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Sano, Hiroyuki ; Tanaka, Hidekazu ; Motoji, Yoshiki ; Mukai, Jun ; Suto, Makiko ; Takada, Hiroki ; Soga, Fumitaka ; Hatani, Yutaka ;…

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Echocardiography during Preload Stress for Evaluation of Right Ventricular Contractile Reserve and Exercise Capacity in Pulmonary Hypertension

[1]Hiroyuki Sano, MD, PhD, [1]Hidekazu Tanaka, MD, PhD*, [1]Yoshiki Motoji, MD, PhD
[1]Jun Mukai, MD, [1]Makiko Suto, MD, [1]Hiroki Takada, MD, [1]Fumitaka Soga, MD
[1]Yutaka Hatani, MD, PhD, [1]Hiroki Matsuzoe, MD, PhD, [1]Keiko Hatazawa, MD
[1]Hiroyuki Shimoura, MD, PhD, [1]Junichi Ooka, MD, PhD
[1]Kazuhiko Nakayama, MD, PhD, [1]Kensuke Matsumoto, MD, PhD
[2]Hirotsugu Yamada, MD, PhD, [1]Noriaki Emoto, MD, PhD, [1]Ken-ichi Hirata, MD, PhD

[1]Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[2]Department of Community Medicine for Cardiology, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

***Corresponding Author**
Hidekazu Tanaka, MD, PhD, FAHA, FACC, FASE
Division of Cardiovascular Medicine, Department of Internal Medicine,
Kobe University Graduate School of Medicine, Kobe, Japan
7-5-2, Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan
Tel; +81-78-382-5846, Fax; +81-78-382-5859
E-mail; tanakah@med.kobe-u.ac.jp

Running Head: RV Contractile Reserve and Exercise Capacity in PH

Abstract

Objectives: Pulmonary hypertension (PH) is characterized by marked and sustained elevation of pulmonary vascular resistance and pulmonary artery pressure, and subsequent right-sided heart failure. Right ventricular (RV) function and exercise capacity have been recognized as important prognostic factors for PH. Our aim was to investigate RV contractile reserve and exercise capacity during a leg-positive pressure (LPP) maneuver.

Methods: The study population comprised 43 PH patients and 17 normal controls. All patients underwent echocardiography at rest and during LPP stress. Exercise capacity was assessed by 6-min walk distance for PH patients. RV relative wall thickness was calculated from dividing by RV free-wall thickness by basal RV linear dimensions at end-diastole. RV function was calculated by averaging peak speckle-tracking longitudinal strain from the RV free-wall. RV contractile reserve was assessed as the difference in RV-free wall strain at rest and during LPP stress. Changes in left ventricular stroke volume (ΔSV) during LPP stress were also calculated.

Results: ΔSV and RV contractile reserve of PH patients were significantly lower than of controls (3.6 ±6.0ml vs. 8.5 ±2.3ml, and 8.2 ±11.9 % vs. 14.5 ± 6.6 %; both $p<0.01$). RV contractile reserve of PH patients with ΔSV<3.3mL was significantly lower than of PH patients with ΔSV>3.3mL (3.9 ± 13.2% vs 12.3 ± 8.9%; $p=0.02$). ΔSV had also significant correlation with 6-minute walk distance ($r=0.42$, $p=0.006$). Multivariate regression analysis showed that RV relative wall thickness was an independent determinant parameter of ΔSV during LPP stress for PH patients ($\beta=3.2$, $p=0.003$).

Conclusions: Preload stress echocardiography in response to LPP maneuver, a non-invasive and easy-to-use procedure for routine clinical use, proved to be useful for the assessment of RV contractile reserve and exercise capacity of PH patients.

Key words; Echocardiography; Pulmonary hypertension; Right ventricular function; Stress echocardiography

Introduction

Pulmonary hypertension (PH) remains a poor prognosis disease by progressive obstructive pulmonary vasculopathy leading to increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Right ventricular (RV) contractility in PH patients frequently improves to preserve cardiac output (CO) as an adaptation for the increase in afterload, while wall thickness also increases. However, if RV cannot adapt, an increase in afterload can result in RV enlargement and eccentric hypertrophy, leading to subsequent right-sided heart failure and death[1-3]. Because RV remodeling as well as RV systolic function is closely related to survival of PH patients, its assessment can be one of the most important determinant factors[4-10]. Left ventricular (LV) contractile reserve is reported closely related to prognosis for patients with left-sided heart failure[11, 12], coronary artery disease[13], and valvular heart disease [14]. However, the utility of RV contractile reserve for PH patients remains uncertain. Grunig et al reported that RV contractile reserve may decrease in the early stage of PH before resting RV function and CO start to decline[15]. They also showed that a decline in RV contractile reserve as assessed by stress echocardiography represented subclinical RV dysfunction, which is useful for early diagnosis and associated with prognosis for PH patients[16]. Therefore, the assessment of RV contractile reserve by means of exercise echocardiography for PH patients can be useful, although it can be technically demanding due to exercise intolerance or tachycardia developing during exercise. On the other hand, echocardiography for the evaluation of preload stress in response to a leg-positive pressure (LPP) maneuver which provides a continuous external pressure of 90mmHg around both lower limbs and an effective increase in ventricular preload without a significant increase in either heart rate or blood pressure, has been found to be

useful[17-19]. In addition, this method also makes it possible to assess exercise capacity and is reportedly useful for patients with left-sided heart failure[17-19]. The aim of our study was to investigate whether it is possible to use preload stress echocardiography in response to an LPP maneuver in PH patients for predicting their RV contractile reserve and exercise capacity.

