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Original Article

Bi-Ventricular Interplay in Patients with Systemic Sclerosis-Associated Pulmonary Arterial Hypertension; Detection by Cardiac Magnetic Resonance

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Abstract

Objectives. Pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc) has a poor prognosis compared to PAH associated with other connective tissue diseases (CTD). The objective of this study was to examine the difference in hemodynamic state between SSc-PAH and other CTD-PAH by performing cardiac magnetic resonance (CMR) imaging.

Methods. A single center retrospective analysis was conducted comprising 40 consecutive CTD patients who underwent right heart catheterization and CMR at the same period from January 2010 to October 2015.

Results. Thirty-two patients had pre-capillary pulmonary hypertension. Of these, 15 had SSc and 17 had other CTD. CMR measurements, particularly the ratio of right to left end-diastolic volume (RVEDV/LVEDV), correlated well with mean pulmonary arterial pressure (mPAP). Conversely, RVEDV/LVEDV and mPAP correlated differently in SSc and non-SSc patients. In SSc patients, the ratio of RVEDV/LVEDV to mPAP was significantly higher compared to non-SSc patients. In the follow-up study, 2 SSc patients exhibited increased RVEDV/LVEDV in spite of decreased mPAP following treatment. Kaplan-Meier analysis revealed poor prognosis of patients with increased RVEDV/LVEDV following treatment.

Conclusions. Our data indicate that altered bi-ventricular interplay detected at CMR may represent SSc-related cardiac involvement and reflect poor prognosis of SSc-PAH.

Introduction

Pulmonary arterial hypertension (PAH) is of clinical significance in connective tissue diseases (CTD) because of its high mortality. In particular, several studies have demonstrated poor prognosis of patients with PAH associated with systemic sclerosis (SSc) compared to those with PAH associated with other CTD (1-3) or idiopathic PAH (4-7). Furthermore, PAH is a relatively common complication of SSc, occurring in about 10 to 12% of the patients (8-10). Early detection as well as accurate evaluation of the severity of PAH is therefore critical in order to improve the prognosis of patients with SSc.

Cardiac magnetic resonance (CMR) imaging has recently been performed in PAH patients. CMR is useful in the estimation of right heart catheterization (RHC) measurements, such as mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) and therefore represents a non-invasive diagnostic tool of PAH (11-13). In addition, CMR has been shown to sensitively detect clinical and subclinical cardiac involvement. At least one cardiac abnormality, such as reduced ejection fraction and diastolic dysfunction, was observed at CMR in up to 75% of patients with SSc (14).

Here we hypothesized that CMR may detect some difference in the hemodynamic state between SSc-PAH and other CTD-PAH to differentiate prognosis in SSc patients.

Materials and methods

Study design

The present retrospective, observational clinical study was conducted in a single center to assess the value of CMR imaging in patients with CTD-PAH. We enrolled 40 consecutive CTD patients who had undergone RHC and CMR within one week from January 2010 to October 2015. All patients had been suspected of having PAH with either unexplainable dyspnea or increased tricuspid regurgitation velocity (>2.8 m/s) measured with echocardiography. CTD-PAH patients were defined as those who had any CTD and met the criteria of pre-capillary pulmonary hypertension (PH) [mPAP of 25 or more mmHg and pulmonary arterial wedge pressure (PAWP) of 15 or less mmHg] (15). Each patient with SSc, systemic lupus erythematosus, mixed connective tissue disease, polymyositis, primary Sjögren's syndrome, primary antiphospholipid syndrome and rheumatoid arthritis fulfilled the 2013 ACR/EULAR SSc criteria (16), 2012 Systemic Lupus International Collaborating Clinics Classification criteria (17) or 1982 ACR criteria for systemic lupus erythematosus (18), at least one of three mixed connective tissue disease criteria [Sharp, Alarcón-Segovia, or Kasukawa] that Ortega-Hernandez OD *et al.* reviewed (19), Bohan and Peter's criteria for polymyositis (20), the 2012 ACR classification criteria for Sjögren's syndrome (21), the classification criteria for definite antiphospholipid syndrome (22), and 2010 ACR/EULAR classification criteria for rheumatoid arthritis (23), respectively. All non-SSc patients did not meet any criteria of SSc (1980 ACR SSc criteria (24), LeRoy/Medsger SSc criteria (25), nor 2013 ACR/EULAR

SSc criteria (16)). The study protocol was approved by the ethics committee of the Hokkaido University Hospital. The present study complied with the Declaration of Helsinki.

Cardiac Magnetic Resonance Imaging

CMR was performed using a 1.5-Tesla Philips Achieva magnetic resonance imaging system (Philips Medical Systems, Best, The Netherlands) with a cardiac five-channel coil, equipped with Master gradients (maximum gradient amplitude, 33 mT/m; maximum slew rate, 100 mT/m/m). Imaging was performed with breath-holding in expiration, using a vector-cardiographic method for electrocardiogram gating. Images were evaluated using commercially available software (Extended MR Work Space: ver. 2.6.3, Philips Medical Systems, Amsterdam, The Netherlands). Left ventricle (LV) volumes were measured using LV short axis images obtained from coronal and sagittal scout images, and manual tracing of LV endocardial borders of contiguous short axis slices at end-diastole and end-systole allowed the calculation of LV ejection fraction. Right ventricle (RV) volumes and ejection fraction were measured in transaxial orientation, as Alfakih *et al.* had demonstrated that the transaxial orientation resulted in better observer variability when compared with the short axis orientation (26). Endocardial and epicardial ventricular borders were manually contoured for quantification of the volume of RV and LV wall. The interventricular septum was regarded as a part of LV wall.

