

Pulmonary fibrosis as a risk factor for thromboembolic disease

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Background Chronic obstructive pulmonary disease (COPD) and lung cancer are well known to be associated with increased risk for venous thromboembolism (VTE). However, there are few data about the association between idiopathic pulmonary fibrosis (IPF) and VTE.

Aim of this study The aim of the study was to investigate the prevalence of venous thromboembolic events in hospitalized IPF patients and compare it with the incidence in COPD patients.

Patients and methods We retrospectively analyzed the database of interstitial lung disease from 2007 to 2013. We included 629 IPF patients after exclusion of patients with secondary pulmonary fibrosis and those with a concurrent diagnosis of COPD or lung cancer. VTE disease was defined as either deep venous thrombosis, pulmonary embolism, or both deep venous thrombosis and pulmonary embolism. For comparison, we also analyzed the database of COPD patients.

Results Out of the 629 included IPF patients, 13 had thromboembolic events, showing a prevalence for VTE in

IPF that is significantly higher than that in COPD (2.1 vs. 1.1%; odds ratio: 1.9; confidence interval: 1.039–3.530; $P = 0.035$). The prevalence is also significantly higher in female and nonsmoker IPF patients compared with COPD patients ($P = 0.008$ and 0.011 respectively). Among IPF patients, men had significantly lower risk for VTE compared with women ($P = 0.045$).

Conclusion IPF, especially in women, is associated with increased risk for VTE, being greater than the risk in COPD. *Egypt J Broncho* 2015 9:160–164
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Egyptian Journal of Bronchology 2015 9:160–164

Keywords: idiopathic pulmonary fibrosis, prevalence, venous thromboembolism

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Received 18 November 2014 **Accepted** 05 December 2014

Introduction

Common respiratory diseases, especially chronic obstructive pulmonary disease (COPD) [1] and lung cancer [2], are well known to be associated with increased risk for venous thromboembolism. Over the last decade, awareness has also been increased on the association between idiopathic pulmonary fibrosis (IPF) and venous thromboembolic disease (VTE), which may significantly affect survival [3,4].

Data suggest dysregulation of fibrinolysis [5] as well as activation of the extrinsic [6] and intrinsic [7] coagulation cascade. Imokawa *et al.* [6] identified tissue factor (TF) antigens in lung tissues of IPF patients. These findings suggest that the extrinsic pathway of the coagulation system is activated in interstitial lung disease (ILD), but this may be a response to generic lung injury, rather than a mechanism specific to IPF. Fujii *et al.* [8] found that more advanced IPF (defined by a PaO_2 of <55 torr while breathing room air, or a vital capacity of <50% predicted) was associated with higher levels of TF in the lung, suggesting that activation of the coagulation cascade reflects IPF progression. Also, the fibrinolysis pathway may be downregulated (or at least not upregulated proportionally to the increases in procoagulant activity), resulting in persistent fibrin deposition. Levels of plasminogen activator inhibitor-1 were reduced, and levels of α_2 -antiplasmin were increased, in patients with ILD compared with controls [9].

Clinical studies also confirmed the relation between IPF and VTE. A clinical trial in Japan indicated improvement in survival in severe IPF patients receiving anticoagulation [10]. Epidemiological studies using UK primary care data and American death certificate data also demonstrated that people with IPF are at increased risk of having VTE [11,12].

On the basis of these data, we aimed to study the prevalence of venous thromboembolic events in hospitalized IPF patients and to compare it with that in COPD patients.

Patients and methods

This retrospective study was conducted in the Chest Department of Assiut University Hospital. The study was approved by the Faculty of Medicine Ethics Committee, Assiut University.

For this study, we analyzed the database of ILD from 2007 to 2013. We included only data of IPF patients after exclusion of patients with any condition that might be associated with secondary PF, including connective tissue diseases, radiation fibrosis, asbestosis, pneumoconiosis, sarcoidosis, and extrinsic allergic alveolitis. In addition, we excluded patients with a concurrent diagnosis of COPD or lung cancer. Data including age, sex, smoking status, presence of comorbidities, pulmonary function

tests, pulmonary artery systolic pressure, and computed tomography (CT) pattern were included in the study. HRCT or multislice CT findings were classified into either usual interstitial pneumonia (UIP) pattern or non-UIP pattern [13]. VTE disease was defined as either deep venous thrombosis (DVT), pulmonary embolism (PE), or both DVT and PE. For comparison, we also analyzed the database of COPD patients (but not of those with IPF or lung cancer).