Methods

Study population

We prospectively recruited 43 PH patients diagnosed with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who were admitted to the PH Clinic of Kobe University Hospital between December 2014 and February 2017. PH was defined as resting mean PAP (mPAP) >25mmHg measured by means of right-heart catheterization (RHC). Patients were excluded from the study were those with: (1) pulmonary capillary wedge pressure ≥15mmHg as measured with RHC; (2) atrial fibrillation; (3) coronary artery disease, defined as a single coronary artery stenosis of >50% of the diameter of a major epicardial vessel or a previous history of myocardial infarction; (4) more than moderate mitral and aortic valvular heart disease; and (5) respiratory disease. For comparison, a control group similar in age, gender and LV ejection fraction (LVEF) distribution, consisting of 17 subjects with no history of cardiovascular disease and with completely normal electrocardiograms as well as two-dimensional and Doppler echocardiograms. This study was approved by the ethics committee of our institution (No. 180063).

Echocardiographic examination

All echocardiographic studies were performed with commercially available

echocardiography systems equipped with a 3.5-MHz transducer (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). Digital routine grayscale 2-D cine loops and tissue Doppler cine loops were obtained from three consecutive beats with end-expiratory apnea from standard apical and parasternal views. Mean frame rates were 62±11 Hz for grayscale imaging from the RV-focused apical 4-chamber view used for speckle-tracking analysis. Sector width was optimized to allow for complete myocardial visualization while frame rate was maximized regardless of heart rate. Standard echocardiographic measurements were obtained according to the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[4, 9]. In addition, the assessment of RV relative wall thickness (RV-RWT) was calculated from RV free-wall thickness/basal RV linear dimensions at end-diastole according to the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[4, 9, 20]. Digital data were transferred to dedicated offline software (EchoPAC version BTO8; GE Vingmed Ultrasound AS) for subsequent offline speckle-tracking analysis.

Assessment of RV function by speckle-tracking strain

The assessment of RV function by means of two-dimensional longitudinal speckle-tracking strain from RV free wall was previously described in detail[4, 7-10, 21-25]. Briefly, a region of interest was traced on the RV endocardium at the end-diastole from the RV-focused apical 4-chamber view and a larger region of interest was generated and manually adjusted near the epicardium. The RV was then divided into six standard segments, and six corresponding time-strain curves were generated. RV free-wall longitudinal strain was calculated by averaging each of the three regional peak systolic strains along the entire RV free wall, and was expressed as an absolute

value.

Preload stress echocardiography during LPP maneuver

Preload stress echocardiography during an LPP maneuver was performed for all PH patients and normal controls by using a commercially available leg-positive pressure machine (Dr. Medomer DM-5000EX, Medo Industries Co., Ltd., Tokyo Japan). Details of the LPP maneuver for generating preload stress are described in elsewhere (Figure 1)[17-19]. Briefly, the device is designed to provide a continuous external pressure of 90mmHg around both lower limbs. The findings from preliminary invasive hemodynamic studies have proven that this pressure provides an effective increase in ventricular preload without a significant increase in either heart rate or blood pressure[17-19]. Echocardiographic measurements were assessed at rest and during LPP stress, and RV contractile reserve was defined as the relative increase between RV free wall strain obtained at rest and LPP stress (%ΔRV free wall strain). Written informed consent was obtained from all PH patients and normal controls when the LPP maneuver was performed for preload stress echocardiography. The procedure did not result in any complications in either PH patients or normal controls.

Hemodynamic measurements and exercise capacity

All PH patients underwent RHC for hemodynamic measurements, while the Fick principle for estimations was used for calculating mPAP, PVR, right atrial pressure and stroke volume (SV). Pressure was measured by an investigator who was blinded to the echocardiographic data. In addition, PH patients underwent the 6-minute walk distance (6MWD) test for evaluating exercise capacity. 6MWD was measured for Borg rating at the end of the test to determine the level of effort as recommended in the guideline of the European Society of Cardiology[4].

Statistical analysis

All group data were compared by using the two-tailed Student's t test for paired and unpaired data and are presented as mean ± SD. Proportional differences were assessed by means of Fisher's exact test as appropriate. The associations between ΔSV and 6MWD were explored by means of linear regression analysis, after which Pearson's correlation coefficients were calculated. The initial univariate regression analysis to identify univariate predictors of changes in SV at rest during LPP stress was followed by multivariate regression analysis using enter selection. For all tests, a p value <0.05 was considered statistically significant. All the analyses were performed with commercially available software (MedCalc software version 10.4.0.0; MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

The baseline characteristics of the 43 PH patients and 17 age-, gender-, and LVEF-matched normal controls are summarized in Table 1. Of the PH patients, 19 (44%) had CTEPH and 24 (56%) had had various types of PAH such as idiopathic pulmonary arterial hypertension, connective tissue disease, portopulmonary hypertension, and congenital heart disease. Five patients (12%) were classified as World Health Organization functional class I, 16 (37%) as class II, 21 (49%) as class III, and one (2%) as class IV. As expected, PH patients exhibited significant RV and RA dilation and RV hypertrophy in comparison with normal controls. In addition, RV function in PH patients was significantly less than that in normal controls (RV free wall strain: 18.5 % vs 24.2 %; $p<0.01$).

