Klin Wochenschr (1991) 69:522–526
0023217391001343

Klinische Wochenschrift

Fibrin Degradation Product D-Dimer in the Diagnosis of Pulmonary Embolism

J. Lichey[1], I. Reschofski[1], T. Dissmann[2], M. Priesnitz[1], M. Hoffmann[1], and H. Lode[1]

[1] Innere Medizinische Abteilung, Lungenfunktionslabor, [2] Innere Medizinische Abteilung, Allgemeinmedizin, Klinikum Steglitz, Freie Universität Berlin

Summary. The study objective was to determine the specificity and sensitivity of plasma concentrations of D-dimer, a fibrin degradation product, as a marker for ongoing thrombotic and thrombolytic events in pulmonary embolism. A prospective study was performed in 74 patients with suspected pulmonary embolism who appeared in the emergency room with dyspnea and/or chest pain.

The presence of pulmonary embolism was established by positive findings either in pulmonary angiography or lung scan. D-dimer concentrations were determined in all patients. In 11 patients with positive pulmonary angiography, D-dimer concentrations were monitored for 6–12 days.

D-dimer concentrations were determined by a quantitative enzyme-linked immunoassay. Plasma probes of 26 patients (16 with/10 without positive pulmonary angiography) were reassayed with a semiquantitative latex agglutination assay. D-dimer levels were significantly higher in patients with pulmonary embolism (>1000 ng/mL in 41 out of 43) than in those without (<1000 ng/mL in all 21 patients) ($p < 0.01$).

The sensitivity and specificity for the ELISA were found to be 95% and 100%, respectively, for establishing the diagnosis of pulmonary embolism. In the latex assay the values were 81% and 60%, respectively.

It is concluded that in patients with dyspnea and/or chest pain, determination of D-dimer in plasma by ELISA adds a valuable tool to the noninvasive diagnostic procedure for pulmonary embolism. From the time-course of D-dimer values we conclude that this assay might be valuable up to at least 6 days after symptom onset. The assay, however, is unreliable in malignancies or after surgery.

Key words: Pulmonary embolism – D-dimer

Abbreviations: apPE = angiographically proven pulmonary embolism; hpPE = highly probable pulmonary embolism; imPE = highly improbable pulmonary embolism; rPE = pulmonary embolism ruled out; pPE = possible pulmonary embolism

Pulmonary embolism is one of the most frequently underdiagnosed of acute serious disorders [8]. This is because the pattern of signs, symptoms, and laboratory data are often deceivingly nonspecific [7, 21]. However, rapid diagnosis and treatment are required, since failure in the diagnosis and treatment of acute pulmonary embolism increases mortality considerably [2, 8]. On the other hand, exclusion of suspected minor pulmonary embolism is of equal importance because unjustified anticoagulant therapy bears life-threatening risks, too [6].

Pulmonary angiography is accepted as the gold standard for the diagnosis of pulmonary embolism, but it is a time-consuming and invasive procedure with its own risks, and requiring specialized equipment and personnel. Thromboembolic events are either often obscured or mimicked by other diseases, such as chronic obstructive pulmonary disease and pleuritis. The specificity of isotope lung scan is low in these patients. Thus, especially in these patients, it is often difficult to decide who should be submitted to pulmonary angiography. In order to circumvent these problems, several laboratory tests have been suggested in the search for the noninvasive diagnosis of pulmonary embolism, but none of them has reached clinical relevance [21, 23]. Recently, a monoclonal ELISA and a latex agglutination assay have been developed which may indicate an active fibrin clot lysis [12, 20]. Therefore, in a prospective study we examined the value of the D-dimer ELISA and latex agglutination assay for the diagnosis of thromboembolism.

