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Heart Failure

Correlation of Right Ventricular Wall Stress With Plasma B-Type Natriuretic Peptide Levels in Patients With Pulmonary Hypertension

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Background: This study was designed to investigate the relationship between right ventricular wall stress (RVWS) and plasma B-type natriuretic peptide (BNP) levels in patients with pulmonary hypertension (PH).

Methods and Results: The 57 consecutive PH patients and 8 control subjects were enrolled. Right heart catheterization (RHC), echocardiography, and BNP measurements were performed, and RVWS and left ventricular wall stress (LVWS) were calculated with the formula based on Laplace's law. Systolic RVWS and end-diastolic RVWS were higher in PH patients compared with controls (systolic RVWS: 77±41 vs. 17±5 kdynes/cm^2 (P<0.0001), end-diastolic RVWS: 15±12 vs. 8±2 kdynes/cm^2 (P<0.0005)). Univariate analyses showed that logBNP at baseline correlated with systolic RVWS (r=0.58, P<0.0001) and end-diastolic RVWS (r=0.61, P<0.0001). We performed multivariate regression analysis and determined that end-diastolic RVWS was an independent determinant of logBNP in patients with PH. In addition, change in plasma BNP levels after treatment correlated with change in systolic RVWS (r=0.70, P<0.0001) and change in end-diastolic RVWS (r=0.68, P<0.0001).

Conclusions: Both systolic and end-diastolic RVWS were elevated in patients with PH, and correlated with the symptoms of PH. End-diastolic RVWS was an independent determinant of plasma BNP levels in PH patients.

Key Words: B-type natriuretic peptide; Pulmonary hypertension; Right ventricular wall stress

Over recent decades numerous therapies have been developed to treat pulmonary hypertension (PH), but an aggressive approach targeting multiple pathways in PH may lead to better treatment outcomes.[1–5] The functional status of the right ventricle (RV) remains the key determinant of prognosis, and the management of right heart failure (RHF) is essential for many PH patients,[6,7] whose RV function can become impaired, even though pressure overload is reduced after PH treatment.[7] The increased ventricular wall stress (WS) is the main determinant of changes to the ventricles, and reduction of right ventricular WS (RVWS) is an important treatment strategy for PH patients.[8] WS is a parameter related to the ventricular dimensions and pressure and is inversely proportional to wall thickness. WS cannot be measured directly, but its value can be estimated using the formula based on Laplace's law: WS=0.334×D×P/WT (1+WT/D); where D=dimension, P=pressure, and WT=wall thickness. D and WT are measured by echocardiography or magnetic resonance imaging (MRI), and P is determined by right heart catheterization (RHC).[9] In the case of left ventricular (LV) disease, the LV end-diastolic WS correlates with plasma B-type natriuretic peptide (BNP) levels.[10–13] BNP is a natriuretic hormone, used as a biomarker of RV dysfunction in patients with PH.[14,15] Plasma BNP levels are associated with disease severity and exhibit a strong independent association with mortality rates in these patients;[16,17] thus, the normalization of BNP levels has been suggested as a goal in PH treatment.[18,19] BNP is secreted from the ventricles in response to stretching of cardiac myocytes, and plasma BNP levels are demonstrated to be increased in LV and RV diseases.[7] Previous studies reported the main stimulus of BNP secretion as cardiac WS in patients with LV disease,[10,11,20,21] but no studies have investigated the association between RVWS

