Prognostic Role of Brain Natriuretic Peptide in Acute Pulmonary Embolism

Nils Kucher, MD; Gert Printzen, MD; Samuel Z. Goldhaber, MD

Background—Rapid, noninvasive, and accurate prognostic assessment with an inexpensive cardiac biomarker is an appealing approach for patients with acute pulmonary embolism (PE).

Methods and Results—We measured at the time of admission the plasma level of plasma brain natriuretic peptide (BNP) to determine its utility in prognosticating the clinical course of 73 consecutive patients with acute PE. We used a prespecified BNP cut-off level (<90 pg/mL) for the prediction of the absence of a major adverse cardiovascular event, defined as any of the following: death, cardiopulmonary resuscitation, mechanical ventilation, or use of pressors, thrombolysis, catheter fragmentation, or surgical embolectomy. In the 20 (27%) patients with adverse events, median BNP (194.2, range 3.7 to 1201.1 pg/mL) was higher than in patients with a benign course (39.1, range 1.0 to 1560.0 pg/mL; \(P<0.001\)). However, 3 patients with adverse outcomes had low BNP levels on admission: 1 death, BNP 52 pg/mL; 1 patient with prolonged cardiopulmonary resuscitation, BNP 3.7 pg/mL; and 1 patient undergoing rescue thrombolysis, BNP 75 pg/mL. Sensitivity, specificity, and negative and positive predictive value of BNP levels <90 pg/mL for absence of adverse outcomes were 85% (64% to 95%), 75% (62% to 85%), 93% (95% CI 81% to 98%), and 57% (39% to 73%), respectively. The optimal BNP cut-off level, identified by receiver operating characteristic analysis, was <50 pg/mL.

Conclusions—Low BNP levels do not guarantee an uncomplicated hospital course in patients with acute PE, using a “congestive heart failure” cut-off level of 90 pg/mL. A lower cut-off level of <50 pg/mL identifies 95% of patients with a benign clinical course. (Circulation. 2003;107:2545-2547.)

Key Words: natriuretic peptides ■ heart diseases ■ prognosis ■ embolism ■ thrombosis

Accurate risk stratification is of paramount importance in selecting the optimal management strategy for patients with acute pulmonary embolism (PE). Rapid, noninvasive, and accurate prognostic assessment with an inexpensive and widely available cardiac biomarker is an appealing approach. Plasma B-type natriuretic peptide (BNP) is a useful diagnostic and prognostic biomarker for patients with congestive heart failure.1,2 Levels of BNP and related peptides increase in disorders that cause right ventricular dysfunction such as primary pulmonary hypertension, chronic obstructive pulmonary disease, chronic thromboembolic pulmonary hypertension, and left-to-right cardiac shunts.3–6 Therefore, we studied the utility of plasma BNP levels for risk stratification of patients with acute PE.

Methods
We obtained blood samples for BNP testing within 4 hours of admission in 73 consecutive patients with acute PE (average age 61±18 years, 43 men/30 women) from a study of the prognostic role of N-terminal pro B-type natriuretic peptide in PE.7 The local ethics committee approved the study protocol, and written informed consent was obtained from all patients.

The diagnosis of PE was confirmed using spiral chest computed tomography in 63, pulmonary angiography in 4, high probability ventilation perfusion scan in 3, and surgical embolectomy in 3 patients. Echocardiography was performed in all patients, and right ventricular systolic dysfunction was diagnosed in the presence of moderate to severe right ventricular hypokinesis in 33 (46%) patients.

Adverse events were defined according to the Management Strategy And Prognosis of Pulmonary Embolism Trial-3 (MAPPET-3) criteria as the combined end-point of death or the need for at least one of the following: cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, or surgical embolectomy.8 Twenty (27%) patients reached the end-point of an adverse event. In-hospital mortality was 7%, and all 5 deaths were attributed to right ventricular failure. The 15 surviving patients had the following combinations of adverse events: 2 patients were treated with catecholamines, 3 with thrombolysis, 3 with thrombolysis and catecholamines, 1 with thrombolysis and cardiopulmonary resuscitation, 1 with thrombolysis, cardiopulmonary resuscitation, and mechanical ventilation, 2 with surgical embolectomy and catecholamines, and 2 with catheter fragmentation, thrombolysis, and catecholamines, and 1 with catheter fragmentation and catecholamines.

