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NT-proBNP can be used to detect RV systolic dysfunction in pulmonary hypertension

Short Title

NT-proBNP and RV failure in PH

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ABSTRACT

Background

Right ventricular systolic dysfunction (RVSD) at baseline (pre-treatment) predicts early death in patients with pulmonary hypertension (PH). RVSD can, however, only be detected reliably by prohibitively invasive or expensive techniques. N-terminal B-type natriuretic peptide concentration ([NT-proBNP]) correlates with RV function in PH, however, an [NT-proBNP] threshold that indicates RVSD in individual patients has not previously been determined.

Methods

25 patients with PH (Pulmonary Arterial Hypertension (19) or Chronic Thromboembolic PH (6)) underwent Cardiovascular Magnetic Resonance (CMR) imaging and NTproBNP measurement at baseline. [NT-proBNP] was correlated against RV dimensions and ejection fraction (RVEF) measured directly by CMR imaging. The ability of NT-proBNP to detect RVSD (defined as a CMR-derived RV ejection fraction (RVEF) > 2 standard deviations below control values) was tested and predictors of [NT-proBNP] identified.

Results

[NT-proBNP] correlated negatively with RVEF. RVSD was present in 9/25 patients. An [NT-proBNP] threshold of 1685 pg/ml was sensitive (100 %) and specific (94 %) in detecting RVSD. RVEF and RV mass index independently predicted [NT-proBNP].

Conclusion

In PH, a baseline [NT-proBNP] > 1685 ng/l suggests RVSD, and thus an increased risk of early death. NT-proBNP could prove useful as an objective, non-invasive means of identifying patients with PH who have RVSD at presentation.

INTRODUCTION

Pulmonary Hypertension (PH) is a rare condition characterised by increased resistance to pulmonary blood flow, progressive right ventricular (RV) systolic dysfunction (RVSD) and early death. Without specific treatment up to 50 % of patients diagnosed with PH will die within 2 years; usually as a result of RVSD. (1) Evidence of RVSD at baseline (i.e. pre-treatment) has previously been associated with an increased mortality risk in earlier studies that identified RVSD either by invasive haemodynamic measurements (1-5) or by the detection of overt clinical signs of RV failure (i.e. patients within Class IV of the WHO classification of disease severity). (1)

Accurate assessment of baseline RV function is therefore desirable in all patients with PH. This information can help identify individuals in whom prompt invasive assessment ± the initiation of disease targeted therapy is appropriate. Because early RV dysfunction is difficult to detect on clinical examination, trans-thoracic echocardiography is often used for this purpose. (6) Although inexpensive and widely available, RV ejection fraction (RVEF) can only be estimated indirectly from measurements acquired in two dimensions by echocardiography. Variables derived by this method that reflect RV function and provide useful prognostic information in PH are either complicated to define and therefore reliant upon an experienced operator (e.g. the Tei index) (7) or detected most frequently in patients in whom RV failure is already clinically overt (e.g. a pericardial effusion). (2)

Cardiac Magnetic Resonance (CMR) imaging has recently emerged as the new gold standard for assessment of the RV in PH and other diseases (8, 9); it allows image acquisition in any plane and at almost any angle, allowing direct measurement of RV volumes and RVEF. At present, CMR imaging remains too expensive for routine clinical use and is therefore not available in many PH centres, an alternative non-invasive method of identifying baseline RVSD in PH that was objective, operator independent and widely available would, therefore, be clinically useful.

B-type natriuretic peptide (BNP) and N-terminal-pro BNP (NT-proBNP) are released from both cardiac ventricles in response to raised chamber pressure or volume overload. (10) Previous studies have shown that circulating BNP concentration correlates with invasive pulmonary haemodynamics, (11, 12) RVEF measured by computed tomography (CT), (12) survival (13, 14) and the response to therapy (15, 16) in PH patients. NT-proBNP, which is biologically inactive, is more stable *in vivo* and *in vitro* than BNP (17) and can therefore be used instead of BNP as cardiovascular biomarker in various disease states. Circulating NT-proBNP concentration ([NT-proBNP]) has recently been shown to correlate with invasive pulmonary haemodynamics (18), survival and echocardiography derived measures of RV function in PH, (19) however a threshold [NT-proBNP] which indicates that RVSD is present in an individual patient has yet to be determined, perhaps because of insufficient precision in the previous reference method of RV systolic function measurement (echocardiography).

