Clinical review

Fortnightly review

The diagnosis of pulmonary embolism

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BMJ 1997;314:425–9

Pulmonary emboli are responsible for 10% of all deaths in hospital (medical and surgical), and contribute to a further 10%.[1] Death occurs in a heterogeneous group of patients ranging from those who are terminally ill to those who are convalescent. It is usually a sudden event but not always unheralded and often predictable. Thromboprophylaxis and a high level of suspicion are the only means by which any impression is likely to be made on the current death rate, which has not changed in the past 30 years.[1] Once treatment is started death from pulmonary embolism is rare, the problem is diagnosing it. The only confirmatory test available to most clinicians is ventilation perfusion lung scanning, but it is truly diagnostic in only about 30% of cases. The remaining 70% of scans—that is, low and intermediate probability scans, sometimes referred to as non-diagnostic scans—may represent a probability for an underlying embolus of between 4% and 66%, depending on the clinical circumstances and the scan abnormality.[2] Most clinical guidelines refer patients with a non-diagnostic scan for pulmonary angiography, the gold standard diagnostic test for pulmonary embolus, ignoring the fact that angiography is not available to many clinicians in the United Kingdom. Clinicians thus have to make clinical decisions on the basis of somewhat broad diagnostic probabilities.

How do they cope? We do not know for sure, but in most cases treatment is probably withheld.[3] When an uncertain diagnosis is balanced against the perceived risks and inconveniences of anticoagulant treatment concerns about anticoagulants are likely to win over any concerns over dying of pulmonary embolism. But how fatal is pulmonary embolism?

Remarkably little is known about the natural course of the condition, but a death rate of 30% for an untreated pulmonary embolus is often quoted and accounts for why guidelines inevitably proceed to angiography, the diagnosis being too dangerous to miss. This figure is based on a pioneering study in patients with massive pulmonary emboli,[4] but can it reasonably be extrapolated to patients presenting with a non-diagnostic scan? Some disagree and believe that most patients will come to little harm if left untreated, but the morbidity associated with this approach is unknown.

Summary points

- Anticoagulants reduce the risk of recurrent pulmonary embolism—they do not treat an existing embolus
- Non-invasive investigation of the leg veins is an insensitive test for diagnosing pulmonary embolism
- Patients with a non-diagnostic scan and negative results on non-invasive investigation of the leg veins have a less than 5% risk of having a further clinically detectable thromboembolic event
- Using published protocols the mortality associated with anticoagulant treatment for thromboembolic disease is 0.1%
- Mortality associated with a suspected but untreated pulmonary embolus in patients with reduced cardiorespiratory reserve is high, even in those with a low probability scan

Aim of review

Some important studies have been published over the past six years that have improved interpretation of a lung scan and understanding of the natural course of what might be called "non-diagnostic scan disease," as well as describing ways of diagnosing pulmonary emboli without resort to angiography. I aim to put these studies into a context where angiography is not generally available, where for 70% of patients with suspected pulmonary embolism the decision to treat has to be clinical, and where, as a result, pulmonary emboli are probably undertreated.

Methods

The review was prepared from a prospective review of the following major general medical journals and respiratory journals from January 1989 to May 1996: *Annals of Internal Medicine*, *Archives of Internal Medicine*, *JAMA*, *BMJ*, *Lancet*, *New England Journal of Medicine*, *Chest*, and *Thorax*. Reference lists and the relevant papers were handsearched and supplemented by a Medline search over the same dates, using the key words Doppler ultrasound and venous thrombosis and impedance plethysmography.

