Pulmonary arterial hypertension in systemic sclerosis

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Different right ventricular filling pattern in systemic sclerosis-associated pulmonary arterial hypertension compared with idiopathic pulmonary arterial hypertension

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Abstract

Introduction: Since systemic sclerosis (SSc) also affects the heart, we assessed differences in right ventricular (RV) filling patterns in SSc-associated pulmonary arterial hypertension (SScPAH) and idiopathic PAH (IPAH), while afterload between both groups was similar.

Methods: Ten SScPAH, 14 IPAH and 10 healthy subjects were studied. SScPAH was age-matched with controls. SScPAH and IPAH were matched for afterload, i.e., similar pulmonary vascular resistance and compliance. RV mass index (RVMI) and diastolic function, described by early peak filling rate (E), normalized atrium-induced peak filling rate (A), and E/A ratio, were measured with MRI.

Results: E was lower in SScPAH *vs*. IPAH (geometric mean and 95% Confidence Interval (CI) (150 ml/s (109 to 208) *vs.* 333 ml/s (237 to 468); p=0.002), and *vs.* controls (409 ml/s (294-568); p<0.0001). A was not different between SScPAH and IPAH. However, A was higher in SScPAH *vs.* controls (499 ml/s (394 to 632) *vs.* 194 ml/s (116 to 324); p=0.001). E/A ratio in SScPAH was lower *vs.* IPAH (0.3 (0.2 to 0.4) *vs* 0.8 (0.5 to1.3); p=0.004). RVMI was higher in SScPAH *vs.* controls ((mean ± SD) (37.8 ± 12.2 *vs.* 20.5 ± 3.4 g/m^2, p=0.002), but did not differ from IPAH.

Conclusions: RV filling pattern in SScPAH is more impaired than IPAH with similar afterload. This difference might be explained by intramyocardial pathology in SScPAH.

Introduction

Systemic sclerosis (SSc) is characterised by vasculopathy, inflammation and excessive deposition of collagen in multiple organ systems. Pulmonary arterial hypertension complicates SSc in 8-12% of the cases[1,2]. PAH leads to increased afterload, right heart failure and ultimately death, with a 3-year survival rate of 55% despite treatment[3].

Right ventricular (RV) diastolic function is influenced by afterload, wall thickness and intra-myocardial factors such as changes in the structures within the extracellular matrix (ECM) or abnormalities that are intrinsic to the cardiac muscle cells themselves[4,5]. As SSc-disease can also involve the myocardial tissue, [4-6]diastolic function in SScPAH might be influenced by both increased afterload and intramyocardial pathology[6-8].

Several studies have shown that diastolic properties measured by (tissue) Doppler echocardiography of the RV are altered in SSc in comparison with non-SSc controls[9-11] and that this may occur due to latent pulmonary hypertension. However, it is unclear from these studies to what extent abnormalities due to increased afterload or due to SSc-specific intra-myocardial pathology play a role.

To evaluate whether disease specific changes of the myocardium could contribute to altered RV filling patterns in SScPAH, we performed a study comparing a group of SSc patients with proven PAH with a group of patients with idiopathic PAH (IPAH) with similar afterload.

Methods

Patients

Ten consecutive SScPAH patients (all female) and 14 consecutive IPAH patients (3 males, 11 females) were included, ensuring comparable parameters defining the RV afterload, *i.e.* pulmonary vascular resistance (PVR) and Compliance, between the groups [12]. Ten healthy, non-smoking control subjects (4 males, 6 females), recruited among (family members from) hospital personnel, were studied as well. Controls were age-matched with the SScPAH group. IPAH patients were taken from a previously studied patient cohort[13]. Nine SScPAH patients and 11 IPAH patients were referred to our hospital for the initial evaluation of PAH; 1 SScPAH patient and 3 IPAH patients were evaluated for the evaluation of treatment effects. One SScPAH and 2 IPAH patients were treated with epoprostenol, 1 IPAH patient was treated with bosentan. Pulmonary hypertension was confirmed by a mean pulmonary artery

pressure (mPpa) of > 25 mmHg at rest, and a pulmonary capillary wedge pressure (PCWP) of ≤ 15 mmHg and a PVR > 240 dynes×s×cm^{-5}. The diagnosis of systemic sclerosis was based on the classification criteria proposed by LeRoy *et al*.[14]

Pulmonary function testing ($\dot{V}$max 229 and 6200; SensorMedics; Yorba Linda, CA) and high resolution computed tomography (HRCT; CT Somatom Plus 4; Siemens; Erlangen; Germany) were used to exclude underlying fibrotic lung disease as a cause of pulmonary hypertension.