We aimed to relate [NT-proBNP] to RV volumes and systolic function measured directly by CMR imaging and to identify an [NT-proBNP] threshold for the detection of RVSD in patients with PH at baseline.

METHODS

Patients

We performed a prospective cross-sectional study and recruited 30 consecutive patients who attended for diagnosis and baseline assessment at the Scottish Pulmonary Vascular Unit (Glasgow, UK). All subjects underwent routine clinical assessment including right heart catheterisation to establish a diagnosis of PH. The following were used as inclusion criteria for the study:

1. A diagnosis of either Pulmonary Arterial Hypertension (PAH) or Chronic Thromboembolic PH (CTEPH) reached by conventional diagnostic methods. (6)

2. Informed written consent to a study protocol approved by our local institutional review committee.

Patients were excluded from the study (after review of their past medical history, admission blood tests and transthoracic echocardiogram and before CMR imaging and NT-proBNP measurement) if they met any of the following exclusion criteria:

1. Evidence of congenital heart disease (CHD), either at echocardiography or as a previous diagnosis. Patients with CHD were excluded because differing patterns of natriuretic peptide release have been demonstrated in conditions that cause RV volume overload, such as CHD, in comparison to those that cause RV pressure overload (e.g. PAH and CTEPH). (20)

2. A history of any other condition that might cause elevation of [NT-proBNP]. These include:

    a. Ischaemic heart disease (21)

    b. Myocardial infarction (22)

    c. LV systolic dysfunction (23)

    d. Systemic hypertension (24)

    e. Left-sided valvular heart disease (25)

    f. Chronic renal impairment (26) or an abnormal serum creatinine on admission to our unit (normal was defined as < 120 $\mu moll^{-1}$)

    g. Diabetes Mellitus (27) or a fasting blood glucose on admission to the SPVU of > 6.1 $mmoll^{-1}$

3. CMR-related exclusion criteria included:

    a. Indwelling cardiac pacemaker

    b. Claustrophobia.

On the basis of these criteria, 5/30 patients were excluded from the final analysis (atrial septal defect (2/5), chronic renal impairment (1/5), significant mitral regurgitation (1/5) and systemic hypertension (1/5)). The remaining 25 subjects

underwent CMR imaging and venous blood sampling for [NT-proBNP] within 24 hours of invasive assessment. The final diagnoses reached in these 25 patients were, idiopathic PAH (IPAH) in 11/25, CTEPH in 6/25 and PAH associated with connective tissue disease (PAH-CTD) in 8/25. At the time of the study no patient had received any disease-targeted therapy (i.e. Prostacyclin analogues, Bosentan, Sildenafil or calcium channel blockers) for PH.

Twelve control subjects, with no history of any cardio-respiratory disease underwent CMR imaging to provide local control values for ventricular dimensions and function. All control subjects were staff of the Western Infirmary, Glasgow, UK and were subject to the same exclusion criteria as PH patients. Controls were approached individually and asked to participate. All controls gave informed written consent but did not undergo right heart catheterisation or NT-proBNP measurement.

Between PH patients and controls there were no significant differences in mean age (PH: 60 (± 12), Controls: 57 (± 12), $p = 0.455$) or mean systemic blood pressure (PH: 95 (± 13), Controls: 92 (± 17), $p = 0.536$). PH (17 ♀: 8 ♂) and control populations (8 ♀: 4 ♂) were well sex-matched.

Venous blood sampling and measurement of NT-proBNP

After at least 20 minutes of recumbent rest, 5 mls of venous blood was drawn from the antecubital fossa of all 25 PH patients immediately prior to CMR imaging. Blood samples were drawn into vacuum-sealed containers containing ethylenediamine tetraacetic acid and immediately centrifuged at 3000 rpm for 15 minutes using a

PK110 centrifuge (ALC, Winchester, VA, USA). Supernatant was then removed and individual samples were coded, labelled and stored at -80˚C until analysis. NT-proBNP analysis was performed on an ELECSYS 2010 bench top analyser utilising a chemiluminescent assay with a CV < 5 % (Roche Diagnostics, Lewes, UK). All biochemical analyses were performed by a single operator (JJM) who was blinded to haemodynamic, CMR and clinical results. NT-proBNP measurements are subsequently quoted as plasma concentration (ng/l).

