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ORIGINAL INVESTIGATION

Prognostic value of 6-min walk stress echocardiography in patients with interstitial lung disease

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Abstract

Background The 6-min walk test (6MWT) provides prognostic information for patients with interstitial lung disease (ILD). Parameter determined by Doppler echocardiography after the 6MWT (6 MW stress echocardiography) is shown to be a predictor of future development of pulmonary hypertension in patients with connective tissue disease. However, the clinical utility of 6 MW stress echocardiography in predicting cardiopulmonary events in patients with ILD remains unknown. We examined whether parameters determined by 6 MW stress echocardiography independent predictors of adverse events in patients with ILD.

Methods Echocardiographic examinations were performed in 68 consecutively enrolled patients with ILD (age, 65 ± 10 years, 65% men). A pressure gradient of tricuspid regurgitation (TRPG) and pulmonary vascular resistance (PVRecho) calculated using the following formula [PVRecho = (peak velocity of TR × 10/time-velocity integral of right ventricular outflow (RVOT-VTI)) + 0.16] were measured at baseline and at post 6MWT. Data for parameters of pulmonary functional tests and for 6MWT were collected.

Results During a mean follow-up period of 22 ± 12 months, 22 patients experienced cardiopulmonary events. In univariate analysis, %VC, TRPG, PVRecho, TRPG post 6MWT, and PVRecho post 6MWT were significantly associated with cardiopulmonary events. Multivariate analysis using the Cox proportional hazards model indicated that %VC [hazard ratio (HR): 0.97, $p = 0.009$] and PVRecho post 6MWT (HR: 1.77, $p = 0.004$) were independent predictors of cardiopulmonary events in patients with ILD.

Conclusions In addition to parameters of pulmonary function tests, increased PVRecho post 6MWT is a significant predictor of cardiopulmonary events in patients with ILD. A 6 MW stress echocardiography is useful in assessing the risk of adverse events in patients with ILD.

Keywords Interstitial lung disease · Pulmonary vascular resistance · Prognosis · 6-min walk test · Stress echocardiography

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Introduction

Interstitial lung disease (ILD) is a heterogeneous group of diseases resulting from damage to the lung parenchyma by inflammation and fibrosis of the interstitium [1–3]. Decreased lung volume and diffusion capacity, increased mean pulmonary artery pressure (mPAP), and increased pulmonary vascular resistance (PVR), which are assessed at rest, are independent predictors of mortality in patients with ILD [4–7] and idiopathic pulmonary fibrosis (IPF) [8–11]. Furthermore, oxygen saturation has been shown to predict survival in patients with ILD, not only at rest [8], but also during exercise using a bicycle ergometer [12], and during a cardiopulmonary exercise test [13]. These reports [12, 13] suggest that exercise-induced hypoxia is an important prognostic factor. Exercise-induced hypoxia could be also assessed by the 6-min walk test (6MWT), which is a less-invasive and simple method. The 6MWT has been widely used in the clinical setting, and the minimum oxygen saturation (SpO2) at the end of the 6MWT [12, 14, 15] and walk distance in the 6MWT (6-min walk distance) [16] provide prognostic information in patients with ILD.

Doppler echocardiography, which is also a non-invasive, simple, and reproducible modality, is useful for the prediction of mortality in patients with ILD [7, 9, 10]. Exercise stress echocardiography has been used for the assessment of prognosis in patients with coronary artery disease [17]. Furthermore, exercise stress echocardiography has been applied to assess the cardiopulmonary vascular system in patients with congenital heart disease, pulmonary hypertension (PH) and connective tissue disease (CTD) [18]. Recently, the parameter determined by Doppler echocardiography after the 6MWT (6 MW stress echocardiography) has been shown to be a predictor of future development of PH in patients with CTD [19]. This suggests that a 6 MW stress echocardiography might identify subclinical pulmonary circulatory impairment, which is a probable prognosis predictor in patients with ILD [3, 20]. However, the clinical utility of a 6 MW stress echocardiography in the prediction of cardiopulmonary events in patients with ILD remains unknown. The aim of this study was to determine whether parameters determined by 6 MW stress echocardiography were independent predictors of adverse outcomes in patients with ILD.

Methods

Study patients

This single-center prospective study was conducted at the Sapporo Medical University Hospital. A total of 98 consecutive patients with ILD who were referred to the echocardiographic laboratory at the Sapporo Medical University Hospital for screening of PH from Jul 29, 2016 to Jan 21, 2020 were enrolled. ILD was diagnosed according to the criteria proposed by the American Thoracic Society and European Respiratory Society (ATS/ERS) [1]. ILD was mainly diagnosed on the basis of a combination of clinical and radiological features. All patients showed lung interstitial abnormalities on high-resolution computed tomography (HRCT) images. Of the initially enrolled patients, the following patients were excluded: patients with ILD with follow-up data for less than 3 months ($n = 18$), patients without a measurable tricuspid regurgitation (TR) velocity at post 6 MW stress echocardiography ($n = 3$), patients without pulmonary functional tests data ($n = 3$), ILD patients with concomitant lung cancer ($n = 4$), atrial fibrillation ($n = 1$), and left ventricular (LV) ejection fraction < 30% ($n = 1$). Significant LV hypertrophy (mean wall thickness ≥ 12 mm), significant mitral and/or aortic valve diseases were not included. Finally, 68 consecutive patients [25 patients with IPF, 28 patients with idiopathic interstitial pneumoniae (IIP) other than IPF, and 15 patients with CTD associated ILD] were included in this study. Most patients with IIP other than IPF were patients with nonspecific interstitial pneumonia ($n = 28$), clinically diagnosed using HRCT. Most patients with CTD-associated ILD were patients with interstitial pneumoniae with autoimmune features ($n = 11$) [21]. The other causes of CTD-associated ILD were anti-neutrophil cytoplasmic antibody-associated vasculitis ($n = 2$) and rheumatoid arthritis ($n = 2$). None of the patients with CTD-associated ILD had systemic sclerosis mixed connective tissue disease or systemic lupus erythematosus.

