Part II: Respiratory Failure

Chapter 26: Pulmonary Embolism

T E Oh

Pulmonary embolism (PE) is a complication of deep vein thrombosis (DVT). The actual incidence is difficult to ascertain, but may be as high as 630,000 cases annually in the USA. It is a frequent cause of morbidity and mortality in both postoperative and medical patients. In autopsy reports, death has been directly attributed to PE in 15% of cases. The mortality in treated patients is significantly lower than those undiagnosed or untreated. Hence, prophylactic measure against DVT, and early diagnosis and treatment of PE is important, especially in critically ill ICU patients.

Aetiology

Almost all pulmonary emboli result from frequently asymptomatic thromboses from deep veins of the lower limbs, pelvis and inferior vena cava (proximal DVT), and rarely from thromboses in the upper limbs, right atrium or ventricle. Thrombosis limited to calf veins (distal DVT) seldom results in clinically obvious PE, but progression to a proximal thrombus and direct embolization from a calf-only thrombus are possible.

Predisposing factors for thrombosis are best considered in terms of Virchow's triad (a) stasis of blood flow, (b) damage to vessels, or (c) alterations in coagulation mechanism (Table 1). High risk patients for DVT and PE are those with heart failure, cancer, prolonged bed rest, obesity (especially females), and hip fracture, and aged over 65 years and receiving oestrogen therapy. Other less well known, but significant risk factors are heritable disorders. Inherited deficiencies of protein C, protein S, and antithrombin III (ATIII) have recently been discovered. Protein C and S are vitamin K-dependent antithrombotic proteins. Inherited abnormalities of fibrinogen and plasminogen also increase the risk of PE.

Clinical Presentation

Pulmonary embolism has a varied non-specific presentation, largely dependent on the severity and multiplicity of the embolic episode. Symptoms and signs may be mistaken for manifestations of coexistent diseases. Such diseases of the heart and lungs is likely to influence the outcome of PE. Small "herald" emboli may precede a major embolus by days or weeks. The majority of emboli are multiple.

1. Symptoms

The most common symptom is dyspnoea of sudden onset (85% of patients). Chest pain of substernal or pleuritic type occurs in 70%, and apprehension and non-productive cough occur in 60% of cases. Syncope (14% of patients) is usually only associated with massive pulmonary embolism. Classic symptoms of pleuritic pain and haemoptisis are not early symptoms and are present only if infarction has occurred (10% of patients).

2. Physical Signs

There may be no helpful clinical signs. Those present are usually non-specific and include:

(a) *Respiratory*

Tachypnoea with shallow breaths (> 20/min) is seen in 80% of patients. Cyanosis is usually restricted to cases of massive embolism. A pleural effusion and friction rub may be found if infarction has occurred, usually in the lower lobes. Wheezing is present infrequently. Rales may be a manifestation of coexisting cardiopulmonary disease.

(b) *Cardiovascular*

Tachycardia (> 100/min) may relate to the site of the obstruction. Onset of bradycardia is an ominous sign. Accentuation of the pulmonary valve closure sound and widened splitting of the 2nd heart sound may reflect a rise in pulmonary arterial pressure. Mean pulmonary artery pressure is elevated by 5 mmHg (0.67 kPa) when more than 50% of the pulmonary vasculature is acutely obstructed. A right ventricular heave may be palpable. S_3 and S_4 gallop heart sounds may be detected, often associated with extensive embolism. A high jugular venous pressure and prominent "a" waves may be seen. Systemic hypotension and shock occur in the presence of massive embolization; a small sharp peripheral pulse may be palpated.

(c) *Lower Limbs*

Clinical evidence of DVT may be present, but is found in only about 30% of patients with PE. A "normal" leg may give rise to emboli, more so than an overly thrombophlebitic (calf-vein thrombus) leg.

(d) *Other Signs*

A modest fever (38-39 °C) is found in 45% of patients, and diaphoresis in one third.

Many of the above signs may be transient and persist for only a few hours after the acute embolization, perhaps signifying early lysis and fragmentation, with more distal distribution of the embolus. The pathophysiological bases of the clinical features are shown in Table 2. Differential diagnosis includes myocardial infarction, acute left ventricle failure, aspiration pneumonitis, acute pneumonia, fat embolism, pneumothorax, and dissecting aortic aneurysm.

Investigations

Objective diagnostic tests are essential, as the clinical examination and readily available tests (i.e. chest X-ray) are unreliable to diagnose or exclude PE. Investigation include those to diagnose DVT as well as PE.

