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Laboratory Diagnosis of Pulmonary Thromboembolism

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Abstract

Twenty five patients with clinically suspected pulmonary embolism were studied by ventilation-perfusion lung scan (V/Q). Twenty patients showed positive scan (low, indeterminant and high probability) and 5 patients had negative scan. ß-mode ultrasound with doppler showed evidence of deep venous thrombosis in 50% of cases. Laboratory findings showed a raised plasma cross linked fibrin degradation products (FDP's) above 500 ng/ml in 85.7% of cases with high probability positive lung scan and an elevated serum levels of C-reactive protein (CRP) above 50 mg/L in 85.7% of high probability scan. A normal level of serum CRP and/or plasma cross linked FDP's in blood taken within 4 days of onset of symptoms virtually excluded the diagnosis of pulmonary embolism. Other positive laboratory data in cases of pulmonary embolism diagnosed by lung scan were disturbed arterial blood gases in 90% of cases, raised serum lactate dehydrogenase enzyme above 300 IU/L in 57.2%, aspartate transaminase enzyme above 40 IU/L in 28.6% of cases and low platelet count below 100.000/Cmm in 25% of cases.

Introduction

THE clinical diagnosis of pulmonary embolism is incorrect in 50% of patients on further investigation or at post mortem [1]; conversely, pulmonary embolism is often undiagnosed, despite being the cause of 8 to 21% of hospital deaths [2], this mortality rate falls well if patients are treated with anticoagulants or thrombolysis.

At autopsy, most patients with pulmonary embolism had evidence of previous emboli [3] and in retrospect nearly 50% have had symptoms of herald emboli.

Pulmonary angiography is the most accurate method of diagnosis of plumonary embolism, but is an invasive procedure. Ventilation-perfusion (V/Q) scanning is much more frequently done, but less accurate because of more non-diagnostic results (indeterminate) [4]. Unfortunately, it may not be possible to perform scanning at the proper time and it is not universally available.

Lung scanning has to be performed as soon as possible after the onset of clinical

symptoms to increase diagnostic value [4].

It would be valuable if one or more laboratory tests could be shown to be of value in establishing or excluding the condition.

The aim of the present study was to assess clinical and laboratory findings in a group of patients with suspected pulmonary embolism, diagnosed by V/Q lung scan.

Material and Methods

Twenty five patients (mean age 58.5±15.4 male and 10 females) admitted to intensive care unit because of clinically suspected pulmonary embolism were included in this study.

Patients, included in this study, bad acute onset of symptoms. Lung scan was performed and blood samples taken for specific assays, within 3 days of the onset of symptoms and before anti-coagulant therapy.

Electrocardiogram and plain X-ray chest were performed for all cases.

I- Lung scanning:

All patients without the clinical history of chronic lung disease and a normal chest X-ray were initially investigated by perfusion scan only. In patients with clinical history of chronic lung disease or abnormal chest X-ray, a ventilation/perfusion lung scan was performed initially. In those patients with combined ventilation/perfusion lung scan, the ventilation scan was performed before perfusion scan after inhalation of Xe^{133}. Static images were obtained with gamma camera in six projections (anterior, posterior, left lateral, right lateral, left and right posterior oblique). Perfusion lung scan was performed after I.V. injection of (2.70 mCi) technetium -99m. Labelled macroaggregated albumin. Static images were performed in six projections [5].

Classification of lung scan was done according to the study of Biello et al. which has been modified [6].

High probability scan: two segmental or multiple subsegmental regions of ventilation perfusion mismatch.

Low probability scan: Small (<25% of a segment) defects or only matching ventilation/perfusion defects with normal X-ray chest. Indeterminate; one subsegment or segment of V/Q mismatch or multiple subsegmental defects of V/Q mismatch or perfusion abnormality matching radiological change. No patients underwent pulmonary angiography.

II- Real time B-mode venous ultrasound imaging, combined with Doppler on both lower limbs was performed for all patients.

