Brain Natriuretic Peptide as a Predictor of Adverse Outcome in Patients With Pulmonary Embolism

M. ten Wolde, MD, PhD; I.I. Tulevski, MD; J.W.M. Mulder; M. Söhne, MD; F. Boomsma, PhD; B.J.M. Mulder, MD, PhD; H.R. Büller, MD, PhD

Background—Despite effective treatment with anticoagulants, 2% to 7% of patients with pulmonary embolism will die as a result of their disease.

Methods and Results—We examined in 110 consecutive patients with pulmonary embolism whether plasma brain natriuretic peptide (BNP), a novel marker of (right) ventricular dysfunction, is a predictor of fatal pulmonary embolism. The relationship between BNP concentration measured at presentation and clinical outcome was assessed by comparing the proportion of outcome events among tertiles. Positive and negative predictive values of BNP levels in the highest and lowest tertiles were calculated. The risk of death related to pulmonary embolism if the BNP level is >21.7 pmol/L is 17% (95% CI, 6% to 33%). The negative predictive value for uneventful outcome of a BNP value <21.7 pmol/L is 99% (95% CI, 93% to 100%).

Conclusion—This is the first study to show that plasma BNP levels seem to predict adverse outcome in patients with acute pulmonary embolism. (Circulation. 2003;107:2082-2084.)

Key Words: embolism ■ mortality ■ natriuretic peptides ■ pulmonary heart disease ■ thrombosis

Hemodynamically stable patients with pulmonary embolism are initially treated with heparin and subsequently with vitamin K antagonists. Although this therapy is very effective, during 3 months of follow-up, 2% to 7% of patients will die as a result of pulmonary embolism.1–7 Mortality likely occurs in those patients with right ventricular dysfunction at presentation.5–7 Brain natriuretic peptide (BNP) is a plasma neurohormone secreted in the cardiac ventricles in response to stretch and/or pressure increase.8 BNP levels are known to correlate with left ventricular dysfunction and are used for the diagnosis of left ventricular failure.9,10 We recently showed that BNP levels are also associated with right ventricular dysfunction in patients with pulmonary embolism.11 Because right ventricular dysfunction in these patients is a likely marker for long-term adverse outcome, we hypothesized that this may be predicted by high BNP levels at presentation.

Methods

Study Population
Consecutive patients presenting with clinically suspected pulmonary embolism, referred for diagnostic work-up, were eligible for this study. Only patients with objectively confirmed pulmonary embolism on spiral CT were included. Patients requiring thrombolytic therapy because of hemodynamic instability were excluded. The Institutional Review Boards approved the study protocol, and participants gave informed consent. Because renal insufficiency can result in elevated BNP levels, we excluded patients with known renal insufficiency. Sixteen of the patients in this study were previously included in a study evaluating the relationship between echocardiographic right ventricular dysfunction and BNP levels.11

Blood Sampling
At presentation, blood was collected in citrated tubes and centrifuged for 15 minutes. Plasma was stored at −80°C, and BNP concentrations were determined with an immunoradiometric assay (Shionoria) without knowledge of the clinical outcome. In healthy volunteers, the normal values (±2SD) of BNP range between 0.4 and 4.6 pmol/L.

Outcome Events
All adverse events occurring during 3 months of follow-up were reviewed by a blinded and independent adjudication committee. Deaths were subcategorized as deaths definitely due to pulmonary embolism, possibly due to pulmonary embolism, or due to other causes. The following outcomes were used for our analysis: deaths due to pulmonary embolism, deaths related to pulmonary embolism (ie, those patients with pulmonary embolism as a definite as well as a possible cause of death), and all-cause mortality.

Statistical Analysis
Patients were divided into tertiles on the basis of their BNP level. The χ² test was used to analyze the differences in proportions of outcome events. The positive and negative predictive values for
death related to pulmonary embolism of a BNP level in the highest and lowest tertiles, respectively, were calculated. Their exact 95% confidence intervals were calculated using Confidence Interval Analysis. To evaluate the effects of other variables on mortality, multiple logistic regression analysis was performed using SPSS (SPSS for Windows, release 10.0.7). BNP was entered as a dichotomous variable using the 67th percentile as the cutoff value. Values of \( P<0.05 \) were considered statistically significant. Standard deviations were reported for a mean, whereas the interquartile range was given for a median.

