Use of Fibrinogen/Fibrin Degradation Products and Soluble Fibrin Complexes for Differentiating Pulmonary Embolism from Nonthromboembolic Lung Disease[1-3]

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SUMMARY

To help differentiate pulmonary embolism from other lung diseases, we measured the degradation products of fibrinogen and fibrin and soluble fibrin complexes in normal control subjects and patients with pulmonary embolism, lung cancer, pneumonia, chronic obstructive pulmonary disease, tuberculosis, asthma, and several miscellaneous disorders. A separate group of patients, who were suspected of having pulmonary embolism but had negative pulmonary angiography, were also tested. Many nonthromboembolic lung diseases frequently were associated with positive fibrinogen/fibrin degradation products or soluble fibrin complexes, but those with high positivity rates for one test tended to have low rates for the other test. Both fibrinogen/fibrin degradation products and soluble fibrin complexes were positive in 55 per cent of patients with pulmonary embolism but only in 4 per cent with nonthromboembolic conditions ($P < 0.001$), in 7 per cent of patients with negative pulmonary angiography ($P < 0.001$), and in none of the normal subjects ($P < 0.001$). Both tests were negative in only 3 per cent of patients with pulmonary embolism but in 35 per cent of nonthromboembolic diseases ($P < 0.005$), 54 per cent of those with negative pulmonary angiography ($P < 0.001$), and 79 per cent of normal control subjects ($P < 0.001$). The combination of fibrinogen/fibrin degradation products and soluble fibrin complexes is more valuable than either test alone in the diagnostic separation of thromboembolic from nonthromboembolic pulmonary diseases.

Introduction

Because pulmonary embolism is difficult to differentiate from other pulmonary disorders with similar clinical features, embolic disease is frequently misdiagnosed (1–3). Tests for fibrinogen/fibrin degradation products (FDP/fdp) and soluble fibrin complexes (SFC) have proved useful in the diagnosis of thromboembolic disorders in several clinical series (4–9). However, these determinations have not been evaluated systematically in many of the illnesses that can mimic thromboembolism. The present study was designed to assess the usefulness of FDP/fdp and SFC in differentiating pulmonary embolism from nonthromboembolic lung diseases.

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Materials and Methods

Fibrinogen/fibrin degradation products and soluble fibrin complexes. A single blood sample was obtained from each subject. Measurement of FDP/fdp was done by a tanned red cell hemagglutination inhibition immunoassay (7); serum was obtained from 2 ml of blood drawn in Vacutainer tubes (Becton Dickinson Co., Rutherford, N. J.) containing 20 NIH units of thrombin and 3,670 NF units of soybean trypsin inhibitor. Because of the antithrombin effect

of heparin, the blood was further clotted by the addition of 1.7 mg of Reptilase® (Abbott Laboratories, South Pasadena, Calif.) with incubation for 2 hours at 37° C; these modifications have previously been found to be necessary to avoid factitious elevations of FDP/fdp (10). Measurement of SFC was done by the serial dilution protamine sulfate test of Gurewich and Hutchinson (5), using a grading system to semiquantify results as described previously (11). Plasma samples were obtained from 4.5 ml of blood drawn into siliconized Vacutainer tubes containing 0.5 ml of sodium citrate (3.8 per cent) and 1,000 units of aprotinin (Trasylol®, FBA Pharmaceutical Inc., New York, N. Y.). The tubes were placed immediately on ice and samples were centrifuged promptly at 1,500 × *g* in a refrigerated centrifuge at 4° C. Normal values were considered to be less than 10 μg per ml for FDP/fdp and less than a grade of 10 for SFC.

