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NT-proBNP reflects right ventricular structure and function in pulmonary hypertension

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ABSTRACT: The aim of the current study was to investigate whether alterations in N-terminal pro brain natriuretic peptide (NT-proBNP) reflect changes in right ventricular structure and function in pulmonary hypertension patients during treatment.

The study consisted of 30 pulmonary hypertension patients; 15 newly diagnosed and 15 on long-term treatment. NT-proBNP, right heart catheterisation and cardiac magnetic resonance imaging measurements were performed, at baseline and follow-up.

There were no significant differences between newly diagnosed patients and those on treatment at baseline or follow-up with respect to NT-proBNP, haemodynamics and right ventricular parameters. Relative changes in NT-proBNP during treatment were correlated to the relative changes in right ventricular end-diastolic volume index (r=0.59), right ventricular mass index (r=0.62) and right ventricular ejection fraction (r= -0.81).

N-terminal pro brain natriuretic peptide measurements reflect changes in magnetic resonance imaging-measured right ventricular structure and function in pulmonary hypertension patients. An increase in N-terminal pro brain natriuretic peptide over time reflects right ventricular dilatation concomitant to hypertrophy and deterioration of systolic function.

KEYWORDS: Magnetic resonance imaging, N-terminal pro brain natriuretic peptide, pulmonary hypertension, right ventricle

Pulmonary hypertension (PH) is a disease characterised by increased pulmonary vascular resistance leading to chronic right ventricular (RV) pressure overload. Without treatment, patients have a poor prognosis and die of right heart failure. Right atrial pressure, measured by right heart catheterisation, has been shown to be an important prognostic parameter in pulmonary arterial hypertension (PAH) [1]. Recently, the search for a less invasive prognostic marker was successful with the detection of the cardiac hormone brain natriuretic peptide (BNP) and its biologically inactive alternative N-terminal pro brain natriuretic peptide (NT-proBNP). Research performed in patients with a diseased left ventricle, *i.e.* ischemia, pressure or volume overload, showed the clinical and prognostic value of this hormone [2–5]. NAGAYA *et al.* [6] showed in idiopathic PAH patients that a high BNP level at baseline and a further increase in BNP at follow-up was associated with a poor prognosis. In patients with increased RV load it has been shown that BNP is related to: functional status, initial haemodynamics, RV systolic function and structure [7–9]. In PAH patients, BNP parallels alterations in haemodynamics and functional status during treatment [10]. Although these findings emphasise the clinical significance of the change in BNP after long-term therapy in PAH patients, insight into changes in RV structure and systolic function in relation to BNP are lacking. Furthermore, in previous reports BNP was measured, however, it is unclear whether measurements of NT-proBNP show similar relations. Therefore, the aim of the current study was to assess the temporal relationships of NT-proBNP with RV structure and systolic function in PH patients.

METHODS

Study design

In total, 30 PH patients with a mean (range) age of 48 (21–80) yrs and a male to female ratio of eight to 22 were studied. Of these, 15 patients were newly diagnosed and 15 patients were receiving long-term treatment (27±16 months) at the start of the study and were being

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re-evaluated for treatment effect and/or add on therapy. All patients had a mean pulmonary artery pressure >25 mmHg, pulmonary capillary wedge pressure <15 mmHg at right heart catheterisation and normal systemic blood pressure and renal function (serum creatinine <120 $\mu ml \cdot L^{-1}$).

PH due to left sided heart diseases, interstitial lung disease or hypoxemia, was excluded by further diagnostic tests (echocardiography, high-resolution computed tomography scan and lung function test) following the 2003 Venice consensus guidelines on the diagnosis and treatment of PAH [11]. The different aetiologies of PH were distributed as follows: idiopathic PAH (n=19); PAH related to the limited type of systemic sclerosis (n=7); PAH related to HIV (n=1); PAH related to porto-pulmonary shunts (n=1); and PH due to chronic thrombo-embolic disease (n=2).