Gd-DTPA (0.1mmol/kg, Magnevist; Berlex Laboratories, Wayne, NJ) was intravenously administered.

Ten minutes after the injection, a breath-holding, inversion recovery-prepared, three dimensional turbo field echo pulse sequence with electrocardiogram gating was performed to obtain a delayed enhancement image with fat saturation of spectral presaturation with inversion recovery.

Statistical analysis

Categorical variables are expressed as percentages, and continuous variables are expressed as mean $\pm$ standard deviation (SD) for those normally distributed or otherwise as medians and interquartile ranges (IQR). *P*-values less than 0.05 were considered significant. Correlation coefficients were assessed by Spearman rank method. Analysis of covariance (ANCOVA) was used to compare two regression slopes. Kaplan-Meier survival estimates were stratified by the optimal cut-off values and compared by log-rank tests. All statistical analyses were carried out with IBM SPSS Statistics (version 22.0.0, Inc.).

Results

Patients' characteristics

A total of 40 CTD patients were enrolled in this study (Table 1). Of 40 patients, 32 (80%) met the criteria of pre-capillary PH, 2 (5%) had isolated post-capillary PH, and 6 (15%) did not have PH. Thirty-seven (93%) were female. Mean age on the enrollment was 53.8 ± 14.5 years. WHO functional class on the enrollment was I, II, III and IV in 1 (3%), 14 (35%), 22 (55%) and 3 (8%) patients, respectively. Twenty-one (53%) patients had SSc, 8 (20%) had systemic lupus erythematosus, 5 (13%) had mixed connective tissue disease, and 6 (15%) had other CTD including polymyositis, primary Sjögren's syndrome, primary antiphospholipid syndrome and rheumatoid arthritis.

RHC and CMR measurements at baseline

All patients enrolled in this study underwent RHC and CMR at the same period. Systolic, diastolic and mean PAP, PAWP, cardiac index (CI), and PVR were measured at RHC. Left and right ventricular end-diastolic volume index (LVEDVI and RVEDVI), left and right ventricular end-systolic volume index (LVESVI and RVESVI), and left and right ventricular ejection fraction (LVEF and RVEF) were measured at CMR. To analyze the interplay between right and left ventricle, the ratio of RVEDV to LVEDV, RVESV to LVESV, and RVEF to LVEF were calculated. The mean value of mPAP was $35.0 \pm$

11.9 mmHg. The median value of PVR and RVEDV/LVEDV were 5.71 [IQR 3.76 - 9.29] wood units (WU) and 1.43 [IQR 1.20 - 1.99], respectively (Table 1).

Difference in RHC and CMR measurements between SSc and non-SSc patients

To evaluate the difference in hemodynamic state between SSc and non-SSc patients with pre-capillary PH, we next compared RHC and CMR measurements in the two groups (Table 2). In SSc patients, mPAP was lower than in non-SSc patients. Conversely, WHO functional class, PVR and CMR measurements were not different in the two groups. These results indicate that RHC measurements alone may not reflect the severity of PAH in SSc patients, presumably due to the presence of clinical or subclinical cardiac dysfunction in that population.

Correlation between mPAP and CMR measurements

To detect SSc-related cardiac dysfunction, we analyzed the correlation between mPAP and CMR measurements in either SSc or non-SSc patients. Among 9 parameters measured at CMR (Table 2), RVEDV/LVEDV, RVESV/LVESV and RVEF/LVEF exhibited a good correlation with mPAP and PVR compared to other RV or LV parameters (Figure 1A, 1B, 1C, Supplementary Figure 1, 2), suggesting these parameters as indicators of PAH severity. Interestingly, in the scattergram of mPAP-RVEDV/LVEDV correlation, the approximate line of SSc patients was dissociated from that of

non-SSc patients (Figure 1D). Conversely, in the scattergrams of mPAP-RVESV/LVESV or mPAP-RVEF/LVEF correlation, approximate lines were similar in the two groups (Figure 1E, 1F). Among the 9 CMR parameters, although not statistically significant, the difference between two slopes, SSc and non-SSc, was the largest in RVEDV/LVEDV (Table 3). To confirm the difference in mPAP-RVEDV/LVEDV correlation between SSc and non-SSc patients, we also evaluated the ratio of RVEDV/LVEDV to mPAP. In SSc patients, (RVEDV/LVEDV)/mPAP was significantly higher compared to non-SSc patients (Table 2). Although duration from PH onset to study entry was shorter and treatment with vasodilators was less frequent in SSc than non-SSc patients (Table 2), no significant relationship was observed between these factors and (RVEDV/LVEDV)/mPAP (data not shown). These results indicate that RVEDV/LVEDV reflects not only the severity of PAH but also SSc-related cardiac dysfunction.

