The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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Citation for published version (APA):

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INCREASED BRAIN AND ATRIAL NATRIURETIC PEPTIDES IN PATIENTS WITH CHRONIC RIGHT VENTRICULAR PRESSURE OVERLOAD: CORRELATION BETWEEN PLASMA NEUROHORMONES AND RIGHT VENTRICULAR DYSFUNCTION

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{Heart 2001; 86:27-30}
ABSTRACT

Objective: To evaluate the role of plasma neurohormones in diagnosis of asymptomatic or minimally symptomatic RV dysfunction.

Methods: Plasma brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) levels were measured in 21 asymptomatic or minimally symptomatic patients with chronic RV pressure overload due to a congenital heart disease and in seven healthy volunteers. RV ejection fraction (EF) was determined using magnetic resonance (MR) imaging.

Results: RVEF of the volunteers was significantly higher than RVEF of the patients (69.0(8.2)% v 58.0(12.0)%, respectively, p<0.006). Left ventricular (LV) EF in volunteers and patients was 72.3(7.8)% v 68.1(11.0)%, respectively, p=NS. Between patients and volunteers there was a significant difference in the plasma concentrations of BNP (5.3(3.5)pmol/L v 2.3(1.7)pmol/L, respectively, p<0.009) and ANP (7.3(4.5)pmol/L v 3.6(1.4)pmol/L, respectively, p<0.05). Both in patients and volunteers mean ANP plasma concentrations were higher than mean BNP plasma concentrations. RVEF was inversely correlated with BNP and ANP (r=0.65; p<0.0002 and r=0.61; p<0.002, respectively). No correlations were found between LVEF and BNP (r=0.2; p=NS), and LVEF and ANP (r=0.52; p=NS). Similarly, no correlation was shown between the level of RV systolic pressure and plasma neurohormones BNP (r=0.20) and ANP (r=0.07) respectively.

Conclusions: Our study shows a significant inverse correlation between RVEF and the plasma neurohormones BNP and ANP in asymptomatic or minimally symptomatic patients with RV pressure overload and congenital heart disease. Monitoring of changes in BNP and ANP levels may provide quantitative follow up of RV dysfunction in these patients.
INTRODUCTION

Early diagnosis of right ventricular (RV) dysfunction is difficult but of great importance in patients with chronic RV pressure overload due to congenital heart defects. Absence of accurate RV function parameters precludes the estimation of the optimal moment for medical or surgical intervention in order to prevent or delay irreversible RV failure. Recent literature has shown that plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated in patients with asymptomatic left ventricular (LV) systolic dysfunction and these parameters are highly accurate for the detection of LV failure. BNP is a marker for ventricular distention and is secreted in both atria and ventricles, especially in failing ventricles. In normal subjects ANP is synthesized and secreted almost exclusively in the atrium, but patients with congestive heart failure have increased production in both atria and ventricles in response to increased atrial stretch. Although previous studies suggest that neurohumoral markers not only play a role in LV dysfunction but also in RV dysfunction, their applicability in detection of RV dysfunction and their relation with other quantitative determinants of RV function in asymptomatic or minimally symptomatic patients with congenital heart disease are yet unknown.

In the present study plasma levels of BNP and ANP were investigated in asymptomatic or minimally symptomatic patients under circumstances of chronic RV pressure overload. Plasma neurohormones were related to RV ejection fraction (RVEF) determined by magnetic resonance (MR) imaging. MR imaging is an accurate and reproducible method in the quantitative assessment of RV function and allows in-vivo assessment of various RV function parameters.

METHODS

STUDY DESIGN AND PATIENT POPULATION
Twenty one consecutive asymptomatic or minimally symptomatic patients (NYHA Class I and II) from the cardiology outpatient clinic with chronic RV pressure overload due to a congenital heart disease were included in this study. Seven healthy volunteers matched for sex and age served as controls. Chronic RV pressure overload was diagnosed by Doppler echocardiography (RV systolic pressure >35 mm Hg). All patients were studied off medication. In each subject valvular regurgitation (>10 ml per cardiac cycle) was ruled out by means of MR flow measurements. Patients with atrial arrhythmias were excluded from this study for two reasons: 1. Arrhythmias make MRI images unreliable for analysis because of the triggering problem and 2. Atrial arrhythmias are known to influence natriuretic peptide levels. Patients with chronic renal impairment (serum creatinine >133 µmol/liter) or significant LV abnormalities were not included in this study. Informed consent was obtained from all patients and volunteers. The study was approved by the Local Ethical Committee. Clinical characteristics of the study population are listed in Table 1.
Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Volunteers</th>
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<tbody>
<tr>
<td>Men/women</td>
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<td>4/3</td>
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<tr>
<td>Age, y</td>
<td>26.6 (8.6)</td>
<td>26.9 (3.9)</td>
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<tr>
<td>NYHA class I/II</td>
<td>13/8</td>
<td>7/0</td>
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<tr>
<td>ccTGA</td>
<td>2</td>
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<td>TGA (Mustard or Senning)</td>
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<td>Corrected Tetralogy of Fallot</td>
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<tr>
<td>Pulmonary artery stenosis</td>
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<td>RV systolic pressure (mmHg)</td>
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<td>RV EDV / BSA (ml/m²)</td>
<td>65.3 (23.3)</td>
<td>66.8 (17.6)</td>
</tr>
</tbody>
</table>