Measurements were repeated after a mean (range) follow-up period of 10.5 (3.7–15.6) months. Patients were treated with bosentan (n=11), nifidipine (n=1), epoprostenol (n=6), sitaxentan (n=2) and combination therapy consisting of epoprostenol-sildenafil (n=5) or bosentan-sildenafil (n=5). The study was part of a project that evaluates and monitors cardiac function in PAH by magnetic resonance imaging (MRI), approved by the Committee on Research Involving Human Subjects of the VU University medical centre (Amsterdam, Netherlands). Written informed consent was obtained from all patients.

Cardiac catheterisation

Diagnostic right heart catheterisation was performed with a balloon tipped, flow directed 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp, Irvine, CA, USA). The patient was in a stable condition lying supine and breathing room air. Right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressures were measured. Blood was sampled, with the catheter positioned in the main pulmonary artery to assess mixed venous oxygen saturation. Left ventricular pressure measurements and coronary angiogram were performed in two patients with PAH associated with systemic sclerosis and old age (>70 yrs) to exclude coronary artery disease. Arterial oxygen saturation was measured from blood sampled from the radial or femoral artery. Cardiac output was assessed by the Fick method and pulmonary vascular resistance was calculated using the standard formula.

MRI measurements

MRI was performed on a Siemens 1.5T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), using a four-element phased array cardiac receiver coil, according to the MRI protocol described previously [12]. Perpendicular to the four chamber end-diastolic image, a stack of consecutive short-axis breath hold cine images were made with temporal resolution of 34 ms, and slice distance of 10 mm. From the stack of parallel short-axis cine images, quantitative analysis of volumes and geometry was performed by manual detection of endocardial and epicardial borders on each slice, using the MR Analytical Software System (Medis, Leiden, Netherlands).

The MRI data was analysed blind to the NT-proBNP levels at the time of analysis. The interventricular septum was considered part of the left ventricle. RV end-diastolic volume (RVEDV) and RV myocardial mass (RVM) were calculated and indexed (indicated with suffix I). Stroke volume (SV) was measured using magnetic resonance phase-contrast flow quantification (velocity sensitivity 150 $cm \cdot s^{-1}$, and temporal resolution 22 ms). The ejection fraction (EF) was calculated as right ventricular (RVEF=100 × SV/RVEDV) and left ventricular EF LVEF=100 × (SV/left ventricular end-diastolic volume).

Plasma NT-proBNP levels

Blood was sampled from a peripheral vein with the patient at rest, within 24 h of MRI measurements and right heart catheterisation. NT-proBNP plasma levels were analysed on an ELECSYS 1010 bench top analyser (Roche Diagnostics, Almere, Netherlands). Temporal changes were expressed as percentage of the baseline values.

Statistical analyses

Results are reported as median and interquartile range, unless otherwise indicated. Wilcoxon signed rank test was performed for comparison of baseline and follow-up values. Baseline NT-proBNP was correlated to haemodynamics and MRI measurements. Similar correlations were assessed for the relative changes in NT-proBNP, haemodynamics and MRI measurements. Correlation analyses were performed with a Spearman rank correlation test. A p-value <0.05 was considered statistically significant.

RESULTS

At the start of the study 6-min walk distance, haemodynamics and MRI measurements were not different between newly diagnosed and patients on long-term treatment. Furthermore, there was no clinically relevant difference in functional class among the newly diagnosed patients and those on treatment. The coronary angiogram performed in the two patients with PAH associated with systemic sclerosis did not reveal coronary artery disease. Furthermore, LVEF measured by MRI was >60% in all patients.

Haemodynamics and MRI measurements

The functional status, haemodynamics and MRI measurements at baseline and follow-up are summarised in table 1. At baseline most patients were in New York Heart Association functional class III. Haemodynamic measurements showed that all patients had significant pulmonary hypertension, which is also reflected by the MRI measured RV parameters; *i.e.* RV dilatation, hypertrophy and impairment of systolic function. A small but significant haemodynamic improvement in pulmonary artery pressure and pulmonary vascular resistance index was observed during follow-up. However, this improvement was not reflected by RV parameters or a decrease of NT-proBNP (normal values 68–112 $pg \cdot mL^{-1}$) [13].

