The assessment of left heart disease in patients with systemic sclerosis and pulmonary hypertension

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ABSTRACT

Objective. *Systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH) is of clinical significance owing to its poor outcome. One of the explanations for the outcome is the copresence of left heart disease (LHD). The aim of this study is to assess LHD phenotype in patients with SSc and pulmonary hypertension (PH).*

Methods. *This study included consecutive patients with SSc who underwent right heart catheterisation to diagnose PAH. Heart failure with preserved ejection fraction (HFpEF) was evaluated according to the recommendation of 6th WSPH and to the Framingham criteria.*

Results. *In total, 76 patients were enrolled in this study. Of them, 42 had PH (mPAP >20 mmHg) with a normal left ventricle ejection fraction (≥50%). Among the 42 patients, four and three patients were classified "HFpEF not excluded" and "HFpEF confirmed" whereas 10 had a clinical diagnosis of HFpEF according to 6th WSPH and Framingham criteria, respectively. These differences were due mainly to relatively low PAWP (<13 mmHg). By a combination of ROC curve and logistic regression analyses, left atrial dimension and left ventricular end-diastolic volume index assessed with echocardiography and cardiac MRI, respectively, had significantly higher predictive values for detecting the complication of HFpEF rather than PAWP.*

Conclusion. *Morphological evaluation using echocardiography and cardiac MRI, compared with haemodynamic evaluation by PAWP, may better reflect the copresence of LHD phenotype in patients with SSc and PH. Our data would also indicate a limited elevation of PAWP in patients with SSc, PH and HFpEF.*

Introduction

Pulmonary arterial hypertension (PAH), also referred to as group 1 pulmonary hypertension (PH), is an increased blood pressure in the circulation of the lung as a consequence of remodelling and constriction of the pulmonary arteries and arterioles, leading to right heart failure in advanced cases. PAH occurs either primarily (idiopathic PAH) or in association with other diseases such as connective tissue diseases. Of connective tissue diseases, systemic sclerosis (SSc) is of particularly clinical significance as an underlying disease of PAH, as the outcome of SSc-PAH is less favourable than that of other PAH (1, 2). There are several potential explanations for the poor outcome of SSc-PAH (3-5). First, pulmonary vasculopathy of SSc-PAH does not always share the histopathological aspects with that of other PAH. Compared to plexogenic pulmonary arteriopathy including endothelial and smooth muscle cell proliferation observed in idiopathic PAH or PAH associated with non-SSc connective tissue diseases, histopathological characteristics of SSc-PAH are more fibrotic, with some cases showing collapse of small vessels (6). Moreover, remodelling of the pulmonary veins and venules is seen in SSc-PAH (7). Second, left heart disease (LHD) due to fibrotic myocardial damages may develop frequently (8, 9) and contribute to PH (group 2 PH) and subsequent pulmonary vascular remodelling (10). Third, interstitial lung disease, which also leads to pre-capillary PH (group 3 PH), coexists in most cases (11). These pathophysiological complexities may be related with a blunted response to current PAH therapies.

Recently, the 6th World Symposium on PH (WSPH) has proposed a probability stratification model on LHD phenotype

in patients with PH, including those with a pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg and thus classified as pre-capillary PH (12). However, this model focuses on aging- or atherosclerosis-related LHD, therefore remains to be validated independently in patients with SSc. In this study, we raised a question which clinical parameters best reflect the presence of heart failure with preserved ejection fraction (HFpEF) in patents with SSc and group 2 PH. This study was aimed to assess and identify group 2 PH spectrum/LHD phenotype in patients with SSc and PH.

Methods

Patients and data extraction

This retrospective cross-sectional, single-centre study involved a cohort of consecutive patients who underwent right heart catheterisation (RHC) to diagnose PAH from July 2010 to July 2019 in Hokkaido University Hospital and met the 2013 American College of Rheumatology/European League against Rheumatism classification criteria of SSc (13). Patients being unwilling to make their clinical data available were excluded. This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval was obtained from the Institutional Review Board of Hokkaido University Hospital (Approval number: 17-0327). Patients' privacy data were strictly protected. Demographic, laboratory and radiological findings were extracted from the medical records. SSc was divided into three subsets, including diffuse cutaneous, limited cutaneous and mixed type, according to the classification of LeRoy *et al*. (14) and the Tanaka's criteria of mixed connective tissue disease (15). In this study, PH was defined as a mean pulmonary arterial pressure (mPAP) of >20 mmHg according to the statement of 6th WSPH (16). MK has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RHC and clinical evaluation

RHC was performed using a balloon-tipped 7.0F thermodilution catheter (Becton-Dickinson, Franklin Lakes,

Table I. Characteristics of enrolled patients.

