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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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Abstract

Objective—To evaluate the role of plasma neurohormones in the diagnosis of asymptomatic or minimally symptomatic right ventricular dysfunction.

Setting—Tertiary cardiovascular referral centre.

Methods—Plasma brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) concentrations were measured in 21 asymptomatic or minimally symptomatic patients with chronic right ventricular pressure overload caused by congenital heart disease, and in seven healthy volunteers. Right ventricular ejection fraction was determined using magnetic resonance imaging.

Results—Right ventricular ejection fraction in the volunteers was higher than in the patients (69.0 (8.2)% *v* 58.0(12.0)%, respectively; $p < 0.006$). Left ventricular ejection fraction was 72.3(7.8)% in volunteers and 68.1(11.0)% in patients (NS). There was a significant difference between patients and volunteers in the plasma concentrations of BNP (5.3 (3.5) *v* 2.3 (1.7) pmol/l, respectively; $p < 0.009$) and ANP (7.3 (4.5) *v* 3.6 (1.4) pmol/l; $p < 0.05$). In both patients and volunteers, mean plasma ANP was higher than mean plasma BNP. Right ventricular ejection fraction was inversely correlated with BNP and ANP (respectively, $r = 0.65$; $p < 0.0002$ and $r = 0.61$; $p < 0.002$). There was no correlation between left ventricular ejection fraction and BNP ($r = 0.2$; NS) or ANP ($r = 0.52$; NS). Similarly, no correlation was shown between the level of right ventricular systolic pressure and either plasma BNP ($r = 0.20$) or plasma ANP ($r = 0.07$).

Conclusions—There was a significant inverse correlation between right ventricular ejection fraction and the plasma neurohormones BNP and ANP in asymptomatic or minimally symptomatic patients with right ventricular pressure overload and congenital heart disease. Monitoring changes in BNP and ANP may provide quantitative follow up of right ventricular dysfunction in these patients.

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Keywords: natriuretic peptides; right ventricle; pressure overload; congenital heart disease

Department of Cardiology, Academic Medical Centre, Meibergdreef 9, 1100 DD Amsterdam, Netherlands
I I Tulevski
M Groenink
A Hirsch
J S Lemkes
B J M Mulder

Department of Radiology, Academic Medical Centre, Amsterdam
J Stoker

Department of Cardiology, Leiden University Medical Centre, Leiden, Netherlands
E E van der Wall

Department of Cardiology, University Hospital, Groningen, Netherlands
D J van Veldhuisen

Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, Netherlands
F Boomsma

Correspondence to:
Dr Mulder
b.j.mulder@amc.uva.nl

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Early diagnosis of right ventricular dysfunction is difficult but very important in patients with chronic right ventricular pressure overload caused by congenital heart defects.[1] Absence of an accurate measure of right ventricular function makes it impossible to estimate the optimal moment for medical or surgical intervention so as to prevent or delay irreversible right ventricular failure.[2 3] Recent reports have shown that plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are raised in patients with asymptomatic left ventricular systolic dysfunction, and these variables are highly accurate for detecting left ventricular failure.[4] BNP is a marker of ventricular distension[4 5] and is secreted in both atria and ventricles, especially in failing ventricles.[6–8] In normal subjects ANP is synthesised and secreted almost exclusively in the atrium, but patients with congestive heart failure have increased production in both atria and ventricles in response to increasing atrial stretch.[6 7] Previous studies suggest that neurohumoral markers play a role not only in left ventricular dysfunction[9] but also in right ventricular dysfunction.[10 11] However, their value as markers of right ventricular dysfunction and their relation to other quantitative determinants of right ventricular function in asymptomatic or minimally symptomatic patients with congenital heart disease are as yet unknown.