Clinical, echocardiographic, and laboratory test data were collected from the patient's hospital charts. Clinical and laboratory test data collected within 3 months before and after echocardiographic examinations (mean: 6 ± 9 days) were used for analyses of their correlations. Surfactant protein (SP)-A and Krebs von den Lungen-6 (KL-6) were measured using commercially available chemiluminescent enzyme immunosorbent assay kits (SP-A: Sysmex Co., Japan; KL-6: Sekisui Medical Co., Japan). SP-D was measured using an enzyme immunoassay kit (Yamasa Co., Japan). Follow-up data were obtained by reviewing each patient's hospital chart. Follow-up of the patients was started on the day of the echocardiographic

examination and finished by Apr 30, 2020. All-cause mortality and hospitalization due to heart failure (HF) or exacerbation of interstitial pneumoniae during the follow-up period were selected as endpoints. This study was approved by the institutional ethics committee of Sapporo Medical University (IRB number 282-26) and written informed consent was obtained from all the patients.

Pulmonary functional test

Pulmonary functional tests were performed according to the method described by the ATS/ERS task force [22]. The tests were performed within 3 months (mean: 16 ± 18 days) before and after echocardiographic examinations. Vital capacity (VC) and diffusion capacity of the lungs for carbon monoxide (DLco) were measured using CHESTAC-8900 (Chest M.I., Inc., Japan). The results were expressed as the percentage of predicted performance using standard values [i.e., percentage of predicted VC (%VC) and percentage of predicted DLco (%DLco)].

Echocardiography

Conventional transthoracic echocardiography and tissue Doppler echocardiography were performed using Vivid E9 (GE Healthcare Japan Co., Japan). Two-dimensional echocardiography was performed using the standard echocardiographic views, including parasternal long-axis and apical four-, three- and two-chamber views at a left lateral decubitus position. LV ejection fraction (%) was calculated using the biplane modified Simpson's method. Left atrial volume (ml/m^2) was measured using the biplane Simpson's method and was normalized for body surface area [23, 24]. Transmitral flow velocities were determined using pulsed-wave Doppler echocardiography. Mitral flow parameters, including peak velocities during early diastole (E) and late diastole (A), were measured and E/A ratio was calculated. The peak early diastolic myocardial velocity (e') at the medial site of mitral annulus was measured using tissue Doppler echocardiography, and the E/e' ratio was calculated. Tricuspid annular plane systolic excursion (TAPSE) was assessed in the apical four-chamber view with the M-mode cursor through the lateral tricuspid annulus. Right ventricular (RV) end-diastolic dimension was measured at the basal level of the RV cavity on the apical four-chamber view [25]. Pressure gradients of TR and pulmonary regurgitation (PR) at the end-diastole were calculated by applying the simplified Bernoulli equation: $4v^2$ [v = peak velocity of TR (TRV) and PR, (m/sec)]. Inferior vena cava dimension was measured at end-expiration and just proximal to the junction of the hepatic vein. Right atrial pressure (RAP) was estimated using the inferior vena cava diameter and respiration index. RV systolic pressure was calculated by adding the RAP to pressure gradient of TR (TRPG) [25]. Mean pulmonary artery pressure (MPAP) assessed by Doppler echocardiography (MPAPecho) was calculated using the following formula: MPAPecho = 0.6 × RV systolic pressure + 2 [19]. Cardiac output (CO) was calculated using the following formula: CO = [left ventricular outflow tract (LVOT) diameter)^2 × 0.785 × velocity time integral (VTI) of LVOT (LVOT-VTI) × heart rate [18]. A sample volume of tissue Doppler echocardiography was placed at the lateral tricuspid annulus in the apical four-chamber view, and the peak myocardial velocity during systole (RV s') was measured. PVR assessed by Doppler echocardiography (PVRecho) was calculated using the following formula: PVRecho = [TRV × 10/VTI of right ventricular outflow (RVOT-VTI)] + 0.16 [26] (Fig. 1A, B).

6-MW stress echocardiography

The 6MWT was performed indoors along a flat, straight, enclosed corridor with a hard surface [14, 19]. The walking course distance was 50 m. The transcutaneous arterial SpO2 was determined by pulse oximetry. Blood pressure, heart rate, and SpO2 at baseline and post 6MWT and 6-min walk distance were measured. Post 6MWT, TRV, TRPG, RVOT-VTI and LVOT-VTI were obtained by Doppler echocardiography within 30 s. MPAPecho post 6MWT and CO