### Results

#### Study Population

Patients \((n=110)\) with confirmed pulmonary embolism were included. The mean \((\pm SD)\) age was 58 \((\pm 18)\). The median BNP level was 9.4 pmol/L \((1.7 \text{ to } 37.1)\). Eleven patients \((10\%)\) died during 3 months of follow-up. Seven deaths were related to pulmonary embolism, of which 5 deaths were definitely \((3 \text{ of these patients died 2 days after presentation, whereas the others died on days 5 and 38) and 2 possibly due to pulmonary embolism (days 8 and 34). The remaining 4 deaths were attributable to cancer (38, 43, 76, and 87 days after presentation). None of the 5 patients who died as a consequence of pulmonary embolism had a history of heart failure. Of the 2 patients who possibly died of pulmonary embolism, heart failure contributed to the cause of death. The 11 patients who died were older \(\text{mean age } 66 \pm 15\) and more often had cancer \((36\%)\) as compared with those who survived \(\text{mean age } 56 \pm 18; 14\% \text{ suffered from cancer); } P=0.074 \text{ and } 0.064, \text{ respectively. No differences were observed between those who died and survivors with regard to the prevalences of chronic obstructive pulmonary disease and vascular disease, including cerebrovascular, coronary artery, and peripheral artery disease. The median BNP in the patients who died was 71.6 pmol/L \((47.4 \text{ to } 117.1)\), compared with 8.7 pmol/L \((1.5 \text{ to } 29.3)\) in those who survived \((P<0.001)\). The median BNP value in the 5 patients who died due to pulmonary embolism was 80.5 pmol/L \((25.8 \text{ to } 101.5); P=0.030 \text{ for the comparison with the median BNP level of the other patients).}

#### Plasma BNP Concentrations and Clinical Outcome

Patients with events had BNP levels at presentation belonging to the highest tertiles (Table). High BNP levels were associated with all-cause mortality and death related to pulmonary embolism. Of the 36 patients in the highest tertile, 4 died of pulmonary embolism, whereas in another 2 patients, pulmonary embolism was a possible cause of death. Hence, the positive predictive value for pulmonary embolism–related death of a BNP level \(>21.7 \text{ pmol/L} \) was 17\% \((95\% CI, 6\% \text{ to } 33\%). \) The negative predictive value for an uneventful outcome of a value \(<21.7 \text{ pmol/L} \) was 99\% \((95\% CI, 93\% \text{ to } 100\%).\) Survival was significantly worse in patients with BNP concentrations in the highest tertile (Figure). As shown by multiple logistic regression analysis, the odds ratio for the risk of all-cause death \(\text{adjusted for age and cancer) of levels above the 67th percentile (ie, } 21.7 \text{ pmol/L) was } 9.4 \text{ (95\% CI, 1.8 to 49.2). The adjusted odds ratio of a BNP level } >21.7 \text{ pmol/L for death related to pulmonary embolism was 14.1 (95\% CI, 1.5 to 131.1).}

### Discussion

This analysis demonstrates that the BNP plasma concentration in patients with pulmonary embolism, measured at presentation, seems to predict adverse outcome during 3 months of follow-up. Patients with pulmonary embolism are part of a clinically heterogeneous group, which ranges from patients with minimal pleuritic chest pain to those who are hemodynamically compromised. Attempts have been made to stratify patients to select those with a high risk of fatal pulmonary embolism, with the eventual aim to guide more aggressive therapy. Previous studies have shown that echo-
cardiography to assess right ventricular dysfunction appears to be such a tool. However, the positive predictive value of echocardiographically assessed right ventricular dysfunction for pulmonary embolism–related death in hemodynamically stable patients appears to be only 5%. More recently, cardiac troponins T and I have been advocated as possible candidates for risk stratification. Konstantinides and colleagues found that 35% to 40% of patients with pulmonary embolism have elevated levels of cardiac troponins, which were associated with overall mortality and a complicated in-hospital course. However, cardiac troponins are released as a consequence of myocardial injury, whereas the triggering factor for release of BNP is an increase in stretch or pressure of the ventricles, which precedes right ventricular failure. Five percent of the patients in the study of Konstantinides were hemodynamically unstable, and 28% of the patients suffered from syncope, which might have resulted in the high percentage of elevated troponins and (overall) mortality. The results of the present study are of particular interest because only hemodynamically stable patients were included. These patients are currently treated with heparin and vitamin K antagonists but might benefit from more aggressive treatment (e.g., thrombolysis) if their BNP levels are high at presentation. Hemodynamically unstable patients already have an indication for thrombolytic therapy.

One of the limitations of this study is that causes of death might be incorrectly attributed to pulmonary embolism. We do not believe that this has affected our findings because an independent, blinded committee adjudicated the outcome events. Another potential bias relates to the fact that in addition to angiography, other diagnostic methods were used to diagnose pulmonary embolism, such as lung scintigraphy, spiral computed tomography, and compression ultrasonography of the legs. However, in the past 10 years, these methods have been extensively investigated and are now generally accepted for the diagnosis of pulmonary embolism. In conclusion, our results indicate that high BNP levels, measured at presentation, are associated with mortality during 3 months of follow-up in patients with pulmonary embolism. It needs to be investigated whether BNP, troponin, or a combination of both is the best predictor of adverse outcomes in hemodynamically stable patients with acute pulmonary embolism. If proven to be effective, this easy-to-perform blood test might be a simple tool to stratify patients for more aggressive therapy such as thrombolysis or percutaneous embolectomy.

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References
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