

VENOUS THROMBOEMBOLIC DISEASE

Acute pulmonary embolism 1: pathophysiology, clinical presentation, and diagnosis

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Thrombotic pulmonary embolism is not an isolated disease of the chest but a complication of venous thrombosis. Deep venous thrombosis (DVT) and pulmonary embolism are therefore parts of the same process, venous thromboembolism. Evidence of leg DVT is found in about 70% of patients who have sustained a pulmonary embolism; in most of the remainder, it is assumed that the whole thrombus has already become detached and embolised. Conversely, pulmonary embolism occurs in up to 50% of patients with proximal DVT of the legs (involving the popliteal and/or more proximal veins), and is less likely when the thrombus is confined to the calf veins. Rarely, the source of emboli are the iliac veins, renal veins, right heart, or upper extremity veins; the clinical circumstances usually point to these unusual sites.

Risk factors, epidemiology, and risk stratification

As pulmonary embolism is preceded by DVT, the factors predisposing to the two conditions are the same and broadly fit Virchow's triad of venous stasis, injury to the vein wall and enhanced coagulability of the blood (table 1). The identification of risk factors not only aids clinical diagnosis of venous thromboembolism, but also guides decisions about prophylactic measures and repeat testing in borderline cases.

Primary "thrombophilic" abnormalities are usually discovered after the thromboembolic

Table 1 Risk factors for venous thromboembolic disease

Venous stasis or injury, secondary hypercoagulable states:

- Immobilisation or other cause of venous stasis—for example, stroke
- Major trauma or surgery within 4 weeks
- Active cancer (treatment within previous 6 months or palliative therapy)
- Prior history of thromboembolism
- Reduced cardiac output (congestive heart failure)
- Obesity, advanced age
- Pregnancy, early puerperium, contraceptive pill with high oestrogen content
- Indwelling catheters and electrodes in great veins and right heart
- Acquired thrombotic disorders—for example, antiphospholipid antibodies, heparin induced thrombocytopenia, thrombocytosis, post-splenectomy

Primary hypercoagulable states (thrombophilia):

- Deficiency of antithrombin III, protein C or S
- Resistance to activated protein C (factor V Leiden)
- Elevated plasminogen activator inhibitor
- Hyperhomocysteinaemia
- High plasma concentration of factor VIII
- Prothrombin gene mutation (G2010A polymorphism)

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event. Therefore, the risk of venous thromboembolism is best assessed by recognising the presence of known "clinical" risk factors. However, investigations for thrombophilic disorders at follow up should be considered in those without another apparent explanation. In many patients, multiple risk factors are present, and the risks are cumulative.

The overall incidence and mortality of pulmonary embolism in the population is unknown because the clinical diagnosis is unreliable, many events are asymptomatic, variable methods of prophylaxis are applied, necropsy rates are low, and death certification is inaccurate. Nevertheless, DVT and pulmonary embolism constitute some of the most common cardiovascular diseases in the western world. Many cases go unrecognised and hence untreated, with serious outcomes. The case fatality rate is less than 5% in treated patients who are haemodynamically stable at presentation but approximately 20% in those with persistent hypotension. Most deaths directly attributable to acute pulmonary embolism occur before the diagnosis can be confirmed and effective treatment implemented, which makes prevention in high risk patients imperative.

Although the overall frequency of pulmonary embolism cannot be accurately estimated, it is possible to assess incidence in particular groups at risk (table 2). In surgical series the risk of venous thromboembolism rises rapidly with age, length of anaesthesia, and the presence of previous venous thromboembolism or cancer. The incidence is highest in those undergoing emergency surgery following trauma (for hip fractures, for example) and pelvic surgery. Fatal pulmonary embolism occurs in 0.5–0.8% of unprotected patients older than 40 years undergoing major abdominal surgery. About one in 20 patients after total hip replacement will have a pulmonary embolism, nearly half of these being fatal. In obstetrics there is a high incidence of venous thromboembolism, particularly if operative delivery is used. Clinically important pulmonary embolism occurs in at least 3% of patients after coronary bypass surgery. Surgery predisposes patients to pulmonary embolism even as late as one month postoperatively.

In medical patients, venous thromboembolism is frequent in cardiorespiratory disorders (for example, congestive cardiac failure, irreversible airways disease), with leg immobility (caused by stroke and other neurological diseases), and in cancer. The increase in the prevalence of pulmonary embolism with increasing age may be only due to the relation between age and other comorbidities, which are the actual risk factors for venous thromboembolism.

The relative risk of suffering a venous thromboembolism episode is about three times higher in oral contraceptive users compared with non-users. This risk has to be interpreted in light of a low basal risk in the non-user population (about 2 per 10 000 women years) and the fact that fatal pulmonary embolism occurs only in a minority of treated cases. The

Table 2 Incidence of thromboembolic disease in various risk categories

Risk category	Low risk	Medium risk	High risk
General surgery	Age < 40 years Surgery < 30 minutes No risk factors	Age > 40 years Surgery > 30 minutes No other risk factors	Age > 60 years Surgery > 60 minutes Plus additional risk factors
Orthopaedic surgery, traumatology	Minor trauma	Leg plaster cast	Hip or knee surgery, hip fracture, polytrauma
Medical conditions	Pregnancy	Heart failure, stroke, malignancy	Long immobility
Incidence (%)			
Distal DVT	2	10–40	40–80
Proximal DVT	0.4	6–8	10–15
Symptomatic PE	0.2	1–2	5–10
Fatal PE	0.002	0.1–0.8	1–5

DVT, deep vein thrombosis; PE, pulmonary embolism.

third generation oral contraceptives carry an excess risk of 1.5–2 for venous thromboembolism as compared with the second generation preparations containing low doses of oestrogens. This may transfer to one extra death per million women per year.