Blood (4 mL) for BNP was collected into a tube containing ethylene-diamine-tetra-acetate. The plasma was immediately sepa-
rated by centrifugation at 2500g and then stored at −70°C until analysis. Quantitative BNP levels were measured using a fluorescence immunoassay kit (Triage, Biosite Diagnostics Inc). The analytical sensitivity or lowest detectable concentration that is distinguishable from zero for the Triage BNP Test is <5 pg/mL (95% confidence interval 0.2 to 4.8 pg/mL). The intraday/interday coefficients of variation range from 8.8/9.9% for low to 11.6/12.2% for high BNP concentrations, respectively.

Commonly used cut-off levels of the Triage BNP assay for diagnosing congestive heart failure as the cause of dyspnea range between 80 and 100 pg/mL. Therefore, we chose <90 pg/mL as the cut-off level for a normal BNP. In addition, we performed a receiver operating characteristic (ROC) analysis to identify the most sensitive BNP cut-off level for identifying low-risk patients. BNP levels were adjusted for univariately significant clinical variables. We used multivariate logistic regression analysis to investigate the predictive value for adverse clinical events.

Results

In the 20 patients with adverse clinical events, median BNP (194.2, range 3.7 to 1201.1 pg/mL) was higher than in patients with a benign hospital course (39.1, range 1.0 to 1560.0 pg/mL; P < 0.001) (Figure, A). Forty one (56%) patients had BNP levels <90, and 32 (44%) had BNP levels ≥90 pg/mL. Between the BNP groups, there was no difference in either a history of coronary artery disease (6 patients in the high and 4 in the low BNP group) or of congestive heart failure (3 patients per group). In patients with BNP levels ≥90 pg/mL, systolic blood pressure was lower (108±21 versus 121±22 mm Hg; P = 0.031) and heart rate was higher (101±19 versus 84±16 bpm; P = 0.014). Twenty-nine (88%) of 33 patients with moderate or severe right ventricular dysfunction had BNP levels ≥90 pg/mL.

Three patients with adverse events had low BNP levels on admission. The first patient, a 29-year-old female, suffered cardiogenic shock after syncpe. BNP, taken during cardiopulmonary resuscitation approximately 3 hours after the onset of symptoms, was 52 pg/mL. This patient died 36 hours later despite emergency surgical embolectomy. The second patient, a 61-year-old male, had a massive PE with pulseless electrical activity in the Emergency Department, approximately 2 hours after the onset of symptoms. BNP, taken during prolonged cardiopulmonary resuscitation, was 3.7 pg/mL. The third patient, a 72-year-old male, was treated with rescue systemic thrombolysis due to a systolic blood pressure of 90 mm Hg, a heart rate of 121 bpm, and severe right ventricular dysfunction on echocardiography. This patient had a BNP level of 75 pg/mL, 6 hours after the onset of symptoms.

Five patients with a benign outcome had BNP levels >200 pg/mL: a 71-year-old male had chronic lung disease and non-small cell lung cancer (251 pg/mL); an 87-year-old male had chronic lung disease and systemic hypertension (390 pg/mL); a 83-year-old female had coronary artery disease (317 pg/mL); a 84-year-old male had New York Heart Association function class II congestive heart failure (564 pg/mL); and a 75-year-old male patient had New York Heart Association function class III congestive heart failure (1560 pg/mL).

After multivariate analysis, plasma BNP >90 pg/mL remained an independent predictor for adverse outcomes (odds ratio 8.0, 95% confidence interval [CI] 1.3 to 50.1; P = 0.026) (Table). However, the diagnostic value of other clinical variables did not remain significant after adjustment in the multivariate model. Diabetes mellitus (4 versus 2 patients; P = 0.59) and peripheral vascular disease (2 versus 1 patients; P = 0.71) were similarly present in patients with BNP < and ≥90 pg/mL.

