Egyptian Journal of Bronchology

Vol 2, No 2, December, 2008

ORIGINAL ARTICLE

PREDICTORS FOR PULMONARY EMBOLISM IN PATIENTS WITH ACUTE EXACERBATION OF COPD

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Background: *Diagnosis of pulmonary embolism (PE) is difficult in patients complaining of acute exacerbation of chronic obstructive pulmonary disease (AECOPD).*

Objective: *to detect the numerical predictors in clinical, gasometric and laboratory findings for PE in patients with AECOPD. Will be used cut – off point of the different factors to reach a definite clue for this diagnostic dilemma.*

Patients and Methods: *Ninety patients with acute exacerbation of COPD who were admitted to Chest department or Respiratory Intensive Care Unit in Assiut University Hospitals. They were 66 males and 24 females with the mean age (61.9 years). All of them underwent the following clinical examination chest X-ray CBC, ABG, ECG; echocardiography, Duppler US of the lower limbs to diagnose DVT. Spiral CT, pulmonary angiography was performed to all patients to confirm the diagnosis of PE. Indices of coagulation, fibrinolysis and platelet activity were performed to all patients.*

Results: *PE was present in 25 of 90 patients (27.8%) while DVT was diagnosed in 14 cases (15.6%). Ten patients (11.1%) have both DVT and PE. Spiral CT pulmonary angiography (SCTPA) was the diagnostic tool and the patients were divided into positive for PE 25 (27.8%) and negative [65 (72.2%)]. The Cut off points were used to give the definite diagnosis of PE among those critical patients with AECOPD as the following: Respiratory rate >35 cycles/min, heart rate > 120 beats. Hematocrite value > 56%, platelet count < 200.000/mm3, mean pulmonary artery pressure >60mmHg, P (A-a) O2 >25mmHg, D-dimer >1000ng/ml, thrombin >15µg/dL, B-Thromboglobulin > 80 IU/mL, P-selectin > 300ng/mL, duration of illness > 12 years, frequency of exacerbation > 5/year, no. of hospital admission > 4/year.*

Conclusion: *This study showed a 27.8% prevelance of PE in patients with COPD hospitalized for severe exacerbation. These clinical and laboratory cut-off points can facilitate the diagnosis by a high sensitivity yield with a highly significant importance (P<0.001 - <0.02).*

INTRODUCTION

The management of patients with suspected acute pulmonary embolism (PE) has greatly improved in recent years because of clinical probability of PE, ultrasonography, ventilation perfusion scanning and spiral pulmonary angiography (SCTPA) (Wells et al., 2001). However, clinical diagnosis of acute PE is difficult in patients with COPD. Pulmonary embolism resembles COPD exacerbation so closely that these 2 entities often impossible to distinguish clinically (Lesser et al., 1992). The reported incidence of PE in studies done postmortem of patients with COPD ranges from 28% to 51% (Baum and Fisher, 1960). In this study, risk factors, symptoms, and arterial blood gases values were similar in patients with and without PE. In addition, by Hartmman, et al., (2000), showed that the presence of COPD does not affect the diagnostic performance of D-dimer testing, CTPA for PE. The true frequency of PE in patients with COPD in whom PE is clinically suspected ranges from 19% to 29%, (Tillie-Leblond, et al., 2002). Thus, clinical detection of PE in these patients is particularly difficult.

Objectives: To detect different variables among basic clinical, radiological and laboratory investigations that predict for the presence of pulmonary embolism in patients presented with acute exacerbation of COPD in order to overcome this diagnostic problem especially when more sophisticated investigations is invaluable or hazards.

METHODS AND SUBJECTS

Ninety patients with acute exacerbation of COPD were included in this prospective study. They were 66 males and 24 females (mean 61± 0.94) the age ranged between 37- 82 years.