Pathophysiology and clinical presentation

The effects of an embolus depend on the extent to which it obstructs the pulmonary circulation, the duration over which that obstruction accumulates, and the pre-existing state of the patient, which has been defined only imprecisely. Some humoral mediators (for example, serotonin or thromboxane from activated platelets) can probably produce vasospasm in non-embolised segments of the lung. As a result, a degree of pulmonary hypertension may develop disproportionate to the amount of vasculature that is mechanically occluded. In general, a patient who has pre-existing cardiopulmonary disease or who is old, frail or debilitated will be more sensitive to the effects of pulmonary embolism than a patient who was well until the embolic event occurred. Most emboli are multiple. As both the extent and chronicity of obstruction vary so widely, pulmonary embolism can produce widely differing clinical pictures. Disregarding chronic thromboembolic pulmonary hypertension, it is convenient to classify pulmonary embolism into three main types (table 3). The first and most common presentation is dyspnoea with or without pleuritic pain and haemoptysis (acute minor pulmonary embolism). The second presentation is haemodynamic instability, which is associated with acute massive pulmonary embolism. The third and least common

presentation mimics heart failure or indolent pneumonia, especially in the elderly (subacute massive pulmonary embolism).

Acute minor pulmonary embolism

If an embolus obstructs less than 50% of the pulmonary circulation, it often produces no symptoms. For example, about 40% of patients with DVT who have no symptoms of pulmonary embolism have evidence of the condition on lung scans. If symptoms do develop the most common is dyspnoea, possibly upon minor exertion. Sometimes, the first abnormality the patient notes results from pulmonary infarction, which occurs in obstruction of medium sized pulmonary artery branches. Sharp pleuritic pain develops, and there may be associated haemoptysis. Pulmonary infarction occurs in only about 10% of patients without pre-existing cardiopulmonary disease. If, however, there is already compromise of the oxygenation of the embolised area—either because the airways are abnormal or pulmonary venous outflow is impaired as a result of pre-existing left heart disease—then the incidence of infarction rises to 30%.

If there are any physical signs, they are those of pulmonary infarction. The patient is distressed with rapid and shallow breathing because of the pleuritic pain, but is not cyanosed because the disturbance of gas transfer is only slight. Signs of pulmonary infarction may be found in the lungs: a mixture of consolidation and effusion, possibly with a pleural rub. Fever is common and sometimes differentiation from infective pleurisy is difficult. The fever and pain often produce a sinus tachycardia. Pulmonary artery mean pressure rarely exceeds 25 mm Hg. As minor pulmonary embolism does not compromise the right ventricle, cardiac output is well maintained,

Table 3 Clinical forms of pulmonary embolism

Pulmonary embolism	History	Vascular obstruction	Presentation	Typical pressures	
				PAP	RAP
Acute minor	Short, sudden onset	< 50%	Dyspnoea with or without pleuritic pain and haemoptysis	Normal	Normal
Acute massive	Short, sudden onset	> 50%	Right heart strain with or without haemodynamic instability and syncope	45/20	12
Subacute massive	Several weeks	> 50%	Dyspnoea with right heart strain	70/35	8

PAP, pulmonary artery pressure; RAP, mean right atrial pressure.

hypotension does not occur, and the venous pressure and heart sounds are normal. A common misapprehension is that there is often a loud pulmonary component of the second heart sound; this is not the case because the right heart pressures are normal or only slightly elevated.

Acute massive pulmonary embolism

When more than 50% of the pulmonary circulation is suddenly obstructed, the pathophysiology and clinical signs become dominated by the severe derangement of cardiac and pulmonary function. Obstruction of the pulmonary artery and mediator induced vasoconstriction cause a substantial increase in right ventricular afterload and, if the cardiac output is to be maintained, consequent elevation of pulmonary artery systolic pressure and an increase in right ventricular work. If this work cannot be sustained, acute right heart failure occurs. The thin walled right ventricle is designed to work against the normally low pulmonary vascular resistance; it performs poorly against a sudden obstruction. As a result, it dilates, and a moderate rise in the right ventricular and pulmonary artery systolic pressure occurs which rarely exceeds 55 mm Hg because the ventricle, lacking time to develop compensatory hypertrophy, is unable to generate a higher pressure. The right ventricular end diastolic pressure and right atrial pressure rise to about 15–20 mm Hg as the ventricle fails. Right ventricular dilatation leads to tricuspid regurgitation and may compromise the filling of the left ventricle. Cardiac output falls and the patient becomes hypotensive. This may occur so rapidly that syncope is either the presenting feature or easily induced by a relatively minor cardiovascular stress. If the degree of obstruction is sufficient, death occurs almost immediately. The fall in aortic pressure and the rise in right ventricular pressure may cause ischaemia of the right ventricle through a critical reduction of right coronary perfusion. Electro-mechanical dissociation is the most frequent cause of final cardiac arrest.

Arterial hypoxaemia correlates roughly with the extent of embolism if there is no prior cardiopulmonary disease. Massive pulmonary embolism without hypoxaemia is so rare that if the arterial oxygen tension (P_{aO_2}) is normal an alternative diagnosis should be considered. Hypoxaemia decreases tissue oxygen delivery and can impede circulatory adaptation through its vasodilating effects.

The main causes of hypoxaemia in pulmonary embolism seem to be as follows:

- (1) *Ventilation-perfusion mismatch.* Unembolised areas of the lung are relatively overperfused, so that the ventilation in these areas may be insufficient to oxygenate fully the extra blood flow.
- (2) *Shunting* occurs through areas of collapse and infarction that are not ventilated but retain some blood flow. This may become more important a few days after the initial episode. In patients with a patent foramen ovale, raised right atrial pressure may open the foramen and cause right-to-left shunt-

ing at the atrial level. This should be considered if the degree of hypoxaemia is more profound than would be expected from other clinical features, if it cannot be corrected by oxygen administration and if it is accompanied by hypercapnia.

- (3) *Low mixed venous oxygen saturation* caused by the reduced cardiac output causes hypoxaemia because there is insufficient time for the extremely desaturated blood to become fully saturated as it passes through the alveolar capillaries in the overperfused areas of the lung.

Although pulmonary embolism impairs the elimination of CO_2 , hypercapnia is rare because compensatory hyperventilation eliminates CO_2 in all but the most extensive embolism. In cases with a sufficient degree of vascular obstruction to produce hypercapnia, the haemodynamic sequelae of acute right ventricular failure usually prove fatal.