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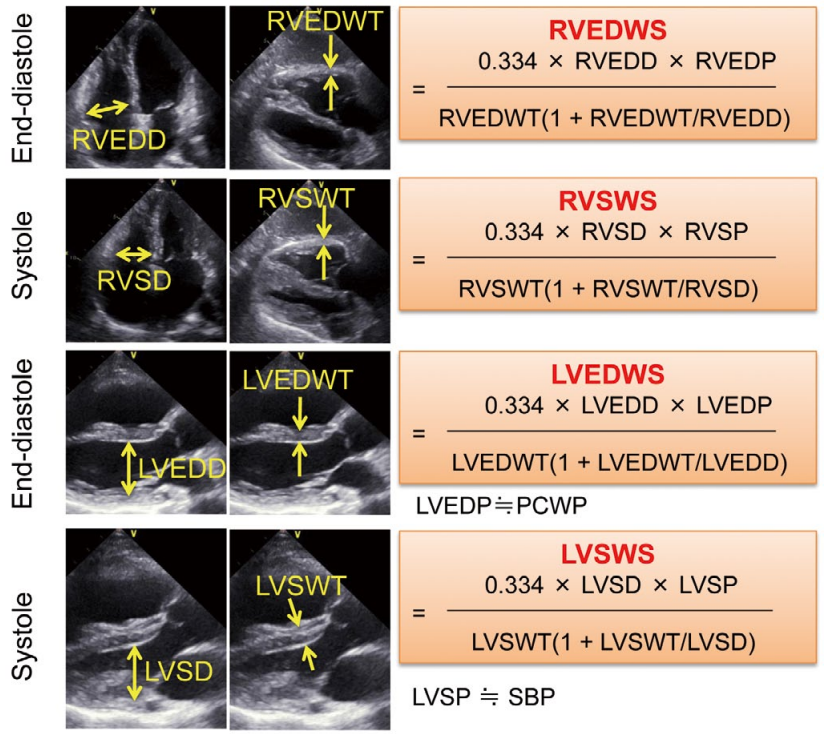

Figure 1. Measurement of wall stress (WS) in the right and left ventricles using data obtained from echocardiography and right heart catheterization. LVEDWS, left ventricular end-diastolic wall stress; LVEDD, left ventricular end-diastolic dimension; LVEDP, left ventricular end-diastolic pressure; LVEDWT, left ventricular end-diastolic wall thickness; LVSD, left ventricular systolic dimension; LVSP, left ventricular systolic pressure; LVSWS, left ventricular systolic wall stress; LVSWT, left ventricular systolic wall thickness; PCWP, pulmonary capillary wedge pressure; RVEDD, right ventricular end-diastolic dimension; RVEDP, right ventricular end-diastolic pressure; RVEDWS, right ventricular end-diastolic wall stress; RVEDWT, right ventricular end-diastolic wall thickness; RVSD, right ventricular systolic dimension; RVSP, right ventricular systolic pressure; RVSWS, right ventricular systolic wall stress; RVSWT, right ventricular systolic wall thickness; SBP, systolic blood pressure.

Table 1. Characteristics of the Study Patients With PH

	PH group
N (total)	57
Age (years)	60±15
Male	13 (23)
Body mass index	22.6±4.3
BNP, pg/mL	262±602
WHO functional class	
I	0 (0)
II	20 (35)
III	25 (44)
IV	12 (21)
Type of PH	
CTEPH	25 (44)
CTD-PAH	20 (35)
IPAH	6 (10)
Other	6 (10)
Therapy	
Balloon pulmonary angioplasty	23 (40)
Anticoagulation	29 (51)
Diuretics	24 (42)
Vasodilator	
Endothelin-receptor antagonist	26 (46)
PDE-5 inhibitor	21 (37)
Beraprost	16 (28)
Epoprostenol	9 (16)

Values are mean±SD, n (%). CTD-PAH, connective tissue disease-associated pulmonary artery hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary artery hypertension; PDE-5, phosphodiesterase type 5; PH, pulmonary hypertension; WHO, World Health Organization.

and BNP in patients with RV dysfunction caused by PH. The purpose of the present study was to investigate the clinical significance of RVWS and to clarify the relationship between RVWS and BNP in patients with PH.