Subjects and Methods

The study was undertaken in four hospitals of the Free University of Berlin. Patients who appeared in the emergency room with dyspnea and/or chest pain were considered for participation in the study. Patients suffering from non-thromboembolic diseases such as myocardial infarction, bronchial asthma, pneumothorax, or hyperventilation-syndrome, which could be clearly diagnosed by physical examination (e.g., bilateral wheezing in the presence of a history of bronchial asthma), ECG (e.g., typical S-Tsegment elevation), and chest X-ray (e.g., partial or total collapse of the lung) were excluded from further diagnostic procedures following our protocol and did not participate in the study.

Seventy-four patients (35 men, 39 women; aged from 20 to 84 years, mean age 59.2) who did not meet the exclusion criteria were enrolled in the study according to the following protocol. Each patient was examined on the day of referral by a consulting physician. Clinical history and physical findings were evaluated and recorded. In each of these patients an ECG and a two-view chest X-ray were performed. The patients were submitted to an additional four-view lung perfusion scan with technetium-99M-labeled macroaggregated albumin. If lung scans were negative we refrained from performing further diagnostic procedures for pulmonary embolism. In case of a positive lung scan, with segmental or larger lung scan perfusion defects, or an indecisive lung scan, in which scintigraphic defects match abnormalities on the chest X-ray [10], contrast venography and arterial blood gas analysis were performed. No venography was performed if immediate pulmonary angiography was necessary or indecisive lung scans were obtained in combination with low clinical probability for pulmonary embolism.

A selective pulmonary angiography was performed within 24 h after admission in 24 patients having no contraindication for thrombolytic or long-term anticoagulant therapy. Pulmonary angiography was also performed when contraindication for anticoagulant therapy existed or if surgical therapy was contemplated (as in venous interruption), but a diagnosis of pulmonary embolism could not be established sufficiently without angiography (indecisive or indeterminate lung scan). Pulmonary angiography was not performed when results would not have affected therapy; thus, anticoagulation would in any event be indicated for deep-vein thrombosis.

Briefly, the decision-making process for diagnostic procedures was performed mainly as described by Reilly [19].

On the basis of the diagnostic procedures listed above, patients were assigned to the following subgroups irrespective of the results of fibrin D-dimer degradation product determination:

1. Angiographically proven pulmonary embolism (apPE, $n=24$): vascular cut-offs or intraluminar filling defects were present on pulmonary angiograms.
2. Highly probable pulmonary embolism (hpPE, $n=19$): segmental or larger lung scan perfusion defects in the presence of a normal chest X-ray and when, additionally, deep-vein thrombosis was shown by contrast venography.
3. Highly improbable pulmonary embolism (imPE, $n=17$): presence of a normal lung scan.
4. Pulmonary embolism ruled out (rPE, $n=4$): presence of a normal pulmonary angiogram.
5. Possible pulmonary embolism (pPE, $n=10$): segmental or larger lung scan perfusion defects in the presence of an abnormal chest X-ray or subsegmental defects in the presence of a normal chest X-ray and deep-vein thrombosis shown by venography or, alternatively to venography (in 4 patients), acute right ventricular strain as shown by ECG or hypoxia confirmed by arterial blood gas analysis. Since pulmonary embolism was uncertain in these patients, the current study does not evalu-

Table 1. Frequency of concomitant diseases in patient groups included in the study

Disease	Patient group			
	apPE	hpPE	imPE	rPE
Recurrent thromboembolic event	7	5	2	3
Chronic obstructive lung disease	2		1	1
Pneumonia	1	1	1	1
Pleuritis			4	1
Chronic heart failure	3	5	5	1
Coronary artery disease	3	3	6	
Functional heart complaints			1	1
Arterial hypertension	1	6	2	
Diabetes mellitus	1		4	
Malignancy (operated, no metastasis)	1			
Malignancy (not operated)	1			
Surgery (<3 weeks before admission)	1			
Surgery (>3 weeks before admission)	2	2		

apPE: angiographically proven pulmonary embolism; hpPE: highly probable; imPE: improbable; rPE: pulmonary embolism ruled out

ate patients classified as "possible pulmonary embolism".