Statistical analysis

Statistical package for the social sciences (version 16) software was used for analysis of results. The results of this study are presented as mean \pm SD or as number and percentage. We used the χ^2 -test to compare qualitative data between IPF patients with or without VTE. The quantitative data were compared using a two-sampled unpaired *t*-test. We also used the χ^2 -test to determine the risk for VTE in patients with IPF in reference to the COPD group. A *P*-value less than 0.05 was considered to represent statistical significance in all analyses.

Results

From 2007 to 2013, 820 patients were admitted to our department with ILD; 629 patients with IPF were included in this study after exclusion of patients with ILD secondary to connective tissue diseases or occupational lung diseases and those with combined COPD or lung cancer, a known risk factor for VTE.

Table 1 shows the demographic data of our study group. The mean age of the patients was 44.62 ± 9.8 . Out of all patients, 426 (67.7%) were female. Only 40 (6.4%) were smokers and 284 (45.2%) met the criteria for UIP pattern in HRCT.

Among them, 13 had thromboembolic events, showing a prevalence of VTE in IPF that was significantly higher than that in patients admitted with COPD [2.1 vs. 1.1%; odds ratio (OR): 1.9; confidence interval (CI) 1.039–3.530; *P* = 0.035] (Table 2).

Compared with COPD patients, female and nonsmoker IPF patients had significantly greater risk for VTE (*P* = 0.008 and 0.011, respectively). However, the risk for VTE was the same among men (*P* = 0.405), current smokers (*P* = 0.417), and among patients falling under the same age groups as COPD patients (Table 3).

Table 1 Demographic data of IPF patients (*n* = 629)

Variables	
Age	
Mean \pm SD	44.62 \pm 9.8
Range	18–66
Sex [<i>n</i> (%)]	
Male	203 (32.3)
Female	426 (67.7)
Smoking habit [<i>n</i> (%)]	
Smoker	40 (6.4)
Exsmoker	107 (17)
Nonsmoker	482 (76.6)
HRCT pattern [<i>n</i> (%)]	
UIP pattern	284 (45.2)
Non-UIP pattern	345 (54.8)
Comorbidities [<i>n</i> (%)]	
Diabetes mellitus	141 (22.7)
Hypertension	56 (9)
IHD	16 (2.3)

Data are expressed as number (%) or mean \pm SD; IHD, ischemic heart disease; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

Table 2 Prevalence of thromboembolic events in IPF patients compared with COPD

Event	IPF (<i>n</i> = 629)	COPD (<i>n</i> = 4171)	<i>P</i> -value	OR (95% CI)
DVT	2 (0.3)	17 (0.4)		
PE	9 (1.4)	20 (0.5)		
Both DVT and PE	2 (0.3)	8 (0.2)		
Total	13 (2.1)	45 (1.1)	0.035*	1.9 (1.039–3.537)

Data are expressed as number (%); CI, confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; IPF, idiopathic pulmonary fibrosis; OR, odd ratio; PE, pulmonary embolism; *Significant.

Table 3 Prevalence of thromboembolic events in different categories of IPF patients compared with COPD

Event	IPF (<i>n</i> = 629)	COPD (<i>n</i> = 4171)	<i>P</i> -value	OR (95% CI)
Sex				
Male	1/203 (0.5)	34/3050 (1.1)	0.405	0.442 (0.061–3.261)
Female	12/426 (2.8)	11/1121 (0.9)	0.008*	2.871 (1.276–6.456)
Age				
<45	8/315 (2.5)	0/19 (0)	0.482	1.469 (0.587–3.678)
\geq 45	5/314 (1.6)	45/4151 (1.1)	0.409	
Smoking habit				
Smoker	1/40 (2.5)	17/1525 (1.1)	0.217	2.243 (0.306–16.442)
Exsmoker	0/107 (0)	17/1435 (1.2)	0.258	–
Nonsmoker	12/482 (2.5)	11/1210 (0.9)	0.011*	2.744 (1.219–6.177)

Data expressed as number (%); CI, confidence interval; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; OR, odd ratio; *Significant.

