Plasma D-Dimer: A Useful Tool for Evaluating Suspected Pulmonary Embolus

Katherine A. Harrison, William D. Haire, Alex A. Pappas, Gary L. Purnell, Sharon Palmer, Karen P. Holdeman, Lou M. Fink and Glenn V. Dalrymple

Departments of Radiology and Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska; Departments of Pathology and Radiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; and Department of Pathology, John L. McClellan Memorial Veterans Medical Center, Little Rock, Arkansas

Although ventilation-perfusion lung scanning is widely used in evaluating patients with suspected pulmonary embolus, additional rapid screening tests are needed to supplement scintigraphy in patients in whom the scan is indeterminate or the scan results are discordant with clinical suspicion. D-dimer is a fibrin degradation product which should be elevated in the presence of intravascular coagulation. We prospectively studied patients referred for lung scanning by obtaining a plasma D-dimer latex agglutination assay at the time of the scan. Of 64 patients who had pulmonary angiography to confirm the diagnosis, 16 were positive for pulmonary embolus and only one had a normal D-dimer. The D-dimer was normal in 27 of 48 patients without embolus and elevated in 21. Although an elevated D-dimer level is a nonspecific finding, we conclude that a normal D-dimer is a good negative predictor for pulmonary embolus, with a negative predictive value of 0.97.

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Pulmonary embolism (PE) is a potentially life threatening occurrence which has numerous clinical presentations. Therapy, either with anticoagulation, fibrinolysis or inferior vena cava interruption, carries a significant risk of morbidity and mortality. Reliable noninvasive screening techniques have been sought for decades.

Currently, one of the most widely used screening tests is ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scanning. Unfortunately, a substantial percentage of scans will fall into the indeterminate (or intermediate probability) category, meaning that approximately one-third of these patients will have PE. Even scans that can be classified as high or low probabilities have error rates of about 10%–12% (*1,2*).

D-dimer (D-D) is a plasmin degradation product of fibrin. D-D levels are increased in the presence of acute intravascular coagulation of any etiology, including acute PE (*3,4*). An enzyme-linked immunoassay (ELISA) for D-D has been found to be a good predictor of the absence of PE in patients with normal levels. Elevated levels are regarded as too nonspecific to assist in the identification of PE (*5,6*).

One problem with the ELISA test is the time and effort required before results are available. This limits its use as a screening test in the emergency room or outpatient setting. A simple, rapid latex agglutination assay is also available for D-D (*3*) but has been reported by some investigators to be too insensitive to be valuable in excluding intravascular coagulation (*7–9*). In order to further investigate the use of D-D latex agglutination assays in the urgent setting, we assessed the D-D levels of patients referred for $\dot{V}/\dot{Q}$ scans who later underwent pulmonary angiography (PAG).

MATERIALS AND METHODS

Five hundred eighty-eight patients with suspected PE in a major Veterans Administration Medical Center and two university hospitals who were referred for $\dot{V}/\dot{Q}$ scanning had blood samples drawn for plasma D-D latex agglutination assay at the time of or shortly after imaging. Based on clinical suspicion after scintigraphic findings were known, 63 patients also underwent PAG within 48 hr. In addition, one patient did not have $\dot{V}/\dot{Q}$ scanning, but proceeded directly to PAG and had blood drawn for a D-D latex agglutination assay.

$\dot{V}/\dot{Q}$ scans were obtained with a large field of view gamma camera using 10–20 mCi (370–740 MBq) ^{133}Xe gas in a closed-loop system. Single-breath, equilibrium and washout images were obtained in the posterior projection as well as equilibrium images in both posterior oblique projections. Perfusion images were obtained after the intravenous injection of 4 mCi (148 MBq) of ^{99m}Tc-macroaggregated albumin (MAA) with the patient in the supine position whenever possible. Eight view static images were then obtained. A chest radiograph obtained within 24 hr prior to scintigraphy was used for comparison during interpretation. Scans were interpreted by one or more of the investigators (KAH, KPH, GLP or GVD) using previously published criteria (*1,2*).

PAG was performed in a standard fashion (*10*) using the $\dot{V}/\dot{Q}$ scan to guide the angiographer to segments most likely involved and was interpreted by the angiographer performing the study. Once an embolus was identified, the remainder of the lung was not studied.

Citrated whole blood was obtained in all patients at the time of $\dot{V}/\dot{Q}$ scintigraphy or shortly thereafter. Testing was performed in duplicate according to the manufacturer's recommendations (D-Di Test, American Bioproducts Company, Parsippany, NJ). The technologist performing the analysis was not aware of either

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For correspondence or reprints: Katherine A. Harrison, MD, Department of Radiology, University of Nebraska Medical Center, 600 S. 42nd St., Omaha, NE 68198-1045.

TABLE 1
V/Q Results Versus D-D Results

	PAG+			
	Low	Indeterminate	High	Total
D-D Elevated	4	8	3	15
D-D Normal	0	1	0	1
Total	4	9	3	16
	PAG−			
	Low	Indeterminate	High	Total
D-D Elevated	5	13	1	19
D-D Normal	12	15	1	28
Total	17	28	2	47

the V̇/Q̇ or PAG results. An elevated level was reported when agglutination was observed in an undiluted sample or in any of serial dilutions. A normal result was recorded if there was no agglutination in an undiluted sample. This D-D level is approximately equivalent to 250 ng/ml when compared to the same manufacturer's ELISA assay for D-D.

RESULTS

Of the 588 V̇/Q̇ scans, 91 were interpreted as normal, 282 as low probability, 159 as indeterminate and 56 as high probability.

Of 64 patients who had PAG, 16 were positive for PE and 48 were negative. One of the patients with PE had a normal D-D (<250 ng/ml), whereas the other 15 had elevated D-D levels. Of the 48 patients without PE, 27 had normal D-D and 21 had elevated levels. A summary of this data is given in Table 1.

