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FULL PAPER

The impact of saddle embolism on the major adverse event rate of patients with non-high-risk pulmonary embolism

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Objective: Wider application of CT angiography (CTA) improves the diagnosis of acute pulmonary embolism (PE). It also permits the visualisation of saddle embolism (SE), namely thrombi, which are located at the bifurcation of the main pulmonary artery. The aim of this study was to assess the prevalence of SE and whether SE predicts a complicated clinical course in patients with non-high-risk PE.

Methods: In total, 297 consecutive patients with non-high-risk PE confirmed using CTA in the emergency department were studied. The presence of SE and its ability to predict the occurrence of major adverse events (MAEs) within 1 month were determined.

Results: Of the 297 patients, 27 (9.1%) had an SE. The overall mortality at 1 month was 12.5%; no significant difference

was observed between the SE and non-SE groups (18.5% vs 11.9%, $p=0.32$). However, patients with SE were more likely to receive thrombolytic therapy (29.6% vs 8.1%, $p<0.01$) and had significantly more MAEs (59.3% vs 25.6%, $p<0.01$).

Conclusion: At the time of diagnosis, SE, as determined using CTA, is associated with the development of MAE within 1 month. It may be a simple method for risk stratification of patients with non-high-risk PE.

Advances in knowledge: The prognosis of patients with SE, especially those who are haemodynamically stable, is unclear. This study shows that patients with SE, determined with CTA, is associated with the development of MAE.

Acute pulmonary embolism (PE) is a potentially life-threatening disease and remains one of the leading causes of cardiovascular morbidity and mortality [1]. However, depending on the clinical presentation, the mortality rate associated with acute PE ranges from 50% to <1% [2,3]. Thus, patient risk stratification has focused on identifying those at risk for shock and death, to identify those who could benefit from aggressive therapy such as thrombolysis.

Saddle embolism (SE) is defined as a visible thromboembolus that straddles the bifurcation of the main pulmonary artery trunk [4–6]. Radiological evidence of SE is found in approximately 2–5% of all patients with PE [7,8]. However, its true frequency may be underestimated because many patients are too unstable to undergo CT angiography (CTA), and the diagnosis is often established at autopsy. The diagnosis of saddle PE causes clinical alarm because it signals an unstable, large clot burden in the pulmonary artery and the possibility of sudden haemodynamic collapse. Nonetheless, the clinical presentation and outcomes of these patients vary widely [9–13]. In particular, an

unresolved issue is the prognosis of patients with SE in haemodynamically stable (non-high-risk) PE. Although a few studies have documented the clinical outcomes of SE in non-high-risk PE, its effect on prognosis remains unclear.

The aim of this study is to assess the incidence of SE (determined with CTA) in patients with non-high-risk PE at the time of diagnosis. It was also determined whether the presence of SE is predictive of major adverse events (MAEs), namely PE-related shock, mechanical ventilation, in-hospital mortality, thrombolysis and thrombectomy, within 30 days.

METHODS AND MATERIALS

Study design

This retrospective cohort single-centre study was conducted at the Asan Medical Center, a 2800-bed, university-affiliated tertiary referral centre in Seoul, Republic of Korea. The cohort consisted of 347 consecutive patients with non-high-risk acute PE, as diagnosed using chest CTA in the emergency department (ED) between January 2006

and October 2010. The diagnosis of PE was confirmed by the CT scans that demonstrated the presence of at least one intraluminal filling defect in an interlobar or more proximal pulmonary artery. The diagnosis of non-high-risk PE, which is defined as acute PE initially with normal blood pressure, was based on the guidelines on the diagnosis and management of acute PE [14]. Patients were excluded if they were under 18 years of age or had been transferred from another hospital. In the case of multiple admissions, only the first was considered. This study and protocol were approved by the institutional review board of Asan Medical Center (ASAN-IRB number 2010-0410) and informed consent was waived.

Data collection

The clinical and demographic characteristics of all patients, including their age, gender, symptoms, medical history, initial vital signs, blood sample results, echocardiographic findings, CT angiographic findings and in-hospital course, were retrieved from electronic hospital records.

Chest CTA was performed using a 16-detector row CT scanner (Sensation 16; Siemens Medical Solutions, Forchheim, Germany) with a standard imaging protocol, which included contiguous axial images of 1.5-mm slice thickness from the lung apices to below the costophrenic angles during a single 32-s breath hold. Coronal reformatted images were also obtained. All images were reviewed by a board-certified radiologist who was unaware of the clinical outcome. This radiologist selected those patients who had a radiological finding of SE, which was defined as a low-attenuation filling defect that extended across the bifurcation of the pulmonary artery trunk. The scans were also used to measure the minor axes of the right ventricle (RV) and the left ventricle (LV) of the heart in the transverse plane at their widest points between the inner surface of the free wall and the surface of the interventricular septum. These maximum dimensions may be found at different levels. The RV/LV ratio was then calculated. The diameters of the main pulmonary artery and ascending aorta (the diameters of the inner lumina) were measured at a single transverse scanning level at which the right pulmonary artery is in continuity with the main pulmonary artery and sweeps across the midline.

The echocardiographic data were extracted from the cardiology reports. Only two-dimensional echocardiograms performed within the first 72 h of admission were included.

Patients who had SE on CTA were compared with those who did not. The clinical, echocardiographic findings and CT parameters were analysed to determine their ability to predict the development of MAEs within 30 days.

Statistical analysis

The data are presented as mean $\pm$ standard deviation for continuous variables and as absolute or relative frequencies for categorical variables. In the primary analysis, the SE group was compared with the non-SE group. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Student's *t*-test was used to compare the means of continuous variables if a normal distribution was detected; otherwise, the

Mann–Whitney *U*-test was used. Categorical variables were compared using the χ^2 test. Univariate and multivariate logistic regression analyses were used to identify the independent predictors of developing MAE. Stepwise modelling was used to screen the potential variables for inclusion in the final model. The results of multivariate logistic regression analysis were reported as odds ratios (OR) and 95% confidence intervals (CI). $p \leq 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS® for Windows v. 18.0 (SPSS Inc., Chicago, IL).

RESULTS

In total, 347 patients were diagnosed with non-high-risk acute PE in the ED during the study period. Of these, 50 patients were excluded from the final analysis. These included 37 patients with recurrent PE and 13 patients whose initial chest CTA images were inadequate for evaluation. The final study group consisted of 297 patients with non-high risk PE. There were 143 males and 154 females, and the mean age was 62 years. The patient demographic characteristics and laboratory findings are summarised in Table 1. The prevalence of SE in these patients was 9.7% (27/297). On non-electrocardiographic-gated CTA, the patients with SE had significantly longer RV and LV end diastolic dimensions and greater RV/LV ratios than the patients without SE (Table 1). Echocardiographic D-shaped LV was also observed more frequently in the patients with SE. The overall mortality at 30 days was 12.5%, and no significant difference was seen between the SE and non-SE groups (18.5% vs 11.9%, $p=0.32$). However, the patients with SE were more likely to be treated with thrombolytic therapy (29.6% vs 8.1%, $p<0.01$) (Table 2) and also had a significantly higher rate of MAE (59.3% vs 25.6%, $p<0.01$). The results of multivariate logistic regression analysis of factors that are associated with the development of MAE are presented in Table 3. The presence of SE and a high RV/LV ratio are associated independently with the development of MAE within 30 days of ED admission (OR: 2.48, 95% CI: 1.10–6.04, $p=0.03$ and OR: 3.34, 95% CI: 1.46–7.46, $p<0.01$, respectively).

DISCUSSION

The present study evaluated whether the presence of SE (as determined by CTA at the time of diagnosis) in patients with non-high-risk PE can predict the development of PE-related MAEs (shock, mechanical ventilation, in-hospital mortality, thrombolysis and thrombectomy) within 30 days. The prevalence of SE in the 297 consecutive patients at ED admission was 9.7%. SE was also an independent predictor of the development of MAE within 30 days (OR: 2.48, 95% CI: 1.10–6.04, $p=0.03$).

The SE frequency of 9.7% is slightly higher than the frequencies recorded by previous studies: Pruszczyk et al [9], Ryu et al [7] and Sardi et al [12] found frequencies of 5.2%, 2.6% and 5.4%, respectively. This disparity probably reflects the fact that the present study was only conducted with patients at ED admission, whereas all of the previous studies also examined patients at non-ED admission. This fact is supported by the report by Sardi et al [12], in which 81% of the SE cases were diagnosed in the ED and another 19% developed SE during hospitalisation.

Table 1. Baseline clinical characteristics of patients with non-high-risk pulmonary embolism who do or do not have a saddle embolus, as diagnosed using CT angiography

Variables	Non-saddle (<i>n</i> =270)	Saddle (<i>n</i> =27)	<i>p</i> -value
Demographic factors			
Age (years)	62.1±15.4	62.5±12.1	0.90
Male	131 (48.5)	12 (44.4)	0.84
Comorbidities			
Diabetes	48 (17.8)	7 (25.9)	0.30
Heart failure	7 (2.6)	1 (3.7)	0.54
COPD	7 (2.6)	0 (0.0)	1.00
Cancer	112 (41.5)	9 (33.3)	0.53
DVT	75 (27.7)	5 (18.5)	0.49
Clinical feature			
Dyspnoea	203 (75.2)	24 (88.9)	0.12
Haemodynamics			
Systolic BP, mmHg	124.8±22.8	116.4±27.0	0.06
Diastolic BP, mmHg	78.8±16.6	77.3±16.2	0.65
Laboratory findings			
PaO ₂ , mmHg	72.5±22.2	63.2±14.8	0.26
FiO ₂ , %	25.4±16.5	24.0±15.0	0.69
D-dimer, µg ml ⁻¹	11.4±16.1	14.4±12.2	0.30
C-reactive protein	5.4±7.0	5.4±5.5	0.81
Creatinine	0.9±0.6	0.9±0.3	0.99
Echocardiographic findings ^a			
LV ejection fraction, %	60.7±6.9	59.7±9.5	0.58
TR velocity, m s ⁻¹	3.1±0.7	3.2±0.8	0.52
RV dysfunction	75 (48.1)	11 (61.1)	0.29
D-shape LV	39 (25.2)	9 (60.0)	<0.01
CT findings			
LV end diastolic dimension, mm	39.8±8.0	34.9±9.0	0.01
RV end diastolic dimension, mm	42.1±8.0	48.7±7.2	<0.01
RV/LV ratio	1.1±0.4	1.6±0.5	<0.01
PA diameter, mm	32.1±5.5	32.4±5.0	0.80
Aorta diameter, mm	35.0±5.3	35.7±4.3	0.46
SVC diameter, mm	18.3±3.4	19.3±3.9	0.17
Azygos vein, mm	9.5±2.3	9.5±2.5	0.97
IVC diameter, mm	22.3±4.3	23.3±3.9	0.25

BP, blood pressure; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; FiO₂, fraction of inspired oxygen; IVC, inferior vena cava; LV, left ventricle; PA, pulmonary artery; PaO₂, partial oxygen tension in arterial blood; RV, right ventricle; RV/LV ratio, ratio of right ventricular diameter to left ventricular diameter; SVC, superior vena cava; TR, tricuspid regurgitation.

Values are expressed as mean ± standard deviation or *n* (%).

^aThe total number of patients with available echocardiography data within 24 h is 182.

The clinical presentation and outcomes of patients with SE vary widely. Previous studies have suggested that SE requires aggressive therapy, such as surgical embolectomy or thrombolysis, owing to

an increased risk of mortality [9,15,16]. However, other contemporary studies have reported successful recovery after less aggressive treatment and have suggested that SE is not associated

Table 2. Treatment and outcomes of patients with non-high-risk pulmonary embolism who do or do not have a saddle embolus, as diagnosed using CT angiography

Variables	Non-saddle (<i>n</i> =270)	Saddle (<i>n</i> =27)	<i>p</i> -value
Treatment, <i>n</i> (%)			
Vasopressor	40 (14.9)	8 (29.6)	0.05
Inferior vena cava filter	51 (18.9)	10 (37.0)	0.03
Thrombolytics	22 (8.1)	8 (29.6)	<0.01
Thrombectomy	3 (1.1)	2 (7.4)	0.07
30 day all-cause mortality, <i>n</i> (%)	32 (11.9)	5 (18.5)	0.32
Major adverse events, <i>n</i> (%)	69 (25.6)	16 (59.3)	<0.01

with worse short-term outcomes [4,5,7,9,12]. Therefore, for appropriate risk stratification, it is necessary to know the prognosis of SE, especially in patients with non-high-risk acute PE. Recent studies have shown that the mortality rate associated with SE is low: none of the 14 patients with SE in the study by Ryu et al [7] died; 1 of the 17 patients in the study by Pruszczyk et al [9] died; 2 of the 37 patients in the study by Sardi et al [12] died; 2 of the 31 patients in the study by Gandara et al died [17]; and Vedovati et al [18] said that saddle emboli were not predictors of all-cause death or clinical deterioration. In all three studies, the mortality rates of the SE and non-SE groups did not differ significantly. In the present study, 5 of the 27 patients with SE died, and the SE and non-SE groups also did not differ in terms of overall mortality at 30 days (18.5% vs 11.9%, $p=0.32$). However, the patients with SE were also more likely to receive thrombolytic therapy (29.6% vs 8.1%, $p<0.01$). This suggests that thrombolytic therapy may have been beneficial and improved the overall mortality rate of the patients with SE, which is why the SE and non-SE groups did not differ in terms of mortality. This observation requires further evaluation with a well-designed study.

Some authors believe that the diagnosis of SE is not associated with mortality and therefore should not affect the outcome or management of PE. However, this notion may be based on studies that have some limitations. First, previous studies on SE only had between 14 and 37 patients. Second, most of these studies were case series; there was only one case-control study, namely that by Pruszczyk et al [9], which compared 17 patients with SE with 44 patients who had been selected from a non-SE group. To our knowledge, the present study is the first and largest study to

compare the outcomes of patients with and without SE in non-high-risk PE. Unlike previous studies, the present study showed that patients with SE had a significantly higher rate of MAEs (59.3% vs 25.6%, $p<0.01$). Moreover, it showed that the presence of SE was an independent predictor of the development of MAE within 1 month, with an OR of 2.48 (95% CI: 1.10–6.04, $p=0.03$). A recent study by Yusuf et al [11] supports our finding that SE is associated with a poor PE outcome: although the SE and non-SE groups did not differ in terms of mortality rates at 1 month, the SE group had a significantly higher mortality rate at 1 year than the non-SE group. The presence of SE was also associated with an OR of death within 1 year of 7.41 (95% CI: 1.75–31.46, $p=0.007$).

The RV/LV ratio is widely accepted as a measure of RV dilatation on CTA [19–21]. In the present study, the RV/LV ratio was associated independently with the development of MAE within 30 days of ED admission (OR: 3.34, 95% CI: 1.46–7.46, $p<0.01$). However, the cut-off RV/LV ratio values that are used to signify RV dysfunction vary between reports from 0.9 to 1.5 [18–20]. Another concern that has arisen is whether non-electrocardiographic-gated CT is accurate in terms of measuring ventricular chamber size because the images are acquired in different phases of the cardiac cycle. Thus, the RV/LV ratio may be too inaccurate to be useful for clinicians comparing to check for the presence of SE. Moreover, it is impractical in emergency situations.

The limitations of the current study mainly relate to its retrospective nature: there is always the possibility that selection bias may have influenced the results. Moreover, the sample size was relatively limited, although this is the largest study to date of

Table 3. Multivariate logistic regression analysis to identify independent factors that associate with the occurrence of major adverse events in patients with non-high-risk pulmonary emboli

Variables	Adjusted OR	95% CI	<i>p</i> -value
Age	1.00	0.99–1.03	0.48
Gender	1.01	0.62–1.92	0.76
Concave interventricular septum	1.48	0.70–3.18	0.31
Saddle embolism	2.48	1.10–6.04	0.03
RV/LV ratio	3.34	1.46–7.46	0.01

CI, confidence interval; OR, odds ratio; RV/LV ratio, ratio of right ventricular diameter to left ventricular diameter.

patients with SE in the setting of an ED. Another potential concern is the fact that only overall mortality rates were reported. In addition, 47% of the patients of this study had malignancies, which are generally associated with high mortality. This may have had an impact on the overall mortality. Finally, the effect of thrombolysis on mortality could not be assessed. Large-scale studies may be needed to clarify this possible association.

In summary, although the presence of SE (as determined by CTA) at the time of diagnosis did not associate with mortality in patients with non-high risk PE in the ED, it was predictive of their development of PE-related MAE (namely shock, mechanical ventilation, in-hospital mortality, thrombolysis and thrombectomy) within 30 days. Therefore, patients with SE should not be overlooked. Instead, they should be observed closely for signs of MAEs.

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