

Risk factors associated with provoked pulmonary embolism

Endri Gjonbrataj^{1,*}, Ji Na Kim^{2,*}, Juarda Gjonbrataj^{1,3}, Hye In Jung¹, Hyun Jung Kim¹, and Won-Il Choi¹

¹Department of Internal Medicine, Keimyung University School of Medicine, Daegu; ²Department of Internal Medicine, Daegu Fatima Hospital, Daegu, Korea; ³Department of Internal Medicine, Mother Theresa University Hospital Centre, Tirana, Albania

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Correspondence to
Won-Il Choi, M.D.

Department of Internal Medicine,
Keimyung University School of
Medicine, 56 Dalseong-ro, Jung-
gu, Daegu 41931, Korea
Tel: +82-53-250-7572
Fax: +82-53-250-8379
E-mail: wic Choi@dsmc.or.kr

*These authors contributed
equally to this work.

Background/Aims: This study aimed to investigate the risk factors associated with provoked pulmonary embolism (PE).

Methods: This retrospective cohort study included 237 patients with PE. Patients that had transient risk factors at diagnosis were classified as having provoked PE, with the remaining patients being classified as having unprovoked PE. The baseline clinical characteristics and factors associated with coagulation were compared. We evaluated the risk factors associated with provoked PE.

Results: Of the 237 PE patients, 73 (30.8%) had provoked PE. The rate of respiratory failure and infection, as well as the disseminated intravascular coagulation score and ratio of right ventricular diameter to left ventricular diameter were significantly higher in patients with provoked PE than in those with unprovoked PE. The protein and activity levels associated with coagulation, including protein C antigen, protein S antigen, protein S activity, anti-thrombin III antigen, and factor VIII, were significantly lower in patients with provoked PE than in those with unprovoked PE. Multivariate analysis showed that infection (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.4 to 7.4) and protein S activity (OR, 0.97; 95% CI, 0.95 to 0.99) were significantly associated with provoked PE.

Conclusions: Protein S activity and presence of infection were important factors associated with provoked PE. We should pay attention to the presence of infection in patients with provoked PE.

Keywords: Coagulation; Infection; Protein S; Provoked; Pulmonary embolism

INTRODUCTION

Pulmonary embolism (PE)—as a subset of venous thromboembolism (VTE)—is a common, potentially lethal disorder that affects hospitalized and non-hospitalized patients. It recurs frequently and is often overlooked, resulting in long-term complications. PE is the third most common cause of hospital-related death and the most common preventable cause of hospital-related death [1,2].

Although the pathophysiology of PE is not well understood, the predisposing factors broadly fit Virchow's

triad of blood stasis, endothelial injury, and enhanced blood coagulability [3]. Pulmonary emboli usually arise from the thrombi that originated in the deep venous system of the lower extremities. PE occurs in approximately 15% to 32% of cases following deep vein thrombosis (DVT) in the lower extremities [4].

A provoked PE is associated with acquired risk factors, either transient or persistent, whereas an unprovoked or idiopathic PE is associated with no apparent clinical risk factors [5]. Death, recurrence, and long-term mortality can often be avoided by identifying and treating the risk factors. The risk factors for provoked PE include

age, personal history of VTE, active malignancy, or other disabling conditions such as heart or respiratory failure, coagulation disorders, hormone replacement therapy, oral contraception, immobilization, and surgery or trauma within the last 3 months [6]. However cancer associated VTE can be classified separated from provoked VTE [7]. Patients with unprovoked PE—when compared with their provoked counterparts—are at higher risk for recurrent PE [8,9], cardiovascular events [10], cancer [11], and chronic thromboembolic pulmonary hypertension [8]. The risk of recurrence is low if the VTE is provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked [12-16].