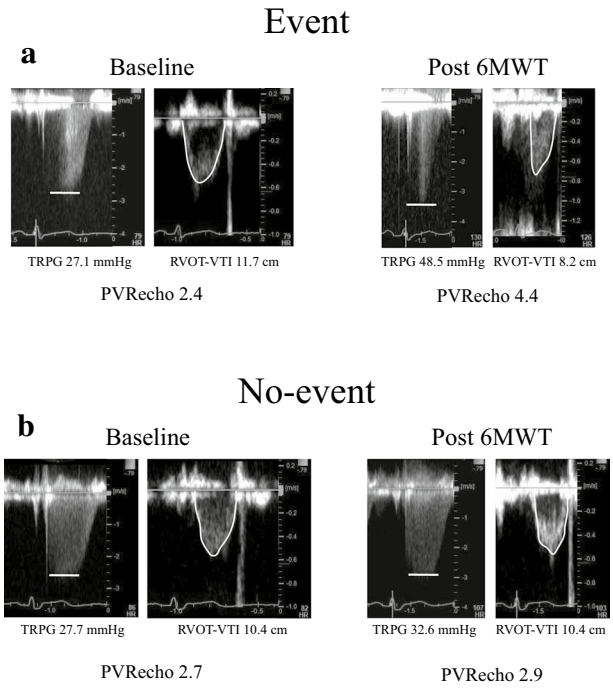

Fig. 1 Representative measurements of pulmonary vascular resistance estimated by Doppler echocardiography (PVRecho) in a patient with (**A**) and without (**B**) cardiopulmonary event during the follow-up period. RVOT, right ventricular outflow; TRPG, pressure gradient of tricuspid regurgitation; VTI, velocity time integral

post 6MWT were calculated using the formulas [18, 19] as shown. Differences of MPAPecho and CO at baseline and post 6MWT (ΔMPAPecho and ΔCO, respectively) were calculated. ΔMPAPecho divided by ΔCO (ΔMPAPecho/ΔCO) was calculated as a parameter of the PAP-CO relationship [19]. PVRecho post 6MWT was also calculated using the formula [26] as shown above. The rate of change in PVRecho from baseline to post 6MWT was calculated using the following formula: rate of change in PVRecho = (PVRecho post 6MWT–PVRecho)/PVRecho × 100.

Statistical analysis

Continuous variables are expressed as means ± standard deviations or medians and interquartile ranges, as appropriate. Differences in continuous variables between the two groups were assessed using the unpaired Student's *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were analyzed by the chi-square test, and Fisher's exact test was used when appropriate. A paired *t* test was used to compare the variables at baseline and post 6MWT. Correlations of both PVRecho and PVRecho post 6MWT with parameters of the pulmonary functional test, serum biomarkers, and data of 6MWT were analyzed using Pearson's method. Correlations of both MPAPecho and MPAPecho post 6MWT with parameters of the pulmonary functional test, serum biomarkers, and data of 6MWT were also analyzed using Pearson's method. To identify independent predictors of cardiopulmonary events in patients with ILD, we established an appropriate prediction model with Cox proportional hazard analysis. A stepwise variable selection procedure was used for the multivariate analysis. Variable selections in the stepwise multivariate regression analysis were performed based on age and variables with assessed in univariate analysis as shown in Table 2 (i.e., male, body surface area, heart rate, systolic blood pressure, IPF, PaO2, KL-6, %VC, 6-min walk distance, minimum SpO2, TAPSE, RV-s', TRPG, MPAPecho, CO, RVOT-VTI, PVRecho, TRPG post 6MWT, MPAPecho post 6MWT, CO post 6MWT, RVOT-VTI post 6MWT, PVRecho post 6MWT, and ΔMPAPecho/ΔCO). We analyzed two different models to avoid interference between TRPG and MPAPecho. In model 1, all variables, except for MPAPecho and MPAPecho post 6MWT, assessed in the univariate analysis were entered into the multivariate analysis. In model 2, all variables, except for TRPG and TRPG post 6MWT, assessed in the univariate analysis were entered into the multivariate analysis. The optimal cutoff values for %VC and PVRecho post 6MWT for differentiation of the patients with cardiopulmonary events (events group) from those without cardiopulmonary events (no-events group) were defined using receiver operating characteristic curves. Event-free curves were calculated using the Kaplan–Meier method and were compared using the log-rank test. Data analysis was performed using commercially available statistical analysis software packages (SPSS version 9.0, SPSS Inc., Chicago, IL). A probability value of <0.05 was considered statistically significant.

Results

The baseline clinical characteristics and demographic data of the patients with ILD are shown in Table 1. The mean age of the patients was 65 ± 10 years, and 44 patients (65%) were men. Heart rate and systolic and diastolic blood pressures at baseline were well controlled and these parameters were significantly ($p<0.01$) increased post 6MWT. Of the 68 patients with ILD, only one patient (1%) was diagnosed as elevated left atrial pressure according to the algorithm [27] and no patient had probable PH indicated by Doppler echocardiography at rest (i.e., peak TR velocity > 3.4 m/sec). RAPs in all the studied patients were estimated to be 3 mmHg. PVRecho and RV systolic pressure were 2.2 ± 0.5 and 22 ± 6 mmHg, respectively. No surgical lung biopsy was performed.

Post 6MWT, TRPG ($p<0.01$), RVOT-VTI ($p<0.01$) and PVRecho ($p=0.02$) were significantly increased compared to those at baseline values (Fig. 2). Significant increases in TRPG (20 ± 4 vs. 28 ± 8 mmHg, $p<0.01$), RVOT-VTI (11 ± 2 vs. 13 ± 2 cm, $p<0.01$) and PVRecho (2.1 ± 0.4 vs. 2.3 ± 0.6, $p=0.02$) from baseline to post 6MWT were found in the no-events group ($n=46$). Similarly, a significant increase in TRPG (25 ± 8 vs. 35 ± 14 mmHg, $p<0.01$) from baseline to post 6MWT was found in the events group ($n=22$). On the contrary, no significant increase in RVOT-VTI (12 ± 3 vs. 13 ± 4 cm, $p=0.06$) and PVRecho (2.3 ± 0.7 vs. 2.7 ± 1.6, $p=0.17$) was observed in the events group ($n=22$). Rates of change in PVRecho from baseline to post 6MWT were comparable in the non-events group and the events group (10 ± 26 vs. 17 ± 50%, $p=0.55$). Two patients had exercise-induced PH as demonstrated by the 6MWT (i.e., estimated peak systolic pulmonary artery pressure > 60 mmHg) [18].