Methods

Patients

We enrolled 57 consecutive patients with PH diagnosed by RHC. Their mean pulmonary artery pressure (PAP) was ≥25 mmHg; they all underwent echocardiographic examinations. We set out the following exclusion criteria to avoid the influence of renal failure or left HF on BNP levels: a serum creatinine level ≥2.0 mg/dL, LV ejection fraction <50%, and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg. The control group comprised 8 subjects who were examined by echocardiography and RHC, and were cleared of cardiopulmonary disease as a result, and whose BNP levels were <18 pg/mL and mean PAP was <20 mmHg. The Ethics Committee of Kagoshima University unanimously approved this study, and informed consent was given by all patients.

Measurement of Plasma BNP Levels

Blood samples from the patients were obtained before performing the echocardiographic examination. Plasma BNP levels were measured using EDTA-plasma samples and a chemiluminescent enzyme immunoassay on the PATHFAST analyzer (Mitsubishi Chemical Medience Co., Tokyo, Japan).

Echocardiographic Measurements

Echocardiographic examinations were performed using the Vivid 7 or E9 (GE Healthcare, Tokyo, Japan) ultrasound systems, and the following parameters were measured

Table 2. Comparison of Wall Stress, Hemodynamics and Echocardiographic Measurements Between the PH and Control Groups at Baseline

	PH (n=57)	Control (n=8)	P value
Age (years)	60±15	65±8	NS
Male	13 (23)	4 (50)	NS
Body mass index	22.6±4.3	24.3±2.7	NS
BNP (pg/mL)	262±602	13±4	<0.005
Wall stress (kdynes/cm²)			
Systolic RVWS	77±41	17±5	<0.0001
End-diastolic RVWS	15±12	8±2	<0.0005
Systolic LVWS	63±22	58±22	NS
End-diastolic LVWS	8±4	6±1	NS
Hemodynamic measurements			
Systolic PAP (mmHg)	61±18	25±3	<0.0001
Mean PAP (mmHg)	37±10	16±2	<0.0001
Systolic RVP (mmHg)	60±18	28±3	<0.0001
End-diastolic RVP (mmHg)	8±4	7±1	NS
PCWP (mmHg)	7±5	8±3	NS
Mean RAP (mmHg)	5±4	5±2	NS
CO (L/min)	4.0±1.0	4.7±0.8	<0.05
SV (mL)	51±16	69±13	<0.01
Echocardiographic measurements			
Systolic RVD (mm)	32±8	14±5	<0.0001
End-diastolic RVD (mm)	40±9	21±4	<0.0001
Systolic RVWT (mm)	7.3±1.6	5.4±0.8	<0.0001
End-diastolic RVWT (mm)	6.4±1.4	4.9±0.8	<0.0005
RV FAC (%)	30±13	42±13	<0.05
LVEF (%)	71±9	65±9	NS
TAPSE (mm)	19±3	NA	
TR PFV (m/s)	3.6±0.7	2.2±0.2	<0.0001

Values are mean±SD, n (%). BNP, B-type natriuretic peptide; CO, cardiac output; FAC, fractional area change; LVEF, left ventricular ejection fraction; LVWS, left ventricular wall stress; NA, not available; NS, not significant; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVD, right ventricular dimension; RVP, right ventricular pressure; RVWS, right ventricular wall stress; RVWT, right ventricular wall thickness; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TR PFV, tricuspid regurgitation peak flow velocity.

according to the guidelines of the American Society of Echocardiography.[22] Systolic RV dimension (RVD) and end-diastolic RVD, of which the basal cavity of the RV was measured in the apical RV-focused 4-chamber view in the systolic and end-diastolic periods. Systolic RVWT and end-diastolic RVWT, which were measured in the subcostal view or apical RV-focused 4-chamber view in the systolic and end-diastolic periods. For calculation of left ventricular WS (LVWS), systolic LV dimension (LVD), end-diastolic LVD, systolic LVWT, and end-diastolic LVWT were measured. For estimation of PH status and RV function, tricuspid regurgitation peak flow velocity (TR PFV), RV fractional area change (RV FAC), and tricuspid annular plane systolic excursion (TAPSE) were measured.

