

# Cardiac Magnetic Resonance Imaging Detects Subclinical Right Ventricular Impairment in Systemic Sclerosis

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**ABSTRACT. Objective.** To assess myocardial involvement in patients with systemic sclerosis (SSc) with no signs or symptoms of cardiac impairment (New York Heart Association functional class I).

**Methods.** Fifty patients (45 women, 5 men, age  $53.3 \pm 12.9$  yrs) who did not complain of serious diseases other than SSc were recruited out of 119 consecutive patients with SSc. Thirty-three were found to have limited cutaneous SSc (lSSc) and 17 diffuse SSc (dSSc). All underwent cardiovascular magnetic resonance imaging (MRI) to determine right and left systolic and diastolic volumes and ventricular ejection fractions (RVEF and LVEF). Thirty-one healthy subjects matched for sex, age, and body surface area (BSA) were studied as controls. Diffusion lung capacity test (DLCO) and high resolution computed tomography were performed to evaluate lung involvement.

**Results.** Disease duration between patients with lSSc ( $14.1 \pm 11.4$  yrs) and those with dSSc ( $6.9 \pm 4.4$  yrs) was found to be significantly different ( $p < 0.003$ ). lSSc patients were older than those with dSSc ( $54.8 \pm 13.7$  yrs vs  $50.4 \pm 9.9$  yrs, respectively;  $p < 0.04$ ). Anticentromere antibodies and Scl-70 were positive in 23 (46%) and 17 patients (34%). Except for the left and right systolic volumes, all unadjusted cardiac MRI measures were significantly reduced in SSc compared to the controls ( $p < 0.001$  and  $p < 0.009$ ). These differences persisted after adjustment for subjects' height and BSA. Raw RVEF data and RVEF data matched for height and BSA were significantly reduced in dSSc patients in comparison to lSSc ( $p < 0.03$ ).

**Conclusion.** Compromised RVF was found in patients with asymptomatic SSc. Unlike standard diagnostic techniques, cardiac MRI appears to be a rapid and noninvasive means of determining subclinical right myocardial involvement that is otherwise undetected in patients with SSc. (First Release Nov 1 2007; *J Rheumatol* 2007;34:2431–7)

## Key Indexing Terms:

CARDIAC MAGNETIC RESONANCE IMAGING

VENTRICULAR IMPAIRMENT

SYSTEMIC SCLEROSIS

Heart involvement in systemic sclerosis (SSc) has been reported since the 1960s on the basis of autopsy observations, which show in 70%–80% of cases a myocardial fibrosis pathway characterized by contraction band necrosis of both ventricles and replacement fibrosis in the absence of concomitant major coronary artery disease<sup>1</sup>. Since cardiac involvement was detectable at bedside in only 20%–25% of patients, such alterations were clinically underestimated<sup>2</sup>. The exact mechanism leading to myocardial fibrosis in SSc remains unknown.

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Myocyte replacement by collagen and coronary vasospasm seem to be the most relevant pathological factors. The reported increased deposition of collagen into the extracellular matrix of the myocardium leads to a progressive increase of myocardial mass, causing wall stiffness of the cardiac cavities<sup>3,4</sup>. When clinically evident, myocardial involvement is recognized as a poor prognostic factor, since the overall mortality rate of SSc patients with proven cardiovascular alterations is above 70% at 5 years<sup>5</sup>. This finding stresses the need for early detection of SSc cardiac disease; this may improve prognosis via early administration of appropriate treatment, but the diagnosis may be late or missing because of the frequent discrepancy between clinical manifestations and actual cardiac involvement. For this reason, use of all the available procedures is recommended to achieve timely diagnosis<sup>6</sup>.

Cardiovascular magnetic resonance imaging (MRI) has developed from an effective research tool into a clinically proven, safe, and comprehensive imaging method. It provides anatomic and functional information in acquired and congenital heart disease and is one of the most precise techniques for

quantification of ventricular volumes, function, and mass with excellent reproducibility<sup>7</sup>. Our aim was to evaluate myocardial involvement in patients who had SSc with no apparent symptoms of cardiac impairment [New York Heart Association (NYHA) functional class I].

