Emerg Radiol (2015) 22:257–260
DOI 10.1007/s10140-014-1280-7

ORIGINAL ARTICLE

The prevalence of pulmonary embolism among patients suffering from acute exacerbations of chronic obstructive pulmonary disease

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Received: 20 August 2014 / Accepted: 15 October 2014 / Published online: 26 October 2014

Abstract The clinical diagnosis of acute pulmonary embolism (PE) in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) is often difficult due to the similarity in the presenting symptoms of the two conditions. The purpose of this study was to determine the prevalence of PE in patients with acute exacerbation of COPD. Forty-nine consecutive patients admitted to our medical center for acute exacerbation of COPD were investigated for PE (whether or not clinically suspected), following a standardized algorithm based on D-dimer testing and computed tomography pulmonary angiography (CTPA). PE was ruled out by a D-dimer value <500 μg/L in 20 (41 %) patients and by negative CTPA in 40 (82 %). PE was confirmed in 9 patients. The prevalence of PE was 18 %. One patient with normal D-dimer had PE. Presenting symptoms and signs were similar between patients who did and did not have PE. PE was detected in 18 % of COPD patients who were hospitalized for an acute exacerbation. This finding supports the systematic evaluation of PE in hospitalized COPD exacerbated patients.

Keywords Pulmonary embolism · Chronic obstructive pulmonary disease (COPD) · Exacerbation · D-dimer · Pulmonary CTA

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic progressive respiratory disease; smoking is the leading cause. The clinical course of COPD includes both a progressive decline in respiratory functions and acute exacerbations. The global initiative for chronic obstructive lung disease (GOLD) defines a COPD exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations" [1]. The median exacerbation frequency among COPD patients has been estimated at 2.5–3 events per year [2]. Acute exacerbations of COPD are associated with increased mortality and morbidity and may have profound impact on patients' quality of life [3]. Although most exacerbations are related to infectious agents, up to 30 % are of unknown etiology [3]. These "unknown" etiologies include myocardial infarction, heart failure, aspiration, and pulmonary embolism (PE) [1, 4]. Patients suffering from acute exacerbations of COPD are at increased risk of *venous thromboembolism* (VTE); the latter includes both deep vein thrombosis and PE [5]. The reasons for this are numerous and include the effects of smoking, immobilization and increased blood levels of pro-coagulant factors such as fibrinogen and factor XIII [6]. One quarter of patients with PE die within 1 year [7]. Moreover, PE has been shown to increase the death rate from COPD in the following year [8, 9]. Thus, diagnosing PE in patients suffering from COPD is important for patient care and prognosis. However, PE cannot be diagnosed from clinical information alone, since the signs and symptoms are non-specific. Further, the high resemblance in the clinical presentation of PE and COPD exacerbation (especially the "non-infectious" type) poses a clinical challenge; specifically, should COPD exacerbation be an indication for a systematic evaluation of PE?

The literature regarding this issue is not conclusive. A meta-analysis published in 2009 [10] reported a prevalence

rate of PE of 20 % among individuals with acute exacerbation of COPD, which reached 25 % of those who required hospitalization. However, Rutchman et al. detected a rate of only 3.3 % PE among COPD admitted to the emergency department and thus argued against systematic evaluation of PE among COPD patients [11]. The aim of the current study was to evaluate the prevalence of PE among patients suffering from acute COPD exacerbations at our institution and to assess the sensitivity and specificity of the D-dimer test in the diagnosis of PE in these patients.

Materials and methods

Study population

This single-institution prospective study was approved by our institutional review board. Forty-nine consecutive patients diagnosed with acute exacerbation of COPD and admitted to the hospital between February and August 2010 were found eligible for the study. Exclusion criteria were as follows: inability to give informed consent, inability to perform spirometry, impaired renal function, iodine allergy, anticoagulant treatment, and a known hypercoagulable state.

COPD acute exacerbation was defined as any worsening of dyspnea sufficiently severe to warrant an admission to the hospital. COPD was confirmed in all patients by evaluating airflow limitation with simple spirometry. One-second forced expiratory volume (FEV1) and forced vital capacity (FVC) were measured by simple spirometry 15 min after bronchodilator inhalation. A FEV1/FVC ratio of less than 70 % was a study inclusion criterion.

PE was investigated in all patients following a standardized algorithm based on blood sampling and computed tomography pulmonary angiography (CTPA). Blood sampling included measurements of D-dimer and creatinine levels at admission, before CTPA examination. A D-dimer value >500 μg/L was considered abnormal. To determine the frequency of contrast-induced nephropathy (CIN) following CTPA, creatinine level measurements were repeated at 48 h after CTPA performance. CTPA imaging findings (either lungs or pleural) were also reviewed. Findings were compared between those with and without PE.