Hemodynamic Examination

RHC was performed after the echocardiographic examination to measure multiple variables: systolic PAP, diastolic PAP, mean PAP, pulmonary vascular resistance (PVR), systolic RV pressure (RVP), end-diastolic RVP, mean right atrial pressure (RAP), cardiac output (CO), stroke volume (SV), PCWP as a substitute for end-diastolic LV pressure (LVP), and systolic blood pressure (SBP) as a substitute for systolic LVP.

Calculation of WS

WS was calculated using the following formula based on Laplace's law:[9] WS=0.334×D×P/WT (1+WT/D), where D=dimension, P=pressure, and WT=wall thickness. As shown in **Figure 1**, end-diastolic RVWS was calculated using basal end-diastolic RVD, end-diastolic RVWT, and end-diastolic RVP measured by RHC. Systolic RVWS was calculated using systolic RVD, systolic RVWT, and systolic RVP. End-diastolic left ventricular WS (LVWS) was calculated using end-diastolic LVD, end-diastolic LVWT, and PCWP as a substitute for end-diastolic LVP. Systolic LVWS was calculated using systolic LVD, systolic LVWT, and SBP as a substitute for systolic LVP. We then compared these RV and LV functional parameters with BNP levels.

Reproducibility of Measurements

Two independent observers repeated 10 measurements of systolic RVWS and end-diastolic RVWS to investigate the interobserver and intraobserver differences. Differences in the measurements by the 2 observers were obtained to estimate interobserver variability. The same observer repeated the 10 measurements, and intraobserver variability was calculated.

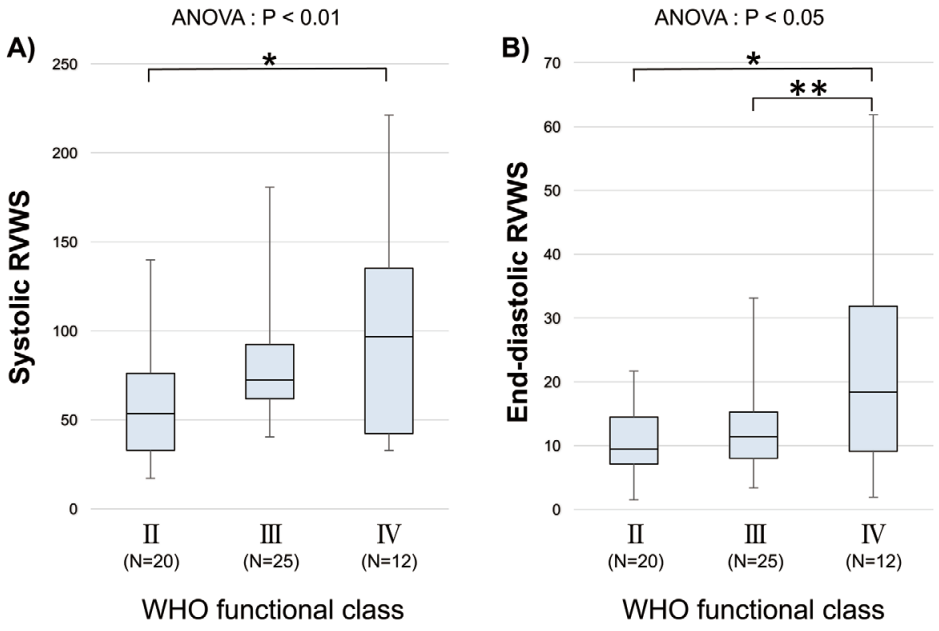

Figure 2. Relationship between WHO functional class and RVWS. Systolic RVWS (**A**) and end-diastolic RVWS (**B**) are presented as box (25th percentile, median, 75th percentile) and whisker (10th and 90th percentiles) plots. *P<0.05 vs. WHO class II, **P<0.05 vs. ANOVA, analysis of variance; WHO class III. RVWS, right ventricular wall stress; WHO, World Health Organization.

