Management of venous thromboembolism. Etiology, diagnosis, prognosis and treatment

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Brain natriuretic peptide (BNP) as a predictor of adverse outcome in patients with pulmonary embolism

Marije ten Wolde, Igor I. Tulevski, Jasper W. M. Mulder, Maaike Söhne, Frans Boomsma, Barbara J. M. Mulder, Harry R. Büller

Despite effective treatment with anticoagulants, 2-7% of patients with pulmonary embolism will die as a result of their disease. 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 above 21.7 pmol/L is 16% (95% CI: 6-32%). The negative predictive value for uneventful outcome of a BNP value below 21.7 pmol/L is 99% (95% CI 93-100%). This is the first study to show that plasma BNP levels seem to predict adverse outcome in patients with acute pulmonary embolism.
Emotionally stable patients with pulmonary embolism are initially treated with heparin and subsequently with vitamin K antagonists. Although this therapy is very effective, still during 3 months of follow-up 2-7% of patients will die as a result of pulmonary embolism. Mortality likely occurs in those patients with right ventricular dysfunction at presentation. Brain Natriuretic Peptide (BNP) is a plasma neurohormone secreted in the cardiac ventricles in response to stretch and/or pressure increase. BNP levels are known to correlate with left ventricular dysfunction and are used for the diagnosis of left ventricular failure. We recently showed that BNP levels are also associated with right ventricular dysfunction in patients with pulmonary embolism. Because right ventricular dysfunction in these patients is a likely marker for long term adverse outcome, we hypothesised 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 the basis of abnormal angiography, a high-probability scintigram, a non-high probability scintigram with abnormal ultrasonography of the legs or the presence of 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. Since 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.

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, Osaka, Japan) 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 subcategorised as deaths definitely due to pulmonary embolism, possibly due to pulmonary embolism or other causes. The following outcomes were used for our analysis: deaths due to pulmonary embolism, deaths related to pulmonary embolism.
(i.e. 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 chi square test was used to analyse 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 (Gardner MJ, BMJ Books 1989, version 1.0). 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 cut-off value. P values <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
Hundred-ten patients with confirmed pulmonary embolism were included. The mean (+/- SD) age was 58 (+/- 18). The median BNP level was 9.4 pmol/L (1.7 - 37.1). Eleven patients (10%) died during 3 months of follow-up. Seven deaths were related to pulmonary embolism of whom 5 deaths were definitely (3 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 died because of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deaths (N=11)</th>
<th>Survivors (N=99)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m)</td>
<td>5 (46%)</td>
<td>48 (49%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Age, mean (+- SD)</td>
<td>66 (+-15)</td>
<td>56 (+-18)</td>
<td>0.074</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (9%)</td>
<td>7 (7%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>1 (9%)</td>
<td>9 (9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>4 (36%)</td>
<td>14 (14%)</td>
<td>0.064</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>1 (9%)</td>
<td>16 (16%)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

COPD = Chronic Obstructive Pulmonary Disease, VTE = Venous thromboembolism, * Vascular disease includes cerebrovascular, coronary artery and peripheral artery disease. † Of 2 patients it is unknown whether they had cancer
Table 2. Distribution of outcome events during 3 months follow-up among BNP tertiles in patients with pulmonary embolism

<table>
<thead>
<tr>
<th>Concentration BNP (pmol/L)</th>
<th>Patients</th>
<th>Deaths related to pulmonary embolism</th>
<th>All-cause mortality</th>
<th>Deaths due to other causes‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>n</td>
<td>n</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>≤ 2.5</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.5 - ≤ 21.7</td>
<td>37</td>
<td>1* (2.6%)</td>
<td>2 (5.3%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>&gt; 21.7</td>
<td>36</td>
<td>6+ (16.2%)</td>
<td>9 (24.3%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>P=0.003</td>
<td>P&lt;0.001</td>
<td>P=0.067</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This death was definitely due to pulmonary embolism. † 4 of these deaths were definitely due to pulmonary embolism.
‡ All these patients died as a consequence of cancer.

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. Table 1 details the baseline characteristics of the survivors and those who died during follow-up. The median BNP in the patients who died was 71.6 pmol/L (47.4-117.1), compared with 8.7 pmol/L (1.5-29.3) in those who survived (P<0.001). The median BNP in the 5 patients who died due to pulmonary embolism was 80.5 pmol/L (25.8-101.5; P=0.030 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 2). High BNP levels were associated with all-cause mortality and death related to pulmonary embolism. Of the 38 patients in the highest tertile, four died of pulmonary embolism, whereas in another 2 patients pulmonary embolism was a possible cause of death. Hence, the positive predictive value of a BNP level above 21.7 pmol/L was 16% (95% CI: 6-32%). The negative predictive value for an uneventful outcome of a value below 21.7 pmol/L was 99% (95% CI: 93-100%). Survival was significantly worse in patients with BNP concentrations in the highest tertile (figure 1). As shown by multiple logistic regression analysis, the odds ratio for the risk of all-cause death - adjusted for cancer and age - of levels above the 67th percentile (i.e. 21.7 pmol/L) was 9.4 (p=0.008).
Figure 1. Kaplan-Meier survival curve for 110 patients during 3 months after the diagnosis of pulmonary embolism. There were 0 deaths in the first tertile (BNP level 0-2.5 pmol/L), 2 deaths in the second (2.5-21.7 pmol/L), and 9 in the highest tertile.

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 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 in order 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 echocardiography, 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 only 5% 7. More recently, cardiac troponine T and I have been advocated as possible candidates for risk stratification. Konstantinides and colleagues found that 35-40% of patients with pulmonary embolism has elevated levels of cardiac troponines which were associated with overall mortality and a complicated inhospital course 12. However, cardiac troponines 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 troponines 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 level is high at presentation. Hemodynamically unstable patients already have an indication for more 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 since an independent blinded committee adjudicated the outcome events. Another potential bias concerns 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, troponine 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.

Acknowledgements
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3. van Beek FJ, Kuijper PM, Buller HR et al. The clinical course of patients with suspected pulmonary embolism. Archives of Internal Medicine 1997; 157:2593-98.