- COPD was suspected in patients with either history of symptoms or clinical signs suggestive of COPD or history of exposure to risk factors and was confirmed by spirometeric postbronchodilator FEV1/FVC < 70% (ATS/ERS, 2004 and GOLD, 2007).
- Acute exacerbation was diagnosed according to the following criteria:

A. Symptoms of AECOPD: major symptoms as increased breathlessness, increase in sputum purulence and/or volume and minor symptoms as increased chest wheezes, cough, sore throat and nasal congestion or discharge

B. Lung function tests: FEV1< 1 liter indicates a severe exacerbation.

C. Arterial blood gases: PaO2 < 60 mmHg and / or SaO2 < 90% with or without PaCO2 > 50 mmHg when breathing room air indicate respiratory failure and severe exacerbation (Bartter et al., 2003).

All the studied patients underwent the following:

- Full medical history and clinical examination
- Chest X-ray; posteroanterior and lateral views
- Venous blood sample to measure complete blood count (CBC) including WBCs, RBCs, hemoglobin concentration, hematocrit value and platelet count.
- Arterial blood sample for arterial blood gas analysis were obtained.
- ECG and Echocardiography to detect signs of PE as RV strain, and to measure mean pulmonary artery pressure
- Doppler US of the lower limbs to diagnose DVT
- Spiral CT pulmonary angiography was performed to all patients to confirm the presence of PE.
  - Indices of coagulation were assessed by measuring Thrombin antithrombin (TAT) level using Enzygnost TAT micro, which is a microtitration plates coated with rabbit antibodies against human thrombin (Normal values: 1-4 µg/l).
  - Indices of fibrinolysis was assessed by measuring plasma D-dimer level using

Zymutest D-dimer, which is complete ELIZA kit for the assay of human D-dimer (N: <500 ng/mL).

- Assessment of platelet activity by P-selectin (using sP-selectin ELIZA) (N: 110—260 ng/mL) and Beta-thromboglobulin (using Asserachrom B-thromboglobulin, which is Enzyme Immunossay for B-thromboglobulin (N < 50 IU/mL).

Table I. Characteristic data of patients included in the study.

	Range	Mean ± SE
- Age & Sex		
- Males (66, 73.3%) Age (years)	46 - 82	68 ± 1
- Females (24, 26.7%) Age (years)	37-69	54 ± 0.8
- Duration of illness (years)	2-18	8.1 ± 0.35
- Frequency of exacerbations / year	1-5	2.7 ± 0.08
- No. of hospital admission/ year	1-4	1.7 ± 0.01
- No. of ICU admission/year	0-3	0.5 ± 0.06

RESULTS

PE was present in 25 of 90 patients (27.8%) while DVT was diagnosed in 14 cases (15.6%). Ten patients (11.1%) have both DVT and PE (Table 1). Spiral CT pulmonary angiography (SCTPA) was the diagnostic tool in 21 (23.3%) cases, Doppler ultrasound (DUS) of the lower limbs was the diagnostic tool in 14 of 90 (15.6% of cases).

Table 1. Frequency of pulmonary embolism (PE) and DVT among patients with AECOPD.

Studied patients (n=90)	Present		Absent	
	No.	%	No.	%
Pulmonary embolism	25	27.8	65	72.2
Deep venous thrombosis	14	15.6	76	84.4
Combined (DVT & PE)	10	11.1	80	88.9

Characteristics of patients according to the Presence or absence of PE

The mean heart rate and respiratory rate were very highly significantly increased in patients with PE than in those without PE while the mean of temperature showed no statistically significant difference between both groups (Table 2).

Table 2. Mean heart rate (HR), respiratory rate (RR) and temperature in studied patients (n = 90).

	Total patients	PE present	PE absent	P-value
	Mean ± SE	M ±SD	M ±SD	
HR	99.5 ± 1.4	112 ± 2.4	94.7± 1.3	< 0 .001
RR	25.4 ± .5	31.3 ± .87	23 ± .44	< 0.001
Temperature	37.4 ± .3	37.48 ± .04	37.3 ± .05	0.38

Table 3 showed statistically significant difference between COPD patients with PE and those without PE as regard to duration of illness (years), frequency of exacerbation /year and number of previous ICU admissions.

Table 3. The effect of COPD as a risk factor for PE.

