Ultrasound of iliac and femoral veins. As venous thromboembolism is one disorder which may be asymptomatic or present with features of pulmonary embolism, with or without DVT, ultrasonography is often performed to assess the integrity of the lower limb veins when the diagnosis of pulmonary thromboembolism is being considered.

Pulmonary artery catheterisation. Special balloon catheters have been developed which enable angiography to be performed at the bedside. These may then be replaced by standard Swan-Ganz catheters which are then used for fibrinolytic treatment and haemodynamic monitoring to guide therapy. In one study of patients with a previously normal cardiovascular system, a MPAP of 22 mmHg correlated with a 30% pulmonary vascular obstruction and a MPAP of 36 mmHg correlated with a 50% pulmonary vascular obstruction. The MPAP rarely exceeded 40 mmHg, even with massive pulmonary thromboembolism in patients with a previously normal cardiovascular system, and therefore if it exceeded 40 mmHg or the pulmonary arterial systolic pressure exceeded 50 mmHg, chronic pulmonary hypertension with right ventricular hypertrophy must have been present previously.

Treatment

In patients who have signs of mild pulmonary thromboembolism, the thrombus will either undergo natural fibrinolysis (and resolve), or undergo organis-
ation. Resolution may be enhanced by administering heparin to allow natural fibrinolysis to continue without thrombogenesis and is often the only therapy required. Substantial angiographic resolution normally occurs within the first 24 hr, with further resolution being complete within 4 - 6 weeks. In approximately 10% of patients with pulmonary thromboembolism, the clot undergoes organisation and the pulmonary defect remains after 6 weeks, and 2 - 5% of patients develop recurrent pulmonary emboli (in the absence of prolonged anticoagulation) with progressive pulmonary hypertension, hypoxaemia and right ventricular failure. Thus, in a group of susceptible patients, prolonged anticoagulation is required. Patients with normal blood pressure and signs of acute pulmonary hypertension should be treated with thrombolytic agents and heparin.

Management of a patient with massive or severe pulmonary embolism often requires:

**Resuscitation**

*Respiratory resuscitation*

Inspired oxygen concentrations between 40 and 80% are administered by facemask. In patients who are in extremis, endotracheal intubation and mechanical ventilation may be required, although high peak inspiratory pressures and PEEP are avoided.

*Cardiovascular resuscitation*

This may require intravenous fluids (to optimise preload without increasing right atrial or pulmonary artery pressures to levels which reduce left ventricular performance), inotropic agents (to improve right ventricular perfusion, reduce pulmonary resistance and improve cardiac output) and pulmonary vasodilators (to reduce right ventricular afterload).

While left ventricular perfusion occurs largely during diastole, right ventricular perfusion occurs during both systole and diastole and both may be reduced with a massive pulmonary embolism. The maintenance of the right ventricular perfusion pressure (i.e. mean systemic blood pressure - mean right ventricular pressure; where mean right ventricular pressure may be measured directly or calculated from the formula: right atrial pressure (RAP) + 1/3 (pulmonary artery systolic pressure - RAP)) of greater than 30 mmHg may be required to reduce right ventricular ischaemia associated with massive pulmonary embolism, although the pulsatile nature of the right ventricular pressure may provide intermittent yet adequate right ventricular perfusion at mean pressures of less than 30 mmHg. Left ventricular dysfunction may also occur during massive pulmonary embolism largely due to a reduced preload (due to reduced right ventricular stroke volume, intraventricular septal shift and pericardial constraint caused by right ventricular dilation).

In general, cardiovascular resuscitation is needed only in massive thromboembolism, unless cardiac failure has existed previously, and involves treatment that improves right ventricular preload, contractility and afterload (although the major focus should be to reduce the afterload by reducing the mechanical obstruction caused by the embolus).

**Intravascular fluid.** A moderate increase in intravascular volume (e.g. 500 mL of 4 - 5% albumin) may be beneficial, although volume expansion must be performed cautiously as an increase in right atrial pressure to greater than 20 mmHg may be associated with a reduction in left ventricular filling as well as acute tricuspid regurgitation, due to acute right ventricular dilation and septal shift.

**Inotropic agents.** Adrenaline is often considered the inotropic agent of choice as it provides a positive inotropic effect, systemic vasoconstriction and adequate coronary and cerebral perfusion. Nevertheless, some studies using a canine model of pulmonary embolism and shock conclude that noradrenaline is the drug of choice, although it may have shown this effect as it has a greater positive inotropic effect in the canine model than in man. If low cardiac output is present without hypotension (i.e. if right ventricular perfusion is adequate) then isoproterenol may be beneficial as it is associated with a greater haemodynamic improvement when compared with noradrenaline.

**Pulmonary vasodilators.** While platelet release from thromboxane A2 and serotonin may be responsible for pulmonary vasocostriction as well as bronchodilation, inhibitors of both these substances have not been of value in the management of patients with pulmonary embolism. However, there have been sporadic reports of beneficial effects of inhaled nitric oxide in patients with massive pulmonary embolism.

**Anticoagulation**

Unless there is a contraindication, intravenous UF heparin (80 U/kg as an intravenous bolus dose, followed by 18 U/kg/hr as an intravenous infusion or 5500 U stat) is recommended in a 70 kg adult and adjusted to keep the APTT 1.5 - 2.5 x the control value and oral warfarin (5mg daily), are initiated as soon as the diagnosis is suspected. Therapy is begun as soon as possible because untreated pulmonary thromboembolism has a mortality of 15%, which is reduced to 8% (i.e. two-fold) if it is treated with anticoagulants, whereas haemorrhage from heparin occurs in only 4% of patients (causing death in less than 0.5%).
pulmonary embolism should be confirmed with objective tests and anticoagulants discontinued if pulmonary embolism is not confirmed.