Table 1. Values are mean (SD); NYHA, New York Heart Association; ccTGA, congenitally corrected transposition of the great arteries; TGA, transposition of the great arteries; RV, right ventricle; EDV, end diastolic volume.

**IMAGING PROTOCOL**

Study subjects were placed supine in a 1.5 Tesla MR imaging scanner (Vision, Siemens, Erlangen, Germany). MR imaging acquisition involved a standardized protocol. Imaging sessions were initiated with scout images to determine the position of the heart in the thoracic cavity. Based on these images an electrocardiogram (ECG) triggered T1-weighted series of axial images was acquired. A gradient-echo cine sequence was then performed in a plane bisecting the mitral valve orifice and passing through the apex visualizing the long-axis view in order to localize the atrioventricular valve plane. An ECG-triggered, ultrafast, breath-held gradient-echo cine sequence (TR = R-R interval, TE = 4.8 msec, matrix size = 256x256, field of view = 350 mm, Flip angle = 20°) was then used to acquire images in the short axis plane in contiguous 10mm slices encompassing the valve plane to the apex of the heart. Velocity maps were acquired with a flip angle of 30°, TE = 5 ms, slice thickness = 6 mm, FOV = 320 mm and imaging matrix = 256x256, Velocity encoding = 250 cm/s.

**IMAGE ANALYSIS**

A Unix workstation was used for analysis of the MR images. MASS® (Medis, Leiden, The Netherlands) image analysis software was used to display multi-slice, multi-phase images individually and in a movie loop mode. End-diastolic (maximal ventricular volume) (EDV) and end-systolic (minimal ventricular volume) (ESV) frames were determined by manual outlining of a mid-ventricular slice in all phases. On end-diastolic and end-systolic time frames endocardial borders of the RV and the LV were outlined manually. Papillary muscles and the moderator band were not included in the ventricular volume measurements. The enclosed RV and LV cross-sectional areas were measured by computer, multiplied by section thickness, and summed up according to Simpson’s rule to provide LV and RV volumes.
The Flow® (Medis, Leiden, The Netherlands) image analysis software was used to calculate volumetric flow. Contours of the great artery arising from the RV were drawn manually on the modulus images of all time frames. Flow (ml/s) per cardiac cycle was calculated using the velocity values of the corresponding velocity encoded images.

**PLASMA NEUROHORMONES**

Prior to the MRI examination we obtained blood samples 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 centrifuged (3000 rotations/minute for 10 minutes) and stored at minus 70°C until final analysis. ANP and BNP concentrations were determined with immunoradiometric assay kits (Shionoria, Osaka, Japan).

**STATISTICAL ANALYSIS**

Differences between the groups were assessed by the unpaired Student’s t test. P values <0.05 were considered statistically significant. All p values presented are two-tailed. Linear regression analysis was performed to correlate neurohumoral factors and systolic RV function. For descriptive purposes, quantitative variables with a normal distribution were presented as mean standard deviation (SD).

**RESULTS**

RVEF of the volunteers was significantly higher than RVEF of the patients (69.0 (8.2)% v 58.0 (12.0)%, respectively, p<0.006) (Figure 1a). LVEF in volunteers and patients was 72.3 (7.8)% v 68.1 (11.0)%, respectively, p=NS. There was a significant difference in the plasma concentrations of BNP and ANP between the patients and the volunteers. BNP in patients was 5.3 (3.5) pmol/L v BNP in volunteers 2.3 (1.7) pmol/L, p<0.009; ANP in patients was 7.3 (4.5) pmol/L v ANP in volunteers 3.6 (1.4) pmol/L, p<0.05 (Figure 1b). Both in patients and volunteers mean ANP plasma concentrations were higher than mean BNP plasma concentrations. RVEF was inversely correlated with BNP (r=-0.65;p<0.0002; Figure 2a), and ANP (r=-0.61;p<0.002 Figure 2b). No correlation was found between LVEF and BNP (r=0.2;p=NS), ANP (r=0.52;p=NS).

