Plasma cross linked fibrin degradation products in pulmonary embolism

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Abstract

Plasma concentrations of cross linked fibrin degradation products, a marker of intravascular thrombosis and fibrinolysis, were measured in 495 patients with suspected pulmonary embolism referred for ventilation-perfusion lung scanning to determine whether concentrations are increased in pulmonary embolism and their potential use in diagnosis. Lung scans were described as normal (n = 66) or as showing a low (n = 292), indeterminate (n = 58), or high probability (n = 79) of pulmonary embolism. There was a difference between the mean levels of cross linked fibrin degradation products in each scan category: normal scans, 142 ng/ml; low probability scans, 295 ng/ml; indeterminate probability scans, 510 ng/ml; high probability scans, 952 ng/ml ($p < 0.001$). Of the patients with high probability scans, 96% had raised concentrations. Explanations for discrepant low results include incorrect scan diagnosis, delay in blood sampling, and anticoagulation. Of the patients with a low or indeterminate probability of pulmonary embolism, 43% had increased concentrations of cross linked fibrin degradation products that could be attributed in most cases to another illness. Owing to the wide range of values in each lung scan diagnostic category, raised concentrations of these fibrin degradation products cannot be used without reference to the patient's clinical state as a discriminatory test for pulmonary embolism. Further evaluation of the significance of normal concentrations in excluding a diagnosis of pulmonary embolism appears to be warranted.

A simple, non-invasive blood test for the diagnosis of pulmonary embolism has long been sought. Measurement of markers of thrombosis, such as fibrinopeptide A and β thromboglobulin,¹⁻³ and of fibrinolysis, such as fibrin[ogen] degradation products,⁴⁻⁶ was considered but abandoned because of a lack of sensitivity and specificity. With monoclonal antibody technology, a new generation of assays for fibrin degradation products is now available.⁷ Several of these assays react with epitopes related to the cross linking between γ chains introduced by factor XIIIa during stabilisation of the fibrin clot. They identify the derivatives of cross linked fibrin

specifically and are uninfluenced by fibrinolysis. The assays can be performed in plasma, eliminating the artefact seen in results obtained from serum,⁸ and they provide a simple and accurate measurement of the derivatives of cross linked fibrin, the major fibrin form found in *in vivo* thrombi.

As well as indicating fibrinolysis, increased levels of cross linked fibrin degradation products are an indirect but apparently accurate marker of intravascular thrombosis. Raised concentrations occurred in all patients with clinical or occult deep vein thrombosis confirmed by venography,^{9,10} and their measurement has been proposed as a screening test for the condition. We investigated the value of the measurement in patients with suspected pulmonary embolism.

Methods

Six hundred and fourteen consecutive patients (aged 19-92 years) undergoing ventilation-perfusion lung scanning because of suspected pulmonary embolism were enrolled prospectively in the study. Data collected before scanning included clinical history and examination findings, chest radiograph, electrocardiogram, arterial blood gas tensions, venogram, the full blood count, and a biochemical screen. Patients were classified as inpatients if the suspected embolism complicated another medical or surgical illness, such as myocardial infarction or the aftermath of surgery, and as outpatients if there was no other disorder requiring hospital admission.

Citrated plasma for assay of cross linked fibrin degradation products were taken immediately before scanning. Samples were assayed by both enzyme immunoassay¹¹ (Dimertest EIA, Agen) and latex assay¹² (Dimertest Latex Agen). Both assays use the monoclonal antibody DD-3B6/22 to the D dimer and other cross linked derivatives. The normal ranges produced by these assays are: enzyme immunoassay 0-250 ng/ml; latex 0. Acquisition of lung scans was by a modification of the method of Smart *et al*,¹³ with a six view technetium-99m diethyltriamine pent-acetic acid (DTPA) aerosol ventilation study and a six view ^{99m}Tc macroaggregated albumin perfusion study. A high resolution collimator was used with a large field of vision camera to obtain anterior, posterior, and both right and left anterior and posterior oblique views. All patients had a chest radiograph within 12 hours of their scans.

All scans were interpreted by a single

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Table 1 Criteria used for classification of ventilation-perfusion lung scans

Definition of a defect	
Small:	<25% of segment
Subsegmental:	25–75% of segment
Segmental:	75–100% of segment
Whole lobe:	multiple segments
Normal scan	
Normal ventilation and perfusion	
Scans with the following probabilities of pulmonary embolism:	
High probability	
Two or more segmental or subsegmental regions of ventilation-perfusion mismatch	
Low probability	
Small defects or only matching ventilation-perfusion defects	
Indeterminate probability	
Single ventilation-perfusion mismatch	
or	
Perfusion abnormality matching radiographic change	
or	
Diffuse ventilation abnormalities such that there are uncertainties about whether areas are matched or mismatched	

nuclear physician (JE-V) and classified according to Biello *et al*,¹⁴ with modifications by Alderson *et al*¹⁵ and Davis *et al*¹⁶ (table 1). This classification was made without knowledge of the concentration of cross linked fibrin degradation products. No patient underwent pulmonary angiography.

