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Brief communication (Original)

Pulmonary embolism in patients with chronic obstructive pulmonary disease and exacerbations of unknown origin

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Background: Despite important advances in the diagnosis and treatment of acute pulmonary embolism (APE), diagnosis of pulmonary embolism (PE) is difficult in patients with chronic obstructive pulmonary disease (COPD) and exacerbation.
Objective: We evaluated PE in patients with chronic obstructive pulmonary disease and exacerbations of unknown origin.
Methods: Two-hundred and eight patients with COPD and severe exacerbations were studied. All patients had CT pulmonary angiography (CTPA) and lower limb ultrasonography. Arterial blood gas measurements, D-dimers and endothelin-1 (ET-1) levels were recorded.
Results: The frequency of PE was 33%. The following were more common in the PE group ($\chi^2 = 4.32–6.79$, mean $p < 0.05$): immobilization ≥ 7 days; a ≥ 1 cm difference in edema of the lower limbs; deep venous thrombosis; syncope; S1Q3T3 syndrome; and a decrease in $PaCO_2$ ≥ 5 mm Hg. Plasma D-dimers and ET-1 levels were significantly higher in the PE group. Risk factors identified from logistic regression analysis were immobilization ≥ 7 days, ≥ 1 cm difference in lower limb edema, and deep venous thrombosis.
Conclusions: Overall, 33% of 208 patients had a PE, and the risk was greater in those who had been immobilized, those who had a ≥ 1 cm difference in edema of the lower limbs, and those who had a deep venous thrombosis.

Keywords: Chronic obstructive pulmonary disease, D-dimer, endothelin, pulmonary embolism

The management of patients with suspected acute pulmonary embolism (PE) has greatly improved in recent years as a result of better awareness and clinical assessment, and the increasing use of ultrasonography, ventilation perfusion scanning, and CT pulmonary angiography (CTPA). However, the clinical diagnosis of APE can be difficult in patients with chronic obstructive pulmonary disease (COPD), as the clinical presentation is similar to that of an acute exacerbation of the underlying condition. Respiratory infections are the most common cause of acute exacerbations of COPD. These are usually accompanied by symptoms such as increased sputum volume and viscosity, fever, chills, and a sore throat [1].

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Previous studies estimated that from 50% to 70% of all COPD exacerbations are precipitated by an infectious process, while 10% are because of environmental pollution [2]. Up to 30% of exacerbations are of an unknown etiology [2]. Exacerbations are typically characterized by an increase in cough and dyspnea. Because thromboembolic events can also lead to a cough and dyspnea, PE may be another common cause of exacerbations. However, unlike infections that can be effectively treated by antimicrobials and systemic corticosteroids, thromboembolic disease requires anticoagulant therapy, and significant delays in treatment are associated with a poor outcome [1]. We designed this study to explore the frequency of PE in patients with COPD and exacerbations of unknown etiology. In addition, we also examined factors associated with the presence of a PE.

Methods

Enrollment and exclusion criteria

Inclusion criteria

The study was conducted in the pulmonary department of the First Affiliated Hospital of Henan University of Science and Technology. Between September 2006 and June 2011, all consecutive patients with COPD referred to the pulmonary department with severe exacerbations of unknown etiology were assessed for the presence of a PE. The diagnosis of COPD was confirmed, and its severity was determined according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease [3]. Severe exacerbations were defined as an acute deterioration from a stable condition that required hospitalization. The exacerbation was classified as of "unknown origin" if it met the following criteria: the absence of a lower respiratory tract infection (increased sputum volume and/or increased sputum purulence, fever, history of a cold, and sore throat); the absence of a pneumothorax; and the presence of a discrepancy between clinical and radiologic features and hypoxemia [4]. Physicians were required to discuss each case of COPD with two of the referring physicians.

Exclusion criteria

Criteria included the following: (1) patients requiring invasive mechanical ventilation; (2) patients with exacerbations because of a pneumothorax or iatrogenic causes; (3) patients in whom the CTPA had not been completed and lower limb venous ultrasound was not performed within 24 hours of admission; and (4) iodine intolerance, serious endocrine disease, and liver and kidney dysfunction.

