

Incidence of deep venous thrombosis in patients with both pulmonary embolism and COPD

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Abstract. *Introduction.* There are no studies investigating populations of patients with both pulmonary embolism and chronic obstructive pulmonary disease (PE-COPD) with and without deep venous thrombosis (DVT). *Aim of the study.* To define the prevalence of DVT in COPD with PE and to compare the characteristics of COPD patients who develop PE, with and without DVT. Secondly, we aimed to assess differences in the localization of PE among study groups. *Methods.* 116 patients with pulmonary embolism (PE) were enrolled in a retrospective study. Clinical data as well as echocardiographic and lower limb ultrasonography records were collected for all subjects. Subjects were divided into two groups according to the presence of COPD: Group 1, 54 patients with diagnosis of PE without COPD and Group 2, 66 patients diagnosed of PE with COPD. Then, individuals of Group 2 were subdivided in two subgroups according to the presence (n=21) or absence (n=45) of DVT. *Results.* 33% of patients with COPD and PE showed DVT. These subjects had higher PaCO₂ and ejection fraction (p<0.05 for all) and higher percentage of chronic renal failure and diabetes mellitus compared to those without DVT (p<0.05 for all). Moreover, in COPD-PE patients with DVT, the most frequent localization was proximal (54% of total), whereas COPD-PE patients without DVT showed a more frequent segmental localization (60% of total). No difference was found in clinical presentation and blood chemistry tests. *Conclusions.* DVT was non common in PE-COPD patients. Chronic renal failure, and type 2 diabetes mellitus are more frequent in PE-COPD patients with DVT, that showed a higher frequency of proximal localization, thereby indicating a greater risk of more severe clinical implications. Conversely, PE-COPD subjects without DVT showed a more frequent segmental localization and were less hypercapnic. PE should be taken into account in COPD with worsening of respiratory symptoms, also in absence of DVT. (www.actabiomedica.it).

Key words: Venous thromboembolism, Chronic Obstructive Pulmonary Disease, Pulmonary embolism, In situ thrombosis.

Introduction

Venous Thromboembolism (VTE) is a spectrum of diseases ranging from Pulmonary Embolism (PE) to deep venous thrombosis (DVT) and pulmonary infarction [1]. The most frequent clinical presentation

of VTE in general settings is DVT, with two cases of DVT for one PE case [1].

Like other cardiovascular diseases, VTE is more prevalent among patients with Chronic Obstructive Pulmonary Disease (COPD) than those without COPD [2,3]. Indeed, compared to the general

population, the risk of PE is greater than the risk of DVT in both stable and exacerbated COPD. Interestingly, PE is described in up to 25% of hospitalized patients with COPD [5]. Aleva et al found that the pooled prevalence of PE in unexplained acute exacerbation of COPD (AE-COPD) was 16.1% (95% CI, 8.3%-25.8%), whereas the pooled prevalence of DVT in AE-COPD was 10.5% (95% CI, 4.3%-19.0%) [6].

Furthermore, the diagnosis of PE in COPD is made difficult by the fact that the symptoms of these conditions can overlap [7]. The latter is a serious problem, considering that patients with COPD and PE have 70% higher rate of in-hospital death and twice the rate of dying within 30 days from diagnosis of VTE compared to those without COPD [8]. Similarly, patients with concomitant COPD and PE show an increased 1-year mortality compared to those without COPD (53.3%, relative risk 1.94) [6,9,10]. Based on the above, chronic respiratory diseases have been integrated in Pulmonary Embolism Severity Index [11].

Moreover, COPD may be an independent risk factor for PE, especially in subjects under 60 years old [12].

In light of these premises, the aim of our study was to define the prevalence of DVT in COPD with PE and to compare the characteristics of COPD patients who develop PE, with and without DVT. Secondly, we

aimed to assess differences in the localization of PE among study groups.

Materials and Methods

Patients and Study design

The current retrospective study was performed in the units of respiratory diseases and internal medicine of the University hospital Policlinico of Bari, Italy.