The frequency of concomitant diseases in the different patient groups is shown in Table 1. Blood samples for fibrin D-dimer degradation product determination were taken on the day of admission (day 1) from all patients who were included in the study at the time they underwent lung scanning. This means that blood specimens were obtained from these patients between 3 and 12 h after onset of symptoms, depending on the time of admission to the hospital. Eleven patients with proven pulmonary embolism were able to be followed up for D-dimer determination on day 1 (day of hospital admission), days 3, 6, 9, and 12, since they were not receiving fibrinolytic therapy.

Blood samples (10 mL) were collected in polystyrene tubes containing 1 ml sodium citrate (0.11 M and 250 KIU aprotinin. Blood was immediately centrifuged and the plasma stored at −35° C until assayed.

Fibrin D-dimer degradation product determination was performed by a quantitative enzyme-immunoassay (ELISA D-dimer, Boehringer Mannheim, FRG) and by a latex agglutination assay (D-Dimer-Test, Boehringer Mannheim, FRG) as described earlier [20].

Values were obtained from a standard curve of D-dimer. The curve was linear over the range of 10–10000 ng/mL. Values over 5000 ng/mL were expressed as >5000 ng/mL. Samples of 16 patients with proven pulmonary embolism (apPE) and 10 without (imPE) were reassayed by the semiquantitative latex agglutination assay. It is considered positive when macroscopic agglutination occurs after 3 min. When no agglutination is seen in the undiluted sample, the D-dimer concentration is <500 ng/mL. We used sample dilutions (glycine buffer, pH 8.2) of 1:1, 1:4, 1:8, 1:16, and 1:32.

The Kruskal-Wallis test was used to test for overall equality of means in all groups. Multiple pairwise comparisons were carried out with the use of the Mann-Whitney test. The time-related course of D-dimer concentrations was tested by means of Friedman's two-way analysis of variance. A difference is described as significant if the p value is less than 0.05. For the evaluation of sensitivity and specificity, the diagnostic subgroups "apPE" and "hpPE" were considered as "pulmonary embolism present" (considered as true positive), the groups "im PE" and "rPE" as "pulmonary embolism absent" (considered as true negative). The group of "possible pulmonary embolism" of course was not included in statistical analysis because it was not completely diagnosed.

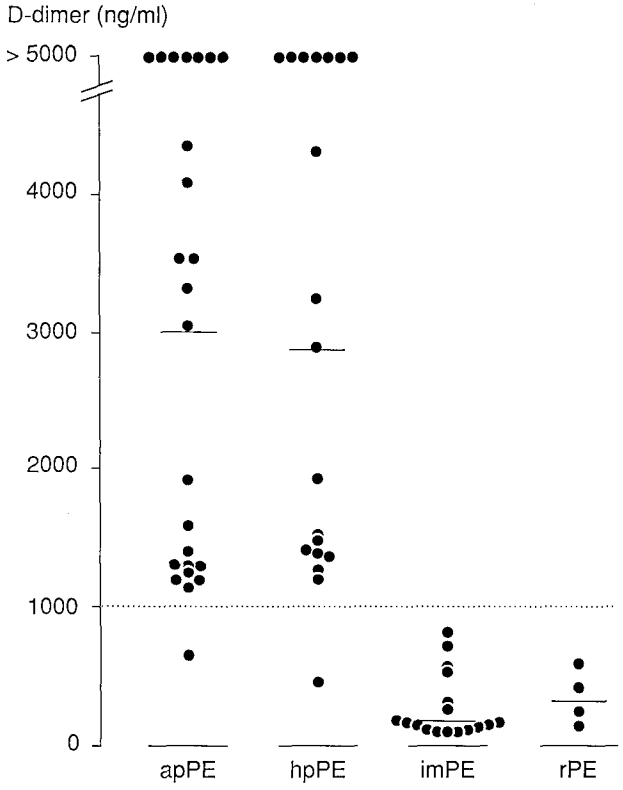

Fig. 1. D-dimer plasma concentrations in patients with angiographically proven pulmonary embolism (apPE), highly probable pulmonary embolism (hpPE), highly improbable pulmonary embolism (imPE), and pulmonary embolism ruled out (rPE). Horizontal bars = medians; broken line = cutoff level

Results

All but one patient in the group of angiographically proven and highly probable pulmonary embolism (apPE and hpPE, pulmonary embolism present) showed D-dimer plasma levels above 1000 ng/mL, whereas none in the group of highly improbable and ruled out pulmonary embolism (imPE and rPE, pulmonary embolimsm absent) reached the cutoff level of 1000 ng/mL level (Fig. 1).

