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The prognostic value of pro-B-Type natriuretic peptide in acute pulmonary embolism

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ABSTRACT

Aims: To assess the clinical performance of pro-B-type natriuretic peptide 1-108 (proBNP) for the prognosis of acute pulmonary embolism.
Methods: This study was ancillary to a recently published multicentre study including 570 patients with acute pulmonary embolism. ProBNP values were analysed using a new sandwich immunoassay proBNP1-108, Bioplex2200™ (Bio-Rade Laboratories). Data was compared with BNP and N-terminal (NT) proBNP values. Adverse outcomes at 30 days were defined as death, secondary cardiogenic shock, or recurrent venous thromboembolism.
Résults: ProBNP values were analysed in 549 patients, with 39 (7.1%) presenting adverse outcomes. All three natriuretic peptides were significantly elevated in these 39 patients compared with the group without adverse outcomes (BNP: $p < 0.001$; NT-proBNP: $p < 0.001$; proBNP: 0.044), with median proBNP values being 605 pg/ml (113-1437) and 109 pg/ml (30-444), respectively. Multivariate analyses revealed that proBNP significantly depended on patient age ($p < 0.001$) and renal failure ($p = 0.001$), with proBNP values increasing with both factors. The areas under the receiver operating curve were 0.74 (95% CI 0.69-0.79) for BNP, 0.76 (95% CI 0.72-0.80) for NT-proBNP, and 0.70 (95% CI 0.65-0.75) for proBNP, meaning that the performance of proBNP was significantly lower than that of the two other peptides ($p = 0.017$).
Conclusion: ProBNP, BNP, and NT-proBNP values were significantly increased in patients with adverse outcomes after acute pulmonary embolism. However, the prognostic performance of proBNP for predicting adverse versus favourable outcomes was lower than that of the other natriuretic peptides, thus limiting the clinical relevance of proBNP as a prognostic marker in pulmonary embolism.

Introduction

Pulmonary embolism (PE) is a challenging disease, as clinicians are simultaneously required to establish an appropriate diagnosis, assess short-term prognosis, and initiate therapy during the initial workup in the emergency department. Assessing the prognosis of PE at the bedside involves two issues regarding the destination of the patient and type of therapy, namely outpatient treatment of low-risk PE patients or more aggressive treatment with thrombolysis for high-risk patients.

Acute complications of PE in terms of mortality, haemorrhage under treatment, and recurrence affect approximately 10% of patients [1]. However, mortality varies according to the patient's condition, being greater than 25% in the case of shock [2], between 3 and 15% for stable patients with right heart dysfunction [3], and less than 2% for patients without right heart dysfunction [4]. More than half of patients belong to this latter category, with current guidelines allowing outpatient treatment for low-risk patients [5,6]. In contrast, 5% of patients are high-risk, presenting clinical shock or arterial hypotension and justifying thrombolysis (level A evidence) [6]. The remaining group of PE patients carry an intermediate risk, presenting so-called sub-massive PE [3,7]. The potential benefits of thrombolysis for these patients combining right cardiac dysfunction and cardiac ischemic signs are currently being investigated in a large randomised multicentre study known as the PEITHO trial [8].

Abbreviations: PE, Pulmonary Embolism; proBNP, pro-B-type natriuretic peptide 1-108.

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In addition to clinical prognostic variables, cardiac biomarkers such as troponin, B-type natriuretic peptide (BNP), or N-Terminal Pro-BNP (NT-ProBNP) are associated with a poor outcome in patients with acute PE [9–12]. Nevertheless, the lack of test standardisation and validated outcome studies prevents the confident use of these cardiac biomarkers for assessing the short-term prognosis of PE at the bedside [13].

The pro-B-type natriuretic peptide 1-108 (proBNP) is a cardiac prohormone cleaved into the two well-known cardiac biomarkers, BNP and NT-proBNP. The recent emergence of assays for measuring proBNP allowed the evaluation of its clinical usefulness for the diagnosis and prognosis of heart failure [14]. Although the performance of proBNP for left ventricular dysfunction has not yet proved to be superior to BNP or NT-proBNP, the potential advantages of pro-BNP assays concern their greater specificity and the absence of cross-reactivity with other natriuretic peptides [15].

The objectives of this study were first to assess the clinical performance of proBNP in the initial risk stratification of PE and secondly, to compare it with BNP and NT-proBNP.

Materials and Methods

Study Design and Patients

This study was ancillary to a recently published multicentre study comprising 570 patients with acute PE [13]. Data was collected during a prospective, multicentre, observational cohort study evaluating the additional prognostic value of echocardiography and biomarkers in determining the risk categories of PE. The study was conducted in 11 university hospitals across France, Belgium, and Switzerland, with the referent study taking place between January 2006 and May 2007. Written informed consent was obtained from all patients, while the study was approved by the local ethics committees.

Eligible patients were aged over 18 years with an objectively confirmed PE. Exclusion criteria were the following: curative anticoagulant treatment for more than 24 hours, unavailability for follow-up, inability to give informed consent, and life-expectancy less than 1 month.