Diagnosis of DVT

About 90% of pulmonary emboli are thought to arise in the deep veins of the lower extremities and pelvis. Diagnosis of DVT may help to diagnose PE, if specialized facilities to confirm PE are unavailable, and also in the decision to use thrombolytic therapy. Studies of the lower extremities for DVT are:

1. Radiolabelled Fibrinogen Scan

Radioisotope I^{125} fibrinogen is injected IV and the legs are scanned for up to 7 days. The test is good to detect calf-vein (distal) thrombi, but relatively insensitive for thrombi in the thigh and pelvis. It is also only effective prospectively, i.e. when the thrombosis is still developing, and has to be performed over several days.

2. Impedance Plethysmography

This is a new noninvasive technique sensitive for proximal, but not distal DVT. Electrical impedance is measured distally, during inflation and deflation of a mid thigh pneumatic cuff. Change of impedance reflects change in blood volume, indicating venous obstruction. Diagnostic reliability has been verified with serial impedance plethysmography over 10-14 days. This combined with fibrinogen leg scanning, is equal in sensitivity to invasive venography.

3. Doppler Ultrasonography

Doppler ultrasound detects flow changes in veins. The technique is sensitive for obstruction of popliteal and more proximal veins. However, interpretation is subjective.

4. Contrast Venography

Venography is the most accurate diagnostic technique. However, visualization of external and common iliac veins may be inadequate in some patients. A negative venogram cannot exclude a DVT with utmost certainty, as embolism may have arisen from sources other than the lower extremities. It is invasive and expensive, and complications inslude pain and a very low incidence of DVT itself.

Diagnosis of PE

Diagnostic investigations include routine laboratory and bedside tests, although these are generally non specific.

1. Blood

White cell count may be elevated (> 15,000 x 10^6 cells/L). Serum lactic dehydrogenase, transaminase enzymes and billirubin levels may rise infrequently and late in the illness. However, they lack specificity to be of any use in the acute situation. The elevation of fibrinogen degradation products is currently more of research than clinical interest.

2. Chest X-ray

This is not specific or diagnostic, but comparison with previous films may be helpful. The chest film may be normal. Focal pulmonary oligaemia, localized infiltrates, consolidation, raised diaphragms, pleural effusion, and "plump" pulmonary arteries are seen in up to half the cases.

3. Electroencephalograph

The classic pattern of a deep S-wave in lead I, and a Q-wave and inverted T-wave in lead III (S1Q3T3) is not frequently seen. Non-specific S-T depression and T wave inversion in anterior leads is the most common finding, reflecting right heart strain. P pulmonale, right bundle branch block, and atrial arrhythmias are also occasionally present, and persistent if embolization is massive. A normal ECG is present in 6% of cases with massive embolization. The ECG may be useful, however, in excluding acute myocardial infarction.

4. Arterial Blood Gases

Hypoxaemia is frequently present, but an arterial PO_2 over 80 mmHg (10,6 kPa) is not uncommon in PE. Hypocarbia may be present, as a result of the tachypnoea. It is important to know the inspired oxygen concentration at the time of arterial blood sampling. Metabolic acidosis will be present if a shock state follows a large embolus.

5. Ventillation/Perfusion Lung Scans

A perfusion lung scan (using IV technetium-99m labelled albumin) is a sensitive non-invasive test which should be performed whenever PE is suspected. Perfusion defects may be classified as single or multiple, and as subsegmental, segmental, or lobar. A ventilation scan (inhalation of xenon-133) performed in conjunction, markedly improves specificity over a perfusion scan alone. Defects may "mismatch" (with normal ventilation at the site of a perfusion defect) or "match" (when the ventilation defect corresponds with the perfusion defect). The probability of PE may be deduced from V/Q lung scans as being high, low, or intermediate (Table 3). Presence of pre-existing lung disease makes interpretation of V/Q abnormalities difficult, and false positive findings may be made. The diagnostic value of the low probability category is currently debatable; 25-40% of such cases show abnormalities on subsequent angiography. Nevertheless, general management guidelines based on V/Q lung scans are possible.

(a) A normal perfusion scan virtually rules out significant PE.

(b) A high probability V/Q scan with significant risk factors reliably establishes the diagnosis of PE.

(c) A low probability V/Q scan with a high clinical index of suspicion warrants pulmonary angiography.

(d) A high probability V/Q scan with normal non-invasive tests for DVT and low risk factors should also be confirmed by pulmonary angiography.

