

Longitudinal strain of right ventricular free wall by 2-dimensional speckle-tracking echocardiography is useful for detecting pulmonary hypertension

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Abstract

Aims: Echocardiography is widely used for screening of pulmonary hypertension (PH). More recently developed two-dimensional speckle-tracking echocardiography (2D-STE) can assess regional deformation of the myocardium and is useful for detecting left ventricular dysfunction. However, its usefulness to assess right ventricular (RV) dysfunction is not clear. Therefore, the aim of this study was to investigate the ability of peak systolic strain (PSS) and post-systolic strain index (PSI) at the RV free wall determined by 2D-STE to detect PH.

Main methods: Thirty-six images (27 images from PH patients, nine from patients with connective tissue disease without PH) obtained by 2D-STE were analysed. We investigated the relationship between RV hemodynamics measured by right heart catheterization and PSS, PSI and other echocardiographic parameters reflecting RV overload including RV end-diastolic diameter (RVDD) and tricuspid valve regurgitant pressure gradient (TRPG).

Key findings: PSS, PSI, RVDD and TRPG were all correlated with mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance (PVR). Furthermore, when PSS and MPAP were measured twice, the change in PSS was correlated with the change in MPAP ($r=0.633$, $p=0.037$). Multivariate logistic regression analysis identified PSS as the only independent factor associated with $MPAP \geq 35$ mmHg [odds ratio (OR), 1.616; 95% confidence interval (CI) 1.017-2.567; $p=0.042$] and $PVR \geq 400$ dyne·sec·cm⁻⁵ (OR, 1.804; 95% CI 1.131-2.877; $p=0.013$). Furthermore, the optimal PSS cut-off value to detect an elevated MPAP and PVR was -20.75%, based on receiver operating characteristic curve analysis.

Significance: PSS of the RV free wall might serve as a useful non-invasive

indicator of PH.

Key words: pulmonary hypertension, echocardiography, speckle tracking, peak systolic strain, post systolic index, tricuspid valve regurgitant pressure gradient

Introduction

Pulmonary hypertension (PH) is severe and life-threatening syndrome associated with poor outcome; therefore, early diagnosis and treatment are important for PH patients to improve their prognosis. A definite diagnosis of PH is required for invasive right heart catheterization (RHC) which does not always proceed due to patient concerns about cost and potential complications. Transthoracic echocardiography and Doppler imaging represents the most widely-available non-invasive tool for the evaluation of PH.(Bossone et al. , 2005, Currie et al. , 1985) Among the echocardiographic parameters for estimating pulmonary arterial pressure (PAP), tricuspid valve regurgitation velocity (TRV) is widely used; however, a recent meta-analysis showed that its sensitivity and specificity for estimating pulmonary arterial pressure were only 83% and 72%, respectively.(Janda et al. , 2011) Although several other Doppler imaging-based methods have been proposed to estimate PAP, none of them has yet eliminated the need for invasive evaluation.(Chemla et al. , 2009, Gurudevan et al. , 2007, Lang et al. , 2010, Vlahos et al. , 2008)

Recent advances in echocardiography have allowed quantification of regional and global myocardial function. Regional deformation and deformation rate using Doppler tissue imaging (DTI) and 2-dimensional speckle-tracking echocardiography (2D-STE) can provide quantitative information on regional myocardial dysfunction.(Teske et al. , 2007) 2D-STE, which can quantify complex cardiac motion based on frame-to-frame tracking of ultrasonic speckles in grayscale images, has the advantage that it is angle-independent and shows less preload dependency compared with DTI in the clinical setting.(Biswas et al. , 2013) The clinical usefulness of 2D-STE has been shown in patients with left ventricular (LV) dysfunction, such as myocardial ischemia, heart

failure with or without a decrease in LV ejection fraction, valvular heart disease, chemotherapy-induced cardiotoxicity and cardiomyopathy.(Biswas, Sudhakar, 2013) This technique has been introduced to evaluate regional right ventricular (RV) function, which is difficult due to complex RV anatomy and physiology. However, the usefulness of 2D-STE for evaluating RV dysfunction has not been fully elucidated.

The aim of this study was to determine whether strain parameters derived from 2D-STE, peak systolic strain (PSS) and post-systolic strain index (PSI) of the RV free wall obtained by 2D-STE, can estimate RV hemodynamics measured by RHC. In addition, we examined whether these parameters are superior to TRV and other parameters obtained by conventional echocardiography as indicators of PAP and pulmonary vascular resistance (PVR)

Methods

Study population

Between October, 2010 and May, 2013, 36 images obtained by transthoracic echocardiography were analyzed. The images were obtained from 17 patients with idiopathic pulmonary arterial hypertension, 3 with chronic thromboembolic pulmonary hypertension, 7 with PH due to connective tissue disease (CTD) and 9 with CTD without PH. The patients underwent RHC within 2 weeks of echocardiographic examination (average, 9.11 days after echocardiography). PH was defined as a mean PAP (MPAP) ≥ 25 mmHg assessed by RHC. Patients with left-sided heart failure, moderate to severe aortic and/or mitral valvular heart disease, coronary artery disease and atrial fibrillation/flutter were excluded. This study complied with the Declaration of Helsinki with regard to investigations in humans, and all participants provided written,

informed consent before RHC.