Patients without thromboembolism. Patients admitted to Parkland Memorial Hospital with pneumonia, lung cancer, tuberculosis, asthma, and chronic obstructive pulmonary disease were studied because these conditions are commonly confused with pulmonary embolism. Also included in this category were patients with a variety of miscellaneous pulmonary disorders (pulmonary fibrosis, bronchiolitis obliterans, bronchiectasis, residua of previous tuberculosis, empyema, pneumothorax, and atelectasis). Blood samples were obtained from 80 patients at the time of admission to the hospital, before institution of therapy. Although in these cases it was not feasible to perform lung scanning or pulmonary angiography routinely to rule out pulmonary embolism, careful clinical evaluation was performed in each, and no patient was included in this category with any clinical suspicion of thromboembolic disease. All patients were followed and re-evaluated throughout their hospital course to confirm the diagnosis, and 10 months after discharge the records of all patients were again reviewed to determine if thromboembolic events had occurred in the interim. Four patients had clinical or autopsy evidence of thromboembolism demonstrated within 4 weeks of measurement of FDP/fdp and SFC; another patient developed thrombophlebitis 6 months later.

A separate group of 28 patients, originally believed to have pulmonary embolism by clinical criteria but subsequently found to have negative pulmonary angiograms, were tested at the time of their initial evaluation. These patients subsequently proved to have a variety of diagnoses, including chronic obstructive pulmonary disease (4 patients), pneumonia (4 patients), viral pleurodynia (3 patients), psychoneurosis (4 patients), congestive heart failure (3 patients), tuberculosis (2 patients), cancer, primary pulmonary hypertension, pulmonary fibrosis, and pancreatitis (1 patient each); the etiology of symptoms was never definitively established in 4 patients.

Patients with pulmonary embolism. Measurement of FDP/fdp and SFC was performed in 29 patients with pulmonary embolism. In each patient, the diagnosis was suggested by compatible clinical and radiographic findings and subsequently established in 12 patients by a "high probability" lung scan (12) and in 17 patients by a pulmonary angiogram showing cut-offs or filling defects (13). Blood samples for FDP/fdp and SFC were obtained as part of the initial evaluation before heparin therapy was begun. Each patient was followed closely throughout his or her hospital stay to ensure that all features of the illness were compatible with pulmonary embolism. Twelve of these patients had concomitant deep venous thrombosis (10 confirmed by positive venograms); the remaining 17 had no clinical evidence of venous disease (8 confirmed by negative venograms).

Normal subjects. Measurement of FDP/fdp and SFC was performed in 24 normal subjects selected from hospital personnel. None had symptoms suggesting pulmonary or cardiovascular disease. None was taking oral contraceptive hormones at the time these determinations were made.

Statistical analysis. Data were analyzed by the chi square test with Yates' correction, the Fisher exact test, or "Student's" t test for unpaired data (14). $P < 0.01$ was considered significant when multiple comparisons were made.

Results

The frequency with which each test showed increased values (i.e., positive results) or normal values (negative results) is shown in table 1. Normal subjects rarely had positive tests, whereas patients with pulmonary embolism had significantly higher positivity rates for both FDP/fdp ($P < 0.001$) and SFC ($P < 0.005$). Patients with nonthromboembolic pulmonary diseases, when compared as a group to those with pulmonary embolism, had significantly lower rates of positive FDP/fdp ($P < 0.005$) and positive SFC ($P < 0.001$). An interesting trend was apparent in the group with nonthromboembolic conditions; i.e., in general, those disorders associated with high rates of positivity for one test were associated with low rates for the other test, and one or the other test was significantly different from those in patients with pulmonary embolism in most instances ($P < 0.01$). Patients who were suspected of having pulmonary embolism but who had negative pulmonary angiograms also had lower rates of positivity for FDP/fdp and SFC when compared to patients with positive angiograms, but the differences were significant only with FDP/fdp ($P < 0.001$).