Duplex examination of the deep venous system was done with Helwett Packard Sonos 1000 colored coded system using 7.5 Mz linear transducer. The courses of the deep veins of both legs were scanned first by B mode from the posterior tibial veins to the inferior vena cava. Compressibility of the vein lumen was assessed by applying light transducer pressure while scanning. Absence of compressibility is interpreted as a sign of recent thrombosis. Other points were also noted, the patency of the lumen, the presence of intraluminal echoes and the change in the diameter of the vein by respiration and valsalva maneuver. When a thrombus was proved to be present, its echo characteristics were thoroughly looked for to differentiate acute from chronic thrombosis.

Colored coded Doppler is then turned

on and the spontaneous flow of the color map was noted as a measure of patency of the vein. A sample Doppler was then taken to confirm the patency of the vein.

Absence of spontaneous phasic variation with respiration of the color flow map or the Doppler sample was taken as criteria of obstruction of the vein.

III- Laboratory investigations:

1- Blood picture including neutrophil and platelet counts on counter.

2- Arterial blood gases done on ABL 30 automated blood gas analyzer.

3- Serum total bilirubin by calorimetric method, serum aspartate aminotransferase enzyme (AST) done by an optimized calorimetric method [7], serum creatine kinase (CK) [8] and lactate dehydrogenase (LDH) enzyme [0].

4- Estimation of serum C-reactive protein (CRP) by radial immunodiffusion method [10].

5- Estimation of plasma cross-linked fibrin degradation products (FDP's) D-dimers by dimer test agglutination latex assay (commercial latex Agen kit). Samples of plasma were separated within 2hs of collection and stored at-18 °C. The normal result is O and according to the instructions of the manufacturer, a positive agglutination is seen with plasma containing more than 500 ng/ml D-dimer [11].

Results

Clinical:

Of the 25 scans, 5 were considered to be normal, 5 low, 8 intermediate and 7 a high probability scan of pulmonary embolism.

The median age of patients with positive scans was 59 years. The most common symptoms in our patients with pulmonary embolism were dyspnea (75%), acute chest pain (60%), and pleuritic chest pain. Cough and hemoptysis occurred much less often. The most common physical findings were sinus tachycardia above 100 beats/min. (80%), tachypnea (respiratory rate above 25/min) 75% and pulmonary rates (60%). Right ventricular gallop rhythm, accentuated pulmonary sound and a murmur of tricuspid insufficiency occur less often.

Hypotension, syncope with congested neck veins were other clinical findings. A variety of less common and non-specific clinical features including the following: confusion, chest wheezing, unexplained arrhythmias, pyrexia and right sided heart failure. Leg pain with edema, tenderness discoloration occurred in 25% of cases.

X-ray:

Plain X-ray chest showed pulmonary infiltrate in 75% and unilateral pleural effusion is found in 30% of cases.

Other radiological findings are elevation of the hemidiaphragm and areas of plate-like atelectasis. Normal chest X-ray occurred in 4 cases (25%).

E.C.G.:

The electrocardiogram showed in most cases sinus tachycardia and non-specific changes.

Classic findings of right axis shift and S_1, Q_1T_3 pattern were uncommon occurring only in 2 cases (10%).

Duplex:

Recent-deep venous thrombosis involving the popliteal vein on one side was detected by Duplex in 10 cases (50%) of pos-

itive lung scan. In three cases the process extended to the common femoral vein and in one case extension to common iliac vein was detected.

Table (1) shows the clinical data of the 20 patients with suspected pulmonary embolism. The hematological and biochemical features of the 25 cases studied are presented in table (2).

All patients with high probability lung scans had raised serum levels of C.R.P. (> 10 mg/L) and more than 85% of them had positive plasma cross linked FDP's (levels above 500 ng/ml).

Discriminant analysis, form of multivariant analysis, identified 10 items that were significant, independent diagnostic predictors of pulmonary embolism (Table 3). 4 of these variables were clinical items, 3 were radiological items and 3 were laboratory items.

A decision rule was created by rounding the discriminant function coefficients for the 10 variables. A patients decision rule score was calculated by summing the individual scores of all findings that were present.

The higher the score, the more likely the patient was to have a positive diagnosis of pulmonary embolism.

Table (1): Clinical Data in 20 Patients with Suspected Pulmonary Embolism.