COPD illness	Present	Absent	P-value
	Mean ±SE	Mean ±SE	
Duration of illness (years)	9.8 ± 0.7	7.4 ± 0.35	0.01
Frequency of exacerbations / year	3.1± 0.1	2.6 ± 0.07	NS
No. of hospital admissions / year	2.1 ± 0.3	1.62 ± 0.02	NS
No. of previous ICU admissions	0.8 ± 0.2	0.37 ± 0.02	0.02

Table 4 showed statistically significant reduction in PaO^2, SaO^2 and P (A-a) O2mmHg with significant alkalosis in pH due to CO^2 wash.

Table 4. Means of blood gas values in patients with and in those without PE.

PE / ABG	Present (25)	Absent (65)	P-value
	M ±SE	M ±SE	
pH	7.43 ± 0.006	7.37 ± 0.005	< 0 .001
$PaCO^2$ mmHg	59.1 ± 1.38	61.54 ± 0.8	0.1
PaO^2 mmHg	43.8 ± 0.87	51.8 ± 0.8	< 0.001
SaO^2 %	76.4± 1	81.1 ± 0.8	0.002
P (A-a) O^2 mmHg	31.4 ± 1.34	15 ± 0.9	< 0.001

As regard to complete blood count, there was statistically significant increase in hematocrit value (49.2 ±1.3) and very highly significant reduction in the platelet count in COPD patients with PE (184.2 ± 8.2 versus 232.7± 6.3).

Table 5. Complete blood count (CBC) in the studied patients.

PE / ABG	Total patients	PE Present	PE Absent	P-value
	Mean ± SE	Mean ± SE	Mean ± SE	
WBCs $x10^3/mml^3$	11.1 ± .3	11.2 ± .53	11.06 ± .38	0.8
RBCs x106/mml^3	4.2 ± .1	4.5 ± .27	3.9 ± .23	0.4
Hgb g/dL	13.9 ± .62	14.6 ± .63	13.2 ± .61	0.3
Hct %	45.8 ± .6	49.2 ± 1.3	44.5 ± .64	0.001
Platelet $x10^3/mml^3$	219.3 ± 5.5	184.2 ± 8.2	232.7± 6.3	< 0 .001

The mean pulmonary artery pressure was very highly statistically significantly increased in patients with PE in comparison to those without PE and there was very highly significant increase in the frequency of PE (54.2 ± 1.05 versus 42.5 ± 0.9).

Table 6. Mean pulmonary artery pressure (MPAP) in studied patients.

Mean pulmonary artery pressure	Total patients	Patients with PE	Patients without PE	P-value
	M ± SE	M ± SE	M ± SE	
	45.9 ± 0.9	54.2 ± 1.05	42.5 ± 0.9	< 0.001

Table 7 showed statistically very highly significant increase in the level of plasma D-dimer, thrombin antithrombin (TAT), p-selectin and ß-thromboglobulin (ß -TG) in patients with AECOPD with PE than in those without PE.

Table 7. Coagulation profile in AECOPD patients with and in those without VTE.

VTE / Coagulation profile	Total patients	Present	Absent	P-value
	Mean ± SE	Mean ± SE	Mean ± SE	
D- dimer (< 500 ng/mL)	539 ± 30	810 ± 38	436 ± 31	< 0 .001
Thrombin-antithormbin (1-4 µg/l)	11.5 ± 1	22.3 ± 2.3	7.4 ± 0.6	< 0.001
Betathromboglobulin (β-TG) (< 50 IU/mL)	56 ± 2.9	67 ± 6.3	51 ± 3.1	0.02
P-Selectin (110-260 ng/mL)	205 ± 9.8	277 ± 21	177 ± 8.6	< 0.001

Table 8 Show significant frequency of PE among patients with AECOPD reach to 100% with the application of these cut of points of different variables as regards the clinical examination, CPC values, echocardiographic examination, arterial blood gases analysis, the effect of chronic obstructive pulmonary disease duration as a risk factor and finally the laboratory indices with specific numerical values.

Table 8. Bivariate analysis of the cut-off points of different variables associated with significant increase in the frequency of PE.