True-positive (TP) was defined as D-D elevated and PE present, true-negative (TN) as D-D normal and PE absent, false-positive (FP) as D-D elevated and PE absent, and false negative (FN) as D-D normal and PE present. The sensitivity (sens), specificity (spec), positive predictive value (PPV) and negative predictive value (NPV) were calculated using the following standard formulas (*11*):

$$\text{Sens} = TP/[TP + FN]$$

$$\text{Spec} = TN/[TN + FP]$$

$$\text{PPV} = TP/[TP + FP]$$

$$\text{NPV} = TN/[TN + FN].$$

Thus, the sensitivity of an elevated D-D for PE was 0.94 and the specificity was 0.58. The PPV of an elevated D-D for the presence of PE was 0.43. The NPV of a normal D-D for the absence of PE was 0.97.

DISCUSSION

A review of the literature reveals two studies using D-D ELISA and PAG in evaluating patients for suspected PE (*12,13*). Although both studies included small numbers of patients, they result in essentially the same sensitivity (1.0–0.89) and negative predictive value (1.0–0.92) as our study (Table 2). This would seem to indicate that the D-D latex agglutination assay, as well as the D-D ELISA, can be used as a negative predictor of PE.

Other studies (*7–9*) suggesting that the latex agglutination assay is too insensitive for exclusion of thrombotic or embolic disease used different manufacturers' products. In one case (*7*), it is reported that although the lowest concentration detectable by the assay was stated to be 200 ng/ml, the actual level detected, when compared to ELISA assay on the same sample, was 400 ng/ml. Another author (*9*) states that a comparison of the two latex agglutination assays tested were less sensitive than that stated by the manufacturer when compared to ELISA assays. The third (*8*) did not state the lowest detectable D-D concentration for the latex agglutination assay used in the study. One might suspect that these studies may have been using assays that were less sensitive than that used in our study, even if the stated lower limits of detectability were similar.

A relatively large number of V̇/Q̇ scans on patients suspected of having PE are interpreted as indeterminate. This setting could prove to be one in which the finding of a negative D-D will be the most valuable. In fact, of 159 patients with indeterminate V̇/Q̇ scans, 86 had negative D-D levels. The sensitivity, specificity, PPV and NPV of D-D in each subset of patients based on V̇/Q̇ results are shown in Table 3. Even for patients with indeterminate V̇/Q̇ results, the NPV is still quite good. Unless clinical suspicion is very high, PAG with its attendant risks and cost may be avoided in many patients such as these.

Of concern is our single patient and the two other reported cases with positive PAG and negative D-D. D-D is the result of fibrin *degradation* not fibrin *formation*. Generation of D-D requires both formation of fibrin and gen-

TABLE 2
Comparison of Current Study with Published Data

		PAG+		PAG−					
	No. PAG	D-D+	D-D−	D-D+	D-D−	Sens	Spec	PPV	NPV
Nebraska/Arkansas	64	15	1	20	28	0.94	0.58	0.43	0.97
Boston (*11*)	19	17	2	28*	22*	0.89	0.44	0.38	0.92
Clamart (*12*)	29	29	0	0	1	1.00	1.00	1.00	1.00
Total	112	61	3	48*	51*	0.95†	0.62†	0.57†	0.97†

*Absence of PE indicated by "normal" V̇/Q̇ or by absence of PE on PAG.
†Weighted average.

TABLE 3
V̇/Q̇ Results Versus D-D Results

		PAG+		PAG−					
	No. PAG	D-D+	D-D−	D-D+	D-D−	Sens	Spec	PPV	NPV
Low probability	21	4	0	5	12	1.00	1.00	1.00	1.00
Indeterminate	37	8	1	13	15	0.89	0.54	0.38	0.94
High probability	5	3	0	1	1	1.00	1.00	1.00	1.00
Total	63	15	1	19	28	0.94	0.59	0.44	0.97

eration of plasmin, which is responsible for degradation of fibrin to its components, including D-D. Consequently, situations in which conversion of plasminogen to plasmin is impaired may limit generation of D-D from fibrin. The most physiologically relevant plasminogen activator is probably tissue plasminogen activator (tPA). Its physiologic inhibitor is plasminogen activator inhibitor type-1 (PAI-1) (*14*). Many conditions associated with pulmonary emboli such as deep vein thrombosis (*15,16*), malignancy (*17*), obesity (*18*), inflammatory bowel disease (*19*) and the postoperative state (*20*) are associated with either high levels of PAI or poor release of tPA into the plasma from its intracellular storage sites. Consequently, it is not surprising that some patients with PE have normal levels of D-D, possibly resulting from either impaired release of tPA into the circulation or high levels of PAI.

Another factor which could potentially result in a negative D-D in the presence of proven emboli is the decreasing D-D level with time after onset of symptoms (*6*) or anticoagulation therapy (*13*).

Ideally, the D-D latex agglutination assay would be used in the acute setting as an independent predictor of PE in addition to clinical evaluation and V̇/Q̇ scanning. Results can be obtained within approximately 10 min of the arrival of the patient's blood in the laboratory. No specialized training of laboratory personnel is required. It should be stressed that a negative D-D latex agglutination assay should never be used to deny further evaluation (e.g., PAG) to a patient for whom the clinical suspicion of PE is high.

CONCLUSIONS

Our results confirm previous studies which concluded that the D-D assay is not specific for PE and cannot be used to confirm this diagnosis. In fact, any of a large number of pathologic states characterized by intravascular coagulation, including deep vein thrombosis, postoperative state, traumatic hematoma and malignancies to name but a few, may result in a positive D-D. However, a negative D-D is strongly associated with the absence of acute PE.

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