

D-Dimer testing: the role of the clinical laboratory in the diagnosis of pulmonary embolism

B H Mavromatis, C M Kessler

Abstract

Pulmonary embolism is a common, yet often unsuspected and unrecognised disease associated with a high mortality. New, objective, “user friendly” and cost effective diagnostic strategies are being explored. D-Dimers, the fibrinolytic degradation products of crosslinked fibrin, have emerged as the most useful of the procoagulant activity and ongoing fibrinolysis markers. D-Dimer measurements are very sensitive in excluding a diagnosis of pulmonary embolism in the setting of normal values, a low clinical suspicion, and non-diagnostic lung scans. Several assays have been developed and are reviewed.

(*J Clin Pathol* 2001;54:664–668)

Keywords: pulmonary embolism; D-dimer assay

The clinical condition now known as pulmonary embolism was described initially by RTH Laënnec in his 1819 exposé on “pulmonary apoplexy” (Greek *αποπληξια*). This sudden impairment of pulmonary function was part of a syndrome characterised by extensive parenchymal haemorrhage (“haemoptoic engorgement”) and symptomatic haemoptysis (“haemoptysical infarctus”). (“The lesion consists in an induration, which is partial, and never occupies a larger portion of the lung; . . . it is always well defined, of even character in its center and periphery. The surrounding parenchyma is entirely normal—the swollen part is very dark red.”)¹ Three decades later, the pathologist R Virchow established in an animal model that the pathophysiology of the disease was embolic, a concept rather unique for the time.¹ According to insurance statistics, pulmonary embolism is diagnosed at least 300 000 times/year (23/100 000 patients/year) in the USA, with an expected one year mortality rate of 19%.² Ten per cent of affected patients will experience recurrent events, with a subsequent death rate of 45%. The introduction of new and innovative therapeutic modalities for the treatment of pulmonary embolism, including the recent availability of low molecular weight heparin preparations and increasing use of thrombolytic treatments, have not altered the mortality and morbidity of this condition. In part, this can be attributed to the fact that most pulmonary emboli remain unsuspected and unrecognised before death³; necropsy studies indicate that pulmonary emboli are overlooked as the primary or contributory cause of death in up to 84% of cases.³ Thus the crucial challenge of this disease resides in the development of new, rapid, specific, non-invasive, and “user friendly” objective diagnostic strategies, which can be used in a cost effective

manner to amplify the accuracy of subjective clinical judgment and suspicion. The considerable morbidity and life threatening nature of thromboembolic diseases, such as pulmonary embolism, require prompt and accurate diagnosis so that appropriate treatment can be initiated. Diagnostic tests should ideally be highly specific and sensitive enough to provide accurate diagnoses so that expensive and invasive procedures can be avoided. Diagnostic test results should also help the clinician to assess the risk–benefit ratio of certain treatment modalities—for example, would the benefits of thrombolytic treatment for suspected massive pulmonary emboli, or for multiple small emboli with evidence of right ventricular dilatation, or for emboli associated with proximal deep vein thrombosis in the lower extremities outweigh the risks of treatment?

Clinical diagnosis

Clinical evaluation of the patient as an independent diagnostic modality for pulmonary embolism has been considered insufficiently accurate to yield rapid and definitive diagnoses in most cases. Among patients in a large general hospital who died from pulmonary embolism, the diagnosis (confirmed at necropsy) was unsuspected in 70% of patients.⁴ Ninety three per cent of these deaths occurred within 2.5 hours of the onset of symptoms, emphasising the importance of clinical suspicion and timely initiation of diagnostic testing and subsequent treatment. The prevalence of pulmonary emboli found in published postmortem studies has not changed over three decades, despite the availability of sensitive and specific non-invasive (ventilation perfusion lung scan, cine computed tomography (CT) scans, etc) and invasive (pulmonary arteriograms) screening techniques. The prospective investigation of pulmonary embolism diagnosis (PIOPED) study data suggest that clinical acumen can improve the accuracy of diagnosis and reduce the need for expensive confirmatory tests.⁵ That is, the combination of low clinical suspicion of pulmonary embolism and a low probability lung scan yields a very low post-scan incidence of pulmonary embolism (4%), thus obviating the need for pulmonary angiography. In contrast, approximately 90% of patients with high probability scans and high or intermediate clinical suspicion for pulmonary embolism do have emboli. Yet, the so called “classic” clinical and laboratory characteristics of pulmonary embolism are not evident in all patients.⁶ Neither dyspnea nor tachypnea was observed in 12% of patients with the pulmonary infarction syndrome; a large number of patients with circulatory collapse attributable to pulmonary emboli were not dyspneic, tachypneic, or

