Research

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Serial Measurements of Tricuspid Regurgitation Pressure Gradient by Echocardiography Predict Prognosis in Idiopathic Pulmonary Fibrosis

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ABSTRACT

Background and Objectives: Idiopathic Pulmonary Fibrosis (IPF), especially with emphysema, reportedly involved with Pulmonary Hypertension (PH). However, it is not elucidated whether pulmonary arterial pressure changes serially during the course and influence on prognosis in IPF. We examined whether serial measurements of Tricuspid Regurgitation Pressure Gradient (TRPG) by echocardiography were meaningful predictors of IPF patient survival.
Methods: We retrospectively investigated 83 IPF patients. The echocardiographic TRPG cutoff was set at 30 mmHg, and the subjects were divided into two groups: high TRPG and normal TRPG. We also evaluated the relationship between serial TRPG changes during follow-up.
Results: A total of 28 patients were included in the high TRPG group. The high TRPG group showed significantly lower %FVC and %DLco, higher A-aDO$_2$, shorter 6-minute walk test distance, and more frequent emphysema than the normal TRPG group. The high TRPG group also had poorer survival than the normal TRPG group. A multivariate Cox proportional hazard model demonstrated that TRPG, %FVC, and A-aDO$_2$ significantly affected patient survival. Thirty-six patients underwent echocardiography twice. At the time of the second echocardiography, 7 patients with normal TRPG at baseline (n=22) increased to a TRPG of more than 30 mmHg. These patients had significantly showed poorer survival.
Conclusions: TRPG is an independent prognostic factor in IPF. Emphysema involvement, decreased DLco, and decreased FVC were associated with an increase in TRPG. Serial measurements of TRPG are recommended for the early detection of PH and predict prognosis in IPF patients.

KEYWORDS: Tricuspid regurgitation pressure gradient; Idiopathic pulmonary fibrosis; echocardiography; Combined pulmonary fibrosis and emphysema.

ABBREVIATIONS: 6MWD: 6-minute walk test distance; A-aDO2: Alveolar-arterial oxygen difference; ATS: American Thoracic Society; BNP: Brain natriuretic peptide; CPFE: Combined Pulmonary Fibrosis and Emphysema; DLco: Diffusing capacity of the lung for carbon monoxide; ERS: European Respiratory Society; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; HOT: Home Oxygen Therapy; IPF: Idiopathic Pulmonary Fibrosis; KL-6: Krebs vonden Lungen-6; LAA: Low Attenuation Area; LDH: Lactate Dehydrogenase; PAP: Pulmonary Arterial Pressure; PH: Pulmonary Hypertension; RHC: Right Heart Catheterization; RVSP: Right Ventricular Systolic Pressure; SP: Surfactant Protein; TRPG: Tricuspid Regurgitation Pressure Gradient.

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a progressive fibrotic disorder of unknown etiology with no cure.[1] The prediction of individual patient survival is difficult because of its heterogeneity, although the overall prognosis is poor with a median survival of 2.4-3.5 years.[2-4] Pulmonary Hypertension (PH) is an important comorbidity of advanced IPF that has a significant negative impact on survival.[5-7] Variable prevalence (range, 32%-84%) of PH has been reported.[5,6]

Combined Pulmonary Fibrosis and Emphysema (CPFE) has been proposed as a new phenotype of pulmonary fibrosis, defined by the presence of emphysema of upper lobe and fibrosis of the lower lobe.[8] PH involvement is more frequent in IPF with emphysema than in IPF without emphysema, and PH is believed to be a poor prognostic factor of CPFE.[7,8] In IPF, there is a possibility that CPFE patients are substantially included among IPF patients with PH. However, it is not clear how many CPFE patients were included in IPF with PH and related with prognosis.

