Mechanics of early ventricular impairment in systemic sclerosis and the effects of peripheral arterial haemodynamics

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ABSTRACT

Objective. *Multiple mechanisms commonly lead to severe cardiac involvement in systemic sclerosis (SSc), an autoimmune disease characterised by microvascular lesions, systemic inflammation and fibrosis. Herein, we examined the mechanics of right and left ventricles (RV, LV) at the early stage of impairment and tested the hypothesis that peripheral vasculopathy influences the possible early compromise of LV.*

Methods. *Ninety-five SSc patients free of any cardiovascular disease or related symptoms (88% women, 53±14 years) and 54 subjects matched for age, gender, arterial hypertension, dyslipidaemia, and diabetes mellitus underwent echocardiography, including multilayer speckle-tracking, and tonometry-based pulse wave analysis of the peripheral arteries; 66 SSc patients were prospectively assessed after 32±7 months. Indices of ventricular and arterial structure and function, as well as LV-arterial coupling, were calculated.*

Results. *At baseline, patients presented RV diastolic/systolic impairment, as well as LV remodelling and diastolic/systolic impairment in terms of reduced deformation parameters versus controls. No association was found between RV and LV strain within individual patients, whereas both RV and LV abnormalities progressed independently during follow-up. Moreover, in the absence of differences in aortic stiffening and LV-arterial coupling between patients and controls, arterial pressure wave reflections assessing small vessel function and/or microcirculation were abnormal in SSc patients and strongly correlated with impaired indices of LV diastolic function and remodelling.*

Conclusion. *Speckle-tracking echocardiography demonstrates the mechanics of RV early impairment in SSc that develops and progresses independently from the concomitant LV impairment, which, in turn, may be influenced by peripheral microvascular abnormalities in the absence of macrovascular damage.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by vasculopathy, inflammation and fibrosis of the skin and internal organs. Microvascular abnormalities precede fibrosis and play a major role in the disease process. Endothelial injury, affecting mostly small and medium arteries, occurs early in the course of disease and is the main contributor of vasculopathy. In addition to small vessel disease, there is accumulating evidence for macrovascular damage, contributing to the increased prevalence of cardiovascular mortality observed in SSc (1-3).

Cardiac involvement is a well-known complication of SSc, affecting all structural components of the heart and associated with poor prognosis and increased mortality (4-6). Several factors including the low discriminatory capacity of the available diagnostic methods, the complexity of clinical manifestations and definitions, and the concomitant pulmonary abnormalities, contribute to a rather poor understanding of the mechanisms underlying cardiac impairment in SSc (7). The newly developed techniques, such as cardiovascular magnetic resonance (8-10) and speckle tracking echocardiography (11, 12) permit a more detailed study of cardiac structure and function, whereas their results correlate with autopsy findings (13). While functional and structural abnormalities of coronary microcirculation and cardiac tissue inflammation and fibrosis seem to be the main contributors in primary heart impairment (14), the possible contribution of the peripheral vascular

Table I. Demographics and characteristics of patients with systemic sclerosis and age- and gender-matched subjects.

		Patients at baseline (n=95)	Control subjects (n=54)	*p**	Patients at follow up (n=66)
Age in years (mean ± SD)		53.3 ± 13.7	53.5 ± 12	0.909	53 ± 12.2
Gender (women, %)		88	87	0.803	-
BSA (m^2) (mean ± SD)		1.7 ± 0.2	1.8 ± 0.2	***0.018***	1.71 ± 0.16
Diabetes Mellitus (type 1 or 2) (%)		2	2	0.916	7
Arterial hypertension (%)		60	68	0.362	62
Dyslipidaemia (%)		21	28	0.370	22
Smoking (%)		17	42	***0.001***	20
SSc disease characteristics					
SSc disease duration in years (range)		7 (4-12)	n/a	-	9 (6-15)
SSc subtype	Limited (%)	59	n/a	-	45
	Diffuse (%)	41	n/a	-	55
Antibody status	ACA (%)	10	n/a	-	6
	Anti-SCL70 (%)	67	n/a	-	71
Organ involvement	Pulmonary fibrosis (%)	65	n/a	-	n/av
	Renal crisis (%)	2	n/a	-	n/av
	Upper Gastrointestinal involvement (%)	65	n/a	-	n/av
	Lower Gastrointestinal involvement (%)	32	n/a	-	n/av
	Contractures (%)	28	n/a	-	n/av
	Digital ulcers (%)	53	n/a	-	n/av
	Digital Absorptions (%)	10	n/a	-	n/av
	Calcifications (%)	17	n/a	-	n/av
Medication					
Medications	ASA (%)	33	6	***<0.001***	38
	Ca blockers (%)	47	13	***<0.001***	47
	ACE inhibitor (%)	16	9	0.251	17
	ARBS (%)	7	26	***0.005***	5
	Diuretics (%)	7	15	0.141	3
	Cortizone (%)	57	n/a	-	64
	Methotrexate (%)	24	n/a	-	30
	Phosphodiesterase 5 Inh. (%)	20	n/a	-	24