SV and RV free wall strain at rest and during LPP

Figure 2 shows comparisons of SV and RV free wall strain at rest and during LPP stress for PH patients and normal controls. The LPP stress resulted in significant increases in SV and RV free wall strain in both normal controls and PH patients (SV: from 60.8 ± 15.8mL to 69.2 ± 16.8mL in normal controls and from 65.8 ± 18.5mL to 69.4 ± 19.7mL in PH patients, both $p<0.01$; RV free wall strain: from 24.3 ± 3.2% to 27.8 ± 4.1% in normal controls and from 18.5 ± 5.2% to 20.0 ± 6.1% in PH patients, both $p<0.01$). Figure 3 shows differences in SV (ΔSV) and RV free wall strain between at rest and during LPP stress. ΔSV for PH patients was significantly less than that for normal controls (3.6 ± 6.0mL vs. 8.5 ± 2.3mL; $p<0.01$) and %ΔRV free wall strain for PH patients was also significantly less than that for normal controls (8.2 ± 11.9% vs. 14.5 ± 6.6%, $p<0.01$).

Correlation between RV contractile reserve and exercise capacity

Next, a median ΔSV increase of 3.3 mL was used as the criterion for dividing the PH patients into two groups. The two groups had similar baseline clinical, hemodynamic and echocardiographic parameters, except that 6MWD and RV-RWT for PH patients with ΔSV≥3.3mL were significantly higher than those for PH patients with ΔSV<3.3mL (6MWD: 389 ± 75 m vs. 300 ± 111 m; $p<0.01$, RV-RWT: 0.21 ± 0.03 vs. 0.18 ± 0.04; $p=0.02$), while %RV free wall strain for PH patients with ΔSV<3.3mL was significantly lower than that for PH patients with ΔSV≥3.3mL (3.9 ± 13.2% vs. 12.3 ± 8.9 %; $p=0.02$; Figure 4). In addition, ΔSV for all PH patients showed significant correlation with 6MWD ($r=0.42$; $P=0.006$; Figure 5).

Predictor of ΔSV during LPP stress of PH patients

Table 2 shows the results of univariate and multivariate regression analyses for

associations with ΔSV for PH patients. The univariate regression analysis showed that %ΔRV free wall strain, RV-RWT, mPAP and PVR were associated with ΔSV. An important finding of the multivariate regression analysis was that RV-RWT was the independent determinant parameter of ΔSV for PH patients (β=3.2, p=0.003).

Discussion

The findings of our study indicate that the RV contractile reserve following preload augmentation was significantly reduced for PH patients in comparison with normal controls, and the echocardiography following preload stress generated by the LPP maneuver in PH patients made it possible to predict RV contractile reserve and exercise capacity. In addition, it was found that RV-RWT may be a significant parameter for predicting exercise capacity.

RV contractile reserve and exercise capacity of PH patients

The assessment of LV contractile reserve by means of stress echocardiography is a well-established technique, and the incremental prognostic value of LV contractile reserve rather than of resting measurements has been demonstrated for various left-sided heart disease[26-28]. On the other hand, the utility of assessment of RV contractile reserve by means of echocardiography in PH patients remains uncertain. The natural progression of PH is an increase in PVR, resulting in secondary RV dysfunction. Furthermore, RV dysfunction limits CO in the advanced stages of disease, while CO starts to decline even at rest[15]. Sharma et al demonstrated the utility of dobutamine stress echocardiography for determining RV contractile reserve in PH patients[29]. They also showed that RV contractile reserve in PH patients revealed subclinical RV dysfunction that is not apparent at rest, and that it correlated significantly with exercise

capacity. RV contractile reserve determined by means of echocardiography may therefore show subclinical RV dysfunction in PH patients, which is useful for early diagnosis and reportedly associated with prognosis. In our study, it during an LPP maneuver may indicate subclinical RV dysfunction, and that it correlated significantly with exercise capacity assessed with the 6MWD test for PH patients.

Adapted and maladapted right ventricle in PH patients

A chronic increase in PAP and PVR leads to RV remodeling in PH patients to enable the RV to compensate by means of RV hypertrophy for the increase in afterload. When the right ventricle is continually exposed to increases in afterload, it can respond with myocardial hypertrophy as an adaptive response tempered by an increase in wall thickness in accordance with Laplace's law [30]. However, RV remodeling is heterogeneous, with the characteristic forms consisting of two patterns. Adaptive remodeling is generally characterized by concentric hypertrophy with minimal RV dilation, and maladaptive remodeling by eccentric hypertrophy accompanied by RV dilation [1, 2]. Maladaptive remodeling is characterized by a disproportionally thin RV thickness in relation to the high level of PVR. Such an RV is therefore dilated and exhibits high wall stress in accordance with Laplace's law. The high afterload then leads to further CO reduction and compensatory RV dilation, while maladaptive RV remodeling causes further thinning due to wall stretching, resulting in a vicious cycle and RV dysfunction. Our group recently reported that RV-RWT is an independent parameter for predicting mid-term RV reverse remodeling, and is associated with long-term post-treatment survival of PH patients[20]. Moreover, incremental changes in RV-RWT proved to be of significant value for prediction of survival, and the combined assessment of RV-RWT and mid-term RV reverse remodeling resulted in more accurate

prediction of outcome for PH patients. In the current study, multivariate regression analysis demonstrated that RV-RWT was the independent determinant parameter of ΔSV for PH patients while further evidence clearly demonstrated the importance of RV-RWT.

Clinical implications

Since some PH patients may exhibit exercise tolerance and adverse cardiac events despite even maintaining RV function at rest, it would be difficult to predicting the pathophysiological progression of the disease and its prognosis by performing evaluations only under at rest conditions. The severity of the disease state of PH patients such as a change in the cardiac index (CI) can be more accurately assessed when determined as a change in values from rest to exercise than only at rest [31, 32]. In addition, Blumberg et al reported that RV contractile reserve is the main determinant of the increase in CI during exercise[33]. However, the assessment of RV contractile reserve by means of exercise echocardiography for PH patients can be technically demanding due to exercise intolerance or tachycardia developing during exercise. On the other hand, the preload stress echocardiography during an LPP maneuver as described in this study, which is non-invasive, easy-to-use, and safe for routine clinical use, is effective for the assessment of RV contractile reserve in PH patients.