Although, Right Heart Catheterization (RHC) is the gold standard for PH diagnosis,[9] this procedure is not easy to perform routinely because of its invasiveness. On the other hand, echocardiography is a noninvasive screening modality that can be useful for detecting the cause of suspected or confirmed PH.[9,10] Although echocardiography is inferior to RHC in accuracy,[11,12] several reports have suggested that it can provide a useful prognostic value of IPF.[6,13] However, most previous studies on the relationship between PH and IPF were cross-sectional analyses. Therefore, it is unknown whether clinical parameters, including Pulmonary Arterial Pressure (PAP), change serially during the natural course of IPF. The risk of PH onset is also unclear.

In the present study, we focused on PH and estimated the significance of the Tricuspid Regurgitation Pressure Gradient (TRPG), a noninvasive indicator relevant to PAP, to predict the survival of IPF patients with or without emphysema in both early stage and advanced stage disease. We also evaluated the relationship between serial changes in TRPG during follow-up and clinically practical indicators associated with the increased risk of mortality in IPF patients.

METHODS

Subjects

We performed a retrospective cohort study of 83 IPF patients at Sapporo Medical University Hospital between April 2007 and December 2013. This study was approved by the Institutional Review Board of the Sapporo Medical University Hospital. All subjects provided written informed consent. The diagnosis of IPF was made in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) statement.[1] All patients underwent High Resolution Computed Tomography (HRCT), pulmonary function tests, 6-minute walk tests, blood gas analysis, blood sample measurements, and echocardiography. Thirty-two of 83 patients underwent these examinations again after an appropriate interval. We excluded patients with cardiovascular diseases, infectious diseases, allergic diseases, collagen vascular diseases, granulomatous diseases, or neoplastic diseases and the patients who underwent lung operation.

HRCT and Evaluation of Emphysema

Patients were examined by chest HRCT within one month prior to echocardiography. CT scans were obtained on a Light Speed Ultra scanner (GE Health Care, Tokyo, Japan) using 1.25 mm collimation at 5 mm intervals from the sternal notch to below the diaphragm during breath-holding after a deep inspiration in a supine position at 140 kVp, 170 mA. The lungs were imaged at the window width of 1000 HU and the window level of 700 HU.

We evaluated the extent of emphysema by visual scoring in bilateral lung fields according to the method of Goddard.[14] In brief, both lungs were divided into a total of six areas consisting of three lung fields: the aortic arch, carina, and inferior pulmonary vein levels. The extent was estimated using a 5 points scale for each lesion. Total scores were calculated (maximum total: 24 points) and the severity of emphysema was graded as follows: 0 point (no emphysematous lesions), 1 point (LAA <25% of the entire lung field), 2 points 25% ≤low attenuation area (LAA) <50% of the entire lung field, 3 points (50% ≤LAA <75% of the entire lung field), and 4 points (75% ≤LAA of the entire lung field). HRCT scans were independently reviewed by 3 experienced pulmonologists. Emphysema was defined as a LAA lacking a distinct wall on HRCT. The total emphysema scores of %LAA ≥25% were categorized as IPF patients with emphysema.[15]

Pulmonary Function Tests

Patients were examined by pulmonary function tests within a month before the echocardiography. Chestac 9800 (Chest Co, Tokyo, Japan) was used for pulmonary function tests. We used parameters as follows: forced vital capacity (FVC), predicted percentage of forced vital capacity (%FVC), and forced expiratory volume one second percent (FEV_1/FVC). We measured diffusion capacity (DLco) and predicted the percentage of diffusion capacity (%DLco) according to single-breath carbon monoxide uptake. The alveolar-arterial oxygen difference ($A-aDO_2$) was estimated based on arterial blood gas analysis.

