

## A practical approach to the diagnosis of venothromboembolism

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Although there is now a wealth of information that allows a rational approach to the management of suspected venothromboembolism (VTE), ignorance is widespread and much current practice is unsatisfactory. There is an assumption that, because urgent anticoagulation is mandatory in major pulmonary embolus (PE), minor episodes in otherwise fit people must not be missed and require similar urgent treatment. In a teaching hospital clinicians commonly make dubious management decisions on the basis of inadequate imaging information<sup>1</sup>. In any case, most patients with suspected VTE are not initially seen by a well informed specialist but are referred to middle-grade physicians by colleagues in emergency, general surgical, orthopaedic and obstetric departments who are often unaware of the literature. Most published guidance does not translate well into clinical settings in which:

- there are several clinical patterns of PE
- urgent action may be required
- there are usually other diagnoses that need to be considered
- access to appropriate investigations can be a major problem.

There is not wide application of the concept that a small PE in a patient with underlying severe pre-existing cardio-pulmonary disease may require a different investigational approach from that in a previously fit person<sup>2</sup>. The perceived danger of failing to treat a patient with PE is more than matched by the consequences of overdiagnosing the condition. This inevitably leads to worry

and further unnecessary treatment if chest symptoms recur, inappropriate withdrawal of oral contraceptives and, in females, mandatory anticoagulation during future pregnancies.

The problem of both underdiagnosis and overdiagnosis is in part due to a traditional over-reliance on the ability of ventilation/perfusion (V/Q) scanning to diagnose or exclude PE. The Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) study<sup>3</sup>, primarily designed to assess the value of V/Q scanning using pulmonary angiography (PA) as the definitive test, emphasised the poor predictive value of scans reported as ‘intermediate probability’ – a common occurrence in routine clinical practice.

The limitations of V/Q scanning may be one reason why many clinicians are prepared to make management decisions without any specific imaging for PE. A recent American study found no imaging evidence to support the diagnosis in almost half of those with a discharge diagnosis of PE<sup>4</sup>. A Canadian study showed that in some clinical situations physicians did not anticoagulate patients with V/Q scans and clinical features suggestive of PE, with disastrous results<sup>5</sup>.

More recently, the development and widespread introduction of helical computed tomographic (CT) scanning (‘spiral CT’) and markers of fibrin degradation (D-dimer) which can be measured in plasma have offered new algorithms for investigation in the patient with superior VTE. This article discusses newer approaches to investigation and management.

### Predisposing factors

The recognised risk factors for VTE also include those for both PE and deep vein thrombosis (DVT) because they are closely related (Table 1). Over 70% of fatal<sup>5,6</sup> or non-fatal<sup>7</sup> proven PE cases have proximal thrombus, even though

this is usually clinically undetectable. It is assumed that failure to find DVT in the leg in the other 30% is due to the leg thrombus having already become dislodged, although this is unproven. Conversely, half of those with proximal DVT have concurrent PE<sup>8–13</sup>. Controversy remains as to whether isolated calf vein DVT carries a significant risk of subsequent PE; distal clot undergoes spontaneous lysis, but proximal propagation and PE have been reported to occur in those who are symptomatic<sup>14</sup> and after hip arthroplasty<sup>15</sup>. The most common predisposing factors are:

- immobilisation for more than one week
- a history of previous VTE<sup>16</sup>
- recent surgery or fractures, particularly of the lower limb<sup>17</sup>.

The presence of risk factors not only aids clinical diagnosis of VTE<sup>18</sup> but may also guide decisions about repeat testing in borderline cases<sup>19</sup>. The incidence of VTE is particularly high when there are multiple risk factors.

The incidence of PE increases exponentially with age<sup>4</sup>, which may reflect the high prevalence of medical illnesses and major operations with increasing age. In several studies age over 40 is included as an independent risk factor. Apart from long-distance travel, where lower limb immobility can lead to VTE<sup>20,21</sup>, most immobile patients with PE have other risk factors.

In surgical series, the risk of VTE rises rapidly with:

- age
- length of general anaesthesia
- site of surgery (especially abdominal and lower limb)
- the presence of advanced cancer or previous thromboembolic disease.

