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Full Length Article

Clinical relevance of syncope in patients with pulmonary embolism

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ABSTRACT

Background: Syncope is an unusual clinical manifestation of pulmonary embolism (PE), and the clinical significance of syncope in PE patients remains controversial. We investigated the incidence of syncope, examined the clinical factors associated with syncope, and assessed the association between syncope and the short-term outcomes of PE.

Methods: We retrospectively classified patients presenting with PE into 2 groups: patients with syncope and those without syncope. We compared the clinical and computed tomography parameters between the groups.

Results: Among 1084 patients diagnosed with PE, 45 (4.2%) presented with syncope. Four patients which presented with cardiac arrest were excluded from the study. The syncope group showed significantly higher blood biomarker levels and higher rates of central PE and right ventricular dilation than the control group. Unprovoked PE (odds ratio [OR] 8.046, 95% confidence interval [CI] 3.073–21.069, $p < 0.001$), female sex (OR 3.419, 95% CI 1.348–8.675, $p = 0.010$), central PE (OR 2.854, 95% CI 1.298–6.278, $p = 0.009$), and troponin I level (OR 2.812, 95% CI 1.765–4.480, $p < 0.001$) were observed to be independent factors associated with syncope in PE patients. However, multivariate analysis showed that the presence of syncope was not a significant predictor of adverse outcomes and recurrent venous thromboembolism in PE patients.

Conclusions: Although syncope is associated with a more severe form of PE, it does not influence the short-term prognosis of PE. Central PE, blood troponin I level, unprovoked PE, and female sex were observed to be clinical factors related with syncope in patients with PE.

1. Introduction

Acute pulmonary embolism (PE) is usually associated with nonspecific symptoms and signs. The clinical presentation of this disease entity is variable, ranging from asymptomatic incidental findings to hemodynamic instability and consequently even death [1]. The common symptoms of PE include dyspnea, chest pain, and hemoptysis [2], and syncope is an unusual clinical manifestation associated with this condition. Syncope has been reported to occur in 5.5–16% of patients with PE, depending upon the study design and the population in which these findings were noted [2–11]. Data regarding the incidence of syncope in Asian patients with PE are lacking. Based on previous studies, PE is a rare underlying cause in patients presenting with syncope with its incidence ranging between 1% and 2.3% of patients [12–14], although a much higher incidence has been reported in a recent study [15].

PE is known to cause hemodynamic disturbances as follows: pulmonary emboli with a high clot burden cause acute right ventricular (RV) failure, impair left ventricular (LV) filling, cause cerebral hypoperfusion, and eventually lead to syncope [16]. Given that massive PE causes syncope, syncope is expected to play a role in determining the short-term prognosis of PE. However, studies investigating the association between syncope and mortality in patients with PE have shown conflicting results. A few studies have demonstrated that the presence of syncope was associated with a higher mortality of PE [11,16,17], whereas others have not shown any such association [3–5,18–21]. Notably, a study has even shown that mortality was lower in PE patients with syncope than in those without syncope [10].

Our present study retrospectively investigated the incidence of syncope in Korean patients with PE and assessed the association of syncope with outcome variables of PE. Additionally, we examined the clinical factors associated with syncope in these patients.

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2. Methods

2.1. Study design

This study was retrospectively performed at a tertiary referral center, the Kyungpook National University Hospital (KNUH) in Daegu, South Korea. Consecutive patients diagnosed with PE using multidetector-row computed tomography (CT) between March 2003 and December 2016 were enrolled into the PE registry. Syncope was defined as a symptom due to cerebral hypoperfusion, presenting with an abrupt, transient, complete loss of consciousness, associated with inability to maintain postural tone, with rapid and spontaneous recovery [22]. Syncope was determined by consensus between 2 chest physicians (Y.H.L. and S.I.C.) based on patients' medical records. Clinical characteristics, blood biomarkers, and CT findings were compared between patients with syncope (syncope group) and those without syncope (control group). 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.

2.2. Data collection

Data regarding demographics, symptoms, vital signs, risk factors of venous thromboembolism (VTE), and comorbidities, were obtained. Unprovoked PE was defined as the absence of reversible provoking risk factors, including trauma, surgery, cancer, pregnancy and puerperium within 3 months of the event, and immobilization (bed rest for most of the day for ≥3 consecutive days) within 1 month of the event [23]. The PE Severity Index (PESI) [24] was retrospectively calculated. Based on the 2008 European Society of Cardiology (ESC) guidelines [25], the severity of PE was classified into three categories: high, intermediate, and low risk. Outcome variables, including PE-related in-hospital mortality, adverse outcomes, and recurrence of VTE, were determined. As reported in a previous study [26], a PE-related in-hospital death was defined as an in-hospital death that met 1 of 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. An adverse outcome was defined as a PE-related in-hospital death or PE resulting in a serious clinical condition requiring intensive care treatment, such as inotropic support and mechanical ventilation, impending respiratory failure or refractory hypoxia, cardiopulmonary resuscitation, or secondary thrombolysis [26]. Measured blood biomarker levels, including N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and troponin I, were recorded.

