The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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PEPTIDE (BNP) AS A PREDICTOR OF ADVERSE OUTCOMES IN PATIENTS WITH PULMONARY EMBOLISM

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ABSTRACT

Background: Despite effective treatment with anticoagulants, 2-7% 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.

Results: 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%).

Conclusion: This is the first study to show that plasma BNP levels seem to predict adverse outcome in patients with acute pulmonary embolism.
INTRODUCTION

Hemodynamically stable patients with pulmonary embolism are treated with an initial course of (low molecular weight) heparin and subsequently vitamin K antagonists for 3-6 months. Although this therapy is very effective, still during 3 months of follow-up approximately 2-7% of patients will die as a result of pulmonary embolism. Mortality likely occurs in those patients having right ventricular dysfunction at presentation. Brain Natriuretic Peptide (BNP) is a plasma neurohormone mainly secreted in the cardiac ventricles in response to stretch and/or pressure increase. BNP levels are known to correlate with left ventricular dysfunction and used for the diagnosis of left ventricular failure. We recently showed that increased levels of BNP are also associated with right ventricular dysfunction in patients with pulmonary embolism. Because right ventricular dysfunction in patients with pulmonary embolism 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

Data from a prospective cohort study of patients presenting with clinically suspected pulmonary embolism, referred for diagnostic work-up, were available for analysis. Patients requiring thrombolytic therapy because of hemodynamic instability were excluded from this study. The Institutional Review Boards approved the study protocol and participants gave informed consent. For the present analysis only patients with objectively confirmed pulmonary embolism on the basis of 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 used. Since renal insufficiency can result in elevated BNP levels, we excluded patients with known renal insufficiency.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deaths</th>
<th>Survivors</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=11</td>
<td>N=99</td>
<td></td>
</tr>
<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>

Table 1. Baseline clinical characteristics of 110 patients with pulmonary embolism who died (N=11) and survived (N=99) during 3 months of follow-up. 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.
**BLOOD SAMPLING**

At the time of enrolment, blood specimens were collected in citrated tubes and centrifuged for 15 minutes. The plasma was stored at -80 °C and at the end of the study BNP concentrations were determined with immunoradiometric assay kits (Shionoria, Osaka, Japan) without knowledge of the clinical outcome. According measurements 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 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 at the time of inclusion. The chi square test was used to test the difference in proportions of outcome events between the three groups. 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 death, and whether these potential cofounders influenced the association between high BNP levels and death, multiple logistic regression analysis was performed using SPSS (SPSS for Windows, release 10.0.7) and Excel (Microsoft® Excel 97 SR-1). BNP was entered as a dichotomous variable using the 33rd and 67th percentile as the cut-off value.

<table>
<thead>
<tr>
<th>Concentration BNP (pmol/L)</th>
<th>Patients n</th>
<th>Deaths related to pulmonary embolism n</th>
<th>All cause mortality n</th>
<th>Deaths due to other causes‡ n</th>
</tr>
</thead>
<tbody>
<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></td>
<td></td>
<td>P=0.003</td>
<td>P&lt;0.001</td>
<td>P=0.067</td>
</tr>
</tbody>
</table>

Table 2. Distribution of outcome events during 3 months follow-up among BNP tertiles in patients with pulmonary embolism. *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.
RESULTS

STUDY POPULATION
A total of 110 consecutive patients with objectively confirmed pulmonary embolism were included. The mean age was 58 (+/- SD: 18). The mean baseline level of BNP was 32.4 pmol/L, with a median of 9.4 pmol/L. Eleven patients died during 3 months of clinical follow-up (10%). 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 (they died on days 8 and 34). The remaining 4 deaths died as a result of 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 at presentation. Of the 2 patients who possibly died of pulmonary embolism heart failure contributed to the cause of death. Table 1 gives the baseline characteristics of the patients who survived and those who died during 3 months of follow-up. Patients who died had more often cancer (p=0.084) and were older (p=0.074). The median BNP in the patients who died was 71.6 pmol/L (interquartile range 47.4-117.1), compared with 8.7 pmol/L (interquartile range 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 (interquartile range 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 adverse outcome 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%). On the other hand, the negative predictive value for uneventful outcome of a BNP value below 21.7 pmol/L was 99% (95% CI 93-100%). As shown in Figure 1, survival is significantly worse in patients with BNP concentrations in the highest tertile. As shown by logistic regression analysis, the odds ratio for the risk of all cause death - adjusted for cancer and age - of BNP 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. BNP= Brain Natriuretic Peptide.](image-url)
DISCUSSION

This analysis demonstrates for the first time that the plasma concentration of BNP 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 pleuritic chest pain as the only physical sign to those who are severely dyspnoeic and/or hemodynamically compromised. In the past years attempts have been made to stratify this patient group in order to select patients 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%, whereas the positive predictive value of a high BNP level for this outcome event as found in our study is 16% (95% CI: 6-32%). 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 in-hospital course. 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 that 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 conservative therapy (i.e. 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 aggressive therapy. It needs to be investigated in a larger group of patients 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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