Variable	Sign.
Respiratory rate > 35 cycle / minute	< 0.001
Heart rate > 120 beats / minutes	< 0.001
Hematocrit value > 56%	< 0.001
Platelet count < 200,000/mm3	< 0.001
Mean pulmonary artery pressure > 60 mmHg	< 0.001
P (A-a) O2 > 25 mmHg	< 0.001
D-dimer > 1000 ng/mL	< 0.001
Thrombin-antithrombin > 15 µg/l	< 0.001
B-Thromboglobulin > 80 IU/mL	0.02
P-selectin > 300 ng/mL	0.005
Duration of illness > 12 years	0.02
Frequency of exacerbations > 5/year	0.003

DISCUSSION

COPD is considered a risk factor for PE, and PE may occur as a serious complication of COPD. In many cases PE is part of the differential diagnosis of an acute exacerbation of COPD. However, differentiating a PE from an exacerbation of COPD is difficult, since the clinical signs and symptoms of these two conditions overlap to a considerable extent and the investigation of PE is often ignored in those patients (Hartmann et al., 2000). Moreover, the radiological and blood gas studies; in most cases do not permit differentiation between PE and exacerbation of the underlying respiratory disease. Therefore the true prevalence of PE in this situation is unknown (Tillie-Leblond et al., 2002 and Perreir et al., 2004).

In our study, out of 90 patients with AECOPD, 25 (27.8%) had PE. We discuss there the clinical, laboratory and radiological variables associated with increased risk of PE. Tachypnea and tachycardia were present in a significantly higher percentage in COPD patients with PE in comparison to those without PE (96% versus 55% and 92% versus 47%, respectively) ($p < 0.001$). The mean heart rate was 112 ± 2.4 beats/ minute in COPD patients with PE versus 94.7± 1.3 in patients without PE, while the mean respiratory rate was 31.3 ± 0.87 cycles/ minute in COPD patients with PE versus 23 ± 0.44 in patients without PE, the difference was highly statistically significant. Pulse rate > 120 beats/ minutes had a good positive predictive value where at a cut-off point of 120 beats / minute more than 75% of cases had PE. Also respiratory rate > 35cycles / minutes is a good predictors.

The explanation of the previous results could be attributed to the higher burden on respiratory and cardiovascular system from AECOPD and PE. These findings were in consistent with Palevsky et al., 1998 who reported that tachypnea is the hallmark of embolization of the lung and attributed it to stimulation of irritant receptors and juxtacapillary receptors in the alveolar capillary membrane by swelling of the alveolar interstitial space. This stimulation increases reflex vagal afferent activity, which stimulates medullary respiratory neurons. Hypoxemia increases sympathetic tone and together with decreased CPO, and chest pain all reflex increase in the heart rate observed in those patients.

In this work, the duration of COPD illness ranged from 2 – 18 years with a mean of 8.1 ± 0.35. Patients with VTE had a longer duration of illness than those without PE, the difference was statistically significant. The risk of PE increased with increased COPD duration and at a cut off-point of the duration of COPD illness more than 12 years this risk increased significantly. The explanation for this may be due to the enhanced prothrombotic process that increased as the disease becomes advanced. This in turn account for the increased thrombosis in pulmonary vessels in those patients, which increase significantly the risk of pulmonary thromboembolism. This result is in agreed with that of Mariinov et al., 1988 and Stibbing and Lim., 1998 who reported similar results.

The frequency of PE increased with the increase in the frequency of COPD exacerbation and this will be more significant if exacerbations were more than 5 times/ year. This may be explained by the fact that patients with frequent exacerbations have more increase in fibrinogen level and prolonged periods of recumbancy and subsequent venous stasis. This observation agreed with that of Wedzicha et al., 2000 who stated that acute exacerbation of COPD further increases the risk of PE as there is transit acute increase in plasma fibrinogen in patients with AECOPD (mediated through a rise in IL-6).

Patients with PE had a higher number of hospital admissions/ year than other patients and this may be due to the fact that patients with PE had more severe underlying COPD disease and more severe exacerbations than others, which necessitate frequent hospital admission. The frequency of PE increased significantly in COPD patients admitted more than 4 times per year because of acute exacerbation. This may be attributed to the prolonged periods of immobility, medications and increased hypercoagulability in those patients.