BSA: body surface area; SSc: systemic sclerosis; ACA: anti-centromere antibodies; ASA: aspirin; Ca: calcium; ACE: angiotensin-converting-enzyme; ARBS: angiotensin receptor blockers; n/a: non-applicable; n/av: non-available.
*p: comparison between "SSc patients at baseline(n=95)" and age- and gender-matched "control subjects".

abnormalities has not been addressed. Therefore, the present study aimed to investigate the mechanics of right and left ventricle (RV, LV) impairment at the early phases and test the hypothesis that peripheral arterial dysfunction and impaired ventricular-arterial coupling is associated with the possible early abnormalities of LV structure and function.

Methods

Study population

Consecutive SSc patients fulfilling the 2013 ACR/EULAR classification criteria for SSc (15) were recruited from the outpatient Rheumatology Unit of Laikon University Hospital and 95 patients, free of any cardiovascular disease or related symptoms, were finally included in the study. The following clinical and echocardiographic exclusion criteria were applied: history of palpitations, angina, myocardial infarction or stroke and the presence of peripheral macrovascular disease, pulmonary arterial hypertension, moderate or severe valvular abnormalities, left ventricular hypertrophy more than 11mm, atrial fibrillation, cardiac pacing or left bundle branch block. Fifty-four subjects, free of connective tissue or cardiovascular disease matched for age, gender, arterial hypertension, dyslipidaemia, and diabetes mellitus, served as the control group. At baseline, all participants underwent a thorough physical examination and echocardiography, including multilayer speckle tracking. In addition, indices of ventricular and arterial properties and ventricular-arterial coupling were assessed by pulse wave analysis techniques. Sixty-six SSc patients were re-examined by echocardiography after a mean follow-up of 32±7 months. The study was performed in accordance with the international guidelines on clinical investigation of the World Medical Association's Declaration of Helsinki and was approved by local ethics committee. All subjects gave written consent.

Echocardiography and speckle tracking study

All subjects underwent a comprehensive conventional two-dimensional (2D) and Doppler echocardiography study, by the same certified operator blinded to other clinical data. An ultrasound system (Vivid 7 pro, General Electric Medical Systems, Horten, Norway) with a 2.5 MHz transducer was used. All data were stored for off-line analysis (EchoPAC 113.05 version, GE Healthcare, Horten, Norway). All images were obtained according to the recent recommendations with a frame rate above 50 frames/sec. The study protocol is described in detail in the supplement.

Arterial haemodynamics, ventricular-arterial coupling and cardiovascular performance indices

All participants, after a 12-hour abstinence from food, caffeine, smoking, alcohol, and drugs, underwent arterial haemodynamic measurements by the same experienced physician. After a 10-min resting period in the supine position, the carotid to femoral pulse wave velocity was non-invasively calculated with the available SphygmoCor system (Sphygmocor Atcor medical, Australia) (16). Using the same system and a validated transfer function, aortic pressures and central haemodynamics were obtained from the radial artery waveform (17). To further investigate the arterial and left ventricular properties, indices of LV ventricular-arterial

coupling and performance were calculated. Detailed analysis of the relevant methodology is also described in the supplement.

Statistical analysis

Data were analysed using the Stata 14 (StataCorp, Texas). Shapiro-Wilk test was performed to test the normality. Variables with normal distribution were expressed as mean±SD while those with non-normal distribution were shown as median (25–75% quartiles). Comparisons between categorical variables were made with the chi-square test, while those between continuous variables with the t-test (values with normal distribution) and Mann-Whitney U-test (values without normal distribution). Paired *t*-test was used for comparison of SSc patients' data between the baseline and end of follow-up. Correlations were tested by Pearson and Spearman tests, as appropriate. Single and multivariate stepwise regression analysis was performed to assess the association between echocardiographic findings, vascular findings and disease characteristics. Adjustment for confounders such as age, gender, cardiovascular risk factors (smoking, body surface area (BSA), diabetes, dyslipidaemia, arterial hypertension), anti-hypertensive drugs and mean arterial pressure was performed, and a *p*-value ≤0.05 was defined as statistically significant.