Follow-up study

Of 32 patients with pre-capillary PH enrolled in this study, 17 patients underwent follow-up CMR as well as follow-up RHC synchronously. All patients were treated with at least one vasodilator during follow-up. In most of the patients, mPAP, PVR and RVEDV/LVEDV were decreased following treatment (Figure 2A, 2B, 2C), again suggesting RVEDV/LVEDV as an indicator of PAH severity. RVEDV/LVEDV was increased in 3 patients (Figure 2F) while mPAP and PVR were decreased in 2 of the 3 patients (Figure 2D,

2E). Both of these 2 patients had SSc and one of these 2 patients (Case 2) died due to right heart failure within 2 years since the development of PAH (Table 4). Furthermore, using Kaplan-Meier estimate, our results demonstrated poor prognosis of patients with increased RVEDV/LVEDV following treatment (Figure 3A). The prognosis of patients was much poorer if either mPAP or RVEDV/LVEDV increased following treatment (Figure 3B). Taken together, the change of RVEDV/LVEDV following treatment might be a novel prognostic factor particularly in SSc-PAH patients.

Discussion

We here demonstrate the altered bi-ventricular interplay detected at CMR as SSc-related cardiac involvement which reflects poor prognosis of SSc-PAH. To date, several studies have indicated the poor prognosis of patients with SSc-PAH compared to those with other CTD associated or idiopathic PAH, however the reason for this remains to be elucidated (1, 4, 5). In those studies, mPAP and PVR were similar or even lower in SSc-PAH patients compared to other PAH patients (4). Consistent with these data, mPAP was lower and PVR was similar in SSc patients compared to non-SSc patients in our study. It is therefore suggested that RHC measurements do not always predict the prognosis of patients with SSc-PAH correctly.

CMR has been shown to estimate RHC measurements as well as to provide functional and morphological cardiac information. A recent study performed by Swift AJ, *et al.* (11) indicated that mPAP could be accurately estimated using ventricular mass index, defined as RV mass divided by LV mass, and intraventricular septal angle, both of which represent the interplay between right and left ventricle. They also showed that these two parameters, compared to other LV or RV indexes, better correlated with mPAP. Consistent with these data, RVEDV/LVEDV, RVESV/LVESV and RVEF/LVEF, which also represent bi-ventricular interplay, correlated well with mPAP in our study.

Conversely, a novel aspect of this study was the examination of differences between RHC and CMR measurements. RVEDV/LVEDV and mPAP were differently correlated in SSc and non-SSc patients. In

SSc patients, the ratio of RVEDV/LVEDV to mPAP was significantly higher compared to non-SSc patients. Furthermore, in our follow-up study, RVEDV/LVEDV was increased with high mortality in 2 SSc patients with decreased mPAP and PVR whose PAH were conventionally considered ameliorated. These results indicate that the changes of RHC and CMR measurements following treatment or over time may not always be synchronized. In contrast to other PAH patients, SSc-PAH patients may develop “primary” cardiac involvement due to fibrotic, inflammatory or ischemic myocardial damage as well as “secondary” cardiac dysfunction due to elevated pulmonary arterial pressure (8). Cardiac involvement has been found to be more common than previously expected in SSc patients (27). CMR detected clinical or subclinical cardiac involvement, such as LV diastolic dysfunction and myocardial delayed contrast enhancement, in up to 75% of patients with SSc (14). Taken together, CMR can detect “primary” cardiac involvement of SSc which is difficult to evaluate with RHC and may be an indicator of a poor prognosis in SSc-PAH patients.

Myocardial remodeling has been shown to occur in PAH patients (28). RV adapts to the increased afterload by thickening its wall. In SSc-PAH patients, however, RV mass was less increased compared to idiopathic PAH patients, indicating an impaired cardiac adaptation in SSc-PAH (29). Another study performed by Tedford RJ, *et al.* indicated an impairment of RV contractility, evaluated with RV pressure-volume relations, to compensate for the high afterload in SSc-PAH patients (30). Furthermore, they recently demonstrated the depressed contractile reserve of RV and consequent exercise-associated

RV dilation in SSc-PAH patients (31). In our follow-up study, 2 SSc patients exhibited deteriorated RVEDV/LVEDV in spite of ameliorated mPAP and PVR following treatment. These patients were not likely to compensate even for the decreased afterload following treatment because of the deterioration of “primary” cardiac involvement (Figure 4).

LV kinetic abnormalities such as LV reduced ejection fraction and diastolic dysfunction, compared to RV kinetic abnormalities, have been shown to be 3 times more frequently detected with CMR in SSc patients (14). In our study, LVEDVI and LVEDVI/mPAP were higher in SSc patients than in non-SSc patients, but the differences were not statistically significant. Conversely, RVEDVI/mPAP was higher with statistical significance in SSc patients than in non-SSc patients. These results suggest that SSc patients do not only have left heart disease frequently, but they also easily develop right heart dilation, which may be due to impaired compensation for afterload, if PAH is complicated.

