Pulmonary embolism in chronic hypoxemic patients with and without secondary polycythemia - analysis of risk factors in prospective clinical study

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ABSTRACT

Aim Prospective evaluation of the incidence of pulmonary embolism and risk factors for this life-threatening disease on chronic hypoxemic patients treated in intensive respiratory care unit.

Methods The study enrolled 842 consecutive patients with severe exacerbation of chronic obstructive pulmonary disease or respiratory failure. The initial assessment included clinical history collection, physical examination, hematological and biochemical analysis, gas analysis, chest X-ray, 12 lead electrocardiography and determination of value of D-dimer. Of all enrolled patients, 211 met the exclusion criteria. Of 631 included patients, 269 (42.6%) had normal D-dimer. D-dimer level ≥500 μg/L was found in 362 (57.5%) patients who were referred to Doppler echocardiography, lower limb color Doppler ultrasonography and thoracic multidetector helical computed tomography. According the value of hematocrit, all patients were divided in two groups: group I (100 patients) with polycythemia and group II (262 patients) without polycythemia.

Results The first outcome of the study was the significantly higher incidence of pulmonary embolism in group I of patients than in group II, 39 (39%) and 29 (11.06%), respectively. Patients in group I had significantly worse disturbance of pulmonary function and higher degree of pulmonary hypertension (58.4±3.66 vs. 30.3±9.41). Apart from polycythemia in group I, the most common risk factors were arrhythmia, absolute and varicose veins.

Conclusion Polycythemia is a single most significant risk factor for pulmonary embolism in chronic hypoxemic patients. Value of D-dimer ≥500 μg/L, as well as presence of comorbidity, particularly vein varicose, in these patients should raise clinical suspicion of PE.

Key words: chronic obstructive pulmonary disease, multidetector computed tomography, arrhythmia, varicose veins, pulmonary hypertension
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and disability, and by 2020 it is predicted to become the third greatest cause of death worldwide (1,2). As pulmonary function deteriorates, and as the COPD progresses, the risk of alveolar hypoxia and consequent hypoxemia increases (2,3). Exacerbations of COPD are frequently associated with deterioration in gas exchange and associated hypoxemia (3). Uncorrected chronic hypoxemia is associated with the development of adverse effects, including secondary polycythemia, and systemic inflammation (3-5). When chronic hypoxemia is present in patients with severe COPD exacerbations or respiratory failure, it can contribute to the development of pulmonary hypertension, and leads to pulmonary endothelial dysfunction, reduced cerebral blood flow, and increased risk of venous thromboembolic disease (3,4,6). Low oxygen levels in blood cause a high production of erythropoietin. This enzyme enters red bone marrow and causes it to start making red blood cells in an erythropoiesis (3). Red blood cells carry oxygen in blood, so more red blood cells are made in the body’s attempt to raise blood oxygen levels (7,8). The exact mechanism of this form of secondary polycythemia is not yet fully understood, but angiotensin II may be responsible for inappropriately sustained erythropoietin secretion (9) or direct stimulation of erythroid progenitors (5). The normal range of hematocrit is defined and quoted as 0.45 ± 0.05 in males and 0.41 ± 0.05 in females (6). A rise in hematocrit is associated with greater blood viscosity that may cause hemodynamic and rheological problems (7,8). It is believed that hematocrit values above 0.50 increase the risk of acquiring hypertension, heart failure, myocardial infarction, and especially thrombosis (6,8). The incidence of pulmonary embolism (PE) in patients with COPD and respiratory failure is uncertain, depending on whether the ante-mortem or autopsy studies (10-12), prospective or retrospective (13,14), in outpatients or in hospitalized patients (15,16), or on consecutive or in patients are evaluated according to score systems, etc. (17,18). A compilation of studies examining the incidence of PE in patients with COPD reported a rate of 3.3%–25%, with the majority discovered by surveillance studies and those clinically asymptomatic (17). Autopsy studies have reported the incidence of PE in COPD patients to be 28%–30% without defining the percentage of suspected antemortem diagnoses (14,15,17,19). Considering the fact that chronic hypoxemia and secondary polycythemia are particularly strong risk factors for pulmonary embolism, it was hypothesized that PE is more frequent in the population of patients with severe COPD or respiratory failure with secondary polycythemia than in patients without it.