The clinical features of acute massive pulmonary embolism can be explained in terms of these pathophysiological changes (table 3). The patient becomes acutely distressed, severely short of breath, and may be syncopal because of the combination of hypoxaemia and low cardiac output. The combination of hypotension, hypoxaemia, and increased cardiac work may cause anginal chest pain. The physical signs are those of reduced cardiac output—that is, pronounced sinus tachycardia, hypotension, and a cool periphery, sometimes with confusion. The patient is obviously dyspnoeic (but not orthopnoeic), cyanosed both centrally and peripherally, and has signs of acute right heart strain: a raised venous pressure, which is often difficult to appreciate because of the respiratory distress; a gallop rhythm at lower sternum; and a widely split second heart sound due to delayed right ventricular ejection, which is difficult to detect because of the accompanying tachycardia. The pulmonary component of the second heart sound is usually not loud because the pulmonary artery pressure is only moderately raised.

Subacute massive pulmonary embolism

This is caused by multiple small or moderately sized emboli that accumulate over several weeks. Because the obstruction occurs slowly, there is time for the right ventricle to adapt and for some hypertrophy to develop; consequently, the right ventricular systolic pressure is higher than in acute pulmonary embolism. The rises in the right ventricular end diastolic and right atrial pressures are of a lesser extent than in acute massive pulmonary embolism since there is time for adaptation to occur and the degree of right ventricular failure is less for a given degree of pulmonary artery obstruction. The main symptoms are increasing dyspnoea and falling exercise tolerance. There is often an associated dry cough. The breathlessness is usually out of proportion to all other findings, and there may be central cyanosis. The blood pressure and pulse rate are usually normal because the cardiac output is well maintained. Commonly, the venous pressure is raised and a third heart sound is audible at the

Table 4 Estimation of the (pretest) clinical likelihood of pulmonary embolism

High (> 85% likely)	Otherwise unexplained sudden onset of dyspnoea, tachypnoea, or chest pain and at least 2 of the following: Significant risk factor present (immobility, leg fracture, major surgery) Fainting with new signs of right ventricular overload in ECG Signs of possible leg DVT (unilateral pain, tenderness, erythema, warmth, or swelling) Radiographic signs of infarction, plump hilum, or oligemia
Intermediate (15-85% likely)	Neither high nor low clinical likelihood
Low (< 15% likely)	Absence of sudden onset of dyspnoea and tachypnoea and chest pain Dyspnoea, tachypnoea, or chest pain present but explainable by another condition Risk factors absent Radiographic abnormality explainable by another condition Adequate anticoagulation (INR > 2 or aPTT > 1.5 times control) during the previous week

INR, international normalised ratio; aPTT, activated partial thromboplastin time

lower sternum which may be accentuated by inspiration. The pulmonary component of the second heart sound is sometimes loud. There may also be intermittent symptoms and signs of pulmonary infarction that occurred during the build up of the obstruction. In advanced cases, cardiac output falls and frank right heart failure develops. A further pulmonary embolus may change the picture to that resembling acute massive pulmonary embolism.

Diagnostic procedures

The clinical diagnosis of pulmonary embolism is difficult, particularly when there is coexisting heart or lung disease, and it is notoriously inaccurate when based on clinical signs alone. About two thirds patients who present with suspected DVT or pulmonary embolism do not have these conditions.^{1,2} Very rarely, pulmonary embolism presents in such a dramatic fashion that the diagnosis is intuitively obvious and treatment will be started, but the usual presentation is frequently vague and variable in severity, so that further testing is necessary to establish or exclude the diagnosis.² Diagnostic evaluation is best carried out by first attempting to identify a provable alternative diagnosis that can explain the patient's symptoms.

Estimating pretest clinical likelihood of venous thromboembolism

Until the 1970s, the diagnosis or exclusion of pulmonary embolism was made on clinical grounds alone. In the UPET (urokinase pulmonary embolism trial) study, several clinical findings, previously considered valuable in the diagnosis of pulmonary embolism, were not present in many patients with the condition, and less than one third of the 2200 patients with suspected pulmonary embolism actually had the disease after objective testing.¹ These results led clinicians to virtually abandon clinical examination and diagnose pulmonary embolism solely based on the results of objective tests. A number of recent studies, however, have suggested that combining the individual components of clinical assessment, risk factors for venous thromboembolism, and simple investigations reliably categorises the likelihood of pulmonary embolism as low, moderate, or high in an individual patient.³⁻⁶

By adopting a thorough stratification system the clinician can more appropriately select further investigations to prove or exclude pulmonary embolism. Establishing the pretest clinical likelihood of pulmonary embolism is especially helpful in interpreting the scintigraphy. Clinical likelihood of pulmonary embolism is determined after consideration of risk factors (the most common being immobilisation, a history of previous venous thromboembolism, lower limb fractures, and recent surgery), presentation, and basic investigations (ECG and plain chest radiograph). Although the characteristics of these clinical estimates have not been extensively validated, those generally accepted are given in table 4.

Nearly all patients with pulmonary embolism will have one or more of the following clinical features—dyspnoea of sudden onset, tachypnoea (> 20 breaths/minute), or chest pain (pleuritic or substernal)²; if the clinician remembers these three features, the possibility of pulmonary embolism will rarely be overlooked. When these clinical features are associated with ECG signs of right ventricular strain and/or radiologic signs of plump hilum, pulmonary infarction or oligemia, the likelihood of pulmonary embolism is high, and it is further strengthened in the presence of risk factors for venous thromboembolism and arterial hypoxaemia with hypocapnia.⁴ On the contrary, the absence of all these three clinical features virtually excludes the diagnosis of pulmonary embolism.

Electrocardiography

ECG changes are usually non-specific. In minor pulmonary embolism there is no haemodynamic stress and thus the only finding is sinus tachycardia. In acute or subacute massive pulmonary embolism, evidence of right heart strain may be seen (rightward shift of the QRS axis, transient right bundle branch block, T wave inversion in leads V1-3, P pulmonale), but the classic S₁Q_{III}T_{III} pattern occurs in only a few cases.² The main value of ECG is in excluding other potential diagnoses, such as myocardial infarction or pericarditis.