PVRecho was significantly correlated with %VC ($r=-0.35$, $p<0.01$), SP-D ($r=0.29$, $p<0.05$), 6 MW distance ($r=-0.27$, $p<0.05$) and with minimum SpO2 ($r=-0.31$, $p<0.01$), but not with %DLco, SP-A or KL-6. PVRecho post 6MWT was also significantly correlated with %VC ($r=-0.25$, $p<0.05$), SP-D ($r=0.36$, $p<0.01$), and minimum SpO2 ($r=-0.29$, $p<0.05$), but not with %DLco, SP-A, 6 MW distance or KL-6. MPAPecho was significantly correlated with %VC ($r=-0.39$, $p<0.01$) and with minimum SpO2 ($r=-0.33$, $p<0.01$) but not with %DLco, SP-A, SP-D, 6 MW distance or KL-6. MPAPecho post 6MWT was also significantly correlated with %VC ($r=-0.36$, $p<0.01$), SP-D ($r=0.31$, $p<0.05$), and minimum SpO2 ($r=-0.33$,

Table 1 Baseline clinical characteristics and demographic data of patients with interstitial lung disease

Variables	All patients ($n=68$)	Events group ($n=22$)	No-events group ($n=46$)	p value
Age (years)	65 ± 10	68 ± 9	64 ± 10	0.15
Male	44 (65%)	15 (68%)	29 (63%)	0.68
Body syrface area (m^2)	1.7 ± 0.2	1.6 ± 0.2	1.7 ± 0.2	0.39
Heart rate (beats/min)	76 ± 11	73 ± 11	77 ± 11	0.20
Systolic blood pressure (mmHg)	117 ± 11	118 ± 11	117 ± 10	0.86
Diastolic blood pressure (mmHg)	67 ± 10	67 ± 9	66 ± 10	0.72
Heart rate post 6MWT (beats/min)	105 ± 15	105 ± 16	104 ± 14	0.83
Systolic blood pressure post 6MWT (mmHg)	150 ± 25	150 ± 27	150 ± 25	1.00
Diastolic blood pressure post 6MWT (mmHg)	76 ± 19	71 ± 12	79 ± 20	0.13
Hypertension	16 (23%)	8 (36%)	8 (17%)	0.08
History of smoking	49 (72%)	17 (77%)	32 (70%)	0.35
IPF	25 (37%)	8 (36%)	17 (37%)	0.93
Idiopathic IP other than IPF	28 (41%)	12 (55%)	16 (35%)	0.09
Connective tissue disease-associated ILD	15 (22%)	2 (9%)	13 (28%)	0.08
Medications				
ACE-I or ARB	10 (15%)	1 (5%)	9 (20%)	0.10
Oral corticosteroids	8 (12%)	3 (14%)	5 (10%)	0.74
Immunosuppressants	2 (3%)	1 (5%)	1 (2%)	0.59
Antifibrotic drugs	0	0	0	–
Laboratory data				
Estimated GFR (ml/min/1.73m^2)	75 ± 20	70 ± 20	78 ± 21	0.12
Brain natriuretic peptide (pg/mL)	21 (11–47) ($n=50$)	23 (10–75) ($n=16$)	21 (14–43) ($n=34$)	0.76
LDH (IU/L)	211 (181–251)	191 (169–242)	217 (194–253)	0.12
PaO_2 (mmHg)	84 ± 10	83 ± 11	85 ± 4	0.37
SP-A (ng/mL)	50 (39–87)	45 (33–100)	56 (40–84)	0.34
SP-D (ng/mL)	207 (116–307)	197 (104–323)	208 (129–301)	0.82
KL-6 (U/mL)	773 (435–1763)	606 (436–1459)	971 (429–1905)	0.50
Pulmonary function data				
VC % predicted (%)	89 ± 22	79 ± 16	94 ± 23	< 0.01
DL_{CO} % predicted (%)	58 ± 18	54 ± 23	59 ± 16	0.35
6MWT data				
6-min walk distance (m)	416 (352–476)	382 (342–475)	450 (376–489)	0.22
Minimum SpO2 (%)	89 ± 5	89 ± 4	90 ± 5	0.65
Minimum SpO2 < 88%	19 (28%)	7 (32%)	12 (26%)	0.62
Echocardiographic data at baseline				
Left atrial volume (mL/m^2)	25 ± 8	28 ± 11	24 ± 6	0.11
LV ejection fraction (%)	62 ± 6	63 ± 7	61 ± 5	0.31
E/A ratio	0.8 ± 0.3	0.8 ± 0.4	0.8 ± 0.2	0.86
E/e' ratio	10 ± 5	9 ± 3	10 ± 6	0.67
RV end-diastolic dimension (mm)	36 ± 4	36 ± 4	35 ± 5	0.68
Inferior vena cava dimension (mm)	13 ± 2	13 ± 2	13 ± 2	0.28
TAPSE (mm)	18 ± 3	18 ± 3	18 ± 3	0.95
RV s' (cm^2)	11 ± 2	11 ± 2	11 ± 2	0.96
TRPG (mmHg)	22 ± 6	25 ± 9	20 ± 3	< 0.05
MPAPecho (mmHg)	17 ± 4	19 ± 5	16 ± 2	< 0.05
CO (L/min)	4.1 ± 1.4	4.0 ± 0.7	4.2 ± 1.7	0.51
RVOT-VTI (cm)	12 ± 2	12 ± 3	12 ± 2	0.94
PVRecho	2.2 ± 0.5	2.3 ± 0.7	2.1 ± 0.4	0.05
Echocardiographic data post 6MWT				
TRPG post 6MWT (mmHg)	30 ± 11	35 ± 14	28 ± 9	< 0.05