The study was approved by the Institutional Review Board on Research Involving Human Subjects of the VU University Medical Center.

Study Design

All patients underwent an MRI-scan and right heart catheterisation on two consecutive days. Control subjects were only studied by MRI. There was no significant difference in heart rate during cardiac catheterization and MRI. All patients were in sinus rhythm. The six-minute walk test was performed one day before right heart catheterization. Blood was sampled for analysis of N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels, within 24 hours of MRI measurements and right heart catheterization. Values were analyzed on an ELECSYS 1010 bench top analyzer (Roche Diagnostics Netherlands).

Cardiac catheterisation

Right heart catheterisation was performed with a 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA). Right atrial pressure (Pra), systolic (sPrv) and end-diastolic (edPrv) RV pressure, pulmonary artery pressure (Ppa) and PCWP were measured. Blood was sampled to assess mixed venous oxygen content. Arterial oxygen content was measured from blood sampled from the radial or femoral artery. VO_2 was measured during right heart catheterization (($\dot{V}$max 229 and 6200; SensorMedics; Yorba Linda, CA). Cardiac output (CO) was measured by the Fick method and PVR was calculated using the standard formula (mPpa – PCWP)/CO. Stroke volume index (SVI) was calculated as cardiac index (CI) divided by heart rate (HR). Total pulmonary arterial compliance was calculated as stroke volume divided by pulse pressure (PP)[15,16]. PP was calculated as systolic Ppa minus diastolic Ppa.

MRI measurements

MRI was performed on a Siemens 1.5T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) as described previously[17]. Four-chamber cine images were acquired by steady state free precession imaging, with 11 phase-encoding lines per heartbeat in a 14-heartbeat breath hold. With 30 reconstructed phases, the effective

temporal resolution was in the range between 25 and 34 ms. Perpendicular to the four chamber end- diastolic image, a stack of consecutive short-axis breath hold cine images were acquired with the same sequence parameters as used for the 4-chamber cine, and with slice distance of 10 mm. From this stack of parallel short-axis cine images, quantitative analysis of RV volumes and mass (RVM) was performed using the MR Analytical Software System (Medis, Leiden, The Netherlands).

Stroke volume was measured using MR phase-contrast flow quantification in an image plane orthogonal to the main pulmonary artery, at 1 cm distance downstream from the pulmonary valves. Velocity sensitivity was 150 cm/s, and temporal resolution 22 ms. RV ejection fraction was obtained by the ratio of RV stroke volume and RV end-diastolic volume (RVedv).

Quantification of RV diastolic function

RV filling was quantified from the RV volumetric filling curves as assessed from the stack of short-axis cine images[18]. RV early- (E), atrium-induced (A) peak filling rate and E/A quantified RV diastolic filling pattern. Measurements were performed independently by two observers (MJO and CTG) to check the reproducibility of data. Data from observer 1 were taken. The reproducibility coefficient was assessed to determine the interobserver variability.

Statistical analyses

SPSS 12.0 software package was used for statistical analyses, and $p < 0.05$ was considered statistically significant. Normal distribution was evaluated by Shapiro-Wilkinson's test; tests with a skewed distribution underwent natural log-transformation before analysis (NT-proBNP, E, A and the E/A ratio). These data are presented as their geometric mean; the confidence intervals presented for these data are the confidence limits for the ratio of the geometric mean. One-way analysis of variance was performed for comparisons between groups. Because of multiple testing the threshold for significance was adjusted using the Bonferroni correction for families of tests.

Student t test was used for comparison of parameters of hemodynamics between the PAH groups. These results are reported as mean ± standard deviation for descriptive statistics. Non-parametric Spearman's correlation was used to evaluate the relation between parameters of increased afterload and parameters of diastolic dysfunction.

Results

Patients

Patient characteristics are listed in Table 1. Ten patients with SScPAH, 14 patients with IPAH and 10 healthy non-smoking control patients were studied. Controls and SScPAH did not differ significantly in age (64 ± 11 and 59 ± 11 years, p = 1.00, respectively). IPAH patients were significantly younger than both the SScPAH patients and the control subjects (42 ± 14 years; p= < 0.0001 and p = 0.007 for comparison with SScPAH and with controls, respectively). SScPAH patients and the majority of the IPAH patients were female. NT-proBNP values did not demonstrate significant differences. The SScPAH patients were classified as having the limited cutaneous form of SSc[19].