We also evaluated myocardial abnormalities with CMR. Although not statistically significant, myocardial delayed contrast enhancement was frequently found in SSc patients (80%) compared to non-SSc patients (59%) (Table 2). Myocardial abnormalities have been shown to be observed not only in patients with SSc but also in those with idiopathic or CTD associated PAH (32, 33). Further studies are needed to evaluate whether these changes are useful to detect “primary” cardiac involvement of patients with SSc-PAH.

The limitations of our study are the small sample size, single center design, and retrospective observations. Due to the limited sample size, we included all patients who met the criteria of pre-capillary PH but did

not exclude patients who had lung diseases concomitantly. The impact of pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis on CMR parameters was not evaluated due to the lack of histopathological assessment. In the comparison of mPAP-RVEDV/LVEDV correlation between SSc and non-SSc patients, we could obtain statistical significance only with unpaired t-test by comparing the ratio of RVEDV/LVEDV to mPAP but not with ANCOVA by comparing two regression slopes.

Although CTD-PAH is a rare disease and CMR is not widely performed, prospective multi center studies in a large sample may confirm our findings.

In summary, our data provides the first evidence of SSc-related bi-ventricular interplay and its prognostic value in CTD-PAH patients. CMR provides additional information on RHC in terms of monitoring the effect of treatment and predicting the prognosis particularly in SSc-PAH patients. SSc-related bi-ventricular interplay may in part explain the poor prognosis of patients with SSc-PAH compared to those with other CTD associated PAH, therefore, SSc associated CTD-PAH and non-SSc associated CTD-PAH could be discriminated as classification category.

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Conflict of interest

T. A. received research grants/honoraria from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Daiichi Sankyo Co. Ltd. and Otsuka Pharmaceutical Co., Ltd..

The other authors declare no conflict of interest associated with this manuscript.

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Figure legends

Figure 1. Correlation between mPAP and RVEDV / LVEDV (A), RVESV / LVESV (B), or RVEF / LVEF (C) measured at CMR in patients with pre-capillary PH. D, E and F shows sub analysis of A, B, and C respectively, in SSc-patients and non-SSc patients. mPAP: mean pulmonary arterial pressure.

Figure 2. Changes of mPAP (A), PVR (B), and RVEDV / LVEDV (C) following treatment of PAH in 17 patients who underwent follow-up CMR as well as follow-up RHC synchronously. D, E, F shows sub analysis of A, B and C, respectively, in patients with increased RVEDV / LVEDV in spite of treatment with vasodilators. **P*-values <0.05, ***P*-values <0.01. *P*-values were calculated for comparison between baseline and follow-up period, using either paired t-test or Wilcoxon signed-rank test.

Figure 3. A shows landmark analysis of patients with increased RVEDV / LVEDV (*n* = 3) and patients with decreased RVEDV / LVEDV (*n* = 14). B shows landmark analysis of patients with either mPAP or RVEDV / LVEDV increased (*n* = 4) and patients with both of them decreased (*n* = 13).

Figure 4. A scheme of discrepant time courses in SSc-PAH patients exhibiting improved PAP and PVR following treatment with vasodilators. According to the novel findings of our study, the level of RVEDV / LVEDV does not always decrease synchronically with PAP and PVR. One possible reason for this is because deteriorated “primary” cardiac involvement may cause the irreversible dysfunction to compensate for afterload. Other factors, such as gender, age, and duration from PAH onset to treatment start, might also change the course, but further studies are needed.