6-Minute Walk Test

6-minute walk test was conducted for patients according to the ATS statement, and the distance on 6-minute walk test (6MWD) was evaluated.[16]

Echocardiography

Conventional transthoracic echocardiography was performed using Vivid7 or VividE9 (GE Health Care, Tokyo, Japan) with M5S transducer. Two-dimensional echocardiography was performed using the standard echocardiographic views, including parasternal long-axis and apical 4-, 3-, and 2-chamber views at a left lateral decubitus position. TRPG was calculated by applying the simplified Bernoulli equation: $4V^2$ (v=peak velocity of tricuspid regurgitation, m/s); and high TRPG was defined as TRPG $\geq$30 mmHg.[9,17]

Blood Sample Measurements

Plasma brain natriuretic peptide (BNP), surfactant protein (SP)-A, SP-D, and Krebs vonden Lungen-6 (KL-6) in sera were measured using commercially available ELISA kits at enrollment (STACIA CLEIA BNP kit, LSI medience, Tokyo, Japan; SP-A test Kokusai-F kit, SYSMEX CORPORATION, Kobe, Japan; SP-D kit YAMASA EIA II, Yamasa, Chosi, Japan; Picolumi KL-6 kit, EIDIA Co., Ltd, Tokyo, Japan).

Statistical Analysis

All data were expressed as the mean ± standard deviation (SD) or 95% confidence interval (CI). Differences between the two groups were assessed using the Mann-Whitney test. A chi-square test or Fisher's exact test was used to compare categorical data. Correlations were calculated using Spearman's correlation test. The differences between the three groups were assessed by one-way analysis of variance (one-way ANOVA). Tukey HSD post hoc tests were used for differences between each pair of groups. The survival analysis was completed according to the method of Kaplan-Meier, and the log-rank test was used to compare survival curves. The multivariate Cox's proportional hazard model was used to examine the association of selected variables with survival. Variables that were significant ($p<0.05$) in the univariate analysis were included in the multivariate model.

All tests were performed at a significant level of $p<0.05$. Analyses were completed using IBM SPSS statistics version 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

IPF Patient Demographic Features

Based on echocardiographic TRPG measurements, 83 patients with IPF were classified into two groups named high TRPG (TRPG $\geq$30 mmHg) and normal TRPG (TRGP <30 mmHg) (Table 1). The high TRPG group included 28 patients (33.7%). They had significantly lower values of FVC, %FVC, DLco, and %DLco; higher values of A-aDO$_2$; and a shorter distance in 6MWD as compared with the normal TRPG group. The prevalence of emphysema in 83 IPF patients was 35% (29 of 83 patients). Emphysema was more common in the high TRPG group than in the normal TRPG group (50% *versus* 27%, $p<0.05$). There was no significant difference between the high TRPG group and normal TRPG group in terms of other demographics or serum biomarkers.

Next, we examined the relationship between TRPG and other parameters. TRPG showed significantly weak to moderate correlations with 6MWD, FVC, %FVC, FEV$_1$/FVC, DLco, %DLco, and A-aDO$_2$ (Table 2). On the other hand, no significant difference was found in the relation of TRPG with age, BNP, lactate dehydrogenase (LDH), KL-6, SP-A, and SP-D.

Prediction of Survival

Kaplan-Meier survival analysis showed that high TRPG patients had significantly worse survival than normal TRPG patients (p=0.004) (Figure 1).

Evaluation of Prognostic Factors

The univariate Cox's proportional hazard model demonstrated that TRPG (HR=1.095; 95% CI, 1.045-1.148; $p<0.001$) and several other variables had a statistically significant impact on survival (Table 3). The multivariate Cox's proportional hazard model demonstrated that TRPG (HR=1.059; 95% CI, 1.010-1.110; p=0.017), A-aDO$_2$ (HR=1.031; 95% CI, 1.008-1.053; p=0.007), and %FVC (HR=0.930; 95% CI, 0.904-0.957; $p<0.001$) significantly affected survival.

Serial Changes in TRPG during Follow-Up and Survival

Of the 83 patients, 36 underwent echocardiography twice (mean interval, 14.6±6.6 months). Among these patients, 14 and 22 were classified into the high TRPG group and the normal TRPG group, respectively, at first echocardiography. At the second echocardiographic assessment, 7 (31.8%) patients in the normal TRPG group increased to TRPG more than 30 mmHg (named "increased TRPG") (Table 4). However, the other showed TRPG less than 30 mmHg at the second assessment (named "maintained TRPG").