Combined rates of positivity and negativity

TABLE 1

FREQUENCY OF POSITIVE AND NEGATIVE RESULTS FOR FIBRINOGEN/FIBRIN DEGRADATION PRODUCTS (FDP/fdp) AND SOLUBLE FIBRIN COMPLEXES (SFC)

Category	No. of Patients	FDP/fdp Positive		SFC Positive		Both Positive		Both Negative	
		(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)
Pulmonary embolism	29	24	83	21	72	16	55	1	3
Normal	24	1	4*	4	17*	0	0*	19	79*
Nonthromboembolic pulmonary disease	80	40	50*	16	20*	3	4*	28	35*
Cancer	6	5	83	0	0*	0	0*	1	17
Pneumonia	20	15	75	1	5*	0	0*	5	25
Chronic obstructive pulmonary disease	13	7	54	2	15*	1	8*	5	38*
Tuberculosis	7	3	43	1	14	0	0	3	43
Asthma	13	2	15*	6	46	1	8	6	46*
Miscellaneous	21	8	38*	6	29*	1	5*	8	33*
Negative angiograms†	28	5	18*	10	36	2	7*	15	54*

*Significant compared to pulmonary embolism ($P < 0.01$).
†Patients who were suspected of having pulmonary embolism but had negative pulmonary angiograms.

for both measurements are also shown in table 1. Patients with pulmonary embolism had positive results for both tests more frequently than did patients with nonthromboembolic lung diseases ($P < 0.001$), normal subjects ($P < 0.001$), or patients with negative pulmonary angiograms ($P < 0.001$). Negative results for both tests were associated significantly less often with pulmonary embolism than with nonthromboembolic diseases ($P < 0.005$), normal subjects ($P < 0.001$), or patients with negative angiograms ($P < 0.001$). No patients with nonthromboembolic disease and negative results for both tests had clinical or autopsy evidence of thromboembolism within 10 months.

Mean values for both tests in all groups studied are compared in table 2. As a group, patients with nonthromboembolic lung diseases had significantly lower mean concentrations of FDP/fdp ($P < 0.005$) and SFC ($P < 0.001$) than did patients with pulmonary embolism. Patients with negative pulmonary angiograms also had significantly lower values for FDP/fdp ($P < 0.01$) and SFC ($P < 0.005$) when compared as a group to patients with pulmonary embolism.

Discussion

Many of the clinical features used in the differential diagnosis of pulmonary embolism have been shown to have poor discriminative value (7, 15, 16). Even the most reliable diagnostic procedures, radioactive lung scanning and pulmonary angiography, can be misleading (12, 17, 18). Therefore, substantial benefit might derive from any additional means of separating pulmonary embolism from other pulmonary diseases with which embolic disease is frequently confused. It has been suggested that the measurement of FDP/fdp and SFC could assist in making this distinction because these tests have repeatedly been shown to be elevated in patients with venous thromboembolism (1, 3, 5, 6, 19). However, no study has reported results of these determinations in a large number of patients with nonthromboembolic lung diseases. Thus, their value in differentiating pulmonary embolism from other lung diseases is uncertain.

It is well established that products of coagulation and fibrinolysis may circulate in the blood of patients with a number of neoplastic, hematologic, and infectious diseases (2, 7), so that elevated concentrations of FDP/fdp or SFC would be expected in many diverse pulmonary disorders. The present study was designed to

TABLE 2

MEAN ± SEM VALUES FOR FIBRINOGEN/FIBRIN DEGRADATION PRODUCTS (FDP/fdp) AND SOLUBLE FIBRIN COMPLEXES (SFC)

Category	FDP/fdp *(μg/ml)*	SFC *(grade of/reaction)*
Pulmonary embolism	23.2 ± 6.8	10.0 ± 0.8
Normal	1.2 ± 0.5*	5.3 ± 0.7*
Nonthromboembolic pulmonary disease	5.9 ± 1.2*	3.5 ± 0.6*
Cancer	15.9 ± 3.0	2.0 ± 0.8*
Pneumonia	9.7 ± 4.2	1.9 ± 0.8*
Chronic obstructive pulmonary disease	3.5 ± 1.3	3.5 ± 1.4*
Tuberculosis	5.1 ± 1.8	2.4 ± 1.8*
Asthma	2.5 ± 1.2	7.4 ± 2.0
Miscellaneous	4.5 ± 1.3	4.0 ± 1.3*
Negative angiograms†	5.2 ± 0.8*	7.1 ± 0.8*

*Significant compared to pulmonary embolism ($P < 0.01$).

