Low Pro-Brain Natriuretic Peptide Levels Predict Benign Clinical Outcome in Acute Pulmonary Embolism

Nils Kucher, MD; Gert Printzen, MD; Tanja Doernhoefer, MD; Stephan Windecker, MD; Bernhard Meier, MD; Otto Martin Hess, MD

Background—The role of pro-brain natriuretic peptide (proBNP) for the prediction of clinical outcome has not been examined in patients with acute pulmonary embolism (PE).

Methods and Results—ProBNP levels were measured in 73 patients with acute PE within 4 hours of admission. Adverse clinical outcome was defined as in-hospital death or the need for at least 1 of the following: cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, or surgical embolectomy. In the 53 patients with a benign clinical outcome, proBNP (median 121, range 16 to 34,802 pg/mL) was lower than in 20 patients with adverse clinical outcome (median 4250, range 92 to 49,607 pg/mL; \( P < 0.0001 \)). The negative predictive value of proBNP levels <500 pg/mL to predict adverse clinical outcome was 97% (95% confidence interval 84 to 99). ProBNP remained an independent predictor for adverse clinical outcome (odds ratio 14.6; 95% confidence interval 1.5 to 139.0; \( P = 0.02 \)) after adjusting for severity of PE (submassive/massive), troponin T levels >0.01 ng/mL, age >70 years, gender, and history of congestive heart failure.

Conclusions—Low proBNP levels predict an uneventful hospital course in patients with acute PE. A proBNP level <500 pg/mL identifies patients who will be potential candidates for an abbreviated hospital length of stay or care on a completely outpatient basis. (Circulation. 2003;107:1576-1578.)

Key Words: natriuretic peptides ■ pulmonary heart disease ■ prognosis

There is an increasing interest in risk stratification of patients with acute pulmonary embolism (PE) using standardized blood tests. Accurate identification of low-risk patients might assist in appropriate triage of those who would do well clinically with an abbreviated hospitalization or even with treatment conducted completely on an outpatient basis.

Recently, increases in cardiac troponins I and T in patients with PE have been shown to be associated with early mortality and a complicated course.1–3 Brain natriuretic peptide is accurate for the diagnosis and prognosis in patients with left ventricular dysfunction.4–6 We investigated the role of N-terminal pro-brain natriuretic peptide (proBNP) for the prediction of adverse clinical outcomes in patients with acute PE.

Methods

Seventy-three consecutive patients with acute PE were enrolled from a prospective diagnostic and treatment study of patients with suspected PE at the emergency department of the University Hospital Bern, Switzerland, between April 2000 and October 2001.7 The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

In 59 hemodynamically stable patients with a shock index <1 (heart rate divided by systolic blood pressure), PE was confirmed with a high probability ventilation perfusion scan (n=3) or a positive spiral computed tomogram (CT) (n=56). PE was diagnosed by spiral CT when there was at least 1 intravascular filling defect in a pulmonary artery using a standard protocol.8 Submassive PE, ie, the presence of right ventricular dysfunction with a shock index <1, was present in 19 of the 59 patients. In 14 hemodynamically unstable patients (shock index \( \geq \)1) with a high pretest probability according to the Wells criteria,9 emergent transesophageal echocardiography revealed severe right ventricular dysfunction, and massive PE was subsequently confirmed in all patients after initiation of reperfusion treatment by spiral CT after initiation of thrombolysis in 7 patients, at catheter fragmentation during pulmonary angiography in 4 patients, and at surgical embolectomy in 3 patients.

ProBNP was measured on admission using Elecsys proBNP (Roche), a quantitative electrochemiluminescence immunoassay. Troponin T (TnT) was measured on admission using Elecsys Troponin T STAT (Roche), a quantitative electrochemiluminescence immunoassay. Both proBNP and TnT were measured using the Elecsys 2010 immunoassay analyzer (Roche).

Echocardiography was performed using an Acuson Sequoia C256 system with a 3.5 MHz probe within 4 hours after admission in all patients. Right ventricular end-diastolic diameter was measured either from the apical or subcostal 4-chamber view. Systolic right ventricular dysfunction was diagnosed in the presence moderately to severely depressed right ventricular free wall kinesis.10

Adverse clinical outcome was defined as in-hospital death or escalation of therapy with the need for at least 1 of the following: cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, or surgical embolectomy.11
The cut-off value for the prediction of adverse outcomes was 500 pg/mL for proBNP, which was identified by receiver operating characteristic (ROC) analysis. Because of reduced precision of the TnT assay at concentrations below 0.03 ng/mL, 2 predefined cut-off levels (0.01 and 0.1 ng/mL) were investigated. Differences in the endpoint according to proBNP and TnT levels were analyzed with Fisher’s exact test. Cumulative adverse events between patients with and without proBNP elevation were analyzed with a log rank test. ProBNP levels were adjusted for important clinical variables using multivariate logistic regression to investigate the predictive value for adverse events.