The increased TRPG group showed significantly lower values of FVC, %FVC, and DLco when compared with the maintained TRPG group. The rate of emphysema involvement was higher in both the increased TRPG and the high TRPG group than in the maintained TRPG group. Increased TRPG showed significantly worse survival of the maintained TRPG group (p=0.042) (Figure 2). Patient survival in the increased TRPG group was similar (1-year mortality: 55.6%; mean survival: 7.8 months) to that of the high TRPG group at first echocardiography (61.2%, 10.8 months; p=0.168).

DISCUSSION

The main purpose of the present study was to clarify whether the TRPG measurement by echocardiography was a meaningful

	All	high TRPG	normal TRPG	*p* value	No
	(n=83)	(n=28)	(n=55)		
Sex M/F	62/21	23/5	39/16	NS	
Age	70±8.0	70±7.5	69±8.2	NS	
Smoker /never-smokers	68/15	23/5	45/10	NS	
Pack-yrs smoking	39±26	38±22	40±28	NS	
IPF specific treatment				NS	
oral corticosteroids	15	6	9		
immunosuppressant drugs	13	6	7		
Pirfenidone	27	6	21		
PH specific treatment	2	2	0		
HOT	15	8	7		
emphysema (+/-)	29/54	14/14	15/40	*p*<0.05	
6MWD (meters)	358±117	301±127	388±101	*p*<0.05	n=76
FVC (L)	2.4±0.8	2.1±0.8	2.6±0.8	*p*<0.05	n=83
FVC % pred (%)	80±24	69±24	86±22	*p*<0.05	n=83
FEV1 /FVC (L)	84±10	87±8.8	82±10	*p*<0.05	n=83
DLco (ml/min/mmHg)	9.8±3.4	7.5±2.5	11±3.3	*p*<0.05	n=72
DLco % pred (%)	47±15	36±12	50±15	*p*<0.05	n=72
A-aDO$_2$ (mmHg)	20±16	27±20	17±13	*p*<0.05	n=83
BNP (pg/ml)	50±76	37±27	57±90	NS	n=83
LDH (IU/l)	230±57	243±58	223±55	NS	n=83
KL-6 (U/ml)	1124±712	1289±901	1040±586	NS	n=83
SP-A (ng/ml)	78±30	81±29	77±31	NS	n=83
SP-D (ng/ml)	273±191	316±239	251±159	NS	n=83
TRPG (mmHg)	26±10	36±7.6	21±6.1	*p*<0.05	n=83

Data given as mean ± SD or numbers. IPF: Idiopathic pulmonary fibrosis; PH: pulmonary hypertension; HOT: home oxygen therapy; 6MWD: six minutes walk test distance; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; A-aDO$_2$: alveolar-arterial oxygen difference; BNP: brain natriuretic peptide; LDH: lactate dehydrogenase; KL-6: krebs von den lungen-6; SP: surfactant protein; TRPG: tricuspid regurgitation pressure gradient.
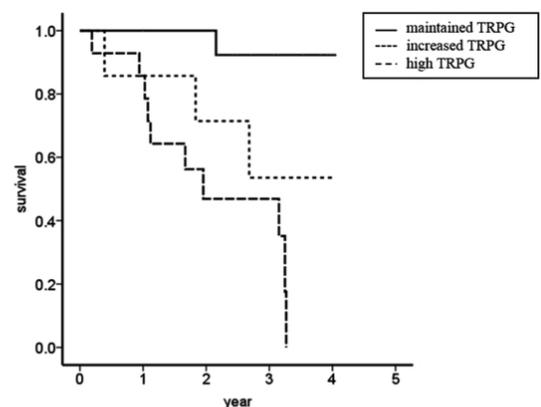
Table 1: The baseline characteristics at initial assessment.
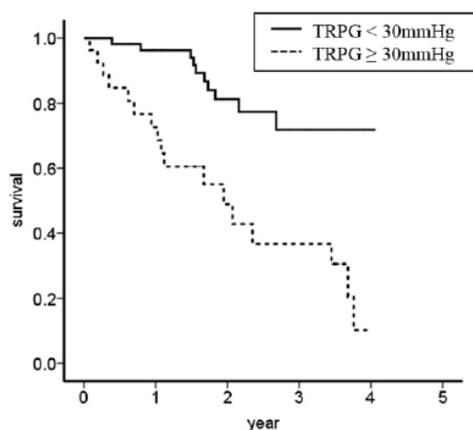
Figure 1: Kaplan-Meier survival curves for patients with IPF according to the baseline assessment of TRPG. Survival time was significantly lower in the patients with TRPG ≥30 mmHg than in those with TRPG <30mmHg (*p*=0.004 log-rank test).