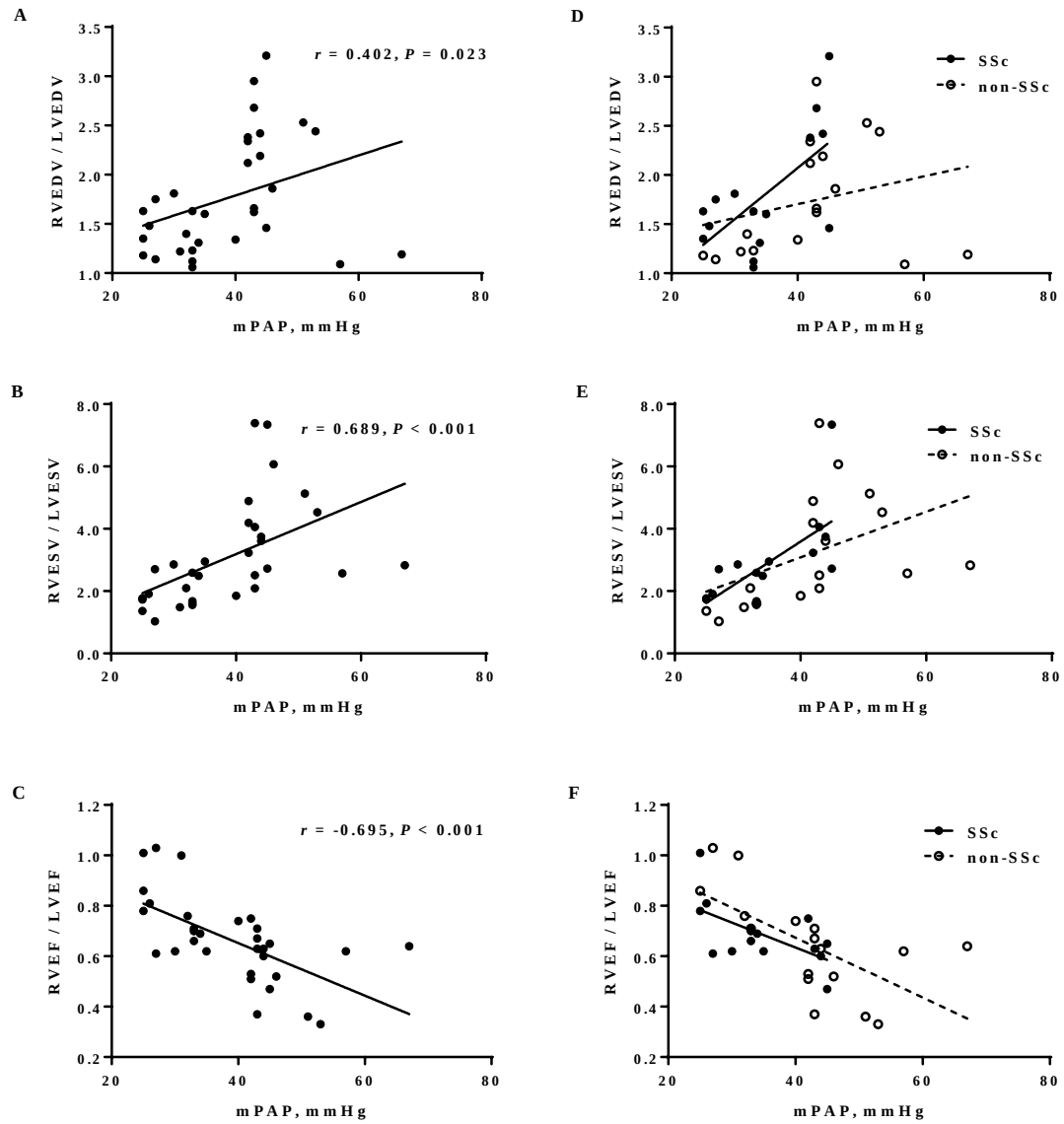


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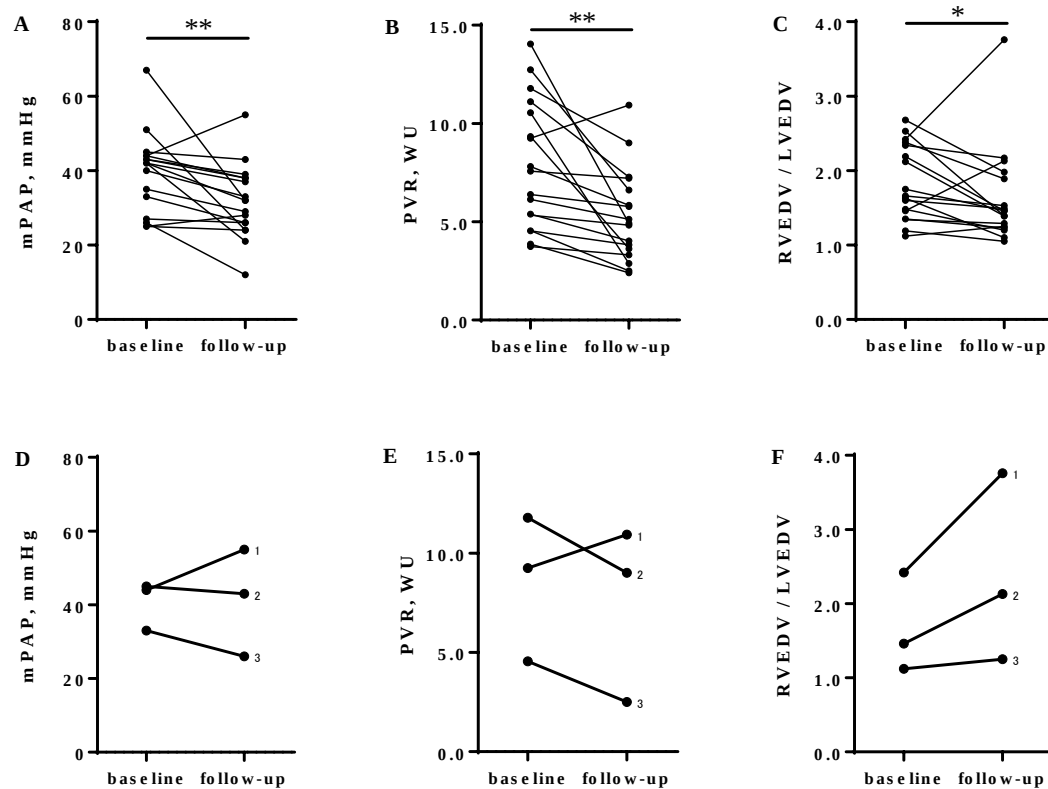