Table 1 (continued)

Variables	All patients ($n=68$)	Events group ($n=22$)	No-events group ($n=46$)	p value
MPAPecho post 6MWT (mmHg)	22 ± 7	25 ± 8	21 ± 5	< 0.05
CO post 6MWT (L/min)	4.3 ± 1.1	4.4 ± 1.1	4.3 ± 1.0	0.57
ΔMPAP/ΔCO (mmHg/L/min)	1.0 ± 1.6	1.1 ± 1.6	1.0 ± 1.6	0.75
RVOT-VTI post 6MWT (cm)	13 ± 3	13 ± 4	13 ± 2	0.80
PVRecho post 6MWT	2.4 ± 1.0	2.7 ± 1.6	2.3 ± 0.6	0.19

Data are presented as the mean value ± SD or median (25th–75th percentile) or number (%) of patients. Brain natriuretic peptide, LDH, SP-A, SP-D, KL-6 and 6-min walk distance between two groups were assessed by the Mann–Whitney *U* test

A peak velocity of transmitral flow during late diastole, *ACE* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *CO* cardiac output, *DLco* diffusion capacity of lungs for carbon monoxide, *E* peak velocity of trasmitral flow during early diastole, *e'* peak myocardial velocity during early diastole, *GFR* glomerular filtration rate, *ILD* interstitial lung disease, *IP* interstitial pneumonia, *IPF* idiopathic pulmpnary fibrosis, *KL-6* Krebs von den Lungen-6, *LDH* lactic acid dehydrogenase, *LV* left ventricular, *MPAP* mean pulmonary artery pressure, PaO_2 arterial partial pressure of oxygen, *PG* pressure gradient, *PVRecho* pulmonary vascular resistance estimated by Doppler echocardiography, *RV* right ventricle, *RVOT* right ventricular outflow, *s'* peak myocardial velocity during systole, *6MWT* six-minute walk test, *SP-A* surfactant protein-A, *SP-D* surfactant protein-D, *SpO2* oxygen saturation, *TAPSE* tricuspid annular plane systolic excursion, *TRPG* pressure gradient of tricuspid regurgitation, *VC* vital capacity, *VTI* velocity time integral

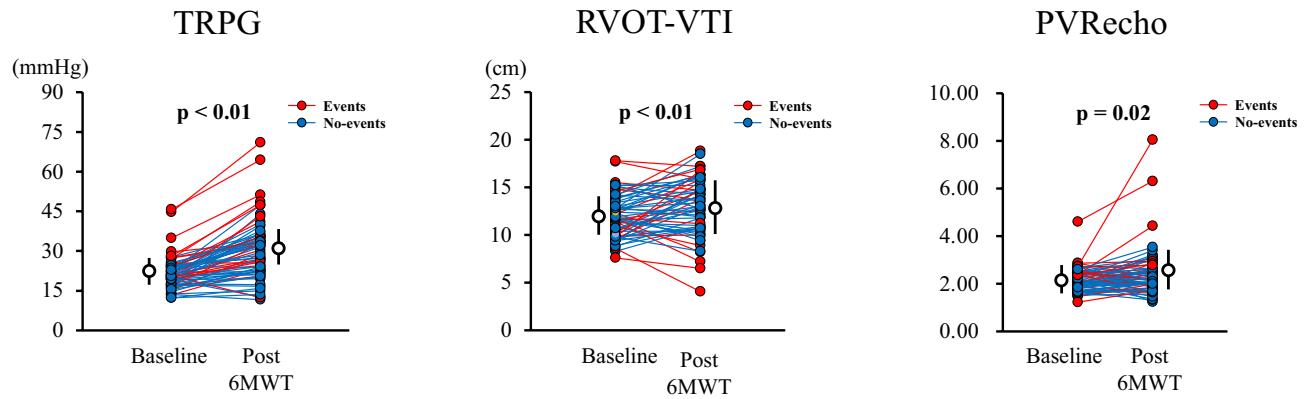

Fig. 2 Doppler echocardiographic parameters at baseline and post 6-min walk test (6MWT). *PVRecho* pulmonary vascular resistance estimated by Doppler echocardiography; *RVOT* right ventricular outflow, *TRPG* pressure gradient of tricuspid regurgitation, *VTI* velocity time integral. Red circles, patient with events; blue circles, patient without events

$p < 0.01$) but not with %DLco, SP-A, 6 MW distance or KL-6.

Eight patients (12%) were treated with oral corticosteroids and two patients (3%) were treated with immunosuppressants. No patient was treated with antifibrotic drugs (i.e., pirfenidone and nintedanib). These choice of treatment was determined by the treating physicians.