Chest radiography

Chest radiograph findings are also non-specific but may be helpful. A normal film is compatible with all types of acute pulmonary embolism; in fact, a normal film in a patient with severe acute dyspnoea without wheezing is very

suspicious of pulmonary embolism. The lung fields may show evidence of pulmonary infarction: peripheral opacities, sometimes wedge shaped or semicircular, arranged along the pleural surface (so called Hampton's hump). Atelectasis, small pleural effusions, and raised diaphragm have low specificity for pulmonary embolism. In massive pulmonary embolism a plump pulmonary artery shadow may be seen when the pulmonary artery pressure is elevated. It may be possible to detect areas of oligoemia in the parts of the lung affected by emboli (Westermarck sign), but this is difficult on the type of film usually available in the acute situation. The radiograph is especially valuable in excluding other conditions mimicking pulmonary embolism (pneumothorax, pneumonia, left heart failure, tumour, rib fracture, massive pleural effusion, lobar collapse), but pulmonary embolism may coexist with other cardiopulmonary processes. The radiograph is also necessary for the proper interpretation of the lung scan.

Echocardiography

Transthoracic echocardiography rarely enables direct visualisation of the pulmonary embolus but may reveal thrombus floating in the right atrium or ventricle. With transoesophageal echocardiography, it is possible to visualise massive emboli in the central pulmonary arteries. In the presence of thrombi in right heart chambers, pulmonary angiography is not necessary and, indeed, is contraindicated because of risk of thrombus dislodgement.

In massive pulmonary embolism the right ventricle is dilated and hypokinetic, with abnormal motion of the interventricular septum. The inferior vena cava does not collapse during inspiration. Unfortunately, the finding of right ventricular dysfunction is non-specific and certain conditions commonly confused with pulmonary embolism (such as chronic obstructive pulmonary disease (COPD) exacerbations or cardiomyopathy) are also associated with abnormal right ventricular function. There is some evidence that regional right ventricular dysfunction (akinesia of the mid-free wall with apical sparing) may be more common in acute pulmonary embolism. The Doppler technique allows the pulmonary artery pressure to be estimated and together with contrast echocardiography it is useful in diagnosing patent foramen ovale which may indicate impending paradoxical embolism.

Although direct echocardiographic visualisation of intraluminal thrombi in patients with suspected pulmonary embolism is not frequent, and even when echocardiography provides only indirect signs compatible with haemodynamic consequences of massive pulmonary embolism, it is helpful in excluding or suggesting alternative causes for haemodynamic instability (aortic dissection, ventricular septal rupture, cardiac tamponade, etc). In an unstable hypotensive patient requiring immediate treatment, such information is of great importance. However, because the right ventricle may show no dysfunction even in patients with massive pulmonary embolism, echo-

cardiography should be considered an ancillary rather than a principal diagnostic test for the diagnosis of pulmonary embolism.

Arterial blood gases

The characteristic changes are a reduced P_{aO_2} , and a P_{aCO_2} that is normal or reduced because of hyperventilation. The P_{aO_2} is almost never normal in the patient with massive pulmonary embolism but can be normal in minor pulmonary embolism, mainly due to hyperventilation. In such cases the widening of the alveolo-arterial P_{O_2} gradient ($AaP_{O_2} > 20$ mm Hg) may be more sensitive than P_{aO_2} alone. Both hypoxaemia and a wide AaP_{O_2} may obviously be due to many other causes. Blood gases, therefore, may heighten the suspicion of pulmonary embolism and contribute to the clinical assessment, but they are of insufficient discriminant value to permit proof or exclusion of pulmonary embolism.²

Biochemistry

No blood test will diagnose venous thromboembolism. Although endogenous fibrinolysis is indicated by the sensitive assay of cross linked fibrin degradation products (D-dimers), this test has low specificity and is positive not only when there is venous thromboembolism but also in the presence of disseminated intravascular coagulation, malignancy, and after trauma or surgery. Although a negative test may be strong enough evidence that clotting has not occurred and that anticoagulants can be withheld, a positive test cannot confirm venous thromboembolism. The test could reduce the number of investigations in outpatients with suspected pulmonary embolism and a low pretest likelihood for venous thromboembolism, and may be useful as a screening test in an emergency unit when lung scintigraphy or computed tomography (CT) is not immediately available. However, if there is a high clinical suspicion of acute pulmonary embolism, diagnostic tests should proceed in spite of a normal D-dimer. In elderly or inpatients, D-dimer retains a high negative predictive value, but is normal in less than 10% of patients, and, hence, not very useful. Not all D-dimer testing methods have equal and sufficient sensitivity (the latex agglutination test is not reliable in excluding pulmonary embolism), but the rapid assays with a negative predictive value approaching 100% are comparable to the reliable but labour and time consuming ELISA (enzyme linked immunosorbent assay) tests.

Lung scintigraphy

A normal perfusion scan essentially excludes the diagnosis of a clinically relevant recent pulmonary embolism because occlusive pulmonary embolism of all types produces a defect of perfusion. Normal results are almost never associated with recurrent pulmonary embolism, even if anticoagulants are withheld. However, many conditions other than pulmonary embolism, such as tumours, consolidation, left heart failure, bullous lesions, lung fibrosis, and obstructive airways disease, can also produce

Table 5 Probability (%) of underlying pulmonary embolism according to the criteria of PIOPED study³

	Scan probability			
	Normal/very low	"Non-diagnostic"		
		Low	Intermediate	High
Clinical likelihood:				
Low	2	4	16	56
Intermediate	6	16	28	88
High	0	40	66	96

perfusion defects. Addition of a ventilation scan increases the specificity of scintigraphy. Pulmonary embolism usually produces a defect of perfusion but not ventilation ("mismatch") while most of the other conditions produce a ventilation defect in the same area as the perfusion defect (matched defects). Pulmonary embolism can also produce matched defects when infarction has occurred, but in this situation the chest radiograph nearly always shows shadowing in the area of scan defect.