Study design

The study group included 208 patients with COPD with severe exacerbation of unknown origin. There were 158 men and 50 women. Their age ranged from 50 to 82 years, with a mean of 62 ± 12 years. Patients were classified as PE positive (positive results on CTPA) or PE negative (negative results on CTPA) [5]. There were 69 patients in the PE positive group: 59 were men and 10 were women, and their age ranged from 55 to 79 years, with a mean of 65 ± 10 years. There were 139 patients in the PE negative group: 99 were men and 40 were women, and their age ranged from 50 to 82 years, with a mean of 62 ± 12 years. This prospective study complied with the ethical standards of human trials and obtained the approval of the Ethical Committee of the First Affiliated Hospital of Henan University of Science and Technology (No.20060909), which necessitated informed patient consent.

Methods

A medical history was obtained from all patients and a detailed physical examination was performed within 24 hours of admission. Epidemiological data, characteristics of the exacerbation and patient mobility were noted. Lower limb venous ultrasonography and CT pulmonary angiography (CTPA) were undertaken within 24 hours of admission.

Computed tomographic pulmonary angiography (CTPA)

All patients were evaluated with a 64-detector helical CT system (Light-speed 64-detector CT GE, USA), using 64 × 0.625 mm collimation and a table feed of 44.3 mm/revolution, a pitch of 1.11, 120 kV, 400 mA, and a 0.5 second rotation. On the basis of these datasets, transverse images were reconstructed with an interval of 0.7 mm. The mean duration of data acquisition was from 2 to 4 seconds. All studies were performed with 120 ml of 370 mg/ml Iopamiro (Iopamiro 370; Bracco, Sine Pharmaceutical, Shanghai, China) administered at a rate of 4 ml/s using an automatic dual chamber injector (Medrad). The start delay time was determined by adding 2 seconds to the time-to-peak value. Scanning delays were from 8 to 14 seconds (mean 12 seconds). Pulmonary embolism was diagnosed if contrast material outlined an intraluminal defect, or if the vessel was totally occluded by low attenuation material [6-8].

Pulmonary function tests

For each patient, classification of COPD severity was made according to the GOLD criteria, depending on stable-state spirometric measurements [3]. Pulmonary function was evaluated with body plethysmography (Jaeger, Wuerzburg, Germany). All testing was performed in accordance with the GOLD standards, with the patient in a sitting position at the same time of day and with the same technician, in order to ensure consistency of the technique. Three technically acceptable measurements were performed for each patient, and the highest one was included in the analysis.

Ultrasonography

Venous compression ultrasonography of both legs was performed from the common femoral vein to the popliteal vein including the calf vein, and noncompressibility was considered to indicate a deep venous thrombosis (DVT). The criteria were [9]: (1) a strong or weak solid echo pattern demonstrated within the venous lumen; (2) the compressed lumen could not be flattened or only partially flattened; and (3) blood flow could not be detected by pulse and color Doppler.

Measurement of ET-1, arterial blood gases and D-dimers

In all patients, peripheral venous blood samples from the antecubital vein were collected between 6 and 8 am. Serum was separated from blood cells by centrifugation at 3,000 rpm. All samples were stored at –70°C until analyzed. ET-1 levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits. D-dimer levels were measured immediately using ELISA kits (rapid ELISA assay, Vidas DD; BioM rieux, Marcy l'Etoile, France). D-dimer levels below 0.5 µg/l were considered normal. At the time of collection of venous blood samples, an arterial blood sample, while breathing room air, was obtained by puncture of the radial artery for blood gas analysis.

Statistical analysis

Data analysis was performed using SPSS version 17.0 (SPSS, Chicago, USA). Mean values of the groups were compared using a two-tailed unpaired *t* test for normally distributed variables and a Mann–Whitney *U* test for non-normally distributed variables. Qualitative data was assessed using a χ^2 test. Risk factors were analyzed using logistic regression analysis. A $p < 0.05$ was considered to indicate statistical significance.