	All patients (n=76)	Patients with PH (n=43)	Patients without PH (n=33)	*p*-value
Age at initial RHC, years	63.5 [50.3-70.0]	60.0 [48.5-70.0]	65.0 [32.0-80.0]	0.44
Sex female	64 (84.2%)	37 (86.0%)	26 (78.7%)	0.34
Height, m	1.55 [1.48-1.61]	1.56 [1.50-1.60]	154.6 [139-179.3]	0.72
Weight, kg	49.7 [43.1-58.6]	50.9 [45.5-61.2]	47.1 [35.7-71.9]	0.05
BMI, kg/m^2	20.8 [18.5-23.5]	21.6 [19.5-24.6]	20.0 [15.8-28.9]	0.03
Antibodies				
Anti-Scl-70	20 (26.3%)	6 (14.0%)	14 (42.4%)	0.0081
Anti-U1-RNP	24 (31.6%)	17 (39.5%)	7 (21.2%)	0.13
Anti-centromere	24 (31.6%)	14 (32.6%)	10 (30.3%)	0.99
Anti-RNA polymerase III	1 (0.02%)	1 (0.03%)	0 (0.0%)	0.99
Disease subtype				
dcSSc	29 (38.2%)	12 (27.9%)	17 (51.5%)	0.05
lcSSc	22 (28.9%)	11 (25.6%)	11 (33.3%)	0.61
Mixed	25 (32.9%)	20 (46.5%)	5 (15.1%)	0.006
Organ involvement				
Interstitial lung disease	60 (78.9%)	33 (76.7%)	27 (81.8%)	0.77
Renal crisis	6 (7.90%)	2 (4.70%)	4 (12.1%)	0.39
GERD	63 (82.9%)	37 (86.0%)	26 (78.7%)	0.54
Raynaud's phenomenon	70 (92.1%)	39 (90.7%)	31 (93.9%)	0.69
Digital ulcer	31 (40.7%)	15 (34.8%)	16 (48.4%)	0.24
PVOD	4 (5.30%)	4 (9.30%)	0 (0.0%)	0.12
Complications				
Hypertension	25 (32.9%)	12 (27.9%)	12 (36.3%)	0.61
Dyslipidaemia	25 (32.9%)	13 (30.2%)	11 (33.3%)	0.99
Obesity	13 (17.1%)	11 (25.6%)	2 (6.06%)	0.03
Diabetes mellitus	18 (23.7%)	10 (23.3%)	8 (24.2%)	0.99
Atrial fibrillation	18 (23.7%)	9 (20.9%)	9 (27.2%)	0.59
ECG				
Right axis deviation	10 (13.2%)	9 (20.9%)	1 (3.03%)	0.03
Atrial fibrillation	18 (23.7%)	9 (20.9%)	9 (27.2%)	0.59
LBBB	11 (14.5%)	5 (11.6%)	6 (18.1%)	0.51
RBBB	5 (6.6%)	3 (7.0%)	2 (6.06%)	0.99
LVH	9 (11.8%)	3 (7.0%)	6 (18.1%)	0.16
RVH	10 (13.2%)	9 (20.9%)	1 (3.03%)	0.03
AVB, SAB	4 (5.3%)	1 (2.3%)	3 (9.09%)	0.31
Spirometry				
VC (L)	2.17 [1-5.32]	2.23 [1.03-4.35]	2.16 [1.00-5.32]	0.65
%VC	83.1 [30.1-147.6]	81.4 [30.1-147.6]	86 [43.2-120.3]	0.41
FVC (L)	2.16 [0.9-5.53]	2.23 [1.02-4.36]	2.15 [0.9-5.53]	0.55
%FVC	85.2 [24.2-150]	81.4 [24.2-150]	91.4 [42.2-123.5]	0.25
TV	0.6 [0.23-1.11]	0.63 [0.23-1.07]	0.55 [0.25-1.11]	0.17
FEV1.0	1.71 [0.8-4.26]	1.6 [0.83-3.53]	1.80 [0.8-4.26]	0.15
FEV1.0/FVC	80.9 [51.6-98.7]	79.3 [51.6-98.7]	82.6 [59.3-97.8]	0.18
DLco (%)	44.9 [10.0-105.8]	31.8 [10.1-78.1]	57.7 [22.9-105.8]	<0.0001
DLco/VA (%)	55.5 [12.6-165]	48.2 [12.6-99.0]	64.2 [28.4-165.0]	0.0001
FVC/DLco	1.73 [0.63-7.71]	2.98 [1.30-7.71]	1.52 [0.63-4.17]	<0.0001
Laboratory data				
BNP (pg/dl)	52.2 [8.6-13.7x10^3]	58.9 [8.6-1.25x10^3]	49.0 [10.9-13.7x10^3]	0.47
UA (mg/dl)	5.20 [2.20-13.1]	5.30 [2.20-13.1]	4.6 [2.3-7.8]	0.10
Serum creatinine (mg/dl)	0.64 [0.4-7.08]	0.61 [0.4-1.9]	0.66 [0.4-7.08]	0.29
Estimated GFR (ml/min)	75.2 [6.8-138.9]	74.8 [22.9-123.5]	75.4 [6.8-138.9]	0.79
RHC				
mPAP (mmHg)	24 [9-65]	36 [21-65]	16 [9-20]	<0.0001
PAWP (mmHg)	8 [2-26]	8 [2-26]	7 [2-12]	0.03
PVR (Wood Unit)	3.60 [0.98-19.3]	5.81 [2.43-19.3]	2.01 [0.98-3.78]	<0.0001
sPAP (mmHg)	37 [16-105]	55 [33-105]	27 [16-37]	<0.0001
dPAP (mmHg)	14 [4-50]	22 [7-50]	8 [4-15]	<0.0001
CO (L/min)	4.02 [2.27-6.59]	4.00 [2.27-6.59]	4.11 [2.82-6.44]	0.27
CI (L/min/m^2)	2.70 [1.59-4.37]	2.57 [1.59-4.37]	2.97 [1.99-4.03]	0.01
RAP (mmHg)	4 [-1-19]	5 [0-13]	3 [-1-19]	0.02
SvO2 (%)	73.0 [41.0-81.0]	71.5 [41.0-81.0]	74.1 [53.3-79.4]	0.02
TTE				
ePASP (mmHg)	44.0 [20.0-117]	55.0 [20.0-117]	36.5 [21.0-60.0]	<0.0001
TRV (m/s)	3.12 [1.94-5.29]	3.54 [1.94-5.29]	2.80 [2.00-3.70]	<0.0001
LAD (mm)	34.0 [20.0-72.5]	35.0 [20.0-54.0]	33.0 [27.0-72.5]	0.76