The lung scan is an indirect method of diagnosis since it does not detect the embolus itself but only its consequence, the perfusion abnormality. The probability that perfusion defects are caused by pulmonary embolism can be assessed as high, intermediate or low depending on the type of scan abnormality (although there are significant variations in the interpretative patterns and diagnostic accuracy even between experienced readers using standard algorithms).^{3,7} If the scan is of a high probability type (basically multiple segmental or larger perfusion defects with a normal ventilation scan) there is a more than 85% chance that the patient has pulmonary embolism. However, the majority of patients with clinically suspected pulmonary embolism do not have high probability scans and instead have ones that suggest either low or intermediate probability (= non-diagnostic scans); in these patients the prevalence of pulmonary embolism is about 25%. Taking the clinical assessment into account improves diagnostic accuracy (when the clinical likelihood of pulmonary embolism and scan interpretation is concordant, the ability to diagnose or exclude pulmonary embolism is optimised (table 5)), but the diagnosis can still be made or excluded with accuracy in only about a third of patients. A low probability scan does not rule out pulmonary embolism, but in fact there is up to a 40% probability of pulmonary embolism when clinical likelihood is high.³

In theory the addition of ventilation scanning should improve the usefulness of perfusion imaging, but the PIOPED (prospective investigation of pulmonary embolism diagnosis) study showed such benefit to be marginal. Perfusion defects caused by pulmonary embolism are most often wedge shaped. In the PISA-PED (prospective investigation study of acute pulmonary embolism diagnosis) study, when only wedge-shaped defects were classified as suspect for pulmonary embolism, perfusion scintigraphy without the use of ventilation scans, combined with clinical as-

Table 6 Probability (%) of underlying pulmonary embolism (PE) according to the criteria of PISA-PED study⁸

	Scan probability	
	PE-	PE+
Clinical likelihood:		
Low	3	55
Intermediate	12	92
High	39	99

essment of pulmonary embolism likelihood (table 6), made it possible to confirm or exclude the condition in 76% of patients with abnormal scans, with an accuracy of 97%.^{4,8} Angiography was then required only in about one fourth of patients with abnormal scans. This suggests that where ventilation imaging is unavailable, perfusion scanning alone is acceptable. The simple PISA-PED criteria are likely to become an attractive alternative to the complex PIOPED criteria.

Although the lung scan is often an imprecise guide it is useful in clinical decision making: a normal scan or a low probability scan with low clinical likelihood of pulmonary embolism means that treatment for suspected pulmonary embolism can be withheld, and a high probability scan with a high clinical likelihood of pulmonary embolism means that treatment is mandatory. Objective tests for DVT and pulmonary angiography or CT must be used to decide on the treatment in patients between these extremes and in whom the clinical likelihood of pulmonary embolism and scan interpretation are discordant.

Planar scintigraphy is the standard technology in most institutions. With SPECT (single photon emission CT) technology, pictures can be reconstructed in any plane and the specificity of scintigraphy substantially improves because of the reduction in the frequency of non-diagnostic scans.⁹

Scanning should be performed within 24 hours of the onset of symptoms of pulmonary embolism, since some scans revert to normal quickly. A follow up scan at the time of discharge is helpful in establishing a new baseline for subsequent episodes of suspected pulmonary embolism. The only clinically important cause of a false positive study is prior pulmonary embolism that has not resolved, leaving a lung scan pattern that remains in the high probability category.

Computed tomography (CT, spiral or electron beam CT)

Contrast enhanced spiral or electron beam CT have emerged as valuable methods for diagnosing pulmonary embolism and, because of its availability, spiral CT is becoming the first choice method at many institutions. The technique is faster, less complex, and less operator dependent than conventional pulmonary angiography, and has about the same frequency of technically insufficient examinations (about 5%). The thorax can be scanned during a single breath hold. There is better interobserver agreement in the interpretation of CT than for

Pulmonary scintigraphy

- Significant variations in scan interpretation exist even between experienced readers using standard algorithms
- Normal perfusion scan excludes clinically important pulmonary embolism and makes further testing unnecessary. It is safe to withhold anticoagulants in patients with suspected pulmonary embolism and normal perfusion scan
- Scan is diagnostic in a minority of cases. Only normal and high probability scans are clear in terms of clinical implications. The utility of scans is optimised when interpreted as representing a low or high probability of pulmonary embolism with concordant clinical likelihood of pulmonary embolism
- Patients with non-diagnostic scans require further imaging rather than management based on clinical features

scintigraphy. Another advantage of CT over scintigraphy is that by imaging the lung parenchyma and great vessels, an alternative diagnosis (for example, pulmonary mass, pneumonia, emphysema, pleural effusion, mediastinal adenopathy) can be made if pulmonary embolism is absent. This advantage of CT also pertains to pulmonary angiography, which images only the arteries. CT can also detect right ventricular dilatation, thus indicating severe, potentially fatal pulmonary embolism.

Criteria for a positive CT scan result include a partial filling defect (defined as intraluminal area of low attenuation surrounded by a contrast medium), a complete filling defect, and the “railway track sign” (masses seen floating in the lumen, allowing the flow of blood between the vessel wall and the embolus). The procedure has over 90% specificity and sensitivity in diagnosing pulmonary embolism in the main, lobar, and segmental pulmonary arteries. When CT is used to evaluate patients with a non-diagnostic lung scan, the sensitivity is lower.^{10 11}

Although recent advances in CT technology enable better visualisation of subsegmental arteries, these small vessels remain difficult to evaluate. The clinical significance of isolated subsegmental emboli is unclear, and it is not current practice to ignore them. They may be of importance in patients with poor cardiopulmonary reserve, and their presence is an indicator for current DVT, which thus potentially heralds more severe emboli. One recent study showed, however, that patients with pulmonary embolism negative spiral CT do well without anticoagulation treatment.¹² This should be especially true when these patients also have a leg venous study that is negative for thrombus.

Other reasons for falsely negative results may be inadequate visualisation of a portion of the lung, difficulty in evaluating non-vertically ori-

ented arteries (particularly of the lingula and the middle lobe), and difficulty in opacifying the arteries in patients with superior vena caval obstruction or intracardiac or intrapulmonary shunts. These sources of falsely negative results are significant and one cannot therefore regard CT as a new “gold standard” to replace angiography. If clinical suspicion for pulmonary embolism is high and the CT is interpreted as negative or inconclusive, further investigation should be performed.