Fatal PE occurs in less than one in 10,000 minor elective operations, but in up to 5% of high-risk procedures such as extensive surgery for advanced abdominal or pelvic malignancy, major orthopaedic lower limb surgery or post-operative intensive care. Pharmacological and physical measures are increasingly used to reduce the risk of postoperative DVT in high-risk patients,

with substantial reduction in the incidence of fatal PE. However, there are wide variations in practice<sup>22</sup>, and even in highly motivated units protocols may be overlooked in patients who need emergency surgery<sup>23</sup>. In obstetrics, there is a higher incidence of VTE, particularly if operative delivery is used, and also in the early puerperium.

There are three major risk factors in non-surgical patients:

- 1 Cardiorespiratory disorders, particularly myocardial infarction (MI), congenital heart disease<sup>24</sup>, congestive cardiac failure and chronic airflow obstruction.
- 2 Lower limb immobility due to stroke and other neurological diseases such as brain tumour and acute spinal injury<sup>25</sup>.
- 3 Malignancy, particularly of the uterus, pancreas, breast and stomach<sup>6</sup> as well as advanced metastatic cancer. The reported association between PE and occult malignancy refers mainly to those with no risk factors and/or recurrent thromboembolism<sup>26–28</sup>.

The previous significant association with the use of oral oestrogens appears to be less with current low-dose formulations, whether used as oral contraception<sup>29</sup> or replacement therapy<sup>30</sup>. Although VTE and PE are 2–4 times more common than in controls, PE is uncommon in women on oestrogens with no other risk factors. There is an increasing recognition of the importance of clotting disorders in VTE, although it is unusual for them to be present as unheralded PE. Investigations for thrombogenic disease at follow-up

Table 1. Major risk factors for venous thromboembolism.

Category	Comments
<b>Surgery</b>	Major abdominal pelvic surgery Hip/knee surgery Postoperative intensive care
<b>Obstetrics</b>	Pregnancy/puerperium
<b>Cardiorespiratory disease</b>	Acute myocardial infarction Disabling disease
<b>Lower limb problems</b>	Fracture Varicose vein Stroke/spinal cord injury
<b>Malignant disease</b>	Abdominal/pelvic Advanced/metastatic Concurrent chemotherapy
<b>Miscellaneous</b>	Increasing age Previous proven PE/DVT Immobility Thrombotic disorders Trauma

DVT = deep vein thrombosis; PE = pulmonary embolism.

should be considered in those without another apparent explanation, including proteins S and C deficiency, and mutation of factor V leading to factor V Leiden deficiency. Lesser risk factors include prolonged air travel, oral oestrogens and central vein catheters.

### Clinical features

A simple screening system to assess clinical features can be a great help in estimating the probability of VTE. The presence of certain clinical features cannot be used to make a diagnosis of PE, but their absence makes such a diagnosis unlikely. Large studies have shown that dyspnoea plus tachypnoea (defined as respiratory rate >20/min) is absent in only 10% of patients with PE, while fewer than 3% will have neither of these

features nor pleuritic pain. The remainder will have either chest radiographic changes or a low PaO<sub>2</sub><sup>31,32</sup>. The absence of all these clinical features virtually excludes the diagnosis of PE.

One of the main values of standard investigations is that they may help to eliminate other cardiac and respiratory diagnoses. Thus, conditions that may present with similar features to PE (including MI, left heart failure, pericarditis, dissecting aneurysm, pneumothorax, pneumonia and lobar collapse) can often be detected by routine investigations such as ECG, chest radiography and lung function tests.

The studies mentioned above assessed the clinical characteristics of all patients with PE, but in practice there are subgroups with distinctive features. Table 2 summarises the findings of several

Table 2. Main clinical presentations of pulmonary embolism.