## MATERIALS AND METHODS

**Patients.** Fifty patients (45 women, 5 men, age  $53.3 \pm 12.9$  yrs) who did not complain of signs and symptoms of cardiovascular disease or serious diseases other than SSc (American College Rheumatology classification criteria<sup>8</sup> and more recently proposed criteria for early SSc<sup>9</sup>) were recruited out of 119 consecutive patients with SSc at the outpatient division of clinical immunology of our institution. Duration of disease in the SSc population was calculated from the onset of Raynaud's phenomenon. Patients who were taking calcium channel-blockers, corticosteroids, D-penicillamine, or immunosuppressive drugs were excluded. Patients treated with vasodilators (bufomedil or prostanooids) or with nonsteroidal antiinflammatory drugs underwent a 1-month washout period before physical and laboratory examinations. In order to evaluate cardiopulmonary involvement, the following tests were performed: complete physical examination, chest radiograph, surface electrocardiography, and a treadmill effort test (Bruce's protocol).

All patients underwent M-mode and 2-D measurements obtained with a C256-Acuson Sequoia™ ultrasound unit (Siemens). The left ventricular regional wall motion score index (WMSI) and left ventricular ejection fraction (LVEF; biplane Simpson rule) were calculated according to the American Society of Echocardiography (ASE) recommendations<sup>10</sup>. The normal cutoff values were considered for WMSI = 1 and for LVEF  $\geq 55\%$ . LV mass was derived using the formula described by Devereux and associates<sup>11</sup>. The presence of LV hypertrophy was defined as LV mass index  $> 125 \text{ g/m}^2$  in men and  $> 110 \text{ g/m}^2$  in women<sup>12</sup>. Systolic pulmonary artery pressures (PAPS) were estimated based on tricuspid regurgitation with a cutoff value of normal range of 36 mm Hg<sup>13</sup>.

**Autoantibody detection.** We tested all patients for serum antitopoisomerase I antibodies (Scl-70) and for anticentromere antibodies (ACA). Antinuclear antibodies were detected by indirect immunofluorescence using HEp-2 cells as substrate (Euroimmun, Lubeck, Germany). ACA and Scl-70 were measured using an ELISA (Euroimmun).

**Diffusion lung capacity (DLCO test).** Diffusion lung capacity was measured using the single-breath technique. The following pulmonary function variables were measured with spirometric and CO diffusion tests: total lung capacity, residual volume, forced expiratory volume in 1 second (FEV1), vital capacity, total lung CO diffusion, and CO diffusion corrected for lung volume (data not shown). All values were evaluated as the percentage of predicted values. Abnormal diffusing capacity was defined as DLCO  $< 80\%$  of predicted value<sup>14</sup>.

**Doppler echocardiography.** The diastolic function indices were derived from the Doppler mitral and pulmonary venous flows. The Doppler mitral-flow evaluation was performed from the apical 4-chamber view with pulsed sample volume between the tips of mitral leaflets during diastole as described<sup>15</sup>. Peak velocities of early (E) and late (A) filling, the E/A ratio, and deceleration time of E wave (DTE) were measured following the ASE recommendations<sup>15a</sup>. Pulmonary venous (PV) flow measures were also performed from the apical 4-chamber view and color Doppler imaging was used to obtain a beam direction parallel to the right or the left upper PV flow. Peak velocities of systolic (S) and diastolic (D) PV flow and their ratio (S/D) were measured. The pattern of abnormal LV relaxation was defined according to the standard definition<sup>16,17</sup>.

**High resolution computed tomography (HRCT).** HRCT using an X-Vision CT unit (Toshiba, Otawara, Japan) was performed without intravenous contrast material, with patients in supine position. A modified score<sup>18</sup> was used to assess pulmonary interstitial disease: score 0 = normal, 1 = any lung lesion caused by scleroderma, save for honeycombing (e.g., ground-glass opacities, parenchymal or subpleural micronodules, septal or nonseptal linear opacities,

bronchiectasis, bronchiolectasis, pleural thickening, and subpleural plaques), and 2 = honeycombing.

