The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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INCREASED BRAIN NATRIURETIC PEPTIDE AS A MARKER FOR RIGHT VENTRICULAR DYSFUNCTION IN ACUTE PULMONARY EMBOLISM

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Objective: Right ventricular (RV) function is of major prognostic significance in patients with acute pulmonary embolism (PE). The aim of the present study was to evaluate the role of neurohormone plasma brain natriuretic peptide (BNP) in assessing RV function in patients with acute PE.

Methods: BNP levels were measured in 16 consecutive patients with acute PE as diagnosed by high probability lung scintigraphy or pulmonary angiography. Twelve healthy age-matched volunteers served as controls. All 16 patients underwent standard echocardiography and blood tests during the first hour of presentation. In the patient group survival was studied for a period of 30 days.

Results: Plasma BNP levels in patients with acute PE were higher than in controls (7.2 (95% CI 0.4 to 144.6) versus 1.4 (95% CI 0.4 to 4.6) pmol/L, p=0.0008). Plasma BNP was significantly higher in 5 patients with RV dysfunction compared to 11 patients with normal RV function (40.2 (95% CI 7.5 to 214.9) versus 3.3 (95% CI 0.4 to 24.9) pmol/L, p=0.0003). RV systolic pressure was not significantly correlated with BNP (r=0.42, p=ns).

Conclusion: Plasma BNP neurohormone levels might be of clinical importance as a supplementary tool for assessment of RV function in patient with acute PE.
INTRODUCTION

Pulmonary embolism (PE) is associated with a varying degree of pulmonary vascular obstruction due to embolism and vasoconstriction. Increased pulmonary vascular resistance results in increased workload of the right ventricle (RV) and eventually in RV failure. From a therapeutic point of view it has been suggested that it may be important to divide hemodynamically stable patients into those with and without evidence of RV dysfunction. RV function is of major prognostic significance in patients with acute pulmonary embolism. Early diagnosis of RV dysfunction is difficult and once identified, patients with PE and RV dysfunction need close monitoring and appropriate therapy. Thrombolysis, embolectomy or placement of an inferior caval vein filter in conjunction with anticoagulation, are necessary to prevent recurrent PE or death in cases of hemodynamic instability.

Recently, neurohumoral activation of the RV in state of overload has gained increased attention. Brain natriuretic peptide (BNP) is a marker for left-ventricular dysfunction and is secreted mainly in ventricles. BNP has potent diuretic and systemic vasorelaxant properties.

Although it has been reported that BNP is rapidly produced and secreted by acute overload in the left ventricle (LV) there has been only one case report demonstrating the changes in the BNP plasma concentrations in response to acute RV overload. The role of plasma neurohormones and their applicability in detection of RV dysfunction in patients with acute pulmonary embolism are yet unknown.

Accordingly we hypothesized that plasma BNP would enable assessment of RV function in patients with PE in case of a significant correlation with currently used clinical parameters for RV function in PE.
Clinical characteristics

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<tr>
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<th>Patients</th>
<th>Controls</th>
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<tr>
<td>n</td>
<td>16</td>
<td>12</td>
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<tr>
<td>Male/female</td>
<td>8/8</td>
<td>8/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (28 - 84)</td>
<td>51 (42 - 62)</td>
</tr>
<tr>
<td>Hemodynamically stable/unstable</td>
<td>14/2</td>
<td>12/0</td>
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<tr>
<td>BNP (pmol/L)</td>
<td>20.2 (0.7 - 117.1)</td>
<td>1.7 (0.7 - 4.8)</td>
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<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>37.7 (22 - 56)*</td>
<td>-</td>
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</tbody>
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Echocardiography

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<tbody>
<tr>
<td>RV dilatation</td>
<td>8</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1. Values are expressed as mean (range) or as number of patients. * n = 12 (RV systolic pressure could not be assessed in 4 patients by the means of echocardiography) BNP, brain natriuretic peptide; RV, right ventricular.

PATIENTS AND METHODS

**Patients**
We studied 16 consecutive patients (age 57 ± 19 years, 8 males) with acute PE as diagnosed by high probability lung scintigraphy or pulmonary angiography. Twelve healthy volunteers served as controls (age 51 ± 7 years, 8 males). There were no significant differences in age between the groups and subgroups examined in this study. In addition, all study patients had a follow-up of 30 days considering cardiovascular mortality. Patients with renal impairment (serum creatinine >133 μmol/liter) or with left ventricular dysfunction, documented by echocardiography, were not included in the study. Informed consent was obtained from all study subjects. The study was approved by the Local Ethical Committee. Informed consent was obtained from all patients and volunteers. Clinical characteristics of the study population are listed in Table 1.