Echocardiography

All echocardiographic studies were performed with a Vivid E9 or Vivid q echocardiographic system (GE Healthcare Japan, Tokyo, Japan) in the left lateral position. Images were acquired from apical and parasternal views during breath holds with stable electrocardiographic recordings, and were then digitally stored for subsequent offline analysis using an EchoPAC version 110.X.X workstation (GE Healthcare Japan).

2D-STE strain was analyzed using conventional echocardiographic grayscale apical 4-chamber images with a frame rate of 70 - 80 frames/s. For post-processing analysis, the region of interest (ROI) was obtained by tracing the endocardial borders of RV free wall in a still frame at end-systole. An automated software program calculated the frame-to-frame displacements of the speckle pattern within the ROI throughout the cardiac cycle. Longitudinal strain curves were obtained for the basal and mid-segments of the RV free wall, and the global RV strain curve was based on the average of the 2 regional strain curves (Figure 1A). The end of systole was set at the time of pulmonary valve closure. PSS was the lowest strain value during the ejection period, and the value was expressed as a percentage of the longitudinal shortening in systole compared with diastole for each segment of interest (Figure 1B). Peak strain was the lowest strain value over entire RR interval (Figure 1B). The post-systolic strain index (PSI) was calculated from the following formula: $PSI = (\text{peak strain} - PSS) / \text{peak strain}$. (Meris et al. , 2010, Teske, De Boeck, 2007) Both PSS and PSI at the basal and mid-RV free wall were averaged.

RV fractional area change (FAC) was obtained by measuring the RV area at

end-diastole and end-systole in the 4-chamber view and then dividing the difference between the end-diastolic and end-systolic areas by the end-diastolic area.(Anavekar et al. , 2007) RV end-diastolic diameter (RVDd) was obtained by measuring RV mid-cavity diameter from the apical 4-chamber view at end-diastole. Tricuspid valve plane systolic excursion (TAPSE) was obtained by drawing a straight line (M-mode) through the lateral tricuspid valve annulus, and TAPSE was expressed as the length of the excursion of the tricuspid annular plane during systole.(Bleeker et al. , 2006) Tricuspid regurgitant flow was identified by color flow Doppler techniques, and the maximum jet velocity was measured by continuous wave Doppler. The tricuspid valve regurgitant pressure gradient (TRPG) was calculated from the velocity of the regurgitant jet using the modified Bernoulli equation, since the regurgitant jet is thought to be correlated with systolic PAP in the absence of RV outflow obstruction.(Arcasoy et al. , 2003, Galie et al. , 2009b, Lang, Plank, 2010) An investigator (sonographer) blinded to the RHC data performed all of the echocardiographic measurements.

Right heart catheterization

All patients underwent RHC for measuring RV hemodynamics. Values for PAP and pulmonary capillary wedge pressure (PCWP) were recorded at end expiration. PVR ($\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$) was calculated using the formula: $\text{PVR} = (\text{MPAP} - \text{mean PCWP}) / \text{cardiac output} \times 80$. The averaged A-wave of PCWP served as mean PCWP.

Statistical analysis

Continuous values are expressed as the mean \pm standard deviation (SD). Relationships between the echocardiographic parameters and RV hemodynamic parameters measured by RHC were evaluated using Spearman's rank correlation coefficient. Significant factors associated with $\text{MPAP} \geq 35 \text{ mmHg}$ and $\text{PVR} \geq 400 \text{ dyne}$

$\cdot \text{sec} \cdot \text{cm}^{-5}$ were determined using univariate and multivariate logistic regression analysis. Factors with $p < 0.05$ in univariate analysis were entered into the multivariable model. Receiver-operating characteristic curves (ROCs) were constructed to identify the optimal cut-off values of various parameters to detect an elevated MPAP and PVR. The optimal cut-off values were defined as the point closest to 1 in the top left corner. A p value < 0.05 was considered statistically significant. All data were statistically analyzed using SPSS version 18 (IBM Corp., Somers, NY).

Results

Table 1 shows the characteristics of the patients. Patients were predominantly female, and had moderately elevated pulmonary pressures (average MPAP, 37.6 mmHg) and exercise intolerance (mean 6-minute walk distance, 386.8 m).