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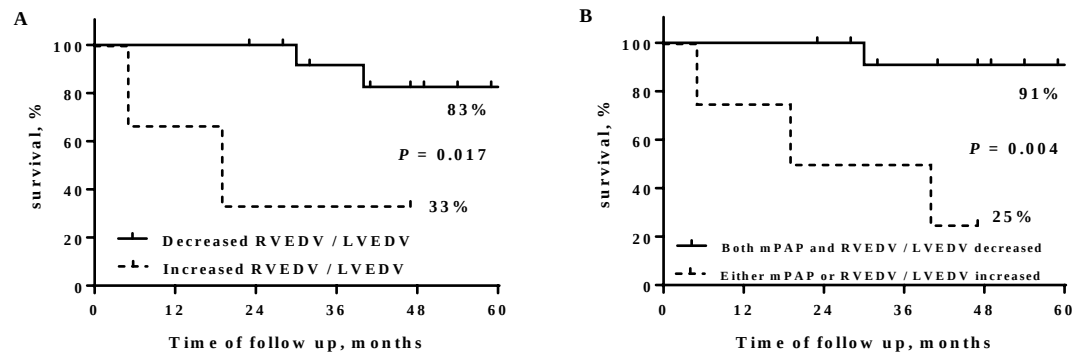


Figure 3. A shows landmark analysis of patients with increased RVEDV / LVEDV ($n = 3$) and patients with decreased RVEDV / LVEDV ($n = 14$). B shows landmark analysis of patients with either mPAP or RVEDV / LVEDV increased ($n = 4$) and patients with both of them decreased ($n = 13$).

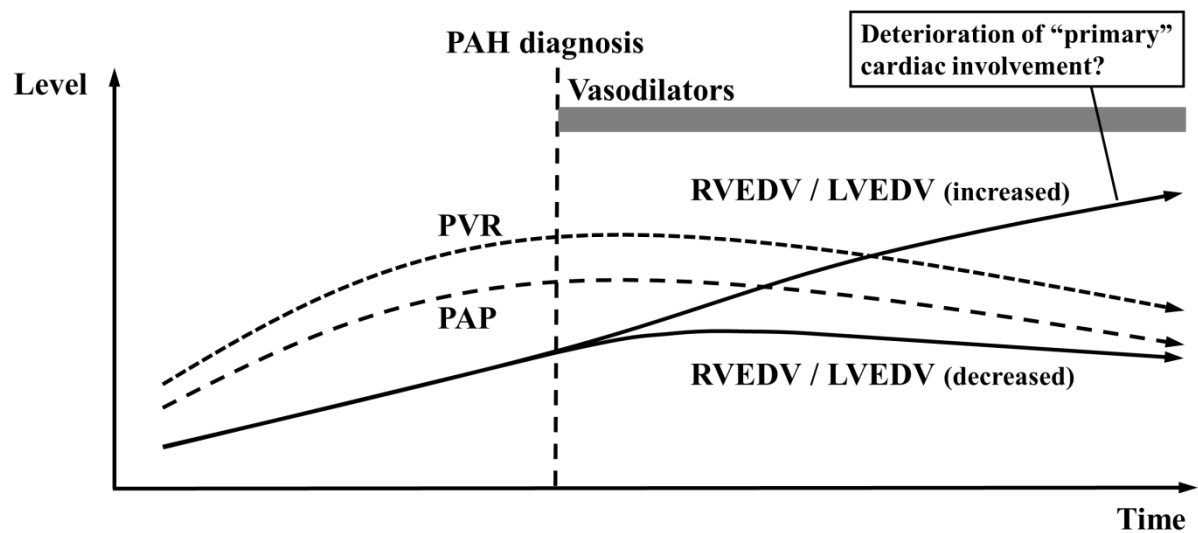


Figure 4. A scheme of discrepant time courses in SSc-PAH patients exhibiting improved PAP and PVR following treatment with vasodilators. According to the novel findings of our study, the level of RVEDV / LVEDV does not always decrease synchronically with PAP and PVR. One possible reason for this is because deteriorated “primary” cardiac involvement may cause the irreversible dysfunction to compensate for afterload. Other factors, such as gender, age, and duration from PAH onset to treatment start, might also change the course, but further studies are needed.