Table 1 Percentage probability of underlying pulmonary embolism according to the criteria of PIOPED study[2]

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

Ventilation-perfusion lung scanning

The prospective investigation of pulmonary embolism diagnosis study (PIOPED) confirmed and extended the criteria for assessing the probability of an underlying pulmonary embolus on isotope lung scanning (box 1).[2] Importantly, it also showed that clinical assessment may be helpful in interpreting the scan and that this knowledge could usefully be incorporated routinely into the management strategy. The clinician should estimate the likelihood of an underlying pulmonary embolus before the scan, according to three groups.[5]

- A high clinical probability (80-100% sure) would be based on the presence of one or more predisposing factors, appropriate signs, and symptoms and the absence of other diseases to account for these. Risk factors for pulmonary embolism are surgery, particularly orthopaedic surgery on the legs; trauma or burns; malignancy; immobility; paralysis of the legs; pregnancy or the puerperium; increasing age; heart failure; thrombophilia; the nephrotic syndrome; and inflammatory bowel disease. Suspicious symptoms and signs include dyspnoea, tachypnoea, pleuritic pain, haemoptysis, and syncope or shock
- A low probability (0-19% sure) would be based on the absence of underlying risk factors and the presence of other diseases to account for the presentation

Box 1–PIOPED study[2]

Objective: To assess (*a*) the sensitivity and specificity of ventilation-perfusion lung scanning in diagnosing pulmonary emboli and (*b*) the value of a pretest clinical estimate and the likelihood of an underlying embolus.
Design: Prospective 12 month follow up of patients undergoing ventilation-perfusion lung scanning and pulmonary angiography for investigation of suspected pulmonary embolism.
Setting: Six acute medical centres in the United States.
Subjects: 933 of 1493 eligible patients were randomly chosen to undergo both a lung scan and pulmonary angiography. 755 patients completed both investigations.
Main outcome measure: Pulmonary embolism on pulmonary angiography.
Results: 30% of patients had a pulmonary embolus on angiography. Isotope lung scanning had a sensitivity of 98% but a specificity of only 10% for detecting pulmonary emboli. 97% of high probability scans, 33% of intermediate scans, and 12% of low probability scans had pulmonary emboli visible on angiography.
Conclusions: A high or low pretest clinical likelihood combined with a matching high or low probability scan made a pulmonary embolus highly likely or unlikely as diagnosed by angiography. A normal or very low probability scan excluded the diagnosis of a pulmonary embolus. Such diagnostic certainty, however, applied to only a minority of patients.

- An intermediate probability (20-79% sure) would not fall easily into either of the above categories. The patient then has a lung scan, which is classed according to the study criteria (appendix). The scan report is interpreted in the light of the pretest clinical estimate (table 1). The PIOPED study differentiated between a segmental and subsegmental perfusion defect.[2] A subsegment was classed as being between 25% and 75% of a segment. A high probability scan is defined as two unmatched segmental perfusion defects or four subsegmental defects, highly specific (96%) but very insensitive (fig 1). Subsequent reanalysis of the data suggests that a single unmatched segmental or indeed subsegmental defect represents an 80% chance of an underlying pulmonary embolus,[6] and many clinicians would consider this sufficiently high odds to treat.

Modified criteria have also now been described for interpreting scans in patients with cardiorespiratory disease. Thus, when two segmental or subsegmental defects are present in these patients they have an 80% probability of an underlying pulmonary embolus, if clinical suspicion is intermediate or high.[7] The presence of cardiorespiratory disease or indeed any critical illness should not deter clinicians from requesting a lung scan.[8] The PIOPED study suggests that patients with normal or very low probability scans should be left untreated, while patients with high probability scans should be treated.[2] At what level of risk should a patient with a non-diagnostic scan be treated? A low probability scan with a low clinical likelihood can probably be left untreated, on the basis of results in a small series of 48 such patients followed up for one year.[9] Thereafter, however, it is up to the individual clinician to decide up to what level of risk, 16% through to 66%, treatment can safely be withheld. On weighing up the risks and benefits of anticoagulation, it should be appreciated that by using published guidelines mortality due to treatment is low.[10] Thus in the British Thoracic Society's study of treatment duration, there was one death due to haemorrhage in 712 treated patients, a mortality of 0.1%.[11]

Investigation of leg veins

If clinicians require more information before committing themselves to treatment, the current favoured strategy is non-invasive examination of the leg veins, from where over 90% of emboli originate.[12] If the leg veins are clear it is reasonable to assume that the patient is not in imminent danger of a fatal recurrence and treatment could safely be withheld. There are two immediate drawbacks with this approach.