CT may also be falsely positive for pulmonary embolism. Enlarged hilar lymph nodes and volume averaged atelectatic lung or mediastinal fat may be misinterpreted as emboli. Perivascular oedema (such as occurs in congestive heart failure) may appear as an embolus. An insufficient delay from the administration of contrast to the initiation of the scan can lead to filling defects that can be misinterpreted as emboli.

Additional research is required to establish the place of CT in clinical practice. In particular, the sensitivity of CT for small clots should be carefully examined and the utility of testing strategies employing CT must be determined in outcome studies and compared with currently employed algorithms. Because of the small number of non-diagnostic results and a potentially greater out-of-hours availability, spiral CT may replace scintigraphy as the primary test in patients with suspected pulmonary embolism.

After performing lung CT (involving intravenous injection of contrast medium) to diagnose pulmonary embolism, sufficient opacification of the venous system remains to evaluate the veins of the legs, pelvis, and abdomen for DVT, without additional venepuncture or contrast medium. Such an examination is a continuous study, adding approximately five minutes to pulmonary scanning, with the added expense of only one sheet of film. The pelvic and abdominal images screen the iliac veins and vena cava for thrombosis, an important advantage over sonography, particularly when caval filter placement is considered. This potential for performing in a single study both venography and pulmonary CT angiography is promising. If the accuracy of venous imaging after lung scanning is confirmed in large studies, its use should be considered whenever CT pulmonary angiography is indicated.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) offers both morphological and functional information on lung perfusion and right heart function, but its image quality still needs improvement to be comparable with CT. MRI has several attractive advantages, including the avoidance of nephrotoxic iodinated contrast and ionising radiation, and excellent sensitivity and specificity for DVT, together with the potential for performing lung perfusion imaging. This technique may ultimately allow simultaneous and accurate detection of both DVT and pulmonary embolism. Additional data are needed, however. A disadvantage of MRI compared to CT is the long time (15–30

Spiral or electron beam CT

- Emerging as a non-invasive testing modality to complement or replace the standard lung scintigraphy
- Can directly visualise intravascular thrombus, but smaller, subsegmental emboli can be overlooked
- Greater sensitivity and specificity for pulmonary embolism than lung scintigraphy. Agreement among readers of CT better than among readers of scintigrams
- CT scans, like angiograms, are either positive or negative for pulmonary embolism in the majority of cases. Only 10% of CT scans are non-diagnostic (compared to 70% non-diagnostic scintigrams)
- Can diagnose alternative causes of dyspnoea
- Currently, because of significant sources of both false negative and false positive examinations, CT cannot yet be regarded as a gold standard alternative to angiography.

minutes) needed to perform the examination, which is not suitable for clinically unstable patients. Improvements in MRI angiographic techniques will inevitably produce better results in the future.

Pulmonary angiography

Catheter pulmonary angiography remains the “gold standard” and the only technique that can diagnose or exclude pulmonary embolism with relative certainty. It should be considered, first, if cardiovascular collapse or hypotension are present and, second, when other investigations are inconclusive. However, angiography has disadvantages of limited availability and a small (< 0.3%) but definite risk of mortality.^{7 13} This risk gets higher the more seriously ill the patient is, particularly when there is significant pulmonary hypertension. Relative contraindications include pregnancy, significant bleeding risk, renal insufficiency, and known right heart thrombus. The presence of a left bundle branch block is an indication for a temporary pacemaker during the procedure. The safety of the procedure is enhanced by monitoring (ECG, pulse oximeter, automated blood pressure device), ready oxygen availability, and by reducing the amount of contrast material given at lower pressure.

Injection of low osmolar non-ionic contrast through a pigtail catheter into the main pulmonary artery, with radiographs of the whole chest in two projections taken in rapid succession using an automatic film changer, is sufficient to delineate the emboli in most cases. Where prior scintigraphy is non-diagnostic, angiography can be first confined to the more abnormal side. When the embolus is small,

selective injections into subdivisions of the arteries, oblique views and cineangiography, which can separate superimposed vessels as they move apart due to the pulsation of the arteries, improves diagnostic accuracy. The digital subtraction technique makes the examination easier and faster (because of the cinematic review and work station manipulation) and results in comparable image quality and improved interobserver agreement compared with conventional cut-film angiography. An embolus appears as an abrupt vessel cutoff or a convex filling defect often with contrast leaking beyond its edges and the sides of the vessel containing it. The overall perfusion of the affected region is reduced.

The assumption that life threatening pulmonary embolism is not missed by pulmonary angiography seems to hold true. However, although false positives are difficult to prove and probably scarce, false negative examinations can occur despite important intravascular embolus. Non-diagnostic pulmonary angiography can also occur.

Pulmonary angiography can be performed by the femoral, brachial, subclavian or internal jugular approaches. The femoral venous approach is useless in patients who have had an inferior caval interruptive procedure. Disadvantages of the femoral approach relate to the possibility of dislodging iliofemoral or caval thrombus and a high risk of bleeding from a fresh femoral venous puncture site during thrombolytic treatment. This risk can be reduced by leaving the catheter in the vein for mechanical haemostasis during the thrombolysis. The main difficulty with catheterisation from the brachial approach relates to the possibility of catheter induced venous spasm with inability to advance the catheter into the central veins; this may be particularly problematic in patients with excessive circulating catecholamines caused by shock or vasopressor administration. In fully anticoagulated patients the internal jugular and, especially, the subclavian approach are contraindicated.

The changes in the right heart pressures that occur in pulmonary embolism are summarised in table 3. It is important to measure the pressures and oxygen saturations before angiography so that the haemodynamic situation, including cardiac output and any intracardiac shunting, can be assessed. This facilitates determination of the patient's underlying cardiopulmonary reserve, identification of any haemodynamic derangements that might require specific treatment to increase the safety of angiography, and more careful selection of the contrast agent and dose to maximise diagnostic information while minimising the risk of hypotension, myocardial depression or a further increase in ventricular filling pressures. Occasionally if the diagnosis of pulmonary embolism before catheterisation is wrong the haemodynamic data may suggest the correct diagnosis and lead to appropriate treatment.