Similarly, no correlation was shown between the level of RV systolic pressure and plasma neurohormones BNP (r=0.20;p=NS) and ANP (r=0.07;p=NS) respectively. End-diastolic RV volume corrected for body surface area was not different between patients and controls (65.3 (23.3) ml/m2 v 66.8 (17.6) ml/m2, respectively, p=NS). There were no differences in ventricular volumes between the different patient groups included in this study.

![Figure 1](image-url) A. Scatter graph showing RVEF in patients and controls. RVEF, right ventricular ejection fraction. B. Scatter graph showing plasma levels of BNP and ANP in patients and controls. Vertical bars show mean values SD. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.
**DISCUSSION**

Our study showed that RVEF was significantly lower in asymptomatic and minimally symptomatic patients with chronic RV pressure overload than in healthy volunteers. In addition, both BNP and ANP levels were significantly raised in patients. A significant inverse correlation between RVEF and neurohumoral factors BNP and ANP was observed. There was no difference in LVEF between patients and controls, and we found no correlation between LVEF and the plasma neurohormones.

To our knowledge, this is the first study to demonstrate a correlation between RV systolic function and the neurohumoral factors BNP and ANP in asymptomatic or minimally symptomatic patients with chronic RV pressure overload due to congenital heart disease. Raised plasma levels of BNP and ANP have been reported previously in patients with LV systolic dysfunction. Tsutamoto et al. stated that a high BNP level may predict mortality and morbidity in asymptomatic patients with LV dysfunction. Until now, the relation between neurohumoral factors and RV function has received little attention. Only one previous study by Nagaya et al. demonstrated increased BNP and ANP levels in symptomatic patients with RV pressure and volume overload. In the current study, we observed increased plasma levels of natriuretic peptides in asymptomatic or minimally symptomatic patients with chronic RV pressure overload.

Previous reports have indicated that ANP plasma levels in healthy subjects are higher than BNP plasma levels whereas patients with manifest LV or RV failure show a much larger increase of BNP relative to ANP. In our patients BNP plasma levels did not exceed the plasma levels of ANP, and both BNP and ANP remained relatively low. This can be explained by the asymptomatic nature of early RV dysfunction. Based on these data one could speculate that, analogous to the conditions in LV failure, BNP plasma levels will exceed ANP levels in case of deterioration from asymptomatic to severe symptomatic RV failure.

No correlation was found between the level of RV systolic pressure and plasma neurohormones, indicating that elevated plasma neurohormones are markers for RV dysfunction rather than for...
elevated RV pressure in patients with congenital heart disease. This is consistent with the results described by Nagaya et al.\textsuperscript{10} concerning patients with pulmonary hypertension.

Despite the importance of detecting early RV failure, diagnosis of early asymptomatic RV dysfunction remains difficult\textsuperscript{2}. Although noninvasive imaging techniques permit evaluation of RV function, they are not suitable for large-scale, cost-effective application. Our data suggest that elevated BNP and ANP plasma levels in asymptomatic or minimally symptomatic patients might be helpful as early markers of RV systolic dysfunction and therefore potentially cost-effective for patients at risk for RV dysfunction. Monitoring of changes in the BNP and ANP plasma levels may provide quantitative follow up of RV dysfunction in these patients.

Interpretation of BNP plasma levels must be done within an appropriate clinical context, because levels of BNP may also arise as a consequence of diverse pathological processes\textsuperscript{18} for example renal failure\textsuperscript{19} significant LV diseases\textsuperscript{4} or atrial arrhythmias\textsuperscript{14}.

CONCLUSIONS

Our study shows a significant inverse correlation between RVEF and the plasma neurohormones BNP and ANP in asymptomatic or minimally symptomatic patients with chronic RV pressure overload and congenital heart disease. Increased BNP and ANP plasma levels in these patients might be used as early indicators of RV systolic dysfunction and monitoring of changes in the BNP and ANP plasma levels may provide quantitative follow up of RV function. These results set the scene for larger studies of hormone-guided follow-up of asymptomatic patients with congenital heart disease at risk for RV failure.
REFERENCES
