Should pulmonary embolism be suspected in exacerbation of Chronic Obstructive Pulmonary Disease?

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Abstract

Background: The cause of acute exacerbation of chronic obstructive pulmonary disease (COPD) is frequently difficult to determine. Pulmonary embolism may be a trigger of acute dyspnea in patients with COPD. We aimed to determine the prevalence of pulmonary embolism in patients with acute exacerbation of COPD.

Methods: We included 123 consecutive patients admitted to the emergency departments of two academic teaching hospitals for acute exacerbation of moderate to very severe COPD. Pulmonary embolism was investigated in all patients (whether or not clinically suspected) following a standardized algorithm based on D-dimer testing, lower limb venous ultrasonography and multidetector helical CT-scan.

Results: Pulmonary embolism was ruled out by a D-dimer value < 500 µg/L in 28 (23%) patients and a negative chest CT-scan in 91 (74%). CT-scan showed pulmonary embolism in 4 patients (3.3%, 95% CI 1.2-8.0%), including 3 lobar and one sub-segmental embolisms. The prevalence of pulmonary embolism was 6.2% (n=3) (95% CI 2.3-16.9%) in the 48 patients who had a clinical suspicion of pulmonary embolism and 1.3% (n=1) (95% CI 0.3-7.1%) when there was no suspicion. In two cases with positive CT scan, the venous ultrasonography also showed a proximal deep-vein thrombosis. No other patient was diagnosed with venous thrombosis.

Conclusions: the prevalence of unsuspected pulmonary embolism is very low in patients admitted in the emergency department for an acute exacerbation of their COPD. These results argue against a systematic work-up for pulmonary embolism in this population.
Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and represents a huge economical burden for the healthcare system.1,2 Acute exacerbation of COPD is a frequent reason for emergency department (ED) visit. 3 The most common triggers of exacerbations are infections of the tracheobronchial tree4,5 and air pollution6 but the cause of exacerbation is impossible to determine in up to 30% of cases.7

Clinical presentation of COPD exacerbation includes worsening of dyspnea, increased cough and sputum, and changes in the aspect of expectorations. Although clinical criteria have been used to determine which patient should be treated with antibiotics,8 these criteria are neither sensitive not specific enough to exclude other causes of dyspnea in this population. Other frequent clinical conditions may mimic the symptoms of COPD exacerbation, including congestive heart failure, pneumonia, pneumothorax, pleural effusion, and pulmonary embolism (PE).7

On the other hand, COPD is often cited among risk factors for acute venous thromboembolism and was recently identified as an independent predictor of PE.9 In small series of patients, the prevalence of deep vein thrombosis in patients admitted with acute exacerbation of COPD was 31%.10,11 Similarly, based on ventilation-perfusion lung scintigraphy, the prevalence of PE in patients admitted with acute exacerbation of COPD was as high as 20%.12,13 More recently, Tillie et al. explored the prevalence of PE in a cohort of COPD patients with unexplained dyspnea and found a prevalence of 25% in this population.14 However, that study was performed in a highly selected subgroup of patients and does not resolve the dilemma that primary care and emergency physicians face when taking care of acute exacerbation of COPD.

Our prospective study aimed to determine the prevalence of PE in patients presenting to the emergency department with acute exacerbation of COPD using a validated diagnostic strategy based on the use of D-dimer, lower limb ultrasonography and multi-detector computed tomography (CT).15

Materials and Methods

Study design and setting

This was a cross-sectional study performed in the emergency departments of two general teaching hospitals in Geneva and Lausanne, Switzerland, admitting 60'000 and 35'000 patients a year each respectively.

Study population

All consecutive adult patients known for moderate to very severe COPD accordingly to GOLD definition7 and admitted for an acute exacerbation of their COPD were eligible for the study. COPD had to be confirmed by pulmonary testing during the index admission. Exacerbation was defined as any worsening of dyspnea sufficiently severe to warrant an admission to the emergency room. Patients with renal failure...
(plasma creatinin > 150 µmol/l), allergy to IV contrast medium, on long-term anticoagulation therapy at admission, or in respiratory distress requiring intubation/non-invasive ventilation were excluded. Patients with an obvious alternative cause of dyspnea (lobar pneumonia, pneumothorax, pulmonary edema, and other obvious causes) were also excluded.