The area under the receiver operating characteristic curve for adverse outcomes was 0.83 (95% CI 0.73 to 0.94, Figure, B). Sensitivity, specificity, and negative and positive predictive value of BNP levels <90 pg/mL for absence of adverse events were as follows: 85% (64% to 95%), 75% (62% to 85%), 93% (95% CI 81% to 98%), and 57% (39% to 73%), respectively. The most sensitive BNP cut-off, identified by receiver operating characteristic analysis, was <50 pg/mL. Sensitivity, specificity, and negative and positive predictive value of BNP levels <50 pg/mL for absence of adverse outcomes were: 95% (76% to 99%), 60% (47% to 72%), 97% (85% CI 81% to 99%), and 48% (33% to 63%), respectively.

Discussion

Plasma BNP elevation in acute PE is probably caused by increased myocardial shear stress, mainly in the right ventricle, and depends on the degree and dynamics of embolic events. Among patients with acute PE, plasma BNP levels help prognosticate and differentiate between a benign versus a complicated hospital course. Most patients who died and most who required escalation of therapy had elevated BNP levels. The overlap between PE patients with adverse and benign outcomes (Figure, A), however, argues for the limited specificity of this assay. Normal BNP levels, using a frequently used BNP cut-off level, do not guarantee an uncomplicated course in patients with PE. Indeed, 3 of our patients

### Multivariate Analysis for the Prediction of Adverse Clinical Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP &gt;90 pg/mL</td>
<td>8.0</td>
<td>1.3–50.1</td>
<td>0.026</td>
</tr>
<tr>
<td>Troponin T &gt;0.01 ng/mL</td>
<td>4.3</td>
<td>0.8–24.1</td>
<td>0.09</td>
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<td>Age &gt;70 y</td>
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<td>0.1–2.7</td>
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<tr>
<td>Female gender</td>
<td>2.1</td>
<td>0.5–8.4</td>
<td>0.31</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>2.6</td>
<td>0.5–12.2</td>
<td>0.24</td>
</tr>
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with major adverse events, including 1 who died, had BNP levels <80 pg/mL. The symptom duration in these 3 patients was less than 12 hours. One possible explanation is that we obtained BNP levels in these patients too early in their clinical course, before BNP release from right ventricular myocardium. The negative predictive value using the 90 pg/mL cut-off level for BNP (93%) was similar to that of cardiac troponins I ≥0.07 ng/mL (92%) and T ≥0.04 ng/mL (93%) using the same end-point definition for adverse clinical outcomes in a study of 106 patients with acute PE. In our multivariate analysis, BNP appeared to have independent predictive value after factoring in the contribution of troponin levels.

In the present study, receiver operating analysis revealed a high-sensitivity cut-off level for BNP of 50 pg/mL for predicting the absence of major cardiovascular adverse events. Sensitivity and negative predictive value for predicting the absence of adverse events, using this post hoc newly derived cut-off level, were 95% and 97%, respectively.

The study interpretation is limited by its sample size. Variables in the multivariate analysis for risk stratification had wide confidence intervals. Future studies of the prognostic role of BNP in PE should be designed with serial BNP testing of individual patients. These studies should explore new BNP cut-off levels for risk stratification in PE, because the values established for left ventricular congestive heart failure may not be optimal for the population of patients with acute PE. Finally, future trials will confirm or refute our finding that BNP levels provide complementary information to troponin levels in determining individual patients’ prognosis. If both the troponin and BNP levels are normal, a low-risk population free of adverse clinical outcomes likely exists, and right ventricular function on echocardiography will almost certainly be normal. These patients may be suitable for an abbreviated hospital length of stay or even for outpatient management. In contrast, those with elevated cardiac biomarkers may require immediate triage to intensive care units and urgent consideration for thrombolysis, catheter embolectomy, or open surgical embolectomy.

References

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Circulation. 2003;107:2545-2547; originally published online May 12, 2003;
doi: 10.1161/01.CIR.0000074039.45523.BE
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
http://circ.ahajournals.org/content/107/20/2545

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