CMR image acquisition

CMR imaging was undertaken on a 1.5 T MRI scanner (Sonata Magnetom, Siemens, Germany) using a protocol that we have recently described in detail. (28) An identical CMR protocol was followed in control subjects. Fast imaging as steady state free precession (SSFP) cines (TrueFISP by Siemens) were utilised throughout. Methodological details which are of particular importance include standardised imaging parameters of: TR/TE/flip angle/voxel size/FoV = 3.14 ms/1.6 ms/60°/2.2 x 1.3 x 8.0 mm/340 mm; 8-mm imaging slices were used with a 2-mm inter-slice gap. Short axis imaging was initiated at the atrioventricular valve plane identified on a horizontal long axis view of the heart, and then propagated sequentially to the cardiac apex, providing complete coverage of left and right ventricles.

CMR image analysis

CMR images in PH patients and controls were analysed by a single operator (KB) using the Argus analysis software (Siemens, Erlangen, Germany). Individual scans

were coded by number and analysed in batches by KB who was blinded to the identity and haemodynamic results of any given subject at the time of analysis. CMR analysis was performed before blood samples were analysed for NT-proBNP levels. RV and LV volumes (RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV)) were determined by manual planimetry of selected short axis images as described previously. (29, 30) Right and left ventricular stroke volume (RVSV & LVSV), ejection fraction (RVEF and LVEF) and mass (RVM and LVM) were determined as previously described. (29, 30) RV mass was determined as RV free wall mass. The Interventricular Septum (IVS) was considered part of the LV. RVM index (RVMI) was determined as RVM/LVM. (31) Left and right ventricular volumes were corrected for Body Surface Area (BSA) and reported as indexed measurements (RVEDVI, RVESVI, LVEDVI, and LVESVI).

Clinical assessment and right heart catheterisation

A standard diagnostic algorithm (6) was employed in the clinical assessment of all PH patients studied. This included right heart catheterisation using established techniques (6), isotope perfusion lung scanning and CT pulmonary angiography in all patients. If CTEPH was suspected following these initial investigations selective pulmonary angiography was performed in the catheterisation laboratory (CTEPH was confirmed using this algorithm in 6/25 PH patents).

Statistical analysis

For all variables a normal distribution was verified using histograms and Kolmogorov-Smirnov tests. Non-normally distributed values ([NT-proBNP] and right atrial pressure) were logarithmically transformed and all correlation analyses were performed using Pearson's method. Comparisons between PH patients and controls (and between sub-groups of PH patients) were made using an independent samples (unpaired) t-test (using Welch's correction if appropriate).

2x2 contingency tables were used to calculate the sensitivity and specificity of various plasma concentrations of NT-proBNP as a means of detecting RVSD. RVSD was defined as an RVEF < 42 % (this constituted an RVEF > two standard deviations below the mean RVEF of the control population (66 (±7) %)). The plasma [NT-proBNP] with the greatest diagnostic accuracy (that which produced the lowest number of false positive and false negative results) was chosen as a "threshold" value for the detection of RVSD. Negative and positive predictive values ((NPV and PPV) for results either side of this NT-proBNP threshold were then calculated. The implications of an above threshold result were quantified by likelihood ratios and Fisher's exact test.

To identify independent predictor(s) of circulating [NT-proBNP], variables significantly associated with [NT-proBNP] (RVEDVI, RVESVI, RVEF, RVMI, LVSVI, mean PAP, systolic PAP, diastolic PAP, cardiac index, pulmonary vascular resistance and mixed venous oxygen saturation (MVO_2) (see table 3)) were entered into a multivariable stepwise linear regression model, in which NT-proBNP was the

dependent variable. Co-variables with a correlation co-efficient ≥ 0.8 were tested within separate regression models to avoid the effects of co-linearity. All statistical analyses were performed using GraphPad Prism 4 for Windows (GraphPad Software Inc., San Diego, USA), were two-sided and assumed a significance level of 5 %. All values are presented as mean (±1SD) unless otherwise stated.

RESULTS

Right heart catheterisation

Invasive measurements acquired in the PH patients are summarised in Table 1.