In this study we investigated plasma concentrations of BNP and ANP in asymptomatic or minimally symptomatic patients who had chronic right ventricular pressure overload. Plasma neurohormones were related to right ventricular ejection fraction, determined by magnetic resonance imaging (MRI). MRI is an accurate and reproducible method of determining various quantitative indices of right ventricular function in vivo.[12 13]

Methods

STUDY DESIGN AND PATIENT POPULATION

We studied 21 consecutive asymptomatic or minimally symptomatic outpatients (New York Heart Association functional class I and II) with chronic right ventricular pressure overload caused by congenital heart disease. Seven healthy volunteers matched for sex and age served as controls. Chronic right ventricular pressure overload was diagnosed by Doppler echocardiography (right ventricular systolic pressure > 35 mm Hg). All patients were studied off drug treatment. In each subject valvar

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Table 1 Clinical characteristics of the study population

	Patients	*Volunteers*
Male/female	12/9	4/3
Age (years)	26.6 (8.6)	26.9 (3.9)
NYHA class I/II	13/8	7/0
ccTGA	2	
TGA (Mustard or Senning)	9	
Corrected tetralogy of Fallot	10	
Pulmonary artery stenosis	2	
RV systolic pressure (mm Hg)	36 to 134	
RV EDV/BSA (ml/m^2)	65.3 (23.3)	66.8 (17.6)

Values are mean (SD) or n.
BSA, body surface area; ccTGA, congenitally corrected transposition of the great arteries; EDV, end diastolic volume; NYHA, New York Heart Association; RV, right ventricular; TGA, transposition of the great arteries.

regurgitation (> 10 ml per cardiac cycle) was ruled out by MRI flow measurements. Patients with atrial arrhythmias were excluded from the study for two reasons: first; arrhythmias make MRI images unreliable for analysis because of the triggering problem; second, atrial arrhythmias are known to influence natriuretic peptide concentrations.[14] Patients with chronic renal impairment (serum creatinine > 133 μmol/l) or significant left ventricular abnormalities were also excluded. Informed consent was obtained from all patients and volunteers. The study was approved by the local ethics committee. Clinical characteristics of the study population are listed in table 1.

IMAGING PROTOCOL

Study subjects were placed supine in a 1.5 Tesla MR imaging scanner (Vision, Siemens, Erlangen, Germany). MRI acquisition involved a standardised protocol. Imaging sessions were initiated with scout images to determine the position of the heart in the thoracic cavity. Based on these images an 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, visualising the long axis view in order to localise the atrioventricular valve plane. An ECG triggered, ultrafast, breath held, gradient echo cine sequence (time of repetition (TR) = RR interval, time of echo (TE) = 4.8 ms, matrix size = 256 × 256, field of view (FOV) = 350 mm, flip angle = 20°) was then used to acquire images in the short axis plane in contiguous 10 mm 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, imaging matrix = 256 × 256, and velocity encoding = 250 cm/s.

IMAGE ANALYSIS

A Unix workstation was used for analysis of the magnetic resonance images. MASS (Medis, Leiden, Netherlands) image analysis software was used to display multislice, multiphase images individually and in a movie loop mode. End diastolic (maximum ventricular) and end systolic (minimum ventricular) volume 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 right and left ventricles were outlined manually. Papillary muscles and the moderator band were not included in the ventricular volume measurements. The enclosed right ventricular and left ventricular cross sectional areas were measured by computer, multiplied by section thickness, and summed up according to Simpson's rule to provide left ventricular and right ventricular volumes.

Flow (Medis) image analysis software was used to calculate volumetric flow. Contours of the great artery arising from the right ventricle 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

Before 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 (1111 g for 10 minutes) and stored at −70°C until final analysis. ANP and BNP concentrations were determined using immunoradiometric assay kits (Shionoria, Osaka, Japan).

STATISTICAL ANALYSIS

Differences between the groups were assessed by the unpaired Student's *t* test. Probability values of $p < 0.05$ were considered significant. All p values are two tailed. Linear regression analysis was performed to correlate neurohumoral factors and systolic right ventricular function. For descriptive purposes, quantitative variables with a normal distribution are presented as mean (SD).