**Magnetic resonance imaging.** Cardiac MRI was performed using a superconducting 1.5 Tesla cardiac MR unit. All patients underwent morphological and functional evaluation. Morphological assessment through T1 and T2 weighted turbo spin-echo sequences and fat-suppression turbo spin-echo sequences was carried out. Each image was acquired with a cardiac phased-array coil (with prospective gating) and by using scansion levels of cardiac long and short axis. Hypointense areas in T1 and T2 sequences were considered suggestive of fibrosis, while hyperintense areas in T2 sequences were suggestive of interstitial edema. Cine-MRI was performed with a segmented ECG-gated breath-hold cine gradient-echo sequence to acquire 6 to 11 short-axis contiguous 10 mm slices covering the entire length of the LV cavity. To encompass the entire heart, cine-MR images were acquired in the anatomic short-axis planes of both left and right ventricles by using a breath-hold Flash-2-D technique (TR/TE 100/6.1 ms; FA 25°; section thickness 10 mm). Cardiac volume testing was carried out using standard cardiac MRI software and all images were stored on magnetic tape. The window settings were standardized with the high level set just below the pericardial fat signal intensity and the lower level set slightly above the interventricular signal intensity (noise). Series of manual contours of LV and RV end-diastolic and end-systolic images were created starting from the base of the heart and moving forward through the ventricle to the apex at 10 mm intervals. LV myocardial volumes were calculated using the Simpson rule<sup>19</sup>. LVEF and RVEF were calculated as follows: end-diastolic volume – end-systolic volume/end-diastolic volume  $\times 100$ <sup>20</sup>.

**Control group.** Thirty-one healthy subjects (26 women, 5 men, mean age  $55 \pm 9.0$  yrs) matched with the SSc group for sex, age, and body surface area (BSA; Table 1), who were taking no medication and who reported no cardiovascular risk factors, were recruited based on a recent report by Maceira, *et al*<sup>21</sup>, who showed that many clinical parameters of RV volume and systolic/diastolic function are significantly dependent on sex, age, and BSA. After giving informed consent, these individuals underwent physical and metabolic blood tests, ultrasound examination, effort stress test, and cardiac MRI.

**Statistical analysis.** All data are expressed as mean  $\pm$  SD. All statistical analyses were performed using JMP statistical database software (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as  $p < 0.05$ . Differences among variables were assessed using the appropriate statistical test, based on the underlying distribution of the variables. Comparisons between 2 different groups were done using independent sample Student t test and one-way analysis of variance with Bonferroni or Tukey multiple comparison post-test as appropriate. Raw cardiac MRI volumes and EF were divided by height and BSA to obtain adjusted values. Tables 3 and 4 show raw and height and BSA-indexed cardiac MRI variables expressed as mean values (SD) with fifth and 95th percentiles. Between-groups differences were assessed using Student t tests. The multivariate regression model was used to simultaneously assess the relationship between cardiac MRI and different variables.

To determine intraobserver variability, 15 cardiac MRI scans were randomly selected, and an observer, blinded with respect to the initial values, subsequently reevaluated copies of these images at least 2 weeks after the first analysis. For each variable, the mean + SD of the differences between the 2 measurement results was calculated and the coefficient of variability (expressed as percentage) was calculated as the SD of the differences divided by the mean of the variable under consideration. To test interobserver variability, the same scans were reevaluated by a different observer blinded to the results obtained by the previous investigator, and the coefficient of variability was obtained in a similar way.

## RESULTS

**Clinical characteristics (Table 1).** All patients were asymptomatic for cardiovascular symptoms (NYHA functional class I)

Table 1. Clinical characteristics of SSc population and control group. Data are mean  $\pm$  SD or percentage.