Statistical Analysis

Data are expressed as mean±SD or median (interquartile range) as appropriate. Comparisons between the PH group and controls were performed using Student's t-test. BNP levels were log-transformed (logBNP) to obtain a normal distribution. Comparisons of parameters among 3 groups (WHO functional classes II, III and IV) were performed using analysis of covariance (ANOVA) followed by Tukey-Kramer's HSD post hoc test. The relationships between logBNP and RV measurements (RVWS, echocardiographic measurements, and RHC data) were analyzed with simple linear regression analyses. Determinants of logBNP and BNP changes after treatment (ΔBNP) were explored by multiple stepwise regression analyses. All statistical analyses were performed with JMP version 6 (SAS Institute, Cary NC, USA). A P-value <0.05 was considered to be statistically significant.

Results

Patients' Characteristics

The patients' characteristics are summarized in **Table 1**. The mean age of the patients was 60±15 years, and 13 patients (23%) were male; all patients were diagnosed as having PH by RHC studies. The subtypes of PH in these patients were: chronic thromboembolic PH (CTEPH: 44%), connective tissue disease-associated PH (CTDAPH: 35%), idiopathic pulmonary artery hypertension (10%), and others (10%); 34 patients (60%) were de novo patients at baseline who were diagnosed as having PH for the first time. The mean BNP level was 262±602 pg/mL. After measurements at baseline, the PH patients had the following therapies: balloon pulmonary angioplasty for CTEPH (40%), anticoagulation (51%), diuretics (42%), endothelin-receptor antagonist (46%), phosphodiesterase type 5 inhibitor (37%), beraprost (28%), and epoprostenol (16%).

Comparison of RVWS Between PH Patients and Controls

As shown in **Table 2**, we compared RVWS, LVWS, echocardiographic measurements and cardiac hemodynamic values between the PH and control groups. Both systolic RVWS and end-diastolic RVWS were higher in PH patients compared with controls (systolic RVWS: 77±41 vs. 17±5 kdynes/cm^2 (P<0.0001), end-diastolic RVWS: 15±12 vs. 8±2 kdynes/cm^2 (P<0.0005)). As compared with controls, the PH group showed significant increased systolic PAP or RVP, enlarged RV dimensions, increased RVWT and decreased RV FAC.

RVWS and WHO Functional Class

To determine the relationship between the functional status of PH and RVWS, the relationships between RVWS and WHO functional class of PH patients were assessed by ANOVA and Tukey-Kramer's HSD post hoc test. **Figure 2** shows that both systolic and end-diastolic RVWS increased significantly with worsening WHO functional class (systolic RVWS: P<0.01, end-diastolic RVWS: P<0.05). Systolic RVWS in patients with WHO class IV was significantly higher than in patients with WHO class II (**Figure 2A**). End-diastolic RVWS in patients with WHO class IV was significantly higher than in patient with WHO class II or III (**Figure 2B**).

Relationship Between LogBNP and RVWS at Baseline

To investigate the determinants of plasma BNP levels in patients with PH, we analyzed the correlation between logBNP and various parameters (**Table 3**). Univariate analyses demonstrated that logBNP at baseline positively correlated

Table 3. Correlation Between LogBNP and Various Parameters in PH Patients at Baseline (n=57)

	Univariate		Multivariate
	R	P value	P value
Age	0.23	0.09	
Male	0.06	0.65	
Body weight	−0.11	0.43	
Body mass index	−0.14	0.30	
Hb	−0.04	0.75	
Cr	−0.09	0.49	
Wall stress			
Systolic RVWS	0.58	<0.0001	0.086
End-diastolic RVWS	0.61	<0.0001	0.0008
Systolic LVWS	0.03	0.80	
End-diastolic LVWS	−0.06	0.68	
Hemodynamic measurements			
Systolic PAP	0.45	<0.0005	0.94
End-diastolic PAP	0.45	<0.0005	0.31
Systolic RVP	0.44	<0.001	0.70
End-diastolic RVP	0.51	<0.0001	0.85
PVR	0.43	<0.001	0.15
PCWP	0.11	0.43	
Mean RAP	0.44	<0.0001	0.86
CO	−0.32	<0.05	0.64
SV	−0.36	<0.01	0.17
Echocardiographic measurements			
Systolic RVWT	−0.05	0.71	
End-diastolic RVWT	0.06	0.88	
Systolic RVD	0.54	<0.0001	0.43
End-diastolic RVD	0.41	<0.005	0.39
RVFAC	−0.23	0.082	
TAPSE	−0.086	0.53	