(e) V/Q lung scans are used to document resolution of confirmed emboli.

6. Pulmonary Angiography

This is a specific "gold standard" test. Unfortunately, it is invasive and specialized, with an associated mortality and morbidity (albeit small and probably less than that of empirical anticoagulation). A positive angiogram shows consistent defects in multiple films or sharp cut-offs in vessels over 2.5 mm diameter. Massive PE produce significant filling defects or obstruction in 2 or more lobar arteries. Indications for pulmonary angiography include the above considerations with V/Q scans, confirmation of PE in a patient at increased risk of bleeding from anticoagulants, and massive PE to decide choice of thrombolytic, embolectomy, or vena caval interruption therapy. The pulmonary angiogram catheter can be left in situ for measurements of pulmonary arterial pressures, direct infusion of thrombolytic drugs and repeat angiography.

7. Angioscopy

A pulmonary fiberoptic angioscope is directed percutaneously via the jugular vein into the heart and pulmonary arteries. Direct visualization of pulmonary arteries from the main trunk to 3.5 mm diameter vessels is then possible. This new technique may be helpful when the diagnostis remains equivocal or if the patient is allergic to angiographic contrast media. It may also help to identify and localize suspected chronic pulmonary emboli.

Management

General Measures

General measures in the acute situation include oxygen therapy, haemodynamic support, and treating shock in massive PE. Cardiopulmonary resuscitation is undertaken in acute cardivascular collapse.

1. Oxygen Therapy

Oxygen is given by mask. High flows should be used because air entrainment from marked hyperventilation will result in a lower than expected inspired oxygen concentration. Intubation and mechanical ventilation may be necessary.

2. Haemodynamic Support

It is imperative to maintain right heart filling pressures. Elevation of the lower limbs will increase venous return by autotransfusion, and thus assist right heart filling pressures (Starling effect). Placement of a Swan-Ganz catheter, although not essential, will enable monitoring of responses to vasoactive and thrombolytic agents. Fluid infusion and positive inotropes may help to maintain systemic and pulmonary circulations. Isoprenaline, although a potent inotrope and pulmonary vasodilator, is less useful, as it is also arrhythmogenic and a systemic vasodilator (and thus decrease right heart filling pressures). Femoro-femoral partial cardiopulmonary bypass has been used to support the circulation until thrombolytic therapy or embolectomy can be undertaken.

Radiographic contrast injection can cause systemic vasodilation and a decrease in right heart filling pressures, with possible catastrophic effects. Atropine and phenylephrine should be readily available. An intravenous line should be inserted in the left arm as angiographic procedures are usually performed from the right arm.

Definitive Therapy for DVT and PE

Definitive treatment is directed towards prevention of new thrombus formation, thrombolysis, blocking migration of emboli, and emboli removal.

1. Heparin Therapy

Heparin enhances the inhibitory effect of ATIII on thrombin and Factor Xa. Heparin anticoagulation by infusion is safer and more efficacious than intermittent IV bolus doses for preventing new thrombus formation. A bigger IV bolus of 15,000-20,000 units is advocated, followed by an infusion of 1000-1500 units/h. Heparin is known to antagonize platelet-released serotonin and histamine, which are known to cause acute pulmonary vasoconstriction, and further exacerbate pulmonary hypertension associated PE.

The dose of heparin is adjusted to maintain partial thromboplastin time (APPT) at 1.5-2.5 times the control level. Heparin anticoagulation may be achieved in a patient with ATIII deficiency by simultaneous administration of plasma to provide exogenous ATIII. Therapy is usually continued for 7-10 days with a 5 day overlap with the start of oral warfarin therapy. Starting warfarin soon after heparin (even the same day), with a similar 5 day overlap, reduces exposure to heparin and is reported to be effective and safe.

Heparin may induce thrombocytopenia and a paradoxical thrombotic thrombocytopenia syndrome. In severe cases, heparin should be discontinued, and other treatment measures instituted.

2. Warfarin Therapy

Warfarin and other coumarin derivatives inhibit synthesis of vitamin K-dependent clotting factors, i.e. prothrombin and Factors VII, IX and X. In addition, it reduces anti-thrombotic protein C levels. Thus, during the early stages of warfarin therapy, a hypercoagulable state may exist, before all vitamin K-dependent factors with longer half-lives (II, IX and X) are sufficiently inhibited. Hence, heparin therapy must continue for 5 more days after the start of warfarin, even though the prothrombin time may reflect a therapeutic warfarin effect after 2-3 days.