Variables	SSc	dSSc	ISSc	Control
Subjects, n	50	17	33	31
Age, yrs	53.3 $\pm$ 12.9	50.4 $\pm$ 9.9 <sup>†</sup>	54.8 $\pm$ 13.7	55.0 $\pm$ 9.0
Women/men	45/5	14/3	31/2	26/5
Body surface area, m <sup>2</sup>	1.66 $\pm$ 0.12	1.65 $\pm$ 0.1	1.66 $\pm$ 0.1	1.67 $\pm$ 0.1
Heart rate, beats/min	75.0 $\pm$ 8.0	75.8 $\pm$ 7.6	74.0 $\pm$ 8.4	72.0 $\pm$ 4.0
Mean arterial pressure, mm/Hg	96.9 $\pm$ 7.0	95.9 $\pm$ 9.5	99.6 $\pm$ 8.4	93.0 $\pm$ 6.2
Disease duration, yrs	12.2 $\pm$ 10.2	6.9 $\pm$ 4.4*	14.1 $\pm$ 11.4	—
ACA, %	38.0	41.0	36.4	—
Scl-70, %	34.0	59.0	21.2	—
DLCO, %	83.1 $\pm$ 16.1	75.0 $\pm$ 8.9*	84.9 $\pm$ 16.8	—
FEV1, %	95.7 $\pm$ 16.0	95.4 $\pm$ 14.2	95.4 $\pm$ 18.0	—

DLCO: lung diffusion for CO; ACA: serum anticentromere antibodies; Scl-70: antitopoisomerase antibodies.

<sup>†</sup> p < 0.04 between dSSc and ISSc. \* p < 0.003 between dSSc and ISSc.

with unremarkable physical examinations. No differences of age, sex, BSA, heart rate, or mean arterial pressure were found between SSc patients and controls. Nine SSc patients were smokers and 10 showed elevated serum cholesterol levels (normal value < 190 mg/dl). Glucose serum levels were within the normal range. All electrocardiograms showed normal sinus rhythm without rhythm disturbances, conduction defects, or abnormal morphology. According to LeRoy and Medsger<sup>9</sup>, 17 subjects had the limited form (ISSc; mean age 50.4  $\pm$  9.9 yrs) and 33 the diffuse form (dSSc; mean age 54.8  $\pm$  13.7 yrs) of the disease. The difference in mean disease duration between the 2 subgroups (ISSc 14.1  $\pm$  11.4 yrs and dSSc 6.9  $\pm$  4.4 yrs) was statistically significant (p < 0.003). Further, patients with ISSc were older (p < 0.04) than those with dSSc (54.8  $\pm$  13.7 vs 50.4  $\pm$  9.9 yrs). Serum ACA and Scl70 were positive in 23 (46%) and 17 patients (34%), respectively. No statistical differences were found in the remaining variables when SSc patients were evaluated on the basis of ISSc and dSSc. Ultrasound examination showed no significant valvular heart disease or pericardial effusion. The LV regional wall motion score index (WMSI = 1), LVEF (> 55%), and PAPS were all within the normal ranges. The LV mass index was in the normal range among all SSc patients (67.11  $\pm$  15.17 g/m<sup>2</sup>), with no significant differences compar-

ing dSSc (68.27  $\pm$  14.02 g/m<sup>2</sup>) and ISSc (67.72  $\pm$  15.28 g/m<sup>2</sup>) patients.

**Doppler echocardiography** (Table 2). The E/A ratio at the mitral level was significantly lower in SSc patients than in controls (p < 0.01). Indeed, an inverted left ventricular E/A ratio was detected in 25 of 77 SSc patients (32%) and in 4 of the 36 controls (11%). E/A ratio seemed to be related to increased peak A (p < 0.05) with a slight but not significant decrease of peak E (NS). Consistent with an abnormal left ventricular filling, SSc patients showed significantly longer DTE (p < 0.05). Peak velocities of systolic (S) and diastolic (D) PV flow and their ratio (S/D) were reduced in SSc in comparison with controls, and this difference was mainly due to a significant reduction in the peak D (p < 0.001), while peak S was not reduced (NS). Comparing the dSSc with ISSc patients, no significant differences among variables were found.

**Pulmonary function tests** (Table 1). Morphological evaluation by HRCT revealed honeycombing pattern (score 2) in 8 patients (3 with dSSc and 5 with ISSc). Functional evaluation by respiratory tests showed significant reduction in DLCO between dSSc and ISSc (p < 0.05), while FEV1 was not significantly different between subgroups. Statistical analysis of

Table 2. Doppler mitral and pulmonary venous flow variables of the SSc and control groups. Data are mean  $\pm$  SD.

