Impact of Pulmonary Embolism on Acute Chronic Obstructive Pulmonary Disease Exacerbation

Pulmoner Emboli ve Akut Kronik Obstrüktif Akciğer Hastalığı Alevlenmesi Birlikteliği

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ABSTRACT

Purpose: This study aims to assess effect of pulmonary embolism (PE) on clinical and laboratory parameters of patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Risk factors for PE development were also evaluated.
Methods: In this retrospective study, patients who were hospitalized for AECOPD and underwent computed tomographic pulmonary angiography scan (CTPA) between 2009 and 2011 were included. Patients with PE were evaluated separately as those diagnosed at initial examination and those suspected during exacerbation therapy since they had inadequate response. Binary logistic regression analysis was used in order to determine risk factors on PE development.
Results: The study consisted of 36 patients, 13 patients (36.1%) had PE. FEV_1 and FEV_1/FVC values were higher in PE group (53.7% vs 41.4%; 62.3% vs 52% respectively; p<0.05). There was no difference between D-dimer levels of PE and non-PE patients. Risk of PE development did not differ with analyzed variables. Those diagnosed at initial examination had significantly less number of exacerbations in the last one year than those diagnosed during therapy (1.1 vs 3.2; p<0.05).
Conclusion: PE should always be considered in AECOPD etiology, particularly in patients with frequent exacerbation history and D-dimer levels may be misleading.

Key Words: Pulmonary embolism, chronic obstructive pulmonary disease, exacerbation

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ÖZET

Amaç: Bu çalışma ile kronik obstrüktif akciğer hastalığı akut alevlenmesi (KOAHA) nedeniyle hastane yatışı yapılan hastalarda tespit edilen pulmoner embolinin (PE), hastalığın klinik ve laboratuvar parametreleri üzerindeki etkisinin değerlendirilmesi amaçlanmıştır. PE gelişimine ait risk faktörleri ayrıca araştırılmıştır.
Yöntem: Bu retrospektif çalışmaya 2009-2011 yılları arasında, KOAHA nedeni ile hastane yatışı yapılan ve bilgisayarlı tomografi pulmoner anjiyografi (BTPA) tetkiki bulunan hastalar dahil edilmiştir. PE tanısı alan hastalar ilk değerlendirme esnasında tanı alanlar ve tedavi sürecinde yetersiz klinik yanıt alınması nedeniyle araştırılırken tanı alanlar şeklinde ayrı ayrı değerlendirilmiştir. PE gelişimi için risk faktörlerinin belirlenmesi için ikili lojistik regresyon analizi kullanılmıştır.
Bulgular: Çalışmaya alınan 36 hastanın 13'ünde (%36.1) PE mevcuttu. FEV1 ve FEV1/FVC değerleri PE grubunda daha yüksek bulundu (sırasıyla %53.7 vs %41.4; %62.3 vs %52; p<0.05). PE tespit edilen ve edilmeyen hastaların D-dimer seviyeleri arasında farklılık bulunmadı. Araştırılan parametrelerin PE gelişimi üzerinde etkisi tespit edilmedi. İlk değerlendirme esnasında PE tanısı alan hasta grubunun son 1 yıldaki atak sayısı takip esnasında tanı alan hastalara göre belirgin daha düşüktü (1.1 vs 3.2; p<0.05).
Sonuçlar: Özellikle sık atak öyküsü bulunan KOAHA hastalarının etyolojisinde mutlaka PE varlığı araştırılmalıdır. Bu hasta grubundaki D-dimer sonuçlarının yanıltıcı olabileceği unutulmamalıdır.

Anahtar Sözcükler: Pulmoner emboli, kronik obstrüktif akciğer hastalığı alevlenmesi

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a worldwide common public health problem (1). It is the third most common cause of mortality and 2.9 million people die of COPD every year (2). Exacerbations (AECOPD), defined as acute deterioration of daily symptoms despite routine treatment during course of the disease, are the most important cause of morbidity and mortality (3). Tracheobronchial infections comprise 50–70% and are the most common among factors causing exacerbations. However, etiologic factors cannot be identified in approximately 30% of cases (4). It was shown that pulmonary embolism (PE) was the cause in 25% of severe exacerbations with unknown etiology that required hospitalization (5).