### Baseline Characteristics of 73 Patients With Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Pro BNP ≥500 pg/mL</th>
<th>Pro BNP &lt;500 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>73</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±18</td>
<td>65±15*</td>
<td>55±20</td>
</tr>
<tr>
<td>Men</td>
<td>43 (59)</td>
<td>24 (57)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Submassive PE</td>
<td>19 (26)</td>
<td>16 (38)†</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Massive PE</td>
<td>14 (19)</td>
<td>14 (33)†</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>47 (65)</td>
<td>38T(90)†</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>34 (47)</td>
<td>20 (47)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Syncope</td>
<td>10 (14)</td>
<td>9 (21)†</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Symptom duration before hospitalization, d</td>
<td>3.5±3.1</td>
<td>3.1±2.9</td>
<td>3.8±3.2</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>17 (23)</td>
<td>11 (26)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (8)</td>
<td>4 (10)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (14)</td>
<td>6 (14)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5 (7)</td>
<td>2 (5)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Hemodynamic and echocardiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>116±22</td>
<td>111±22*</td>
<td>121±21</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>93±23</td>
<td>101±25*</td>
<td>82±15</td>
</tr>
<tr>
<td>PO2, mm Hg</td>
<td>67±22</td>
<td>62±21*</td>
<td>75±24</td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>34±6</td>
<td>32±5*</td>
<td>35±4</td>
</tr>
<tr>
<td>Right ventricular end-diastolic diameter, mm</td>
<td>42±8</td>
<td>45±7†</td>
<td>38±6</td>
</tr>
<tr>
<td>Tricuspid systolic gradient, mm Hg</td>
<td>46±17</td>
<td>52±17†</td>
<td>35±10</td>
</tr>
<tr>
<td>Moderate to severe RV dysfunction</td>
<td>33 (46)</td>
<td>32 (76)†</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%). *P<0.05; †P<0.001.

The cut-off value for the prediction of adverse outcomes was 500 pg/mL for proBNP, which was identified by receiver operating characteristic (ROC) analysis. Because of reduced precision of the TnT assay at concentrations below 0.03 ng/mL, 2 predefined cut-off levels (0.01 and 0.1 ng/mL) were investigated. Differences in the endpoint according to proBNP and TnT levels were analyzed with Fisher’s exact test. Cumulative adverse events between patients with and without proBNP elevation were analyzed with a log rank test. ProBNP levels were adjusted for important clinical variables using multivariate logistic regression to investigate the predictive value for adverse events.

### Results

Patients with proBNP ≥500 pg/mL were older and more often presented with dyspnea and syncope (Table). Hemodynamic and respiratory compromise was more severe in patients with proBNP ≥500 pg/mL. Echocardiographic signs of right ventricular strain were less severe in patients with proBNP <500 compared with patients with levels ≥500 pg/mL.

Twenty (27%) of the 73 patients had adverse outcomes. Twelve of these patients had massive PE, 6 had submassive PE, and 2 had non-massive PE. Median time from admission to adverse events was 8 hours (range 0.5 to 144 hours). In-hospital mortality was 7%, and all 5 deaths (3 massive, 2 submassive PE) were attributed to right ventricular failure. Cardiopulmonary resuscitation was performed in 3 patients (4%), mechanical ventilation in 5 (7%), pressors in 6 (8%), thrombolysis in 10 (14%), surgical embolectomy in 3 (4%), and catheter fragmentation in 4 (5%).

In the 53 patients with a benign outcome, proBNP (median 121, range 16 to 34 802 pg/mL) was lower than in 20 patients with adverse outcome (median 4250, range 92 to 49 607 pg/mL; P<0.0001). Most adverse events occurred within the first 2 days of admission in patients with proBNP levels ≥500 pg/mL (Figure). Thirty of 31 patients with a proBNP level ≤500 pg/mL had a benign clinical course. This resulted in a negative predictive value and a sensitivity of proBNP ≤500 pg/mL for adverse outcomes of 97% (95% confidence interval [CI] 84 to 99) and 95% (95% CI 76 to 99), respectively.