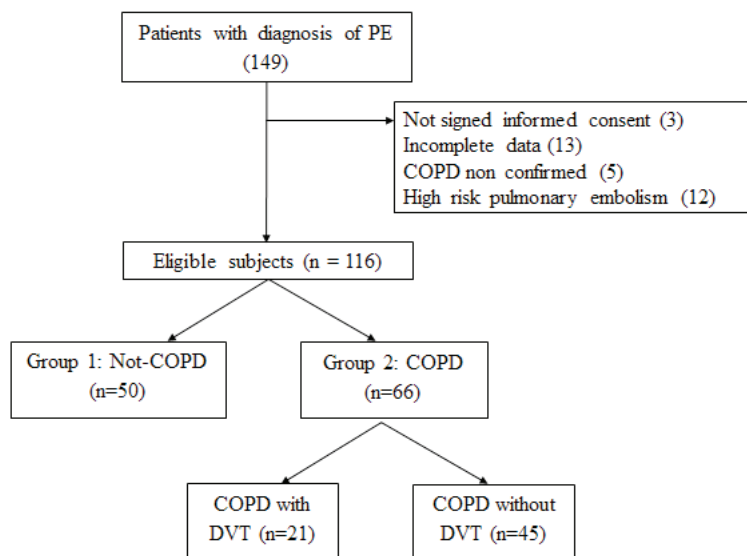
We investigated all patients admitted to the above wards who were diagnosed with PE (n=149) according to the ESC ERS guidelines 2014 [11] from January 2014 to February 2016.

Patients were divided into two groups according to the presence of COPD, strictly following GOLD guidelines 2017 [13]: Group 1, consisting of 54 patients with diagnosis of PE without COPD and Group 2, made of 66 patients diagnosed of PE with concurrent COPD.

Subsequently, individuals of Group 2 were subdivided in two subgroups according to the presence or absence of DVT. (see Figure 1)

This study was conducted in accordance with International Conference on Harmonization guidelines

Figure 1: Design of the Study



and the Declaration of Helsinki. All procedures performed in the present study were approved by the ethical institutions at which the study was conducted and an informed consent was required to all participants.

Exclusion criteria were as follows: absence of informed consent, incomplete data, failure to confirm the diagnosis of COPD, high risk pulmonary embolism.

Diagnosis of PE was conducted at the Emergency Department (ED) of Policlinico, Bari with Computed tomographic pulmonary angiography (CTPA) or ventilation-perfusion scan according to ESC ERS guideline 2014 [11], with definition of localization (proximal, segmental or subsegmental).

Afterwards, if not performed at the ED, upon admission to the wards of respiratory medicine or internal medicine, each patient underwent the following investigations: collection of full medical history (including confirmation of COPD diagnosis and PE risk factor), clinical evaluation, arterial blood gas analysis, routine blood tests including D-dimer and NT-pro-BNP, echocardiography with estimation of ejection fraction and pulmonary artery systolic pressure (PASP) and lower limb ultrasonography for research of DVT. COPD was confirmed by medical data provided by patients or present in the ward archives.

We considered the following risk factors for PE: obesity, defined by BMI>30; recent trauma; immobility, defined as complete bed rest; use of contraceptive medications; current malignancy; active pneumonia; atrial fibrillation (AF); type 2 diabetes mellitus; current smoking. We have also evaluated presence of ischemic heart disease, systemic hypertension and chronic renal failure.

Lower limb ultrasonography

Complete lower limb compression ultrasonography was performed within 24h of the diagnosis of PE by the same operator with extensive experience in echo-colour Doppler (7,5 Mhz linear probe, Ascendus, Hitachi, Japan).

In detail, common iliac vein, common femoral vein, superficial femoral vein, saphenofemoral junction, popliteal vein and posterior tibial vein were investigated. Each vein was examined in both longitudinal

and cross-section scans. Ultrasonographic criteria for deep-vein thrombosis were non-compressibility or incomplete compressibility of the vein [14].

Statistical Analysis

Baseline characteristics of patients were reported as mean \pm standard deviation (SD) for continuous variables and as a percentage (%) for categorical variables. Continuous variables were compared using Student's t-test for independent samples and Chi-Square Test for dichotomous variables. Univariate analysis was used for significant parameters.

Data analyses were conducted using SPSS (version 16 for Windows; SPSS, Chicago, Ill., USA). Values of $p < 0.05$ were considered as statistically significant.

Results

Baseline characteristics of our population are shown in Table 1.

After ruling out 33 subjects which did not satisfy inclusion criteria, a total number of 116 patients with diagnosis of PE were enrolled in the study. COPD was documented in 66 patients (56% of the total), whereas DVT was described in 45 individuals (39% of the total), with higher prevalence in patients without COPD than those with COPD (48% vs 32%, $p < 0.05$).

Main risk factors for PE in our population were: obesity, immobility, malignancies and type 2 diabetes mellitus. Furthermore, patients with COPD were older and had lower PaO₂, higher PaCO₂ and lower prevalence of DVT ($p < 0.05$ for all).

Only 32% of patients with COPD and PE showed DVT. These subjects had higher PaCO₂ and ejection fraction ($p < 0.05$ for all) and higher percentage of chronic renal failure and type 2 diabetes mellitus if compared to those without DVT ($p < 0.05$ for all, see Table 2).