Study limitations

This study covered a small number of patients in a single-center retrospective study, so that future studies involving larger numbers of patients are required to verify our findings.

Conclusion

Preload stress echocardiography following an LPP maneuver proved to be useful for estimating RV contractile reserve and exercise capacity. Our findings may thus have clinical implications for better management of PH patients.

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Disclosures:

We have no disclosures.

Author Contributions:

Hiroyuki Sano: Concept/design, data analysis/interpretation, drafting article, statistics, and data collection

Hidekazu Tanaka: Concept/design, data analysis/interpretation, drafting article, statistics, and data collection

Yoshiki Motoji: Concept/design, data analysis/interpretation, approval of article

Jun Mukai: Concept/design, data analysis/interpretation, approval of article

Makiko Suto: Concept/design, data analysis/interpretation, approval of article

Hiroki Takada: Concept/design, data analysis/interpretation, approval of article

Fumitaka Soga: Concept/design, data analysis/interpretation, approval of article

Yutaka Hatani: Concept/design, data analysis/interpretation, approval of article

Hiroki Matsuzoe: Concept/design, data analysis/interpretation, approval of article

Keiko Hatazawa: Concept/design, data analysis/interpretation, approval of article

Hiroyuki Shimoura: Concept/design, data analysis/interpretation, approval of article

Junichi Ooka: Concept/design, data analysis/interpretation, approval of article

Kazuhiko Nakayama: Concept/design, data analysis/interpretation, approval of article

Kensuke Matsumoto: Concept/design, data analysis/interpretation, approval of article

Hirotsugu Yamada: Concept/design, data analysis/interpretation, approval of article

Noriaki Emoto: Concept/design, data analysis/interpretation, approval of article

Ken-ichi Hirata: Concept/design, data analysis/interpretation, approval of article

Figure Legends

Figure 1: A scheme of preload stress echocardiography during leg positive pressure (LPP). The device is designed to provide a continuous external pressure of 90mmHg around both lower limbs. Echocardiographic measurements were assessed at rest and during LPP stress.

Figure 2: Comparison of stroke volume (SV) and right ventricular (RV) free wall strain at rest and during leg positive pressure (LPP) stress for pulmonary hypertension (PH) patients and normal controls, showing that the LPP stress resulted in significant increases in SV and RV free wall strain in both normal controls and PH patients

Figure 3: Differences in stroke volume (ΔSV) and right ventricular (RV) free wall strain between at rest and during LPP stress in normal control and pulmonary hypertension (PH) patients, showing that ΔSV as well as the %ΔRV free wall strain for PH patients were significantly less than those for normal controls.

Figure 4: %right ventricular (RV) free wall strain in pulmonary hypertension (PH) patients with a difference in stroke volume (ΔSV) between at rest and during leg positive pressure stress <3.3mL was significantly lower than that in PH patients with ΔSV≥3.3mL.

Figure 5: Relationship with significant correlation between 6-minute walk distance (6MWD) and the difference in stroke volume between at rest and during leg positive

pressure stress (ΔSV) in pulmonary hypertension patients.

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Table 1

Baseline characteristics of patients

Variables	Normal controls (n=17)	PH patients (n=43)	p value
Age (years)	56 ± 18	57 ± 17	0.70
Gender (female), n (%)	13 (77%)	38 (88%)	0.25
Systolic blood pressure (mmHg)	123 ± 17	118 ± 19	0.05
Diastolic blood pressure (mmHg)	68 ± 11	70 ± 9	0.74
Heart rate (bpm)	63 ± 5	69 ± 10	0.02
BNP (pg/mL)		43(17-89)	
6MWD (m)		348 ± 102	
WHO Functional Class, n (%)			
I		5 (12)	
II		16 (37)	
III		21 (49)	
IV		1 (2)	
Etiology of PH, n (%)			
Pulmonary arterial hypertension		23 (54)	
Idiopathic PH		7 (16)	

Connective tissue disease		8 (19)	
Portopulmonary hypertension		5 (12)	
Congenital heart disease		3 (7)	
Atrial septal defect		2 (5)	
Patent ductus arteriosus		1(2)	
CTPH		20(47)	
Treatment, n (%)			
Baseline PH-specific drugs			
Prostacyclines		6 (14)	
Endothelin receptor antagonists		18 (42)	
Phosphodiesterase 5 inhibitors		23 (54)	
Pulmonary endarterectomy		5 (12)	
Balloon pulmonary angioplasty		11 (26)	
Hemodynamic parameters			
mPAP (mmHg)		31.8 ± 12.2	
PVR (dyne· s^{-1}· cm^{-5})		484 ± 340	
Cardiac output (L/min)		5.0 ± 5.5	
Cardiac index (L/min/m^2)		2.7 ± 1.1	
Mean RA pressure (mmHg)		4.6 ± 3.5	
Echocardiographic parameters			
LVEF (%)	67.3 ± 4.3	69.7 ± 9.7	0.55
Stroke volume (mL)	60.8 ± 15.8	65.8 ± 18.5	0.32

RV wall thickness (mm)	4.1 ± 0.9	7.1 ± 1.1	<0.01
RV free-wall strain (%)	24.2 ± 3.2	18.5 ± 5.0	<0.01
RVEDA (cm^2)	13.3 ± 3.4	21.7 ± 7.0	<0.01
RVESA (cm^2)	7.6 ± 2.1	15.4 ± 6.4	<0.01
RA area (cm^2)	10.3 ± 2.0	15.4 ± 2.2	<0.01
Tricuspid Regurgitation, n (%)			
None or Trace	15 (88)	22 (51)	<0.01
Mild	2 (12)	6 (14)	0.83
Moderate	0 (0)	12 (28)	0.01
Severe	0 (0)	3 (7)	0.27

Data are expressed as mean ± SD.