In a population-based prospective cohort study with 21,680 participants from six communities in the USA, there were 366 validated thromboses during a 10-year follow-up period. Among the 366 patients with thrombosis, 99 were diagnosed as having PE. Fifty patients had idiopathic PE, and 49 patients had a secondary (provoked) PE [17]. Although several studies have evaluated the factors that influence the development and recurrence of unprovoked PE, the information on the risk factors associated with provoked PE is limited. Therefore, we aimed to investigate the risk factors associated with provoked PE, which may result in earlier evaluation of the patients at high risk for PE, and earlier decisions about prophylactic measures.

METHODS

Study design

This retrospective cohort study was conducted between January 2009 and December 2012. This study was approved by the institutional review board at Keimyung University Dongsan Medical Center with waived informed consent.

Study subjects

During the study period, 583 new adult cases aged ≥ 20 years were diagnosed as acute PE in our hospital. We excluded patients who had active cancer before diagnosis of PE [7]. We selected cases whose coagulation factors and profiles were measured at the time of PE diagnosis before starting warfarin treatment. A total of 237 PE patients were enrolled (Fig. 1).

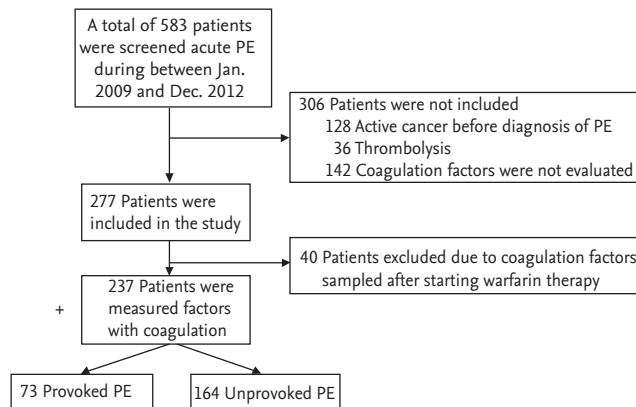


Figure 1. Flow-chart of the study. PE, pulmonary embolism.

Imaging studies

PE was diagnosed based on the presence of intraluminal filling defects in the pulmonary arteries on chest computed tomography (CT) or CT pulmonary angiography, or the findings of a ventilation perfusion scan [18]. DVT diagnosis was confirmed via ultrasound examination or CT venogram of the lower extremities in patients with clinically suspected PE.

Study methods

We reviewed the electronic medical records of all PE patients. We defined provoked PE as patient has transient (within 3 months) risk factors such as surgery, trauma, immobility (bedbound), pregnancy or puerperium, or history of hormonal therapy (oral contraceptive or hormone replacement therapy) [19]. Patients who do not have transient risk factors, we regarded them as an unprovoked PE. The risk factors for PE were as follows: renal dysfunction, defined as serum creatinine level > 1.3 mg/dL; active cancer, defined as treatment with an anti-cancer agent within 3 months of PE diagnosis; and shock, defined as a systolic blood pressure of < 90 mmHg. CT was performed using a 16- or 128-slice detector. The reconstruction interval of the scan was 3 mm. The right ventricular to left ventricular diameter (RV/LV) ratio was calculated using CT images showing the interventricular septum and myocardium from the longitudinal axis of the heart [20,21]. We retrospectively collected the clinical characteristics and laboratory data on factors such as co-morbidity, symptoms, chest CT findings, vital signs, RV/LV ratio, N-terminal prohormone of brain natriuretic peptide, and complete blood count

at the time of PE diagnosis. Coagulation profiles were measured before starting warfarin therapy. The disseminated intravascular coagulation (DIC) score was calculated based on the International Society on Thrombosis and Haemostasis scoring system [22].

Protein C and protein S activities were measured using factor V and VII as substrates (Diagnostica Stago, Asnieres, France). Total protein C, total protein S, and free protein S were measured by radial immunodiffusion. Antithrombin III (AT-III), factor VIII, and factor IX were automatically measured (ACL Top 500, Instrumentation Laboratory, Bedford, MA, USA).