There was a significant difference between the D-dimer values of group apPE and hpPE on one hand and group imPE and rPE on the other ($p <$ 0.01). But there was none between group apPE and hpPE or between group imPE and rPE.

Thus, the specificity of the diagnosis of pulmonary embolism was 100% and the sensitivity was 95%.

In the follow-up of D-dimer plasma levels which could be obtained in 11 patients up to the 6th day, in 10 patients up to the 9th day, and in 9 patients up to the 12th day, all but two were still above 1000 ng/mL (Fig. 2).

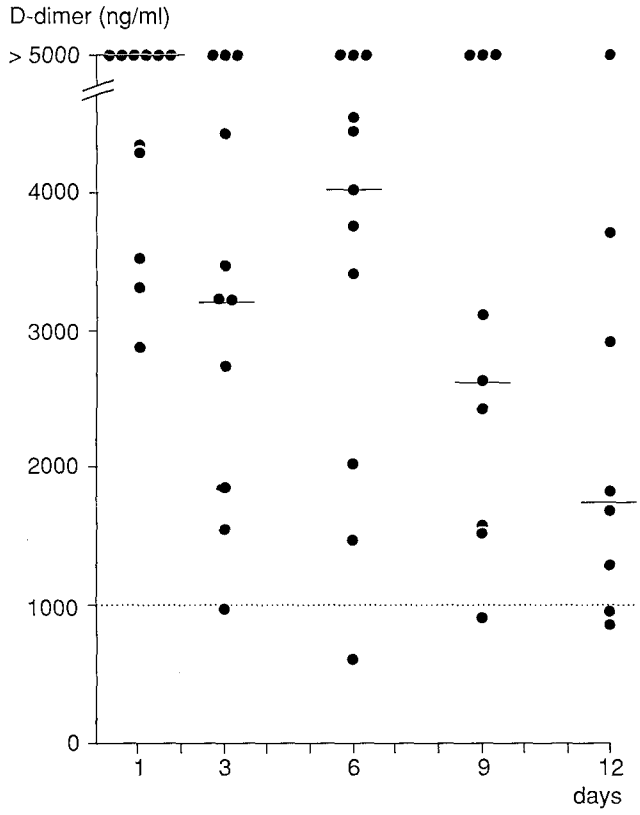

Fig. 2. Time-course of D-dimer plasma concentrations in eleven individual patients with pulmonary embolism. Horizontal bars = medians; broken line = cutoff level

The best discrimination between patient groups with the latex agglutination assay was obtained when used in a dilution of 1:16; 13 out of 16 patients with proven pulmonary embolism showed a macroscopic agglutination, and 6 out of 10 without, a negative one. Thus, the sensitivity and specificity were 81% and 60%, respectively.

Discussion

Our study concerning pulmonary embolism confirmed recent results showing elevated D-dimer plasma concentrations in this disease [5, 9, 15, 17, 24]. However, either these were not prospective studies, or confirmation of diagnosis concerning pulmonary embolism was poorly characterized. In a recent prospective study [13] a slightly lower sensitivity of elevated D-dimer levels for the diagnosis of pulmonary embolism was found – 89% vs 95% in our study – but specificity was considerably lower in that study at 44% vs 100%, respectively. Unfortunately however in that study, neither the duration of symptoms in patients with pulmonary embolism nor the occurrence of concomitant diseases in patients without pulmonary embolism was specified. This could help to explain the differences in our results, since in patients with malignant tumors and after operation, our data (unpublished) and those of other workers [12, 17] show that the D-dimer values can be as high as in thromboembolic events, thus invalidating the diagnosis of pulmonary embolism.

