The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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COMBINED UTILITY OF BRAIN NATRIURETIC PEPTIDE AND CARDIAC TROPONINE T MAY IMPROVE RAPID TRIAGE AND RISK STRATIFICATION IN PATIENTS WITH PULMONARY EMBOLISM

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{Submitted for publication}
ABSTRACT

Background: Evaluation of the combined utility of brain natriuretic peptide (BNP) and cardiac troponin T (cTnT) for risk stratification in patients with acute pulmonary embolism (PE).

Methods: BNP and cTnT levels were measured in 28 patients (age 53±18 years) with acute PE. Twenty-seven healthy age-matched volunteers served as controls (age 42±12 years). Blood samples from all patients were obtained during the first hour of presentation. All patients were treated with intravenously administered heparin. Follow-up blood samples were acquired after 90 days.

Results: Six patients (21%) had increased BNP (59 ± 30 pmol/L) and cTnT (0.044 ± 0.025 ng/mL) and RV dysfunction as diagnosed by echocardiography. Two of these patients died during follow-up as a consequence of RV failure due to PE. In the remaining four patients BNP and cTnT normalized and these patients were in good clinical condition at the end of the follow-up. Eight patients (29%) had increased BNP (40.6 ± 32.6 pmol/L) and normal cTnT at presentation. In four of these patients BNP levels remained increased after treatment (46.9 ± 21.0 pmol/L). During follow-up these patients were diagnosed with chronic PE and RV pressure overload (RVSP > 40 mmHg). In the remaining four patients BNP and cTnT levels normalized and these patients were in good clinical condition at the end of follow-up. Fourteen patients (50%) with confirmed PE had normal BNP and cTnT levels at presentation, which remained normal during follow-up. These fourteen patients were in good clinical condition during follow-up.

Conclusion: Patients with acute PE presenting with both increased BNP and cTnT are at higher risk for adverse outcome then patients with increased BNP and normal cTnT levels. Patients with normal BNP and cTnT have no risk for adverse outcome.
INTRODUCTION

In patients with acute pulmonary embolism (PE) risk stratification is important because more aggressive therapies such as thrombolytics, inotropic vasoactive drugs, and embolectomy may improve the outcome in patients at risk for acute RV failure. In-hospital PE mortality rates range from 1% to > 30%, depending on the clinical and hemodynamic profile of the patients included. Another 4% will have recurrent non-fatal pulmonary embolism. Thus noninvasive rapid triage and assessment of the efficacy of therapy and follow-up in these patients is desirable. Recently brain natriuretic peptide (BNP) and cardiac troponin T (cTnT) have been proposed as possible diagnostic tools for optimizing the management strategy in patients with acute pulmonary embolism.

Plasma BNP, a cardiac hormone secreted mainly by the ventricles has potent diuretic and systemic vasorelaxant properties. In two of our recent studies we have shown that plasma BNP levels increased proportioned to with RV dysfunction.

Cardiac troponin T (cTnT) is a highly sensitive and specific marker of myocardial cell injury and its role for risk stratification in acute coronary syndromes is well established. More recently, cTnT has been advocated as possible candidate for risk stratification in patients with acute PE. In this study we have combined these two independent prognostic factors to elucidate their value as complementary quantitative indicators for rapid triage and risk stratification in patients with acute PE. The changing patterns of BNP and cTnT levels during the initial management of PE and their correlation with clinical outcome were the focus of this study.