2.3. Radiological evaluation

CT scans were performed using a MDCT with 16 or 64 detector rows (Light Speed 16 or Optima CT660; General Electric, Milwaukee, Wisconsin, USA; Aquilion 64, Toshiba Medical Systems, Japan). The scan was obtained in the craniocaudal direction during a single inspiratory breath hold from the apex to the diaphragm. The CT parameters used for 16-channel MDCT were 120 kVp and a 16 × 0.75 mm collimation with a pitch of < 1.5. The parameters for 64-channel MDCT were 120 kVp and 64 × 0.5 mm collimation with a pitch of < 1.5. A standard dose (2 mL/kg, up to 150 mL) of low osmolar nonionic contrast media (Optiray 350, Mallinckrodt Inc., Hazelwood, Mo., USA) was injected through an arm vein at 2.5–3 mL/s. Individual optimization of peak enhancement time was achieved by using bolus tracking within the main pulmonary artery. The threshold value for triggering data acquisition was set to 250 Hounsfield units. Indirect CT venography was performed 140 s after the thoracic scan, from the diaphragm down to the ankles, to detect DVT.

As described in a previous study [27], based on CT evidence, PE was diagnosed as a sharply delineated filling defect in a pulmonary artery in at least 2 consecutive image sections. The largest pulmonary artery showing pulmonary emboli was classified as: pulmonary trunk or right atrium, pulmonary (right or left pulmonary artery), interlobar or lobar, segmental, and subsegmental. Central PE was defined as emboli located in the right or left pulmonary artery or more proximal sites. The diameters of the RV and LV were measured at their widest points between the inner surface of the free wall and the surface of the interventricular septum, and the RV/LV diameter ratio was calculated; and the RV/LV diameter ratio ≥ 1 indicated RV dilation [26]. Similar to prior studies [28,29], pulmonary infarction was defined as the presence of peripheral consolidation in the region of the segmental or subsegmental pulmonary emboli.

2.4. Statistical analysis

Data were expressed as medians with interquartile ranges for continuous variables and as numbers with percentages for categorical variables. Continuous variables were compared between groups using the Mann–Whitney U test, and categorical variables were compared using the chi-squared test. Multiple logistic regression analysis was used to identify factors associated with syncope, adverse outcomes, and VTE recurrence. The Hosmer–Lemeshow test was used as a goodness-of-fit test to assess the fit of the logistic regression models. p-Values < 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) software.

3. Results

3.1. Clinical characteristics of patients with pulmonary embolism and syncope

Among the 1084 PE patients, 45 presented with syncope (4.2%), and after exclusion of 4 patients who presented with cardiac arrest, 1035 were included in the control group. The demographic and clinical characteristics of patients are presented in Table 1. Compared with the control group, the syncope group showed a significantly higher percentage of women (37 [82.2%] vs. 581 [56.1%], p = 0.001) and a higher body mass index (BMI) (24.8 kg/m^2 [22.0–28.2 kg/m^2] vs. 23.6 kg/m^2 [21.1–25.8 kg/m^2], p = 0.008). Unprovoked PE was significantly more common in the syncope group than in the control group (35 [77.8%] vs. 327 [31.6%], p < 0.001). As a risk factor for VTE, surgery or trauma (5 [11.1%] vs. 256 [24.7%], p = 0.037), cancer (4 [8.9%] vs. 223 [21.5%], p = 0.041), and immobilization (7 [15.6%] vs. 494 [47.7%], p < 0.001) were significantly less frequently observed in the syncope group than in the control group. Comorbidities and the PESI score did not significantly differ between the groups. In terms of severity, the percentage of patients showing an intermediate risk was significantly higher in the syncope group than in the control group (39 [86.7%] vs. 537 [51.9%], p < 0.001), whereas the percentage of those showing a low risk was significantly lower (4 [8.9%] vs. 460 [44.4%], p < 0.001). Compared to the control group, the syncope group showed a trend toward higher rate of adverse outcomes (8 [17.8%] vs. 97 [9.4%], p = 0.071) and a significantly higher incidence of VTE recurrence (6 [13.3%] vs. 52 [5.0%], p = 0.029), despite no observed difference in PE-related in-hospital mortality. The patients with syncope underwent thrombolysis more frequently than those without syncope (8 [17.8%] vs. 48 [4.6%], p = 0.002).

3.2. Laboratory and computed tomography findings in patients with pulmonary embolism and syncope

Data regarding blood biomarkers and CT findings are summarized in Table 2. Not all patients underwent the measurement of blood biomarkers, including NT-proBNP and troponin I. The syncope group showed significantly higher levels of than the control group with respect to NT-proBNP (1,150 pg/mL [280–3,149 pg/mL] vs. 458 pg/mL

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