Lower-limb venous ultrasonography was not performed because none of the patients of our study group had clinical symptoms or signs of deep venous thrombosis (DVT) on physical examination at hospital admission.

CT parameters

CTPA was performed on 64-detector-row CT instrument (Brilliance-64, Philips Healthcare, Cleveland, Ohio, USA). All patients were examined in the cranio-caudal direction during inspiratory breath-hold. The delay before data acquisition was adapted on an individual basis using the bolus tracking method. Between 60 and 80 mL of iodinated contrast medium (Iomeron 350 mg/mL, Bracco, Milan, Italy) were injected at 4 mL/s, followed by a saline chaser of 40 mL at 4 mL/s. Image acquisition started 5 s after a region of interest in the main pulmonary artery reached 120 HU (bolus tracking).

The scanning protocol included a 64×0.625 mm collimation, 1-mm-thick reconstruction, 0.5-mm reconstruction increment, and 0.5-s rotation time.

The interpretation was made by a senior radiologist. CT analysis was performed on axial slices and coronal, sagittal, and oblique multiplanar reformatted images. Both soft-tissue windows and lung windows were used. Acute PE was diagnosed when embolic material was directly visualized or when vessel truncation implied the presence of occlusion.

Statistical analysis

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as the mean±SD. Mean values were compared between groups by use of the unpaired Student's *t* test. A *P* value <0.05 was considered to indicate significance.

Results

Forty-nine patients were included in the study, 35 men and 14 women, mean age 65.5 years (range 43 to 92). All were current or former smokers with documented airflow limitation by spirometry. D-dimer levels were considered abnormal (>500 μg/L) in 29 patients (59 %). Of them, CTPA detected PE in 8 (27.6 %). One patient with confirmed PE had a normal D-dimer value. Altogether, 9 of the 49 patients (18.4 %) were diagnosed with PE.

CTPA detected atelectasis and pulmonary artery enlargement in a significantly higher proportion of patients with PE than in those without ($P<0.02$) (Table 1); no other statistically significant differences were detected in CT findings between the groups. An example of PE in a patient with unexplained exacerbation of COPD is shown in Fig. 1.

The sensitivity of D-dimer was calculated as 88.9 %, specificity as 42.5 %, and negative predictive value as 94 %. The mean FEV1 was 36 % of predicted. Patients with PE had more severe airflow limitation than did those without PE: the mean FEV1 was 28 % of predicted in patients with PE and 38.8 % in

Table 1 CTPA findings in COPD patients, with and without PE

CT finding	All patients PE=49	Patients without PE=40 (%)	Patients with PE=9 (%)
Enlarged PA	9	3 (7 %)	6 (70 %)*
Emphysema	23	18 (45 %)	5 (55 %)
Bronchiectasis	5	4 (10 %)	1 (11 %)
Atelectasis	14	9 (22 %)	5 (55 %)*
Consolidation/GGO	7	6 (15 %)	1 (11 %)
Solitary pulmonary nodule	2	2 (5 %)	0 (0 %)
Multiple pulmonary nodules	3	3 (7 %)	0 (0 %)
Interstitial changes	8	8 (20 %)	0 (0 %)
Pleuropulmonary fibro	14	11 (27 %)	3 (33 %)
Pleural effusion	11	9 (22 %)	2 (22 %)
Pulmonary edema	1	1 (2 %)	0 (0 %)
Peribronchial cuffing	4	4 (10 %)	0 (0 %)
Granulomas	4	3 (7 %)	1 (11 %)

PA pulmonary arteries

*$P<0.02$

those without PE ($P=0.02$). None of the patients developed renal failure attributable to contrast-induced nephropathy.