MPAP was correlated with TRPG, RVDD, PSS and PSI (Figure 2), and all of these parameters were significantly associated with $\text{MPAP} \geq 35$ mmHg in univariate logistic regression analysis (Table 2). Multivariate stepwise logistic regression analysis, in which variables with a p value < 0.05 in univariate analysis were incorporated into the model, identified PSS as the only independent factor associated with $\text{MPAP} \geq 35$ mmHg (Table 2). The areas under the ROC curves for detecting $\text{MPAP} \geq 35$ mmHg with PSS, PSI and TRPG were 0.928 ($p < 0.001$), 0.857 ($p = 0.001$) and 0.801 ($p = 0.004$), respectively (Figure 3). The optimal cut-off value of PSS for detecting $\text{MPAP} \geq 35$ mmHg was -20.75% with a sensitivity of 87.5% and a specificity of 87.5%. In 11 patients who underwent RHC and echocardiographic examination at least twice, only changes (difference between 2 measurements) in PSS, but not changes in PSI and TRPG, was correlated with changes in MPAP ($r = 0.633$, $p = 0.037$). The associations between

PVR and echocardiographic parameters were similar to those between MPAP and the other parameters (Figure 4). Multivariate stepwise logistic regression analysis identified PSS as the only independent factor associated with a $PVR \geq 400 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ (Table 3). Furthermore, the optimal cut-off value of PSS to detect an elevated PVR determined from ROC curve analysis was -20.75% with a sensitivity of 94.1% and a specificity of 94.4% (Figure 5).

Discussion

In the present study, we demonstrated that PSS, PSI, TRPG and RVDd had significant correlations with MPAP and PVR, and multivariate logistic regression analysis identified PSS as the only independent predictor for $MPAP \geq 35 \text{ mmHg}$ and $PVR \geq 400 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$. Furthermore, ROC curve analysis showed that optimal cut-off value of PSS to detect an elevated MPAP and PVR was -20.75% .

Pulmonary arterial hypertension (PAH) is characterized by a progressive increase of pulmonary vascular resistance leading to right heart failure. Despite recent advances in treatment of PAH, the long-term prognosis for such patients remains poor. Early therapeutic intervention might be required to improve prognoses.(Humbert et al., 2012) Indeed, PAH patients in World Health Organization functional class (WHO-FC) I/II have significantly better long-term survival rates than patients in higher functional classes.(Humbert et al., 2010) Humbert, et al. demonstrated that PAH screening programs in systemic sclerosis (SSc) patients can identify patients with milder forms of the disease, leading to earlier therapeutic intervention and better survival.(Humbert et al., 2011) In addition, recent guidelines recommend annual echocardiographic screening to facilitate earlier detection and management of PAH in SSc.(Galie et al. , 2009a, Galie,

Hoeper, 2009b) Conventional echocardiography has been shown to be useful for the screening of PH, but a new technique with higher sensitivity and specificity for diagnosing PAP and PH is required to further improve the prognosis of PH patients.

A more recent developed echocardiographic method of speckle tracking can assess myocardial deformation or strain by tracking speckles in the myocardium on grayscale images. This method can evaluate both global and regional myocardial strain without being limited by the Doppler beam angle.(Helle-Valle et al. , 2005, Toyoda et al. , 2004) Most studies of speckle-tracking strain have focused on the assessment of regional LV function, but recently this method has been applied for the assessment of regional RV function.(D'Andrea et al. , 2010, Fukuda et al. , 2011, Meris, Faletra, 2010, Pedrinelli et al. , 2010, Pena et al. , 2009, Verhaert et al. , 2010)

PSS is a quantitative indicator of systolic longitudinal deformation; therefore, reduced PSS of the RV can reflect RV dysfunction. Huez et al. demonstrated that strain of the RV free wall, especially at mid-apex, was decreased in PH patients compared with age-matched healthy subjects, and the strain was correlated with MPAP.(Huez et al. , 2007) Lopez-Candales et al. also showed a decrease of RV free wall strain in patients with PH.(Lopez-Candales et al. , 2005) In these studies, tissue Doppler imaging was used and subjects had severe PH, unlike our study. Previous studies using speckle-tracking echocardiography also showed similar findings that RV free wall strain is impaired in patients with PH (Pirat et al. , 2006) or acute pulmonary thromboembolism.(Sugiura et al. , 2009) PSS of the RV free wall has also been shown to detect not only RV dysfunction in severe PH patients, but also early RV dysfunction in patients with mild PH. In addition, RV PSS is also associated with the prognosis of PH.(Haeck et al. , 2012) The subjects in our study had an average MPAP of 37.6 mmHg

and included 9 subjects without PH, which indicates our subjects had moderately elevated pulmonary pressure. Therefore, the results of our study suggest the usefulness of RV PSS for the early diagnosis of PH. Furthermore, we demonstrated that PSS at the RV free wall was superior to TRPG for detecting PH, according to the results of multivariate analysis and ROC curve analysis.