	All patients (n=76)	Patients with PH (n=43)	Patients without PH (n=33)	*p*-value
LVEF (%)	66.0 [33.0-84.0]	62.5 [35.3-84.0]	66.0 [33.0-75.0]	0.82
LAVI (ml/m^2)	33.5 [17.2-80.8]	30 [17.2-80.8]	36.1 [21.4-73.2]	0.15
E (cm/s)	67 [34.0-118.6]	73 [34.0-105.6]	77.6 [44.9-118.6]	0.0003
E/A	0.87 [0.47-4.48]	0.82 [0.50-1.53]	0.97 [0.47-4.48]	0.028
DcT (s)	199 [108-356]	190 [108-356]	200 [113-317]	0.43
e'sep (cm/s)	7.3 [2.5-14.2]	6.7 [2.5-12.7]	8.95 [2.70-14.2]	0.061
e'lat (cm/s)	9.6 [4.4-17.5]	9.25 [4.5-14.5]	10.25 [4.4-17.5]	0.26
E/e'	7.80 [4.00-30.0]	7.80 [4.00-18.9]	7.75 [4.90-30.0]	0.62
Cardiac MRI				
LVEDVI (ml/m^2)	58.1 [32.6-97.1]	56.0 [32.6-93.5]	61.4 [37.5-97.1]	0.03
LV mass Index (g/m^2)	45.5 [13.4-84.7]	48.8 [24.2-84.7]	44.2 [13.4-81.1]	0.27
LVEF (%)	62.6 [25.8-84.3]	61.9 [44.6-84.3]	64.3 [25.8-80.8]	0.45
LVAWT (mm)	8.65 [4.70-27.9]	8.65 [4.70-27.9]	8.5 [4.7-14.8]	0.63
RVEF (%)	46.0 [18.9-67.5]	42.4 [19.0-63.2]	55.4 [18.9-67.5]	<0.0001
RVEDVI (ml/m^2)	76.4 [35.3-172]	92.8 [39.0-172]	58.1 [35.3-112.0]	<0.0001
Delayed enhancement	12 (15.8%)	5 (11.6%)	7 (21.2%)	0.34
WHO-FC				
I		1 (2.30%)		
II		3 (6.98%)		
III		24 (55.8%)		
IV		15 (34.9%)		

Values presented as n (%) or median (interquartile range). *p*-values by Mann-Whitney U-test.
dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; GERD: gastroesophageal reflux disease; PVOD: pulmonary veno-occlusive disease; ECG: electrocardiogram; AF: arterial fibrillation; LBBB: light bundle branch block; RBBB: right bundle branch block; LVH: left ventricular hypertrophy; RVH: right ventricular hypertrophy; AVB: atrioventricular block; SAB: sinoatrial block; VC: vital capacity; FVC: forced vital capacity; TV: tidal volume; FEV: forced wx-piratory volume; DLco: diffusing capacity for carbon monoxide; DLco/VA: diffusing capacity for carbon monoxide/alveolar volume; BNP: brain natriuretic peptide; UA: uric acid; GFR: glomerular filtration rate; RHC: right heart catheterisation; TTE: transthoracic echocardiography; MRI: magnetic resonance imaging; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure; CO: cardiac output; CI: cardiac index; RAP: right atrial pressure; SvO2: mixed venous oxygen saturation; ePASP: estimated pulmonary artery systolic pressure; TRV: tricuspid regurgitant velocity; LAD: left atrial dimension; LVEF: left ventricle ejection fraction; LAVI: left atrial volume index; DcT: deceleration time; LVEDVI: left ventricular end-diastolic volume index; LVAWT: left ventricle anterior wall thickness; RVEF: right ventricle ejection fraction; RVEDVI: right ventricular end-diastolic volume index; WHO-FC: The World Health Organisation functional class; NYHA: New York Heart Association functional classification.