	Collapse, previously well	Pulmonary haemorrhage	Isolated dyspnoea	Collapse, poor reserve
Frequency (%)	5	60	25	10
Pulmonary artery occlusion Examination*	Extensive	Small/moderate	Moderate/large	Small/moderate
Chest radiograph*	Acute right heart strain	May have localising signs	Tachypnoea	
ECG*	Usually normal	Often suggestive	Usually normal	May be suggestive
Arterial gas tensions	Often acute right heart strain	Normal	Non-specific changes	
	Markedly abnormal	May be normal	Usually abnormal	

\* May be helpful in excluding other diagnoses.

studies<sup>33</sup> which confirm the presence of PE in one of three main ways:

### *Circulatory collapse with hypotension and/or loss of consciousness*

Central chest tightness may occur. Signs are faintness on sitting up and jugular venous engorgement. A diagnosis of massive PE is often obvious clinically if the physician is alert to this possibility. Suggestive ECG changes are common, whereas the chest radiograph is often unremarkable. Blood gas analysis shows marked hypoxia, often accompanied by hypocapnia due to hyperventilation. This subgroup has the most extensive vascular occlusion, so echocardiography often shows characteristic features of acute right heart dilatation and dysfunction.

### *Pulmonary haemorrhage with pleuritic pain and/or haemoptysis*

Chest radiographic changes are common, located to the site of pleuritic pain, whereas the ECG is often normal. This large subgroup is the least severe as assessed by PA<sup>34,35</sup> which usually shows the emboli to be peripheral rather than central, so arterial gas tensions may be normal<sup>36</sup>. In otherwise healthy patients, radiographic changes may clear rapidly, suggesting that the underlying pathology may be pulmonary haemorrhage without infarction<sup>34</sup>.

### *Isolated dyspnoea, defined as acute breathlessness in the absence of other symptoms*

Thrombus is more likely to be central, and these patients are usually hypoxic. A pointer to the correct diagnosis is the sudden onset of unexplained dyspnoea in a patient with predisposing factors for VTE<sup>35</sup>.

Most elderly patients with PE present with one of these patterns. The remainder may be diagnosed on the basis of an unexplained opacity on chest radiography, often accompanied by dyspnoea and/or clinical DVT<sup>36</sup>.

### *Other subgroups*

Table 2 also includes the important, but little studied, subgroup of patients with 'poor reserve' (defined as chronic symptomatic cardiorespiratory disease). They can rapidly decompensate with a relatively small embolus. Diagnosis is particularly difficult for this reason and also because the clinical, ECG and radiographic findings may mainly reflect the underlying disease. Recurrent thromboembolism is common and frequently fatal, yet clinicians often misinterpret lung scan reports, ignore the value of CT scanning or PA, and neglect anticoagulation.

Two clinical settings deserve special mention because both are common and often poorly managed. The first is that of a young patient, often a woman on oral contraception, who presents as an emergency with isolated pleuritic chest pain. The fear of missing PE often leads to most of these patients being admitted and given heparin until lung scanning can be performed. However, a large study<sup>37</sup> has shown that PE is unlikely in such patients if there are no risk factors for thromboembolism, if they are under 40 or have a respiratory rate of less than 20/min plus a normal chest radiograph.

Secondly, in the period immediately after upper abdominal surgery when good quality chest radiographs may be hard to obtain, PE is often confused with segmental/lobar collapse or infection and there may be relative contraindications to anticoagulation.

### **Investigations**

The basic tests described below should be performed in all patients both to support clinical suspicion of PE and, in particular, to exclude alternative diagnoses. More specific investigations are always required to confirm a diagnosis of PE.

#### **Basic tests**

##### *Chest radiography*

Although chest radiographic changes in PE are usually non-specific and appearances may be normal, chest radiography helps to exclude other diagnoses such as

heart failure, pneumonia, pneumothorax or tumour. Common findings in PE include focal infiltrate, segmental collapse, raised diaphragm and pleural effusion. A wedge-shaped, pleural-based opacity, though well described, is rare. Hypovascularity described in large embolus is often difficult to detect. A normal chest radiograph in an acutely breathless hypoxic patient increases the likelihood of PE. In acutely ill patients it is often hard to obtain a good quality radiograph, which is also needed for accurate reporting of V/Q scans.

##### *Electrocardiography*

ECG abnormalities in PE are common but are usually non-specific changes in the ST segment and/or T wave. Features of acute right heart strain are common with massive emboli. The ECG is also useful in excluding other diagnoses such as acute MI and pericardial disease.