Statistical analysis

We performed a univariate analysis using logistic regression to determine the variables that were significantly associated with provoked PE. We included in the multivariate analysis all the variables with a $p < 0.2$ on univariate analysis. Multivariate logistic regression analysis identified the independent variables associated with provoked PE. All tests of significance were two-tailed, and a p value of 0.05 was considered significant. Results were analysed with SPSS version 20.0 (IBM Co., Armonk, NY, USA). Values are expressed as mean \pm standard deviation.

RESULTS

Risk factors for provoked PE were present in 31% of cases. The majority of patients with provoked PE were females with a mean age of 64.8 years. Among 73 provoked PE, 33 patients were related with surgery and 40 patients were related with immobilization. The clinical characteristics between patients with provoked and unprovoked PE were not significantly different. However, the rate of respiratory failure and infection, as well as the DIC score and RV/LV ratio were higher in patients with provoked PE than in those with unprovoked PE (1.3-, 2-, 1.3-, and 1.25-fold higher, respectively). Although not statistically significant, the 30-day mortality was 2-fold higher in patients with provoked PE than in those with unprovoked PE. Meanwhile, the recurrence rate in patients with provoked PE was half of that in patients with unprovoked PE. All demographic, clinical, and laboratory data are summarised in Table 1.

Protein and activity levels associated with coagulation were lower in patients with provoked PE than in those with unprovoked PE; the difference was statistically significant for protein C antigen, protein S antigen, protein S activity, and AT-III antigen (Table 2).

As shown in Table 3, the multivariate analysis revealed a significant association between provoked PE, infection, and protein S activity. Infection and protein S activity were the only independent factors associated with provoked PE. The rate of infection was 2-fold higher in patients with provoked PE than in those with unprovoked PE. The most frequent infection associated with PE was pneumonia, with its frequency being 2-fold higher in patients with unprovoked PE than in those with provoked PE (Table 3).

DISCUSSION

We aimed to investigate the risk factors associated with provoked PE, including the alteration of the factors associated with coagulation. We found infection and protein S activity as independent variables associated with provoked PE.

The infection rate was 2-fold higher in patients with provoked PE than in those with unprovoked PE. The most frequent infection associated with PE was pneumonia. However, frequency of pneumonia was 2-fold higher in patients with unprovoked PE than in those with provoked PE. The association between PE and infection is supported by several studies [23-26]. The odds ratio ranged from 1.7 to 5.0 in other studies [24,25,27,28]. In our study, the odd ratio of infection related to provoked PE was 3.2 (95% confidence interval, 1.4 to 7.4).

Meanwhile, sepsis is reported to be associated with haemostatic abnormalities ranging from localized VTE to acute DIC [29]. In sepsis-induced DIC, the activation of the extrinsic coagulation pathway via tissue factor appears to be the primary event [23]. The initial hypercoagulation is followed by the depletion of clotting factors and organ damage, followed by haemorrhage due to consumption coagulopathy [23]. Early DIC is characterized by thrombosis and decreased protein S activity as well as unaltered level of protein S antigen [24]. In our study, protein S activity was lower in patients with provoked PE (56.3%) than in those with unprovoked PE

Table 1. Baseline characteristics for the 237 patients with pulmonary embolism

Variable	Overall (n = 237)	Unprovoked PE (n = 164)	Provoked PE (n = 73)	p value
Age, yr	66.2 ± 13.9	66.8 ± 13.5	64.8 ± 14.9	0.31
Male sex	84 (35.4)	61 (37.2)	23 (31.5)	0.40
Body mass index	24.1 ± 4	23.9 ± 4.2	24.6 ± 3.3	0.27
Comorbidity				
Heart failure	33 (14)	20 (12.2)	13 (17.8)	0.25
Respiratory failure	150 (63.3)	96 (58.5)	54 (74)	0.02
Renal dysfunction	31 (13.1)	19 (11.6)	12 (16.4)	0.31
Previous DVT or PE	13 (5.5)	11 (6.7)	2 (2.7)	0.22
DIC score ^a	2.1 ± 1.4	1.9 ± 1.4	2.4 ± 1.5	0.04
Infection				
Respiratory tract infection	42 (48.8)	27 (60)	15 (36.6)	< 0.01
Urinary tract infection	6 (7)	5 (11.1)	1 (2.4)	
Wound infection	6 (7)	1 (2.2)	5 (12.2)	
Intra-abdominal infection	5 (5.8)	4 (8.9)	1 (2.4)	
Other site infection	23 (26.7)	7 (15.5)	16 (39)	
Unknown infection	4 (4.6)	1 (2.2)	3 (7.3)	
Clinical findings				
Haemoptysis	16 (6.7)	9 (5.5)	7 (9.6)	0.25
Chest pain	37 (15.6)	27 (16.5)	10 (13.7)	0.59
Altered mental state ^b	18 (7.6)	11 (6.7)	7 (9.6)	0.41
Systolic blood pressure, mmHg ^c	122.6 ± 21.5	123 ± 20.4	121.7 ± 23.9	0.66
Shock	14 (5.9)	7 (4.27)	7 (9.56)	0.11
Cardiac chamber ratio and cardiac biomarker				
RV/LV ratio	1.1 ± 0.5	1.0 ± 0.4	1.3 ± 0.6	< 0.01
NT pro-BNP, ng/L	3,005.6 ± 4,669.7	2,617.5 ± 4,001	3,905.5 ± 5,895	0.13
WBC, cells/ μ L	9,436 ± 4,239	9,180 ± 4,135	10,011 ± 4,439	0.16
D-dimer, μ g/mL	6 ± 7.3	5.6 ± 7.8	6.9 ± 5.9	0.33
BUN, mg/dL	19.9 ± 11.7	20 ± 11.6	19.6 ± 11.9	0.83
PT, sec	11.6 ± 3.6	11.4 ± 3.4	12.1 ± 4.2	0.19
Platelets, cells/ μ L	251,729 ± 112,231	249,377 ± 116,297	257,014 ± 103,082	0.63
SIRS total score	38 (16)	23 (14)	15 (20.5)	0.27
Outcome				
30-Day mortality	10 (4.22)	5 (3.05)	5 (6.85)	0.18
PESI	85.9 ± 28.8	85.8 ± 27.6	86.1 ± 31.6	0.96
Lower extremity DVT	77 (32.5)	56 (34)	21 (28.7)	0.42

Values are presented as mean ± SD or number (%).

PE, pulmonary embolism; DVT, deep vein thrombosis; DIC, disseminated intravascular coagulation; RV, right ventricle; LV, left ventricle; NT pro-BNP, N-terminal prohormone of brain natriuretic peptide; WBC, white blood cells; BUN, blood urea nitrogen; PT, prothrombin time; SIRS, systemic inflammatory response syndrome; PESI, pulmonary embolism severity index.

^aDIC score was based on the International Society on Thrombosis and Haemostasis scoring system.

^bAltered mental status was defined as disorientation, stupor, or coma.

^cShock was defined as systolic blood pressure < 90 mmHg.

Table 2. Factors associated with coagulation between patients with unprovoked and provoked pulmonary embolism

Coagulation profile	Overall (n = 237)	Unprovoked PE (n = 164)	Provoked PE (n = 73)	p value
Protein C Ag, %	50.7 ± 48.7	58 ± 48.9	36.5 ± 45.6	< 0.01
Protein C activity, %	82.6 ± 33.6	84 ± 34.2	79.4 ± 32.4	0.34
Protein S Ag, %	50.1 ± 42	57.2 ± 41.3	35.7 ± 40.1	< 0.01
Protein S Ag, free form, %	56.2 ± 30.5	57.6 ± 29.5	53.7 ± 32.5	0.59
Protein S activity, %	66.5 ± 25	71 ± 24.5	56.3 ± 23.2	< 0.01
Antithrombin III Ag, %	74.7 ± 30.9	80 ± 28.1	64.3 ± 33.7	< 0.01
Factor VII, %	69.7 ± 41.2	68.1 ± 38	73.3 ± 47.4	0.49
Factor VIII, %	175.7 ± 56.5	181.7 ± 62	163 ± 40.3	0.03
Factor IX, %	90 ± 44	89.9 ± 45.8	90.2 ± 40	0.96

Values are presented as mean ± SD.

PE, pulmonary embolism; Ag, antigen.

Table 3. Multivariate analysis with the provoked pulmonary embolism group as the dependent variable

Variable	Coefficient	SE	p value	OR	95% CI
Respiratory failure	0.51	0.46	0.27	1.66	0.67–4.10
Infection	1.18	0.42	< 0.01	3.25	1.42–7.42
Protein C Ag	1.18	0.01	0.89	0.99	0.98–1.02
Protein S Ag	–0.003	0.01	0.81	0.99	0.97–1.02
Protein S activity	–0.026	0.01	0.02	0.97	0.95–0.99
Antithrombin III Ag	–0.005	0.01	0.56	0.99	0.98–1.01
Factor VIII	–0.007	0.005	0.15	0.99	0.98–1.00
DIC score	0.038	0.14	0.78	1.04	0.79–1.36

SE, standard error; OR, odds ratio; CI, confidence interval; Ag, antigen; DIC, disseminated intravascular coagulation.

(71%), whereas the DIC score was higher in patients with provoked PE (2.4) than in those with unprovoked PE (1.9). The presence of infection and low protein S activity in patients with provoked PE support our idea that provoked PE is an earlier form of DIC.

Other coagulation factors such as protein C antigen, protein S antigen, AT-III, factor VIII, and factor IX were not associated with provoked PE. In the present study, the AT-III level was lower in patients with provoked PE. The risk of VTE in patients with AT-III deficiency is higher than in those with other coagulation abnormalities [25]. However, the multivariate analysis showed that the AT-III level is not related with provoked PE. Moreover, we did not find any significant difference between factor IX levels in patients with provoked and unprovoked PE.

In our study, patients with unprovoked PE had higher factor VIII levels than those with provoked PE (181.7% vs. 163%, $p = 0.03$). Our findings are in agreement with the well-known association between idiopathic DVT and increased factor VIII levels [26,27].

Although we did not study the genetic abnormalities in patients with protein S deficiency, it is suggested that protein S deficiency might be an acquired form. There was no family history or recurrent thrombosis history in patients with protein S deficiency. Furthermore the mean age of thrombosis patients was 66.2 years in our study, suggesting that protein S deficiency might be acquired; on the other hand, its hereditary form presents at an earlier age—in the third decade of life—with thrombosis [28,30].

In our study, a similar number of patients with pro-

voked and unprovoked PE developed shock during their clinical course. There was no significant statistical difference in the 30-day mortality between the two groups. The 30-day mortality was 3.05% and 6.85% in patients with unprovoked and provoked PE, respectively. The underlying conditions and comorbidities such as higher frequency of respiratory failure and higher DIC score and higher rate of infection in patients with provoked PE may increase mortality compared with unprovoked PE. One of the factors that may contribute to the higher mortality observed in patients with provoked PE is the higher RV/LV ratio compared to patients with unprovoked PE.

Our study has several limitations. This study was limited by the relative small sample size based on single center and the retrospective data collection. Cases were selected based on measuring coagulation factors, which resulted in more than half of the PE patients were not included during study period. However, this study may provide new insights into of potential triggering factors for provoked PE.

A provoked PE is associated with acquired risk factors, either transient or persistent. The risk factors for provoked PE considered as surgery or trauma, immobilization, hormone replacement therapy, or oral contraception. However infection or transient coagulation abnormalities were not included in transient risk factors for provoked PE. In the present study demonstrated that the presence of infection and reduced protein S activity were found to be important factors associated with provoked PE. PE develops after surgery, trauma, or immobilization; we should carefully investigate the presence of infection.

KEY MESSAGE

1. Reduced protein S activity and the presence of infection were associated with provoked pulmonary embolism (PE).
2. This findings support that acquired form of proteins S deficiency in the presence of infection may responsible for developing provoked PE.
3. We should pay attention to the presence of infection in patients with provoked PE.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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