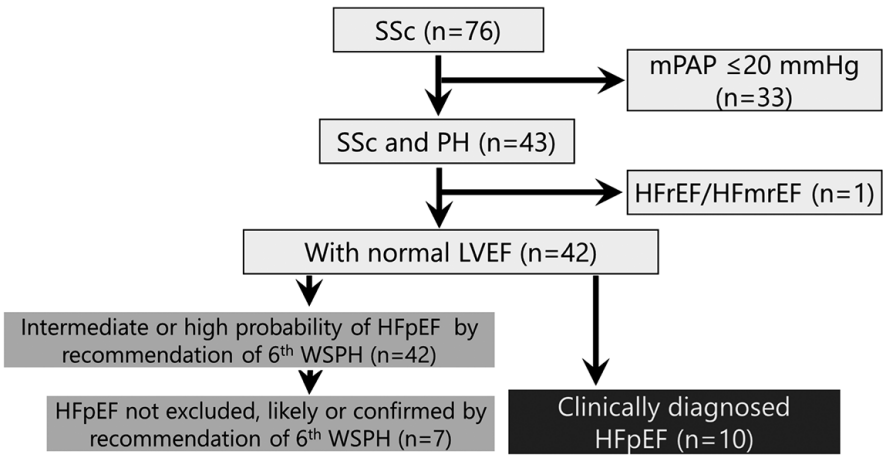

Fig. 1. Evaluation of left heart disease in the patients enrolled in this study.
The total number of systemic sclerosis (SSc) patients was 76, with 43 having pulmonary hypertension (PH, a mean pulmonary arterial pressure of >20 mmHg). One patient had heart failure with reduced ejection fraction (HFrEF). All of 42 patients with SSc, PH and a normal left ventricular ejection fraction (LVEF) were evaluated to have probability of heart failure with preserved ejection fraction (HFpEF) according to the recommendation of 6th WSPH. After considering pulmonary arterial wedge pressure (PAWP), only seven were classified into "HFpEF not excluded, likely or confirmed" group. Conversely, 10 had a clinical diagnosis of HFpEF according to the Framingham criteria.

NJ, USA) via the internal jugular vein or the femoral vein. Pulmonary vascular resistance (PVR) was determined as follows: PVR = (mPAP - PAWP)/CO (cardiac output). CO was measured by the thermodilution technique.

Transthoracic echocardiography (TTE)

Comprehensive TTE was performed in the left decubitus position using commercially available ultrasound systems (Aplio XG/Artida, Canon Medical Systems, Otawara, Japan; Vivid E9, GE Healthcare, Chicago, Illinois, USA; iE33, Philips Medical Systems, Andover, Massachusetts, USA; Prosound F-75, Hitachi Ltd., Tokyo, Japan) according to the guideline (17, 18).

Cardiac magnetic resonance imaging (MRI) acquisition and analysis

We performed cardiac MRI using a 1.5-T scanner (Achieva; Philips Medical Systems, Best, The Netherlands) with a cardiac five-channel phased-array coil, and performed imaging with breath-holding in inspiration for up to 10 seconds. Electrocardiogram-gated cine imaging was performed using a balanced steady-state free precession pulse sequence, during repeated breath-holds. Cine image acquisition parameters were as follows: field of view (FOV), 380mm; repeat time/echo time, 2.8/1.38 ms; acquisition matrix, 192×256 pixels; slice thickness, 10 mm; flip angle, 60 deg; and 20 phases per cardiac cycle. Gadolinium-enhanced cardiac MRI was performed with intravenous administration of 0.1 mmol/kg gadolinium diethylenetriamine penta-acetic acid (Magnevist; Bayer Yakuhin, Osaka, Japan) or gadobutrol (Gadovist; Bayer Yakuhin, Osaka, Japan). After 10 min from the injection, a delayed enhancement image was obtained using an inversion-recovery prepared, 3-dimensional fast field echo pulse sequence with fat saturation. The optimal inversion time was selected to null the signal from normal myocardium using a Look-Locker sequence. The total scan time was about 40 min.
MRI images were analysed with the commercially available software (Extended MR Workspace, Philips Medical Systems, Best, The Netherlands).

The presence of delayed enhancement was visually evaluated.

Definition of LHD phenotype

Heart failure with reduced ejection fraction (HFrEF) and heart failure with midrange ejection fraction (HFmrEF) were defined as a left ventricular ejection fraction (LVEF) of <40% and a LVEF of 40-50%, respectively, measured with TTE (19). HFpEF was evaluated according to the recommendation of 6th WSPH (12) and to the Framingham criteria (20). According to the recommendation of 6th WSPH, patients were evaluated to have low, intermediate or high probability of HFpEF based on clinical parameters including age, metabolic/cardiovascular complications, previous cardiac intervention, and abnormalities on electrocardiogram, TTE or cardiac MRI. Cardiopulmonary exercise testing was not considered to evaluate the probability of HFpEF in this study because of the lack of the data. By combining the probability of HEpEF and PAWP measured with RHC, patients with a PAWP of ≥13 mmHg were further divided into four groups including "Pre-capillary PH" (a PAWP of 13-15 mmHg and low probability of HFpEF), "HFpEF not excluded" (a PAWP of 13-15 mmHg and intermediate or high probability of HFpEF), "HFpEF likely" (a PAWP of >15 mmHg and low probability of HFpEF), and "HFpEF confirmed" (a PAWP of >15 mmHg and intermediate or high probability of HFpEF). In addition, HFpEF is clinically defined by signs and symptoms of heart failure and a LVEF of 50% or greater according to the Framingham criteria.

Statistical analysis

Continuous variables were expressed as median [quartile] and compared using the Man-Whitney U-tests. Categorical variables were expressed as number (percentage) and compared using the Chi-square tests. In multivariate analysis, a forward stepwise approach was adopted for risk factors significant to the necessity of diuretics more than two at univariate analysis. The predictive value of each clinical parameter for detecting the complication of HF-

Table II. Comparison of clinical parameters in patients with and without HFpEF.