**Study protocol**

Every patient was evaluated by the emergency room physician with a standardized protocol including clinical evaluation, chest X-ray, ECG and arterial blood gas analysis. For each patient, the clinician had to determine whether there was a clinical suspicion of PE or not. Absence of suspicion of PE was defined as a patient in whom the physician in charge would not have searched a PE outside the study. Following the initial clinical evaluation, PE was investigated in all included patients following a standardized validated algorithm based on D-dimer (rapid ELISA assay, Vidas-DD Exclusion, BioMérieux) measurement, lower limb ultrasonography and multidetector helical CT scan. A plasma D-dimer value below 500 µg/l ruled out PE and no further examination was performed. For patients with a D-dimer value above 500 µg/l, both lower limb compression ultrasonography of the proximal veins and thoracic multidetector helical CT-scan were performed accordingly to a previously published algorithm.

Ultrasonographic criteria for deep-vein thrombosis were non-, or incomplete compressibility of the vein. CT-scans were obtained using a 16-slice multidetector-row CT. These examinations were performed in breath hold, with the injection of 100 ml of non-ionic contrast material (iopromide; Ultravist-300R™, Schering Ltd, Switzerland), with a power injector at 3ml per second, using a 1.5 millimetre slice thickness, 120 kV tube voltage and 200 mAs tube current. In patients with a BMI of 30 (or higher) the volume of contrast material was increased to 120 ml and the tube voltage to 140 kV. Pulmonary embolism was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material.

**Outcomes**

The main outcome measure was the proportion of patients diagnosed with pulmonary embolism, globally, and in the sub-groups of patients with or without clinical suspicion of PE. These groups were compared in terms of demographic characteristics and clinical presentation using Chi-Square or Fischer exact tests for categorical and t-tests for continuous data (SPSS for windows version 11.0, Chicago, IL).

The full study design was previously reported.

**Ethics**

The protocol was approved by our Institutional Review Board and each patient gave his/her written informed consent to participate.
Results

Five hundred and twenty-one patients were screened for inclusion between February 11, 2003 and December 17, 2004. Three hundred and eighty-five patients were excluded after the initial screening. Reasons for exclusion are summarized in Figure 1. Therefore, 136 patients were initially included. Thirteen patients were further excluded, eleven because COPD was not confirmed on spirometry, and two because CT-scan was not performed. The characteristics of the 123 included patients are summarized in Table 1.

Table 1: Characteristics of patients (n = 123) with acute exacerbation of their COPD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%), mean +/- SD or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 123</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 +/- 8</td>
</tr>
<tr>
<td>Female sex</td>
<td>39 (32%)</td>
</tr>
<tr>
<td>COPD severity</td>
<td></td>
</tr>
<tr>
<td>Very severe (mean +/- SD FEV1: 0.65 l +/- .15)</td>
<td>35 (28%)</td>
</tr>
<tr>
<td>Severe (mean +/- SD FEV1: 0.92 l +/- .26)</td>
<td>61 (50%)</td>
</tr>
<tr>
<td>Moderate (mean +/- SD FEV1: 1.42 l +/- .38)</td>
<td>27 (22%)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Family history of deep vein thrombosis or PE</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Previous deep vein thrombosis or PE</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Know heart failure</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Surgery within 1 month</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>20 (16%)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Other co-morbid conditions</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (33%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>19 (15%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>34 (28%)</td>
</tr>
<tr>
<td>Pleuritic</td>
<td>17 (50%)</td>
</tr>
<tr>
<td>Oppressive</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Reproduced by palpation</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Others non-pleuritic</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Cough</td>
<td>106 (86%)</td>
</tr>
<tr>
<td>Increased frequency</td>
<td>79 (64%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>84 (68%)</td>
</tr>
<tr>
<td>Increased volume</td>
<td>63 (51%)</td>
</tr>
</tbody>
</table>
Based on their initial clinical evaluation, the ED physicians suspected pulmonary embolism in 48 patients (39%), and did not in 75 patients (61%). There were no statistically significant differences between both groups of patients in terms of age groups, sex ratio, PE risk factors, chest X-ray, and ECG findings (data not shown). There were few differences in the clinical presentation: chest pain was present in 42% of the patients with a clinical suspicion of PE, compared to 19% of the patients without suspicion (p = 0.008), but the pain characteristics were similar in both groups. Cough was less frequent when PE was suspected (75% vs. 93%, p=0.009). Similarly, sputum was less frequent when PE was suspected (54% vs. 77%, p=0.016), but sputum characteristics were similar in both groups when sputum was present. Syncope was the presenting complaint in 3 (6%) patients with clinical suspicion of PE and in none of the remaining patients (p=0.051). Finally, severe hypoxemia was more frequent in patients suspected of PE: 48% of the patients suspect of PE had arterial pO2 values below 8.0 kPa compared to 20% in the group of patients without a suspicion of PE (p = 0.003).