The aim of this prospective clinical study on consecutive chronic hypoxemic patients was to evaluate the incidence of PE and risk factors for this life-threatening, but preventable and treatable disease.

PATIENTS AND METHODS

This study was originally designed as prospective clinical management trial on consecutive patients who were hospitalized in the intensive respiratory care unit of the Clinic for Pulmonary Diseases with 16 beds for patients with respiratory disorders requiring continuous monitoring and treatment. This Clinic is the largest in southeast Serbia as tertiary university affiliated Clinic of the Clinical Center Niš. Each year about 20,000 patient visits are performed and about 3000 - 4000 patients are admitted. Data were collected from 20 January 2011 to 20 November 2012. The study protocol was compliant with Helsinki guidelines for human experimentations and approved by an institutional review board, the Ethical Committee of the Clinical Center Niš, and written informed consents were obtained from all patients or their closest relatives at the time of admission to the Clinic.

The study enrolled 842 consecutive patients. The initial assessment of patients admitted with severe exacerbation of COPD according the Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD) (2) criteria or respiratory failure in intensive care unit (ICU) included: clinical history collection, complete physical examination, laboratory biochemical and hematological analysis, arterial gas analysis, chest X ray examination, 12 lead ECG and determination of value of D-dimer. Exclusion criteria were as follows: actual diagnosis of pulmonary embolism (PE) that had been made before admission, ongoing use of anticoagulant therapy for a reason other than pulmonary embolism,
exacerbation of COPD due to pneumothorax, pneumonia, severe neuromuscular disorders in end of life stage, severe impaired renal function, inability to give informed consent, or other iatrogenic reasons (such as known allergy to contrast, extreme obesity). Of 842 consecutive patients, 211 met the exclusion criteria. After the initial clinical evaluation, pulmonary embolism was investigated in 631 included patients following a standardized validated algorithm based on D-dimer. Plasma D-dimer levels by enzyme-linked immunosorbent assay (ELISA) Enzygnost D-dimer micro was measured (Dade Behring, Marburg, Germany), and ruled out pulmonary embolism in patients with a level below the cutoff value of 500 μg/L (Figure 1).

All patients included in the study protocol for evaluation of pulmonary embolism were referred to Doppler echocardiography, lower limb color Doppler ultrasonography (Color Doppler Ultrasound G 40 Siemens, Germany, equipped with high resolution 7.5 -12 MHz transducer), and 64-slice thoracic multidetector helical computed tomography scan (spiral CT, Philips Secura, Netherlands); its parameters were 1.25 mm slice thickness with a 1.2 mm reconstruction interval at 120 kV/150 mAs, and 100 ml of nonionic contrast material containing (iopromide; Ultravist-300R, Schering, Baas, Switzerland), with an injection speed of 3.0 mL/s. The decision of the presence or absence of pulmonary embolism was made by trained attending radiologists who were blinded to any specific patient clinical information. Secondary polycythemia was determined on the basis of hematocrit values higher than 0.5 (50%).

The sample size of this study was determined by a sufficiently large number of patients with chronic hypoxemic patients with secondary polycythemia (100), which could be derived for statistically valid conclusions.

Baseline characteristics are reported as the mean plus or minus standard deviation for continuous variables and as percentages for categorical variables. Differences in baseline characteristics between groups of study participants were determined using the Student t test for continuous variables and the chi-square test, stratified analysis of 2x2 tables, Mantel-Haenszel’s summary chi-square test for dichotomous variables or Fisher’s exact tests for categorical data. Statistical significance for all analyses was accepted at a level of p < 0.05. The variance was of highly statistical significance when p < 0.01.