Recent studies have shown that low-molecular weight heparins (e.g., tinzaparin 175 anti Xa IU/kg daily s.c.) appear to be as effective as intravenous UF heparin (50 U/kg bolus followed by 500 U/day and adjusted to keep the APTT 2 - 3 x the control value) or warfarin in the management of these patients.

Heparin is discontinued, usually after 3 - 5 days, when the prothrombin time is in the therapeutic range (i.e. an international normalised ratio between 2.0 - 3.0), warfarin is then continued for at least 3 months when a transient risk factor is identified (e.g. following surgery), and forever for patients with a second episode. In all other cases anticoagulation for 6 months is recommended.

However, three months of anticoagulant therapy in patients with a transient risk factor may be inadequate, as one study of 162 patients with a first episode of idiopathic venous thromboembolism treated with warfarin for 3 months found that patients treated for a further 24 months with warfarin had a 95% reduction in the risk of recurrent venous thromboembolism compared with the control group (i.e. patients not treated with warfarin), and only a 3.8% per year increase in major bleeding episodes compared with 0% in the control group. In another study of patients with idiopathic thromboembolism, there was an increased incidence of cancer during the following two years which was subsequently reduced in patients who were treated with warfarin for 6 months compared with those who were treated with warfarin for 6 weeks.

Fibrinolytic therapy

Fibrinolytic (thrombolytic) therapy clears the pulmonary arteries of clot and improves the blood pressure and cardiac output more rapidly than heparin. While in one study the mortality of both groups of patients treated by either thrombolysis or heparin was the same after 1 month, in another study, the mortality after one month was lower in the group treated with thrombolytic therapy.

Fibrinolytic therapy should be considered in all patients with venous thromboembolism in whom there are no contraindications, as the improvement in right ventricular function is greater and the pulmonary artery perfusion defect is less 24 hr later and 7 years later, in patients treated with fibrinolytic therapy when compared with those treated with heparin, and the long term morbidity (e.g. chronic pulmonary hypertension and right ventricular failure) is less with fibrinolytic therapy.

One of three standard fibrinolytic agents are often recommended. Streptokinase (250,000 IU over 30 min, followed by 100,000 IU/hr for 12 - 24 hr, then continuous heparinisation), urokinase (4,400 IU/kg in 15 min followed by 4,400 IU/kg/hr for 12 - 24 hr, followed by continuous heparinisation) or alteplase (100 mg over 2 hr with continuous heparinisation). However, the latter may be the treatment of choice as alteplase has a short half-life (i.e. the coagulation defect may be rapidly reversed and an embolectomy may be performed without delay), it has a more rapid effect when compared with urokinase, it does not cause hypotension (c.f., streptokinase), and it may be more effective in fibrinolysing older clots. In one study of 36 patients with massive pulmonary embolism, the standard double bolus regimen of reteplase (10 U i.v. over 2 minutes followed 30 minutes later by 10 U i.v. over 2 minutes) produced the same reduction in pulmonary vascular resistance as the standard dose of alteplase (i.e. 100 mg i.v. over 2 hr).

While post operative thromboembolism during the first 14 days is usually a contraindication for thrombolytic therapy, in one study of 13 postoperative patients who developed significant pulmonary thromboembolism (e.g. > 30% pulmonary vascular obstruction) from 3 - 14 days (mean 9.6 days) of surgery (patients with neurosurgical procedures, cerebrovascular accidents, recent or current gastro-intestinal bleeding, major hepatic renal or other bleeding disorder were excluded), urokinase 2,000 IU/kg followed by 2,200 IU/kg/hr injected directly into the pulmonary artery (until the clot was lysed or serum fibrinogen, which was monitored 6-hourly, was less than 0.6 g/dL, or up to 24 hours) with simultaneous heparin infusion of 500 U/hour, was associated with no bleeding complications.

It is generally thought that there will be little improvement if thrombolytic therapy is delayed for more than 14 days after the onset of symptoms (with a decrease of 0.8% reperfused lung tissue for each 24 hr delay), however one report documented improvement in a patient with massive pulmonary embolism in which thrombolytic therapy was delayed for 1 month. While major bleeding is common (i.e. 9.2%) particularly when administered to patients in the postoperative period, cerebral bleeding is uncommon (i.e. 0.5%).

Pulmonary embolectomy

Surgical embolectomy. Sixty six percent of patients who have massive pulmonary thromboembolism die within the first hour and 80% die within 2 hr. The remaining patients are often able to be managed with inotropic, fibrinolytic and anticoagulant agents without the need for surgery, although embolectomy should be
considered in patients who have more than 50% occlusion of the pulmonary arteries (i.e. massive pulmonary embolism), in whom thrombolytic therapy is contraindicated, or who have continuing deterioration 1 hr after the onset of thrombolytic treatment.\textsuperscript{134} Echocardiography or angiographic evidence is also required to demonstrate a surgically accessible proximal embolus.\textsuperscript{135}

**Percutaneous embolectomy.** Percutaneous embolectomy has been described in specialised centres using catheter devices which aspirate the pulmonary embolus or fragment the pulmonary embolus in situ,\textsuperscript{136-138} (or using catheter devices that both fragment and aspirate the embolus\textsuperscript{139-140}). These devices may be useful in treatment of life threatening pulmonary embolism in patients who have an absolute contraindication to thrombolytic therapy, although they have not yet been compared with surgical or other medical treatments.

**Inferior vena cava interruption**

Methods used to achieve inferior vena cava interruption include vena caval ligation and vena caval filters (see previously), both of which have not been found to reduce long term mortality associated with pulmonary embolism.\textsuperscript{41}

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