A prospective study published recently [3] with design and patient characteristics similar to our own yielded comparable results concerning sensitivity and time-course of D-dimer plasma levels. The specificity, however, was considerably lower (39% vs 100%). This might be due to the lower cutoff level chosen (500 vs 1000 ng/ml) as well as to different patient selection criteria; we included no patients with myocardial infarction, who also can have elevated D-dimer levels (see Table 1).

Other diseases and situations show only slight elevations of D-dimer levels, such as unstable coronary artery disease [16], pregnancy [11], and possibly liver diseases [15]. Elevations as high as in pulmonary embolism are found in arterial embolism [24] and deep-vein thrombosis [15]. However, there should be no problem in discriminating both situations clinically from pulmonary embolism.

Patients with suspected thromboembolism often have coexisting cardiopulmonary diseases such as chronic obstructive lung disease. Diagnosis in these patients may be difficult because physical signs are of little value and lung scans may be difficult to interpret [1], and in some only pulmonary angiography offers diagnostic accuracy [14]. Thus, one would run potential risks associated with performing this procedure too often. On the other hand, this technique is not available in all hospitals. Thus, in those patients the D-dimer ELISA assay is a suitable test which would appear to justify anticoagulant therapy without the need for pulmonary angiography. Another group of patients presenting differential diagnostic problems are those with pleuritic chest pain. In an earlier study in young adults presenting with pleuritic chest pain, a high percentage turned out to be caused by pulmonary embolism [4]. In such patients lung scan is only helpful when it is negative, thus ruling out pulmonary embolism. Even the existence of fever does not rule out pulmonary embolism [18]. Our results indicate that the D-dimer assay may be able to discriminate between pulmonary embolism and pleuritic chest pain of other origin, though further studies in this group of patients are necessary.

A further favorable condition of the D-dimer assay is offered by our finding that in most patients with pulmonary embolism, even after 12 days the

D-dimer levels are above the cutoff of 1000 ng/mL. Thus, this assay seems to be of diagnostic value even for patients appearing late after a thromboembolic event.

In summary, the D-dimer ELISA is a valuable noninvasive test for patients with pulmonary embolism who present with dyspnea and/or chest pain provided that no malignancy is present and no surgery has been performed within two weeks. Though this test, when performed in a larger patient population [3], may not reach the specificity of angiography, it is useful in the decision as to who should be submitted to angiography. This is of special interest since most of the lung scans carried out are inconclusive in establishing or ruling out the diagnosis of pulmonary embolism [22].

The more rapid D-dimer latex agglutination test, which can be performed within 5–10 min, has a poor specificity of 60%. Its sensitivity of 81% may make it a valuable screening test, especially in hospitals with limited laboratory capacity or without angiographic facilities. However, a simpler and more rapid ELISA would be desirable in emergency situations.

Acknowledgement: We are indebted to the following physicians for referring patients to this study: Prof. W. Thimme, Prof. K.-P. Schüren, and Drs. R. Haux, J. Heitz, and v. Herrath.