RESULTS

Among 842 consecutive screened patients treated in ICU from 20 January 2011 to 20 November 2012, 211 patients met the exclusion criteria. Of 631 patients enrolled in study protocol, 269 (42.6%) had normal value of D-dimer below 500 μg/L, and D-dimer levels of 500 μg/L or above were found in 362 (57.4%) patients. According to
the value of hematocrit all patients were divided in two groups: group I (100 pts.) with chronic hypoxemia with secondary polycythemia (hematocrit greater than 0.50) and group II (262) chronic hypoxemic patients without secondary polycythemia (hematocrit less than 0.50).

The first outcome was the significantly higher incidence of pulmonary embolism in group I with chronic hypoxemia and secondary polycythemia than in group II without secondary polycythemia, 39 (39%) and 29 (11.06%), (p<0.001). The patients of the first group with chronic hypoxemia and secondary polycythemia were older on average by 2.95 years (95% CI 0.614 to 5.286 years), (p<0.005). There were no significant differences in the age of the patients in group I and group II with and without PE (p=0.200 and p=0.931, respectively). Between the groups there was not statistically significant difference in the gender structure (p=0.394), as well as between the patients in group I and II with and without PE (p=0.797 and p=0.743, respectively).

Gas analysis of the group I patients showed significantly higher degree of hypoxemia (42.8±5.67 vs. 57.9±6.36) and hypercapnia (63.4±8.4 vs. 45.2±5.3) than patients in group II. The obtained results were in favor of the fact that patients in group I with polycythemia had a significantly higher degree of disturbance of respiratory gas exchange, a higher degree of pulmonary hypertension (58.4±3.66 vs. 30.3±9.41), and more ECG signs of cor pulmonale than patients in group II without secondary polycythemia, 39 (39%) and 29 (11.06%), (p<0.001). The patients of the first group with chronic hypoxemia and secondary polycythemia were older on average by 2.95 years (95% CI 0.614 to 5.286 years), (p<0.005). There were no significant differences in the age of the patients in group I and group II with and without PE (p=0.200 and p=0.931, respectively). Between the groups there was not statistically significant difference in the gender structure (p=0.394), as well as between the patients in group I and II with and without PE (p=0.797 and p=0.743, respectively).

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ups of patients with and without secondary polycythemia was confirmed (Table 5). Comparing the incidence of PE, there was no statistical significance between the patients with (24 patients) and without (15 patients) risk factors for PE in chronic hypoxemic patients with secondary polycythemia (p=0.092).

<table>
<thead>
<tr>
<th>Pulmonary embolism</th>
<th>Risk factor</th>
<th>Risk factor</th>
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</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>29 *</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>128</td>
<td>105</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>208</td>
<td>154</td>
</tr>
</tbody>
</table>

*Pulmonary embolism in chronic hypoxic patients without secondary polycythemia was significantly more frequent in the presence of risk factors (p<0.001);*

In the second group of patients with chronic hypoxemia without secondary polycythemia there was a statistically significant difference between the number of patients with confirmed PE who had risk factors for PE (29 patients), compared to the number of patients without risk factors (0 patients) (p=0.00030 and <0.001, respectively).

In Group II patients with chronic hypoxemia without secondary polycythemia, the Mantel–Haenszel’s summary chi-square test was applied. It was unambiguously found that in chronic hypoxic patients without polycythemia, pulmonary embolism was significantly more frequent when risk factors were present than in their absence (p<0.001), which was not the case with the group of chronic hypoxic patients with secondary polycythemia.

This study clearly demonstrated a significantly higher incidence of pulmonary embolism in chronic hypoxic patients with secondary polycythemia than in those without it (p=0.007 and p<0.001, respectively). The results therefore indicated that secondary polycythemia is the most significant single risk factor for pulmonary embolism in chronic hypoxic patients.

**DISCUSSION**

Chronic obstructive pulmonary disease (COPD), especially during severe exacerbation and as an acute deterioration of chronic respiratory failure, requiring treatment in intensive respiratory care units, is a risk factor for pulmonary embolism (PE) and potentially fatal outcome (14,15). In spite of the awareness of the fact from both the pathophysiologic and clinical perspective, the data on the prevalence and incidence of PE in this large patient population are at least confusing (11,12,14,17).