Post-systolic shortening is myocardial contraction that occurs after end-systole and has been shown to be a sensitive marker of myocardial ischemia that may be superior to systolic strain parameters.(Okuda et al. , 2006, Pislaru et al. , 2001, Voigt et al. , 2003) Asanuma et al. demonstrated use a canine model of coronary occlusion/reperfusion and showed that PSI significantly increased in the risk area until about 10 - 20 min after coronary artery reperfusion, whereas PSS decreased in the risk area during occlusion but recovered to the baseline immediately after reperfusion.(Asanuma et al. , 2012) Hosokawa et al. demonstrated clinically that post-systolic shortening is a marker of recovery in patients with reperfused anterior myocardial infarction.(Hosokawa et al. , 2000) Thus, post-systolic shortening has been shown to be useful for predicting reversible LV injury; however, little is known about the usefulness of PSI in the RV. In patients with PH, there is a delayed time to peak strain of the RV free wall compared with peak strain of the ventricular septum, although peak strains of these areas were synchronized in healthy volunteers.(Lopez-Candales, Dohi, 2005) This may indicate PSI is associated with abnormal RV hemodynamics due to PH. Our study showed that PSI was significantly correlated with MPAP and PVR, and the area under the ROC curves for PSI to detect $MPAP \geq 35$ mmHg and $PVR \geq 400$ dyne \cdot sec \cdot cm⁻⁵ were not lower than those for TRPG. However, multivariate logistic regression analysis did not identify PSI as an independent factor associated with an elevated MPAP and PVR.

In this study, we did not show correlations of TAPSE and RV FAC with MPAP and PVR, although some previous reports showed correlations among these variables.(Fukuda, Tanaka, 2011, Yang et al. , 2013) The difference might be attributed to differences in patients' backgrounds, but the exact reason is unknown. Both TAPSE and RV FAC provide information on global RV function, but do not include potentially important regional variations in contractility and do not assess contraction synchronicity. Our results showed the superiority of RV longitudinal deformation parameters for detecting PH compared with the conventional parameters, TAPSE and RV FAC.

Study limitations

Our study has several limitations. First, the small patient cohort from a single center imposed inherent limitations. For this reason multivariate models may not fit the data very well. ROC curve analysis was done for detecting PH at the median value of MPAP (35 mmHg), but not a MPAP of 25 mmHg that is used clinically to define PH. This was also due to the small number of subjects, especially subjects with MPAP < 25 mmHg, in this study. Therefore, we acknowledge that further validation in a different and larger series of patients is necessary. Second, echocardiographic studies were not performed simultaneously with RHC. Third, RV strain was assessed only in the 4-chamber view of the 2 segments of the RV free wall. Previous studies showed the usefulness of RV free wall longitudinal strain for the assessment of RV performance compared with RV septal wall longitudinal strain.(Fukuda, Tanaka, 2011, Huez, Vachiery, 2007, Lopez-Candales, Dohi, 2005, Utsunomiya et al. , 2011) In the clinical setting, we often find that a fine image of the RV apex cannot be obtained in the 4-chamber view. Pirat et al. showed that magnitude of PSS at apex of RV free wall were similar with that at mid portion in normal subjects.(Pirat, McCulloch, 2006) Therefore, we selected 2 ROIs on the RV free

wall, basal and mid-portion, for simplifying the measurement, and these averaged values were significantly associated with RV hemodynamics. Fourth, RV strain was measured using a speckle-tracking program for LV strain, because definitive speckle-tracking software for RV has not yet been developed. Newly developed software analyzing the complex RV will be required for the accurate measurement of RV performance using speckle-tracking echocardiography.

Conclusions

In the present study, we demonstrated that PSS and PSI of the RV free wall was significantly associated with MPAP and PVR. In particular, PSS was superior to TRPG for the prediction of PH. These findings suggest that myocardial deformation in the RV free wall as assessed by 2D-STE may be useful for detecting PH.

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Figure captions

Figure 1. Speckle-tracking strain imaging.

(A) Regions of interest at the right ventricular (RV) free wall were basal and mid-wall obtained from the apical four-chamber view (left). Speckle tracking-derived RV longitudinal strain curves are automatically generated (right). (B) RV longitudinal strain curves. Peak systolic strain is the lowest strain value during the ejection period (white arrow). Peak strain is the lowest strain value over the entire RR interval (red arrow). Post-systolic strain index was calculated from the formula described in the Methods.

Figure 2. Correlations of MPAP with TRPG, RVDd, PSS and PSI.

MPAP, mean pulmonary arterial pressure; TRPG, tricuspid valve regurgitant pressure gradient; RVDd, right ventricular end-diastolic diameter; PSS, peak systolic strain; PSI, post-systolic strain index.

Figure 3. Receiver operating characteristic curve analysis of the echocardiographic parameters (TRPG, PSS and PSI) for diagnosing $MPAP \geq 35$ mmHg.

MPAP, mean pulmonary arterial pressure; TRPG, tricuspid valve regurgitant pressure gradient; PSS, peak systolic strain; PSI, post-systolic strain index.

Figure 4. Correlations of PVR with TRPG, RVDd, PSS and PSI.

PVR, pulmonary vascular resistance; TRPG, tricuspid valve regurgitant pressure gradient; RVDd, right ventricular end-diastolic diameter; PSS, peak systolic strain; PSI, post-systolic strain index.