Comparisons between survivors and non-survivors

During a mean follow-up period of 22 ± 12 months, 22 patients (32%) had cardiopulmonary events (i.e., events group), including death due to acute respiratory failure ($n=1$), hospitalization due to HF ($n=2$), and hospitalization due to exacerbation of interstitial pneumoniae ($n=19$). The major etiology of interstitial pneumoniae exacerbation was IIP other than IPF ($n=10$). As shown in Table 1, the events group had a significantly lower %VC a higher TRPG and TRPG post 6MWT, and a higher MPAPecho and MPAPecho post 6MWT than those in the no-events group. PVRecho in the events group tended to be higher than that in the no-events group (2.3 ± 0.7 vs. 2.1 ± 0.4, $p=0.05$). There were no significant differences in age, gender, systolic and diastolic blood pressures, heart rate, SP-A, SP-D, and KL-6 levels, LV ejection fraction, E/A ratio, RV end-diastolic dimension, TAPSE, and RV s', CO, CO post 6MWT, and ΔMPAPecho/ΔCO between the two groups.

Univariate and multivariate analyses for prediction of mortality

According to univariate analysis, %VC, TRPG, MPAPecho, PVRecho, TRPG post 6MWT, MPAPecho post 6MWT, and PVRecho post 6MWT, however, not 6-min walk distance nor minimum SpO2 during 6MWT, were significantly associated with cardiopulmonary event in patients with ILD, as shown

Table 2 Univariate and multivariate analysis using Cox proportional hazards model for cardiopulmonary event in patients with interstitial lung disease

	Univariate analysis			Multivariate analysis in model 1[a]			Multivariate analysis in model 2[b]		
Variables	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.03	0.98–1.09	0.26						
Male	0.76	0.32–1.82	0.54						
Body surface area	0.42	0.06–3.08	0.42						
Heart rate	0.98	0.94–1.02	0.29						
Systolic blood pressure	1.01	0.97–1.04	0.80						
IPF (vs. connective tissue disease-associated ILD and idiopathic IP other than IPF)	0.97	0.41–2.32	0.94						
PaO_2	0.99	0.94–1.04	0.58						
KL-6	1.00	0.99–1.00	0.29						
VC % predicted	0.97	0.95–0.99	0.011	0.97	0.94–0.99	0.009	0.97	0.94–0.99	0.009
6-min walk distance	0.99	0.99–1.00	0.06						
Minimum SpO2	1.00	0.92–1.08	0.89						
TAPSE	1.05	0.88–1.24	0.60						
RV s'	0.97	0.79–1.20	0.79						
TRPG	1.10	1.04–1.16	< 0.001						
MPAPecho	1.16	1.06–1.28	< 0.001						
CO	0.85	0.58–1.24	0.41						
RVOT-VTI	0.95	0.78–1.15	0.58						
PVRecho	3.04	1.29–7.15	0.011						
TRPG post 6MWT	1.04	1.01–1.08	0.009						
MPAPecho post 6MWT	1.08	1.02–1.14	0.004						
CO post 6MWT	0.97	0.64–1.46	0.88						
RVOT-VTI post 6MWT	0.97	0.84–1.12	0.70						
PVRecho post 6MWT	1.50	1.06–1.86	0.017	1.77	1.20–2.63	0.004	1.77	1.20–2.63	0.004
ΔMPAP/ΔCO	1.10	0.84–1.44	0.50						

CI confidence interval, *HR* hazard ratio. Other abbreviations as in Table 1

[a]All variables, except for MPAPecho and MPAPecho post 6MWT, assessed in the univariate analysis were entered into the multivariate analysis using Cox proportional hazards model

[b]All vzriables, except for TRPG and TRPG post 6MWT, assessed in the univariate analysis were entered into the multivariate analysis using Cox proportional hazards model

in Table 2. Multivariate analysis using the Cox proportional hazards model 1 indicated that %VC [hazard ratio (HR): 0.97, $p = 0.009$) and PVRecho post 6MWT (HR: 1.77, $p = 0.004$] independently predict cardiopulmonary events in patients with ILD. In model 2, %VC (HR: 0.97, $p = 0.009$) and PVRecho post 6MWT (HR: 1.77, $p = 0.004$) were also selected as independent predictors of cardiopulmonary events in patients with ILD. The receiver operating characteristic analysis indicated that optimal cutoff values for %VC and PVRecho post 6MWT for differentiation of the events group from the non-events group were 91% and 4.4, respectively. Sensitivity, specificity, positive predictive value and negative predictive value of PVRecho post 6MWT ≥ 4.4 for prediction of cardiopulmonary events were 14, 100, 100, and 71%, respectively. Using the cut-off value of %VC ≤ 91%, sensitivity, specificity, positive predictive value and negative predictive value for prediction of cardiopulmonary events were 73, 54, 43, and 81%, respectively. The Kaplan–Meier analysis showed that the cumulative 1-year event-free survival rates were significantly lower in ILD patients with PVRecho post 6MWT ≥ 4.4 than in those with PVRecho post 6MWT < 4.4 (33 vs. 93%, $p < 0.001$, Fig. 3A). They were also significantly lower in ILD patients with %VC ≤ 91% than in those with %VC > 91% (81 vs. 100%, $p = 0.032$, Fig. 3B).