Firstly, 30% of patients with angiographically proved emboli have normal venograms.[13] Although the emboli are assumed to have come from a more proximal site in a few cases, in most cases the thrombus will have dissociated completely from a leg vein and formed an embolus in the lung. In any event, the diagnosis of pulmonary embolism could be missed in a third of patients.

Secondly, whereas current non-invasive tests—impedance plethysmography and Doppler ultrasonography—are highly sensitive and specific for symptomatic proximal vein thrombosis, neither is sensitive when used for screening symptom free patients

at high risk (table 2), presumably because they miss small proximal and calf vein thrombi.[14-17]

Thus, with these tests at least 40% of the asymptomatic thrombi known to be present in patients with proved pulmonary embolism will be missed. Examination of the leg veins then is of little use in diagnosing pulmonary emboli, but perhaps this poor sensitivity does not matter. After all, clinicians are not so much concerned with whether patients have had a pulmonary embolus but rather with whether they are likely to have another, possibly fatal event. Anticoagulants are used prophylactically to prevent such an occurrence. If a significant proximal thrombus is undetected on non-invasive testing, is the patient still vulnerable to a major embolic even? Of course, a small undetectable thrombus might grow and a detached thrombus reform; in addition, 30% of thrombi in the calf vein extend proximally and might all subsequently break off. So perhaps serial testing of leg veins might have more to commend it than a one off test, and if the tests are persistently negative could treatment then be safely withheld?

Serial testing of leg veins for suspected pulmonary emboli

Hull *et al* serially tested leg veins using impedance plethysmography in 711 patients with a non-diagnostic scan[18] (box 2). Sixty eight patients (9.5%) had a positive result on first testing and were treated. During serial testing over 14 days a further 16 (2.5%) patients had positive results and were treated. The remaining 627 were left untreated and followed up for three months. Twelve (1.9% (95% confidence interval 0.8% to 3%)) developed clinical and objectively proved thromboembolic disease (four pulmonary emboli and eight deep vein thrombosis), only one of whom died of a pulmonary embolism after surgery for cancer.

This study may go some way to answering the question of what happens to patients with non-diagnostic scans who are left untreated. A comparatively small proportion, around 14%, are potentially at risk of having a further clinically detectable thromboembolic event. With a comparatively insensitive single screening test this proportion is reduced to less than 5%. With sequential testing there may be a small further reduction to 2% and mortality is low (0.13%). Undoubtedly, many of the patients left untreated in this study would have had a pulmonary embolus at the time of presentation, according to the data from the PIOPED study,[2] but they apparently came to no harm. There is, however, an important subgroup of patients in whom recurrent emboli either are more likely to occur or prove fatal.

Non-diagnostic lung scan and cardiorespiratory disease

A total of 117 patients with inadequate cardiorespiratory reserve were excluded from the original study of Hull *et al* and treated on their own merits at the discretion of the attending clinician.[19] Inadequate cardiorespiratory reserve was defined as pulmonary oedema, right ventricular failure, systolic pressure less than 90 mm Hg, syncope, acute tachycardias, forced expiratory volume in one second of less than 1 litre or forced vital capacity of less than 1.5 litre, and partial pressure of oxygen of less than 6.7 kPa or partial pressure of carbon dioxide greater than 6.0 kPa. These patients had one off screening impedance plethysmography, which gave positive results in 17% of patients, who were given anticoagulants; a further 13% of patients