##### *Arterial blood gas tension*

PE is characterised by ventilation-perfusion mismatch, reduced cardiac output with a low mixed venous oxygen saturation, and hyperventilation, usually accompanied by reduced PaO<sub>2</sub> and normal or low PaCO<sub>2</sub>. The degree of hypoxia roughly correlates with the extent of the embolism as judged by V/Q scanning. However, PaO<sub>2</sub> and PaCO<sub>2</sub> values may be normal, particularly with small emboli, but this does not exclude the need for further investigation. In acute massive PE, cardiovascular collapse may cause a metabolic acidosis.

#### **Specific tests**

##### *D-dimers*

Non-invasive blood tests have been evaluated in the hope of identifying a specific marker of VTE. D-dimer is a degradation product released into the circulation when cross-linked fibrin undergoes endogenous fibrinolysis<sup>38</sup>. Clinical trials have assessed the utility of this test. Strategies have included the combination of V/Q scanning and D-dimer testing. Different assays have

been evaluated using different cut-off values. Generally, either an enzyme-linked immunosorbent assay (ELISA) or a latex agglutination test has been performed. In patients with suspected PE, a low plasma D-dimer concentration (<500 ng/ml) measured by ELISA has a 95% negative predictive power, but low D-dimer levels have been found in only about 25% of patients without PE<sup>39,40</sup>. A latex agglutination test indicating a normal D-dimer level does not appear reliably to exclude PE<sup>41,42</sup>.

A systematic review of the medical literature for reports comparing D-dimer results with the results of other diagnostic tests for VTE shows substantial variability in assay performance, heterogeneity among the patient population, and inconsistent use of definitive diagnostic criteria for VTE<sup>43,44</sup>. More recently, both DVT and PE management studies have been performed, basing therapeutic decisions in part on D-dimer results. Ginsberg and colleagues<sup>45</sup> evaluated the results of a bedside whole-blood agglutination D-dimer assay and impedance plethysmography in patients with suspected DVT. When both studies were negative, anticoagulation was withheld and the patients monitored for three months. The overall negative predictive value for VTE was 98.5%, while for the D-dimer test alone it was 97.2%. In an evaluation of 308 consecutive patients presenting to the emergency room with suspect PE using the same cut-off value for the quantitative D-dimer test, all but two of 198 patients with suspected PE and a D-dimer level below 500 ng/ml were free of PE, one had PE and one was lost to follow-up<sup>46,47</sup>, indicating an approximately 99% negative predictive value. A normal plasma D-dimer, based on a reliable ELISA method, can thus be used to rule out VTE particularly in patients with a low clinical probability.

### Lung imaging

V/Q isotope scanning, which has the advantage of being non-invasive, is widely available. Most acute hospitals in the UK provide regular weekday access, but less than a third of surveyed depart-

ments offer a seven-day on-call service<sup>48</sup>.

Ventilation scans may be obtained with <sup>81m</sup>krypton (Kr), technegas, Tc-DPTA aerosol, or <sup>133</sup>xenon (Xe). Over 80% of nuclear medicine departments have access to <sup>81m</sup>Kr or aerosols. <sup>133</sup>Xe is widely used, but the ventilation images are of inferior quality for comparison with perfusion images. Perfusion scanning is performed by the intravenous injection of <sup>99m</sup>Tc-labelled macroaggregates of albumin or human albumin microspheres with the patient supine to reduce gravitational effects in the pulmonary circulation. After injection, scanning may be performed in either the supine or erect posture, but using the same posture for ventilation and perfusion scans. A minimum of four views should be obtained: anterior, posterior, and right and left posterior oblique. Lateral views may be added.

V/Q scanning should normally be performed within 24 hours of clinical suspicion of PE because some scans revert to normal quickly, and half do so within a week<sup>49</sup>. Delay also increases the potential for misleading reports because of the possible confusion caused by the development of pleural effusion and pulmonary opacities due to lung haemorrhage or infarction. Scans should be reported in conjunction with information on clinical features and a current good quality chest radiograph<sup>50</sup>. The value of the test is likely to be improved by direct communication between the reporter and the requesting clinician. The report should be factual and also give an indication of the probability of PE using the modified PLOPED criteria<sup>51</sup>.