	PH with HFpEF (n=10)	PH without HFpEF (n=32)	*p*-value
Age at initial RHC, years	66 [34-82]	59 [29-78]	0.22
Sex female	7 (70.0%)	30 (93.8%)	0.043
Height, m	155.6 [145.2-171.2]	154.7 [139.7-168.6]	0.80
Weight, kg	53.0 [37.3-77.5]	50.7 [28.0-95.1]	0.87
BMI, kg/m^2	20.6 [14.8-35.2]	22.1 [13.4-35.3]	0.46
Antibodies			
Anti-Scl-70	1 (10.0%)	5 (15.6%)	0.66
Anti-U1-RNP	3 (30.0%)	14 (43.8%)	0.44
Anti-centromere	4 (40.0%)	9 (28.1%)	0.48
Anti-RNA polymerase III	0 (0.0%)	1 (0.31%)	0.57
Disease subtype			
dcSSc	4 (40.0%)	8 (25.0%)	0.36
lcSSc	2 (20.0%)	9 (28.1%)	0.61
Mixed	4 (40.0%)	16 (50.0%)	0.58
Organ involvement			
Interstitial lung disease	9 (90.0%)	24 (75.0%)	0.31
Renal crisis	1 (10.0%)	1 (0.31%)	0.37
GERD	8 (80.0%)	28 (87.5%)	0.55
Raynaud's phenomenon	10 (100.0%)	28 (87.5%)	0.24
Digital ulcer	5 (50.0%)	10 (30.3%)	0.28
PVOD	1 (10.0%)	3 (9.38%)	0.95
Complications			
Hypertension	5 (50.0%)	7 (21.9%)	0.049
Dyslipidaemia	2 (20.0%)	10 (31.3%)	0.59
Obesity	2 (20.0%)	9 (28.1%)	0.72
Diabetes mellitus	2 (20.0%)	8 (25.0%)	0.86
Atrial fibrillation	6 (60.0%)	3 (9.38%)	0.0007
ECG			
Right axis deviation	4 (40.0%)	5 (15.6%)	0.10
LBBB	2 (20.0%)	3 (9.38%)	0.36
RBBB	1 (10.0%)	2 (6.25%)	0.68
LVH	1 (10.0%)	1 (0.31%)	0.37
RVH	2 (20.0%)	6 (18.8%)	0.93
AVB, SAB	1 (10.0%)	0 (0.0%)	0.07
Spirometry			
VC (L)	2.13 [1.33-4.35]	2.31 [1.03-4.29]	0.74
%VC	80.65 [55.2-102.2]	81.4 [30.1-147.6]	0.65
FVC (L)	1.99 [1.29-4.36]	2.26 [1.02-4.27]	0.74
%FVC	79.2 [48.0-106.8]	81.4 [24.2-149.5]	0.79
TV	0.62 [0.23-0.82]	0.66 [0.24-1.07]	0.45
FEV1.0	1.49 [1.01-3.53]	1.66 [0.83-3.06]	0.70
FEV1.0/FVC	79.1 [68.6-87.9]	79.9 [51.6-98.7]	0.76
DLco (%)	29.8 [15.5-78.1]	39.1 [10.1-70.8]	0.69
DLco/VA (%)	46.5 [25.7-74.4]	51.2 [12.6-99.0]	0.61
FVC/DLco	2.52 [1.32-4.16]	2.39 [1.3-7.71]	0.55
Laboratory data			
BNP (pg/dl)	133.5 [9.6-448.7]	44.1 [8.6-1254.1]	0.29
UA (mg/dl)	538 [3.8-10.9]	5.3 [2.2-8.2]	0.31
RHC			
mPAP (mmHg)	33.0 [24.0–46.0]	37.5 [21.0–65.0]	0.50
PAWP (mmHg)	10.0 [5.00-24.0]	8.00 [2.00-26]	0.24
PVR (Wood Unit)	5.13 [2.73-12.9]	6.13 [2.43-19.3]	0.21
sPAP (mmHg)	50.0 [35.0-85.0]	56.0 [33.0-105]	0.63
dPAP (mmHg)	21.0 [10.0-32.0]	22.0 [7.00-50.0]	0.91
CO (L/min)	4.26 [2.81-6.59]	3.97 [2.27-6.00]	0.73
CI (L/min/m^2)	2.68 [1.90-4.37]	2.56 [1.59-3.87]	0.71
RAP (mmHg)	5.50 [1.00-10.0]	4.00 [0.00-13.0]	0.36
SvO2 (%)	69.0 [46.0-79.0]	72.0 [41.0-81.0]	0.42
TTE			
ePASP (mmHg)	51.0 [30.0-85.0]	58.0 [20.0-117]	0.32
TRV (m/s)	3.39 [2.50- 4.47]	3.64 [1.94- 5.29]	0.32
LAD (mm)	42.5 [29.0-54.0]	34.0 [20.0-43.4]	0.007
LVEF (%)	57.0 [56.0-60.0]	68.0 [55.0-84.0]	0.003
LAVI (ml/m^2)	43.2 [17.2-80.8]	29.5 [18.0-47.4]	0.36
E (cm/s)	58.9 [40.5-86.9]	58.7 [34.0-105.6]	0.95
E/A	0.66 [0.51-1.28]	0.82 [0.50-1.53]	0.37