Cr, serum creatinine; Hb, hemoglobin concentration; PVR, pulmonary vascular resistance; RVFAC, right ventricular fractional area change. Other abbreviations as in Table 2.

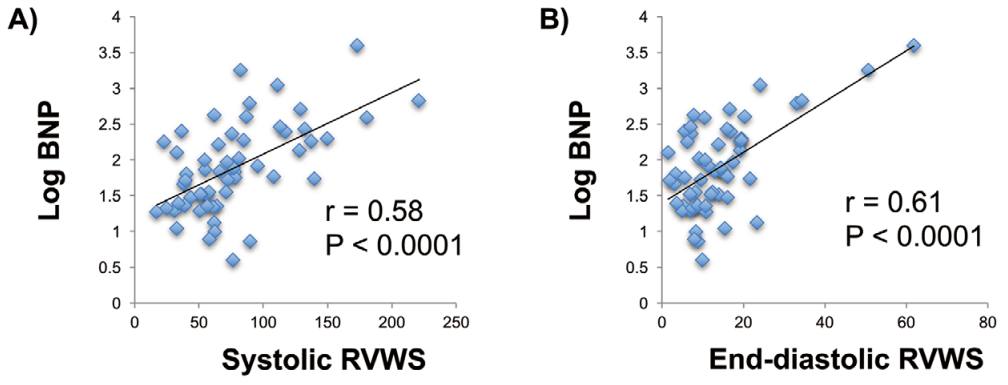

Figure 3. Correlation between logBNP and systolic RVWS (**A**) or end-diastolic RVWS (**B**). BNP, B-type natriuretic peptide; RVWS, right ventricular wall stress.

with systolic RVWS (r=0.58, P<0.0001), end-diastolic RVWS (r=0.61, P<0.0001), systolic PAP (r=0.45, P<0.0005), end-diastolic PAP (r=0.45, P<0.0005), systolic RVP (r=0.44, P<0.001), end-diastolic RVP (r=0.51, P<0.0001), PVR (r=0.43, P<0.001), mean RAP (r=0.44, P<0.0005), systolic RVD (r=0.54, P<0.0001), and end-diastolic RVD (r=0.41, P<0.005) and was negatively correlated with CO (r=−0.32, P<0.05) and SV (r=−0.36, P<0.01). However, logBNP did not correlate with the following variates: age, sex (male), body weight, body mass index, hemoglobin concentration

Table 4. Correlation Between Change in BNP Level and Various Parameters After Treatment of PH (n=45)

	Univariate		Multivariate
	R	P value	P value
Wall stress			
ΔSystolic RVWS	0.70	<0.0001	<0.01
ΔEnd-diastolic RVWS	0.68	<0.0001	<0.005
ΔSystolic LVWS	−0.10	0.51	
ΔEnd-diastolic LVWS	−0.003	0.98	
Hemodynamic measurements			
ΔSystolic PAP	0.58	<0.0001	0.75
ΔEnd-diastolic PAP	0.54	<0.0005	0.18
ΔSystolic RVP	0.62	<0.0001	0.40
ΔEnd-diastolic RVP	0.60	<0.0001	0.89
ΔPVR	0.58	<0.0001	0.06
ΔPCWP	0.15	0.33	
ΔMean RAP	0.47	<0.005	0.70
ΔCO	−0.06	0.67	
ΔSV	−0.25	0.10	
Echocardiographic measurements			
ΔSystolic RVD	0.54	<0.0001	0.93
ΔEnd-diastolic RVD	0.43	<0.005	0.10
ΔSystolic RVWT	0.03	0.86	
ΔEnd-diastolic RVWT	0.10	0.52	

Aabbreviations as in Tables 2,3.

