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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 to 1.3);  $p=0.004$ ). RVMI was higher in SScPAH *vs.* controls ((mean  $\pm$  SD) (37.8  $\pm$  12.2 *vs.* 20.5  $\pm$  3.4 g/m<sup>2</sup>,  $p=0.002$ ), 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.



R1 pressure (mPpa) of > 25 mmHg at rest, and a pulmonary capillary wedge pressure  
R2 (PCWP) of  $\leq 15$  mmHg and a PVR > 240 dynes $\times$ s $\times$ cm<sup>-5</sup>. The diagnosis of systemic  
R3 sclerosis was based on the classification criteria proposed by LeRoy *et al.*[14]

R4 Pulmonary function testing ( $\dot{V}$ max 229 and 6200; SensorMedics; Yorba Linda,  
R5 CA) and high resolution computed tomography (HRCT; CT Somatom Plus 4;  
R6 Siemens; Erlangen; Germany) were used to exclude underlying fibrotic lung disease  
R7 as a cause of pulmonary hypertension.

R8 The study was approved by the Institutional Review Board on Research Involving  
R9 Human Subjects of the VU University Medical Center.

### R10 **Study Design**

R11 All patients underwent an MRI-scan and right heart catheterisation on two  
R12 consecutive days. Control subjects were only studied by MRI. There was no significant  
R13 difference in heart rate during cardiac catheterization and MRI. All patients were in  
R14 sinus rhythm. The six-minute walk test was performed one day before right heart  
R15 catheterization. Blood was sampled for analysis of N-terminal pro brain natriuretic  
R16 peptide (NT-proBNP) plasma levels, within 24 hours of MRI measurements and  
R17 right heart catheterization. Values were analyzed on an ELECSYS 1010 bench top  
R18 analyzer (Roche Diagnostics Netherlands).

### R19 **Cardiac catheterisation**

R20 Right heart catheterisation was performed with a 7F Swan-Ganz catheter (131HF7;  
R21 Baxter Healthcare Corp; Irvine, CA). Right atrial pressure (Pra), systolic (sPrv) and  
R22 end-diastolic (edPrv) RV pressure, pulmonary artery pressure (Ppa) and PCWP  
R23 were measured. Blood was sampled to assess mixed venous oxygen content. Arterial  
R24 oxygen content was measured from blood sampled from the radial or femoral  
R25 artery.  $VO_2$  was measured during right heart catheterization ( $\dot{V}$ max 229 and 6200;  
R26 SensorMedics; Yorba Linda, CA). Cardiac output (CO) was measured by the Fick  
R27 method and PVR was calculated using the standard formula (mPpa – PCWP)/CO.  
R28 Stroke volume index (SVI) was calculated as cardiac index (CI) divided by heart rate  
R29 (HR). Total pulmonary arterial compliance was calculated as stroke volume divided  
R30 by pulse pressure (PP)[15,16]. PP was calculated as systolic Ppa minus diastolic Ppa.  
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### R34 **MRI measurements**

R35 MRI was performed on a Siemens 1.5T Sonata scanner (Siemens Medical Solutions,  
R36 Erlangen, Germany) as described previously[17]. Four-chamber cine images were  
R37 acquired by steady state free precession imaging, with 11 phase-encoding lines per  
R38 heartbeat in a 14-heartbeat breath hold. With 30 reconstructed phases, the effective  
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## 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 ( $64 \pm 11$  and  $59 \pm 11$  years,  $p = 1.00$ , respectively). IPAH patients were significantly younger than both the SScPAH patients and the control subjects ( $42 \pm 14$  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	$64 \pm 11$	$42 \pm 14$	0.001
Gender* (m/f)	0/10	3/11	
BSA, g/m <sup>2</sup>	$1.6 \pm 0.3$	$1.9 \pm 0.2$	0.03
Systolic BP, mmHg	$120 \pm 9$	$124 \pm 13$	0.36
Diastolic BP, mmHg	$65 \pm 8$	$69 \pm 10$	0.30
6 MWD, m	$299 \pm 106$	$443 \pm 126$	0.009
NYHA, no.			
II	4	3	
III	5	11	
IV	1	0	
SaO <sub>2</sub> %	$96 \pm 2.7$	$95 \pm 2.1$	0.33
SvO <sub>2</sub> %	$64 \pm 6.3$	$65 \pm 8.7$	0.49
Hb, mmol/l	$8.2 \pm 0.9$	$8.9 \pm 0.8$	0.053
lnNT-proBNP, pg/ml	gm 1121 <sup>†</sup> (415±3030)	gm 490 (213±1128)	0.17
TLC %	$92 \pm 14$	$99 \pm 11$	0.26
TLCO %	$48 \pm 14$	$79 \pm 16$	0.001
LcSSc, (%) <sup>‡</sup>	13 (100)	-	-
First non-Raynaud SSc-symptom, yrs	$7 \pm 7$	-	-
Raynaud duration, yrs	$22 \pm 18$	-	-
Anti-centromere/ Antinuclear/ Anti-ribonucleoprotein antibodies, n	10/7/1	-	-

Values expressed as mean  $\pm$  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<sub>2</sub>= mixed venous oxygen saturation; TLC %= percentage of predicted total lung capacity. \*Chi square statistic. <sup>†</sup>geometric mean, with 95% confidence intervals. <sup>‡</sup>According to <sup>14</sup>.



**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 <sup>-5</sup>	666 ± 344	750 ± 319	0.55
Compliance, ml/mmHg	1.3 ± 0.5	1.2 ± 0.5	0.70
CI, l/min.m <sup>2</sup>	2.5 ± 0.7	2.8 ± 0.8	0.63
SVI, ml/m <sup>2</sup>	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 <i>vs.</i> Co)	p (SScPAH <i>vs.</i> IPAH)	p (IPAH <i>vs.</i> Co)
RVmassI (g/m <sup>2</sup> )	21 ± 3	38 ± 12	42 ± 17	0.002	0.43	<0.0001
RVedvI (ml/m <sup>2</sup> )	73 ± 24	85 ± 24	87 ± 25	0.43	1.00	0.57
RVesvI (ml/m <sup>2</sup> )	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 <sup>2</sup> )	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





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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 intramyocardial 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], deserving 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.



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