Figure 2: Kaplan-Meier survival curves for IPF patients according to the second assessment of TRPG (*p*=0.001 maintained TRPG *vs.* increased TRPG *p*=0.042, maintained TRPG *vs.* high TRPG *p*<0.001, increased TRPG *vs.* high TRPG *p*=0.168).

	correlation coefficient	p value
Age	0.208	NS
6MWD (meters)	-0.296	$p<0.05$
FVC (L)	-0.284	$p<0.05$
FVC % pred (%)	-0.335	$p<0.05$
FEV1 /FVC (L)	0.239	$p<0.05$
DLco (ml/min/mmHg)	-0.32	$p<0.05$
DLco % pred (%)	-0.247	$p<0.05$
A-aDO$_2$ (mmHg)	0.255	$p<0.05$
BNP (pg/ml)	0.069	NS
LDH (IU/l)	0.158	NS
KL-6 (U/ml)	0.021	NS
SP-A (ng/ml)	-0.015	NS
SP-D (ng/ml)	0.074	NS

TRPG: tricuspid regurgitation pressure gradient; 6MWD: six minutes walk test distance; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; A-aDO$_2$: alveolar-arterial oxygen difference; BNP: brain natriuretic peptide; LDH: lactate dehydrogenase; KL-6: krebs von den lungen-6; SP: surfactant protein.

Table 2: Correlation of parameters with TRPG in 83 IPF patients.

	Parameter	HR(95% CI)	p value
Univariate Cox analysis	Age	1.012(0.965-1.062)	0.612
	Male	2.753(0.826-9.176)	0.099
	emphysema (+)	1.710(0.803-3.641)	0.164
	6MWD (meters)	0.998(0.995-1.001)	0.241
	FVC (L)	0.248(0.128-0.479)	<0.001
	FVC % pred (%)	0.920(0.894-0.946)	<0.001
	FEV1 /FVC (L)	1.136(1.069-1.207)	<0.001
	DLco (ml/min/mmHg)	0.675(0.553-0.824)	<0.001
	DLco % pred (%)	0.924(0.891-0.958)	<0.001
	A-aDO$_2$ (mmHg)	1.032(1.012-1.052)	0.001
	BNP (pg/ml)	0.993(0.984-1.003)	0.152
	LDH (IU/l)	0.998(0.991-1.006)	0.668
	KL-6 (U/ml)	1.000(1.000-1.001)	0.151
	SP-A (ng/ml)	0.995(0.983-1.007)	0.432
	SP-D (ng/ml)	1.002(1.000-1.003)	0.050
	TRPG (mmHg)	1.095(1.045-1.148)	<0.001
	TRPG≥30mmHg	4.510(2.058-9.881)	<0.001
Multivariate Cox analysis	TRPG (mmHg)	1.059(1.010-1.110)	0.017
	A-aDO$_2$ (mmHg)	1.031(1.008-1.053)	0.007
	FVC % pred (%)	0.930(0.904-0.957)	<0.001

IPF, idiopathic pulmonary fibrosis; 6MWD: six minutes walk test distance; FVC: Forced vital capacity; FEV1: forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; A-aDO$_2$: alveolar-arterial oxygen difference; BNP: brain natriuretic peptide; LDH: lactate dehydrogenase; KL-6: krebs von den lungen-6; SP: surfactant protein; TRPG: tricuspid regurgitation pressure gradient.