Figure 5. Receiver operating characteristic curve analysis of the echocardiographic parameters (TRPG, PSS and PSI) for diagnosing $PVR \geq 400 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$.

TRPG, tricuspid valve regurgitant pressure gradient; PSS, peak-systolic strain; PSI, post-systolic strain index; PVR, pulmonary vascular resistance.

Figure 1

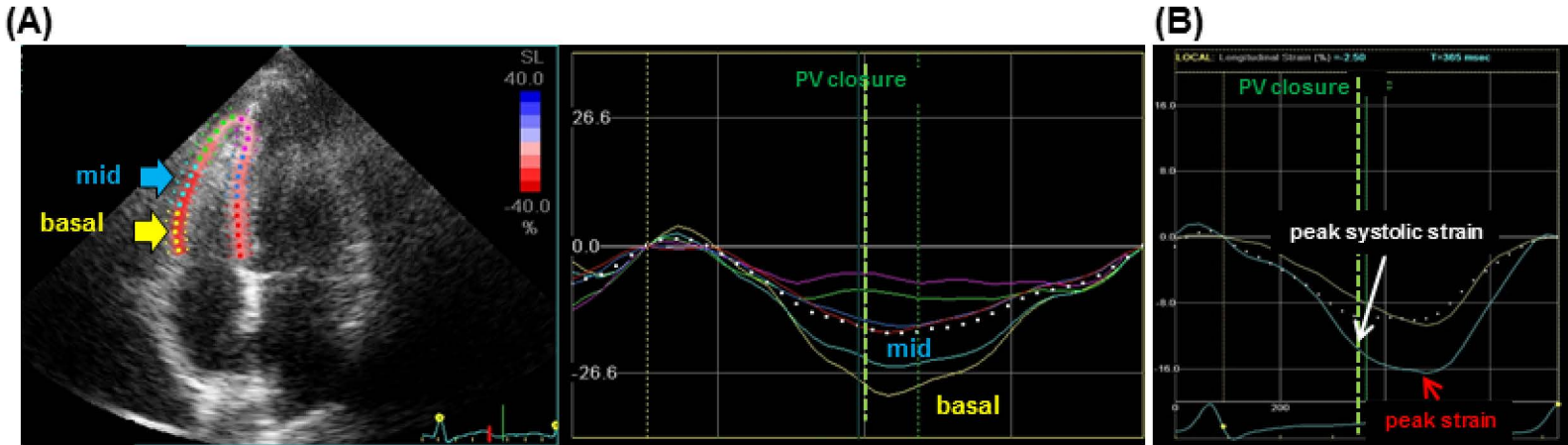


Figure 2

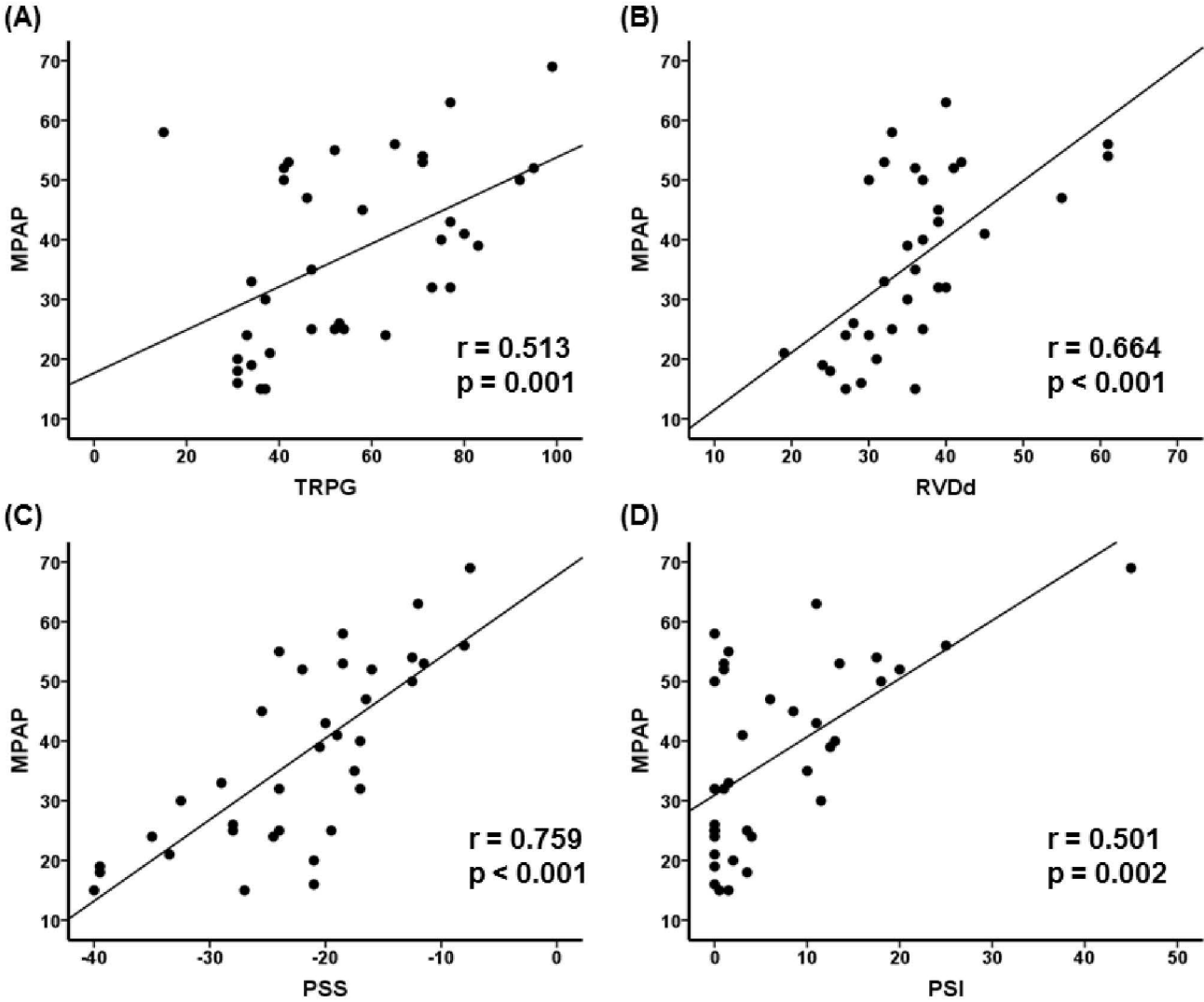
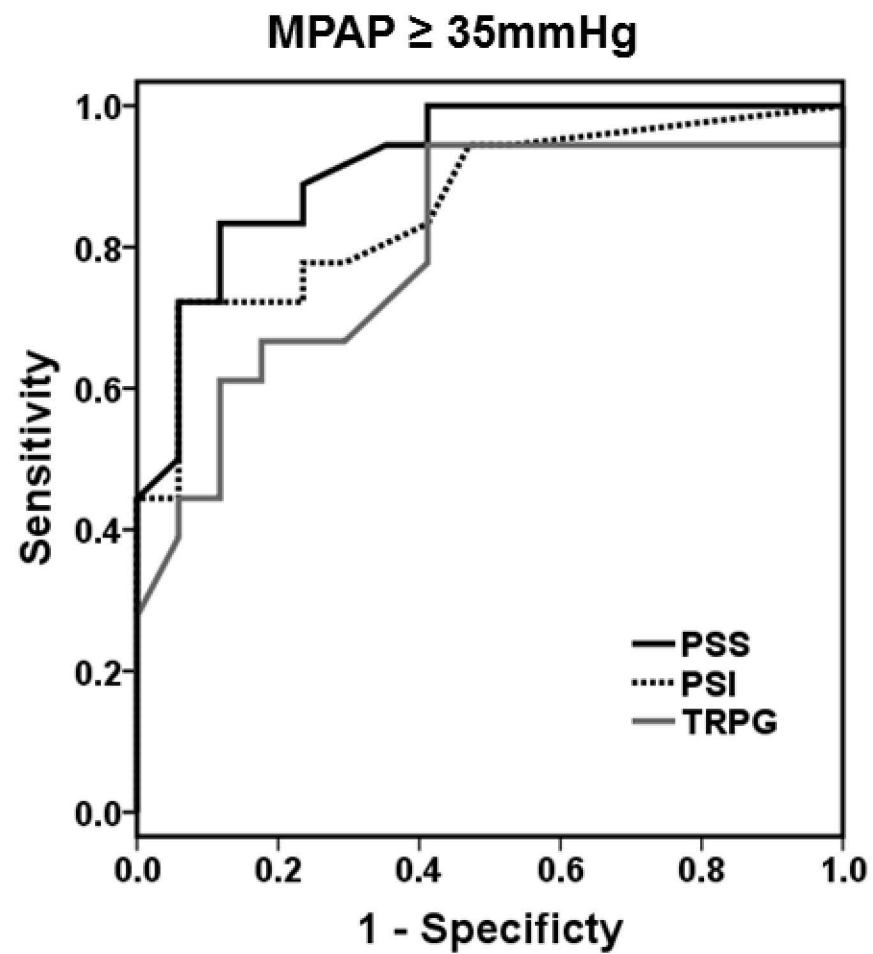


Figure 3



	AUC	P value	Sensitivity	Specificity	Cut-off value
PSS	0.928	<0.001	87.5	87.5	-20.75
PSI	0.857	0.001	75.0	93.7	5.0
TRPG	0.801	0.004	93.8	62.5	39.5