The use of intravenous digital subtraction angiography (DSA) avoids the need for pulmonary artery catheterisation but has been disappointing because opacification of the pulmo-

nary vessels is poor. Although intravenous DSA may be adequate for showing large proximal arterial occlusions, resolution is usually inadequate to identify an embolus in the segmental vessels and beyond. Thus minor pulmonary embolism cannot be excluded on the basis of a normal DSA with peripheral contrast application.¹³

Search for deep venous thrombosis

DVT cannot be reliably diagnosed on the basis of the history and physical examination. Patients with lower extremity DVT often do not exhibit pain, tenderness, erythema, warmth, or swelling. When present, however, these findings merit further evaluation. Impedance plethysmography, compression ultrasonography with venous imaging (colour duplex ultrasound), and MRI are established non-invasive methods for diagnosing DVT. While contrast venography remains the gold standard, it is rarely performed because it is invasive and difficult to carry out in the acutely ill patient. Venography is no longer appropriate as the initial diagnostic test for the evaluation of symptoms that suggest acute DVT; it should be performed whenever non-invasive testing is non-diagnostic or impossible to perform. While plethysmography and ultrasound are reliable for the diagnosis of symptomatic proximal DVT, they are much less reliable for recognising asymptomatic DVT. They are also not able to detect floating thrombus in the vena cava. Plethysmography also has other limitations and is inferior to the latest ultrasound techniques; it is now used in only a few institutions.

Although all the above methods for detecting thrombus in the deep veins do not establish the diagnosis of pulmonary embolism, the confirmation of DVT is of major importance in management decisions. The logic of leg vein imaging is that many patients with pulmonary embolism have residual proximal clot even in the absence of clinical evidence of DVT, itself an indication for treatment even if there is no direct proof of pulmonary embolism. If there is no thrombosis in the proximal leg or pelvic veins the chance of a further significant pulmonary embolism is low; therefore, even if a small pulmonary embolism has occurred already, anticoagulation can be omitted. This approach needs caution if the patient has inadequate cardiorespiratory reserve, is likely to remain immobile, or if there could be an embolic source elsewhere (for example, right atrium or vena cava).¹⁴

Failure to identify thrombosis of the calf veins rarely has serious sequelae, and the investigation can be repeated if there is persisting clinical concern. In patients with documented isolated calf vein thrombosis, repeated impedance plethysmography or compression ultrasonography can be used to separate the 20% of patients who develop proximal extension (and require treatment) from the remaining 80% of patients who do not and in whom the risks of anticoagulant treatment may outweigh the benefits (for example, in patients at high risk of bleeding).¹⁴

The integrated diagnostic approach with management options

The diagnosis requires a high level of clinical suspicion, estimation of the pretest clinical likelihood of pulmonary embolism, and the judicious use of objective investigations to confirm or refute the suspicion. Pulmonary angiography is justly regarded as the final arbiter but is not often performed, because of its limited availability, costs, and invasiveness. Therefore, treatment is often based on the clinical probability of pulmonary embolism rather than on a definite diagnosis or a ruling out of the condition. Consequently, some patients receive anticoagulants without proof of pulmonary embolism and other patients are not treated although they may have it. In either situation, the chance for proper disease management may be lost. For these reasons, much effort has been invested to determine how clinicians could reliably use non-invasive tests, alone or in combination, to replace pulmonary angiography as a diagnostic tool.^{15 16}

Basic tests

Basic tests include the ECG and plain chest radiograph. These must be performed in all patients both to support clinical suspicion of pulmonary embolism and, in particular, to exclude alternative diagnoses. As ECG and chest radiographic abnormalities in pulmonary embolism may be non-specific, absent, transient, or delayed, they cannot be used to confirm the diagnosis. Normal blood gases do not rule out pulmonary embolism; findings of hypoxaemia or hypocapnia may increase the physician's level of suspicion, but they are not specific for pulmonary embolism. More specific investigations are always required, but choosing which road to follow from the myriad of possibilities of imaging examinations can be confusing.

Various combinations of tests have resulted in several elaborate algorithms which, however, are seldom followed in clinical routine. Algorithms that inevitably result in large numbers of patients being referred for angiography are unhelpful. The availability of and familiarity with certain technology may influence the diagnostic approach. The specific clinical scenario also impacts on the diagnostic procedure that is chosen. There is no single algorithm to be recommended for all situations; rather, the investigations should be chosen according to the haemodynamic state of the patient (suspicion of massive versus minor pulmonary embolism), the onset of symptoms (in versus out of hospital), the presence or absence of other cardiopulmonary diseases, and the availability of specific tests.^{15 16}

Haemodynamic instability

In critically ill patients suspected of having a massive pulmonary embolism, particularly those with cardiovascular collapse, echocardiography can be rapidly performed at the bedside to exclude other diseases or, occasionally, to establish the diagnosis by finding clots in the

central pulmonary arteries or the right heart. By visualisation of thrombi further investigations are not necessary. When evidence of right heart strain without clots is present on echo, spiral CT or pulmonary angiography should follow, depending on faster availability.

In patients with life threatening instability where emergency treatment is necessary and CT or cardiac catheterisation is unavailable, intravenous DSA may be adequate for showing large proximal arterial occlusions. Image quality can be improved by delivering the contrast to the pulmonary artery via a flow directed, balloon tipped catheter. The floating catheter may also be useful in showing the characteristic haemodynamic changes with massive pulmonary embolism and suggesting an alternative diagnosis.

Haemodynamically stable patients

The principal challenge in stable patients is to develop a logical sequence of investigations that allow early, cost effective diagnosis and are associated with the most favourable markers of outcome. Depending on timely availability of tests and patient presentation, several approaches are possible.