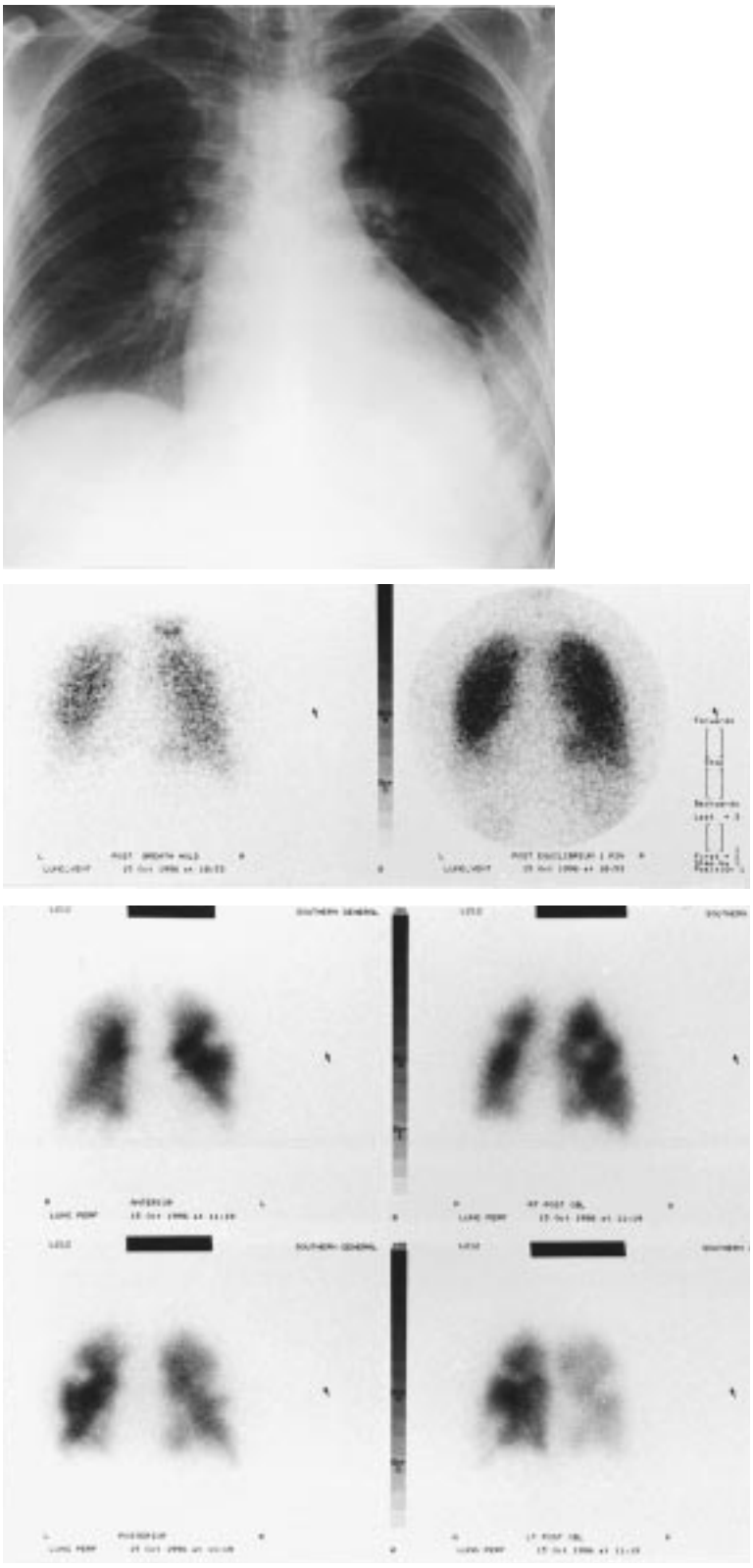

Fig 1 Chest radiograph showing left sided effusion (top). This is matched by ventilation defect after holding breath and after equilibrium phase in ventilation scan (middle). Four view perfusion scan shows multiple, unmatched segmental and subsegmental defects in both lungs (bottom). Thus this is high probability ventilation-perfusion lung scan by criteria of PIOPED study[2]

Table 2 Sensitivity and specificity (percentages) of techniques in detecting proximal vein thrombosis

	Patients with symptoms		Patients at high risk without symptoms	
	Sensitivity	Specificity	Sensitivity	Specificity
Serial impedance plethysmography	95	96	22	?
Doppler ultrasonography	91	99	62	97

were treated at the clinician's discretion, so overall 30% of this group received anticoagulants. The overall mortality due to documented embolism was 6%, with all seven deaths occurring in the untreated group. Six of the seven patients who died had so called low probability scans. Pulmonary embolism was strongly implicated but not proved as a cause of death in a further 6% of patients, all of whom were untreated.