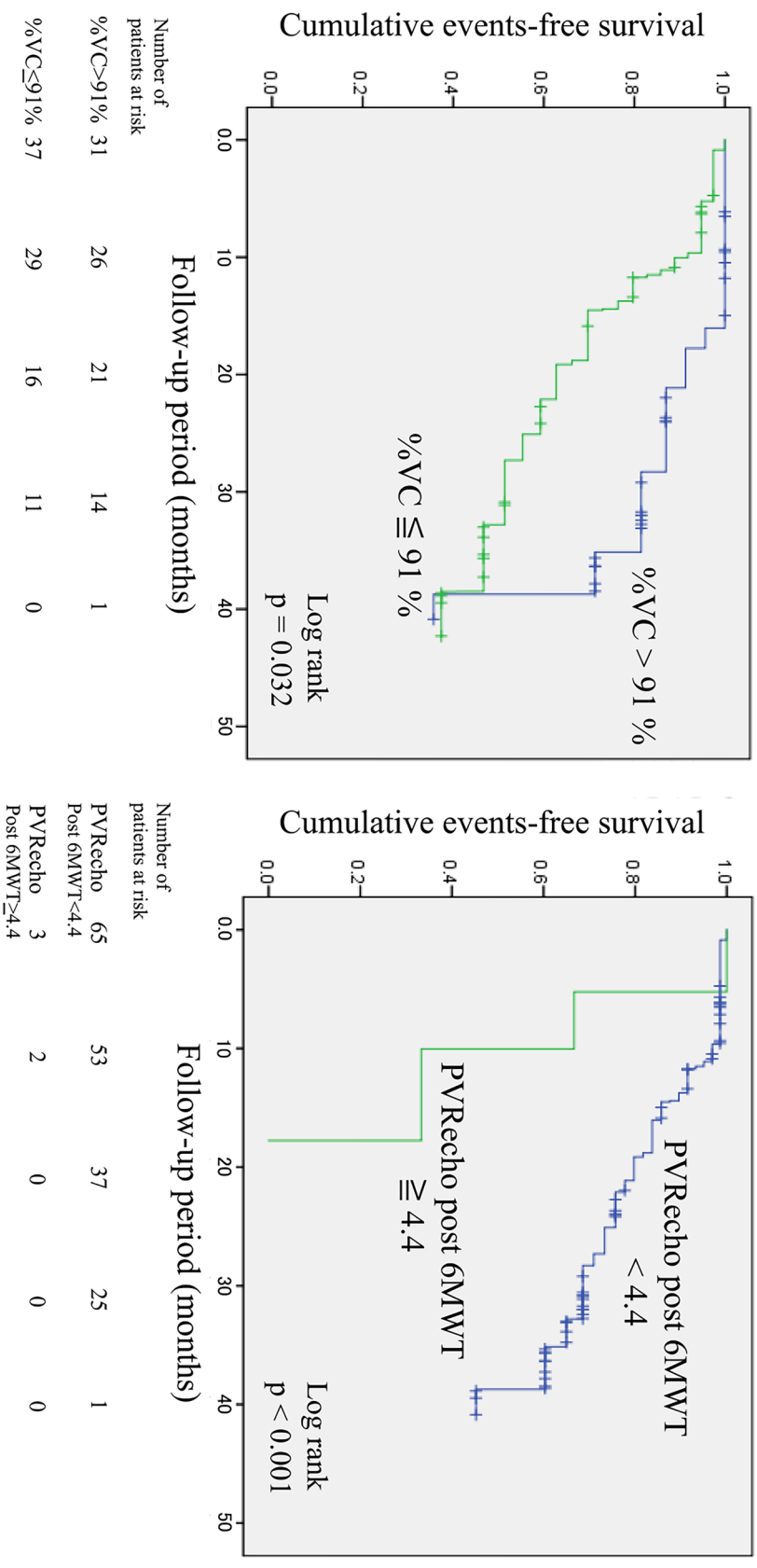

Fig. 3 Kaplan–Meier survival curves for patients with interstitial lung disease who had percentage of predicted vital capacity (%VC) of ≥ 91 versus < 91% (left) and who had pulmonary vascular resistance estimated by Doppler echocardiography (PVRecho) of ≥ 4.4 versus < 4.4 (right)

Discussion

Normal pulmonary circulation has the capacity to accommodate cardiac output at low arterial pressure, even during exercise. This is accomplished by its low-resistance and high-compliance circuit, with large circulatory reserves at rest [28]. During exercise, distension of the pulmonary vasculature and progressive recruitment of the pulmonary circulation result in the maintenance of relatively low arterial pressure despite increasing flow [28]. In this condition, PVR in normal subjects is slightly decreased or maintained, which is dependent on age [29]. In contrast, a significant increase in PVR has been demonstrated during exercise by a bicycle ergometer in patients with IPF [30]. Similar to the findings of an earlier study [30], a significant increase in PVRecho was confirmed in patients with ILD even in the 6MWT, as shown in Fig. 2. Furthermore, we showed for the first time that PVRecho post 6MWT was an independent predictor of cardiopulmonary events in patients with ILD. Collectively, these findings indicate that PVRecho post 6MWT can be used for risk stratification for the development of adverse events, and careful monitoring at the outpatient department might have to be considered for ILD patients with PVRecho post 6MWT ≥ 4.4.