Moreover, in COPD-PE patients with DVT, the most frequent localization was proximal (57% of total), whereas COPD-PE patients without DVT showed a more frequent segmental localization (60% of total, see Table 2).

Table 1. Baseline characteristics of study population. Abbreviations: DVT= Deep venous thrombosis; PE= Pulmonary embolism; PASP= Pulmonary artery systolic pressure.

Parameter	COPD (n=66)	NON COPD (n=50)	p-value
Age (yrs)	71 (14)	65 (18)	<0,05
Males (n)	28 (42%)	36 (72%)	<0.01
DVT (n)	21 (31.8%)	24 (48%)	<0.05
Non-smokers (n)	13 (20%)	42(83%)	<0.01
Current smokers (n)	26 (40%)	5 (11%)	<0.01
Ex-smokers (n)	27 (40%)	3 (6%)	<0.01
PE-central (n)	31 (47%)	12 (25%)	<0.05
PE-segmental (n)	34 (51%)	35 (69%)	ns
PE-subsegmental (n)	1 (2%)	3 (6%)	ns
PaO2 (mmHg)	64 (16)	74 (18)	<0,05
PaCO2 (mmHg)	43 (11)	38 (9)	<0,05
PASP (mmHg)	44 (11)	42 (11)	ns
NT-proBNP (pg/ml)	4870 (11420)	4070 (8023)	ns
D-Dimer (µg/mL)	20 (109)	5 (3,6)	ns
Ejection fraction (%)	50 (9,5)	53 (8)	ns
Obesity (n)	27 (42%)	15 (34%)	ns
Trauma (n)	5 (8%)	1 (2%)	ns
Immobility (n)	17 (27%)	5 (11%)	<0,05
Anticonceptionals (n)	0 (0%)	0 (0%)	ns
Malignancy (n)	12 (19%)	10 (23%)	ns
Atrial Fibrillation (n)	12 (19%)	5 (11%)	ns
Pneumonia	13 (20%)	6 (13%)	ns
Pace Maker (n)	3 (5%)	5 (11%)	ns
Ischemic cardiomyopathy (n)	10 (15,9%)	9 (20%)	ns
Arterial hypertension (n)	38 (60%)	28 (63%)	ns
Diabetes mellitus (n)	15 (24%)	13 (29%)	ns
Chronic renal failure (n)	16 (25%)	10 (22%)	ns

Discussion

To the best of our knowledge, this is the first study which investigates a population of PE-COPD cases with and without DVT.

PE is known to originate from embolization of a DVT, but in up to 50% of patients with PE no DVT is detected by ultrasonography or contrast venography studies [15-16].

We found a somewhat low prevalence of DVT (33%) in patients with both PE and COPD. This is in line with the lower prevalence of DVT compared to that of PE in COPD patients [1-2,4] and confirms

that COPD may be an independent risk factor for PE. On the other hand, higher percentages of DVT (i.e. 60%) were described by Erel et al and Gunen et al (60% and 61%, respectively) [17-18].

Despite similar smoking status, our population of COPD-PE with DVT had higher values of PaCO₂, possibly indicating a higher severity of their respiratory status or the presence of a concomitant COPD exacerbation. The latter condition may lead to patient immobility and promote DVT. Nonetheless, similarly to the findings of Akgun et al [19], no difference in terms of immobility was reported between COPD-PE with and without DVT. Moreover, it has to be highlighted the

Table 2. Characteristics of COPD group, according to the presence or absence of DVT. Abbreviations: PE= Pulmonary embolism; PASP= Pulmonary artery systolic pressure; β -2: Beta-2 agonist; FEV1= Forced expiratory volume in 1 second; FVC= Forced vital capacity.