Among IPF patients, men had significantly lower risk for VTE compared with women (OR: 0.171, CI: 0.022–1.323; OR: 5.718, CI: 0.749–43.676, respectively; $P = 0.045$) (Fig. 1). Furthermore, IPF patients with VTE had significantly lower diffusion capacity (DLCO) compared with those without VTE ($P = 0.017$). Although IPF patients with VTE experienced higher pulmonary artery systolic pressure compared with those without VTE, the difference was not statistically significant ($P = 0.404$) (Table 4).

Discussion

From the data of patients admitted to our Chest Department between 2007 and 2013, we found that the prevalence of VTE in those with IPF was 2.1%.

Only a few studies have examined the relationship between VTE and IPF. Using a longitudinal primary care database from the UK, Hubbard *et al.* [11] found that, in comparison with the general population, the risk for deep venous thrombosis was greater before (OR: 1.98; 95% CI: 1.13–3.48) and even greater after (risk ratio 3.39, 95% CI: 1.57–7.28) the diagnosis of IPF. Using hospital discharge and mortality data of the entire Danish population from 1980 to 2007, Sode *et al.* [14] found an increased risk for the development of ILD in people ever diagnosed with VTE, many of whom probably had IPF. In contrast to our study, they did not exclude patients with a known cause for PF, including those with conditions that might increase the risk for VTE (e.g. connective tissue disease). More recently, using the US Multiple Cause-of-Death mortality database, Sprunger *et al.* [12] determined that the risk for VTE at the time of death from IPF was higher than that for the background population (OR: 1.34; 95% CI: 1.29–1.38).

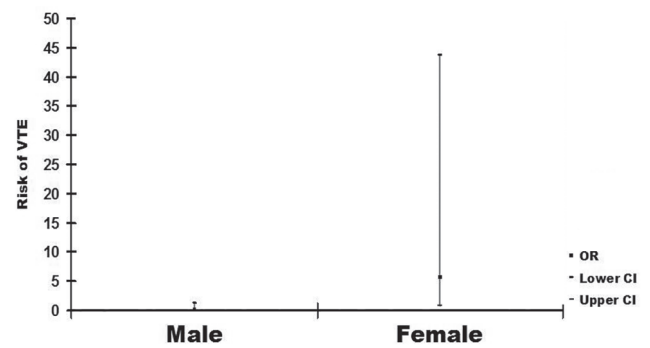
From studies performed on lung transplant recipients, Nathan *et al.* [15] detected post-transplant PE only in patients previously diagnosed with IPF. Similar results were reported in a study carried out on patients receiving transplants at a European center between 1999 and 2009 [16].

Among IPF patients, we found that the risk for VTE in patients with IPF was significantly greater for women than for men. Younger women have an elevated risk for developing VTE because of hormonal influences from the menstrual cycle, from pregnancy, and from contraceptives. This was in contrast to a previous study that found that the risk for VTE in IPF patients was the same regardless of sex [12]. However, this study determined the risk for thromboembolism at the time of death. They also included a more elderly age

group (range 18–85) (the mean age in our study was 44.6 ± 9.8 years). Furthermore, the archived database did not give us information about the risk factors and hormonal status of our female IPF patients.

Somewhat surprisingly, we found that the risk for VTE in those with IPF was about two-fold greater than that

Fig. 1



Risk for VTE in male and female IPF patients. IPF, idiopathic pulmonary fibrosis; VTE, venous thromboembolism.

Table 4 Demographic data, PFTs, PASP, and ABG in IPF patients with or without VTE

Variables	Present (n = 13)	Absent (n = 616)	P-value
Sex [n (%)]			
Male	1 (7.7)	202 (32.8)	0.045*
Female	12 (92.3)	414 (67.2)	
Age [n (%)]			
<45	8 (61.5)	307 (49.8)	0.404
≥45	5 (38.5)	309 (50.2)	
Smoking habit [n (%)]			
Smoker	1 (2.5)	39 (6.3)	0.257
Exsmoker	0 (0)	107 (17.4)	
Nonsmoker	12 (92.3)	470 (76.3)	
HRCT pattern [n (%)]			
UIP pattern	8 (61.5)	276 (44.8)	0.230
Non-UIP pattern	5 (38.5)	340 (55.2)	
Comorbidities [n (%)]			
Diabetes mellitus	1 (7.7)	140 (22.7)	0.192
Hypertension	0 (0)	56 (9.1)	0.251
IHD	0 (0)	14 (2.3)	0.580
PFT (mean ± SD)			
FVC%	44.32 ± 15.3	44.8 ± 10.25	0.868
DLCO%	38.93 ± 16.18	44.65 ± 9.2	0.017*
PASP	56.37 ± 15.36	53.02 ± 14.23	0.404
ABG (mean ± SD)			
PaO ₂	55.2 ± 18.4	55.1 ± 16.5	0.983
PaCO ₂	40.9 ± 9.94	39.4 ± 10.3	0.616