The cumulative rate of adverse clinical outcomes according to proBNP levels <500 pg/mL or ≥500 pg/mL. Logrank=15.2, P<0.0001.
respectively. The positive predictive value and specificity of proBNP levels ≥500 pg/mL for adverse outcomes were 45% (95% CI 31 to 60) and 77% (95% CI 43 to 69), respectively.

Five patients who died in-hospital had a TnT level ≥0.01 ng/mL, and 4 of these patients had a TnT level >0.1 ng/mL. Among the 20 patients with adverse outcomes, 14 had a TnT level ≥0.01 and 16 had a level ≥0.01 ng/mL. Three additional patients (n=19) with adverse outcomes were identified by proBNP ≥500 pg/mL alone.

The negative predictive value and sensitivity of TnT <0.01 ng/mL for adverse outcomes were 91% (95% CI 79 to 96) and 80% (95% CI 58 to 92), respectively. The positive predictive value and specificity of TnT <0.01 ng/mL for adverse clinical outcomes were 15% (95% CI 8 to 22) and 77% (95% CI 62 to 85), respectively. Positive predictive value, negative predictive value, sensitivity, and specificity of the 0.1 ng/mL TnT cut-off level for adverse outcomes were 75% (95% CI 59 to 85%), 89% (95% CI 77 to 95%), 70% (95% CI 48 to 85%), and 89% (95% CI 77 to 95%), respectively.

In a multivariate analysis, proBNP remained an independent predictor for adverse outcome (odds ratio [OR] 14.6, 95% CI 1.5 to 139.0; P = 0.02) after adjusting for TnT >0.01 ng/mL (OR 6.4, 95% CI 1.6 to 25.8; P = 0.01), submassive or massive PE (OR 2.7, 95% CI 0.7 to 10.6; P = 0.17), age >70 years (OR 1.1, 95% CI 0.3 to 4.8; P = 0.87), gender (OR 0.9, 95% CI 0.2 to 3.9; P = 0.84), and history of congestive heart failure (OR 1.2, 95% CI 0.2 to 5.1; P = 0.65).

**Discussion**

In the 73 patients with acute PE, proBNP levels <500 pg/mL predicted a benign clinical outcome. The negative predictive value of proBNP <500 pg/mL for adverse outcomes was 97%. Nevertheless, there was significant overlap in proBNP values between patients with benign and adverse outcomes.

In a previous study of 16 patients with PE, 5 patients with right ventricular dysfunction had higher BNP levels than 11 with preserved right ventricular function. The presence of a troponin leak in PE should alert the clinician because of an increased risk of early death from right ventricular failure in these patients.1–3 TnT levels ≥0.1 ng/mL were superior in detecting high-risk patients as shown by a higher positive predictive value (70% for TnT versus 45% for proBNP), whereas low proBNP levels were superior in detecting low-risk patients, as shown by a higher negative predictive value for adverse outcomes (97% for proBNP versus 91% for TnT <0.01 ng/mL).

ProBNP was also an independent predictor for adverse outcome when adjusted for clinical severity of PE and the presence of a troponin leak. Thus, proBNP and cardiac troponins may be used as complementary biomarker tests for risk stratification in PE.

The 500-pg/mL cut-off level is not a “physiological” threshold but was defined post hoc by ROC analysis. BNP and related peptides show a significant relation to age and gender.11 The 500-pg/mL cut-off level in our study is higher than expected. Reference values for most healthy controls, including older and female subjects, have a maximum 97.5% percentile of 334 pg/mL. In the multivariate analysis, female gender, age >70 years, and a history of congestive heart failure did not influence the predictive role of proBNP for adverse clinical outcomes.

Detection of troponin elevation in PE is possible only during a short diagnostic window.1 Similar to troponin kinetics in PE patients, BNP de novo synthesis and release might also be a transient phenomenon, particularly in patients with initial right ventricular strain that rapidly improves. Although the time interval between symptom onset, biomarker testing, and clinical deterioration was relatively short, serial proBNP and TnT testing would have minimized possible underestimation of biomarker elevation in the present study.

**Conclusions**

A proBNP level <500 pg/mL is highly accurate for the prediction of an uneventful hospital course in patients with acute PE. At the time of admission, cardiac troponins and proBNP may serve as complementary blood tests to risk stratify symptomatic PE patients. Whereas a troponin T leak places the patient at high risk of death and serious adverse events, a low proBNP level <500 pg/mL identifies patients who will do well clinically and who may be potential candidates for an abbreviated hospital length of stay or for care completely on an outpatient basis.

**Acknowledgments**

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**References**


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