Table 1. Patients' characteristics, RHC and CMR measurements

Demographics	
Female, <i>n</i> (%)	37 (93)
Age at study entry, mean $\pm$ SD, years	53.8 $\pm$ 14.5
WHO FC (at study entry) I / II / III / IV, <i>n</i>	1 / 14 / 22 / 3
Classification of PH	
Pre-capillary PH, <i>n</i> (%)	32 (80)
Isolated post-capillary PH, <i>n</i> (%)	2 (5)
Combined post-capillary and pre-capillary PH, <i>n</i> (%)	0 (0)
Non-PH, <i>n</i> (%)	6 (15)
Diseases	
SSc, <i>n</i> (%)	21 (53)
SLE, <i>n</i> (%)	8 (20)
MCTD, <i>n</i> (%)	5 (13)
PM, <i>n</i> (%)	2 (5)
Primary SS, <i>n</i> (%)	2 (5)
Primary APS, <i>n</i> (%)	1 (3)
RA, <i>n</i> (%)	1 (3)
RHC measurements	
systolic PAP, mean $\pm$ SD, mmHg	55.2 $\pm$ 19.4
diastolic PAP, mean $\pm$ SD, mmHg	21.8 $\pm$ 7.8
mean PAP, mean $\pm$ SD, mmHg	35.0 $\pm$ 11.9
PAWP, median (IQR), mmHg	8.0 (5.5 - 10.5)
CI, mean $\pm$ SD, L/min/m ²	2.8 $\pm$ 0.6
PVR, median (IQR), WU	5.71 (3.76 - 9.29)
CMR measurements	
LVEDVI, mean $\pm$ SD, mL/m ²	57.7 $\pm$ 12.7
LVESVI, median (IQR), mL/m ²	19.6 (16.4 - 23.4)
LVEF, mean $\pm$ SD, %	63.8 $\pm$ 8.1
RVEDVI, median (IQR), mL/m ²	83.1 (75.2 - 96.3)
RVESVI, median (IQR), mL/m ²	49.1 (35.9 - 58.2)
RVEF, mean $\pm$ SD, %	44.5 $\pm$ 11.3
RVEDV / LVEDV, median (IQR)	1.43 (1.20 - 1.99)
RVESV / LVESV, median (IQR)	2.31 (1.61 - 3.42)
RVEF / LVEF, mean $\pm$ SD	0.70 $\pm$ 0.17

Continuous values are the mean $\pm$ SD if normally distributed or the median (25 percentile - 75 percentile)

if not. Binary values are number (%) unless otherwise indicated. RHC: right heart catheterization; CMR: cardiac magnetic resonance; SD: standard deviation; WHO: world health organization; FC: functional class; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease; PM: polymyositis; SS: Sjögren's syndrome; APS: antiphospholipid syndrome; RA: rheumatoid arthritis; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; IQR: interquartile range; CI: cardiac index; PVR: pulmonary vascular resistance; WU: wood units; LVEDVI: left ventricular end-diastolic volume index; LVESVI: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction; RVEDVI: right ventricular end-diastolic volume index; RVESVI: right ventricular end-systolic volume index; RVEF: right ventricular ejection fraction; RVEDV / LVEDV: right ventricular end-diastolic volume / left ventricular end-diastolic volume; RVESV / LVESV: right ventricular end-systolic volume / left ventricular end-systolic volume.

Table 2. Comparison between 2 Groups in pre-capillary PH patients; SSc group and non-SSc group

	SSc (<i>n</i> = 15)	non-SSc (<i>n</i> = 17)	<i>P</i> -value
Demographics			
Female, <i>n</i> (%)	14 (93)	17 (100)	-
Age at study entry, mean $\pm$ SD, years	57.0 $\pm$ 11.6	51.8 $\pm$ 13.6	0.250
Duration from PH onset to study entry, median (IQR), months	0.0 (0.0 - 0.0)	33.0 (1.0 - 63.0)	0.001
Follow-up period from study entry, mean $\pm$ SD, months	34.6 $\pm$ 20.3	36.1 $\pm$ 20.5	0.841
WHO FC (at study entry) I / II / III / IV, <i>n</i>	0 / 1 / 12 / 2	1 / 4 / 11 / 1	0.123
Treatment with vasodilators before study entry, <i>n</i> (%)	2 (13)	11 (65)	0.004
ERA / PDE-5i / PGI ₂ (oral) / PGI ₂ (intravenous), <i>n</i>	2 / 1 / 1 / 0	7 / 8 / 6 / 1	
RHC measurements			
systolic PAP, mean $\pm$ SD, mmHg	55.3 $\pm$ 14.2	66.4 $\pm$ 17.0	0.054
diastolic PAP, mean $\pm$ SD, mmHg	22.0 $\pm$ 5.2	26.2 $\pm$ 6.6	0.054
mean PAP, mean $\pm$ SD, mmHg	34.7 $\pm$ 7.4	42.3 $\pm$ 10.9	0.027
PAWP, mean $\pm$ SD, mmHg	6.9 $\pm$ 3.2	8.8 $\pm$ 3.1	0.114
CI, mean $\pm$ SD, L/min/m ²	2.8 $\pm$ 0.6	2.8 $\pm$ 0.5	0.992
PVR, mean $\pm$ SD, WU	7.13 $\pm$ 2.89	8.13 $\pm$ 3.56	0.387
CMR measurements			
LVEDVI, mean $\pm$ SD, mL/m ²	56.2 $\pm$ 13.8	54.1 $\pm$ 10.2	0.639
LVESVI, median (IQR), mL/m ²	20.5 (17.3 - 23.4)	18.4 (15.5 - 19.7)	0.069
LVEF, mean $\pm$ SD, %	61.8 $\pm$ 7.2	66.9 $\pm$ 9.2	0.093
RVEDVI, median (IQR), mL/m ²	93.8 (80.9 - 100)	79.3 (72.2 - 102)	0.246
RVESVI, median (IQR), mL/m ²	53.0 (47.7 - 63.2)	46.1 (32.4 - 71.7)	0.278
RVEF, mean $\pm$ SD, %	41.9 $\pm$ 5.3	43.3 $\pm$ 15.3	0.734
RVEDV / LVEDV, mean $\pm$ SD	1.79 $\pm$ 0.61	1.74 $\pm$ 0.59	0.789
RVESV / LVESV, median (IQR)	2.90 (1.84 - 3.09)	2.57 (1.85 - 4.53)	0.852
RVEF / LVEF, mean $\pm$ SD	0.69 $\pm$ 0.12	0.65 $\pm$ 0.20	0.489
Myocardial delayed enhancement, <i>n</i> (%)	12 (80)	10 (59)	0.265
LVEDVI / mean PAP, mean $\pm$ SD	1.72 $\pm$ 0.63	1.38 $\pm$ 0.51	0.102
LVESVI / mean PAP, mean $\pm$ SD	0.67 $\pm$ 0.33	0.46 $\pm$ 0.20	0.029
LVEF / mean PAP, mean $\pm$ SD	1.84 $\pm$ 0.33	1.68 $\pm$ 0.51	0.317
RVEDVI / mean PAP, mean $\pm$ SD	2.82 $\pm$ 0.67	2.27 $\pm$ 0.83	0.048
RVESVI / mean PAP, median (IQR)	1.65 (1.37 - 1.95)	1.14 (0.98 - 1.57)	0.018
RVEF / mean PAP, median (IQR)	1.25 (1.03 - 1.43)	0.90 (0.75 - 1.39)	0.189
(RVEDV / LVEDV) / mean PAP, mean $\pm$ SD	0.052 $\pm$ 0.013	0.042 $\pm$ 0.012	0.034