Table II. Two-dimensional echocardiographic and speckle-tracking derived parameters for right and left ventricle in patients with systemic sclerosis and age- and gender-matched control subjects.

	SSc patients (n=95)	Control subjects (n=54)	*p**	*p***
	Right ventricle			
EndDiastolic Area, (cm^2/m^2)	9.7 (8.5-10.7)	9.6 (6.8-10.5)	0.444	0.187
EndSystolic Area, (cm^2/m^2)	5.2 (4.6-5.8)	4.6 (4.2-5.5)	0.483	0.758
RV E/e'	4.8 (3.8-5.9)	4.15 (3.4-4.8)	***0.012***	***0.007***
RVSP, (mmHg)	28.6 (23.5-33.1)	13.4 (11.8-14.6)	***<0.001***	n/a
TAPSE, (cm)	2.2 (2.1-2.4)	2.4 (2.3-2.5)	***0.001***	0.356
FAC, (%)	47 (42-51)	50 (46-56)	***<0.001***	0.132
S, (cm/sec)	13 (12-15)	14 (13-15)	***0.05***	0.794
GLS free wall, (%)	-25.7 ± -4.3	-28.3 ± -4.6	***<0.001***	***0.012***
	Left ventricle			
	SSc patients (n=95)	Control subjects (n=54)	*p**	*p****
EndDiastolic Volume, (mL/m^2)	40.3 (36.5-45.5)	43.8 (39.6-49.0)	***0.008***	***0.008***
EndSystolic Volume, (mL/m^2)	16 (12.8-18.7)	16.3 (14.3-19.8)	0.459	0.148
Mass, (g/m^2)	70 (59.6-78.5)	68.1 (57.4-80.9)	0.740	0.09
LV E/e'	8.3 (6.6-9.9)	8.0 (6.8-8.9)	0.116	0.428
EF, (%)	63 ± 3	62 ± 5	0.315	0.484
GLS, Red (sec^{-1})	1.49 (1.2-1.7)	1.54 (1.3-1.8)	0.121	0.059
GLS, (%)	-20.4 ± 2	-21.5 ± -1.9	***0.003***	***0.001***
GCS, (%)	-22.7 (-25 --21.2)	-25.3 (-28.3--23.3)	***0.001***	***0.003***

Data are means ± SD or median value (25, 75 percentile).
RV E/e' ratio: E pulsed-wave Doppler velocity at tricuspid valve over e' pulsed-wave tissue Doppler velocity at tricuspid annulus; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular longitudinal excursion by M-mode; FAC: fractional area changing; S: peak systolic velocity at tricuspid annulus by pulsed-wave tissue Doppler imaging; GLS free wall: global longitudinal strain of right ventricle free wall; n/a: no applicable; EF: ejection fraction; LV E/e': ratio E pulsed-wave Doppler velocity at mitral valve over e' averaged pulsed-wave tissue Doppler velocity at mitral annulus; GLSRed: global longitudinal strain rate in early diastole; GLS: global longitudinal strain; GCS: global circumferential strain.
*Adjusted for age, gender, smoking, body surface area, diabetes, dyslipidaemia, arterial hypertension.
**Adjusted for age, gender, smoking, body surface area, diabetes, dyslipidaemia, arterial hypertension, RVSP.
***Adjusted for age, gender, smoking, body surface area, diabetes, dyslipidaemia, arterial hypertension, mean arterial pressure, calcium channel blockers.

Results

Baseline and follow-up demographic and clinical characteristics, cardiovascular risk factors, and medications of the study population are shown in Table I.

As shown in Table II, although structural and common systolic RV echocardiographic indices were similar between patients and controls, the RV E/e' an index of RV diastolic function and the global longitudinal strain of RV free wall (GLS-RV), were impaired in SSc compared to controls (p=0.007 and p=0.012, respectively). Moreover, by multivariate analysis we found that the GLS-RV was associated only with the presence of diffuse skin involvement (b=2.63, p=0.042) and not with other disease characteristics shown in Table I. Interestingly, we did not find any correlation neither with the presence of RV systolic pressure nor with pulmonary fibrosis, further suggesting the presence of primary RV involvement.