ABG, arterial blood gas; DLCO, diffusion capacity; FVC, forced vital capacity; IHD, ischemic heart disease; IPF, idiopathic pulmonary fibrosis; PaCO₂, partial arterial carbon dioxide pressure; PaO₂, partial arterial oxygen pressure; PASP, pulmonary artery systolic pressure; PFT, pulmonary function test; UIP, usual interstitial pneumonia; VTE, venous thromboembolism; *Significant.

for COPD, a condition known to be associated with VTE. A retrospective study evaluating the risk for thromboembolism in COPD found that the relative risk for PE in adults hospitalized with COPD was 1.92 and that for DVT was 1.30, as compared with the general population [17]. Furthermore, by using data retrieved from Taiwan's National Health Insurance Research Database (from 2000 to 2008), the incidence of PE in COPD patients was determined to be 12.31 per 10 000 person-years (1.37/10 000 persons-years), which was approximately four times higher than in the comparison cohort (0.35/10 000 persons-years) [18]. However, in the studies that prospectively evaluated patients who were hospitalized for COPD exacerbation, the prevalence of PE was 25.5% [19,20]. Although the risk for VTE is elevated in patients with COPD, Sprunger *et al.* [12] found that the risk for VTE associated with IPF was higher than that for COPD (OR: 1.44; 95% CI: 1.39–1.49), which agreed with the results of this study (OR: 1.9; 95% CI: 1.039–3.537). These data open the window for further research on the role of IPF as a risk factor for VTE.

Smoking was considered a risk factor for thromboembolism [21]. A procoagulant state, reduced fibrinolysis, inflammation, and increased blood viscosity might underlie the association between smoking and VTE risk [22,23]. However, that study did not find significant difference as regards smoking habit between IPF patients with and those without venous thromboembolism ($P = 0.257$). Furthermore, compared with nonsmoker COPD patients, nonsmoker IPF patients had significantly greater risk for VTE ($P = 0.011$). Thus, smoking could not be considered a risk factor for VTE in IPF patients.

This can be attributed to the fact that IPF is considered a procoagulant and antifibrinolytic disease [24]. In fact, procoagulant abnormalities (including elevated levels of protein C and reduced thrombomodulin) have been found in the systemic circulation of some patients with IPF during acute exacerbations [25]. In addition, Imokawa *et al.* [6] previously detected TF antigens (markers of active extrinsic coagulation pathways) in type II pneumocytes, in honeycomb cysts, and in some alveolar macrophages. Further, by testing the hypothesis that inhibiting the coagulation cascade would lead to improved outcomes in patients with IPF, Kubo *et al.* [10] observed that patients receiving warfarin plus prednisolone had better 3-year survival (63 vs. 35%) and lower mortality from an acute exacerbation compared with those receiving only prednisolone.

In summary, we conclude that IPF, especially in women, is associated with increased risk for VTE, which is greater than that from COPD. Therefore, we recommend considering thromboembolic events in any patient with an unexplained cause for acute exacerbation of IPF. Further prospective studies should be carried out to detect the role of IPF as a risk factor for VTE, to determine the predictors and risk factors for VTE in IPF, and study the coagulation status in IPF patients.

Limitations

The database restricted us from identifying the risk factors for VTE, including obesity, history of previous surgery, prolonged immobilization, heritable hypercoagulable conditions, and the use of oral contraceptives or female sex hormones.

Acknowledgements

Shereen Farghaly: contributed to the design of the study and analysis and interpretation of data; Ashraf Zein El-Abdin: contributed to the concept of the study and revision and final approval of the version to be published.

Conflicts of interest

None declared.

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