The usual loading dose is 25-30 mg given over 36 hours. Maintenance is often about 5 mg/day but must be controlled by regular prothrombin time estimations (at about 2 times control) or international normalised ratio (INR, 2-3). Haemorrhage is the important side effect of warfarin anticoagulation. Age increases the bleeding risk. Interaction with other drugs (i.e. salicylates, phenothiazines and phenylbutazone) potentiates the action of warfarin. Haemorrhage from warfarin toxicity may occur into kidneys, gastrointestinal tract, lungs, subdural or subarachnoid space, skin, mucous membranes and muscles. Bleeding into the retroperitoneal space is often insidious.

Oral warfarin therapy and monitoring is continued for 1.5-3.0 months for DVT and 3-6 months for PE, and longer in patients at particular risk - one year in those with a previous DVT, and indefinitely if more than 2 episodes of PE have occurred. Contraindications to anticoagulation are given in Table 4. Poor patient compliance with regular medication, and trauma-prone occupation affect long-term anticoagulation.

Table 4. Possible Contraindications to Anticoagulant Therapy

Peptic ulceration
Hiatus hernia
Hepatic disease
Steatorrhoea
Hypertension
Retinopathy
Infective endocarditis
Uraemia
Alcoholism
Pregnancy
Recent surgery and trauma
Cerebral haemorrhage
Haemostatic defect
Poor patient compliance

Reversal of warfarin therapy, if indicated is achieved with vitamin K. A small dose of 5 mg will shorten the prothrombin time. Complete reversal of anticoagulation requires a larger dose, i.e. up to 50 mg. However, if anticoagulation is to be interrupted for an elective surgical procedure, it is best to withhold warfarin for about 3-4 days beforehand. Vitamin K administration will make the control of prothrombin time difficult on recommencement of warfarin, for 2-3 weeks. Acute reversal of warfarin therapy is best achieved by administration of fresh frozen plasma and factor concentrates.

3. Thrombolytic Therapy

Thrombolytic therapy may accelerate resolution of emboli and improve cardiopulmonary status, but improvement in total mortality from PE has not been demonstrated. Nevertheless, thrombolytic therapy is reasonable for extensive proximal DVT, PE with haemodynamic instability, and a perfusion defect of one lobe or greater.

Streptokinase and urokinase activate plasminogen to form plasmin, thereby promoting clot lysis. Streptokinase, despite its potential pyrogenic and antigenic properties, is usually used. It has a MW 43,000, and is rapidly bound to the patient's previously generated circulating antistreptococcal antibodies. Thus a dose must be sufficiently large to provide a free excess for fibrinolytic activity. The dose required may be calculated in vitro. A typical regimen is: 250,000-600,000 units loading infusion over 30 min, followed by an infusion of 100,000 units/h for 24 hours. Longer therapy (3-7 days) may result in better improvements in the pulmonary and leg deep venous circulations. Antihistamines and hydrocortisone (100 mg before and then each 12 hours of therapy) will reduce immunological reactions. High

fevers and rigors are generally uncommon. Adrenaline and resuscitation equipment should be immediately available.

Urokinase has a more rapid onset of action, is non-antigenic and may be used repeatedly, but remains very expensive. It is given 4400 units/kg IV over 10 min as a loading dose, followed by an infusion of 4400 units/h for 12 hours.

Monitoring is achieved by thrombin clotting time (2-4 times the control) and euglobulin lysis time measurements; before therapy, at 4 and 8 hours after commencement for urokinase, and 4 and 12 hours after commencement for streptokinase. Consultation with a haematologist is recommended. Heparin infusion is recommended after the course of thrombolytic therapy is complete.

Main disadvantages of streptokinase therapy are bleeding and allergic reactions. Contraindications to the use of streptokinase or urokinase are given in Table 5. Intramuscular injections must be avoided (as with heparin therapy) and blood sampling minimized and restricted to sites where digitial compression is possible. If complications occur, streptokinase infusion must be stopped (half-life of 15 minutes). If necessary, fresh frozen plasma is given to replenish depleted coagulation factors. Epsilon aminocaproic acid (amicar, 5-8 g) or aprotinin (trasylol; 500,000 units) have been used to antagonize streptokinase fibrinolytic action more rapidly.

New clot-specific thrombolytic agents with less systemic fibrinogenolysis than streptokinase or urokinase have recently been introduced. These include APSAC (anisoylated plasminogen streptokinase activator complex) and rTPA (recombinant tissue plasminogen activator). They have been studied more in acute coronary thrombosis, but also appear to be more beneficial than the first generation thrombolytics.