PE incidence is reported to be nearly 4 times higher in stable COPD patients than normal population (6). PE prevalence ranged from 5% to 29.1% during exacerbation in previous studies (7–11). Although they commonly coexist, the similarity of symptoms and manifestations makes diagnosis of PE in COPD patients difficult. This may lead to delayed diagnosis of PE and even may cause higher mortality if the diagnosis is missed. In patients with PE, COPD was shown to delay diagnosis more than 3 days (12). PE presence is reported to increase mortality 1.5 times in COPD patients who were admitted to emergency room with exacerbation (13).

In this study, we aimed to assess effects of PE on clinical and laboratory parameters of patients hospitalized for AECOPD. Risk factors for PE development were also evaluated.

MATERIALS and METHODS

Database of a university hospital between 2009–2011 was retrospectively analyzed. Patients those who were previously diagnosed as COPD according to current guidelines and hospitalized for AECOPD after the evaluation at the emergency room were identified. Among these patients, those who had computed tomographic pulmonary angiography scan (CTPA) based on clinical manifestations, clinical scoring and D-dimer levels were included in the study. CTPA was obtained for either suspected high probability PE at initial examination, or PE possibility during AECOPD therapy since the patient showed inadequate clinical response. Exacerbation diagnosis was made by new onset activity restriction, respiratory failure or worsening of daily symptoms despite routine treatment regimens. PE was diagnosed by demonstration of a filling defect at any level of one or more than one pulmonary artery on CTPA with consensus of expert pulmonologists and radiologists. All patients had venous thromboembolism prophylaxis with low molecular weight heparin during hospital stay because of severity of exacerbation, age and comorbidities. Patients who were considered as infectious etiology were given proper antibiotic treatment.

Of each patient age, gender, smoking history, initial pulmonary function tests (PFT), Charlson comorbidity score, body mass index (BMI), duration of symptoms before admission, duration of hospitalization, number of exacerbations in the last year, initial C-reactive protein (CRP) level, D-dimer level, hemoglobin concentration, white blood cell count, ejection fraction (EF) and systolic pulmonary artery pressure (sPAB) on echocardiography, and presence of chronic respiratory failure were recorded. Chronic respiratory failure was defined as need for long term oxygen therapy or noninvasive mechanic ventilation. For subgroup analysis, patients who had high probability of PE at initial examination and diagnosed earlier (PE-e) were compared to those that diagnosed during hospitalization (PE-h).

Statistical Analysis

Continuous variables are expressed as mean ± standard deviations (SD) unless otherwise stated. Mann-Whitney U test was used for comparison of PE and non-PE groups. Univariate regression analysis was performed in order to calculate odds ratio (OR) for each variable that may affect PE development. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Database of 180 patients hospitalized for AECOPD between 2009 and 2011 were accessed. Among these, 36 patients (20%) who met the inclusion criteria were included in the study. Twenty-nine patients (80.9%) were male and 7 (19.4%) were female. Mean age was 71.9±9.4. Patient characteristics are listed in Table 1. Thirteen (36.1%) of 36 patients had PE. PE was suspected and diagnosed at initial examination in 7 patients (PE-e, 54%), whereas 6 patients were diagnosed during hospitalization (PE-h, 46%). All patients who had CTPA at initial examination had high pretest probability.

Table 1. General characteristics of all patients.

	Total (n=36)	PE (n=13)	Non-PE (n=23)	*p*
Age (mean ± SD)	71.9 ± 9.4	71.8 ± 9.2	72 ± 9.6	0.95
Gender; female (%)	7 (19.4)	3 (23.1)	4 (17.4)	0.68
Cigarette smoking; package-years ± SD	51.8 ± 29.2	54.7 ± 31.5	50 ± 28.4	0.65
Charlson comorbidity index	6.5 ± 3.5	5.5 ± 2.4	7.1 ± 4	0.31
BMI (kg/m^2)	25.3 ± 5.4	24.6 ± 6.9	25.7 ± 4.5	0.44
Duration of symptoms before admission (days)	15.1 ± 11.8	16.9 ± 16	14 ± 8.4	0.62
Number of exacerbations in last 1 year	1.7 ± 1.1	2 ± 1.5	1.6 ± 0.9	0.5
FEV_1; %pre	45.9 ± 15.3	53.7 ± 16.8	41.4 ± 12.8	**0.047**
FVC; %pre	63.7 ± 14.9	68 ± 14.3	61.3 ± 14.9	0.22
FEV_1/FVC; pre	55 ± 10.3	60.3 ± 10	52 ± 9.5	**0.04**
Hospital stay (days)	13.9 ± 7.9	12.1 ± 8.4	15 ± 7.6	0.13
Hemoglobin (g/dL)	-	12.5 ± 1.5	13.8 ± 2.1	0.07
White blood count (cell/mL)	-	12136 ± 4209	11720 ± 5275	0.81
CRP (mg/L)	-	41.3 ± 44.4	66 ± 73.6	0.48
D-dimer (ng/mL)	-	2039 ± 1960	2208 ± 4020	0.89