**Plasma Neurohormones**
During the first hour after presentation blood samples were obtained from the antecubital vein of all subjects after they had rested for at least 15 minutes. Blood was collected into chilled tubes containing EDTA and aprotinin (1.9 mg and 100 kIU/ml blood, respectively). The blood samples were promptly centrifugated (3000 rotations/minute for 10 minutes) and stored at
minus 70°C until final analysis. BNP concentrations were determined with immunoradiometric assay kits (Shionoria, Osaka, Japan). Details of our methods have been published previously.8

**ECHOCARDIOGRAPHY**

Standard two-dimensional echocardiographic examination with commercially available ultrasound instruments was performed during the first hour of presentation of patients with acute PE and stored on standard S-VHS videotape. The transducer was positioned over standard windows according to the American Society of Echocardiography.18

All studies were performed by physicians and technicians according to a standard clinical protocol used in our institution. The analyses and measurements were performed by the physician, either at the time of investigation in a cine loop mode or later on video recordings. The data were blinded to the clinical outcome of the patient and without the knowledge that the analyses also would be used for research purposes.

The degree of RV dysfunction was assessed by qualitative evaluation (wall motion score) of segmental RV free wall motion. The RV wall motion using standard two-dimensional echocardiography can be judged normal, mildly, moderately or severe hypokinetic.19 However, in the clinical practice it very difficult to differentiate between normal and mildly, mildly and moderate and moderate and severe hypokinetic RV wall. Therefore we classified the echocardiographic findings in two possible to clearly differentiate groups: patients with or without RV dysfunction.

The degree of tricuspid regurgitation was assessed qualitatively by combined analyses of color-flow (size of the largest jet) and continuous-wave Doppler recordings.10

The RV was considered dilated when RV end-diastolic diameter >30 mm or RV/LV end-diastolic diameter ratio >1 in 4-chamber view.20 Continuous wave Doppler of the tricuspid valve was measured to estimate RV systolic pressure, using the following formula: RV systolic pressure = $4v^2 + RA$, where $v$ is the maximal velocity of the tricuspid valve insufficiency signal18. RA is right atrial pressure, assumed to be 10 mm Hg in this population.21 There were no patients in this study with evidence of RV wall hypertrophy (free wall thickness > 7 mm).

**STATISTICAL ANALYSIS**

Differences between the groups were assessed by the unpaired Student's t test. P values <0.05 were considered statistically significant. BNP values were transformed into a logarithmic scale and log values were used for the statistical analysis, means and 95% confidence interval (CI) are expressed on normal scale by taking anti-log. All p values presented are two-tailed. Linear regression analysis was performed to correlate BNP with RV systolic pressure.

**RESULTS**

The baseline characteristics of the patients and the control subjects are shown in Table 1. Plasma BNP levels in patients with acute PE were significantly higher than in controls (7.2 (95% CI 0.4 to 144.6) versus 1.4 (95% CI 0.4 to 4.6) pmol/L, p=0.0008). Plasma BNP was significantly higher in 5 patients with RV dysfunction compared to 11 patients with normal RV function (40.2 (95% CI 7.5 to 214.9) versus 3.3 (95% CI 0.4 to 24.9) pmol/L, p=0.0003) (Figure 1). Plasma levels of BNP were significantly higher in 8 patients with RV dilatation compared to 8 patients without RV dilatation (23.5 (95% CI 3.4 to 162.8) versus 2.2 (95% CI 0.4 to 13.2) pmol/L,
Two patients with the highest BNP plasma levels (117.1 and 80.5 pmol/L) developed RV failure and died within the period of 30 days. RV systolic pressure was not significantly correlated with BNP ($r=0.42$, $p=\text{ns}$).

**DISCUSSION**

In the present study primary emphasis was placed on RV function in patients with acute PE before treatment took place. Our data suggest that the secretion of BNP responds to RV dysfunction in these patients. To the best of our knowledge, for the first time we demonstrated a significant difference in BNP plasma levels between the patient groups with normal and disturbed RV function in acute PE.