BNP= plasma brain natriuretic peptide; 6MWD= 6-min walk test; WHO= World Health Organization; PH= pulmonary hypertension; CTPH= Chronic thromboembolic pulmonary hypertension; mPAP= mean Pulmonary artery pressure; PVR= pulmonary vascular resistance; RA= right atrial; LVEF= left ventricular ejection fraction; RV= right ventricular; RVEDA= right ventricular end-diastolic area; RVESA= right ventricular end-systolic area

Table 2

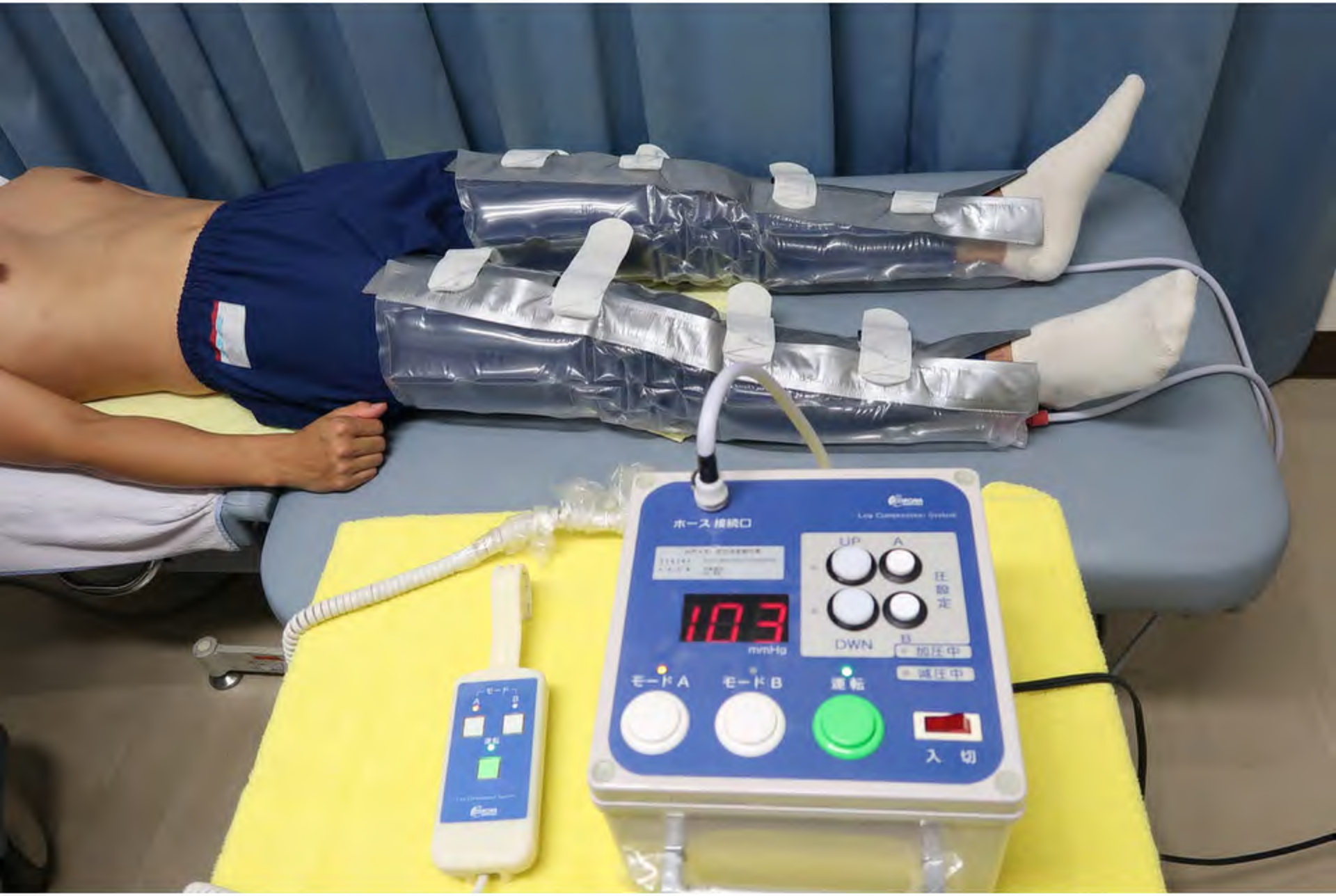
Univariate and Multivariate Regression Analysis