(RVESV / LVESV) / mean PAP, median (IQR)	0.077 (0.070 - 0.090)	0.058 (0.048 - 0.100)	0.313
(RVEF / LVEF) / mean PAP, median (IQR)	0.020 (0.016 - 0.022)	0.014 (0.011 - 0.022)	0.114

P-values were calculated for comparison between SSc group and non-SSc group using Fisher's exact test for binary data and either *t*-test or Mann-Whitney *U*-test for continuous data. ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase type 5 inhibitor; PGI₂: prostacyclin analogue.

Table 3. Correlation between mPAP and CMR parameters and comparison of regression slopes between SSc group and non-SSc group. *: Spearman rank method. **: Analysis of covariance (ANCOVA, SSc vs non-SSc).

	<i>r</i>	<i>P</i> -values (*)	slope (SSc)	slope (non-SSc)	<i>P</i> -values (**)
LVEDVI	-0.309	0.086			
LVESVI	-0.558	0.001	-0.523	-0.164	0.163
LVEF	0.293	0.104			
RVEDVI	0.269	0.137			
RVESVI	0.345	0.053			
RVEF	-0.426	0.015	-0.278	-0.716	0.338
RVEDV/LVEDV	0.402	0.023	0.0522	0.0141	0.112
RVESV/LVESV	0.689	< 0.001	0.131	0.0732	0.362
RVEF/LVEF	-0.695	< 0.001	-0.0099	-0.0119	0.734

Table 4. Characteristics, RHC and CMR measurements of patients who exhibited increased RVEDV / LVEDV following treatment of PAH

	Case 1		Case 2		Case 3	
Characteristics						
Sex, Age at study entry	Female, 71		Female, 66		Female, 40	
Disease	SSc		SSc		SSc	
Comorbidities	ILD		ILD		Renal crisis	
WHO FC at study entry	IV		III		III	
Duration of follow-up	5 months		19 months		37 months	
Duration from study entry to follow-up study	4 months		3 months		3 months	
Treatment and Outcome						
PAH-targeted therapy	Bosentan, Sildenafil		Bosentan		Bosentan, Tadalafil	
Diuretics	None		None		None	
ACEI or ARB	None		None		None	
Prognosis	Dead		Dead		Alive	
Cause of death	Right heart failure		Right heart failure		-	
	baseline	follow-up	baseline	follow-up	baseline	follow-up
RHC measurements						
systolic PAP, mmHg	73	96	85	75	50	45
diastolic PAP, mmHg	25	35	25	25	21	17
mean PAP, mmHg	44	55	45	43	33	26
PAWP, mmHg	13	20	4	10	10	11
CI, L/min/m ²	2.32	2.23	2.26	2.38	2.92	3.25
PVR, WU	9.25	10.94	11.79	9.01	4.55	2.50
CMR measurements						
LVEDVI, mL/m ²	54.7	39.8	58.2	50.9	63.1	69.0
LVESVI, mL/m ²	23.3	12.8	17.0	12.5	23.4	21.7
LVEF, %	57.5	67.7	70.8	75.3	62.9	68.5
RVEDVI, mL/m ²	132.5	149.8	85.1	108.5	70.6	86.0
RVESVI, mL/m ²	87.1	94.5	46.2	60.3	39.2	43.4
RVEF, %	34.3	18.2	45.7	44.4	44.6	49.5
RVEDV / LVEDV	2.42	3.76	1.46	2.13	1.12	1.25
RVESV / LVESV	3.74	7.38	2.72	4.82	1.68	2.00
RVEF / LVEF	0.60	0.27	0.65	0.59	0.71	0.72

ILD: interstitial lung disease; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker