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Central emboli rather than saddle emboli predict adverse outcomes in patients with acute pulmonary embolism

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ABSTRACT

Introduction: In patients with acute pulmonary embolism (PE), the prognostic implications of saddle or central emboli, as observed on computed tomography (CT), remain to be established. The aim of the present study was to assess whether the presence of saddle and central emboli could be used to predict clinical outcomes in patients with PE.
Materials and Methods: The authors retrospectively reviewed 743 consecutive patients hospitalized at a tertiary referral center with a diagnosis of PE based on multi-detector row CT scan.
Results: All the clinical variables did not differ between saddle emboli (5.8% [n = 43]) and right or left pulmonary artery emboli (29.7% [n = 221]), and the frequency of an adverse outcome was not significantly different between the two groups. Saddle emboli and right or left pulmonary artery emboli were grouped into central emboli (35.5% [n = 264]). Patients were allocated to an adverse outcome group (10.5% [n = 78]) or a control group (89.5% [n = 665]). Multivariate analysis demonstrated that PE severity index (PESI) score (class IV-V), N-terminal-pro-B-type natriuretic peptide level (≥1,406 pg/mL), right ventricular dilation on CT (right ventricle/left ventricle diameter ratio ≥1), and central emboli significantly predicted an adverse outcome. The addition of central emboli to other established prognostic factors such as PESI enhanced the positive predictive values and positive likelihood ratios of an adverse outcome for acute PE.
Conclusions: Rather than saddle emboli, central emboli could be an independent prognostic factor of adverse outcomes in patients with acute PE and provide additional prognostic value when combined with other prognostic factors.

Introduction

The presentation of acute pulmonary embolism (PE) is heterogeneous, and its mortality rates vary from < 5% in clinically stable patients to > 30% in hemodynamically unstable patients [1]. Advances in computed tomography (CT) have enabled direct and noninvasive detection of pulmonary emboli. Acute large or multiple pulmonary emboli rather than small and peripheral emboli may cause the hemodynamic consequences of right ventricular dysfunction, left ventricular failure, and hemodynamic collapse [2]. Thus, the presence of large pulmonary emboli on a CT scan is expected to predict a poor prognosis for acute PE. However, measuring clot burden of pulmonary emboli on CT is time consuming, unlikely to be applied in daily clinical practice, and is not a useful prognostic measure in terms of short-term mortality and adverse clinical outcomes [3,4]. The localization of emboli on a CT scan does not seem to improve the risk stratification in the overall population of patients with PE [5]. While clinical prediction models and parameters of right ventricular (RV) dysfunction have been reported to have prognostic value, an obstruction index suggestive of clot burden has not been consistently predictive of clinical outcomes [6].

A saddle embolus, one of the most proximal and large pulmonary emboli, is defined as a visible thromboembolus that straddles the bifurcation of the main pulmonary artery trunk [7]. Visualization of saddle emboli on a CT scan imposes clinicians on having concern about large clot burden, poor prognosis, and impending hemodynamic collapse [7]. However, the clinical course and prognoses of saddle PE vary widely. Unlike past studies suggesting the need for aggressive therapy in saddle PE because of higher mortality [8], recent studies implied that saddle PE itself does not need aggressive therapy [9–11]. In addition, saddle PE has clinical conditions [11] and 30-day prognoses [12,13] similar to non-saddle central PE. In contrast, a recent report indicated that saddle PE was associated with the development of major adverse events within one month [7]. For cancer patients, although the 30-day mortality rate

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of saddle PE was comparable with that of non-saddle proximal PE, the one-year mortality rate of saddle PE was significantly higher than that of non-saddle proximal PE [13]. At present, the prognostic implication of saddle PE remains to be established.

We hypothesized that large pulmonary emboli, such as saddle emboli, could predict an adverse outcome for acute PE. Thus, the aim of the present study was to assess whether saddle or central emboli (saddle emboli or non-saddle right or left pulmonary artery emboli) could be used to predict clinical outcomes in patients with PE. In addition, we investigated whether adding saddle or central emboli to other well-known markers could improve prognostic yield in terms of predicting adverse outcomes.

Methods

Study design

We enrolled 743 consecutive patients with a multidetector-row CT (MDCT)-based diagnosis of PE who had been hospitalized and evaluated or treated in the Department of Pulmonology of Kyungpook National University Hospital (KNUH), a tertiary referral center, in Daegu, South Korea between March 2003 and December 2013. Patients' baseline data were recorded at their charts during their initial contact or consultation, although this study was retrospective. Similar to a previous study [14], all patients were classified into four groups by the PE-involved largest pulmonary arteries: saddle, pulmonary (right or left pulmonary artery), lobar (truncus anterior, interlobar or lobar arteries), and peripheral (segmental or subsegmental arteries). Saddle PE was defined as a thromboembolism at the level of the bifurcation of the pulmonary trunk that extended into the right and left main pulmonary arteries [12,15]. Central PE comprised the saddle and pulmonary groups. To determine the locations of the most proximal pulmonary arteries in which emboli were detected, CT scans were reviewed separately by two experienced radiologists (K.M.S. and J.K.L.) who were blinded to the patients' clinical information. In case of discrepancies in their readings, a final decision was reached by consensus. This study was approved by the Institutional Review Board of the KNUH, which waived the requirement for written informed consent because of the retrospective nature of the study.