METHODS

Data from a prospective cohort study of patients presenting with pulmonary embolism, referred for diagnostic work-up, were available for analysis. We studied 28 consecutive patients (age 53 ± 18 years, 10 males) with acute PE as diagnosed by high-probability scintigram, a non-high probability scintigram with abnormal ultrasonography of the legs or the presence of pulmonary embolism on spiral CT. Patients included in this study had no cardiac or pulmonary medical history. Twenty-seven healthy volunteers served as controls (age 42.4 ± 12.4 years, 17 males). The patient's clinical condition was evaluated according to New York Heart Association (NYHA) classification. Patients with NYHA class I were classified as being in good clinical condition. All study subjects had 90 days follow-up. Those patients requiring thrombolytic therapy because of hemodynamic instability were excluded from this study. Patients with renal impairment (serum creatinine >133 μmol/liter), atrial fibrillation, flutter or with preexisting left ventricular dysfunction, documented by echocardiography, were not included in the study. Informed consent was obtained from all study subjects. The Local Ethical Committee approved the study. Informed consent was obtained from all patients and volunteers. Demographics and clinical characteristics of the study population are listed in Table 1.
Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Male / female</td>
<td>12 / 16</td>
<td>17 / 10</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>53 +/- 18</td>
<td>42 +/-12</td>
</tr>
<tr>
<td><strong>Breathing frequency</strong></td>
<td>19+/−20</td>
<td>16+/−4</td>
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<tr>
<td><strong>Body temperature</strong></td>
<td>37.1+/−0.77</td>
<td>36.5+/−0.5</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>88+/−23</td>
<td>66+/−12</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td>130+/−20</td>
<td>112+/−14</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td>76+/−12</td>
<td>72+/−15</td>
</tr>
</tbody>
</table>

Table 1. Values are expressed as mean (+/− SD).

**ECHOCARDIOGRAPHY**
Standard two-dimensional echocardiographic examination with commercially available ultrasound instruments was performed at physicians discretion according to a standard clinical protocol used in our institution. RV function was assessed by qualitative evaluation and stratified to patients with or without RV dysfunction.

**PLASMA NEUROHORMONES AND cTNT**
Blood samples were obtained at presentation and after 90 days. Blood was collected into chilled tubes, promptly centrifuged (3000 rotations/minute for 10 minutes) and stored at minus 80°C until final analysis. BNP concentrations were determined with immunoradiometric assay kits (Shionoria, Osaka, Japan). Details of our methods have been published previously. From the same blood samples cTnT was determined by means of a qualitative immunological assay.

**RESULTS**
A total of 28 patients with objectively confirmed PE were included. The baseline characteristics of the patients and the control subjects are shown in Table 1.

Mean plasma BNP levels in patients with acute PE, at presentation, were significantly higher than in controls (BNP 29.6 ± 39.2 versus 3.1 ± 3.7 pmol/L; p<0.0006) (Figure 1). In the patient group mean plasma BNP levels significantly decreased after treatment from 29.6 ± 39.2 to 10.8 ± 17.6 pmol/L (p < 0.02) (Figure 2a). Similarly to BNP, mean cTnT levels in patients were significantly higher than in controls (cTnT 0.017 ± 0.017 versus 0.010 ± 0 ng/mL; p< 0.05) and decreased significantly after treatment to 0.010 ± 0 ng/mL; p<0.02 (Figure 2b).
The results are schematically described in flow chart. During initial presentation six patients (21%) had increased both BNP (59 ± 30 pmol/L) and cTnT (0.044 ± 0.025 ng/mL) and RV dysfunction as diagnosed by echocardiography. Two of these patients (7%) died during follow-up (first seven days) as a consequence of RV failure due to PE. The remaining four patients improved after therapy and at the end of follow-up they were in good clinical condition with normalized BNP and cTnT levels.

Eight patients (29%) had increased BNP (40.6 ± 32.6 pmol/L) and normal cTnT at presentation. In four of these patients BNP levels remained increased after treatment (46.9 ± 21.0 pmol/L). During follow-up these patients were diagnosed with chronic PE and RV pressure overload (NYHA II and III). The remaining four patients were in good clinical condition at the end of the follow-up with normalized BNP and cTnT levels.

Fourteen patients (50%) with confirmed PE had normal BNP (3.0 ± 3.0 pmol/L) and cTnT (0.010 ng/ml) levels at presentation that remained normal during follow-up. None of these patients had clinical or diagnostic signs of RV dysfunction during the follow-up period.