CMR imaging

Ventricular dimensions and systolic function of the 25 PH patients and 12 controls are presented in Table 2. In summary, RVEDV, RVESV, RV mass and RVMI were significantly increased, and RVEF significantly depressed in PH patients relative to control subjects. LVEDV and LVSV were significantly lower in PH patients compared with controls. All LV measurements, in both PH patients and controls, were within previously published normal limits. (29, 32) Where available we have used CMR normal ranges determined by SSFP imaging sequences similar to those employed in our own study. (32)

Correlation analyses

[NT-proBNP] was non-normally distributed in the population studied. Median (interquartile range) [NT-proBNP] was 669 (94-2615) ng/l. After logarithmic transformation mean (± 1SD) $\log_{10}$ [NT-proBNP] was 2.71 (± 0.77). A complete list of correlation co-efficients and accompanying p-values for variables compared with [NT-proBNP] is presented in Table 3. There was a powerful negative logarithmic correlation between [NT-proBNP] and RVEF (see figure 1). With the exception of LVSV, there was no significant correlation between [NT-proBNP] and LV measurements (see Discussion).

Differences in $\log_{10}$ [NT-proBNP] in subgroups of PH patients

There were no statistically significant differences in [NT-proBNP] based on gender (mean $\log_{10}$ [NT-proBNP] was 2.7 (± 0.6) in males and 2.7 (± 0.8) in females) or aetiology of PH (mean $\log_{10}$ [NT-proBNP] was 2.6 (± 0.8) in PAH (2.4 (± 0.9) in IPH, 3.0 (± 0.7) in PAH-CTD) and 3.0 (± 0.5) in patients with CTEPH).

RV systolic dysfunction

RV systolic dysfunction (RVSD) was present in 9/25 PH patients (36 %). The distribution of [NT-proBNP] values for the 9 patients with RVSD and the 16 patients without RVSD were normal. Mean [NT-proBNP] was significantly higher in patients with RVSD (4127 (± 2951) ng/l) in comparison to those without RVSD (354 (± 435) ng/l) ($t = 3.813$, $df = 8$, $p = 0.005$).

Diagnostic performance of NT-proBNP

NT-proBNP performed best at a plasma concentration of 1685 ng/l, detecting RVSD with 100 Sensitivity % (95 % CI (63.0 % to 100 %)) and 94 % Specificity (95% CI (71.3 % to 99.9 %)). 1685 ng/l was therefore chosen as the threshold value for RVSD detection.

17/25 patients had an [NT-proBNP] below the 1685 ng/l threshold. 16/17 of these patients were true negatives (i.e. RVEF was normal (≥ 42 %)) and one was a false negative. In the false negative subject RVEF measured 34 % and [NT-proBNP] was 669 ng/l. The negative predictive value of a low [NT-proBNP] was, therefore, 94 %.

8/25 patients had an [NT-proBNP] > 1685 ng/l. RV systolic dysfunction was demonstrated by CMR imaging (RVEF < 42 %) in all of these individuals. Thus, the positive predictive value of a high [NT-proBNP] was 100 %. These results are presented graphically in figure 1. Based on likelihood ratio testing, individuals with an NT-proBNP above the 1685 ng/l threshold were 17 times more likely to have RVSD than those with below threshold results.

Predictors of [NT-proBNP]

Because RVEF correlated powerfully with RVMI ($r = -.854$, $p < 0.001$) these variables were entered into two separate multivariable linear regression models in which [NT-proBNP] was the dependent variable. In these models, RVEF (Odds Ratio = -0.035, 95 % CI (-0.052 – -0.018, $p < 0.001$) and RVMI (Odds Ratio = 2.254, 95 %

CI (1.403 – 3.106, $p < 0.001$) proved the only independent predictors of circulating [NT-proBNP].

Discussion

In the current study we report a close correlation between RVEF, measured directly by CMR imaging and [NT-proBNP] in patients with PH, assessed prior to any treatment. A previous study, reported by Nagaya *et al*, demonstrated a similar relationship between RVEF, measured by electron beam CT imaging, and BNP concentration in a similar cohort of patients. (12) Our study is of additional interest to this previous report for three important and clinically relevant reasons.