Reasons for exclusion from the study were: no sample for assay of cross linked fibrin degradation products (74); second or subsequent progress scans (22); incomplete ven-

tilation-perfusion scan (11); ventilation-perfusion scan films not available for review (12).

Data were analysed by analysis of variance, *t* tests, and Fisher's exact test. The distribution of the concentrations of cross linked fibrin degradation products was skewed, so all analyses were conducted on data transformed to log_e.

Results

Of the 495 scans, 66 were considered to be normal; 292 were considered to have a low, 58 an indeterminate, and 79 a high probability of pulmonary embolism. The mean concentration of cross linked fibrin degradation products increased in each lung scan diagnostic category as the probability of pulmonary embolism increased. Mean concentrations ranged from 142 ng/ml in patients with a normal scan to 952 ng/ml in patients with a high probability scan (*F* = 47.0, 3,491 df; *p* < 0.001) (figure). The mean concentration of cross linked fibrin degradation products in the group with a high probability scan was significantly higher than that of the other diagnostic groups combined (*F* = 11.4, 1,493 df; *p* < 0.001).

There was no difference between mean concentrations of cross linked fibrin degradation products in inpatients and in outpatients in the group as a whole, though inpatients with a normal or low probability scan had higher concentrations than outpatients in this group (inpatients 361 ng/ml, outpatients 185 ng/ml; *t* = 6.41, 356 df, *p* < 0.001).

Seventy six of 79 patients (96%) with a lung scan with a high probability of pulmonary embolism had concentrations of cross linked fibrin degradation products greater than the normal range of 0–250 ng/ml. Raised concentrations were also seen in 179 of 350 patients (43%) with scans having a low or indeterminate probability of pulmonary embolism. The underlying conditions in these patients are listed in table 2. Substantially increased concentrations could be attributed to another condition in 85% of cases, but mild increases (250–400 ng/ml) were unexplained.

In patients with a high probability lung scan the mean concentrations of cross linked fibrin degradation products in patients receiving heparin at presentation for the scan was lower (842 ng/ml) than the concentrations in patients not receiving heparin (1088 ng/ml), but the difference was not significant.

Table 2 Conditions in patients with a low or indeterminate probability of pulmonary embolism on the ventilation-perfusion lung scan

	No of patients
Recent surgery	69
Malignancy	44
Cardiac failure	39
Pneumonia	31
Orthopaedic condition	23
Deep vein thrombosis	16
Peripheral vascular disease	11
Mural thrombosis	2

Concentrations of cross linked fibrin degradation products (XLFDPs) in patients who had ventilation-perfusion lung scans because of suspected pulmonary embolism (means with 95% confidence intervals).

Table 3 Titres of cross linked fibrin degradation products in patients having ventilation-perfusion lung scans for suspected pulmonary embolism

Latex titre	Number of patients				
	Normal scan	Scan with probability of pulmonary embolism:			All scans
		Low	Indeterminate	High	
0	58	176	24	7	265
1	7	59	13	20	99
>1	1	57	21	52	131

$\chi^2 = 121, 1 \text{ df}, p < 0.001.$

The results obtained by latex assay showed changes parallel to those obtained by enzyme immunoassay (table 3). There was a highly significant difference in latex titre in each lung scan diagnostic group ($\chi^2 = 121, 1 \text{ df}, p < 0.001$).

Discussion

This report confirms observations that cross linked fibrin degradation products are increased in patients with pulmonary embolism.^{11 17 18} Although an embolism is an obvious source for these fibrin degradation products in plasma, disseminated intravascular coagulation is frequent and may be an invariable complication of pulmonary embolism.¹⁹ McKay²⁰ proposed that liberation of bound or sequestered thrombin from the embolus as it travels to and disintegrates in the pulmonary vascular bed is responsible for systemic activation of the coagulation system and widespread fibrin deposition. The cross linked fibrin degradation products measured in pulmonary embolism derive then from systemic fibrin and the thromboembolus. As the concentrations derived from latex assay and enzyme immunoassay are similar, only the latter will be discussed.

It is apparent that the rise in cross linked fibrin degradation products after pulmonary embolism is early and short lived. Peak concentrations occur within one hour of experimental pulmonary embolism in dogs, though concentrations were still above normal at 24 hours.²¹ As their half life after generation is about two hours (personal observation), these fibrin degradation products should be measured as close to the event as possible. In most of our patients lung scans were performed within 24 hours of being requested. Clinical suspicion of pulmonary embolism was high in this study (84% of scans were not regarded as having a high probability of pulmonary embolism), but clinical suspicion would not be synchronous with the embolic event; a delay in scanning may have been responsible for normal concentrations of cross linked fibrin degradation products in the three patients with a high probability lung scan.