Results

Clinical characteristics

The frequency of PE was 33%. Differences in the following variables were identified between the PE positive and PE negative groups ($\chi^2 = 4.32–6.79$, mean $p < 0.05$): immobilization ≥7 days: 21.7% (15/208) and 13.7% (19/208), respectively; difference in edema of the lower limbs ≥1 cm: 34.8% (24/208) and 15.1% (21/208), respectively; presence of a deep DVT: 37.7% (26/208) and 12.2% (17/208), respectively; syncope: 11.6% (8/208) and 0.06% (9/208), respectively; S1Q3T3 syndrome: 11.6% (8/208) and 0.04% (5/208), respectively; decrease in $PaCO_2$ ≥5 mmHg (1 mmHg = 0.133 kPa): 27.5% (19/208) and 9.3% (13/208), respectively. No significant differences were found for any of the other variables (**Table 1**).

Table 1. Admission characteristics of patients with and without pulmonary embolism

Characteristics	With PE (n = 69)		Without PE (n = 139)		χ^2	*p*
	Case	n (%)	Case	n (%)		
Age (y)						
≥65	40	58.0	81	58.2	0.00	>0.05
<65	29	42.0	58	41.8		
Smoker (y)	18	26.1	31	22.3	0.56	>0.05
Long-term oxygen therapy	22	31.9	49	35.3	0.80	>0.05
Immobility ≥7 days	15	21.7	19	13.7	4.32	<0.05
Chest pain	17	24.6	39	28.1	0.61	>0.05
Hemoptysis	3	0.04	7	0.05	0.78	>0.05
Palpitations	18	26.1	40	28.8	0.69	>0.05
Dyspnea	60	87.0	120	86.3	0.15	>0.05
DELL ≥1 cm	24	34.8	21	15.1	4.75	<0.05
Syncope	8	11.6	9	0.06	6.79	<0.01
Hypotension	2	0.03	6	0.04	1.43	>0.05
Hypertension	10	14.4	19	13.7	0.21	>0.05
Coronary heart disease	5	0.07	13	0.08	1.07	>0.05
Diabetes	7	10.1	16	11.5	0.18	>0.05
Cerebrovascular disease	3	0.04	8	0.06	1.76	>0.05
Previous thromboemboli	6	0.09	12	0.09	0.03	>0.05
Atrial fibrillation on ECG	4	0.06	8	0.06	0.18	>0.05
S1Q3T3 pattern on ECG	8	11.6	5	0.04	5.87	<0.05

Table 1. Admission characteristics of patients with and without pulmonary embolism (Continue)

Characteristics	With PE (n = 69)		Without PE (n = 139)		χ^2	*p*
	Case	n (%)	Case	n (%)		
PaO_2 (mm Hg)						
<60	31	47.0	74	53.0	0.07	>0.05
≥60	38	63.1	65	46.8		
$PaCO_2$ (mm Hg)						
<39	27	39.1	58	41.7	0.05	>0.05
≥39	42	60.9	81	58.2		
Decrease in $PaCO_2$ ≥5 mmHg	19	27.5	13	9.3	4.97	<0.05
Deep venous thrombosis	26	37.7	17	12.2	6.12	<0.01
D-dimer levels (g/L)						
≥500	67	97.2	2	1.0	6.54	<0.01
<500	2	2.8	137	99.0		
Severity of COPD						
Grade I	12	17.4	22	15.8	0.05	>0.05
Grade II	14	20.2	30	21.6		
Grade III	37	53.6	80	57.6		
Grade IV	6	8.0	7	5.0		

Immobility ≥7 d = in bed more than 60% of waking day, as a result of surgery, fracture, COPD exacerbation, DELL ≥1 cm = difference in edema of the lower limbs ≥1 cm, Decrease in $PaCO_2$ ≥5 mmHg = decrease in $PaCO_2$ of at least 5 mmHg from baseline (baseline = 36 mmHg,1 mmHg = 0.133 kPa).