Figure 4

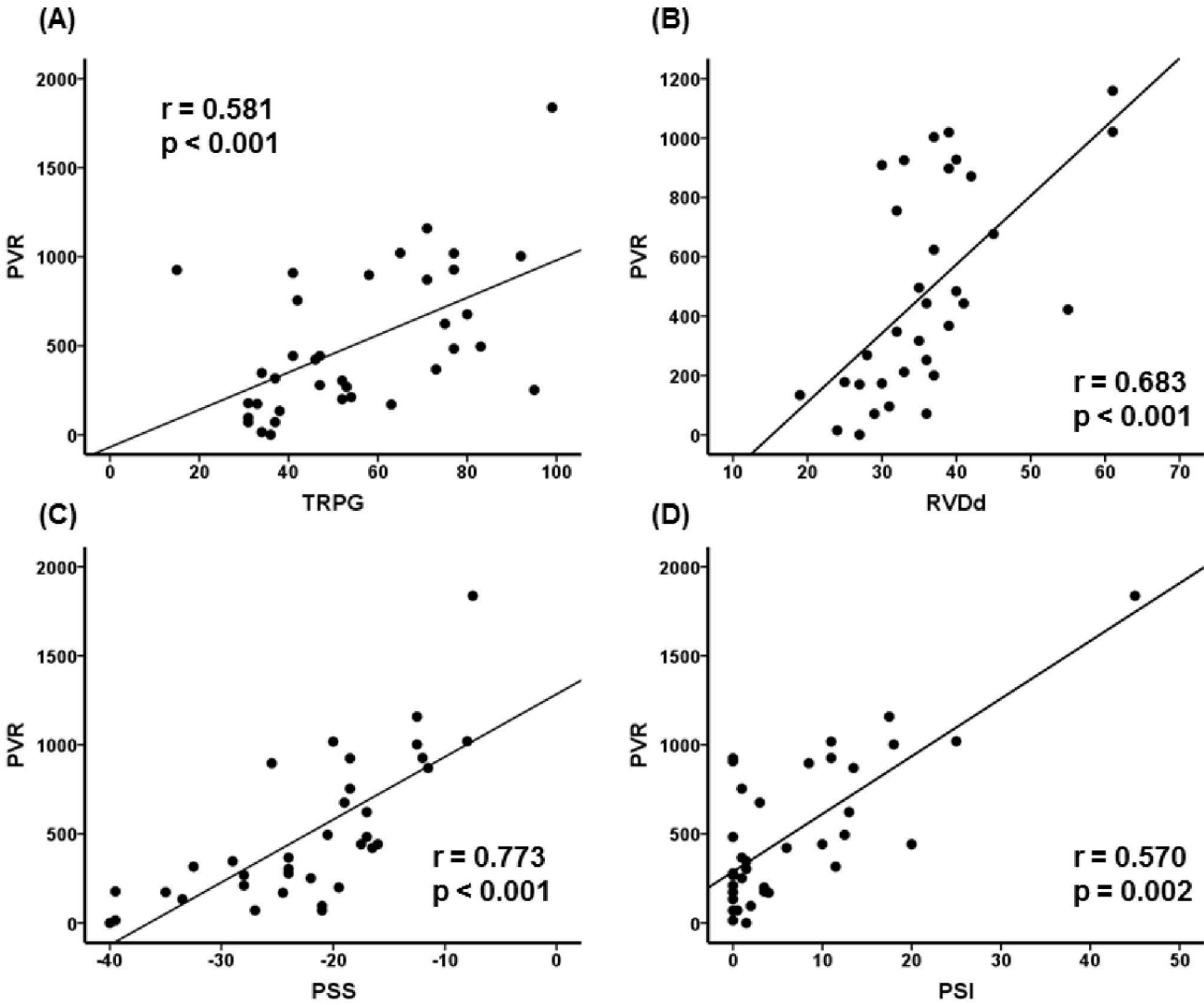
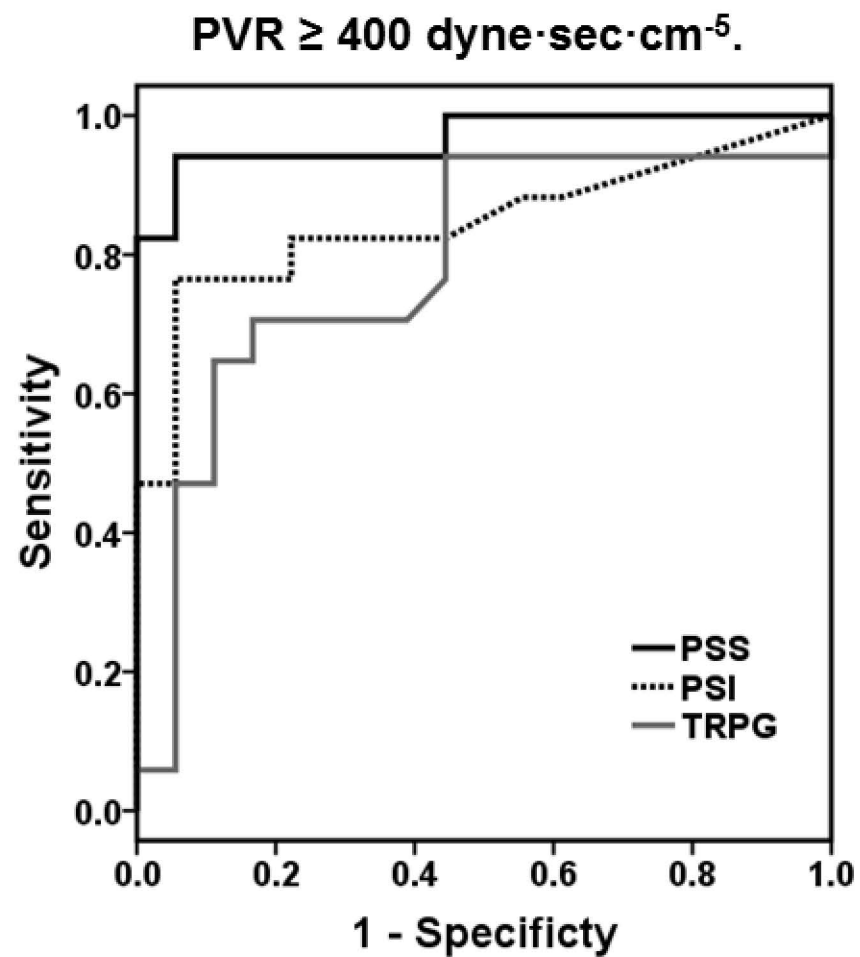