Division of
Hematology/Oncology,
Lombardi Cancer
Center, Georgetown
University Medical
Center, Washington,
DC 20007, USA
B H Mavromatis
C M Kessler

Correspondence to:
Dr Mavromatis
mavromab@
gunet.georgetown.edu

Accepted for publication
26 February 2001

Table 1 Methodologies available for measurement of D-dimers

Assays	Commercial names	Methods	Characteristics	Ref
ELISA assay	Dimertest		Quantitative and reproducible but time consuming limiting their use in emergency situations.	Crippa <i>et al</i> (1997) ¹⁴
	Asserachrom Fibrinostika FnDP D-Dimer micro		High sensitivity, low specificity	Ginsberg <i>et al</i> (1995) ¹⁵
Latex particle assay	Dimertest I D-dimertest Minutex D-dimer FDP-Slidex direct Liatest D-Di	Latex agglutination test	Lower sensitivity, lower NPV when compared with the ELISA method	Laaban <i>et al</i> (1997) ¹⁶ Duet <i>et al</i> (1998) ¹⁷
SimpliRED D-dimer assay	SimpliRED D-dimer assay	Uses bispecific antibody directed against D-dimers and red blood cells	Good interobserver variability. Easier and faster than ELISA and latex assay	Mauron <i>et al</i> (1998) ¹⁸ Turkstra <i>et al</i> (1998) ¹⁹
Immunofiltration assay	NycoCard D-dimer	Uses monoclonal antibodies that are directed against the D-dimer configured molecules	Easy to interpret, rapid, simple	Dale <i>et al</i> (1994) ²⁰
Immunoturbidimetric assay	Boehringer Mannheim	Recognises the D-dimer epitope by antibody coated latex particles	Rapid and fully quantitative	Knecht <i>et al</i> (1997) ²¹

ELISA, enzyme linked immunosorbent assay; NPV, negative predictive value.

experiencing pleuritic pain on presentation. The prospective application of a recently published algorithm in over 1200 patients with suspected pulmonary emboli distinguished between low, moderate, and high probability cohorts based on clinical findings and chest x ray results.⁷ The prevalence of pulmonary emboli was 3%, 28%, and 78%, respectively, in this comprehensively evaluated group. In summary, the estimation of clinical probability can help the clinician develop a cost effective diagnostic strategy for pulmonary embolism by supporting the need or reducing the justification to pursue expensive invasive testing.

The pulmonary arteriogram remains the gold standard for the diagnosis of a thrombotic pulmonary event, and is the imaging technique of choice to establish or exclude pulmonary emboli in patients with non-high probability ventilation perfusion lung scans. However, its use is often hindered by practical factors, such as its invasive nature, the logistical requirement for around the clock availability of properly functioning equipment and appropriately trained staff, its overall expense, and the potential to precipitate acute renal failure in older individuals with underlying arteriosclerotic related renal insufficiency following exposure to the contrast dye load.

The spiral CT has emerged as a promising, convenient, and non-invasive diagnostic technique to visualise directly the pulmonary vessels in patients with suspected pulmonary emboli. However, subsegmental pulmonary emboli are more difficult to visualise in this setting, with both the test sensitivity and specificity decreasing from 94%⁸ to a sensitivity of 63% and a specificity of 89% in the detection of peripheral thrombi.⁹ In a small study,¹⁰ these subsegmental emboli seemed to be less clinically relevant, although larger studies need to be instituted to confirm these preliminary findings.

All these clinical data point to the need for a laboratory test geared to enhance our ability to make an accurate assessment when a pulmonary embolism is suspected.

The role of laboratory testing

The diagnosis of pulmonary embolism is difficult to exclude unless the ventilation perfusion lung scan and/or the spiral CT of the chest are normal. Because most pulmonary emboli are associated with intermediate probability ventilation perfusion lung scans, and because many patients with symptoms consistent with pulmonary emboli frequently have other