Parameter	COPD with DVT (n= 21)	COPD without DVT (n=45)	p-value
Age (yrs)	67 (15)	73 (12)	ns
Males (n)	9 (42%)	24 (54%)	ns
Non-smokers (n)	5 (25%)	17 (39%)	ns
Current smokers (n)	4 (17%)	8 (18%)	ns
Ex-smokers (n)	12(58%)	20 (43%)	ns
PE-central (n)	12 (57%)	17 (37.7%)	<0.05
PE-segmental (n)	9 (46%)	27 (60%)	ns
PE-subsegmental (n)	0 (0%)	1 (4%)	ns
PaO ₂ (mmHg)	58 (14)	66 (20)	Ns
PaCO ₂ (mmHg)	51 (12)	40 (8)	<0,05
PASP (mmHg)	46 (12)	43 (10)	ns
NT-proBNP (pg/ml)	5019 (14900)	4800 (9300)	ns
D-Dimer (μ g/mL)	438 (471)	354(452)	ns
Ejection fraction (%)	54 (7)	49 (10)	<0,05
Obesity (n)	10 (47%)	15 (35%)	ns
Trauma (n)	0 (0%)	1 (3%)	ns
Immobility (n)	5 (24%)	7 (17%)	ns
Anticonceptionals (n)	0 (0%)	0 (0%)	ns
Malignancy (n)	7 (33%)	6 (14%)	ns
Atrial Fibrillation (n)	3 (14%)	7 (17%)	ns
Pneumonia	2 (9,5%)	8 (19%)	ns
Pace Maker (n)	0 (0%)	6 (14%)	ns
Ischemic cardiomyopathy (n)	3 (14%)	9 (21%)	ns
Arterial hypertension (n)	14 (66%)	27 (64%)	ns
Diabetes mellitus (n)	10 (47%)	11 (26%)	<0.05
Chronic renal failure (n)	18 (47%)	8 (13%)	<0,05
Post β -2 FEV1 (%pred)	79 (18)	78 (29)	ns
Post β -2 FVC (%pred)	86 (24)	85 (22)	ns

higher incidence of renal failure in COPD-PE patients with DVT; Wattanakit et al found that middle-aged and elderly patients with chronic kidney disease (stages 3 and 4) have an increased risk for incident DVT [20], but mechanisms linking chronic kidney disease and DVT are not well defined. Moreover, another study showed that patients with DVT and chronic renal disease were younger than those with only DVT [21], and these findings are in line with our data.

COPD-PE Patients with DVT had also higher prevalence of diabetes mellitus, a well-known risk factor for DVT [11,22-23]. Indeed, Diabetes mellitus

is associated with several changes in coagulation and fibrinolysis that may lead to a thrombogenic susceptibility [11,22-23].

Regarding PE-COPD patients without DVT, also known as “de novo PE”, our data showed no differences in prevalence of trauma, active malignancies and right heart thrombi between the subgroups with and without DVT. Undeniably, well-known risk factors for de novo PE reported in literature are trauma [24], active cancer [25], inferior vena cava abnormalities, right heart thrombi and in situ thrombosis [26]. Therefore, based on our findings, we might speculate

a role of COPD as risk factor for the development of PE. Several mechanisms may explain the link between COPD and VTE, such as thrombogenic potential within the pulmonary circulation [4-27], systemic inflammation [28]; elderly, reduced mobility [29], polycythemia [30] smoking [31] and treatment with glucocorticoids for acute exacerbation of disease [32]. Concerning the old age of our cohort, it was previously reported that the diagnostic yield of lower limb compression ultrasonography was greater in the elderly, so the risk of wrong diagnosis on echography is very low in our cohort [33].

The localization of PE was formerly investigated by other authors. In detail, Aleva et al reported that in patients with acute exacerbations of COPD of unknown aetiology 68% of the detected emboli were located in the main pulmonary arteries, lobar arteries, or interlobar arteries [6]. Similar data were reported by Tillie Leblond et al [34]. Contrariwise, Akpınar et al documented a mainly subsegmental localization among hospitalized patients with COPD exacerbation [35].

Our study had several limitations. First, patients did not perform upper-extremity venous duplex scans (UED), even though cases of PE originating from upper limbs DVT are rare and usually linked to traumatic events or presence of central venous catheters [36]. Second, we did not define in our population the prevalence of exacerbated COPD and the severity of COPD. However, a number of studies did not report significant differences in prevalence of PE among COPD-GOLD stages [18-35]. Third, we did not evaluate blood inflammatory markers such as C-reactive protein or leucocytes and haemoglobin and haematocrit, very useful parameters for assessing differences in terms of systemic inflammation and polycythemia. Finally, we did not include in the study data about clinical manifestation and Wells score, since the diagnosis of EP was made at the emergency department. Undoubtedly, further studies with larger sample sizes must include all of the above parameters.

In conclusion, early recognition of PE is of vital importance but is may be challenging in patients with COPD, due to the overlap of clinical symptoms. Moreover, a negative result at venous ultrasonography is more frequent in cases of PE with COPD. Chronic renal failure, and type 2 diabetes mellitus are more

frequent in PE-COPD patients with DVT showed a higher frequency of proximal localization, chronic renal failure and type 2 diabetes mellitus, thereby indicating a greater risk of more severe clinical implications. Conversely, PE- COPD subjects without DVT showed a more frequent segmental localization and were less hypercapnic.

Therefore, PE should be always taken into account in patients with COPD with worsening of symptoms and gas exchange parameters.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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