Correlations of NT-proBNP with haemodynamics and MRI measurements at baseline

At baseline, serum NT-proBNP was related to invasively measured haemodynamic variables, such as right atrial pressure, mixed venous saturation and cardiac index, but not to pulmonary artery pressure or pulmonary vascular resistance index. Furthermore, NT-proBNP was positively related to RVEDV index, and inversely related to RVEF, but not related to RV mass index (table 2).

TABLE 1 Functional status, haemodynamics and magnetic resonance imaging measurements at baseline and follow-up

	Baseline	Follow-up
Functional status		
NYHA II:III:IV	5:22:3	13:15:2
6-MWD m	425 (342–509)	461 (370–591)
Haemodynamics		
P_{ra} mmHg	6 (4–10)	6 (3–10)
P_{rv} syst mmHg	72 (56–93)	65 (56– 82)*
P_{rv} diast mmHg	9 (5–13)	9 (6–13)
mPAP mmHg	47 (38–57)	43 (32–52)*
S_{V,O_2} %	67 (58–71)	66 (61–74)
CI L·min^{-1}·m^2	2.8 (2.0–3.6)	3.1 (2.6–4.0)
PVRI dynes·s·cm^{-5}·m^{-2}	384 (236–528)	324 (160–430)*
P_{pcw} mmHg	6 (5–9)	7 (5–11)
MRI measurements		
RVEDVI ml·m^{-2}	92 (76–111)	98 (76–109)
RVMI g·m^{-2}	38 (29–51)	45 (31–53)
RVEF %	34 (23–50)	38 (31–53)
NT-proBNP pg·mL^{-1}	333 (192–1363)	541 (99–1027)

Data are presented as n or median (interquartile range). NYHA: New York heart association; 6-MWD: 6-min walk distance; P_{ra}: right atrial pressure; P_{rv}: right ventricular pressure; syst: systolic; diast: diastolic; mPAP: mean pulmonary arterial pressure; S_{V,O_2}: mixed venous oxygen saturation; CI: cardiac index; PVRI: pulmonary vascular resistance index; P_{pcw}: pulmonary capillary wedge pressure; RVEDVI: right ventricular end-diastolic volume index; RVMI: right ventricular mass index; RVEF: right ventricular ejection fraction; NT-proBNP: N-terminal pro brain natriuretic peptide. *: $p<0.05$, between baseline and follow-up.

TABLE 2 Correlation of N-terminal pro brain natriuretic peptide with haemodynamics, right ventricular parameters and 6-min walk distance at baseline (6-MWD)

Variable	Correlation coefficient r	p-value
P_{ra} mmHg	0.49	0.008
mPAP mmHg	0.28	0.143
S_{V,O_2} %	-0.64	<0.001
CI L·min^{-1}·m^2	-0.45	0.019
PVRI dynes·s·cm^{-5}·m^{-2}	0.30	0.122
RVEDVI mL·m^{-2}	0.53	0.004
RVMI g·m^{-2}	0.37	0.052
RVEF %	-0.79	<0.001
6-MWD m	-0.51	0.008

Data are presented as n. P_{ra}: right atrial pressure; mPAP: mean pulmonary arterial pressure; S_{V,O_2}: mixed venous oxygen saturation; CI: cardiac index; PVRI: pulmonary vascular resistance index; RVEDVI: right ventricular end-diastolic volume index; RVMI: right ventricular mass index; RVEF: right ventricular ejection fraction.

Correlation of the relative change in NT-proBNP with RV parameters during follow-up

Although for the whole group most of the variables did not change significantly during follow up, there was a considerable individual variation in the relative change of RV parameters, as shown in figure 1. The relative changes in NT-proBNP were closely related to the relative changes in RV end-diastolic volume index ($r=0.59$, $p=0.001$), mass index ($r=0.62$, $p<0.001$) and inversely to RVEF ($r= -0.81$, $p<0.001$; fig. 1). The patient with the significant increase of NT-proBNP at follow-up had an unsuccessful transition on bosentan after being stable on epoprostenol therapy for >4 yrs.