	PH with HFpEF (n=10)	PH without HFpEF (n=32)	*p*-value
DcT (s)	220 [156-260]	187 [108-356]	0.13
e'sep (cm/s)	7.1 [2.5-10.9]	6.6 [3.9-12.7]	0.64
e'lat (cm/s)	9.25 [4.5-14.5]	9.6 [5.2-12.5]	0.99
E/e'	7.45 [6.20-12.7]	8.00 [4.00-18.9]	0.84
Cardiac MRI			
LVEDVI (ml/m^2)	72.4 [40.0-93.5]	52.3 [32.6-79.2]	0.004
LV mass Index (g/m^2)	60.1 [40.1-84.7]	43.6 [24.2-83.1]	0.013
LVEF (%)	59.8 [47.5-84.3]	62.9 [44.6-82.3]	0.27
LVAWT (mm)	9.00 [6.00-27.9]	8.60 [4.70-13.4]	0.52
RVEF (%)	46.2 [29.4-50.8]	42.4 [19-63.2]	0.39
RVEDVI (ml/m^2)	94.0 [61.5-172]	91.8 [39.0-172]	0.78
Delayed enhancement	3 (42.9%)	2 (7.69%)	0.021

Values presented as n (%) or median (interquartile range).
values by Mann-Whitney U-test.

pEF was evaluated by using receiver operator characteristic (ROC) curve. Cut-off levels were defined to maximise Youden Index with sensitivity more than 70% using ROC curve. Screening performance of these parameters were expressed as area under ROC curve (AUC), sensitivity and specificity. All analyses were performed using the JMP Pro software (v. 14.0; SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

In total, 76 patients were enrolled in this study. Of them, 42 had PH (mPAP >20 mmHg) with a normal left ventricle ejection fraction (≥50%). The characteristics of enrolled patients are summarised in Table I. Particularly, interstitial lung disease, gastroesophageal reflux disease and Raynaud's phenomenon were frequently complicated.

Evaluation of HFrEF, HEmrEF and HFpEF in patients with SSc and PH

We first evaluated LHD, including HFrEF, HFmrEF and HFpEF, in patients with SSc and PH (Fig. 1). Of 43 patients with SSc and a mPAP of >20 mmHg, one patient had HFrEF with a decreased LVEF (36%) while the other 42 patients had a normal LVEF (≥50%). Of 42 patients with SSc+PH+normal LVEF, 10 and 32 patients were evaluated to have intermediate and high probability of HFpEF, respectively, whereas no patient had low HFpEF probability, according to the recommendation of 6th WSPH (12). Of note, after considering PAWP, only four, no and three patients were classified into "HFpEF not excluded" group, "HFpEF likely" group and "HFpEF confirmed" group, respectively. These differences were due mainly to relatively low PAWP (<13 mmHg) despite intermediate or high probability of HFpEF, suggesting that PAWP would not well reflect LHD phenotype in patients with SSc and PH. Conversely, 10 patients had a clinical diagnosis of HFpEF according to the Framingham criteria (20).

Comparison of clinical parameters in patients with SSc, PH and HFpEF and those with SSc and PH but without HFpEF

We next compared clinical parameters, including the findings of RHC, TTE and cardiac MRI, in patients with SSc+PH+HFpEF according to the Framingham criteria (20) (n=10) and those with SSc and PH but without HF-

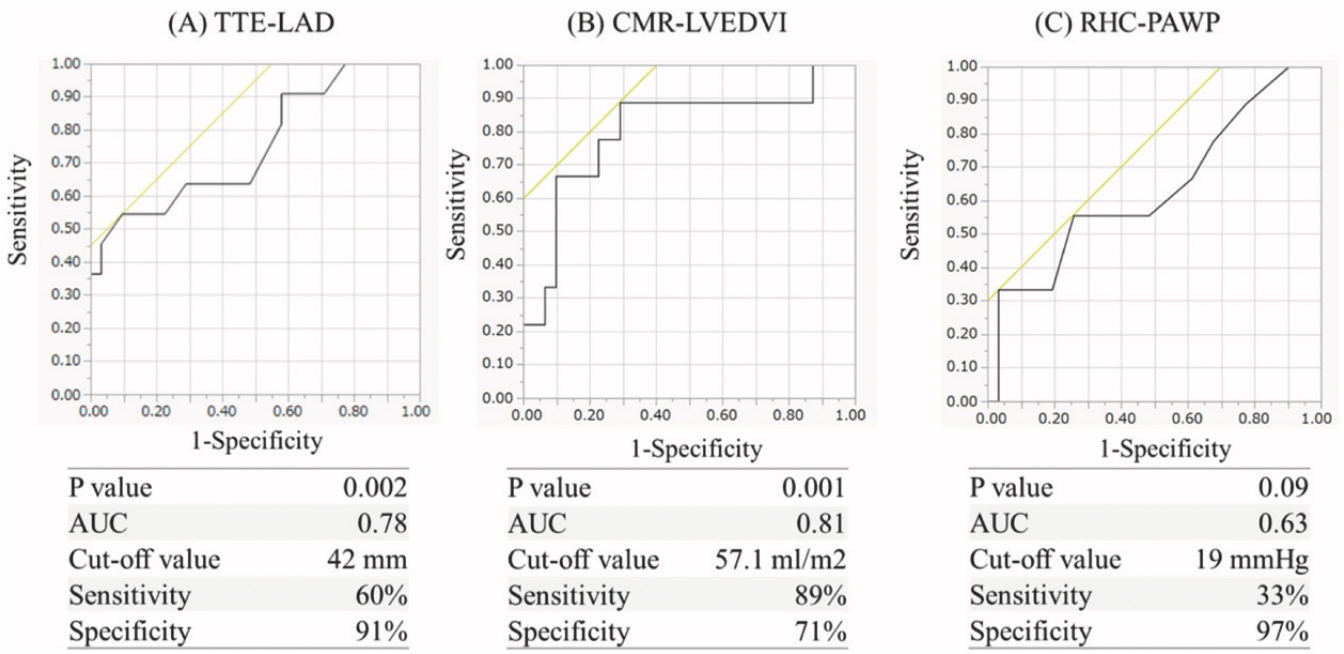

Fig. 2. Predictive values of left atrial dimension (LAD), left ventricular end-diastolic volume index (LVEDVI) and PAWP. They were measured with transthoracic echocardiography (TTE), cardiac magnetic resonance imaging (CMR) and right heart catheterisation (RHC), respectively, for detecting HFpEF (according to the Framingham criteria). AUC: area under ROC curve.