Table 1. Demographic data

	SScPAH (N=10)	IPAH (N=14)	p (SScPAH *vs.* IPAH)
Age, yrs	64 ± 11	42 ± 14	0.001
Gender* (m/f)	0/10	3/11	
BSA, g/m^2	1.6 ± 0.3	1.9 ± 0.2	0.03
Systolic BP, mmHg	120 ± 9	124 ± 13	0.36
Diastolic BP, mmHg	65 ± 8	69 ± 10	0.30
6 MWD, m	299 ± 106	443 ± 126	0.009
NYHA, no.			
II	4	3	
III	5	11	
IV	1	0	
SaO_2 %	96 ± 2.7	95 ± 2.1	0.33
SvO_2 %	64 ± 6.3	65 ± 8.7	0.49
Hb, mmol/l	8.2 ± 0.9	8.9 ± 0.8	0.053
lnNT-proBNP, pg/ml	gm 1121† (415±3030)	gm 490 (213±1128)	0.17
TLC %	92 ± 14	99 ± 11	0.26
TLCO %	48 ± 14	79 ± 16	0.001
LcSSc, (%)‖	13 (100)	-	-
First non-Raynaud SSc-symptom, yrs	7 ± 7	-	-
Raynaud duration, yrs	22 ± 18	-	-
Anti-centromere/ Antinuclear/ Anti-ribonucleoprotein antibodies, n	10/7/1	-	-

Values expressed as mean ± SD or otherwise as stated. Abbreviations: BSA= body surface area; DcSSc= diffuse cutaneous systemic sclerosis; TLCO%= percentage of predicted of the transfer factor of the lung for carbon monoxide; LcSSc= limited cutaneous SSc; 6 MWD= six-minute walk distance; IPAH= idiopathic pulmonary arterial hypertension; NT-proBNP= N-terminal-pro brain natriuretic peptide; NYHA= New York Heart Association; SScPAH= SSc-associated pulmonary arterial hypertension; SvO_2= mixed venous oxygen saturation; TLC %= percentage of predicted total long capacity. *Chi square statistic. †geometric mean, with 95% confidence intervals. ‖According to [14].

Haemodynamic parameters

Afterload as expressed by PVR and Compliance did not differ significantly between the patient groups. Mean Pra was not significantly different between the PAH-groups either. Systolic RV pressure and mPpa were significantly lower in the SScPAH group compared with the IPAH group, whereas CI nor SVI were different between the groups. These parameters are listed in Table 2.

Parameters of diastolic function

End-diastolic Prv did not show significant differences between the SScPAH and IPAH group (Table 2). In both groups the RV was hypertrophied, as shown by increased RVMI (Table 3). The RVedv indexed for body surface was not different between the groups. RV ejection fraction (RVEF) did not differ between IPAH and SScPAH either. However, both patient groups had impaired RVEF when compared with the control group.

The reproducibility coefficient of the quantification of the RV filling between the two observers was $r^2 = 0.97$; $p=<0.0001$. Early peak filling rate (E) was significantly lower in SScPAH than in IPAH. Both SScPAH and IPAH patients had significant lower E than controls. Atrial peak filling rate (A) was not significantly different between SScPAH patients and IPAH. However, A was significantly higher in the patient groups than in the control group. The E/A ratio in SScPAH demonstrated significantly decreased values, compared with both IPAH patients and controls (Figure 1). IPAH patients had significantly lower E/A ratio than controls.

Correlations between parameters of diastolic function and increased afterload

We did not find relations between parameters of diastolic function and increased afterload in the SScPAH group. However, in the IPAH group, we did find a relation between E and mPpa ($r = -0.56$, $p = 0.04$), and a trend towards a relation between E and PVR ($r= -0.53$, $p = 0.054$), whereas no relation was found between E and Compliance.

Table 2. Cardiopulmonary haemodynamics assessed by right heart catheterisation

	SScPAH (N=10)	IPAH (N=14)	p
HR, beats per minute	81 ± 12	83 ± 9	0.56
mPra, mmHg	6 ± 3	7 ± 4	0.44
edPrv, mmHg	11 ± 5	13 ± 4	0.27
sPrv, mmHg	65 ± 20	85 ± 21	0.04
mPpa, mmHg	42 ± 11	55 ± 14	0.006
PCWP, mmHg	10 ± 3	8 ± 4	0.20
PVR, dynes·s·cm^{-5}	666 ± 344	750 ± 319	0.55
Compliance, ml/mmHg	1.3 ± 0.5	1.2 ± 0.5	0.70
CI, l/min.m^2	2.5 ± 0.7	2.8 ± 0.8	0.63
SVI, ml/m^2	31 ± 9	33 ± 7	0.84

Values expressed as mean ±SD. Definition of abbreviations: CI= cardiac index; Compliance= total pulmonary arterial compliance; HR= heart rate; edPrv = end-diastolic right ventricular pressure; mPpa= mean pulmonary artery pressure; mPra = mean right atrial pressure; PCWP = pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; sPrv= systolic RV pressure; SVI= stroke volume index (as measured with Fick method).

Table 3. MRI-derived measurements

	Control (N=10)	SScPAH (N=10)	IPAH (N=14)	p (SScPAH *vs.* Co	p (SScPAH *vs.* IPAH)	p (IPAH *vs.* Co)
RVmassI (g/m^2)	21 ± 3	38 ± 12	42 ± 17	0.002	0.43	<0.0001
RVedvI (ml/m^2)	73 ± 24	85 ± 24	87 ± 25	0.43	1.00	0.57
RVesvI (ml/m^2)	14 ± 6	30 ± 12	32 ± 11	0.005	1.00	0.001
RVEF (%)	71 ± 17	40 ± 16	37 ± 10	< 0.0001	1.00	<0.0001
LVEF (%)	70 ± 8	66 ± 12	65 ± 9	1.00	1.00	0.98
SVI (ml/m^2)	50 ± 13	37 ± 10	41 ± 16	0.001	1.00	<0.0001
E (ml/s)	gm 409	gm 150	gm 333	< 0.0001	0.002	1.00
	294-568	109-208	237-468			
A (ml/s)	gm 194	gm 499	gm 448	0.001	1.00	0.02
	116-324	394-632	339-593			
E/A ratio	gm 2.48	gm 0.30	gm 0.81	< 0.0001	0.004	0.001
	1.56-3.94	0.22-0.41	0.50-1.32			

Values are expressed as mean ± SD; ln-transformed parameters are expressed as geometric mean (gm) with 95% confidence intervals (CI) indicated. RVmass I = right ventricle mass index. Edv = end diastolic volume. A= atrium-induced filling rate. E/edv = early peak filling rate. LVEF = left ventricle ejection fraction. RVEF= right ventricular EF. RVESVI = RV end-systolic volume index. SVI = stroke volume index as measured with MRI

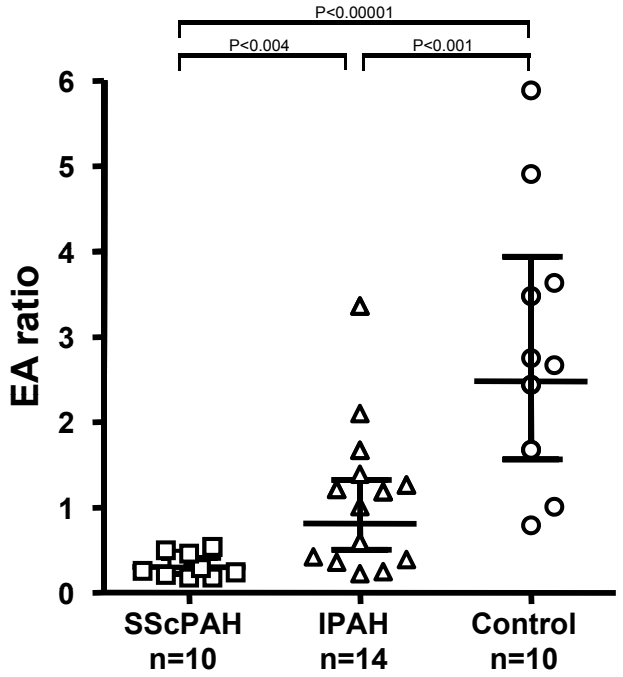

Figure 1

E/A ratio in systemic sclerosis-associated pulmonary arterial hypertension (SScPAH), idiopathic pulmonary arterial hypertension (IPAH) and control. Geometric mean and 95% confidence intervals are show.

Discussion

The results in this study indicate an altered filling pattern of the RV in SScPAH as compared with IPAH patients with similar afterload, demonstrated by a decreased E/A ratio. Therefore, pathology of the myocardium itself might play a role in altered RV filling in SScPAH.

Previous papers have reported an altered diastolic function of the RV in SSc patients[9-11,20]. The first of these studies demonstrated a disturbed ratio between tricuspidal early inflow and peak late inflow velocity[9]. Lindqvist *et al*. [11] demonstrated a prolonged RV-isovolumic relaxation time (IVRT) and a reduced E/A ratio in SSc patients compared with healthy controls. Increased afterload was suggested by increased RV-wall thickness and shortened acceleration time in pulmonary flow. Huez *et al*. [10] suggested an altered diastolic function with increased afterload in SSc, by demonstrating a relation between parameters of

diastolic dysfunction and RV systolic pressure gradients, pulmonary acceleration time and PVR at exercise. Recently, Faludi *et al*.[20] showed a decreased E of the RV in patients with connective tissue disease with PAH at rest and at exercise as compared with healthy controls. The above described studies were performed in unselected patients with SSc without proven pulmonary hypertension and/or were performed with healthy subjects as controls. The individual roles of increased afterload or pathologic changes of the RV myocardial tissue were not investigated in these reports. Our study adds to these reports that a difference between RV filling patterns in SSc patients with proven PAH and patients with IPAH with similar afterload may exist, suggesting that intramyocardial factors may also influence altered RV diastolic function in SScPAH.

The lower E/A ratio in our SSc patient population as compared with other reports[9-11] can be explained by the higher afterload in our group with established PAH. Some trends in the referred studies support this view, for example, Giunta *et al*.[9] demonstrated that in a SSc subgroup with higher echocardiographic pulmonary artery pressures, E/A was disturbed.

Limitations of this study include the small number of patients. Therefore results should be interpreted with caution. The absence of a correlation between parameters of diastolic dysfunction and afterload in the SScPAH group could result from the low patient number, however, this finding might also support the assumption that intramyocardiac pathology, instead of afterload, affects RV filling. A significant age-difference between the SScPAH patients and the IPAH patients exists, reflecting normal epidemiological features [21,22]. Information on the normal age-related influence on parameters of RV diastolic function is scarce[23], disserving further study. We evaluated the influence of age on our results by comparison of the SScPAH group with age-matched controls. Moreover, we did not find correlations between the E and E/A ratio and age in SScPAH (range 53-82 years), IPAH (range 17-71 years) and control (40-71 years). Evaluation of the left ventricle by MRI in SScPAH and IPAH could provide more information concerning the possible role of intramyocardial pathology in the SScPAH group. However, the phenomenon of septal bowing due to dyssynchrony of the right and left ventricle makes interpretation of the described diastolic parameters complex [24,25].

Parameters of diastolic function as assessed by invasive measurements such as RV end-diastolic pressure and mPra [26], were not different between the SScPAH and IPAH groups. The same accounts for the contribution to filling by the atrium, represented by A and A/edv. This indicates that the RV filling in SScPAH may especially be affected in early diastole.

A wide range of intra-myocardial factors is known to alter diastolic filling and some of these occur in SSc cardiac disease, such as changes in the extracellular matrix[27] represented by myocardial fibrosis and[7,28,29], and, speculatively, cross linking of cardiac interstitial collagen[30,31]. Diastolic filling in SScPAH can also be affected by a reduced coronary reserve[6,8,32]. Third, loss of elastic recoil during systole due to impaired ventricular function[33] may impair diastolic relaxation[34]. Finally, speculatively, inflammatory factors in SSc might affect the coronary arterioles and the myocardiocytes, disturbing diastolic function[35-38]. Interestingly, Huez *et al*.[10] demonstrated RV dysfunction in SSc patients with latent pulmonary hypertension. This might be the effect of (the early formation of) intramyocardial changes, supporting above statements.

In conclusion, this study suggests that SScPAH patients may have a different RV filling pattern as compared to IPAH patients, influenced by intra-myocardial pathology. More studies with larger patient groups should confirm these findings. Moreover, studies on the level of the RV myocardium per se and on the RV function in SScPAH should be performed to elucidate underlying pathophysiologic processes and clinical relevance.

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