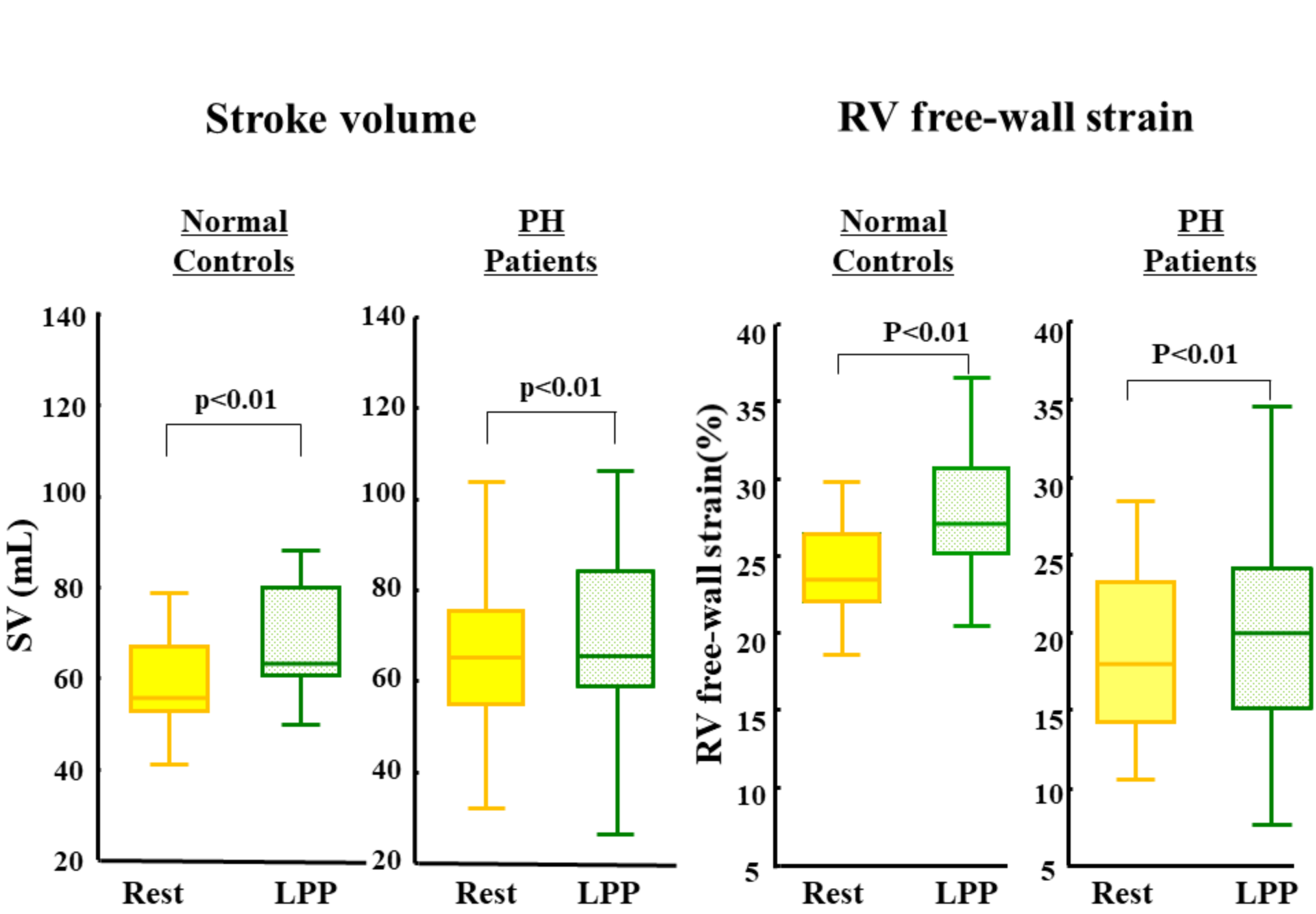
Covariate	Univariate analysis		Multivariate analysis	
	β	p value	β	p value
Clinical Characteristics				
Age	1.332	0.190		
Gender (female)	0.399	0.692		
WHO (III-IV)	-1.761	0.086		
Log-transformed BNP	-1.593	0.119		
Conventional Echocardiographic Parameters				
%ΔRV free-wall strain	3.393	0.002		
RV-RWT (per increase 0.01 increment)	3.039	0.004	3.193	0.003
Hemodynamics				
mPAP	-2.829	0.007		
PVR	-2.855	0.007		