Variables	SSc	dSSc	ISSc	Control	p*
E, cm/s	81.1 $\pm$ 15.8	77.2 $\pm$ 8.4	81.9 $\pm$ 18.9	85.2 $\pm$ 18.2	NS
A, cm/s	70.2 $\pm$ 16.2	73.4 $\pm$ 21.1	70.3 $\pm$ 15.6	63.8 $\pm$ 7.8	0.05
E/A	1.2 $\pm$ 0.29	1.1 $\pm$ 0.3	1.20 $\pm$ 0.29	1.35 $\pm$ 0.1	0.01
DTE, ms	213.5 $\pm$ 43.2	220.4 $\pm$ 44.0	209.57 $\pm$ 43.3	188.6 $\pm$ 22.4	0.05
S, cm/s	51.4 $\pm$ 2.6	53.6 $\pm$ 2.5	50.2 $\pm$ 1.8	52.2 $\pm$ 4.8	NS
D, cm/s	48.3 $\pm$ 5.1	49.3 $\pm$ 3.1	47.7 $\pm$ 5.8	39.5 $\pm$ 3.6	0.001
S/D	1.1 $\pm$ 0.1	1.1 $\pm$ 0.1	1.07 $\pm$ 0.1	1.3 $\pm$ 0.1	0.01

E: peak velocity of early filling wave; A: peak velocity of atrial filling wave; DTE: deceleration time of E wave; S: systolic peak velocity of pulmonary venous flow; D: diastolic peak velocity of pulmonary venous flow.

\* Comparing SSc and control. NS: nonsignificant.

pulmonary evaluation data showed no correlation with cardiac MRI findings.

**Cardiac MRI (Tables 3, 4).** Mean (SD) values and 95th percentile upper limits for cardiac MRI data are given in Table 3. No patient showed regional or global left ventricular abnormalities. The fifth percentile (lower) limits for unadjusted RVEF were 34.3% for SSc and 50.4% for controls, while for LVEF values were 48.0% for SSc and 53.8% for controls. Except for the left and right systolic volumes, all unadjusted cardiac MRI data were significantly reduced in SSc compared to controls ( $p < 0.001$  and  $p < 0.009$ ). These differences persisted after adjustment for subject's height and BSA (Table 3). Table 4 shows mean (SD) values and 95th percentile upper limits for cardiac MRI data. The fifth percentile (lower) limits for the unadjusted RVEF were 32.0% for dSSc and 37.1% for ISSc, while for LVEF, values were 42.0% for dSSc and 47.7% for ISSc. Only unadjusted RVEF was significantly reduced in dSSc in comparison to ISSc ( $p < 0.03$ ). However, this slight significant difference persisted after indexing by subject's height and BSA ( $p < 0.03$ ). The intra- and intervariability were 3.2% and 3.6 %, respectively. No statistically significant correlations were found between RVEF and the other clinical variables we examined.

## DISCUSSION

Subclinical cardiac impairment in our SSc study population

was characterized by a significant reduction in right ventricular end-diastolic volume (RVEDV) and left ventricular end-diastolic volume (LVEDV) with abnormal RVEF compared to the sex, age, and BSA-matched control group. The values of LVEDV, RVEDV, LVEF, and RVEF we observed are in agreement with those reported by Raman, *et al*<sup>22</sup>, who found excellent agreement between multi-detector row cardiac computed tomography and cardiac MRI measurements of both RV and LV size and function. Moreover, a recent report by Maceira, *et al*<sup>21</sup>, showed that RV volumes and function (systolic and diastolic) vary with sex, age, and BSA, and suggested that identification of early abnormality in particular requires reference ranges, normalized for all 3 variables. Thus, the presence of a mild but significant reduction in the LVEDV with LVEF in normal range suggests that, due to anatomical and morphological differences between right and left cardiac chambers, reduced ventricular function is detected in the right ventricle when LVEF is still maintained, even if the myocardial derangements of SSc probably affect left and right sides of the heart.

**Evaluation of cardiac function.** The normal value of RVEF is not well defined and it depends on different variables related not only to the presence/absence of underlying heart diseases but also to morphological variables such as height, BSA, and body mass index as well as the imaging method (nuclear scintigraphy or cardiac MRI), as shown by Meune, *et al*

Table 3. Raw data and height and BSA-matched cardiac MRI variables in SSc and control groups.