Regarding LV, by multivariate analysis after appropriate adjustments we found that an early diastolic impairment was also evident in SSc patients versus controls, as expressed by reduced global longitudinal strain rate in early diastole (p=0.059). In addition, although there was no difference in LV ejection fraction between the two groups, SSc patients displayed early impairment of systolic function in both longitudinal and circumferential level after adjustment for confounders (Table II). Moreover, in multivariate analysis, both global longitudinal (GLS-LV) and circumferential strain (GCS-LV) of LV correlated only with disease duration (b=0.14, p=0.001 and b=0.17, p=0.032, respectively), but not with other disease characteristics shown in Table I.

Repeated echocardiographic studies in a representative subgroup of 66 SSc patients after 32±7 months (Table III) revealed a progression of the early impairment of both ventricles. More specifically, although RV structural indices did not significantly change, RV systolic pressure increased (p=0.016), albeit remaining within normal. The Index of diastolic function RV E/e' (p=0.042) as well as the GLS-RV (p=0.019) showed further deterioration (Table III). Regarding LV, the LV mass index increased remarkably (p<0.001), whereas diastolic (GLSRed; p<0.001)

Table III. Progressive changes in right and left ventricular parameters during a 3-year follow-up in 66 patients with systemic sclerosis.

	Patients at baseline (n=66)	Patients at follow up (n=66)	*p* (paired t-test)
	Right ventricle		
EndDiastolic Area, (cm^2/m^2)	9.6 ± 1.7	9.8 ± 1.6	0.069
EndSystolic Area, (cm^2/m^2)	5.2 ± 1	5.2 ± 1	0.685
RV E/e'	4 (3.4-4.8)	4 (3.6-5.1)	***0.042***
RVSP, (mmHg)	28 ± 7	29 ± 7	***0.016***
GLS free wall, (%)	-25.1 (-28.6--22.7)	-24.9 (-27.9--22.0)	***0.019***
	Left ventricle		
EndDiastolic Volume, (mL/m^2)	40 (36.5–44.8)	39.9 (37.1–43.7)	0.771
EndSystolic Volume, (mL/m^2)	15.5 (13–17.7)	15 (13.1–17.3)	0.680
Mass, (g/m^2)	69.8 ± 12.8	74.3 ± 14.9	***<0.001***
LV E/e'	7.9 (6.5–9.5)	7.7 (6.1–9.9)	0.546
EF, (%)	63 ± 5	63 ± 4	0.474
GLSRed, (sec^{-1})	1.53 (1.3–1.7)	1.38 (1.1–1.6)	***<0.001***
GLS, (%)	-20.4 (-21.6--18.9)	-19.8 (-21.1--18.4)	***<0.001***
GCS, (%)	-22.7 ± -2.8	-22.3 ± -2.8	0.162

Data are means ± SD or median value (25, 75 percentile). RV E/e': ratio E: pulsed-wave Doppler velocity at tricuspid valve over e' pulsed-wave tissue Doppler velocity at tricuspid annulus; RVSP: right ventricular systolic pressure; GLS free wall: global longitudinal strain of right ventricle free wall; EF: ejection fraction; LV E/e': ratio E pulsed-wave Doppler velocity at mitral valve over e' averaged pulsed-wave tissue Doppler velocity at mitral annulus; GLSRed: global longitudinal strain rate in early diastole; GLS: global longitudinal strain; GCS: global circumferential strain.

Table IV. Arterial haemodynamics and vascular-ventricular coupling in systemic sclerosis patients and control subjects.

	SSc patients (n=95)	Control subjects (n=54)	*p**
	Arterial haemodynamics		
SP, (mmHg)	114 (106-126)	127 (118-142)	ns
DP, (mmHg)	69 (64-74)	79 (70-89)	ns
MAP, (mmHg)	85 (79–91)	96 (87–103)	ns
aSP, (mmHg)	108 (97-117)	126 (111-135)	ns
HR, (min^{-1})	70 ± 9	62 ± 8	ns
AP75, (mmHg)	12.3 ± 6.6	12.1 ± 5.2	***0.009***
AIx75, (%)	33 (26.8-38.0)	31.5 (24.0-37.0)	0.061
PWV, (m/s)	7.6 (6.6-9.3)	8.3 (7.3-9.5)	0.602
Aortic stiffness index, (%)	12.4 (8.3-22.4)	12 (7.9-21.4)	0.066
Total arterial compliance, (mL/mmHg)	1.1 (0.9-1.6)	1.1 (0.9-1.5)	***0.032***
	Vascular-arterial coupling and cardiovascular performance indices		
	SSc patients (n=95)	Control subjects (n=54)	*p***
Ea (mmHg/mL)	2.28 (1.82-2.71)	2.26 (1.89-2.60)	0.687
Ees (mmHg/mL)	3.80 ± 1.21	3.93 ± 1.05	0.545
VAC (Ea/Ees)	0.6 (0.5-0.7)	0.6 (0.6-0.7)	0.250
PVA (kg cm)	5.4 (4.6-6.4)	7.4 (5.6-9)	***<0.001***
LV stroke work, (kg cm)	4.2 (3.6-4.8)	5.4 (4.2-6.6)	***<0.001***
LV stroke work index, (g/cm^2)	60.3 ± 10.3	70 ± 11.9	***<0.001***
LV energetic efficiency (%)	76 (73-79)	77 (75-78)	0.086
Cardiac output L/min	2.9 (2.5-3.6)	3.3 (2.9-4.0)	**<0.001**
SVI (%)	133.4 ± 23.1	156 ± 25.3	***<0.001***