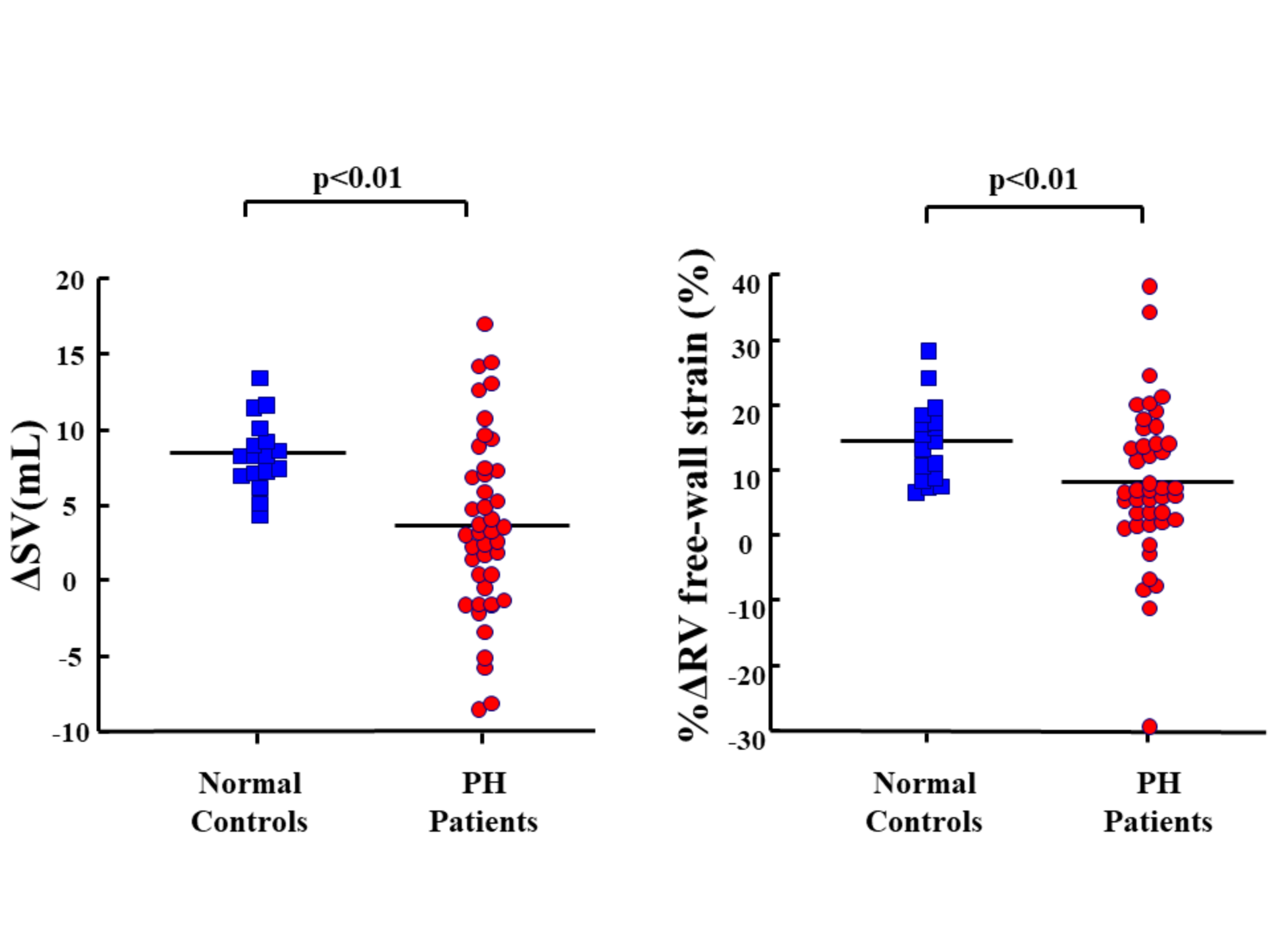
Table 3

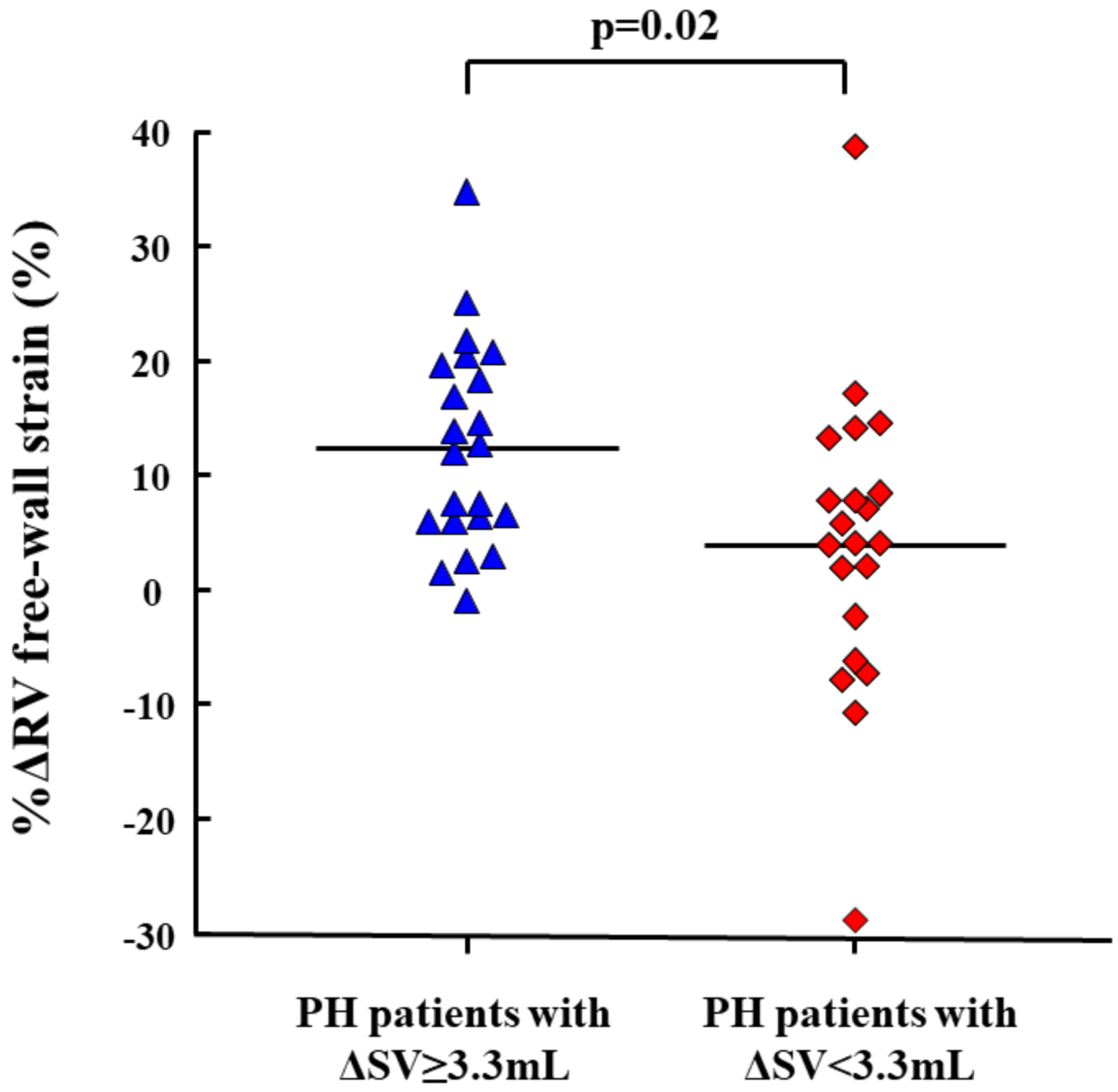
Univariate and Multivariate Regression Analysis