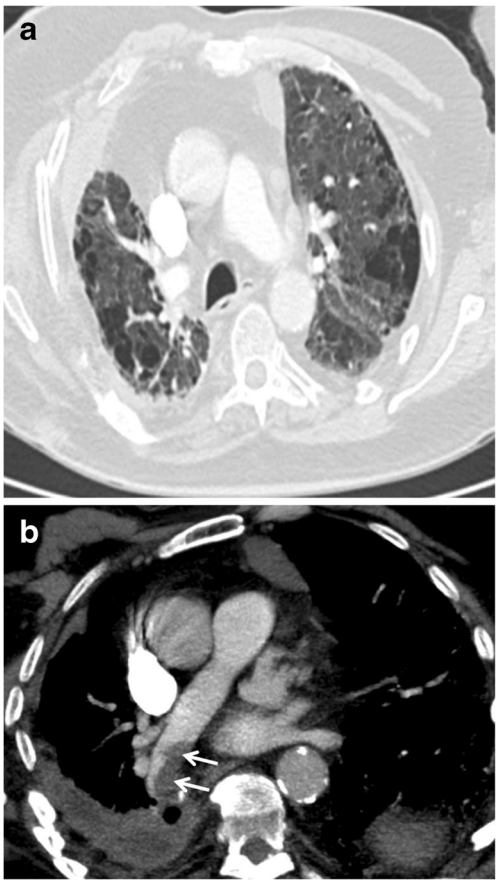

Fig. 1 Pulmonary embolism in a 78-year-old man with unexplained exacerbation of chronic obstructive pulmonary disease (COPD). **a** Axial computed tomography pulmonary angiography (CTPA) image (lung window) shows diffuse emphysematous changes in both lungs. **b** Axial maximum intensity projection (MIP) CT image showing a filling defect (*arrows*) in the right lower lobe pulmonary artery consistent with pulmonary embolism

Discussion

Diagnosing PE in patients with exacerbated COPD is a clinical challenge. However, guidelines for a diagnostic protocol have not been established. In the current study, the negative predictive value of the D-dimer test for the detection of PE among patients with COPD, 94 %, concurs with evidence that a negative D-dimer test excludes the great majority, yet not all cases of PE [12, 13]. Nevertheless, due to the low specificity, the definitive diagnosis of PE requires additional evaluations, mainly ventilation/perfusion lung scan or CTPA [14]. Since many COPD patients undergo abnormal chest X-rays, the preferred study in this scenario is CTPA [15]. Considering the above, the question as to whether to perform CTPA in all COPD exacerbations must be addressed. On one hand, PE diagnosis may be critical to both patients and to caregivers, in light of the association of PE with increased morbidity and mortality. The observation in the current study of more severe airflow limitation among COPD patients with PE than those without PE concurs with such. On the other hand, the performance of CTPA in all COPD patients significantly increases the number of CTPA exams performed and complicates the routine work-up. Also, issues of radiation exposure and the side effects related to iodine injection (allergy, renal impairment, etc.) should be addressed. Therefore, the determination of the frequency of PE in COPD patients is of paramount importance.

In this study, PE was investigated in all patients admitted to the hospital due to COPD exacerbation, regardless of the degree of clinical suspicion. The prevalence of PE observed (18.3 %) concurs with previously reported rates of 20–25 % [10]. In our view, these figures justify a routine-standardized protocol with systematic evaluation of PE in all hospitalized COPD-exacerbated patients, regardless of their D-dimer results. This contrasts with current practice at our center, according to which only 59.2 % (29/49) of the patients in our

cohort would have been referred to CTPA, after the exclusion from this test of the 20 patients who had normal D-dimer results. However, one (11.1 %) of the 9 patients with PE would have been missed. Since only hospital-admitted patients were included in the current study, it is not clear what percentage if any of not admitted patients could also have PE.

Of the 29 patients with abnormal D-dimer results, 21 (72.4 %) did not have PE. This compares with 36 % of the patients with D-dimer >500 μg/L and no PE in Akpinar et al's study [16]. Those authors suggested that the cutoff value for abnormal D-dimer should be elevated, so as to prevent excessive use of CTPA. They claimed that this is possible since those with PE had significantly higher levels than those without. According to their findings, a D-dimer cutoff level of 900 μg/mL would yield sensitivity and specificity of 70 and 71 %. The rate of PE of 37.8 % detected in that study is more than twice that detected in the current study. The older age of their population, mean age 73.4 years, may explain, at least in part, the differences in the findings between the studies.

Pulmonary emboli are detected incidentally in asymptomatic patients at a prevalence of approximately 1.0–1.5 % in the general patient population [17]. Incidental PE has also been reported in several clinical conditions including oncology patients (4 %), mechanically ventilated patients (18.7 %), elderly inpatients (16.7 %), and trauma patients (24 %) [17–20]. In our study, none of the patients had a history of physical trauma or mechanical ventilation in the preceding year or had a known risk factor for thromboembolic disease, such as clotting disorders, recent surgery, or malignancy.

Our study has several limitations including the fact that it was conducted in only one center with a relatively small sample size. In addition, color Doppler and venous lower-limb US was not performed and all patients were referred to CTPA. Adding such examination may affect patient work up and spare CTPA in some cases.

In conclusion, the clinical diagnosis of acute PE in COPD exacerbation patients is often difficult because the presenting symptoms of these conditions are very similar. The diagnosis of PE in the current study, in one of five COPD patients who required hospitalization for an acute exacerbation, supports the systematic evaluation of PE in these patients.

Conflict of interest The authors declare that they have no conflict of interest.

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