Table 3: Prognostic factors for overall survival from initial assessment of 83 IPF patients during the follow-up period.

	maintained TRPG	increased TRPG	high TRPG	p value*
	(n=15)	(n=7)	(n=14)	
observation period (days)	475 ± 198	454 ± 172	442 ± 232	NS
Sex M/F	11/4	5/2	14/0	NS
Age	66±8.8	75±3.4	70±8.9	NS
Smoker /never-smokers	12/3	6/1	31/1	NS
Pack-yrs smoking	37±27	48±26	42±22	NS
emphysema (+/-)	2/13	2/5	8/6	NS
6MWD (meters)	387±76	382±163	340±121	NS
FVC (L)	3.1±0.8	2.1±0.7	2.5±0.7	$p<0.05$
FVC % pred (%)	100±19	74±21	76±21	$p<0.05$
FEV1 /FVC (L)	77±10	81±16	85±7.5	NS
DLco (ml/min/mmHg)	13±3.2	8.4±1.5	8.0±2.7	$p<0.05$
DLco % pred (%)	60±17	44±8.8	38±12	NS
A-aDO$_2$ (mmHg)	13±7.0	23±14	21±12	NS
BNP (pg/ml)	47±60	120±208	37±26	NS
LDH (IU/l)	217±33	226±45	229±49	NS
KL-6 (U/ml)	1006±570	1047±502	1311±1111	NS
SP-A (ng/ml)	73±29	90±40	84±35	NS
SP-D (ng/ml)	218±147	275±168	361±257	NS
TRPG (mmHg)	22±3.1	25±3.4	37±5.7	NS

Data given as mean ± SD or numbers. *p values comparing maintained TRPG and increased TRPG groups. IPF: idiopathic pulmonary fibrosis; TRPG: tricuspid regurgitation pressure gradient; 6MWD: six minutes walk test distance; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; A-aDO$_2$: alveolar-arterial oxygen difference; BNP: brain natriuretic peptide; LDH: lactate dehydrogenase; KL-6: krebs von den lungen-6; SP: surfactant protein.

Table 4: Comparison of the baseline characteristics in 36 IPF patients underwent second echocardiography assessment.

predictor of IPF patient survival. We herein demonstrated that TRPG as well as FVC, DL$_{CO}$, and A-aDO$_2$ reflected IPF patient survival.

The precise prevalence and prognosis of PH in IPF patients remains unknown. Our study showed that 35% of IPF patients had high TRGP and demonstrated that TRPG was an independent prognostic factor for disease and patient outcomes. A previous study conducted to support the validity of our results was reported by Kimura et al.[18] Under the evaluation of 101 mild IPF patients (mean %FVC 70.2±20.1%) undergoing RHC, they showed that 35% of the patients had a mean pulmonary artery pressure (m-PAP)>20 mmHg and suggested that m-PAP is an independent prognostic factor. PH is considered to be present even in mild stages in IPF patients. Therefore, the detection of PH by echocardiography is believed to be required not only for advanced stage but also for mild stage disease.

In our study, IPF patients with high TRPG showed significantly lower %FVC than those with normal TRPG. However, FVC reportedly did not show any significant correlation with the severity of m-PAP and right ventricular systolic pressure (RVSP).[19] The discrepancy may be explained by the difference in the enrolled number of IPF patients with emphysema. CPFE patients had severely impaired DLco with preserved lung volumes, and they may have a high prevalence of PH.[8] The proportion of higher RVSP (>50 mmHg) was higher in IPF patients with emphysema than in IPF patients without emphysema.[7] In our study, IPF with emphysema were consistent with CPFE and 14 of 28 IPF patients with high TRPG were CPFE. The proportion of CPFE in IPF patients may have influenced on the correlation between FVC and PH.