In patients suspected of PE, a high probability V/Q scan report correctly indicates PE in 86–92% of cases, while the accuracy in excluding PE is 86% and 96% for low probability and normal scans, respectively. Agreement among scan readers is good for high probability and normal scans (>90% agreement) but less good (70–75%) for indeterminate and low probability scans. In large studies using single-view <sup>133</sup>Xe ventilation images and conventional reporting criteria, many patients fell into the indeterminate category which is of no

value in discriminating between PE and non-PE. Such patients require further imaging, not a management decision on clinical grounds. The use of newer ventilation scanning agents allowing multiple views should reduce the number of indeterminate scan reports. The interpretation of lung scans may be difficult or misleading in several situations. Alternative imaging investigations should be undertaken in the following situations:

- previous pulmonary embolism, unless a follow-up scan has been performed
- left heart failure, which can cause regional variations in pulmonary perfusion
- chronic obstructive airways disease with local variations in ventilation and in which the vascular bed may be constricted due to local hypoxia
- lung fibrosis with patchy unmatched defects in both ventilation and perfusion
- proximal lung cancer causing vascular occlusion, leading to a marked perfusion defect with preserved ventilation.

### Spiral computed tomographic scanning

Early studies suggest good sensitivity and specificity of spiral CT for central or segmental thrombus. Where available, rapid access to spiral CT scanning may make it the investigation of choice in patients with major embolism and those in the 'isolated dyspnoea' group. However, since not all the lung peripheral is included, and since emboli in subsegmental pulmonary arteries are not reliably visualised, it is less accurate than angiography in minor embolism. A recent report of PA confined to patients with non-diagnostic V/Q scans found that 30% had abnormalities confined to the subsegmental level where spiral CT scanning is less reliable<sup>52</sup>. Sensitivity and specificity appear satisfactory, suggesting spiral CT scanning as the initial confirmatory investigation of choice also in patients with underlying chronic cardiorespiratory disease who present



with clinical features suggesting VTE. Further evaluation of the technique is ongoing.

## Leg imaging

As stated previously, the logic of leg vein imaging is that the majority of patients with PE have proximal clot even in the absence of clinical evidence of DVT, itself an indication for treatment even if there is no direct proof of embolism. Leg vein imaging, which should be performed within 24 hours, is indicated in the assessment of PE as an alternative first-line investigation in those with clinical DVT or who have chronic cardiorespiratory disease, and following an indeterminate V/Q scan.

## Ascending contrast venography

Ascending contrast venography and ultrasound techniques are both widely used to image clot in the veins of the lower limbs and pelvis. Venography is moderately invasive, involving the injection of iodinated contrast agent into a foot vein. Minor complications are less common since the widespread introduction of low osmolar contrast media. Relative contraindications include contrast sensitivity and pregnancy. Technical failures preclude an adequate examination in up to 20% of cases<sup>53,54</sup>. Although venography is considered the 'gold standard' and is accurate in detecting proximal DVT, a recent screening study in orthopaedic patients showed that half the distal DVTs were missed<sup>54</sup>. False positives may also occur<sup>55</sup>.

## Ultrasound techniques

Several different ultrasound techniques are in use and a number of major developments have been made. Compression ultrasound, which can be performed on basic real-time equipment, shows a high degree of accuracy in the femoropopliteal segment<sup>56</sup>. It is enhanced by the addition of colour Doppler imaging which usually allows the iliac and calf veins to be successfully examined<sup>57</sup>. Failure to identify calf veins

rarely has serious sequelae<sup>58</sup>, and the procedure can be readily repeated if there is persisting clinical concern. Where available, colour Doppler imaging is now the investigation of choice in the detection of suspected DVT of the lower limb<sup>59</sup>. However, although accurate at detecting proximal DVT, it is less reliable in screening for asymptomatic distal DVT.

## Other tests

### Echocardiography

Echocardiography can establish the diagnosis, as well as exclude other disease, in patients with major central PE. Using four-chamber, two-dimensional echocardiography, a number of changes have been described in PE<sup>60,61</sup> including:

- right ventricular dilatation and hypokinesis
- pulmonary artery enlargement
- tricuspid regurgitation (from which pulmonary artery pressure can be derived)
- abnormal septal movement
- lack of inferior vena cava collapse during inspiration.

In addition, conditions which may mimic PE (eg MI, aortic dissection, pericardial tamponade) can easily be distinguished<sup>62</sup>.

As expected, changes occur only when there has been significant obstruction to the pulmonary circulation. Diagnostic

abnormalities are typically found in patients with PE who have systemic hypotension. In those with normal blood pressure, right ventricular hypokinesis is likely only if the perfusion defect is more than 30%, but even then a third of investigations are normal<sup>63</sup>. However, there is no doubt that echocardiography is a useful initial investigation in the assessment of patients presenting with cardiovascular collapse. Accuracy can be increased by using the transoesophageal route, which is much more likely to show clot in either the right heart or main pulmonary arteries (an ominous finding).

### Pulmonary angiography

Technical facilities for PA are widely available, but only 15% of UK radiology departments offer this service and even in those only small numbers of procedures are performed<sup>64</sup>. In the UK, only one angiogram is performed for every 95 V/Q scans, probably because of:

- the reluctance of clinicians to consider this investigation
- difficulty in arranging it when indicated
- lack of radiological experience.

Acute hospitals with interventional radiologists should offer a regular service, and be prepared to provide an emergency service.

PA should be considered in patients suspected of PE in whom investigations have failed to give a firm diagnosis. There

## Key Points

**A negative D-dimer result in a patient presenting with signs and symptoms in keeping with venous thromboembolism but with a low clinical probability is sufficient to exclude the diagnosis**

**Ventilation perfusion isotope scanning, although widely available, should only be used in patients with suspected pulmonary embolism who have a normal chest radiograph or no previous chronic cardiopulmonary disease**

**Studies suggest good sensitivity and specificity of spiral computerised tomography (CT) in the diagnosis of central or segmental pulmonary emboli**

**All hospitals receiving acute medical emergencies should devise their own algorithm for diagnosis of venothromboembolism that reflects local expertise and availability of investigations**

are no absolute contraindications, although particular care should be exercised in patients with known sensitivity to contrast media and in those with severe pulmonary hypertension, renal impairment or following acute MI.

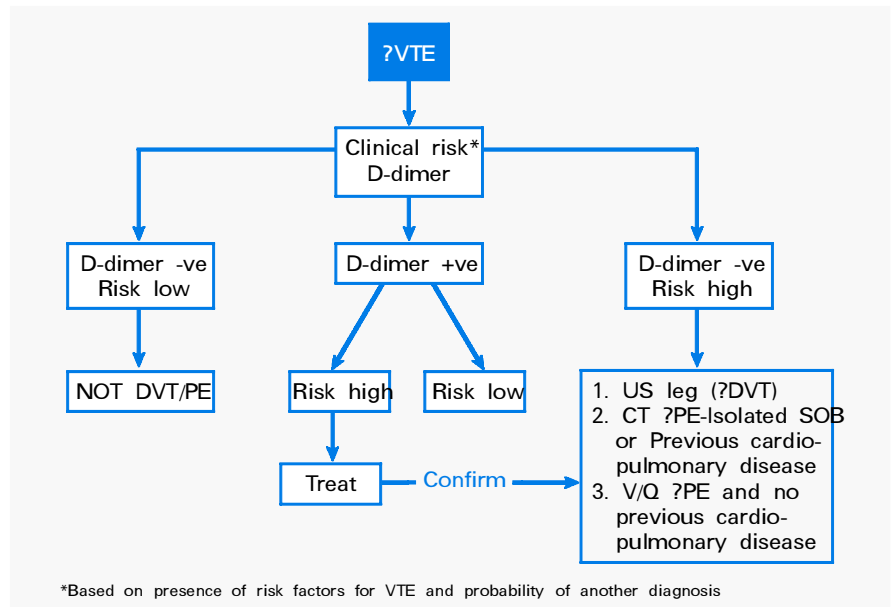
The femoral vein approach is commonly used, but some prefer the internal jugular or subclavian approach because of the reduced risk of disturbing thrombi and the ability to maintain venous access for pressure monitoring and the administration of thrombolytic drugs where indicated. Good liaison between the radiologist and intensive care unit is recommended. Pigtail catheters of sufficient size (7F) to enable high-flow injections of non-ionic contrast media should be used. Volume and flow will depend on facilities available. Superselective injections may be necessary. A main PA injection may be sufficient when prior echocardiography suggests the possibility of a large centrally placed clot. Where prior V/Q scan is non-diagnostic, angiography can be confined to the more abnormal side<sup>65</sup>.