Plasma D-dimers and ET-1 levels

Plasma D-dimers and ET-1 levels were significantly higher in patients with a PE than in those without. D-dimers levels were 760 152 μg/L and 253 ± 56 μg/L (z = –2.946, $p < 0.01$) and ET-1 levels were 5.4 ng/L (1.6–6.9 ng/L) and 1.8 ng/L (1.3–4.8 ng/l) (z = –2.532, $p < 0.01$) in the PE positive and PE negative groups, respectively.

Prevalence of risk factors for PE

Risk factors identified by logistic regression analysis were immobilization ≥7 days ($p < 0.05$; OR = 3.24; 95%CI = 1.56–4.98), a ≥1 cm difference in edema of the lower limbs ($p < 0.05$; OR = 2.56; 95%CI = 1.48–3.93), and the presence of a DVT ($p < 0.05$; OR = 2.31; 95%CI = 1.23–3.58). The prevalence of risk factors for PE in each of the groups is summarized in **Table 2**.

Table 2. Results of logistic regression analysis of baseline characteristics of 208 patients with COPD, according to the presence or absence of pulmonary embolism

Characteristics	With PE (n = 69)		Without PE (n = 139)		χ^2	OR (95%CI)	*p*
	Case	n (%)	Case	n (%)			
Age (y)							
≥65	40	58.0	81	58.2	3.52	0.98 (0.57–1.65)	>0.05
<65	29	42.0	58	41.8			
Smoker (y)	18	26.1	31	22.3	3.21	1.36 (0.66–2.98)	>0.05
Long-term oxygen therapy	22	31.9	49	35.3	2.31	0.99 (0.60–1.75)	>0.05
Immobility ≥7 days	15	21.7	19	13.7	4.97	3.24 (1.56–4.98)	<0.05
DELL ≥1 cm	24	34.8	21	15.1	5.74	2.56 (1.48–3.93)	<0.05
Previous thromboemboli	6	0.09	12	0.09	1.87	4.23 (1.67–15.98)	>0.05
Deep venous thrombosis	26	37.7	17	12.2	8.97	2.31(1.23–3.58)	<0.05

Immobility ≥7 d = stay in bed more than 60% time per day when awaking time including surgery, fracture, COPD exacerbations, DELL ≥1 cm = difference in edema of lower limbs ≥1 cm

Discussion

The prevalence and significance of PE has not yet been precisely determined in COPD and a limited number of studies have reported various prevalence rates varying from 0% and 29% [4, 10-14]. Our results revealed a PE frequency of 33% (69/208) in a series of 208 consecutive Chinese patients with COPD referred with a severe exacerbation of unknown origin. This incidence rate is higher than that previously reported in Europe and the United States. This discrepancy may be explained by differences in study populations. In a study by Mispelaere et al. [14], a group of 31 inpatients with an acute exacerbation of COPD of unknown origin underwent spiral CT following hospital admission, and the frequency of PE was 25%. Rutschmann et al. [12] observed 123 patients with an acute exacerbation of COPD in the emergency department, and found that the frequency of PE was 3.3%. Lesser et al. [11] investigated 108 patients with an acute exacerbation of COPD from both inpatients and outpatients, and reported an incidence of PE of 19%. Rizkallah et al. [12] stated that one in four COPD patients who require hospitalization for an acute exacerbation might have a PE. However, in all of these studies, the relatively small sample size potentially undermines the reliability. In addition, patients with D-dimer levels below 0.5 μg/l were excluded. In our prospective study, all patients were evaluated with CTPA, and two patients with negative D-dimer levels (levels below 0.5 μg/l) were confirmed to have a PE.