1) In routine clinical practice most centres use NT-proBNP, not BNP, to aid clinical decision making in heart failure and a variety of other conditions. As previously discussed, this is because NT-proBNP is more stable *in vivo* and *in vitro* than the active BNP molecule itself. (17)

2) The study by Nagaya *et al* used EBCT imaging to measure RVEF, while we have utilized CMR imaging as our reference method. Temporal resolution is better with CMR imaging (33) without the need for ionizing radiation or intravenous contrast. (34) As a result, CMR has emerged over recent years as the gold standard for detailed study of the RV (9, 35-37) and has become an established modality for the physiological assessment of PH patients in cross-sectional studies, (31, 38-40) longitudinal follow-up studies (41) and clinical trials of therapy (16). EBCT, in contrast, is not used routinely to assess PH patients. The current study is therefore

useful as it defines the relationship between [NT-proBNP] and RV volumes and ejection fraction measured directly by CMR imaging.

3) In addition to a correlation between [NT-proBNP] and RVEF, we found that an [NT-proBNP] > 1685 ng/l (detected in 8/25 patients) proved a sensitive marker of RVSD (sensitivity 100 %). Below this threshold only one false negative result was returned, suggesting that RVSD is very unlikely when circulating [NT-proBNP] is less than 1685 ng/l, at least in patients assessed at baseline, before treatment initiation (negative predictive value 94 %)). Stratifying patients either side of this NT-proBNP threshold may prove useful as an operator independent, objective means of classifying individuals at presentation based upon their probability of having RVSD and thus an increased risk of early death.

Physiological determinants of NT-proBNP

Several variables correlated closely with circulating [NT-proBNP] in our study (see table 3). Of these variables only RVEF and RVMI, analysed within separate regression models to avoid the effects of co-linearity, proved independent predictors of [NT-proBNP]. Although we have previously shown that RVMI relates linearly to mean PAP in PH (31) it has not been proven to predict early death in patients with this condition. For this reason we defined our primary goal as the detection of RVSD, not RV hypertrophy, using [NT-proBNP]. The influence of RV hypertrophy (as RVMI) should, however, be discussed and perhaps acknowledged as a potential confounder of our results. The vast majority (7/8 (88 %)) of patients in our study with above threshold NT-proBNP levels indicative of RVSD also had RV hypertrophy

(defined as a RV mass > 84 g (> 2 SDs above mean RV mass of the control population (48 (± 18) g)) reflecting the co-variation between RVMI, RVEF and [NT-proBNP] that we found. Despite this, RVEF appeared to be an important determinant of circulating [NT-proBNP] in our study.

Clinical implications

A recent study reported by Quaife *et al* (43) demonstrated a close correlation between RVEF and RV wall stress, which is the principal stimulus to NT-proBNP release in PH. This relationship may explain the usefulness of NT-proBNP as a means of detecting RVSD that we report. In interpreting our results it is worth considering the findings of Fijalkowska *et al* who recently examined the prognostic significance of NT-proBNP in PH. (19) Non-survivors in this study were identified by an [NT-proBNP] > 1400 ng/l. Since non-survivors with PH are likely to die from RV failure, and [NT-proBNP] correlated powerfully with echocardiographic measures of RV systolic function in this study, it seems plausible that the 1400 ng/l threshold reported in the Fijalkowska study and our own 1685 ng/l threshold reflect genuine RV systolic dysfunction in the patients studied.

Clearly, the true clinical significance of the [NT-proBNP] threshold for RVSD (1685 ng/l) identified in our study can only be determined in a longitudinal survival analysis. For this reason it is difficult to justify detailed proposals for the future use of NT-proBNP in clinical practice at this time. Our findings indicate, however, that NT-proBNP, measured during a patient's first consultation at a specialist PH centre could, in conjunction with existing means of assessing RV function (i.e. clinical examination

and echocardiography) help identify patients with prognostically significant RVSD. Assuming other reasons for a high NT-proBNP were excluded patients with a high [NT-proBNP] could then be invasively assessed at an early stage and treatment initiated if appropriate. Although there is no evidence yet that early treatment of PH alters prognosis *per se*, it is known that a history of overt RV failure before treatment initiation is associated with an increased mortality risk. (44) Prompt initiation of therapy in patients with high NT-proBNP levels and sub-clinical RVSD may, therefore, avoid the development of overt RV failure and reduce early mortality.

RV ejection fraction

In the current study we utilized RVEF to define RVSD. Although historical data have suggested that RVEF does not reflect RV systolic function alone (since it is also dependant upon right ventricular afterload) (45-47), RVEF determined by echocardiography and radionuclide ventriculography has recently been shown to predict adverse outcomes (cardiac death or deterioration) in patients with PH. (48) Until longitudinal survival studies are reported in which CMR-derived variables are assessed the true prognostic significance of CMR-derived RVEF, and the cut-off value of 42 % used here to define RVSD cannot, however, be known.