The results of the studies about the incidence and prevalence of PE in COPD patients were rather inconsistent (17), ranging from 24.9% in hospitalized patients (18), to 3.3% of those who were evaluated in the emergency departments (19) and in autopsy studies PE was present in 30% of COPD patients (13). The reasons for such findings should be probably sought in the fact that the studies were very different in both the methodology and the number of patients involved, as well as in the degree of severity of COPD and treating institution (11,13,14,17,19). The symptoms of acute COPD exacerbation or acute events in respiratory failure are very similar to PE symptoms, which poses a real clinical challenge in establishing clinical suspicion of PE in these patients (12,15,19). It has been established that in approximately one third of patients there are no clear reasons for a COPD exacerbation on admission for hospital treatment (18), as well as that the risk of PE increases with age, immobilization, and numerous comorbid conditions in these patients (20-22). It has also been found that COPD patients have approximately twice the risk of pulmonary embolism (PE) and other venous thromboembolic events (VTE) than those without COPD (10,14,22). Although it is a well-known fact that COPD is associated with a procoagulant state marked by elevated circulating blood-borne tissue factor-procoagulant activity and increased levels of fibrinogen and factor XIII (5,15,21), secondary polycythemia has not been observed as a risk factor for PE in any of the studies so far. The reason for this lies in the fact that in many health care systems worldwide there has been a large body of patients on long term oxygen therapy (LTOT), used with success to remove the consequences of chronic hypoxemia, such as secondary polycythemia. More recent studies suggest polycythemia is less of an issue in modern COPD populations (7,8). In our patients, LTOT has not been widely administered.

Three aspects of our study findings require comments.

First, this study is a prospective one, a clinical trial enrolling consecutive chronically hypoxe-
mic patients treated in the respiratory intensive care unit for severe COPD exacerbations or acute deterioration of respiratory failure, with a considerable number of patients in both groups, very different by the degree or duration of chronic hypoxemia and its consequences.

Second, the most important result of the study is a statistically significant higher number of patients with chronic hypoxemia and polycythemia, proving PE, compared to the number of those without polycythemia, demonstrating that polycythemia is the most important single risk factor for PE in these patients. The incidence of PE in patients with polycythemia in this study was far higher compared to other studies, exceeding even the incidence of PE in COPD in autopsy studies (13-21). The result is explained by the fact that the patients with polycythemia had very disturbed function of the lungs. Such a degree of pathophysiologic damage is associated with altered rheological blood properties, potentiating a procoagulable state. On the other hand, patients without polycythemia in this study had a PE incidence similar to that in many other studies from 10.4% do 16.5% (10-14, 23).

Our groups of patients did not differ significantly in their gender and age structure, and thus gender and age could not be regarded as especially significant risk factors for PE, which disagreed with the studies in which male gender and age below 60 and over 75 years were found to be significant risks for the occurrence of PE (15,16,21). The patients with polycythemia were significantly older than the patients in the study by Piazza (15) and Agkun (23), with considerably more women and with a much higher incidence of PE. In our patients, other risk factors for PE were also markedly present, except for secondary polycythemia, which was similar to other studies’ results, demonstrating the existence of significant comorbid conditions in chronically hypoxic patients (11, 20-23). Arrhythmia absoluta was a single most commonly present factor in patients with polycythemia, but it was not a statistically significant factor in the occurrence of PE in these patients. In contrast, it was established that venous varices constituted a statistically significant factor for PE in some other studies, which differs from this study results and can be accounted for by different patient populations (10,14,15,18,23).

Third, on admission for treatment, all our patients had clinically suspected pulmonary embolism, while patient categorization based on the Wells or Geneva score was not used. The methodology employed in this study was based on a valid standardized diagnostic algorithm for PE, based on D-dimer patient selection, where values below 500 µg/L exclude the diagnosis of PE with a high degree of probability (24,25). A low D-dimer level remains the single most useful haematological parameter for excluding PE (21,24,25). The present findings have simply pointed out that the general rules for other populations with suspected PE also apply completely to patients with COPD exacerbations (22).