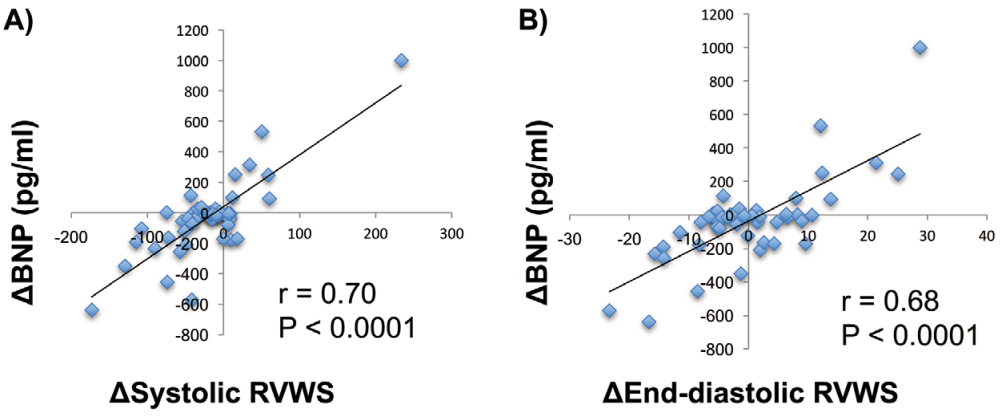

Figure 4. Correlation between changes in BNP and (**A**) change in systolic RVWS and (**B**) end-diastolic RVWS. BNP, B-type natriuretic peptide; RVWS, right ventricular wall stress.

and serum creatinine. **Figure 3** shows that there was a good correlation between logBNP and systolic or end-diastolic RVWS. Multivariate regression analysis identified that end-diastolic RVWS was an independent determinant of logBNP.

Relationship Between Changes in BNP Levels and RVWS

Furthermore, to investigate the association of BNP levels with WS and hemodynamic or echocardiographic data, we analyzed changes in these parameters in 45 patients who underwent echocardiography and RHC before and after PH treatment (**Table 4**). Univariate analyses showed that ΔBNP correlated with Δsystolic RVWS (r=0.70, P<0.0001), Δend-diastolic RVWS (r=0.68, P<0.0001), Δsystolic PAP (r=0.58, P<0.0001), Δend-diastolic PAP (r=0.54, P<0.0005), Δsystolic RVP (r=0.62, P<0.0001), Δend-diastolic RVP (r=0.60, P<0.0001), ΔPVR (r=0.58, P<0.0001), Δmean RAP (r=0.47, P<0.005), Δsystolic RVD (r=0.54, P<0.0001), and Δend-diastolic RVD (r=0.43, P<0.005). As shown in **Figure 4**, there was an excellent correlation between ΔBNP and Δsystolic RVWS (r=0.70, P<0.0001) or Δend-diastolic RVWS (r=0.68, P<0.0001). Multivariate regression analysis showed that Δsystolic RVWS and Δend-diastolic RVWS were independent contributors to ΔBNP.

Reproducibility of Measurements

The mean differences in interobserver and intraobserver variability for the measurement of systolic RVWS and end-diastolic RVWS were: systolic RVWS: 10.6±8.1 or 6.6±7.8%; end-diastolic RVWS: 8.4±4.1 or 5.8±3.5%.

Discussion

The main findings of this study were that BNP elevation correlated with an increase in end-diastolic RVWS, and that RVWS was valuable as a RV-specific parameter to evaluate RV loading conditions.