Similar to a previous study [16], an adverse outcome was defined as PE-related in-hospital death or PE resulting in a serious clinical condition requiring intensive care treatment, including inotropic support, refractory hypoxia (impending respiratory failure or mechanical ventilation), cardiopulmonary resuscitation, or secondary thrombolysis. PE-related in-hospital death was defined as in-hospital death fulfilling the following criteria: objective evidence of death directly caused by PE or death that could not be attributed to other causes and in which PE could not be excluded. The two reviewers (K.J.C. and S.I.C.) identified the occurrence of adverse outcomes and reached a final decision by consensus.

Data collection

Demographic data and risk factors of venous thromboembolism (VTE) were checked. Unprovoked PE was defined as the absence of reversible provoking risk factors, such as surgery, trauma, active cancer, pregnancy and puerperium within 3 months of the event, or immobilization (bed rest within the past month for most of the day for ≥3 consecutive days). The presence of hypotension (systolic blood pressure <90 mm Hg) and tachycardia (heart rate >110/min) were also recorded. The PE severity index (PESI) score [17] was retrospectively calculated for patients before 2007 by a pulmonologist (C.K.J.) and prospectively recorded in their medical records since 2007. Thrombolytic agent use, VTE recurrence, and length of hospital stay were reviewed. Laboratory tests included levels of serum N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and plasma troponin I and arterial blood gas analysis (ABGA) data, including partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), inspired oxygen fraction (FiO_2), and PaO_2/FiO_2 ratio.

Radiological evaluation

As defined in an earlier study [18], PE was diagnosed on CT images as a sharply delineated pulmonary arterial filling defect in at least two consecutive image sections, either located centrally within the vessel or with acute angles at its interface with the vessel wall. The diameters of the right ventricle (RV) and left ventricle (LV) were measured at their widest points between the inner surface of the free wall and the surface of the interventricular septum and were typically measured at the levels of tricuspid valve and mitral valve, respectively [19,20]. Subsequently, the RV/LV diameter ratios were calculated.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Data were expressed as medians with interquartile ranges (IQR) for continuous variables and numbers with percentages for categorical variables. Among the groups, continuous variables were compared using one-way analysis of variance (ANOVA) and the Kruskal-Wallis test for non-normally distributed data. In multiple comparisons, the Scheffe method was used as a *post-hoc* test if equal variances were assumed, and Dunnett's T3 method was adopted if equal variances were not assumed. Categorical variables were compared using the chi-square test among groups, and Bonferroni's correction was used as a post-hoc follow-up test. When continuous variables were converted to categorical variables, cut-off values were determined using receiver operating characteristic (ROC) curves. Unconditional multiple logistic regression analysis was used to identify predictors of adverse outcomes. The Hosmer-Lemeshow test was used as a goodness-of-fit test to assess the fit of logistic regression models. In addition, we calculated sensitivities, specificities, positive predictive values, negative predictive values, positive likelihood ratios, and negative likelihood ratios for predicting adverse outcomes. MedCalc, version 12.0 (MedCalc Software, Ostend, Belgium) was used for analysis of the ROC curve. P-values <0.05 were considered statistically significant.

Results

Baseline characteristics by location of pulmonary emboli

Saddle PE accounted for 5.8% (43/743) of patients with PE. Age, female gender, and smoking history did not significantly differ among the four groups, which consisted of the saddle, pulmonary, lobar, and peripheral groups (Table 1). Although body mass index (BMI) was significantly different among the groups ($p < 0.001$) and the saddle group had significantly higher BMI than the peripheral group ($p = 0.011$ by Scheffe method), no significant difference between the saddle and pulmonary groups was noted. As risk factors for PE, the frequencies of surgery or trauma, cancer, and immobilization significantly differed among the groups ($p < 0.001$, $p = 0.010$, and $p < 0.001$, respectively) but did not significantly differ between the saddle and pulmonary groups. The frequency of unprovoked PE was significantly different among the four groups ($p < 0.001$); unprovoked PE was significantly more common in the saddle group when compared with the peripheral group (Bonferroni's corrected $p < 0.001$) but not when compared with each remaining group.

The frequency of hypotension (systolic blood pressure <90 mmHg) was significantly different among the groups ($p < 0.001$) and was significantly more commonly observed in the saddle group than the peripheral and lobar groups (Bonferroni's corrected $p = 0.006$ or $p < 0.001$, respectively), but no significant difference was found between the saddle and pulmonary groups. Although the distribution of tachycardia