	SSc			Control		
	Mean $\pm$ SD	Upper Limits		Mean $\pm$ SD	Upper Limits	
		5%	95%		5%	95%
<b>Raw</b>						
RVEDV, ml	80.5 $\pm$ 19.3*	54.1	124.4	105.4 $\pm$ 12.6	85.2	124.0
RVESV, ml	42.3 $\pm$ 13.3	24.3	71.9	44.0 $\pm$ 7.1	31.4	55.2
RVEF, %	46.9 $\pm$ 6.9 <sup>†</sup>	34.3	59.9	58.2 $\pm$ 4.3	50.4	65.3
LVEDV, ml	96.5 $\pm$ 18.6*	68.5	130.6	126.8 $\pm$ 29.5	88.7	193.1
LVESV, ml	37.4 $\pm$ 10.7	19.8	62.3	44.7 $\pm$ 17.0	25.3	88.4
LVEF, %	60.8 $\pm$ 6.7**	48.0	69.6	65.2 $\pm$ 7.1	53.8	79.3
<b>Raw/height</b>						
RVEDV, ml/m	49.2 $\pm$ 11.1*	32.7	73.6	65.3 $\pm$ 8.4	51.4	77.7
RVESV, ml/m	26.5 $\pm$ 7.7	15.9	42.0	27.3 $\pm$ 4.7	19.1	54.9
RVEF, %/m	28.8 $\pm$ 4.3 <sup>†</sup>	20.9	37.0	35.6 $\pm$ 2.8	30.9	41.2
LVEDV, ml/m	60.2 $\pm$ 11.6*	44.3	83.3	78.5 $\pm$ 18.3	51.6	119.9
LVESV, ml/m	23.7 $\pm$ 7.5	12.4	42.4	27.6 $\pm$ 10.4	14.8	54.9
LVEF, %/m	37.3 $\pm$ 4.7**	29.5	44.9	40.0 $\pm$ 5.1	30.8	51.2
<b>RAW/BSA</b>						
RVEDV, ml/m <sup>2</sup>	48.5 $\pm$ 9.8*	32.6	65.1	63.2 $\pm$ 8.7	48.8	80.9
RVESV, ml/m <sup>2</sup>	25.8 $\pm$ 7.0	16.0	37.4	26.4 $\pm$ 4.7	17.8	32.9
RVEF, %/m <sup>2</sup>	28.1 $\pm$ 4.6 <sup>†</sup>	19.9	36.7	34.5 $\pm$ 3.6	29.2	41.7
LVEDV, ml/m <sup>2</sup>	58.9 $\pm$ 10.4*	44.8	79.6	76.0 $\pm$ 18.2	47.7	122.4
LVESV, ml/m <sup>2</sup>	23.3 $\pm$ 7.4	12.3	41.4	26.8 $\pm$ 10.6	14.0	55.7
LVEF, %/m <sup>2</sup>	36.4 $\pm$ 5.0**	28.9	45.8	38.6 $\pm$ 5.3	28.9	48.5

BSA: body surface area; RVEF: right ventricular ejection fraction; RVEDV: right ventricular end-diastolic volume; RVESV: right ventricular end-systolic volume; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume. \*  $p < 0.0001$  between SSc and controls. <sup>†</sup>  $p < 0.0001$  between SSc and controls. \*\*  $p = 0.009$  between SSc and controls.

Table 4. Raw data and height and BSA-matched cardiac MRI variables in patients with ISSc and dSSc.