Data are means ± SD or median value (25, 75 percentile).
SP: systolic pressure; DP: diastolic pressure; MAP: mean arterial pressure; aSP: aortic systolic pressure; HR: heart rate; AP75: augmentation pressure at HR 75 min^{-1}; SVI: subendocardial viability index; Aix: augmentation index at HR 75 min^{-1}; PWV: carotid to femoral pulse wave velocity; Ea: effective arterial elastance; Ees: left ventricular elastance; VAC: ventricular arterial coupling; PAV: pressure volume area; LV: left ventricular; n/a: not applicable.
*Adjusted for age, gender, smoking, BSA, diabetes, dyslipidaemia, arterial hypertension, mean arterial pressure
**Adjusted for age, gender, smoking, BSA, diabetes, dyslipidaemia, arterial hypertension.

and systolic function indices (GLS-LV; $p<0.001$) deteriorated. Notably, the absence of association between RV and LV strain within individual SSc patients at baseline was confirmed, since both RV and LV abnormalities progressed independently during follow-up (Supplementary Fig. 1).

Finally, we tested the hypothesis that peripheral arterial dysfunction and/or impaired ventricular-arterial coupling is associated with abnormalities of LV structure and function in SSc patients. Tonometry pulse wave analysis performed in all patients and controls revealed that in the absence of significant aortic stiffening (pulse wave velocity; $p=0.602$, aortic stiffness index; $p=0.066$), the total arterial compliance ($p=0.032$) and pressure wave reflections (augmentation pressure; $p=0.009$ and augmentation index; $p=0.061$) were impaired in SSc (Table IV). Interestingly, in uni- and multivariate analysis no correlation was found between the parameter of vascular properties and SSc characteristics or drugs for SSc. Moreover, although no differences were found in effective arterial elastance ($p=0.687$) and ventricular-arterial coupling ($p=0.250$) between SSc patients and controls, LV performance, as expressed by LV stroke work; ($p<0.001$), LV stroke work index; ($p<0.001$) and pressure-volume area; ($p<0.001$), was reduced in SSc (Table IV). Remarkably, the early LV remodelling as well as diastolic impairment were associated with the impairments of pressure wave reflections and total arterial compliance (Suppl. Table 1a). Furthermore, subendocardial viability ratio, an indirect marker of myocardial ischaemia, correlated with GLS-LV in endocardium derived from multilayer speckle tracking analysis ($p=0.058$) and the calculated indices of the LV performance status correlated with the indices of early LV remodelling and LV deformation parameters (Suppl. Table 1b).

Discussion

In the present prospective controlled study of SSc patients and age- and sex-matched healthy individuals with similar cardiovascular profile, we investigated the very early impairment of right

and left ventricle, arterial properties, and their associations. Taken together, the baseline and follow-up results provide the following novel evidence: (a) early subtle impairment takes place, albeit independently, in both the RV and LV and deteriorates during SSc disease course, (b) the impairment of RV and LV is independently associated with specific SSc characteristics, namely the more severe diffuse subtype and disease duration, respectively; (c) in the absence of significant premature aortic stiffening, existing changes in the peripheral arterial circulation (decreased overall total systemic compliance and increased pressure wave reflections) are associated with early LV diastolic impairment and remodelling; (d) in the absence of overt ventricular-arterial decoupling, LV performance indices are impaired and associated with indices of very early LV remodelling and impairment.