pEF (n=32) (Table II). As indicated in Table II, neither the subsets nor antibodies associated with the complication of HFpEF in the patients with SSc and PH. Male patients tended to be more frequently complicated with HFpEF than female patients. Of note, none of the RHC findings were statistically different between the two groups. The median [range] values of PAWP were 10 [5-24] and 8 [2-26] mmHg in HFpEF group and non-HFpEF group, respectively (p=0.24). Among TTE findings, left atrial dimension (LAD) was higher while LVEF was lower in HFpEF group than in non-HFpEF group with a statistical significance. Among cardiac MRI parameters, left ventricular end-diastolic volume index (LVEDVI) and LV mass index were higher in HFpEF group than in non-HFpEF group with a statistical significance. In addition, delayed gadolinium enhancement in the myocardium was more prevalent in HFpEF group than in non-HFpEF group. We compared the prevalence of arterial hypertension and diabetes, since these are commonly correlated to vascular diseases including LHD or HFpEF. However, these complications did not significantly correlate to LHD or HFpEF in our study.

Predictive values of PAWP, LAD and LVEDVI for detecting the complication of HFpEF

We finally evaluated the predictive values of PAWP, LAD and LVEDVI for detecting the complication of HFpEF using ROC curve. LAD (p=0.002, AUC=0.78) and LVEDVI (p=0.001, AUC=0.81), but not PAWP (p=0.09, AUC=0.63), were significant predictors (Fig. 2), again indicating a limited elevation of PAWP in patients with SSc+PH+HFpEF. Logistic regression analysis also demonstrated the predictive values of LAD and LVEDVI for detecting the complication of HFpEF (Table III). LAD ≥42 mm (OR [95%CI] = 14.5 [2.55–82.2], p=0.003) and LVEDVI ≥57.1 ml/m^2 (OR [95%CI] = 18.6 [2.02–171.0], p=0.01) showed high predictive values, with both cut-off levels defined using ROC curve (Fig. 2). After adjusting for age and sex, the predictive values of LAD ≥42 mm (OR [95%CI] = 12.7 [1.93–83.4], p=0.008) and LVEDVI ≥57.1 ml/m^2 (OR [95%CI] = 20.0 [1.83–218.0], p=0.014) for detecting the complication of HFpEF remained statistically significant.

Table III. Predict values of LAD, LVEDVI and PAWP for detecting HFpEF.

Univariate analysis			
	Odds ratio	p-value	95%CI
LAD≧42.2	14.5	0.003	2.55-82.2
LVEDVI≧57.1	18.6	0.01	2.02-171.0
PAWP≧19	15.5	0.026	1.36-175.0
Multivariate analysis			
	Odds ratio	p-value	95%CI
LAD≧42.2	12.7	0.008	1.93-83.4
LVEDVI≧57.1	20.0	0.014	1.83-218.0
PAWP≧19	13.4	0.048	1.01-177.0

p-values by Logistic Regression Analysis.
The cut-off level of each parameter defined using ROC curve (see Fig. 2).

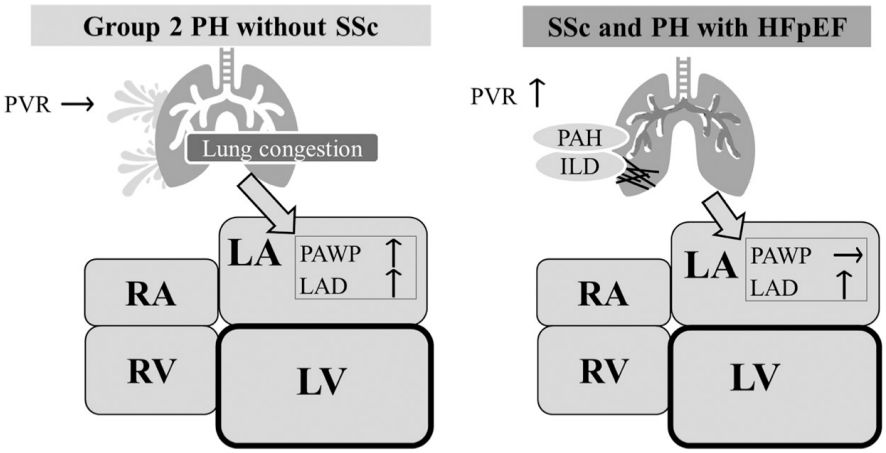

Fig. 3. The scheme regarding the impact of pulmonary vascular resistance (PVR) on PAWP.
The lung condition of SSc may be relatively dry, compared to that of non-SSc group 2 PH, owing to an increased PVR caused by pulmonary arteriopathy (pulmonary arterial hypertension; PAH) and/or interstitial lung disease (ILD).