NT-proBNP and LV stroke volume

We found a statistically significant relationship between [NT-proBNP] and LV stroke volume (LVSV) but no correlation between [NT-proBNP] and RV stroke volume (RVSV). This apparent contradiction reflects the inaccuracy of CMR-planimetry in

determining true (i.e. forward) stroke volume in patients with significant valvular regurgitation. CMR-planimetry of a dilated RV with significant tricuspid valve regurgitation will always overestimate true *forward* RVSV because a proportion of the ejected blood volume will move backwards through the incompetent tricuspid valve. Since *forward* LVSV and *forward* RVSV will, over several heart beats, be equivalent in the absence of any communicating shunt, and since no PHT patient in our study had any evidence of mitral regurgitation, the statistically significant relationship that we found between LVSV and [NT-proBNP] likely reflects an underlying correlation between [NT-proBNP] and true *forward* RVSV that is obscured by this predictable measurement error. Although CMR-planimetry may not always accurately determine forward RVSV in PH patents, RVEF still reflects the systolic contractile function of the ventricle, assessment of which was the primary aim of this study. An alternative confounder to the CMR-planimetry results might be the trabeculation of the RV. Despite this concern, we have found acceptable intra-observer variation for ventricular mass and ejection fraction (3.8-7.4 % and 3.4-4.4 %, respectively) measured by this method in our unit (unpublished data).

Study limitations

The relatively small number of patients involved in our study is of concern in the proposal of a specific cut-off level for use in the detection of RVSD in clinical practice. CMR imaging, however, represents an extremely accurate and reproducible gold standard of RVEF limiting the number of patients required for such studies. [NT-proBNP] can be affected by a number of factors including renal function, left-sided heart disease, age, gender (49) and recent exertion. In the current study we excluded

patients with other reasons for a high [NT-proBNP] and standardised the timing and the conditions surrounding NT-proBNP sampling. A recent study has reported a close relationship between MVO_2 and [NT-proBNP] in patients with cyanotic congenital heart disease and PH (42), however, MVO_2 did not predict [NT-proBNP] in our study and patients with CHD were specifically excluded. We emphasise that our conclusions can only be applied to selected PH patients assessed in this manner. In addition, it is not known whether therapies such as Sildenafil, which acts directly upon the cardiac myocyte, (50) will affect the relationship we report between RVEF and [NT-pro BNP] or whether any observed fall in [NT-pro BNP] during treatment will prove proportional to an improvement in RV systolic function. Further insight into these issues is necessary to understand the clinical significance of changes in [NT-proBNP] during treatment.

Conclusion

We believe that our study is the first to utilise a specific NT-proBNP threshold (1685 ng/l) as a means of detecting RVSD in patients with PH. The method we describe of classifying patients either side of such a threshold is simple, inexpensive and most importantly, non-invasive and may help to inform the largely subjective process of stratifying new patients for invasive assessment and the initiation of disease targeted therapy.

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FIGURE LEGENDS

Figure 1

CMR imaging and NT-proBNP measurements were acquired in 25 patients with Pulmonary Hypertension. [NT-proBNP], after logarithmic transformation correlated powerfully with RV ejection fraction (RVEF) ($r = -0.66$, $p < 0.001$). The horizontal line indicates the [NT-proBNP] threshold chosen (1685 ng/l) for the detection of RV systolic dysfunction (RVSD). The vertical line indicates the RVEF (42%) used to define RVSD. Only one false negative result (solid triangle) was returned.