Our observations regarding the very early RV and LV impairments in SSc patients are consistent with previous studies, that have so far examined either ventricle, albeit separately, using mostly longitudinal strain (18–20). The comparison with well-matched controls allowed us to detect concurrently subtle, early changes in diastolic and systolic function of the RV and the LV in the absence of overt cardiac disease, supporting the presence of global, intrinsic biventricular myocardial involvement in SSc. Although and contrary to LV, it is known that RV function in systemic sclerosis may be affected secondary to pulmonary arterial hypertension and/or pulmonary fibrosis (21), the absence of correlation between RV systolic pressure and pulmonary fibrosis with the impaired GLS RV further supports the primary nature of RV myocardial involvement. Contrary to the findings of a recent study (22), we did not observe any correlation between deformation indices of RV and LV, thus, we hypothesise that, even though the two ventricles are interdependent (23), anatomically and architecturally different (24) and common pathophysiological disease specific mechanisms such as myocardial ischaemia, fibrosis and inflammation may affect both right and left heart, they do respond in a different way.

Having the opportunity to prospectively follow up patients with SSc for almost 3 years we verified that not only LV, but also RV, function continued to deteriorate over time. Our results are consistent with those of a previous study (25), which, however, studied only the LV function impairment. The further reduction in GLS but not in GCS during follow up has never been studied and might be explained by the fact that longitudinal fibbers of left ventricle are more susceptible to subendocardial damage and ischaemia (26). This hypothesis is also supported by the present findings in our population that showed a close inverse association between GLS of the endocardium and the subendocardial index, *i.e.* a biomarker of subendocardial perfusion.

Several previous studies have attempted to investigate the vascular properties in SSc but probably due to methodological issues their results are inconsistent (27-29). Carotid to femoral pulse wave velocity and aortic stiffness index by echocardiography, both measurements of aortic stiffness, were not impaired in our patients, a finding consistent with previous studies (28). However, the increased augmentation pressure and augmentation index have also been demonstrated in a recent study (28), combined with reduced total arterial compliance in SSc, and further support the concept that small arteries and the microcirculation are involved earlier in the disease course of SSc. Interestingly, our findings show that pressure wave reflection abnormalities correlate with the LV remodelling and the diastolic impairment in SSc. As expected, no association between pressure wave reflections and the RV was found. These findings support the hypothesis of a direct causal effect of increased pressure wave reflections on LV diastolic function and structure due to increased afterload, instead of a common pathophysiological mechanism in SSc that underlies both the arterial tree and the heart leading to simultaneous damage.

Finally, in the present study we also evaluated the cardiac performance and cardiovascular coupling using combined data from the cardiac ultrasound and pulse wave analysis. Although we did not identify either ventricular-arterial decoupling or LV mechanical energetic inefficiency, we demonstrated a decreased performance-contractility of the LV (LV stroke work, index, PVA), which was associated with (and potentially explains) impaired deformation parameters. This finding implies that in this very early stage of subclinical cardiac impairment alternations in LV remodelling, cardiac output and aortic pressure may maintain global cardiovascular efficiency. Future studies should evaluate the clinical significance of these findings.

Limitations

Our findings should be interpreted with caution, as although the operator of echocardiography was blinded to all other clinical data, this is a single centre study with a relatively small number of patients and controls. The patient number is limited due to the rarity of SSc, albeit being one of the largest in the literature. Also, we did not re-examine the control group at follow up, but our echocardiographic results verified the presence of myocardial involvement in SSc patients at baseline and the progression at follow up. As far as the speckle tracking multilayer echocardiography is concerned, although it is a novel technique able to study the myocardial mechanics, there are some difficulties when applied to the thin wall of the right ventricle. Moreover, we did not employ right heart catheterisation since this would not be ethical given the very low probability of pulmonary arterial hypertension in our cohort of SSc patients. Finally, instead of using invasive methods for the estimation of ventricular arterial coupling and its components, we used widely accepted, standard non-invasive methods.

Conclusions

Using speckle tracking echocardiography, we demonstrate the mechanics of early primary RV impairment, its specific association with the diffuse SSc subtype and its progression, which occurs independently from the concomitant LV impairment. The latter is as-

sociated with SSc disease duration and may be partly influenced by peripheral microvascular abnormalities in the absence of macrovascular damage. Although we do not assess the prognostic value of our data, our findings support that more detailed systematic echocardiographic protocols including strain parameters as first-line modality should be incorporated into the evaluation of patients with SSc from the early stages of the disease and during the follow up in order to detect selected patients with early primary cardiac impairment. Furthermore, more prospective studies are needed to assess the prognostic as well as the therapeutic implications of these novel findings.

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