Most patients with AECOPD have pulmonary hypertension. The level of pulmonary artery pressure was higher in patients with PE than those without PE and the difference was very highly statistically significant ($p < 0.001$). This is predicted because of the more compromise imposed on the pulmonary vasculature caused by the effect of embolism beside the effect of COPD. The frequency of PE increased with increase in the mean pulmonary artery pressure and at a mean pulmonary artery pressure > 60 mmHg the risk of PE is high which considered as a Cut off point for diagnosis of PE.

Arterial blood gases were abnormal in most patients. pH was statistically higher in COPD patients with PE and this may be due to the lower level of CO2 and respiratory alkalosis in those patients resulting from hyperventilation and increased dead space fraction which occur secondary to embolism. These results were in consistent with those of Lewczuk et al., 1998 who found that patients with COPD and PE had a higher pH and a lower PaCO2 compared to COPD patients without PE. Also these results were in agree with that of Fawzy, 2001 who reported a higher pH in angiographically confirmed PE patients.

Hypoxemia is the most common immediate physiologic consequence of pulmonary embolism. COPD patients with PE are more hypoxemic than those without embolism (43.8 ± 0.87 versus 51.8 ± 0.8) with high statistically significant difference between both groups. This may be attributed to the more gas exchange abnormalities due to presence of two diseases; COPD and PE in those patients and any of them can cause hypoxemia. This was in consistent with that of Jerald et al., 2001 who reported that PE and its mimic conditions as COPD can alone cause great decrease in PaO2.

COPD patients with PE showed lower levels of PaCO2 than COPD patients without PE (59.1 ± 1.38 versus 61.54 ± 0.8), however the difference was not statistically significant. This may be attributed to increased minute ventilation following the embolic events in response to hypoxia-induced intrapulmonary reflex vagal stimulation, with resulting hyperventilation. The resulting alveolar hyperventilation decreases the level of PaCO2. The result of our work was in consistent with those of Rodger et al., 2000 who found hypocapnea in their COPD patients with PE. Moreover, several previous reports showed that a decrease in PaCO2 during COPD exacerbation might indicate PE and a reduction in the PaCO2 in a previously hypercapnic patient might support the diagnosis of acute PE (Lippmann and Fien, 1993 and Rodger et al., 2000).

Tillie-Lebland et al., 2006 found that although the level of PaCO2 or PaO2 on admission did not predict the occurrence of PE, a decrease in PaCO2 of at least 5 mm Hg from the baseline values was the only blood gas abnormality associated with PE.

However, Bartter et al., 2003 stated that patients with COPD and PE had both hypoxemia and hypercapnea that can be attributed to alveolar hypoventilation, resulting from COPD and respiratory muscle and central drive fatigue.

Alveolar - arterial O2 difference {P (A-a) O2} is very useful parameter indicating pulmonary dysfunction. In our work the mean P (A-a) O2 was 22.3 ± 1.00. This mean is abnormally wide, which may be attributed to the fact that most of the studied patients had severe underlying COPD, which cause pulmonary dysfunction. This was in consistent with the results of Bartter et al., 2003 who stated that at any age, P (A- a) O2 difference > 20 mmHg on room air should be considered abnormal and indicative for pulmonary dysfunction. Hyers (1999) reported that wide P (A-a) O2 is the most common arterial blood gas abnormality in patients with PE. On the same hand, some authors suggest that a normal arterial-alveolar gradient (A-a) makes PE very unlikely.

P (A-a) O2 was wider in COPD patients with PE than in patients without PE (31.4 ± 1.34 versus 15 ± 0.9), and the difference was statistically high. P (A-a) O2 > 25 mmHg is a good predictor for PE in COPD patients The cause of this great widening of

P (A-a) O2 may be attributed to the presence of V/Q mismatch and shunt effect in patients with PE, which may be responsible for the general widening of P (A-a) O2 of those patients, while in patients without PE, the difference was variable according to the interaction and severity of the underlying disease process resulting in varying degrees of V/Q mismatch and alveolar hypoventilation..