Finding	No. of cases
Pleuritic chest pain	10 (50%)
Acute chest pain	12 (60%)
Dyspnea	15 (75%)
New hemoptysis	5 (25%)
Leg pain	5 (25%)
Bed rest / inactivity	6 (30%)
Congestive heart failure (chronic) (in-patient diagnosis)	5 (25%)
Chronic obstructive lung disease (in-patient diagnosis)	4 (20%)
Malignancy	2 (10%)
Recent surgery (< 4 weeks)	2 (10%)
Past-history of DVT	3 (15%)
Sinus tachycardia (> 100 /min)	16 (80%)
Tachypnea (> 25 /min)	15 (75%)
Focal rales	12 (60%)
Increased second pulmonary sound	3 (15%)
Audible right ventricle gallop	4 (20%)
Leg tenderness and swelling	5 (25%)
ECG changes	15 (75%)
infiltration on X-ray chest	15 (75%)
Effusion on X-ray chest	6 (30%)
Raised hemidiaphragm on X -ray	1 (5%)
PO_2 < 80 mmHg	18 (90%)
PCO_2 < 35 mmHg	18 (90%)

Table (2): Laboratory Data in the 25 Patients Studied (Mean ± S.D.)

Lung scan	Normal (5 cases)	Low probability (5 cases)	Indeterminate (6 cases)	High probability (7 cases)	Anova+ x^2
Neutrophil Count/Cmm	5.7 ± 206	5.8 ± 2.8	8.2 ± 4.3	10.000 ±4.9	< 0.001
		1 (20%)	2 (25%)	4 (57.1%)	< 0.001
Serum CRP:					
> 10 mg/L.*	2 (40%)	2 (40%)	7 (87.1%)	7 (100%)	< 0.001
> 50 mg / L.	-	1 (20%)	6 (75%)	6 (85.7%)	< 0.001
FDP's		1 case	2 cases	6 cases	< 0.001
(Positive cases > 500 ng/ml)	-	(20%)	(25%)	(85.7%)	
PO_2 mmg < 80	2 (20%)	4 (80%)	7 (87.1%)	7 (100%)	< 0.001
PCO_2 < 35	1 (20%)	4 (80%)	7 (87.1%)	7 (100%)	
Platelets count X $10^{(6)}$ /cmm	290 ± 137	261 ± 105	.256 ± 108	239 ± 117	< 0.001
Serum bilirubin	0.8 mg%	0.9 mg%	0.9 mg%	1.2 mg%	N.S.
Serum LDH (IU/L)	225 ± 73	226 ± 75	310 ± 127	380 ± 152	< 0.001
above 300 mg%8	-	-	2 (25%)	4 (57.2%)	
Serum AST (IU/L)	24.6 ± 14.6	25.7 ± 15	34.6 ± 25.1	33.9 ± 22.8	N.S.
above 40 IU/L*		-	-	2 (28.6%)	
Serum CK IU/L	66.5 ± 42.6	61.5 ± 51	55.3 ±41.1	68.1 ± 42	N.S.

+ Analysis of variance
* Upper limit of normal laboratory range.

Table (3): Decision Rule for Diagnosis of Pulmonary Embolism.

Finding	No. of cases
Substernal chest pain	+ 3
Dyspnea	+ 4
Sinus tachycardia	+ 4
Tachypnea	+ 3
Infiltrate and or/effusion on X-ray	+ 3
Hypoxia	+ 4
Positive duplex on veins of lower limbs	+ 2
Positive C-reactive protein	+ 5
Positive latex dimer test	+ 3
Positive lung scan	+ 5

Discussion

The clinical diagnosis of pulmonary embolism represents a well-known diagnostic problem. None of the clinical features are pathognomonic for this disease and routine laboratory tests fail in differentiating it from other disorders [12].

To avoid an unnecessary and potentially dangerous treatment a high diagnostic accuracy is needed. Yet the gold standard of diagnosis, pulmonary angiography, is invasive and associated with a total morbidity of less than 5% [13].