A further explanation for the discrepant group with normal concentrations of cross linked fibrin degradation products is that the lung scan diagnosis is incorrect. The best estimate of agreement between lung scans considered to show a high probability of pulmonary embolism and pulmonary angiograms

is 90% in both prospective and retrospective series.²²⁻²⁴ Thus the 4% of patients in our series with normal concentrations of cross linked fibrin degradation products fall within the accepted range of possible error in the lung scan diagnosis. A further possible explanation for normal or borderline increases in cross linked fibrin degradation products in patients with a high probability of pulmonary embolism according to the scan relates to heparin treatment. Heparin inhibited the generation of fibrin degradation products after experimental pulmonary embolism in dogs, probably by inhibiting systemic fibrin formation.²¹ Although the mean concentration of cross linked fibrin degradation products in patients receiving heparin at the time of scanning did not differ from that of the patients not receiving it, six of seven patients with a high probability lung scan and low concentrations of the fibrin degradation products (less than 400 ng/ml) were being treated with heparin.

Concentrations of cross linked fibrin degradation products were raised in 43% of patients with normal, low, or indeterminate probability scans. This was anticipated and two explanations are offered. The issue of the accuracy of lung scan diagnosis has already been raised. Whereas a normal perfusion scan is generally agreed to exclude pulmonary embolism, the interpretation of an abnormal perfusion scan is less straightforward.²²⁻²⁴ The incidence of pulmonary embolism, as diagnosed subsequently from the pulmonary angiogram, in patients with lung scans having a low probability of pulmonary embolism is 10% and in those with indeterminate probability scans 25%.²² In the only published prospective study the incidence of pulmonary embolism in such patients was appreciable, 25-40%, depending on the lung scan diagnostic criteria.^{23 24} This is supported by data from the recently completed PIPED study (Prospective Investigation in Pulmonary Embolism Diagnosis; H Salzman, personal communication). Our patients did not have pulmonary angiography as this is not used routinely to diagnose pulmonary embolism because of the risk, the cost, and the need for facilities and experience in interpretation. Even when pulmonary angiography was incorporated in a protocol, 30% of patients did not undergo the procedure, largely because of medical contraindications.²⁴ Some of the patients in our study, however, with increased cross linked fibrin degradation products but lung scans considered to have a low or indeterminate probability of pulmonary

embolism are likely to have had a pulmonary embolism.

Increased cross linked fibrin degradation products in patients with a negative ventilation-perfusion scan may also occur if they are derived from another source of intravascular fibrin. The assay is very sensitive to the products of lysis (1 ng/ml) and although specific for that process it is not specific for disease category. The disorders listed in table 2 are known to be complicated by intravascular fibrin deposition and its attendant lysis.

Reports^{17,18} on the use of measurements of cross linked fibrin degradation products in the diagnosis of pulmonary embolism have produced conflicting results. Goldhaber *et al*¹⁷ measured concentrations of cross linked fibrin degradation products in patients with a normal lung scan and positive pulmonary angiograms (positive diagnosis) and concluded that increased concentrations were not an accurate marker of pulmonary embolism. The quoted sensitivity (89%) was, however, similar to the accepted sensitivity of a high probability lung scan and pulmonary angiogram.²² The high percentage of patients in their study with a normal scan and raised concentrations of cross linked fibrin degradation products without apparent cause is contrary to our experience. Others have claimed high sensitivity (100%) and specificity (81%) and proposed a direct correspondence between concentrations of these fibrin degradation products and risk of pulmonary embolism.¹⁸

Our experience with a large study group indicates that, despite statistically different mean concentrations in the lung scan diagnostic groups, the range of values is such that cross linked fibrin degradation product concentration alone in an individual patient is insufficient to determine the risk of pulmonary embolism. The positive predictive value of the test—that is, in predicting a high probability scan—is only 26%. The negative predictive value of the test is, however, high (98.5%).

Lung scans of low or indeterminate probability may be insufficient grounds for excluding pulmonary embolism.^{23,24} Although pulmonary angiography would help in these cases, it may not be practical. Seventy one per cent of scans in this series were in these categories. Measurement of cross linked fibrin degradation products might prove a useful adjunct in this setting and deserves further study in conjunction with angiography. Normal concentrations in a promptly drawn blood sample before anticoagulation should increase confidence in a lung scan diagnosis of low probability of pulmonary embolism, and a raised concentration without other explanation in patients with a scan having a low or indeterminate probability of pulmonary embolism increases the probability of pulmonary embolism. Although concentrations of cross linked fibrin degradation products offer insights into the pathogenesis of pulmonary embolism and may yet be of clinical use, measurement of their concentration without

reference to the patient's clinical state cannot be recommended as a discriminatory test for pulmonary embolism.

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