DISCUSSION

The present study showed that in PH patients, NT-proBNP parallels changes in RV structure and systolic function. BNP is a cardiac hormone synthesised and cleaved together with NT-proBNP from a pro-hormone in ventricular and atrial cardiomyocytes. The potential advantages of NT-proBNP measurements above BNP are a longer plasma half-life, biological inactivity and lower biological variability [14, 15]. However, head-to-head comparison of BNP and NT-proBNP in patients with left ventricular dysfunction could not confirm a clinically significant advantage of NT-proBNP over BNP [16, 17]. Under normal physiological conditions, the left side of the heart determines BNP and NT-proBNP levels [13]. Elevated NT-proBNP in PH patients presumably results from augmented synthesis and release by the overloaded RV.

In the current study, baseline NT-proBNP was related to haemodynamics characterising RV pressure overload. MRI measurements showed RV dilatation, hypertrophy and impaired function. Compared with earlier studies [7, 8, 18], the present study showed similar, but modest, correlations of NT-proBNP and haemodynamics. In addition, NT-proBNP was related to RV end-diastolic volume index and showed a strong inverse relationship with RV ejection fraction.

The relationship of NT-proBNP and RV mass index was not significant. In the study by NAGAYA *et al.* [8], BNP was correlated to RV mass and systolic function, but not to RV volume. The different findings between the present study and earlier studies might be explained by the small variation on the haemodynamic data at baseline in the current study. Furthermore, RV hypertrophy is a compensatory physiological mechanism aimed at normalising wall stress. In case of RV volume and/or pressure overload, an increase in RV mass decreases wall stress and as a consequence may reduce NT-proBNP. This may explain the absence of a significant correlation between NT-proBNP and RV mass index at baseline.

In the present study, long-term follow-up showed that changes in NT-proBNP paralleled changes in RV structure and function. The long-term follow-up study by LEUCHTE *et al.* [10] has shown that in PH patients there are parallel changes in haemodynamics and BNP confirming the work of a 3-month follow-up study and studies performed in an acute setting [8, 19, 20]. In addition, the current study shows that temporal changes in NT-proBNP are associated with alterations in RV structure and particularly systolic function.