	ISSc			dSSc		
	Mean ± SD	Upper Limits 5% 95%		Mean ± SD	Upper Limits 5% 95%	
Raw						
RVEDV, ml	80.5 ± 17.7	53.9	118.7	80.3 ± 23.8	54.8	127.1
RVESV, ml	40.9 ± 12.2	24.0	65.7	48.1 ± 14.6	27.9	75.5
RVEF, %	47.9 ± 6.8 <sup>†</sup>	37.1	61.9	43.7 ± 5.9	32.0	54.0
LVEDV, ml	96.1 ± 16.6	68.3	126.9	100.6 ± 25.2	74.7	132.5
LVESV, ml	36.7 ± 10.0	18.4	63.14	42.8 ± 16.4	28.5	59.6
LVEF, %	61.3 ± 7.1	47.7	71.8	57.9 ± 7.2	42.0	68.0
Raw/height						
RVEDV, ml/m	49.8 ± 11.1	32.5	74.6	49.4 ± 12.5	33.2	70.6
RVESV, ml/m	25.2 ± 7.4	15.9	41.4	29.8 ± 8.1	16.9	41.9
RVEF, %/m	29.7 ± 4.4 <sup>†</sup>	21.1	38.6	27.1 ± 3.9	20.6	34.6
LVEDV, ml/m	59.4 ± 10.4	43.0	79.9	62.5 ± 15.1	48.1	86.2
LVESV, ml/m	22.6 ± 6.1	11.4	38.5	26.6 ± 10.3	18.3	45.7
LVEF, %/m	37.9 ± 4.5	29.5	46.0	35.9 ± 4.8	25.4	44.6
RAW/BSA						
RVEDV, ml/m <sup>2</sup>	48.7 ± 9.6	31.8	63.9	48.1 ± 11.0	34.0	66.0
RVESV, ml/m <sup>2</sup>	24.7 ± 6.8	15.8	35.5	28.9 ± 7.0	18.4	39.2
RVEF, %/m <sup>2</sup>	29.0 ± 4.7 <sup>†</sup>	21.0	37.7	26.4 ± 4.0	19.6	32.3
LVEDV, ml/m <sup>2</sup>	58.2 ± 9.6	43.9	75.9	60.6 ± 12.9	49.4	83.2
LVESV, ml/m <sup>2</sup>	22.3 ± 6.5	11.2	38.5	25.8 ± 9.5	18.5	44.1
LVEF, %/m <sup>2</sup>	37.1 ± 4.9	30.1	47.2	35.0 ± 5.0	26.2	41.1

Definitions as given in Table 3. <sup>†</sup> p = 0.03 between ISSc and dSSc.

(RVEF of 45.8% ± 5.7%)<sup>23</sup>, Tandri, *et al* (RVEF of 62% ± 6%)<sup>24</sup>, and Rominger, *et al* (62% ± 10% for men and 69% ± 10% for women)<sup>25</sup>, who obtained different normal ranges for RV. The reported cardiac MRI values and differences among these reports persisted after adjustment for sex, height, and BSA, in accord with Pennell's values<sup>21</sup> of normal RV, confirming the presence of scleroderma cardiac impairment in our SSc population. Notably, our cardiac MRI scans were acquired using steady-state free precession, which improves image quality with respect to fast gradient-echo imaging, with better border definition and higher blood-to-myocardium contrast of the ventricles; this improves the inter-study reproducibility of RV measurements, as confirmed by our low intra- and interobserver variability. In contrast with Ferri, *et al*<sup>26</sup>, who found cardiac dysfunction in only a minority of patients with SSc, we detected a significant compromise of RVEF in a higher number of cases. Interestingly, most previous reports have focused on the evaluation of LV anatomy and function. RV function is usually overlooked because RV chamber geometry is very complex in its anatomic configuration. Moreover, the methods for RV functional evaluation are technically difficult to perform and are biased by interobserver variability. Cardiac MRI overcomes such technical limitations since it provides morphological and functional evaluations totally independent from geometric assumptions<sup>27</sup>.

*Duration of disease in the SSc population.* In our study, disease duration was found to be significantly longer in ISSc patients than in dSSc patients. Moreover, patients with dSSc were younger than those with ISSc. These findings are in

agreement with previous studies<sup>28,29</sup> showing that myocardial involvement is more common and severe in patients with dSSc than in ISSc, and that myocardial fibrosis occurs predominantly in patients with diffuse cutaneous disease independently of the duration of the disease<sup>30</sup>.