D-dimer was obtained for all patients. Pulmonary embolism was excluded on the basis of normal (< 500 µg/L) D-dimer levels in 28 (23%) patients (table 2).
Table 2: Results of D-dimer, lower limb ultrasonography (US) and chest CT-scan in 48 patients with a clinical suspicion of PE and in 75 patients without clinical suspicion of PE.

<table>
<thead>
<tr>
<th></th>
<th>PE suspected</th>
<th>PE not suspected</th>
<th>P value (suspected vs not suspected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>48 (39%)</td>
<td>75 (61%)</td>
<td></td>
</tr>
<tr>
<td>D-dimer &lt; 500</td>
<td>11 (23%)</td>
<td>17 (23%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Positive US*</td>
<td>1 (2.1%)</td>
<td>1 (1.3%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Positive CT-scan</td>
<td>3 (6.3%)</td>
<td>1 (1.3%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*The two patients with a deep-vein thrombosis on ultrasonography also had a positive chest CT scan. US: lower limb venous compression ultrasonography.

The percentage of negative D-dimer (< 500 µg/L) was similar in patients with and without a clinical suspicion of PE. Lung CT-scan was performed in 95 patients (77%) and lower limb ultrasonography in 90 patients (73%). In 5 patients (4%), venous ultrasonography could not be performed due to practical reasons.

Lung CT-scan showed pulmonary embolism in 4 patients (3.3%, 95% CI 1.3-8.0%), including 3 lobar and one sub-segmental PE. In two cases the lower limb ultrasonography also showed a proximal deep-vein thrombosis. None of the patients with a negative CT-scan was diagnosed with deep-vein thrombosis at lower limb ultrasonography. PE was diagnosed in 3 patients (6.2%, 95% CI 2.3-16.9%) who had a clinical suspicion of PE and in 1 patient (1.3%, 95% CI 0.3-7.1%) who had no suspicion (table 2).

Discussion

In this prospective series of 123 patients with moderate to very severe COPD admitted with worsened dyspnea, we found that the prevalence of PE was very low. Indeed, a diagnostic procedure based on systematic D-dimer testing, lower limb ultrasonography and lung CT-scan identified PE in only 4 patients (3%, 95% CI 1 to 8%). This prevalence was even lower in the subgroup of patients without a clinical suspicion of PE in the emergency room. In this subgroup, only one PE was diagnosed by our systematic work-up (prevalence of 1.3%). The three remaining cases were suspected by the emergency physician and would have been diagnosed outside the study.

These results contrast strikingly with studies suggesting that the prevalence of PE might be as high as 15 to 25%. These differences may have different explanations. First, the imaging method used for diagnosing PE is crucial in a population of patients
with chronic lung diseases. Ventilation-perfusion scintigraphy was used in previous studies.\textsuperscript{12,13} Although scintigraphy is an acceptable tool for the diagnosis of PE in patients without underlying lung diseases, the interpretation of lung scintigraphy is difficult in patients with COPD, which might have led to an overestimation of the true prevalence of PE in that population.\textsuperscript{19} In contrast, the performance of CT-scan is not altered in COPD patients.\textsuperscript{19,20} We used a validated algorithm based on multidetector CT-scan\textsuperscript{15} which should have minimized the risk of false-positive findings.