Table 2 D-Dimer using ELISA in detection of DVT or PE

Number of patients (PE)	% Sensitivity DVT/PE	% Specificity DVT/PE	% PPV DVT/PE	% NPV DVT/PE	Cut off ng/ml	Ref
69 (19)	89	44	38	92	290	Goldhaber <i>et al</i> (1988) ²²
46 (10)	100	81	69	100	500	Bounameaux <i>et al</i> (1989) ²³
21 (10)	100	36			500	Bounameaux <i>et al</i> (1990) ²⁴
170 (55)	98	39	44	98	500	Bounameaux <i>et al</i> (1991) ²⁵
74 (43)	95	100			1000	Lichey <i>et al</i> (1991) ²⁶
156	96	52		97	300	Demers <i>et al</i> (1992) ²⁷
173(45)	93.3	25	30.4	91.4	500	Goldhaber <i>et al</i> (1993) ²⁸
92	98	38	54	95	250	Dale <i>et al</i> (1994) ²⁹
183	89	76	31	98	300	Veitl <i>et al</i> (1996) ²⁹
117	98	58	97	70	500	Laaban <i>et al</i> (1997) ¹⁶
448	92	36.6	67.7	76.1	500	Leroyer <i>et al</i> (1997) ³⁰

Tables 2–6 list the sensitivities and specificities of the various available D-dimer assays. The sensitivity reflects the probability of a test being abnormal if a patient has the disease. The specificity represents the probability of a test being normal if a patient does not have the disease. The sensitivity and specificity of a test are influenced by the population being studied, and by the threshold (cut off) used to define an abnormal test. These sensitivities and specificities are best interpreted by the physician in the proper clinical context (and based on radiological and other diagnostic procedures). When used alone, and because clinical conditions other than thromboses can be associated with raised D-dimer concentrations, the positive predictive value (the percentage of patients with an abnormal test who have a pulmonary embolus) in these tables remains low. However, the high negative predictive value of these assays (the percentage of patients with a normal test who do not have a pulmonary embolus) allows the physician to rule out the presence of a pulmonary embolism in the setting of a low pretest probability.²² DVT, deep vein thrombosis; ELISA, enzyme linked immunosorbent assay; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

Table 3 D-Dimer latex assays in detection of DVT or PE

Number of patients (PE)	% Sensitivity	% Specificity	% PPV	% NPV	Cut off	Ref
26 (16)	81	60	76	67		Lichey <i>et al</i> (1991) ²⁶
64 (16)	94	58	43	97	500	Harrison <i>et al</i> (1993) ³¹
183	68	77	25	95	350	Veitl <i>et al</i> (1996) ²⁹
117	86	71	84	75	500	Laaban <i>et al</i> (1997) ¹⁶
85 (16)	94			96	500	Duet <i>et al</i> (1998) ¹⁷
386 (146)	100			100	500	Oger <i>et al</i> (1998) ³²
180	95	47	53	96	250	Lindahl <i>et al</i> (1998) ³³
464	94.6	35			400	Escoffre-Barbe <i>et al</i> (1998) ³⁴

See footnotes to table 2.

DVT, deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

cardiopulmonary diseases, which could produce similar symptoms,¹¹ there has been intense interest in including discriminatory laboratory testing in the diagnostic algorithm. Laboratory markers of procoagulant activity and ongoing fibrinolysis have been studied most extensively in the hope that, when combined with imaging tests, they can improve the predictive accuracy and efficiency of diagnosing pulmonary embolism; however, these markers are known to be raised in several medical disorders, which may or may not predispose to thromboembolic events—for example, carcinomas, hepatic and renal insufficiency, surgery, septicaemia, stroke, and major trauma.¹² Measurement of the D-dimer, the fibrinolytic degradation product of crosslinked fibrin, has emerged as the most useful marker. It is very sensitive, but non-specific for the diagnosis of deep vein thrombosis and pulmonary embolism; therefore, high values are not as helpful in establishing the diagnosis of pulmonary emboli as normal values are in excluding the diagnosis of pulmonary emboli. Furthermore, a raised D-dimer concentration does not distinguish between a thrombus arising from a deep vein, a pulmonary vessel, or both concurrently. A recent clinical study comparing the use of the D-dimer assay¹³ in high risk patients with and without a malignancy observed similar high sensitivities for D-dimer assays in the detection of pulmonary emboli. However, the specificity of the assays was considerably lower in those with cancer (48.4%) than those without (82.2%). The respective negative predictive values were also different (78.9 *v* 94.9%). Attempts to improve the specificity of the D-dimer assay, which would increase its value as a diagnostic tool, have resulted in multiple methods for the detection of D-dimers. These are summarised in table 1. Enzyme linked immunosorbent assays (ELISA) have the highest sensitivity (79–