Thus, the mortality in untreated patients with cardiorespiratory disease and non-diagnostic scans was at least 8.5% and probably higher. Hull *et al* point out that a review of case notes showed that most patients were not treated on the basis of a low probability scan report, and a case is made for a change in nomenclature in this group of patients.[19]

Management options

What is the impact of these studies on our current approach to the management of suspected pulmonary embolism? Clinicians should estimate the likelihood of pulmonary embolism before scanning, and scans should be reported in a uniform way that is recognised by both radiologists and clinicians and is according to a local protocol broadly based on the criteria of the PIOPED study.[2] Patients with normal or very low probability scans should not be treated. Patients with high probability scans should be treated.

Box 2–Non-invasive strategy for managing patients with non-diagnostic lung scans[18]

Objective: To assess whether serial non-invasive testing of leg veins is an alternative to pulmonary angiography in the management of patients with normal cardiorespiratory reserve and a non-diagnostic lung scan.
Design: Three month prospective follow up study.
Setting: Two acute hospitals in Hamilton, Ontario.
Subjects: 1564 consecutive patients with suspected pulmonary emboli. Those with non-diagnostic scans underwent serial testing of leg veins.
Main outcome measure: Objectively proved thromboembolic event after investigation and treatment when appropriate.
Results: 711 patients had non-diagnostic scans and normal cardiorespiratory reserve. 84 had developed positive results on serial testing with impedance plethysmography and were treated with anticoagulants. Of the remaining 627 patients, 12 (1.9% (95 confidence interval 0.8% to 3.0%) had a thromboembolic event, one of whom died.
Conclusion: Serial non-invasive investigation of leg veins offers an effective alternative to pulmonary angiography in the management of patients with non-diagnostic lung scans.

Box 3–Management options for suspected pulmonary embolism

- Do not treat patients with normal or very low probability scans
- Treat patients with high probability lung scans (one unmatched segmental or subsegmental perfusion defect)
- Treat patients with non-diagnostic scans according to whether or not they have cardiorespiratory disease

Patients without cardiorespiratory disease
—Do not treat: 14% will be at risk of a further thromboembolic event. Mortality in this group is unknown
—Assess the odds. Balance risks of treatment against risks of recurrent embolism. Patients with high or intermediate clinical suspicion have a 16-66% probability of an underlying embolus and a 14% risk of a recurrence. Anticoagulant treatment using published guidelines is associated with mortality rate of 0.1
—Shorten the odds on a recurrence by performing Doppler ultrasound of the leg veins. Treat if positive. If negative there is less than a 5% risk of a further thromboembolic event. The untreated mortality in this group is unknown but likely to be very low

Patients with cardiorespiratory disease
—Attach equal importance to low and intermediate scan reports
—Mortality of untreated patients will be in excess of 8.5%. Therefore have a low threshold for initiating anticoagulation in this group

Patients with non-diagnostic scans

Patients without cardiorespiratory disease
If clinical suspicion is intermediate or high the probability of an underlying pulmonary embolus will be between 16% and 66% in patients without cardiorespiratory disease. If the clinician cannot proceed to angiography in these patients they have three options (box 3).

In the final option, rather than basing management on assessment of the likelihood of an underlying embolus, the physician may want to shorten the odds on a further potentially fatal thromboembolic event by asking for an examination of the leg veins. Impedance plethysmography is not generally available in the United Kingdom but Doppler ultrasonography is. Two examinations could be performed, the first at the time of the lung scan, the second 10 days later.[20] Given available resources in the United Kingdom, this is probably unrealistic. However, a single examination should be possible and in those with a negative result less than 5% may potentially have a thromboembolic event (this proportion is likely to be lower as Doppler ultrasonography is a more sensitive screening test than impedance plethysmography (table 2)). Many clinicians would feel comfortable withholding treatment with this degree of risk.