References

1. Alderson PO, Biello DR, Sachariah KG, Siegel BA (1981) Scintigraphic detection of pulmonary embolism in patients with obstructive pulmonary disease. Radiology 138:661–666
2. Barritt DW, Jordan SC (1960) Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet I:1309–1312
3. Bounameaux H, Cirafici P, De Moerloose P, Schneider PA, Slosman D, Reber G, Unger PF (1991) Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. Lancet 337:196–200
4. Branch WT, McNeil BJ (1983) Analysis of the differential diagnosis and assessment of pleuritic chest pain in young adults. Am J Med 75:671–679
5. Bridey F, Phlipotteau C, Dreyfus M, Simonneau G (1989) Plasma D-dimer and pulmonary embolism. Lancet I:791–792
6. Cheely R, McCartney WH, Perry JR, Delany DJ, Bustad L, Wynia VH, Griggs TR (1981) The role of noninvasive tests versus pulmonary angiography in the diagnosis of pulmonary embolism. Am J Med 70:17–22
7. Coon WW (1976) The spectrum of pulmonary embolism. Arch Surg 111:398–402
8. Dalen JE, Alpert JS (1975) Natural history of pulmonary embolism. Prog Cardiovasc Dis 17:259–270
9. Elms MJ, Bunce IH, Bundesen PG, Rylatt DB, Webber AJ, Mascí PP, Whithaker AN (1986) Rapid detection of cross-linked fibrin degradation products in plasma using monoclonal antibody-coated latex particles. Am J Clin Pathol 85:360–364
10. Fischer KC, McNeil B (1979) The indeterminate lung scan: its characteristics and its association with pulmonary embolism. Eur J Nucl Med 4:49–53
11. Franke M, Hafter R, von Hugo R, Röbl M, Graeff H (1986) Ein Test zum Nachweis von Fibrin im Plasma. Geburtshilfe Frauenheilkd 46:105–109
12. Gaffney PJ, Creighton LJ, Callus M, Thorpe R (1988) Monoclonal antibodies to crosslinked fibrin degradation products (XL-FDP). II: Evaluation in a variety of clinical conditions. Br J Haematol 68:91–96
13. Goldhaber SZ, Vaughan DE, Tumeh SS, Loscalzo J (1988) Utility of cross-linked fibrin degradation products in the diagnosis of pulmonary embolism. Am Heart J 116:505–508
14. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, Coates G, Gill GJ, Turpie AG, Doyle DJ, Buller HR, Raskob GE (1983) Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Int Med 98:891–899
15. Hunt FA, Rylatt DB, Hart R-A, Bundesen PG (1985) Serum crosslinked fibrin (XDP) and fibrinogen/fibrin degradation products (FDP) in disorders associated with activation of the coagulation of fibrinolytic systems. Br J Haematol 60:715–722
16. Kruskal JB, Commerford PJ, Franks JJ, Kirsch RE (1987) Fibrin and fibrinogen-related antigens in patients with stable and unstable coronary artery diseases. N Engl J Med 317:1361–1365
17. Müller-Berghaus G, Scheefers-Borchel U, Selmayr E, Henschen A (1986) Fibrinogen and its derivatives. Elsevier, Amsterdam New York
18. Murray HW, Ellis GC, Blumenthal DS, Sos TA (1979) Fever and pulmonary thromboembolism. Am J Med 67:232–235
19. Reilly BM (1984) Practical strategies in outpatient medicine. Saunders, Philadelphia
20. Stötzer K-E, Amiral J, Spanuth E (1988) Neue Methoden zur spezifischen Bestimmung von Fibrinspaltprodukten (D-Dimere). Lab Med 12:51–55
21. Szucs MM, Brooks HL, Grossman W, Banas JS, Meister SG, Dexter L, Dalen JE (1971) Diagnostic sensitivity of laboratory findings in acute pulmonary embolism. Ann Intern Med 74:161–166
22. The PIOPED Investigators (1990) Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 263:2753–2759
23. Van Hulsteijn H, Bertina R, Briet E (1982) A one-year follow-up study of plasma fibrinopeptide A and beta-thromboglobulin after deep vein thrombosis and pulmonary embolism. Thromb Res 27:225–229
24. Whitaker AN, Elms MJ, Masci PP, Bundesen PG, Rylatt DB, Webber AJ, Bunce IH (1984) Measurement of cross linked fibrin derivatives in plasma: an immunoassay using monoclonal antibodies. J Clin Pathol 37:882–887

Received: March 1, 1991
Returned for revision: May 10, 1991
Accepted: June 4, 1991

Dr. Jürgen Lichey
Klinikum Steglitz
Freie Universität Berlin
Lungenfunktionslabor
Hindenburgdamm 30
1000 Berlin 45, FRG