Results

Right ventricular ejection fraction in the volunteers was higher than in the patients, at 69.0 (8.2)% *v* 58.0 (12.0)%, respectively; $p < 0.006$ (fig 1A). Left ventricular ejection fraction was 72.3 (7.8)% in volunteers and 68.1 (11.0)% in patients (NS). There was a significant difference in the plasma concentrations of BNP and ANP between patients and volunteers—BNP, patients 5.3 (3.5) pmol/l *v* volunteers 2.3 (1.7) pmol/l ($p < 0.009$); ANP, patients 7.3 (4.5) pmol/l *v* volunteers 3.6 (1.4) pmol/l ($p < 0.05$) (fig 1B). In both patients and volunteers, mean plasma ANP concentrations were higher than mean plasma BNP concentrations. The right ventricular ejection fraction was inversely correlated with BNP ($r = 0.65$; $p < 0.0002$; fig 2A), and ANP ($r = 0.61$; $p < 0.002$; fig 2B). No correlation was found between left ventricular ejection fraction and BNP ($r = 0.2$; NS) or ANP ($r = 0.52$; NS). Similarly, no correlation was shown between the level of right ventricular systolic pressure and plasma BNP ($r = 0.20$; NS) or ANP ($r = 0.07$; NS). End diastolic right ventricular volume corrected for body surface area did not differ between patients and controls (65.3 (23.3) *v* 66.8 (17.6) ml/m^2, respectively; NS). There were no differences in ventricular volumes between the different patient groups included in the study.

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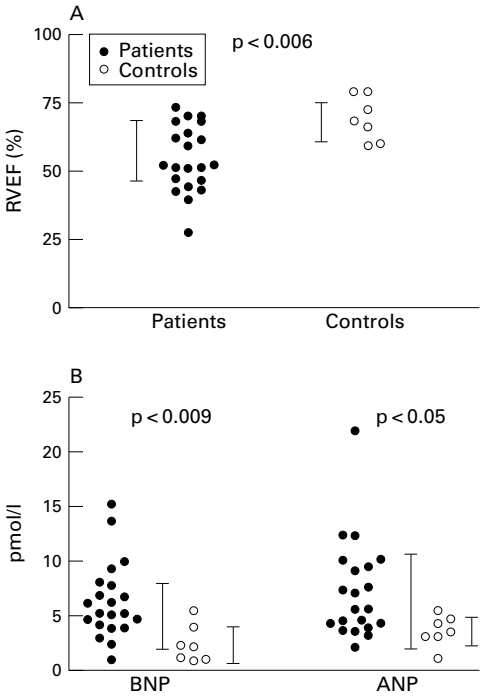

Figure 1 (A) Scatter graph showing right ventricular ejection fraction (RVEF) in patients and controls. (B) Scatter graph showing plasma concentrations of brain (BNP) and atrial (ANP) natriuretic peptide in patients and controls. Values are means; error bars = SD.

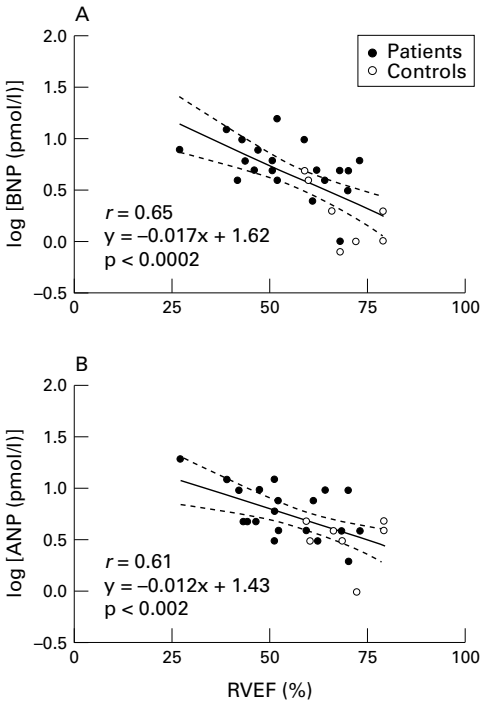

Figure 2 (A) Correlation between plasma brain natriuretic peptide (BNP) and right ventricular ejection fraction (RVEF). (B) Correlation between plasma atrial natriuretic peptide (ANP) and RVEF. Solid lines represent the linear regression and dotted lines are 95% confidence intervals of the regression line.