This study had some limitations. First, we did not observe smoking habits in our examinees (smoking might have had an impact on polycythemia). Second, we assessed immobilization very strictly as a risk factor, confirming it only in literally immovable patients due to cerebrovascular events, in grave general condition due to underlying malignancy, due to obesity, or complications of diabetes. Also, the longitudinal follow up data for patients treated for PE were missing, as well as the data about PE recurrences and treatment outcomes.

In conclusion, our study supports the theory that secondary polycythemia in chronically hypoxic patients hospitalized in intensive respiratory care units for acute exacerbation of COPD or respiratory failure substantially impairs the rheological characteristic of blood and significantly contributes to the procoagulant state, and secondary polycythemia is the most significant single risk factor for pulmonary embolism. Its presence, as well as D-dimer values above 500 µg/L and comorbid conditions as risk factors for PE, especially venous varices, should raise suspicion of pulmonary embolism in this patient population. Future prospective longitudinal studies of pulmonary embolism surveillance in chronically hypoxic patients could evaluate the results of this study.

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TRANSPARENCY DECLARATION
Competing interests: none to declare.
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Plućni embolizam kod hronično hipoksemičnih pacijenata sa i bez sekundarne policitemije – analiza faktora rizika u prospektnoj kliničkoj studiji

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SAŽETAK

Cilj istraživanja je utvrđivanje incidence plućnog tromboembolizma i faktora rizika za nastanak ove potencijalno fatalne bolesti kod konsekutivnih hronično hipoksemičnih pacijenata, lečenih na odeljenju intenzivne respiratorne nege.

Pacijenti i metode U studiju su uključena 842 konsekutivna pacijenta s teškom egzacerbacijom hronične opstruktivne bolesti pluća ili respiratornom insuficijencijom. Inicijalni pregled obuhvatao je uzimanje anamnestičkih podataka, fizički pregled, laboratorijske hematološke i biohemijske analize, gasne analize arterijske krvi, radiografiju grudnog koša, 12-kanalni elektrocardiogram i određivanje vrednosti D dimer. Ekskluzionim kriterijima iz daljeg je istraživanja isključeno 211 pacijenata. Od 631 pacijenta uključenog u dalje istraživanje, 269 (42.6%) je imalo D dimer ispod 500 μg/L, a 362 (57.4%) povećane vrednosti. Pacijenti s vrednostima D dimera upućeni su na Doppler ehokardiografiju, kolor Doppler ehosonografiju donjih ekstremiteta i 64-slajsnu multidetektorsku spiralnu kompjuterizovanu tomografiju grudnog koša u cilju dokazivanja plućnog embolizma. Prema vrednostima hematokrita svi pacijenti su podeljeni u dve grupe: grupu I (100 pacijenata s policitemijom) i grupu II (262 pacijenta bez policitemije).

Rezultati Utvrđena je signifikatno veća incidencu plućnog embolizma kod hronično hipoksemičnih pacijenata s policitemijom u odnosu na pacijente bez policitemije, 39 (39%) vs. 29 (11,06%). Pacijenti s policitemijom imali su teži poremećaj plućne funkcije i veći stepen plućne hipertenzije. Kod ispitanika grupa I najčešći faktori rizika za nastanak plućnog embolizma bili su arrhythmia absoluta i varikoziteti vena.

Zaključak Sekundarna policitemija je pojedinačni najznačajniji faktor rizika za nastanak plućnog embolizma kod hronično hipoksemičnih pacijenata. Vrednosti D dimera iznad 500 μg/L i prisustvo komorbiditeta, posebno varikoziteta vena, trebalo bi da pobude kliničku sumnju na plućni embolizam kod ovih pacijenata.

Ključne reči: hronična opstruktivna bolest pluća, multislasna kompjuterizovana tomografija, aritmija, varikoziteti vena, plućna hipertenzija