PE: pulmonary thromboembolism; SD: standard deviation; BMI: body mass index; FEV_1: forced expiratory volume 1; FVC: forced vital capacity; CRP: C-reactive protein

There was no statistically significant difference in age, gender, smoking history, BMI, duration of symptoms before admission, number of exacerbations in the last one year, Charlson comorbidity score between PE and non-PE groups. FEV_1 and FEV_1/FVC values were higher in PE than non-PE group (53.7% vs 41.4% and 62.3% vs 52% respectively; $p<0.05$). FVC were higher in PE group but this difference was not statistically significant. D-dimer level did not differ between PE and non-PE groups, however, 1 patient with PE (8.3%) had D-dimer <500 ng/mL and 12 patients without PE (80%) had D-dimer >500 ng/mL. PE-e group had significantly less number of exacerbations in the last year than other PE-h group (1.1 vs 3.2; $p<0.05$) (Table 2).

Table 2. Comparison of PE-e and PE-h groups.

	PE-e (n=7)	PE-h (n=6)	*p*
Age (mean ± SD)	75.8±6.7	67±10	0.08
Gender; female (%)	2 (28.6)	1 (16.7)	1
Cigarette smoking; package-years ± SD	56±34.7	53.3±31.3	0.89
Charlson comorbidity index	5.6±2.6	5.3±2.3	0.87
BMI (kg/m^2)	27.4±9.3	21.9±1.7	0.23
FEV_1; %pre	56.6±17	49.6±17.6	0.51
FVC; %pre	71.7±13.4	62.8±15.5	0.31
FEV_1/FVC; pre	60.1±10.5	60.4±10.4	0.97
Number of exacerbations in last 1 year	1.1 ± 0.4	3.2 ± 1.6	**0.02**
Duration of symptoms before admission (days)	18 ± 18.6	15.4 ± 13	0.68
Hospital stay (days)	11.4 ± 7.2	12.8 ± 10.3	0.77
D-dimer (ng/mL)	2288 ± 2360	1690 ± 1380	0.69

PE: pulmonary thromboembolism

Univariate regression analysis was performed for risk factors that may significantly affect PE development and the results are listed in Table 3. None of the variables were identified as a risk factor for PE development.

Table 3. Univariate logistic regression analysis for risk of PE development.

	OR	%95 CI	*p*
Age	0.997	0.927-1.073	0.943
Gender; female	1.425	0.265-7.657	0.68
Cigarette smoking; package-years	1.006	0.981-1.031	0.66
Ever smoker	0.396	0.039-3.977	0.431
Chronic respiratory failure	2.062	0.492-8.654	0.322
Charlson comorbidity index	0.944	0.477-1.869	0.869
Body mass index	0.962	0.827-1.119	0.613
Duration of symptoms before admission (days)	1.022	0.96-1.087	0.498
Number of exacerbations in last 1 year	1.416	0.748-2.681	0.285
EF	1.014	0.949-1.084	0.674
sPAB	1.098	0.98-1.231	0.109
Hemoglobin	0.696	0.468-1.036	0.074

OR: odds ratio, CI: confidence interval, EF: ejection fraction, sPAB: systolic pulmonary artery pressure

DISCUSSION

Our study displayed that pulmonary function tests were better in patients hospitalized with acute COPD exacerbation and concomitant PE and that D-dimer levels may be misleading for PE diagnosis in this patient group. Furthermore, patients who were diagnosed as PE at initial examination had significantly less number of exacerbations in the last year.