100%) for detecting D-dimers; however, their specificities (25–100%) are generally too low to render them useful as diagnostic tests (table 2). In addition, they are too labour intensive, time consuming, and expensive to make them practical to perform in most urgent clinical situations. Latex agglutination assays circumvent these problems, but in the process sacrifice sensitivity (22–88%) (table 3). The SimpliRED D-dimer assay has gained recent popularity because its negative predictive value generally exceeds 95%; however, these data were derived from patients with low pretest clinical probability for deep venous thrombosis or pulmonary embolus (table 4). SimpliRED D-dimer assays have lower sensitivities than ELISA assays. Prospective outpatient studies of the SimpliRED D-dimer assay have validated the negative predictive value of the assay to be as good as a normal ventilation perfusion lung scan, and better than a low probability lung scan.^{41–42} Successful therapeutic management has also been predicated on the results of the SimpliRED D-dimer assay. It may be safe to withhold anticoagulant treatment in those patients with a non-diagnostic lung scan, a normal SimpliRED D-dimer test, and a low clinical probability.³⁸ Negative D-dimer assays may substantially reduce the need for venous ultrasounds and pulmonary angiography to confirm the diagnosis of pulmonary emboli and thus reduce the cost of overall care. D-Dimer assays should not be used in isolation to exclude pulmonary embolism.³⁸ Clinical studies using immunofiltration and immunoturbidimetric techniques for assaying D-dimers are in progress; however, they do not appear to be superior to the SimpliRED D-dimer approach (tables 5 and 6).

Conclusion

In summary, SimpliRED D-dimer assay tests may be useful in the exclusion of pulmonary

Table 4 SimpliRED D-dimer assay in detection of DVT or PE

Number of patients (PE)	% Sensitivity	% Specificity	% PPV	% NPV	Cut off	Ref
86	94	66	38	98		Ginsberg <i>et al</i> (1995) ¹⁵
214	93 (proxDVT) 70 (distDVT)	77				Wells <i>et al</i> (1995) ³⁵
183	88	65	23	98	350	Veitl <i>et al</i> (1996) ²⁹
234	100	58		100		Turkstra <i>et al</i> (1996) ³⁶
45	73–80	77–80		85–89		Mauron <i>et al</i> (1998) ¹⁸
1177 (197)	84.8	68.4				Ginsberg <i>et al</i> (1998) ³⁷
245	90 (PE)					de Groot <i>et al</i> (1999) ³⁸
265	93.3 (DVT) 90.4 (PE)	45.2 (DVT) 62.2 (PE)	34.3 (DVT) 48.7 (PE)	95.6 (DVT) 94.2 (PE)		Siragusa <i>et al</i> (1999) ³⁹
562				98.1		Wells <i>et al</i> (1999) ⁴⁰

See footnotes to table 2.

DVT, deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

Table 5 Immunofiltration D-dimer assay in detection of DVT or PE

Number of patients	% Sensitivity	% Specificity	% PPV	% NPV	Cut off	Ref
92	100	42	57	100	500	Dale <i>et al</i> (1994) ²⁰
183	95	33	14	98	500	Veitl <i>et al</i> (1996) ²⁹
84	95.3	22		81.8	500	Killick <i>et al</i> (1997) ⁴³
180	90	63	60	91	250	Lindahl <i>et al</i> (1998) ³³

See footnotes to table 2.

DVT, deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

Table 6 Immunoturbidimetric D-dimer assay in detection of DVT or PE

Number of patients	% Sensitivity	% Specificity	% PPV	% NPV	Cut off	Ref
183	89	57	21	98	66	Veitl <i>et al</i> (1996) ²⁹
128 (DVT)	98 (DVT)	44 (DVT)				Knecht <i>et al</i>
26 (PE)	100 (PE)	50 (PE)				(1997) ²¹

See footnotes to table 2.

DVT, deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

emboli when negative and accompanied by non-diagnostic lung scans and a low clinical probability. However, when clinically indicated, they would need to be followed up by more costly, perhaps more invasive studies, such a spiral CT scan or an arteriogram. Synthetic peptides designed to attach to a specific active binding site found on activated platelets are now also being evaluated as a potential non-invasive imaging technique in the diagnosis of a pulmonary embolism. Tc-99m (99mTc) or indium labelled antigens have been modelled against the glycoprotein IIb/IIIa platelet receptor complex (Tc-99m-P748, Tc-99m-P280, Tc-99m-DMP444, I-123-Bitistatin).⁴⁴ After injection of the radiotracer, the peptides bind to the activated platelets at the site of thrombosis, potentially enabling the diagnosis and localisation of the clot. However, the sensitivity and specificity in the detection of a thrombus, in addition to the exact role of this methodology in the diagnostic schema of pulmonary embolism, needs to be carefully determined in prospective randomised clinical trials.

The authors thank AH Mavromatis for his help in designing the tables.

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J Clin Pathol 2001 54: 664-668

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