Discussion

SSc-PAH is not just pulmonary artery disease. In the majority of the patients with SSc-PAH, pulmonary venopathy, LHD and interstitial lung disease, as well as pulmonary arteriopathy, may act independently, additively or even synergistically as effectors in the remodelling and constriction of the pulmonary arteries and subsequent right heart failure (3). The 6th WSPH has proposed several important terms and concepts, such as "PAH with overt features of venous/capillaries involvement" (16), "probability of LHD phenotype" (12), "chronic lung disease with severe PH" (21). These concepts attempt to express a spectrum of extensively complicated pulmonary vascular disease.

We herein demonstrated that morphological approach using TTE and/or cardiac MRI, apart from haemodynamic approach by PAWP, well predicted the presence/copresence of LHD phenotype in patients with SSc and PH. The possible explanations for a less elevated PAWP in patients with SSc+PH+HFpEF than those with HFpEF but without SSc are as follows; the lung condition of SSc may be relatively dry, compared to that of non-SSc group 2 PH, owing to an increased PVR caused by pulmonary arteriopathy and/or interstitial lung disease (Fig. 3). Moreover, increased PVR can impair right ventricular function and alter right and left ventricle interdependence, resulting in decreased left

heart filling pressures. A recent study of patients with SSc reported that myocardial inflammation was detected in 73% on cardiac MRI (22, 23). An endomyocardial biopsy study by Fernandes *et al*. (24) demonstrated abnormal myocardial collagen deposition in 15 out of 16 (94%) patients with SSc but no signs or symptoms of left or right heart disease. In an autopsy study, myocardial fibrosis was detected in 66% while lung fibrosis in 50% of mortal SSc cases (25). Another study using right ventricular myofilaments isolated from endomyocardial biopsies showed diminished contractile force and abnormal calcium sensitivity in SSc-PAH, in contrast to hypercontractile compensation in idiopathic PAH (8). Myocardial fibrosis in SSc would occur sequentially after repeated focal ischaemia due to deranged vasoreactivity and microcirculation, with or without associated structural vascular disease (26). Consistently, a study using single photon emission computed tomography indicated myocardial perfusion defects unrelated to coronary artery distribution and the reversibility of some perfusion defects after vasodilator treatment in patients with SSc (27). Of note, asymptomatic left ventricular diastolic dysfunction detected with TTE or cardiac MRI, which is regarded as a precursor of HFpEF, is associated with increased risk of mortality in patients with SSc (28-30). Therefore, there is an emerged need to identify group 2 PH spectrum/LHD phenotype which may benefit from the concomitant therapy for heart failure such as diuretics.

A study by Bourji *et al*. (31) has shown that left atrial enlargement assessed at TTE is the most discriminative parameter for patients with SSc-PAH (PAWP ≤15 mmHg) from those with SSc, PH and haemodynamically defined HFpEF (PAWP >15 mmHg). Our current results are consistent with those reports and further suggest that the size of left atrium reflect occult LHD phenotype in SSc patients with PAWP of ≤15 mmHg. Another recent study by Lammi *et al*. (32) raised an important question about the definition of group 2 PH which relies upon a single PAWP measurement with a cut-off value of 15 mmHg. They demonstrated a "PAWP class change" (group 1/3 PH to group 2 PH and vice versa) over time in about 30% of patients with SSc and PH. In particular, patients started on a PAH-approved medication after initial RHC had a significant increase in PAWP (from 11±5 to 13±6 mmHg), supporting our scheme regarding the impact of PVR on PAWP (Fig. 3).

Cardiac MRI has recently garnered attention in the assessment of patients with PAH because of its high prognostic value (33, 34). Further, myocardial tissue characterisation using cardiac MRI with gadolinium enhancement has a potential to detect SSc-related early histopathological changes (35, 36). Consistent with these previous studies, the current study would support the usefulness of cardiac MRI in the management of SSc and PH by showing the predictive values of LVEDVI and LV mass index for detecting the complication of HFpEF. Delayed gadolinium enhancement in the myocardium would also be useful for the assessment of myocardial fibrosis in those patients.

This study has several potential limitations. First, it was conducted at a single centre, thus having a small sample size, with a retrospective cross-sectional design. Moreover, our study included only Japanese population, therefore it remained uncertain if the data in this study are applicable for other races. Second, fluid challenge and exercise testing, which may contribute to predict the presence/copresence of LHD phenotype, were not performed in our study.

In conclusion, morphological evaluation using TTE and cardiac MRI, apart from haemodynamic evaluation by PAWP, will give additional information for better recognition of the presence or copresence of group 2 PH spectrum/LHD phenotype in patients with SSc and PH. Our data also indicated a limited elevation of PAWP in patients with SSc+PH+HFpEF. In other words, PAWP may have a pitfall for evaluating presence or copresence of group 2 PH spectrum/LHD phenotype in SSc. A multidisciplinary and integrated approach, rather than adopting the haemodynamic approach only, would be closer to the core of this complex and elusive disease.

Take home messages

- PAWP may be only slightly elevated in patients with SSc, PH and HFpEF.
- Morphological evaluation using echocardiography and cardiac MRI well reflect the copresence of HFpEF.
- A multidisciplinary approach, rather than adopting the haemodynamic approach only, would be recommended to evaluate HFpEF in SSc.

Competing interests

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