PE diagnosis during COPD exacerbation is difficult due to similarities between symptoms. PE is common during exacerbations and causes increased mortality. Hasegawa et al. demonstrated that in patients applied to emergency room with exacerbation, presence of PE caused a 1.53 times increase in mortality (%95 CI: 1.15-2.04) (13). Bahloul et al. indicated PE as an independent risk factor for mortality in patients admitted to intensive care unit for severe exacerbations (OR=3.49; %95 CI 1.01-11.1; p=0.035) (14). In our study, no in-hospital mortality was reported and all patients were discharged.

In a meta-analysis, PE prevalence was revealed 24.7% in patients hospitalized for exacerbation (7). A similar study in our country, the number was found 29.1% (10). Even though our study methodologically is not a prevalence study, PE ratio among included patients was 36%.

Although COPD and PE coexist frequently, there is no approved method for differential diagnosis of the two diseases. Previous studies on usage of clinical scoring systems and D-dimer levels during exacerbation have contradictory results. When we look at studies with Wells scoring system, since it can be used in both inpatient and outpatient care, Fernandez et al. reported a lower pretest probability in patients who had PE and COPD than patients who had PE without COPD (12). Akpınar et al. found a Wells score of lower pretest probability in 24% of patients diagnosed as PE during exacerbation (10). On the other hand, in their study Günen et al. did not demonstrate low pretest probability in any of the patients hospitalized for exacerbation and had PE (8). In our study, Wells score of all patients who had CTPA for PE suspicion at initial examination had high probability. 6 patients who were diagnosed PE during hospitalization had low pretest probability at initial examination. Since COPD exacerbation almost always causes tachycardia and can always be an alternative diagnosis to PE, it would be wise to be careful while interpreting Wells scores.

In our study, there was no difference between D-dimer levels of PE and non-PE group. Since almost all previous studies demonstrated significantly higher D-dimer levels in PE groups, our result may be attributed to presence of factors that may increase D-dimer levels such as advanced age, coexisting comorbidities and infection or to the small sample size. Nevertheless, it should always be kept in mind that COPD is a chronic inflammatory and procoagulant disease (15). This will considerably result in false positive D-dimer levels. Consistently, our study revealed high D-dimer levels in 80% of non-PE patients. Hartman et al. showed that presence of COPD did not alter the diagnostic performance of D-dimer testing (COPD (+) sensitivity 82%, specificity 65%, negative predictive value 9%2; COPD (-) sensitivity 82%, specificity 63%, negative predictive value 88%). These results encourage usage of D-dimer testing for exclusion of PE in COPD patients. However, it should be considered that PE can be depicted in patients with normal D-dimer levels as well, as found 8.3% in our study and 10% by Kamel et al. (11).

COPD is an independent risk factor for PE development (16). In univariate analysis, none of the variables were identified as a risk factor for PE development.

Multivariate analysis was not performed due to small sample size and univariate analysis results. In previous two studies on the subject, Tille-Leblond et al. identified malignancy, previous thromboembolism history and drop in PaCO2 more than 5 mmHg; and Chen et al. identified presence of comorbidities and younger age as risk factors for PE development (5, 6).

Our study depicted better PFT results in PE group. However, it is not possible to ascertain whether PE develops in patients with better PFT results or PFT is less affected in exacerbations caused by PE based on the limited available data. In literature, the only study we could find on this subject reported similar PFT results in both PE and non-PE patients with exacerbation. In this prospective study by Choi et al., any value in the last 6 months was accepted as PFT result. In addition, number of PE patients is much lower than that of non-PE patients in this study (5 vs. 98) (9). However, in our study PFT results at admission were compared. This entity may resolve in the future with studies which include comparison with PFT of stable periods.

There was nearly threefold difference between numbers of exacerbations in the last year of patients diagnosed as PE-e and PE-h. Patients who referred to hospital for exacerbation are under risk for re-referral (17). Accepting this as a natural course of the disease and avoiding searching thoroughly for etiology may cause diagnostic delay. Even though it is not proven, an underlying PE may also cause recurrent exacerbation (18).

Our study has several limitations. First of all, it is a single-centered retrospective study with a small sample size, which may cause results different than expected. Secondly, since we did not have PFT results of patients in stable period of the disease, we could not clarify the differences demonstrated between two groups.

In conclusion, PE frequently accompanies acute COPD exacerbations and D-dimer results may misdirect during differential diagnosis. Particularly in patients with frequent exacerbation history, PE should be considered among differential diagnoses each time.

Conflict of interest

No conflict of interest was declared by the authors.

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