Discussion

Our study showed that right ventricular ejection fraction was significantly lower in asymptomatic and minimally symptomatic patients with chronic right ventricular pressure overload than in healthy volunteers. In addition, concentrations of both BNP and ANP were significantly raised in the patients compared with the controls. We found an inverse correlation between right ventricular ejection fraction and the plasma neurohormones. There was no difference in left ventricular ejection fraction between patients and controls, and no correlation between left ventricular ejection fraction and the neurohormones.

To our knowledge, this is the first study to show a correlation between right ventricular systolic function and the neurohormones BNP and ANP in asymptomatic or minimally symptomatic patients with chronic right ventricular pressure overload from congenital heart disease.

Raised plasma concentrations of BNP and ANP have been reported before in patients with left ventricular systolic dysfunction.[4 15 16] Tsutamoto and colleagues stated that a high BNP may predict mortality and morbidity in asymptomatic patients with left ventricular dysfunction.[17] Until now, the relation between neurohumoral factors and right ventricular function has received little attention. Only one previous study, by Nagaya and colleagues,[10] showed increased BNP and ANP concentrations in symptomatic patients with right ventricular pressure and volume overload. In the current study, we observed increased plasma concentrations of natriuretic peptides in asymptomatic or minimally symptomatic patients with chronic right ventricular pressure overload.

Previous reports have indicated that in healthy subjects plasma ANP is higher than plasma BNP,[8] whereas in patients with manifest left or right ventricular failure BNP is increased substantially relative to ANP.[6 10] In our patients plasma BNP did not exceed plasma ANP, and concentrations of both neurohormones remained relatively low. This can be explained by the asymptomatic nature of early right ventricular dysfunction. On the basis of these data one could speculate that—as with left ventricular failure—plasma concentrations of BNP will start to exceed those of ANP as deterioration occurs from asymptomatic to symptomatic right ventricular failure.

No correlation was found between right ventricular systolic pressure and the plasma neurohormones, indicating that a rise in the plasma concentrations of these agents is a marker of right ventricular dysfunction rather than of increased right ventricular pressure in patients with congenital heart disease. This is consistent with the results of Nagaya and colleagues in patients with pulmonary hypertension.[10]

Despite the importance of detecting early right ventricular failure, the diagnosis of early asymptomatic right ventricular dysfunction remains difficult.[2] Although non-invasive imaging techniques allow right ventricular function to be determined, these techniques are not suitable for large scale, cost effective application. Our data suggest that raised plasma BNP and ANP in asymptomatic or minimally symptomatic patients may be helpful as an early

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marker of right ventricular systolic dysfunction, and thus a potentially cost effective investigation in patients at risk of right ventricular failure. Monitoring changes in plasma BNP and ANP may provide quantitative follow up data in such patients.

Interpretation of plasma BNP concentrations must be done within an appropriate clinical context, because BNP may rise in various other pathological processes[18]—for example, renal failure,[19] significant left ventricular disease,[4] and atrial arrhythmias.[14]

CONCLUSIONS

There is a significant inverse correlation between right ventricular ejection fraction and the plasma neurohormones BNP and ANP in asymptomatic or minimally symptomatic patients with chronic right ventricular pressure overload and congenital heart disease. Increased plasma BNP and ANP concentrations in these patients could be a useful early indicator of right ventricular systolic dysfunction, and monitoring changes in plasma BNP and ANP may provide quantitative follow up of right ventricular function. These results set the scene for larger studies of hormone guided follow up of asymptomatic patients with congenital heart disease who are at risk of right ventricular failure.

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