We examined serial changes of TRPG and clinical parameters during patients' follow-up. Approximately 32% of the normal TRPG group experienced an increase in TRPG of more than 30 mmHg after a mean interval of 14.6 months. Song et al. reported that 9 of 36 (25%) patients with IPF but not PH at echocardiography were found to have newly developed PH during a follow-up echocardiography (mean interval of 17.7 months) and showed poor prognosis.[13] Our study also confirmed that IPF patients with increased TRPG at follow-up showed a sig-

nificantly poorer prognosis and lower FVC and DLco at the initial examination when compared with patients who maintained TRPG. Furthermore, the IPF patients with emphysema, even in the absence of FVC decline, tended to show increased TRPG at follow-up echocardiography. Thus, TRPG may be an independent indicator that supplements routine pulmonary function tests. These results suggest the importance of monitoring at routine echocardiography through TRPG measurement in patients with IPF, particularly IPF with emphysema.

The high TRPG group showed significantly lower values in DLco and FVC, higher values in A-aDO$_2$, and a shorter distance in 6MWD than the normal TRPG group. Furthermore, the increased TRPG group showed significantly lower values in DLco and FVC at the initial measurement than the maintained TRPG group. Survival with increased TRPG was significantly worse and was similar to that of the high TRPG group. These results suggest that the TRPG of patients having lower values in DLco and FVC can easily increase during follow-up, even if TRPG values remain in the normal range at the initial investigation.

TRPG showed no significant association with plasma BNP levels. This result was different from previous studies wherein BNP showed a correlation with PH severity and a meaningful prediction of prognosis.[13,20,21] These studies included patients with lower mean FVC values and more severe IPF as compared with our study. Plasma BNP levels lack sensitivity in moderate PH for chronic lung disease and may be confounded by left heart abnormalities.[21] We speculated that right ventricular (RV) overload did not reflect BNP elevations in IPF patients with mild stage disease.

In addition, the serum levels of SP-A, SP-D, and KL-6 are established, useful biomarkers in IPF patients.[22-25] They are associated with rapidly declining lung function and/or poor survival. Although we hypothesized that these serum markers may be used as biomarkers of PH in IPF, we could not find a relationship between TRPG and these serum markers.

There were several limitations to our study. First, this was a retrospective cohort study and conducted at only one institute. Therefore, the number of subjects who could be examined for serial changes in TRPG was small. Second, we did not evaluate other RV function parameters. Several RV echocardiographic parameters have been associated with the prognosis of IPF with PH. Rivera-Lebron et al reported that the ratio of right ventricle to left ventricle diameter, right ventricular dilation, and tricuspid annular plane systolic excursion were associated with an increased risk of death.[26] Further studies are required to examine the relationship between the other RV parameters and IPF. Third, we did not sufficiently evaluate the HRCT findings of emphysema. In the present study, although we checked HRCT to diagnose IPF with emphysema, we did not analyze the relationship between the proportion of patients with emphysema or emphysema subtypes and TRPG. Todd et al reported that a paraseptal emphysema pattern in CPFE patients was an indicator of poor prognosis when compared with a centrilobular or mixed emphysema pattern.[27] Further studies are required to examine relationships between the proportion and subtypes of emphysema and PH in IPF patients.

CONCLUSION

TRPG was an independent prognostic factor of IPF. Particularly, as IPF with emphysema frequently involved PH, measuring TRPG serially was recommended for the early detection of PH. Our results suggest the importance of periodic measurement of TRPG by performing echocardiography during IPF patient follow-up.

AUTHOR'S CONTRIBUTIONS

YK, MO, HC and HT designed the study. SY and AH underwent Echocardiography and analyzed the data. YK, MO, GY, KY, KI, KK, HC and HT checked the diagnosis and eligibility of study subjects. YK, MO, GY, HC and HT analyzed and interpreted the data. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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