**RV DYSFUNCTION**

RV dysfunction occurs in approximately 40% of normotensive patients with acute PE\textsuperscript{18}. At times, acute severe RV dysfunction in patients with PE can be readily detected by physical examination. Very often additional testing is required to identify these patients, for example by electrocardiography or chest radiography. However, the most sensitive tool for diagnosing acute cor pulmonale and RV dysfunction is the echocardiogram\textsuperscript{622}. Identification of patients with PE and RV dysfunction may be associated with some degree of diagnostic uncertainty. Limitations of echocardiography are qualitative assessment of RV function, limitation of acoustic window, and absence of reliable mathematical assumptions due to the complex geometry of RV. Regarding these limitations three dimensional studies of the RV would be helpful in elucidating the full extent of RV function in PE and the relation with plasma neurohormones. Recently, Giannitsis et al. proposed that Troponin T has an independent prognostic value in patients with
confirmed pulmonary embolism. The authors stated that cardiac troponin T is a highly sensitive and specific marker of myocardial injury, and may aid in the identification of patients in whom a more aggressive therapy is warranted. Plasma BNP has the advantage of being an indicator of RV dysfunction, while Troponin T is a product of myocardial injury. Therefore BNP seems to be a more suitable marker than Troponin T for risk stratification in patients with acute PE.

**PLASMA NEUROHORMONES**
BNP may enable assessment of RV function at the patient's bedside. Therefore, invasive diagnostic methods may not be immediately necessary in patients with acute PE in whom RV dysfunction may be assessed by plasma neurohormones (or in combination with echocardiography). Reliable assessment of RV dysfunction would allow risk stratification of the patient population with PE and identification of potential candidates for thrombolytic treatment. Troughton et al showed that treatment of LV failure can be guided by BNP plasma concentrations, speculating that BNP might serve as indicator for the efficacy of treatment in patients with acute PE.

In our patients no correlation was found between RV systolic pressure and BNP. We assume that plasma BNP neurohormone during acute RV overload is a marker for RV dysfunction rather than for elevated RV pressure. This is consistent with the results described by Tulevski et al. and Nagaya et al. concerning patients with chronic RV pressure overload.

A suddenly increased pressure load on the RV is poorly tolerated because of the inability of the normally thin-walled RV to develop and sustain high wall tension and stress. RV function may deteriorate with increase of RV afterload paired with increase in plasma neurohormone levels, but increase of RV systolic pressure will be limited by the RV incapability to cope with acute increasing overload. On the other hand, some patients with acute PE showed normal echocardiographic RV function with RV systolic pressure above 40 mm Hg. In these patients plasma neurohormone levels were not increased.

**PROGNOSTIC SIGNIFICANCE**
The potential prognostic value of BNP has been underscored in several previous studies regarding LV pathology. The results of these studies confirmed that BNP was a powerful predictor of cardiovascular mortality independent of LV ejection fraction. Markedly raised circulating levels of BNP (above 80 pmol/L in two patients, both hemodynamically unstable) in this study were associated with mortality within 30 days. In the patient group with RV dysfunction a significant difference in BNP levels was observed between 3 patients with survival longer than 30 days and 2 patients who died within this period (22.4 (95% CI 11.0 to 45.7) versus 97.1 (95% CI 57.8 to 163.2) pmol/L, respectively, p=0.02).

**CLINICAL SIGNIFICANCE**
The results of this study indicate that BNP has a potential to become a routine measure of substantial practical value as a complementary tool in assessment of RV function in acute PE. Two conclusions with possible clinical applications can be drawn from our data: (1) low BNP plasma levels (<10 pmol/L) indicate normal RV function, and (2) the presence of markedly increased BNP levels may help to target patients for subsequent detailed assessment and monitoring of RV function and the choice of therapy.

**STUDY LIMITATIONS**
Raised levels of BNP are a consequence of hemodynamic and structural abnormalities arising from diverse pathological processes. Hence, the interpretation of BNP plasma levels must be
done within an appropriate clinical context. Examination of small groups entails loss of statistical power and, therefore, the present report requires confirmation in a larger group of patients.

In conclusion our study suggests that the secretion of BNP responds to RV dysfunction in patients with acute PE. Plasma BNP might be of clinical importance as a supplementary tool for assessment of RV function under circumstances of acute RV pressure overload, which can be of substantial importance in the diagnostic process, treatment and prognosis of patients with RV dysfunction in acute PE.
REFERENCES


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