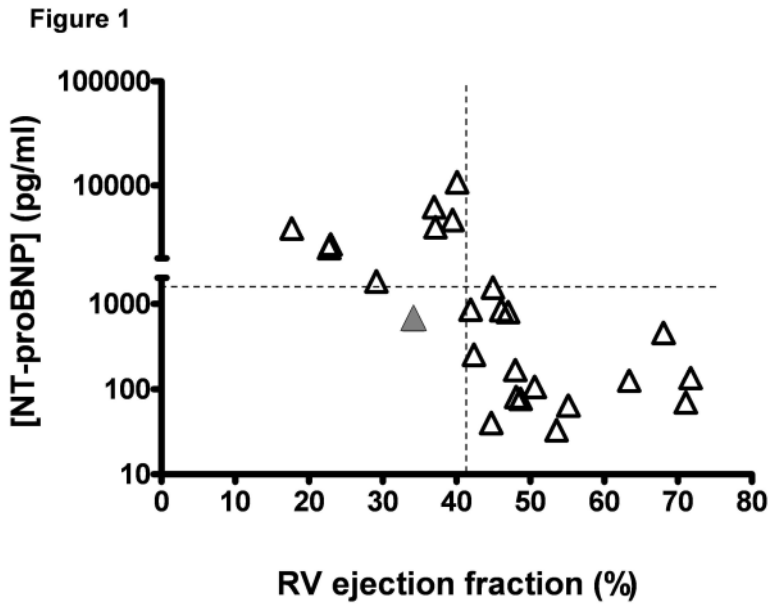

Table 1. Results of right heart catheterisation in 25 patients with Pulmonary Hypertension

		Mean (± SD)
PAP * (mmHg)	Systolic PAP	72 (± 20)
	Diastolic PAP	24 (± 9)
	Mean PAP	43 (± 12)
Cardiac Index (l/min/m2)		2.4 (± 0.6)
PVR † (mmHg/l/min)		10 (± 6)
RAP ‡ (mmHg)		8 (± 8)
MVO_2 § saturation (%)		65 (± 8)

* PAP: Pulmonary Arterial Pressure, † PVR: Pulmonary Vascular Resistance, ‡ RAP: Right Atrial Pressure, § MVO_2: Mixed Venous Oxygen

Table 2. Ventricular dimensions and function by cardiovascular magnetic resonance imaging in patients with Pulmonary Hypertension (PH) and controls. Values are mean (± SD) unless stated.

	PH (n= 25)	Controls (n= 12)	p value
Right Ventricle			
EDV * (ml)	170 (± 57)	129 (± 46)	**0.033**
ESV † (ml)	99 (± 53)	45 (± 22)	**< 0.0001**
Stroke Volume (ml)	71 (± 19)	83 (± 29)	0.126
Ejection Fraction (%)	45 (± 14)	66 (± 7)	**< 0.0001**
Mass (g)	84 (± 34)	48 (± 18)	**0.0002**
RV Mass Index	0.87 (± 0.24)	0.41 (± 0.04)	**< 0.0001**
Left Ventricle			
EDV * (ml)	86 (± 25)	116 (± 36)	**0.005**
ESV † (ml)	28 (± 16)	31 (± 14)	0.579
Stroke Volume (ml)	60 (± 17)	85 (± 24)	**0.0009**
Ejection Fraction (%)	71 (± 9)	74 (± 7)	0.218
Mass (g)	94 (± 23)	120 (± 51)	0.117

* EDV; End-diastolic volume, † ESV; End-systolic Volume

Table 3. Correlation co-efficients between $\log_{10}$ [NT-proBNP] (ng/l) and measurements acquired in 25 Pulmonary Hypertension patients at cardiovascular magnetic resonance imaging and right heart catheterisation

Variable	r co-efficient	p-value
Right Ventricle		
EDVI * (ml/m^2)	0.556	**0.004**
ESVI † (ml/m^2)	0.655	**<0.001**
SVI ‡ (ml/m^2)	-0.279	0.177
Ejection Fraction (%)	-0.66	**<0.001**
Mass (g)	0.613	**0.001**
RV Mass Index	0.713	**<0.001**
Left Ventricle		
EDVI (ml/m^2)	-0.376	0.064
ESVI (ml/m^2)	-0.08	0.705
SVI (ml/m^2)	-0.508	**0.01**
Ejection Fraction (%)	-0.323	0.115
Mass (g)	0.196	0.349
Invasive Measurements		
Mean PAP §	0.501	**0.011**
Systolic PAP	0.435	**0.03**
Diastolic PAP	0.622	**<0.001**
Cardiac Index	-0.523	**0.007**
Pulmonary Vascular Resistance	-0.566	**0.003**
Mixed Venous O_2 Saturation	-0.541	**0.009**

* EDVI; End-diastolic volume index, † ESVI; End-systolic volume index, ‡ SVI; Stroke volume index, § PAP; Pulmonary Artery Pressure