As regard to blood count there was no statistically significant difference between patients with PE and those without PE regarding to the number of WBCs, RBCs and Hgb content while there was statistically significant increase in Hct value and statistically significant decrease in platelet count in COPD patients with PE in comparison with those without PE (P = 0.001 and < 0.001, respectively).

Significant increase in hematocrit value in COPD patients with PE may be attributed to the more severe chronic hypoxemia in those patients with more duration of illness. Hct value > 56 mmHg is a good predictor for PE in COPD patients with acute exacerbation.

Decrease in platelet count in COPD patients with PE may be due to shortened platelet survival time resulting from increased consumption. Chronic hypoxaemia can also affect platelet function and aggregation, (Wedzicha et al., 1991). We found that platelet count < 200 x103/mml3 was associated with increased probability for PE.

D-dimer is highly sensitive for VTE especially when assayed by a quantitative ELIZA or ELIZA-derived method at a cutoff value of 500µg/l. Hence, a D-dimer level below this value reasonably rules out PE (Torbicki et al., 2000). However, specificity of D-dimer is even lower in a variety of physiological and pathological conditions associated with increase fibrin formation other than VTE such as cigarette smoking, old age, during hospital stay, infection and other inflammatory conditions. Hence, D-dimer measurement is unlikely to be useful in such populations and a positive test couldn't confirm the presence of VTE.

In our patients the level of plasma D-dimer showed statistically very highly significant increase in COPD patients with PE in comparison to those without PE (mean ± SE was 810 ± 38 versus 436 ± 31, respectively and p– value was less than 0.001). The explanation for this was that patients with PE had amount of fibrin higher than other conditions, which may increase D-dimer level. Moreover, patients with VTE may have other conditions which increase D-dimer as old age, smoking, hospitalization and infection.

In our work, the frequency of PE increased significantly as the D-dimer level increases. The specificity of D-dimer increased by increase of the cutt- off point of D-dimer level and at a level more than 1000 µg/l, 73% of patients had PE. So the positive predictive value for PE is significantly increased. This was in consistent with the results of Perreir et al., 1997 who found that the specificity of D-dimer would be dramatically increased to 93% when setting the cutoff at 4000 µg/l.

Thrombin antithrombin (TAT), which indicates activation of coagulation system increased significantly in COPD patients with PE than in those without PE. Moreover, the frequency of PE increased significantly as the TAT level increases and at a level more than 20 µg/l, the positive predictive value for PE is significantly increased and 75% of cases were positive for PE while at a level > 30 µg/l, 100% of cases had PE.

Plasma level of bet-TG (a marker of platelet activation) also increased significantly in COPD patients with PE in comparison to those without PE. This was in consistent with those of Smith et al., 1978 who found an association between PE and high betaTG values. De Boer et al., 1981 found that both plasma and urine BTG are significantly elevated (p < 0.005) in patients with PE compared to symptomatic patients with a negative venogram. The positive predictive value for PE is significantly increase with the increase in the level of betaTG and at a cut-off point at 80 IU/mL, 70% of cases was positive for PE

P-selectin, mediates adhesion and migration of leukocytes at sites of inflammation and platelet-

leukocyte interaction, and supports fibrin formation and thrombus growth (Polgar et al., 2005). There was significant increase in P-selectin level in AECOPD patents with PE than among those without PE. This was in consistent with the results of Kyrle et al., 2007 who reported the first clinical evidence of an association between increased P-selectin levels and venous thrombus formation in man and they found that exceeding the high circulating P-selectin is a risk factor of recurrent PE.

The positive predictive value for PE is significantly increased with the increase in the level of p-selectin and at a cut-off point at 400 ng/mL, 80% of cases was positive for PE

In conclusion, this study showed a 27.8% prevalence of PE in patients with COPD hospitalized for severe exacerbation. These clinical and laboratory cut-off points can facilitate the diagnosis by a high sensitivity yield with a highly significant importance (P<0.001 - <0.02)

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