*Cardiovascular remodeling in SSc.* The mechanism underlying impairment in the right ventricle is unclear. RVEF is determined by intrinsic RV contractile function, and by RV preload and afterload. In the normal heart, LV contraction is known to contribute 20% to 40% of RV pressure development and output. Since SSc generally affects both ventricles, the hemodynamic consequences of SSc include a combination of systolic and diastolic dysfunction of both ventricles, such as low cardiac output and increase of the RV and LV filling pressures, that determines RVEF that tends to be lower for any given LVEF. Findings of altered diastolic function in SSc patients with a preserved LVEF have been reported by Lindqvist, *et al*<sup>31</sup> and Giunta, *et al*<sup>32</sup>. However, these studies had limitations: the study populations were not characterized for functional class, the presence of LV hypertrophy was not well stated and, consequently, was excluded, and the presence of hypertension in SSc groups and controls was not fully discussed, thus limiting the attribution of the right and left diastolic alterations to the SSc itself.

Our selected SSc population showed normal PAPS, reduced RVEDV and LVEDV, and no significant difference in heart rate among patients with the 2 cutaneous forms of the disease and controls. In our opinion, these data suggest that reduced RVEF was due to increased ventricular stiffness, like-

ly related to the myocardial fibrosis, with increase in the ventricular filling pressure as shown by the Doppler filling abnormalities in the LV, that is one of the most significant determinants of RV function. In contrast to patients with pulmonary artery hypertension, whose reported reduction in LVEDV and RVEDV reflects the constraining effects of the pericardium due to RV distension, in our subjects the decreased compliance of both ventricles throughout the diastolic phase of the cardiac cycle seems due mainly to the increased stiffness of the cardiac chambers.

Finally, in our series no statistically significant correlation was detected between cardiac MRI data and clinical data potentially associated with heart dysfunction such as serum lipid profile, glucose levels, blood pressure, body mass index, smoking, and lung function measures. These findings support the hypothesis that cardiac involvement in SSc has an autonomous pathogenesis directly related to the fibrotic degeneration of myocardium, similar to the results of Fernandes, *et al*<sup>33</sup>, who used endomyocardial biopsy to show abnormal myocardial collagen deposition in 94% of cases in a consecutive series of 16 SSc patients with no LV dysfunction and no signs or symptoms of heart failure.

*Limitations of the study.* Even if cardiac MRI were able to detect subclinical cardiac abnormalities in SSc, the method should not be considered for routine SSc screening; as suggested by Ferri, *et al*<sup>34</sup>, accurate cardiologic baseline screening and subsequent followup are mandatory for all patients. Initially consisting of noninvasive diagnostic procedures when needed (electrocardiogram, chest radiograph, Doppler echocardiography), these examinations should be integrated by Holter monitoring, cardiopulmonary stress tests, cardiac MRI, nuclear scintigraphy studies of myocardial function and perfusion, and cardiac catheterization to better estimate the presence of cardiac involvement and pulmonary hypertension. We tried to use cardiac MRI as a technique to allow earlier diagnosis of cardiac involvement, although the influence of our results on followup and management of this subgroup of patients with SSc remains to be determined.

The characteristics and different patterns of ventricular filling evaluated by atrioventricular flow are dependent upon loading conditions, heart rate, and myocardial inotropic state. In abnormal ventricular filling, the compensatory increase in atrial pressure determines the pseudonormalization of the atrioventricular flow pattern. The Doppler spectra data acquired in pulmonary veins has been shown to differentiate normal from pseudonormal patterns, while filling velocities through the tricuspid valve are more dependent upon heart rate and respiratory cycles than left atrioventricular flow. Because of these limitations we observed LV filling patterns at the mitral valve and did not evaluate RV filling at the tricuspid valve.

All controls and SSc patients showed unremarkable treadmill stress-test results, suggesting the absence of underlying, fixed, significant coronary lesions. However, these findings should not exclude the presence of microvascular abnormali-

ties<sup>35</sup> such as vasospasms and/or endothelial dysfunction that should be considered responsible for fibrotic alterations in the myocardium.

Compromised right ventricular function was found in asymptomatic patients with SSc. Unlike standard diagnostic techniques, cardiac MRI appears to hold promise as a rapid and noninvasive means of determining subclinical right myocardial involvement that would otherwise be undetected.

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