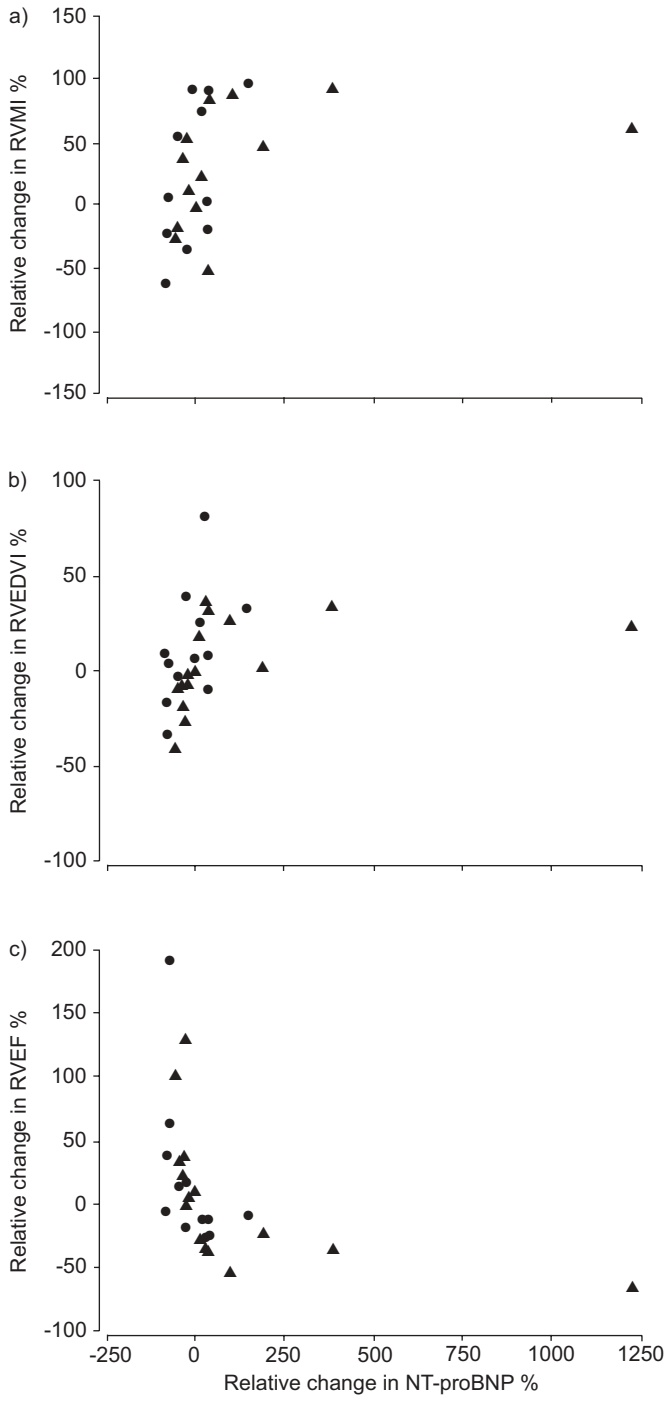

FIGURE 1. Correlation of the relative change in N-terminal pro brain natriuretic peptide (NT-proBNP) with the relative change in a) right ventricular mass index (RVMI), r=0.62, p<0.001; b) right ventricular end-diastolic volume index (RVEDVI), r=0.59, p<0.001; and c) right ventricular ejection fraction (RVEF), r= -0.81, p<0.001, in patients with pulmonary hypertension. ●: newly diagnosed patients (n=15); ▲: patients on treatment (n=15).

Ventricular dilatation has been suggested to be a pathological state of cardiac remodelling. However, data on RV dilatation and outcome in PH patients are lacking. Although an echocardiography study showed that absolute RV end-diastolic area measured as a singular parameter was not a significant predictor of outcome [21], the present finding does not exclude the prognostic importance of a change in RVEDV over time and should be investigated in future studies.

The relative change in NT-proBNP showed a positive correlation with the change in RVM. Since NT-proBNP is produced by the cardiomyocyte, this correlation suggests that hypertrophied RV cardiomyocytes are associated with increased transcription of the proBNP gene and NT-proBNP release. Impaired RV systolic function predisposes to right heart failure which is associated with an increased risk of death [22] in idiopathic PAH patients. The present data shows that NT-proBNP is valuable parameter marking alterations in RV systolic function. The correlations of the change in RV parameters and NT-proBNP were stronger than between baseline RV parameters and NT-proBNP. This supports the idea that serial measurements have higher sensitivity than baseline values. Taking the current results and previous research [18] into account, it may be hypothesised that the importance of an increasing NT-proBNP level, despite treatment, is directly related to failing RV systolic function.

The recent work by FIJALKOWSKA *et al.* [18] has shown that NT-proBNP is related to RV structure and function, and serves as a prognostic parameter in PH patients. The current study showed that serial changes in NT-proBNP closely reflect alterations in RVEDV and EF, which are likely to be important prognostic markers in PH [22]. Since impaired RVEF predisposes to right heart failure, serial measurements might be valuable in monitoring disease. Although it has been shown that singular NT-proBNP measurements are of prognostic value in PH patients [18], longitudinal NT-proBNP measurements might potentially be superior with respect to prognosis, as was shown for BNP [6]. In addition, serial NT-proBNP measurements may be valuable in clinical decisions when there is limited access to MRI or under circumstances where a patient's condition does not allow invasive procedures.

Included in the present study were newly diagnosed patients and patients being initially treated at the beginning of the study. Although there were no clinically relevant differences between the two patient groups, the present study group was too small to draw any conclusion on the influence of treatment on NT-proBNP. The small study group and the limited changes in haemodynamic variables are important limitations of this study, which might explain the absence of significant correlations of several haemodynamic variables with NT-proBNP. An assumption in the present study was that PAH treatment does not directly affect NT-proBNP production. However, there is some evidence from experimental animal research that the phosphodiesterase-5 inhibitor sildenafil might act on the cardiac myocytes directly [23], therefore, a direct effect on the myocardial production of NT-proBNP cannot be excluded.

In conclusion, the data from the present study showed that the change in NT-proBNP over time provides indirect information on right ventricular remodelling and the change in right ventricular systolic function, measured by magnetic resonance imaging. Elevated N-terminal pro brain natriuretic peptide levels over time reflect progressive right ventricular dilatation

and impaired systolic function, and thus should be interpreted as a sign of right ventricular failure.

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