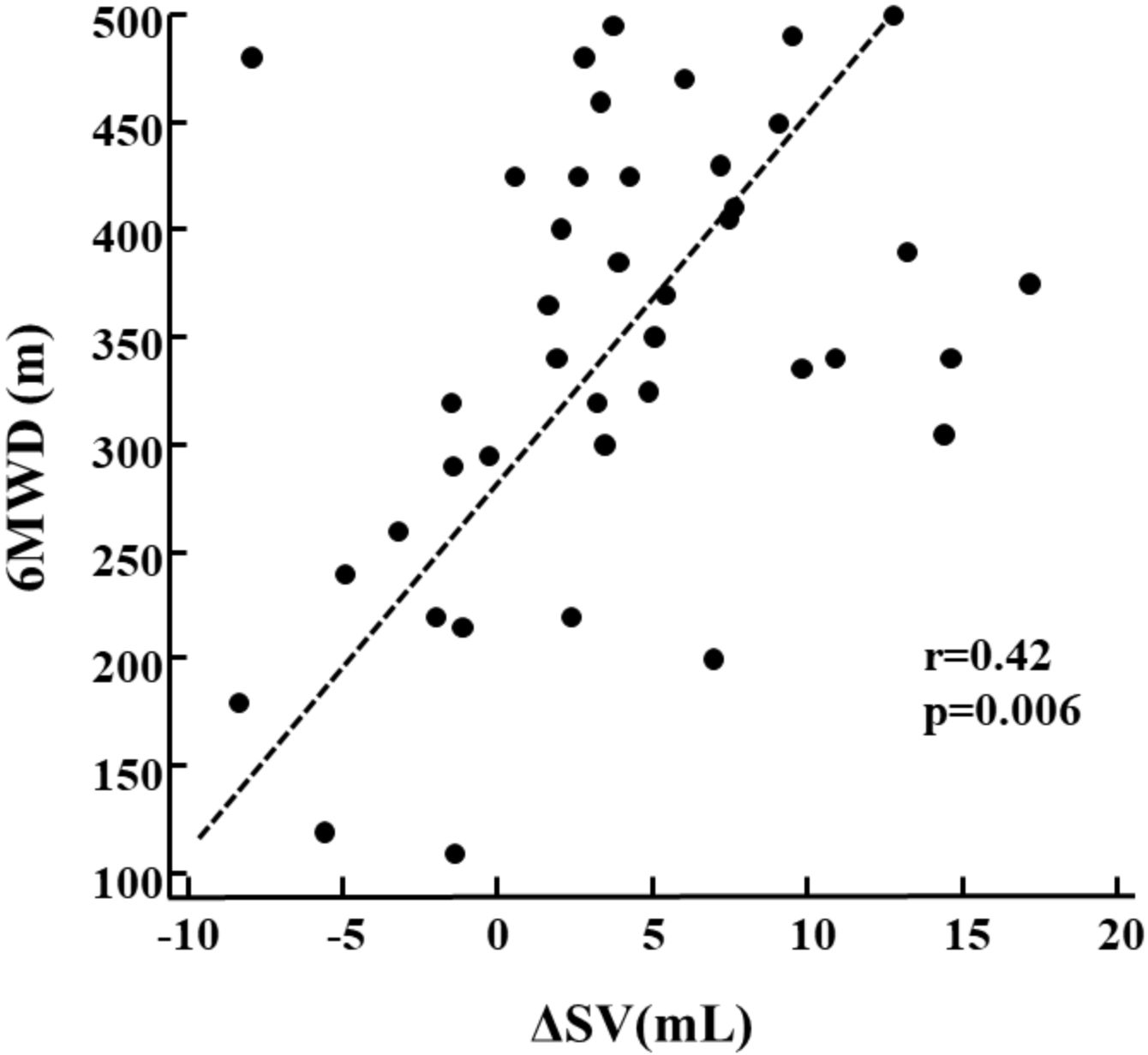
Covariate	Univariate analysis		Multivariate analysis	
	β	p value	β	p value
Clinical Characteristics				
Age	1.332	0.190		
Gender (female)	0.399	0.692		
WHO (III-IV)	-1.761	0.086		
Log-transformed BNP	-1.593	0.119		
Conventional Echocardiographic Parameters				
%ΔRV free-wall strain	3.393	0.002		
RV-RWT (per increase 0.01 increment)	3.039	0.004	3.193	0.003
Hemodynamics				
mPAP	-2.829	0.007		
PVR	-2.855	0.007		


ホース接続口
UP
A
DWN
圧設定
103
mmHg
加圧中
減圧中
モードA
モードB
運転
入 切


Stroke volume
RV free-wall strain
Normal Controls
PH Patients
Normal Controls
PH Patients
SV (mL)
RV free-wall strain(%)
140
120
100
80
60
40
20
40
35
30
25
20
15
10
5
p<0.01
p<0.01
P<0.01
P<0.01
Rest
LPP
Rest
LPP
Rest
LPP
Rest
LPP


p<0.01
ΔSV(mL)
20
15
10
5
0
-5
-10
Normal Controls
PH Patients
p<0.01
%ΔRV free-wall strain (%)
40
30
20
10
0
-10
-20
-30
Normal Controls
PH Patients


p=0.02
40
30
20
10
0
-10
-20
-30
%ΔRV free-wall strain (%)
PH patients with ΔSV≥3.3mL
PH patients with ΔSV<3.3mL


500
450
400
350
300
250
200
150
100
6MWD (m)
-10
-5
0
5
10
15
20
ΔSV(mL)
r=0.42
p=0.006