Proof of DVT without definitive diagnosis of pulmonary embolism

This should be the preferred first procedure in patients with clinical suspicion of DVT in addition to the suspicion of pulmonary embolism. If duplex sonography, MRI, or impedance plethysmography confirms thrombosis, treatment can be started without recourse to lung imaging. Because the treatment of DVT and pulmonary embolism is the same in most patients with stable circulation, establishing the diagnosis of DVT, although it does not confirm that pulmonary embolism has occurred, is sufficient reason for full anticoagulation and avoids the need for additional studies. Leg vein imaging can also be performed as the initial investigation for suspected pulmonary embolism in patients with previous pulmonary embolism or chronic cardiopulmonary disease, where the frequency of non-diagnostic scans is high. If the leg study is negative or inconclusive, however, further investigations are imperative.

Lung scintigraphy

In about one third of cases, lung scan either rules out the diagnosis (normal perfusion or low probability scan with low clinical likelihood of pulmonary embolism) or suggests a high enough probability of pulmonary embolism that, in case of concurrent high clinical likelihood of pulmonary embolism, treatment can be undertaken on the basis of its results without further investigations. The frequency of such diagnostic scans is greater in outpatients with no prior cardiopulmonary disease who have a normal chest radiograph, and especially in these patients scintigraphy is the preferred initial examination. By limiting the patients who undergo scintigraphy to those without demonstrable lung disease at chest radiography, one can reduce the number of indeterminate studies and select a group of

patients whose scintigrams are likely to show normal or high probability results. However, the presence of cardiopulmonary disease or indeed any critical illness should not deter clinicians from requesting a lung scan, if it is readily available.

In patients with a non-diagnostic scan, or whose clinical likelihood of pulmonary embolism does not correlate with the scan result, further investigation is necessary. Of these patients, about 25% will prove to have pulmonary embolism and require anticoagulants; the other 75% will have another disease as the cause of the lung scan defects. CT is especially useful in these patients owing to its efficacy in imaging alternative pulmonary pathology.

If clinical likelihood is intermediate and the scan non-diagnostic, long term anticoagulation treatment can probably be withheld if repeated examination of leg veins over a week is normal and the patient has no underlying cardiopulmonary disease. If the leg veins are clear it is reasonable to assume that the patient is not in imminent danger of a fatal recurrence. Those with underlying cardiopulmonary disease, where only a medium sized embolus could be fatal, require a more aggressive diagnostic approach.¹⁴

In outpatients with a non-diagnostic scan, low clinical likelihood of pulmonary embolism, and no prior cardiopulmonary disease, the finding of a normal D-dimer concentration (measured by a test with nearly 100% sensitivity) can be used to reliably exclude venous thromboembolism. A raised D-dimer concentration, however, is a frequent non-specific finding in hospitalised patients and its clinical usefulness in this setting is low.

Spiral CT

Because the results of scintigraphy are inconclusive in most cases, some authors suggest that CT should be the initial imaging modality of choice, especially in patients known to have a high rate of indeterminate scintigrams (for example, all inpatients, patients with radiographic abnormalities, and patients with COPD). If CT is positive for pulmonary embolism, no further examination is necessary. Also, if it is negative down to the subsegmental arteries, it is not necessary to perform another investigation. However, if the CT findings are normal in the presence of a high clinical likelihood of pulmonary embolism, the patient may undergo leg imaging to detect the presence of a DVT. If this test is negative and the clinical likelihood of pulmonary embolism remains high, catheter angiography that focuses on the distal pulmonary vasculature should be performed. It is important to identify small peripheral emboli not detected by CT, because a major embolus may ensue unless anticoagulation is initiated.

Pulmonary angiography

Depending on local capabilities, this may sometimes be the most readily available investigation. It pinpoints the diagnosis in cases of high clinical likelihood of pulmonary embolism despite non-diagnostic findings on lung and leg

Diagnosing pulmonary embolism

- Clinical assessment is the initial step in identifying patients with possible acute pulmonary embolism. However, objective diagnostic tests are necessary to establish or refute the diagnosis
- The presence of risk factors for thromboembolism should always be rigorously scrutinised
- Clinical features of pulmonary embolism are deceptively non-specific, but pulmonary embolism is highly unlikely in the absence of all of the following: dyspnoea, tachypnoea, and chest pain
- Pulmonary infarction is a relatively rare complication of pulmonary embolism
- Clinical information, ECG, and chest radiography should be used to derive a clinical estimate of prior likelihood of pulmonary embolism before learning the results of imaging studies

imaging. Occasionally, pulmonary angiography is used when the clinical likelihood is low despite the fact that other tests indicate pulmonary embolism. Angiography is also indicated if there are special reasons why the diagnosis must be confirmed beyond doubt (for example, when the risk from anticoagulation is higher than normal or when suspected recurrent emboli have led to frequent admissions to hospital, often in the absence of any firm evidence of venous thromboembolism).

Other combinations of non-invasive tests

Other combinations of non-invasive tests may be useful. For instance, a normal D-dimer and leg imaging can help rule out venous thromboembolism, whereas an echocardiogram showing right ventricular hypokinesia combined with positive leg study is very suspicious of pulmonary embolism.

Finally, if there is no apparent predisposing cause for venous thromboembolism, and particularly if it is recurrent, occurring at a young age (< 50 years) or in an unusual site, or if there is a family history of venous thromboembolism, the patient with pulmonary embolism should be investigated for thrombophilia. If an abnormality is found, consideration should be given to a longer duration of anticoagulation. With limited resources, the testing could be restricted to the activated protein C resistance, because it is the most common cause of thrombophilia; antiphospholipid antibodies, because if present, particularly intensive anticoagulation may be required; and hyperhomocysteinaemia, because it can be readily treated with B vitamins. An extensive screening for occult cancer is usually unrewarding and rarely prolongs life in patients with newly diagnosed venous thromboembolism, because in most cases the cancer has already metastasised and the prognosis is ominous. A pragmatic rec-

ommendation is to use only simple methods of screening (including abdominal CT and sonography, mammography in women, and the test for prostate specific antigen in men) and to look for cancer in patients with symptoms or signs. An idiopathic thromboembolic event should be regarded as a contraindication to use of an oestrogen containing contraceptive.

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