PVR determined by right heart catheterization has been shown to be a predictor of mortality in patients with ILD [4] and in patients with IPF [10]. PVR determined by Doppler echocardiography also has been selected as an independent predictor of mortality in patients with ILD [7]. In this study, PVRecho post 6MWT was a significant predictor of cardiopulmonary events in patients with ILD, as shown in Table 2. The reason for the significant association between adverse events in patients with ILD and PVRecho post 6MWT could not be clarified in this study. However, there are a few possible explanations. Farzaneh-Far et al. [31] demonstrated a significant relationship between increased PVRecho and HF admission in patients with coronary artery disease. They speculated that increased PVRecho indicates adverse structural remodeling in the pulmonary vasculature due to increased left atrial pressure. The main pathological changes of ILD are destruction of the pulmonary capillary bed due to extensive fibrosis and vascular changes, including intimal proliferation and medial thickening of pulmonary arteries [32]. These changes may be related to the loss of vascular distensibility and contribute to the elevated PVR. Hence, increased PVRecho post 6MWT in patients with ILD might reflect advanced adverse structural remodeling in the pulmonary vasculature and severity of pulmonary functional impairment. Our speculation is partially supported by our findings that increased PVRecho post 6MWT was significantly correlated with both reduced %VC and reduced minimum SpO2 at post 6MWT. Degani-Costa et al. [33] reported an abnormal response of MPAP to CO determined during a cardiopulmonary exercise test with right heart catheterization related to pulmonary vascular dysfunction (PVD) in patients with ILD. They also demonstrated a significant relationship between PVR at peak exercise and MPAP/CO slope, which is considered as a surrogate marker of PVD [33]. Furthermore, Lau et al. [34] recently showed that reduction of vascular distensibility, which is similar to increased PVR, during exercise has occurred even in pulmonary vascular disease patients without PH. They suggested that reduced vascular distensibility during exercise could be an index for the detection of early PVD. Collectively, these findings demonstrate that PVRecho post 6MWT may reflect PVD in ILD patients which is associated with adverse events. Several ILD patients with adverse events had extremely elevated PVRecho post 6MWT, although PVRecho at baseline was comparable between ILD patients with and without adverse events, as shown in Figs. 1 and 2. A 6 MW stress echocardiography enables the unmasking of PVD in patients with ILD. Taken together, evaluation of PVRecho obtained during a 6 MW stress echocardiography might contribute to a better clinical assessment of the prognosis in patients with ILD.

ΔMPAPecho/ΔCO determined during 6 MW stress echocardiography with electric cardiometry was shown to be associated with the development of PH in patients with CTD [19]. In contrast to the results of that study [19], ΔMPAPecho/ΔCO determined during 6 MW stress echocardiography failed to predict cardiopulmonary events in patients with ILD. A possible explanation for this discrepancy is the difference between the exercise capacity of patients in this study and that of patients in the earlier study [19]. Patients with ILD in this study had lower 6-min walk distance (416 m) and lower minimum SpO2 (89%) than those in patients with CTD (479 m and 96%, respectively) [19]. Less increased CO from baseline to post 6MWT (4.1 vs. 4.3 L/min, + 5%) than that in the earlier study (4.3 vs. 7.4 L/min, + 72%) [19] might be explained by the low exercise capacity of patients in this study.

An association between %VC and mortality has been shown in patients with IPF [11] and in patients with ILD [7]. We confirmed that %VC was a significant predictor of cardiopulmonary events in patients with ILD, as shown in Table 2. The cutoff value of %VC (> 91%) for the differentiation of the events group from the no-events group was higher than that (> 73%) in an earlier study [7]. A possible explanation for this discrepancy is the difference between the clinical characteristics of the subjects in this study and the earlier study. Patients with ILD in this study had a less decreased arterial partial pressure of oxygen (84%), less impaired %VC (89%) and %DLco (58%), and less increased RV systolic pressure (22 mmHg) than those (79, 88, 50%,

and 24 mmHg, respectively) in an earlier study [7]. Taken together, the findings suggest that %VC could be used for risk stratification in patients with ILD, regardless of disease severity.

It is notable that 6-min walk distance and minimum SpO2 failed to predict cardiopulmonary events in patients with ILD, in contrast to the results of earlier studies [12, 14–16]. A plausible explanation for this discrepancy is the difference between the clinical characteristics of the subjects in this study and the earlier studies [12, 14–16]. Patients with ILD in this study had less impaired %VC (89%) and %DLco (58%) than those in early studies (68–81%, 50–53%, respectively) [14–16]. The less impaired pulmonary function in this study might account for the lack of the predictive value of 6-min walk distance and minimum SpO2 for adverse events. Collectively, these findings suggest that 6 MW stress echocardiography is useful for risk stratification, especially in patients with mild ILD.

Study limitations

This study has several limitations. First, a previous study [35] has already used non-invasive PVRecho evaluation at peak exercise, however, the formula of PVRecho has been validated only at rest [26]. Second, this was a single-center study, and the number of enrolled patients was relatively small. Thus, the possibility of selection bias and insufficient power for detection of statistical differences could not be excluded. A multicenter study with a larger sample size is needed to confirm the prognostic value of PVRecho post 6MWT in patients with ILD. Third, PVRecho post 6MWT had a high positive predictive value but low sensitivity for prediction of cardiopulmonary events in patients with ILD. We consider that the suitable cut-off value of this parameter should be determined in a larger multicenter study. Finally, the wide spectrum and heterogeneity of ILD in this study may be a limitation. However, IPF was not selected as an independent predictor of mortality in multivariate analysis (Table 2), which was also reported in an earlier study [7]. The population in this study reflects the reality for the evaluation of ILD by echocardiography. Hence, the results of this study may be easy to apply in clinical practice.

Conclusions

In addition to the parameter of pulmonary function tests, increased PVRecho post 6MWT is a significant predictor of cardiopulmonary events in patients with ILD. A 6 MW stress echocardiography is useful for assessing the risk of adverse events in patients with ILD.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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