Patients with underlying cardiorespiratory disease
Patients with underlying cardiorespiratory disease require a more aggressive approach as pulmonary embolism seems to be a more dangerous disease in this group. Investigation of the leg veins is twice as likely to give positive results in this group but even if they are negative, the physician should have a low threshold for initiating treatment if clinical suspicion is intermediate or high. Mortality due to pulmonary embolism in

untreated patients in this group is in excess of 8.5%; mortality due to treatment with anticoagulants is 0.1%, although in very sick, unstable patients it may be higher.

The future

The measurement of D-dimer, a fragment produced by the action of the fibrolytic system, may be helpful in refining the diagnosis.[21] In a study of 308 patients the diagnosis of pulmonary embolism was ruled out in 53 out of 202 patients with non-diagnostic scans, with a D-dimer measurement below a predetermined cut off point. None of those patients had a thromboembolic event during six months of follow up.[9]

The D-dimer assay is not, however, currently available for general use, and a much larger number of patients need following up prospectively to assess its true value. So called spiral volumetric computed tomography may prove to be the long sought after non-invasive test that is as effective as angiography in the diagnosis of pulmonary emboli. A recent study showed a sensitivity of 95% and specificity of 97% for the diagnosis of pulmonary emboli, when compared with pulmonary angiography.[22] Small emboli are likely to be missed, the clinical significance of which will need to be assessed.

Summary

Currently, clinicians have to make decisions about how to manage pulmonary embolism on the basis of imperfect tests and assessment of odds. Management protocols that inevitably result in large numbers of patients being referred for angiography are unhelpful. Management decisions based on assessment of odds and investigation of leg veins will inevitably result in some patients who have survived a pulmonary embolus being left untreated. Current evidence suggests that for most patients this is probably not important, the clear exception being those patients with underlying cardiorespiratory disease.

I thank Drs R Monie, E Rimmer, and W Watson and Ms M Kelly for their invaluable help in preparing this manuscript.

Appendix

Amended criteria[23] for interpreting lung scans of PIOPED study[2]

High probability of pulmonary embolism
Two or more large (>75% of a segment) segmental perfusion defects without corresponding ventilation or chest radiograph abnormalities; one large segmental perfusion defect and more than two moderate (26% of a segment) segmental perfusion defects without corresponding abnormalities in ventilation or chest radiograph; four or more moderate segmental perfusion defects without corresponding abnormalities in ventilation or chest radiograph.

Intermediate probability of pulmonary embolism
One moderate or less than two large segmental perfusion defects without corresponding abnormalities in ventilation or chest radiograph; corresponding ventilation-perfusion defects and radiographic parenchymal opacity in lower lung zone; single moderate matched ventilation-perfusion defects with normal findings on chest radiography; corresponding ventilation-perfusion defects and small pleural effusion; difficulty in categorising scan as normal, low, or high probability of pulmonary embolism.

Low probability of pulmonary embolism
Multiple matched ventilation-perfusion defects, regardless of size, with normal findings on chest radiography; corresponding ventilation-perfusion defects and radiographic parenchymal opacity in upper or middle lung zone; corresponding ventilation-perfusion defects and large pleural effusion; any perfusion defects with substantially larger abnormality on chest radiography; defects surrounded by normally perfused lung (stripe sign); more than three small (<25% of a segment) segmental perfusion defects with normal results on chest radiography; non-segmental perfusion defects (cardiomegaly, aortic impression, enlarged hila).

Very low probability of pulmonary embolism
Up to three small (<25% of a segment) segmental perfusion defects with a normal chest radiograph.

Normal findings
No perfusion defects, perfusion outlining the shape of the lung in a chest radiograph.

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(Accepted 6 December 1996)