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Original article

Usefulness of cardiac biomarkers in the prediction of right ventricular dysfunction before echocardiography in acute pulmonary embolism

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ABSTRACT

Background: The aim of this study was to investigate a useful cardiac biomarker for predicting echocardiographic right ventricular (RV) dysfunction in patients with acute pulmonary embolism (APE).
Methods: A total of 84 patients with APE were divided into two groups: patients with RV dysfunction (group I, $n = 51$, 61.8 ± 15.1 years) versus without RV dysfunction (group II, $n = 33$, 66.8 ± 13.6 years). Cardiac biomarkers were compared between the groups.
Results: The level of N-terminal pro-brain-type natriuretic peptide (NT-proBNP), cardiac specific troponin T (cTnt), and I (cTni) was significantly elevated in group I compared to group II, but the level of creatine kinase and high-sensitivity C-reactive protein was not different. By receiver operating characteristic curve analysis, the area under the curve to predict RV dysfunction was 0.912 for NT-proBNP, 0.797 for cTnt, and 0.766 for cTni. The optimal cut-off value to predict RV dysfunction was 620.0 pg/mL for NT-proBNP (sensitivity: 90.2%, specificity: 75.8%), 0.016 ng/mL for cTnt (sensitivity: 82.4%, specificity: 78.8%), and 0.055 ng/mL for cTni (sensitivity: 86.3%, specificity: 66.7%). NT-proBNP > 620 pg/mL and cTnt > 0.016 ng/mL were independent predictors of RV dysfunction on multivariate analysis after adjustment for the baseline characteristics.
Conclusions: NT-proBNP, cTnt, and cTni were significant serologic predictors of RV dysfunction in APE. Measurements of NT-proBNP, cTnt, and cTni are simple and useful in the risk stratification or treatment of APE.

Introduction

Acute pulmonary embolism (APE) is not uncommon in clinical practice, and the mortality of APE is still high despite advances in diagnostic modalities and therapeutic options [1–3]. It has been proved that patients with massive APE, defined by systemic hypotension, should be treated with thrombolysis or embolectomy [4,5].

Right ventricular (RV) dysfunction is a well-known predictor of early death, and thus early identification of RV dysfunction is critical in the risk stratification or management of APE [6–10]. Transthoracic echocardiography (TTE) has been used as a method of choice to identify the patients with RV dysfunction [11]. Cardiac biomarkers such as troponin and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) are known to be useful not only in the diagnosis, but also in the risk stratification of various cardiac diseases [12,13]. Furthermore, recent studies have suggested that cardiac biomarkers are associated with an increased risk of mortality in patients with APE, even in hemodynamically stable patients [14–18], and thus cardiac biomarkers are useful in the risk stratification of APE. It has been suggested that cardiac biomarkers are associated with the presence of RV dysfunction on echocardiography. Although several studies have been conducted to prove the relationship between cardiac biomarkers and RV dysfunction on echocardiography [19–23,10,24], the comparisons among cardiac biomarkers in the prediction of RV dysfunction and the optimal cutoff values of cardiac biomarkers to predict RV dysfunction were poorly evaluated.

Therefore, the aim of the present study was to investigate the most useful serologic predictors of RV dysfunction and to investigate the optimal cutoff values of cardiac biomarkers to predict RV dysfunction in patients with APE.

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Materials and methods

Study design and population

The present study was a single center retrospective observational study, and the study protocol was approved by the Institutional Review Board of Chonnam National University Hospital.

The diagnosis of APE was confirmed by the presence of filling defects within the pulmonary arterial systems on helical computed tomographic pulmonary angiography (CTPA) in patients who presented with dyspnea, tachycardia, chest discomfort, or hemoptysis. From 2004 to 2007, a total of 101 consecutive patients with APE were included initially. Of these, 17 patients were excluded from the study; nine patients with lack of biomarker tests; 3 patients with combined left heart failure; 2 patients with known cor pulmonale; 2 patients without initial echocardiogram; 1 patient with end-stage renal disease. The remaining 84 patients with APE were enrolled finally in the present study, and they were divided into two groups based on the presence of RV dysfunction on echocardiography: patients with RV dysfunction (group I, $n = 51$, 61.8 ± 15.1 years, 31 females) versus patients without RV dysfunction (group II, $n = 33$, 66.8 ± 13.6 years, 20 females). Obesity was defined as body-mass index > 27 kg/m^2, and immobilization as prolonged bed rest associated with orthopedic surgery, major fracture, or cerebrovascular accidents, or prolonged sitting during travel. The thrombophilic condition was defined as the patients with known risk factors for venous thrombosis such as factor V leiden, protein C or S deficiency, anti-phospholipid syndrome, or essential thrombocytosis.

TTE examination

TTE was performed within 6 h after diagnosis of APE by CTPA for the risk stratification or clinical decision-making of therapeutic strategy.