Second, most studies exploring the relationship between COPD exacerbation and deep-vein thrombosis or pulmonary embolism were retrospective or based on autopsy findings.\textsuperscript{9,21,22} Our prospective design and our inclusion criteria limited selection biases.

Third and most importantly, we studied an unselected population of patients admitted to the emergency room of two general teaching hospitals with an acute exacerbation of their COPD. Some studies included only the most severely ill patients admitted to intensive care units.\textsuperscript{11} Others excluded patients with normal D-dimer values.\textsuperscript{13} In our study, 23\% of the patients had D-dimer values below 500 µg/L excluding PE. Excluding these patients would overestimate the true prevalence of PE in an unselected population of COPD patients with acute exacerbation.

Nevertheless, none of those explanations account for the striking difference between our findings and the 25\% prevalence of PE recently reported by Tillie-Leblond et al.\textsuperscript{14} That series was prospective and used multidetector CT. The inclusion criteria appeared similar to those of our study and are summarized as exacerbation of COPD of unknown origin. Their criteria for lower respiratory infection were broad, however, and they excluded patients with increased sputum volume and/or increased sputum purulence, fever, history of cold, and sore throat. We included those patients except when the initial X-ray showed obvious signs of pneumonia. This might account for part of the difference in PE prevalence compared with our series. However, the gap remains large, and we feel that the main difference was truly the clinical setting and patient selection. The French study was conducted in a large referral inpatient respiratory disease department while our population was representative of the patients treated by emergency physicians in general hospitals. Furthermore, 29\% of COPD patients in the French study had cancer compared with only 5\% in our series.

Our study has some limitations. First, the number of excluded patients is relatively high. But 41\% of those patients were excluded for reasons unlikely to have introduced bias (refusal or inability to consent, ongoing oral anticoagulant treatment, allergy or renal failure). Patients who were excluded because exacerbation of their dyspnea was attributed to another cause had very clear alternative diagnoses. In particular, pneumonia was defined by both a consolidation on chest X-ray and a compatible clinical presentation (fever and purulent sputum). Therefore, only 10\% of patients were excluded because they required non-invasive ventilation or intubation and who were not able to undergo a CT-scan procedure. Whether the prevalence in this subgroup could be higher as suggested by Schonhofer et al. is unknown.\textsuperscript{11} Second, the small number of PE did not allow us to explore whether clinical or biological characteristics could identify a sub-group of patients with a higher prevalence of PE.
Despite this limitation and although this was not a primary objective of this study we were able to identify some clinical characteristics that led the emergency physician to suspect PE. PE was more frequently suspected in the presence of chest pain, in the absence of purulent sputum, or when a severe hypoxemia was present.

In conclusion, our results argue against a high prevalence of unsuspected PE in patients admitted for an acute exacerbation of their COPD and against a systematic work-up for PE in these patients but further studies are needed to confirm our findings in similar groups of patients. When PE is clinically suspected, a diagnostic strategy based on D-dimer testing, lower limb ultrasonography and multidetector CT-scan is appropriate.

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Figure 1 legend
Study flow-chart summarizing inclusion and exclusion processes and main outcomes. PE stands for pulmonary embolism, COPD for Chronic Obstructive Pulmonary Disease.
References


Figure 1

Screened for inclusion
N = 521

Excluded after initial screening
N = 385
- Other causes of dyspnea 103 (27%)
  - Pneumonia 73
  - Pulmonary oedema 16
  - Myocardial infarction 5
  - Pneumothorax 5
  - Neurological diseases 3
  - Asthma 1
- Anticoagulation treatment 53 (14%)
- Informed consent impossible (delirium, dementia) 57 (15%)
- Patient refusal 30 (8%)
- Allergy to X-Ray contrast medium 8 (2%)
- Serum creatinin > 150 mol/L 46 (12%)
- Intubated/non invasive ventilation 41 (10%)
- Others 47 (12%)

Included after initial screening
N = 136
- Clinical suspicion of PE 56
- No suspicion 80

Further exclusions
- COPD not confirmed 11
- CT not done 2

Included in final analyses
N = 123
- Clinical suspicion of PE 48
  - Confirmed PE 3
- No clinical suspicion of PE 75
  - Confirmed PE 1
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