The final population comprised 570 patients with objectively confirmed PE. PE was diagnosed on the basis of a positive computed tomography (spiral CT) (n = 471, 83%), ventilation or perfusion scintigraphy (n = 80, 14%), deep vein thrombosis and high clinical suspicion (n = 15, 2.5%), echocardiography and high clinical probability (n = 3, 0.5%), or pulmonary angiography (n = 1, 0.2%).

Outcomes

The following data pertaining to adverse outcomes was collected during the 30-day follow-up: secondary cardiogenic shock defined as systolic blood pressure <90 mmHg, signs of end-organ hypoperfusion and/or requiring catecholamine administration to maintain systolic blood pressure >90 mmHg, all-cause death, or objectively confirmed recurrent thromboembolism. Causes of death were differentiated between those related to PE and those not. An independent committee of two physicians blinded to the clinical and technical results adjudicated all adverse events.

Overall, 42 patients (7.4%) from the original study suffered one or more adverse outcomes: 26 deaths (4.6%) with 12 being related to PE, 25 secondary cardiogenic shocks (4.4%), and 11 recurrent venous thomboembolisms (1.9%).

Cardiac Biomarker Measurement

The determination of circulating natriuretic peptides was centrally performed twice by investigators who were blinded to the clinical patient characteristics and 30-day complicated outcomes, with the evaluation conducted at the end of the original study for BNP and NT-proBNP, and in November 2010 for proBNP levels. Blood was collected on admission in dry tubes (serum) and ethylene diamine tetraacetic acid (EDTA) tubes (Sarstedt, Nümbrecht, Germany). After centrifugation within 1 hour (1500 g at 4 °C for 10 min), EDTA plasma and serum were carefully separated while avoiding contamination by the leukocyte rich layer and then stored at -80 °C until assayed. $ProBNP_{1\text{-}108}$ (proBNP) plasma concentrations were determined on EDTA plasma with the specific BioPlex 2200™ assay (Bio-Rad, Hercules, California). BNP was determined on EDTA plasma using the Access 2® BNP immunoassay based on chemiluminescence detection (Beckman Coulter, Fullerton, CA, USA; Biosite reagents). Nt-proBNP was measured on serum samples with an one step enzyme immunoassay based on the "sandwich" principle and performed using Dimension® RxL –HM (Siemens Healthcare Diagnostics Germany). All automated assays were undertaken according to the manufacturer's specifications.

Statistical Methods

The cardiac biomarkers, BNP, NT-proBNP, and proBNP, exhibited a logarithmic-normal distribution, and thus were expressed as continuous variables with medians and quartiles. The association between biomarkers and the 30-day complicated outcome was compared and expressed using a two-sided p-value.

The three natriuretic peptides were compared in terms of their quality by correlating them with a latent variable, which was the best estimation for the measurement according to the three datasets [16]. Univariate and multivariate non-linear regression analyses were used to assess the independence between cardiac biomarkers, age, renal function, and outcome of patients.

Receiver operating characteristic (ROC) curve analyses were performed in order to assess the prognostic performance of proBNP without taking any cut-off values into consideration. A comparison of the areas under the ROC curve for the three natriuretic peptides was made according to the non-parametric rank method [17].

The additional performance of proBNP for comparing patients who experienced adverse events against those who did not, was analysed according to the reclassification method described by Pencina and colleagues [18].

Results

The initial population comprised 570 patients with objectively confirmed PE. However, as 21 samples were not available for the proBNP dosage, the final population consisted of 549 patients. The characteristics of the studied population are shown in Table 1.

Adverse outcomes after 30-day follow-up were observed in 7.1% of patients (39/549), as shown in Table 1. The results of the cardiac biomarkers in relation to the adverse events are also provided in Table 1. Median BNP, NT-proBNP, and proBNP levels were significantly higher among patients experiencing 30-day adverse events as compared to those not experiencing such events. Fig. 1 describes the logarithmic distribution of BNP, NT-proBNP and proBNP values in patients with versus those without an adverse outcome, expressed as a boxplot (median, 25th and 75th quartiles) with whiskers.

30-day adverse outcome increased with increasing proBNP levels, rising from 2,9% (4/138 patients) in the first quartile (<33 pg/ml) to 16,1% (22/137 patients) in the fourth quartile (>515 pg/ml). Sensitivity, specificity, positive and negative predictive values of proBNP levels >33 pg/ml (first quartile) to predict a 30-day adverse outcome were 89%, 26%, 8% and 97%, respectively; when proBNP was > 515 pg/ml (fourth quartile), sensitivity, specificity, positive and negative predictive values were 56%,77%,16% and 95%, respectively.

Fig. 2 shows the correlation between proBNP values and the estimated latent variable. Results for the three biomarkers are linear compared to the latent variable and in the range of clinical interest. The figure points to non-significant outlier points with regards to proBNP.