The presence of RV dysfunction was confirmed only based on the echocardiographic findings in the present study. The demonstration of RV free wall hypokinesia or akinesia on echocardiographic examination was considered as the definite diagnosis of RV dysfunction in patients with APE. RV enlargement, defined by the ratio of RV to LV size more than 1 in apical 4 chamber view without obvious causes, accompanied by pulmonary hypertension in patients with APE was also considered as RV dysfunction in the present study [11]. Fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and RV systolic pressure were also measured as the additional parameters of RV function according to the current guideline of the American Society of Echocardiography [25]. Eccentricity index (EI) which reflected the degree of RV pressure overload was measured at the parasternal short-axis view during both end-systole and end-diastole. EI was calculated by measuring the ratio D2/D1, where D1 is the antero-posterior dimension and D2 is the transverse dimension of the left ventricle.

Measurement of cardiac biomarkers

NT-proBNP, cardiac specific troponin T (cTnt), I (cTni), creatine kinase (CK), and MB fraction of CK (CK-MB), and high-sensitivity C-reactive protein (hsCRP) were measured as cardiac biomarkers within 1 h after the diagnosis of APE and before the initiation of thrombolytic therapy.

Serum NT-proBNP was measured using an electrochemiluminescence sandwich immunoassay method for NT-proBNP with an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland). This method has high sensitivity and specificity, and large detection range. The analytic range of the NT-proBNP assay extends from 5 to 35,000 pg/mL. The reference value varies according to age and gender, and <88 pg/mL for men and <153 pg/mL for women in our institution. cTnt was measured using electrochemiluminescence sandwich immunoassay method with an Cobas e 411 (Roche Diagnostics), and the reference range for cTnt was <0.1 ng/mL. cTni was also measured using one step Enzyme Immunoassay with a Dimension RxL Max (Siemens, Munich, Germany), and the reference range for cTni was <0.05 ng/mL. And hsCRP was measured by the immunoturbidimetric CRP-Latex (II) high-sensitivity assay using an Olympus 5431 autoanalyzer with reference range of <0.5 mg/dL.

Table 1
Baseline clinical characteristics.

	Group I ($n = 51$)	Group II ($n = 33$)	p-Value
Age (years)	61.8 ± 15.1	66.8 ± 13.6	0.128
Females (%)	31 (60.8)	20 (60.6)	0.987
SBP (mmHg)	113.1 ± 19.8	135.2 ± 16.7	<0.001
DBP (mmHg)	72.7 ± 13.7	82.5 ± 10.5	<0.001
Heart rate (beat/min)	88.1 ± 13.9	81.7 ± 10.6	0.028
Clinical symptoms			
Dyspnea (NYHA class)	2.8 ± 1.0	1.9 ± 0.9	<0.001
Chest pain (%)	21 (41.2)	12 (36.4)	0.659
Hemoptysis (%)	2 (3.9)	6 (18.2)	0.069
Syncope (%)	10 (19.6)	4 (12.1)	0.369
Cyanosis (%)	5 (9.8)	0 (0.0)	0.064
Predisposing conditions			
Previous DVT or PTE (%)	6 (11.8)	5 (15.2)	0.653
Immobilization (%)	7 (13.7)	5 (15.2)	0.855
Smoking (%)	10 (19.6)	12 (36.4)	0.088
Obesity (%)	12 (23.5)	7 (21.2)	0.804
Malignancy (%)	6 (12.2)	4 (12.1)	0.961
Thrombophilic condition (%)	1 (2.0)	1 (3.0)	0.754
Pregnancy (%)	1 (2.0)	0 (0.0)	0.418

SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.

Statistical analysis

The Statistical Package for Social Sciences for Windows (version 17.0, Chicago, IL, USA) was used for statistical analyses. Data were expressed as mean ± standard deviation for continuous variables and percentage for categorical data.

Chi-square test was used to compare differences in categorical values between the two groups. Independent t-test was used to compare differences in continuous variables. Receiver operating characteristic (ROC) curve analysis was conducted to identify the optimal cut-off value of biomarkers to predict RV dysfunction. Correlation analysis between cardiac biomarkers and the parameters of RV dysfunction was established by the Pearson correlation. To identify the independent biochemical predictors of RV dysfunction, multivariate logistic regression analysis adjusted by the baseline clinical characteristics including age, sex, blood pressure, heart rate, and creatinine level was applied to the significant cardiac biomarkers associated with RV dysfunction. A p-value less than 0.05 was considered as statistically significant.

Results

Baseline clinical characteristics

Baseline clinical characteristics are summarized in Table 1. Age, sex, and the predisposing conditions were not different between the groups. Systolic and diastolic blood pressures were significantly lower, and the heart rate was significantly higher in group I than in group II. The degree of dyspnea was significantly more severe in group I than in group II.