Perfusion lung scanning is the key diagnostic test for patients with suspected

pulmonary embolism. Lung scan has to be performed as soon as possible after the onset of clinical symptoms of pulmonary embolism to increase diagnostic accuracy. A normal perfusion lung scan excludes pulmonary embolism [14]. An abnormal scan is, however, non-specific and may occur in conditions that produce either increased radiographic density (e.g. pneumonia), or a regional reduction in ventilation (e.g. bronchitis, which frequently is associated with normal radiography).

Ventilation imaging was introduced to improve the specificity of an abnormal perfusion scan.

Perfusion defects which ventilate normally (V/Q mismatch) are due to pulmonary embolism, whereas matching V/Q abnormalities are due to other conditions. This was shown to be incorrect in recent clinical studies [15].

Ventilation lung scanning is only helpful if the perfusion defect is large (segmental 3-4 cm in diameter or greater) and associated with ventilation mismatch, such patients have a high probability (≥ 86%) of pulmonary embolism by pulmonary angiography [16].

Other abnormal findings on lung scans, such as matching ventilation-perfusion defects (either segmental or subsegmental), subsegmental defects with ventilation mismatch, or perfusion defects which correspond to an area of increased density on the chest X-ray, are associated with a 20-40% frequency of pulmonary embolism [16].

The perfusion lung scan always has to be interpreted with chest radiography, since almost any process causing a radiographic infiltrate results in a compensatory decrease in local perfusion.

A totally normal chest radiography is found in 10% of patients with pulmonary embolism. Up to 75% of patients with pulmonary embolism have pulmonary infiltrate and 45% have pleural effusion [15].

Deep venous thrombosis (DVT) of the legs could be detected in this study by duplex in 10 out of 20 cases (50%) with pulmonary embolism diagnosed by scan. Venography shows DVT in bout 70% of patients with pulmonary embolism diagnosed by pulmonary angiography [17]. Many of these patients have no symptoms or signs of D.V.T. at presentation. Proximal D.V.T. is revealed by impedance plethysmography in 10-25% of patients with abnormal but non-high probability lung scans [18]. This has important implications for management; untreated proximal D.V.T. is associated with a high risk (20-50%) of recurrent thromboembolism [19].

Patients with abnormal, non-high probability lung scans and a negative test for D.V.T (plethysmography or B-mode ultrasound) require pulmonary angiography to diagnose pulmonary embolism [20]. If unavailable, serial testing for D.V.T. is an alternative, based on the concept that clinically important recurrent pulmonary embolism is unlikely (< 1%) in absence of DVT [19].

A simple, non-invasive blood test for the diagnosis of pulmonary embolism has long been sought. Measurements of markers of thrombosis, such as fibrinopeptide A and B-thomboglobulin and of fibrinolysis, such as fibrin (ogen) degradation products [12], was considered but they lack specificity and sensitivity. With monoclonal antibody technology, a new generation of assays for fibrin degradation products is now available [22].

The D-dimer (DD) is a derivative of fi-

brin network after being stabilized and cross-linked by factor XIIIa, to make fibrin network. It measures the activity of plasmin on crosslinked fibrin, the major fibrin found in vivo thrombi.

The assays are performed in plasma, eliminating the artefact seen in results obtained from serum [22].

As well as indicating fibrinolysis, increased levels of cross linked FDP's are an indirect marker of intravascular thrombosis. Raised levels occur in all patients with clinical or occult DVT confirmed by venography [23], or myocardial infarction at presentation [24]. The test is retatively simple taking only a few minutes to perform. In our study 85.7% of patients with high probability lung scan had a positive latex test indicating a plasma level of D-dimer above 500 ng/ml and it was only positive in 20% of these with low probability scan, indicating a high specificity of the test.

Bounameaux et al. [25] found plasma cross-linked FDP to be uniformly above 500 ng/ml in patients with pulmonary thromboembolism and concluded that a level of plasma D-dimer concentration below 500 ng/ml allows exclusion of the diagnosis of pulmonary embolism.

Vaughn et al. [26] found a mean level of cross-linked FDP's by ELISA assay of 2000 ng/ml in 24 patients with positive pulmonary angiogram.

Although an embolism is an obvious source of FDP's in plasma, disseminated intravascular clotting is a frequent complication of pulmonary embolism [27].

Baunameaux et al. [25] proposed that liberation of thrombin from the embolus as it disintegrates in pulmonary vascular bed activates the coagulation system.