Figure 1. Symbols indicate the combination of BNP and cTnT levels at presentation. Two patients died within 7 days (x). In four patients with (†) increased BNP and (=) normal cTnT levels at presentation BNP levels remained elevated during follow-up.

Figure 2a. Changes of BNP levels after treatment.

Figure 2b. Changes of cTnT levels after treatment.
DISCUSSION

This study shows that PE patients with increased BNP and cTnT are at high risk for adverse outcome in terms of mortality. Increased risk for adverse outcomes was also found in the patients with increased BNP and normal cTnT who were diagnosed with chronic PE and RV pressure overload. The patients with normal BNP and cTnT were in good clinical condition and had no signs of RV dysfunction.

IMPORTANCE OF RISK STRATIFICATION IN ACUTE PE

Many patients with PE remain in stable condition, with normal blood pressure and RV function; such patients have a good prognosis with anticoagulants alone. Rarely, patients with PE will present in cardiogenic shock due to RV failure. Thrombolysis, embolectomy or inferior caval vein filter placement in conjunction with anticoagulants are often necessary to prevent recurrent PE or death. Between these two extremes lies a large group of patients characterized by the combination of normal blood pressure and increased RV afterload due to pulmonary hypertension. Such patients may appear to be in deceptively stable condition because their blood pressure and heart rate, at least initially, remain normal. RV dysfunction occurs in approximately 40% of normotensive patients with acute PE and their management is highly controversial.

The current first choice diagnostic tool for RV function in patients with acute PE, echocardiography has certain shortcomings such as the limited acoustic window, operator dependence and the qualitative assessment of RV function. Echocardiographic findings solely are often not conclusive and their contribution to risk stratification and choice of therapy in patients with acute PE is questionable. In our opinion serial quantitative measurements for RV function using BNP, cTnT in combination with echocardiography could markedly improve the risk stratification and point-out patients at imminent risk for RV failure and help in the choice of therapy.

CLINICAL SIGNIFICANCE

Earlier studies showed that BNP or cTnT have a potential to become a routine parameter of substantial practical value as a complementary tool in assessment of RV function in acute PE. In the present study, patients with acute PE with both increased BNP and cTnT levels had most adverse outcomes. Previous results from our group and from the group of Nagaya showed a strong correlation between BNP and RV function. Cardiac TnT is a marker for myocardial damage and it was to be expected that these patients would also have increased BNP levels due to impeded RV function as a consequence of myocardial damage.

Increased BNP levels combined with normal cTnT were measured in eight of our patients. During follow-up, four of these patients retained increased BNP levels due to pulmonary hypertension and as a consequence of PE. In a study performed by Grifoni et al., 10% of the patients developed PE related shock and 5% died. It is reasonable to believe that in some patients subjected to increased RV afterload myocardial damage will occur at some point of time. Therefore these patients should be carefully monitored and they are potential candidates for more aggressive therapy in addition to anticoagulants.

Conservative therapy remains reserved for the majority of patients with acute PE who will present with normal BNP and cTnT. In our study, all patients with normal BNP and cTnT were in good clinical condition and had no signs for RV dysfunction. Accordingly Goldhaber et al.
showed that patients with acute PE and without RV dysfunction are not at risk for adverse outcomes.

CONCLUSION

Patients with acute PE presenting with both increased BNP and cTnT are at higher risk for adverse outcome than patients with increased BNP and normal cTnT levels. Patients with normal BNP and cTnT have no risk for adverse outcome. This study encourages further research for combined utility of BNP and cTnT as noninvasive and quantitative parameters for RV function in patients with acute PE.

Figure 3. Flow chart diagram showing [BNP] brain natriuretic peptide and [cTnT] cardiac troponin T levels at presentation and follow-up.

(↑) increased, (=) normal, (†) dead
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