RVWS as a Parameter of RV Loading Conditions

Norton[23] reviewed definitions of preload and afterload using Laplace's law. The term "preload" can be defined as all factors that contribute to passive ventricular WS at the end of diastole, and the term "afterload" can be defined as all the factors that contribute to total myocardial WS during systolic ejection. Opie and Bers state that preload is often estimated by end-diastolic pressure (EDP), but it is important to remember that the relationship between EDP and end-diastolic volume (EDV) varies between patients.[24] This concept would be more important in RV evaluation that with the LV, because the RV is highly sensitive to changes in afterload, and a minor increase in afterload causes RV enlargement. End-diastolic RVWS can directly reflect both RVEDP and -EDV, so might be a more suitable parameter to assess RV preload compared with RVEDP or -EDV.

RVWS in PH Patients

In the early stages of PH, the RV adapts to the increased PAP by increasing WT to maintain CO. In this compensated phase, RVWS remains normal or is reduced and patients feel few symptoms. Continued pressure overload induces changes in the RV pressure-volume relationship and the increase in RVWS. Finally, in the end stage, the RV dilates, which leads to further increase in RVWS.[25,26] Increased RVWS negatively affects myocardial perfusion,[27] glucose metabolism,[28] and myocardial oxygen consumption.[29,30] RVWS is key to progression of RHF,[8] so evaluation of RVWS is important to assess RV loading conditions in patients with PH.

Measurement of RVWS

RVWS has been estimated using MRI and RHC in patients with PH.[31,32] One study demonstrated that systolic RVWS was significantly higher in patients with idiopathic pulmonary artery hypertension than in controls and that it negatively correlated with the RV EF.[31] Another study demonstrated that end-diastolic RVWS significantly decreased after pulmonary endarterectomy in patients with chronic thromboembolic PH.[32] Further, RVWS can be calculated using echocardiography and RHC and end-diastolic WS correlates with the right atrium size in patients with right-sided congenital heart disease.[9] We used the same method to measure RVWS using echocardiography and RHC. The RV has a complex shape, so its linear dimensions are dependent on probe rotation and different RV views. RVD measurements in the apical RV-focused 4-chamber view are recommended to avoid underestimation.[22] MRI might be more accurate for measuring RV geometry, but it is expensive and not always available.[33] In contrast, the measurement of WS using echocardiography is simpler and a more accepted method compared with MRI; it can be used for frequent evaluations in patients with PH.

Correlation Between WS and BNP

In LV disease, previous studies have reported the relationship between WS and BNP. Wiese et al demonstrated that in isolated atrial and ventricular human myocardium, diastolic overstretch increases BNP gene expression.[34] Iwanaga et al reported that plasma BNP levels strongly correlate with end-diastolic LVWS, not only in patients with systolic HF but also in those with diastolic HF.[11] To our knowledge, no studies have reported a correlation between RVWS and BNP levels. Ours is the first study to demonstrate a good correlation between RVWS and BNP levels. BNP levels can supplement clinical diagnosis of RHF caused by PH, although BNP is a relatively nonspecific biomarker of RV. BNP levels are also higher in patients with LV dysfunction, renal failure, atrial arrhythmia, and so on. On the other hand, RVWS is a RV-specific parameter, and would be useful even for those patients in whom it is not possible to measure BNP. Our results suggested that RVWS was a key factor in BNP secretion, and that estimation of RVWS might be useful for evaluating RV loading conditions in patients with PH.

Study Limitations

First, our study population was not very large, and we did not investigate the correlation between RVWS and BNP levels in each subtype of PH. Therefore, further large studies are needed to confirm our findings and determine the specific relationship between RVWS and BNP levels in each subtype of PH. Second, as the present study was limited to right HF caused by PH, our results cannot be expanded to patients with biventricular HF, in which the major factor in the BNP level is the LV myocardium.

Conclusions

We demonstrated the significance of RVWS measured by echocardiography and RHC in PH patients. Both the systolic and end-diastolic RVWS were associated with the symptoms of PH, and the end-diastolic RVWS was well correlated with plasma BNP levels. RVWS might be a useful parameter to evaluate RV loading conditions in patients with PH.

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Disclosures

The authors have no conflicts of interest to disclose.

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