†Patients who were suspected of having pulmonary embolism but had negative pulmonary angiograms.

measure these products in conditions that share features with pulmonary embolism (dyspnea and cor pulmonale in chronic obstructive pulmonary disease, hemoptysis in cancer and tuberculosis, dyspnea with wheezing in asthma, pleural effusion in tuberculosis, and roentgenographic infiltrates with chest pain in pneumonia) as well as a group of miscellaneous pulmonary diseases. Normal control subjects and patients suspected of having thromboembolism, but with negative pulmonary angiograms, were included for comparison. The conditions studied were all associated with some degree of elevation in FDP/fdp or SFC (table 1). As a group, patients with nonthromboembolic lung diseases had a relatively low incidence of positivity for either test, but patients with some conditions had a frequency of individual positive results approaching that seen in pulmonary embolism. A substantial proportion of patients in whom pulmonary embolism was ruled out by angiograms also had positive tests; therefore, a single test in an individual patient was not very informative.

The greatest discrimination was afforded by a combination of both tests. Normal subjects, although manifesting a small incidence of positive results for one or the other test, did not have concurrent elevations of FDP/fdp and SFC. Patients with lung diseases other than thromboembolism and those suspected of having thromboembolism but who had negative angiograms were similar in that both tests were rarely positive in these groups. On the other hand, pulmonary embolism was associated with abnormalities of both tests in more than one half of the cases (table 1). Additionally, both tests were negative in the majority of normal subjects, in more than one third of patients with other types of pulmonary disease, and in more than one half of those with negative angiograms, but this finding was extremely uncommon in thromboembolism.

The basis for elevation of one test but not the other in nonthromboembolic disorders is not clear; it is especially curious that the data in table 1 suggest an inverse relationship between positivity rates for both tests. This finding may indicate a more limited activation of the coagulation and fibrinolytic systems in these disorders than in pulmonary embolism, because there is evidence that FDP/fdp and SFC derive from different stages of fibrin metabolism (7, 8, 11). SFC are measured in plasma samples and represent complexes of either fibrin monomer, resulting from the recent action of thrombin on fibrinogen, or early fibrin degradation products (fragment X^0), resulting from the action of plasmin. FDP/fdp are measured in serum samples that likely have most early fibrin degradation products removed by clotting and, thus, primarily reflect later products of fibrin breakdown. Nonthromboembolic lung diseases, in the absence of overt thrombosis, cause elevation of early (SFC) or late (FDP/fdp) markers, but not the entire sequence. In acute thromboembolism, fresh thrombi may be formed at the source while emboli are undergoing lysis in the lungs, giving a greater chance for simultaneous elevations of both measurements.

Quantitative differences in these determinations also existed between patients with pulmonary embolism and all other groups studied (table 2). In general, higher concentrations of both

tests occurred in association with pulmonary embolism when compared to normal subjects, patients with nonthromboembolic conditions, and the group with negative pulmonary angiograms. However, the differences were not great, and it appears that the absolute value of either test would be less meaningful in the individual patient than would combined positivity rates.

We concluded that the measurement of only one of these tests of fibrin metabolism is not helpful in distinguishing pulmonary embolism from other lung disease in an individual patient. However, a combination of tests may give more valuable information. If both determinations are positive there is a high likelihood of pulmonary embolism. If both tests are negative, the diagnosis of thromboembolic disease is highly unlikely. When one test is positive and one is negative, interpretation depends on correlation with the findings in table 1; e.g., if pneumonia is the most likely alternative diagnosis, a positive test for FDP/fdp and a negative test for SFC would support the diagnosis of pneumonia, but the reverse would weigh against it. Thus, use of these tests in combination affords more valuable diagnostic assistance than either test alone in differentiating pulmonary embolism from other types of lung disease and may provide an important adjunct to other clinical determinations.

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