Minor complications have been reported in 2% and major or fatal complications in 0.5–1.3% of investigations<sup>66</sup> using these techniques, mainly in patients already severely ill. The introduction of low osmolar non-ionic contrast media has led to a reduction in complications, a recent report finding only one major (non-fatal) complication in every 300 patients<sup>67</sup>.

There may be difficulties in interpretation of PA results, even by experienced radiologists. The PIOPED study found 19% interobserver disagreement, varying from 2% for central to 34% for subsegmental abnormalities<sup>68</sup>, and 11% within-observer discrepancy. A recent study with consensus review in patients with non-diagnostic lung scans led to a change in initial diagnosis in 20%. There was better agreement when digital subtraction was used, but this is not widely available.

**Recommendations**

The algorithm shown in Fig 1 outlines one approach to the investigation of a patient presenting with suspected VTE.



**Fig 1. Algorithm outlining an approach to the investigation of a patient presenting with suspect venothromboembolism (VTE)** (CT = computed tomography; DVT = deep vein thrombosis; PE = pulmonary embolism; SOB = shortness of breath; U/S = ultrasound; V/Q = ventilation/perfusion scan).

**Conclusions**

The investigation of suspected VTE will continue to be refined by further evidence from prospective studies using D-dimers and spiral CT. Moreover, newer modalities such as magnetic resonance imaging (MRI) are beginning to demonstrate diagnostic value, particularly in North America. However, at present, routine use of MRI is not a practical proposition for patients treated in the NHS.

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## Management of alcoholic hepatitis

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It is estimated that there are 3,500–7,000 deaths per year from alcoholic hepatitis and/or cirrhosis in the UK<sup>1,2</sup>. The incidence of cirrhosis in alcoholics at autopsy is about 10%. The average intake of alcohol in male and female alcoholics with cirrhosis is about 175 g/day and 120 g/day, respectively, for approximately eight years, although any alcohol consumption in excess of 60–80 g/day should cause concern. There is evidence of alcoholic hepatitis on liver biopsy in 30–60% of inpatients with alcoholic liver disease, and many patients presenting with alcoholic hepatitis have established cirrhosis at the time of diagnosis. However, the hepatic element is a clinically reversible entity.

### Metabolism of alcohol

Alcohol is oxidised in the liver or stomach by alcohol dehydrogenase to acetaldehyde, which is then metabolised to acetate. It can be oxidised further through the citric acid cycle, or act as a precursor for the synthesis of fatty acids and fat. There are approximately 600 cal in a bottle of wine, one gram of alcohol providing about seven calories. Chronic alcohol abuse will result in induction of

the microsomal P450 ethanol oxidising system. P450 2E1 isoenzyme is the major P450 enzyme involved; it usually metabolises 10–15% of alcohol consumed. Microsomal oxidation of alcohol will generate reactive oxygen species or free radicals. These need to be inactivated or removed by a variety of scavenging or metabolising mechanisms such as catalase, glutathione peroxidase, vitamin C or vitamin E.

### Pathogenesis

The pathogenesis of alcoholic liver disease involves the generation of reactive oxygen species which cause lipid peroxidation and secondary protein modification. Modified proteins may then act as foreign proteins and initiate an inflammatory response. Alcohol also increases the intestinal absorption of endotoxins and secondary activation of a variety of pro-inflammatory and pro-fibrotic cytokines. The combination of activated cytokines and altered cellular epitopes initiates hepatic inflammation and stellate cell activation. Malnutrition, causing depletion of cellular glutathione stores in alcoholics, aggravates this pro-inflammatory cascade (Fig 1).

## Key Points

It is estimated that there are 3,500–7,000 deaths per year from alcoholic hepatitis and/or cirrhosis in the UK.

There is evidence of alcoholic hepatitis on liver biopsy in 30–60% of inpatients with alcoholic liver disease.

Many patients presenting with alcoholic hepatitis also have established cirrhosis at the time of diagnosis.

At the present time, there is no universally accepted treatment of alcoholic hepatitis, although good nutrition and a trial of steroids for one month is common.

Patients die usually from liver failure with a combination of hepatorenal syndrome, plus or minus variceal haemorrhage, plus or minus infections such as spontaneous bacterial peritonitis.