4. Inferior Vena Cava (IVC) Filter

Placement of a mechanical barrier to migration of emboli in the IVC should be considered, if development of a new PE might prove fatal. The indications are:

(a) Recurrent PE despite adequate anticoagulation.
(b) Inability to tolerate anticoagulation.
(c) A large, free-floating thrombus in the ileo-femoral veins.
(d) Immediately following pulmonary embolectomy.

The Greenfield filter is commonly used, placed transvenously under fluoroscopic guidance. It can achieve recurrent PE rates of 5%. Heparin should be started 12 hours after placement of filter in those without contraindications to anticoagulation.

5. Embolectomy

Surgical embolectomy is uncommon, because most patients with massive PE respond well to conservative therapy. Data on its usefulness is unavailable. Specific criteria for pulmonary embolectomy are difficult to derive. Cardiovascular improvement following streptokinase therapy is similar to that of pulmonary embolectomy with cardiopulmonary bypass, but has a higher morbidity and mortality. However, if streptokinase therapy is

contraindicated or unsuccessful, and there is persistent hypotension, oliguria, hypoxia, and metabolic acidosis, with radiological confirmation of greater than 50% occlusion of the pulmonary arterial tree, then pulmonary embolectomy may be all there is to offer. This may be attempted by open thoracotomy or by special transvenous catheters. Venous thrombectomy on the lower limbs is rarely undertaken. Consideration is given to venous thrombectomy if indicated by venography, and if the thrombosis formation is recent.

Prophylaxis Against DVT and PE

Prevention of PE is largely the prevention of DVT. Prolonged anticoagulation with oral agents is useful in those patients at high risk of recurrent emboli. In lower risk or preoperative patients, mobilization exercises in addition to low dose heparin (5000 units subcutaneously 2-3 times daily), offers moderate protection. Low MW heparin appears to be as effective, with less risk of bleeding, but is not generally available. Low dose heparin prophylaxis, however, is not always suitable for neurosurgical, ophthalmic, or orthopaedic joint replacement patients. For such patients, intermittent pneumatic compression of the legs may be as effective. It should be initiated in the operating room and continued for at least 3 days or until fully ambulatory. Elastic stockings donned preoperatively improve venous return from lower extremities, and may be beneficial in conjunction with other measures.

Dihydroergotamine increases tone of capacitance vessels. The combination with subcutaneous low dose heparin appears superior to heparin prophylaxis alone. However, alteration of vascular responses in myocardial and peripheral ischaemia remains a theoretical concern. Other modalities tried with some success, include antiplatelet agents (aspirin or dipyridamole), dextran infusion, and two-stage warfarin. In the last approach, warfarin is started 14 days preoperatively (prothrombin time 1.5 longer than control) and dosage is increased postoperatively (prothrombine time 2-3 times control).

Prognosis

The mortality of treated PE is approximately 5%, and largely dependent on the severity of underlying disease. With continued anticoagulants, the long-term prognosis is good; the haemodynamic problems resolve as the embolus lyses (sponatenously or therapeutically). Pulmonary hypertension is probably only associated with recurrent emboli, and almost never after a single episode.

Other Pulmonary Embolic Pathologies

Pulmonary artery obstruction may result fro embolization with bone marrow, fat, tumour (choriocarcinoma and renal vein tumours), air and amniotic fluid. General principles of resuscitation are enacted. A high mortality is associated with major air and amniotic fluid embolization.

Air embolism may result from the aspiration of air into large open veins at operation, or after inadvertent disconnection of large bore central venous catheters. Additional therapeutic manoeuvres include compression/occlusion of the air source, placing the patient in the left lateral, head down tilt position, and placement of a central venous line such that the tip position allows aspiration of air from the right atrium, ventricle or pulmonary artery.

Anticoagulation may be required to prevent thrombus forming around residual intra-cardiopulmonary air bubbles. Associated acute pulmonary hypertension may facilitate paradoxical embolus across a patent foramen ovale.

Amniotic fluid embolism often results in catastrophic cardiovascular collapse in conjunction with an acute bleeding diathesis and anaphylactic shock. A central venous catheter is placed to aspirate intracardiac amniotic fluid for confirmation of diagnosis and monitoring of cardiovascular status. Cardiopulmonary resuscitation, fresh blood, coagulation factors and fibrinolytic inhibitors may be required.