We did not find any significant differences in age, smoking, long-term oxygen therapy, chest pain, hemoptysis, palpitations, dyspnea, hypotension, hypertension, coronary heart disease, previous thromboemboli, atrial fibrillation on ECG, PaO_2, $PaCO_2$, and the severity of COPD between these two groups. Tille-Leblond et al. [4] and Lesser et al. [11] also failed to find a significant difference in the occurrence of dyspnea, chest pain, hemoptysis, cough, or palpitations between these two groups. However, Rustschmann et al. [12] found that patients with PE were more likely to complain of chest pain and syncope, and less likely to report cough or purulent sputum. Overall, there were no significant differences on physical examination findings between patients who did and did not have a PE. In addition, chest radiographic and ECG findings were similar in both groups. Reports on the results of arterial blood gas analysis have been inconsistent. Tillie-Leblond et al. [4] noted a decrease in $PaCO_2$ of at least 5 mm Hg from baseline in patients with PE (RR, 2.10; 95%CI, 1.23–3.58). This suggests that presenting symptoms, signs, laboratory and epidemiological data are similar in COPD patients with and without PE.

We found only three factors predictive of PE: immobilization e 7 days, a e 1 cm difference in edema of the lower limbs, and the presence of a DVT. Tillie-Leblond et al. [4] found that COPD patients with a PE were more likely to have a history of venous thrombosis (relative risk, 2.43; 95%CI, 1.49 to 3.49) or malignancy (relative risk, 1.82; 95%CI, 1.3 to 2.92) compared with COPD patients without PE. Lesser et al. [11] did not find a difference in mean $PaCO_2$ and PaO_2 levels in patients with COPD with or without a PE. Previous reports have shown that a decrease in $PaCO_2$ during a COPD exacerbation may indicate the presence of a PE. An embolus that obstructs a segmental or large pulmonary artery increases alveolar dead space, which leads to a decrease in exhaled CO_2. Kline et al. [15] reported on a novel device that measures the exhaled CO_2/O_2 ratio, and which is a noninvasive method for assessing increased alveolar dead space with a segmental or large PE. They found that the combination of either a normal end-tidal ratio of CO_2 to O_2 (CO_2/O_2) or normal D-dimer levels was associated with a very low incidence rate of a segmental or large PE [16]. The electrocardiogram can be useful for excluding a myocardial infarction with ST-segment elevation and acute pericarditis. A normal electrocardiogram is very unusual in patients with an acute PE [17]. The chest radiograph cannot be used to diagnose or exclude PE, but it is useful in the differential diagnosis as it can detect pneumonia, pneumothorax, rib fracture, and congestive heart failure.

In this study, we found that plasma D-dimer levels were significantly higher in patients with PE than in those without. The D-dimer blood test is practical for those with a suspected PE [18]. Goldhaber [19] reported that the sensitivity of the D-dimer ELISA for acute PE is 96.4%, and the negative predictive value is 9.9%. Thus, a PE cannot be definitively excluded in those with negative D-dimer levels [20].

We found that ET-1 levels were significantly higher in patients with PE than in those without. The endothelins are a family of naturally occurring peptides that include endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3). They are encoded by three different genes located on chromosomes 6, 1, and 20,

respectively [21]. Endothelins are mainly produced by vascular endothelial cells, and to a lesser extent by vascular smooth muscle cells, airway epithelial cells, macrophages, fibroblasts, cardiac myocytes, brain neurons, and pancreatic islet cells [22]. Of the three subtypes, ET-1 is the most potent and abundant in the human lung, and is one of the most potent and long-lasting vasoconstrictors known to man [22]. Plasma levels of ET-1 correlate with pulmonary pressure, and abnormalities in ET-1 levels have been reported in an experimental PE model [23]. In addition, Han et al. [24] observed the effects of thrombolytic drugs and a selective endothelin-1 receptor (ET-1R) antagonist on acute PE in dogs. They found that selective ET-1R antagonists may be beneficial for the treatment of acute PE. Thus, further studies are needed to confirm the role of ET-1 in patients with COPD and PE.

Our study investigated the incidence of PE in patients with COPD who were hospitalized for severe exacerbations of unknown origin. The incidence was higher in those with the following risk factors: immobilization e 7 days; a difference in edema of the lower limbs e 1 cm; and the presence of a DVT. Preventive measures should be considered in these patients. There is an urgent need for a large-scale multicenter study to evaluate the prevalence of PE in COPD patients, and to confirm the risk factors.

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