Figure 5



	AUC	P value	Sensitivity	Specificity	Cut-off value
PSS	0.967	<0.001	94.1	94.4	-20.75
PSI	0.846	<0.001	76.5	94.4	5.0
TRPG	0.786	0.004	70.6	83.3	56.0

Table 1. Patients' characteristics

Variables	Mean \pm SD
Age (years)	50.0 \pm 19.2
Gender (male : female)	12 : 24
Body mass index	22.6 \pm 4.3
<i>Right heart catheterization</i>	
Mean pulmonary arterial pressure (mmHg)	37.6 \pm 15.4
Mean pulmonary capillary wedge pressure (mmHg)	11.9 \pm 3.5
Cardiac output (L/min)	4.8 \pm 2.4
<i>Blood count and biochemical data</i>	
Red blood cell count ($\times 10^4/\mu\text{l}$)	460.0 \pm 65.6
Hemoglobin (g/dl)	13.6 \pm 2.3
Hematocrit (%)	41.5 \pm 6.0
AST (IU/L)	22.5 \pm 12.7
ALT (IU/L)	18.9 \pm 11.0
Creatinine (mg/dl)	0.77 \pm 0.25
BUN (mg/dl)	14.9 \pm 4.9

Total protein (mg/dl)	7.0 ± 0.9
Uric acid (mg/dl)	6.0 ± 1.5
Fasting blood glucose (mg/dl)	93.4 ± 21.8
Hemoglobin A1c (%)	5.3 ± 0.5
LDL-cholesterol (mg/dl)	95.8 ± 22.4
HDL-cholesterol (mg/dl)	46.5 ± 13.5
Triglyceride (mg/dl)	115.4 ± 55.8
NT-proBNP (pg/ml)	419.2 ± 530.9

Exercise capacity

6 minutes walk distance (m)	386.8 ± 133.2
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AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal-pro brain natriuretic protein.

Table 2. Univariate and multivariate logistic regression analyses of echocardiographic parameters for detecting mean pulmonary arterial pressure ≥ 35 mmHg

	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
TRPG	1.056 (1.013 – 1.100)	0.010		
RVDd	1.319 (1.075 – 1.620)	0.008		
TAPSE	0.900 (0.752 – 1.076)	0.248		
RV FAC	0.943 (0.875 – 1.017)	0.127		
PSS	1.469 (1.126 – 1.917)	0.005	1.616 (1.017 – 2.567)	0.042
PSI	1.326 (1.083 – 1.624)	0.006		

CI, confidence interval; TRPG, tricuspid valve regurgitant pressure gradient; RVDd, RV end-diastolic diameter; TAPSE, tricuspid valve plane systolic excursion; RV FAC, right ventricular fractional area change; PSS, peak systolic strain; PSI, post-systolic strain index.

Table 3. Univariate and multivariate logistic regression analyses of echocardiographic parameters for detecting pulmonary vascular resistance ≥ 400 dyne·sec·cm⁻⁵

	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
TRPG	1.048 (1.009 – 1.090)	0.016		
RVDd	1.378 (1.098 – 1.753)	0.006		
TAPSE	0.860 (0.709 – 1.043)	0.126		
RV FAC	0.947 (0.880 – 1.020)	0.151		
PSS	1.912 (1.177 – 3.105)	0.009	1.804 (1.131 – 2.877)	0.013
PSI	1.337 (1.095 – 1.633)	0.004		

CI, confidence interval; TRPG, tricuspid valve regurgitant pressure gradient; RVDd, RV end-diastolic diameter; TAPSE, tricuspid valve plane systolic excursion; RV FAC, right ventricular fractional area change; PSS, peak systolic strain; PSI, post-systolic strain index.