The rise in cross-linked FDP's after pulmonary embolism is early and short lived [28].

Concentrations of cross linked FDP's above 500 ng/ml were found in 45% of our patients with low and intermediate probability scans. Lung scans of low probability may be insufficient in excluding pulmonary embolism, as 10% of these cases had been subsequently diagnosed as pulmonary embolism by angiography [12]. Seventy one percent of pulmonary scans in one series were in the categories of low or indeterminate probability. Measurement of cross-linked FDP's in this setting is useful in diagnosis or exclusion of pulmonary embolism [25].

The mean platelet count in the 20 patients with high probability lung scan is significantly lower compared to patients with normal lung scan (290 ± 137 versus 239 ± 117, $p < 0.01$).

Five patients with positive lung scan in our study had obvious thrombocytopenia with a platelet count below 100,000/Cmm. Mustafa et al. [29] described cases of pulmonary embolism presented with thrombocytopenia and high FDP's. The authors concluded, that in the case of DVT, or high-risk patients, the coexistence of thrombocytopenia with elevated FDP's should alert the clinician to the possibility of occult pulmonary embolism.

Monreal et al. [30] showed that the platelet count decreased by 20% of the baseline level with the onset of pulmonary embolism and they concluded that a lung scan should be performed only when the platelet count is lower than the baseline value.

A similar fall in platelet count has been found in patients with ischemic cerebral in-

farction and acute myocardial infarction [31].

A raised white cell count due to neutrophilia has been previously reported in patients with pulmonary embolism. Further evidence of an acute-phase response in pulmonary thromboembolism was provided by raised levels of serum C-reactive protein.

C-reactive protein is a sensitive and reliable acute phase protein whose concentration can now be estimated rapidly. The defined upper limit of the normal concentration is < 10 mg/L [19]. Its concentration in plasma increases within 6-8 h. after an inflammatory stimulus, peaking at around 48 hr. Serum C-reactive protein proved very sensitive in that all patients with high probability lung scan had a level of > 10 mg/L, but of low specificity, the latter being improved at a higher concentration of > 50 mg/L.

Our results suggest that a normal C-reactive protein in blood taken within 3 days of the onset of symptoms virtually excludes the diagnosis of pulmonary embolism. Conversely, a markedly raised C-reactive protein level is compatible with a diagnosis of pulmonary embolism and does not necessarily indicate an acute inflammatory condition such as pneumonia [32].

In our study, about 90% of patients with suspected pulmonary embolism have a PaO_2 on room air of less than 80 mmHg. Because of the frequent association of hyperventilation, the Pa Co_2 is lowered. The sensitivity of a low PaO_2 in diagnosing pulmonary embolism is high in many earlier studies [28], however the specificities of both the Po_2 and PCo_2 were low, reducing their usefulness in diagnosis.

Of the biochemical assays, the serum LDH showed the best diagnostic test for pulmonary embolism, a significantly raised proportion of patients (57.2%) with high probability lung scan group had a raised level, this was more than found in the UPET study (41%) [33].

An abnormal serum aspartate transaminase level was found in 28.6% of our patients with high probability lung scans as in the UPET study (27%) [33]. Wackers triad, (raised serum LDH and bilirubin with normal serum A.S.T.) was present in only 3 patients with high and indeterminate lung scan groups.

From the present study in the evaluation of laboratory indices in a group of patients with suspected pulmonary embolism based on lung scanning, we concluded that the most promising assays studied were that of plasma cross-linked FDP's and C-reactive protein concentration. Both represent highly sensitive screening tests which are simple and quick to perform. Normal results of both in our study exclude pulmonary embolism. A delay of tests of up to 3 days from the onset of symptoms was acceptable because the lung scan changes of pulmonary embolism have been shown to persist for this period of time [28].

B-mode ultrasound combined with Doppler is a sensitive and specific method for diagnosing proximal vein thrombosis [2] and should be done in every case of suspected pulmonary embolism. Recent clinical trials [17] have shown that the majority of patients with pulmonary embolism has associated D.V.T. of the legs. Many of these patients do not have symptoms or signs of venous thrombosis at the time of presentation.

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