

Contractile reserve in systemic sclerosis patients as a major predictor of global cardiac impairment and exercise tolerance

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Abstract Several studies have evidenced high prevalence of myocardial systolic and diastolic dysfunction among patients with systemic sclerosis (SSc). Exercise echocardiography has shown a diagnostic and prognostic role in identifying early left ventricular (LV) dysfunction in several myocardial pathological settings. The aim of our study was to evaluate early signs of LV impairment under exercise and their correlation to patient's exercise tolerance. Forty-five patients (age 60.4 ± 10.3 years) with SSc and 20 age and sex comparable controls were enrolled in the study. All patients underwent clinical evaluation, 2D echocardiography associated with Tissue Doppler and speckle tracking to evaluate LV deformation indexes, and an exercise echocardiography to evaluate left ventricle contractile reserve (LVCR) and exercise pulmonary pressures. Finally, a 6-minute walking test (6MWT) to evaluate exercise tolerance was also performed. Compared to controls, SSc patients showed an impaired diastolic function (E/E' 10.9 ± 3.7 vs 8.36 ± 2.01 ; $p < 0.01$) associated with larger left atrial dimensions (LAVI 28.4 ± 8.7 vs 19.3 ± 4.6 mL/m²; $p < 0.01$). During exercise echocardiography, a reduced global longitudinal strain at peak exercise (S-GLS) was highlighted compared to controls (15.7 ± 3.6 vs 18.2 ± 2.2 ; $p = 0.001$). A S-GLS cutoff <18 %, identified by ROC analysis, identified SSc patients with a reduced diastolic function, exercise tolerance at the

6MWT and higher pulmonary pressures. Our data show that in SSc patients a reduced LVCR characterizes the patients with a more extensive cardiovascular impairment in terms of LV diastolic function, pulmonary pressures and exercise tolerance. These data underline the importance of exercise echocardiography for the preclinical screening of the LV impairment in this population.

Keywords Systemic sclerosis · Exercise echocardiography · Speckle tracking echocardiography · Contractile reserve

Introduction

Systemic sclerosis (SSc; scleroderma) is a heterogeneous disease whose pathogenesis is characterized by 3 hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix [1].

Estimated prevalence of 150–300 cases per million are fairly similar for Europe, USA, Australia and Argentina, with a lower prevalence in Scandinavia, Japan, UK, Taiwan and India [2].

Cardiovascular complications proved to be one of the leading causes of mortality in SSc [3], often associated with pulmonary hypertension (PH), which in turn is related to a high mortality rate [4].

Many studies have shown that the left ventricle (LV) is extensively involved in SSc, in terms of myocardial fibrosis and microvascular dysfunction [5, 6]; both these findings could be due to recurrent vasospasm with poor vasodilator reserve, focal ischemia and recurrent ischemia–reperfusion injury and may lead to diastolic and systolic dysfunction [6, 7].

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Two-dimensional (2-D) speckle-tracking (ST) strain analysis has been proposed as a sensitive and accurate method for the evaluation of subclinical myocardial dysfunction, providing measures of LV regional and global strain [8]. The clinical value of measurement of the LV global strain was recently evaluated in relation to functional capacity and ventricular arrhythmias in patients with SSc, showing a subtle LV systolic dysfunction. Notably, LV global longitudinal and circumferential strains were independent predictors of impaired functional capacity, as measured by cardiopulmonary exercise testing [9].

Exercise echocardiography (ExE) has previously been used in the evaluation of patients with scleroderma and in familial forms of pulmonary hypertension [10–12]; more recently, Collins and coll. used this technique to evaluate the change in pulmonary artery pressure in patients with systemic lupus erythematosus and with limited and diffuse SSc. They showed a significant elevation in the systolic pulmonary arterial pressures (sPAP) in all autoimmune subtypes, suggesting an abnormal pulmonary vascular response of these patients to exercise [13].

The method has proved particularly reliable in the assessment of longitudinal LV contractile reserve (LVCR), parameter used to identify early myocardial dysfunction in other settings, such as insulin resistance and type 2 diabetes [14, 15].

The aim of our study was to evaluate the earliest signs of LV impairment using speckle tracking imaging applied to exercise echocardiography. Moreover, our aim was to verify the LV systolic influence to the patient's exercise tolerance and its role in SSc induced left heart remodeling.

Materials and methods

Forty-five patients (age 60.4 ± 10.3 years; 4 male, 41 female) affected by SSc diagnosed at least 2 years before enrollment, in treatment at the Internal Medicine department of our University Hospital have been prospectively enrolled on the study. Twenty healthy subjects who showed no structural heart defects or evidence of CHD, comparable for age (60.8 ± 10.8 years) and BMI, were also enrolled as controls from the cardiology outpatient clinic.

Inclusion criteria for patients were: age >18 and <85 years, a previous diagnosis of SSc according to the American Rheumatism Association classification criteria. Exclusion criteria were: known history of coronary artery disease, reduced echocardiographic LV ejection fraction (LVEF) ≥ 55 %, arterial hypertension with LV hypertrophy (LV mass >104 g/m² measured with 2D echocardiography at rest), moderate to severe heart valve disease, atrial fibrillation or severe arrhythmias, or disabilities that prevented exercise testing.

Most SSc patients were in treatment with endothelin receptor antagonists mainly for digital ulcers (Table 1). No patients were in treatment with other medications affecting pulmonary resistance (i.e. phosphodiesterase-5 inhibitors or prostanoid continuous infusion). All the controls has not history of chest pain or other cardiovascular symptoms. The profiles of patients and controls with respect to cardiovascular risk factors are listed in Table 1.

The physical characteristics, data related to the disease state and the current therapy of the patients studied are summarized in Table 1.

Study protocol

At enrolment all subjects underwent physical examination, blood pressure measurement, 12-lead electrocardiogram, 6-minutes Walking Test (6MWT), and basal and exercise echocardiography with acquisition of raw data for speckle tracking (ST) analysis.

Conventional echocardiography and tissue Doppler imaging (TDI)

The echocardiographic images were recorded using a system equipped with ST raw data acquisition (Toshiba Artida; Toshiba Corp., Tochigi, Japan). Standard 2D measurements (end-diastolic and end-systolic dimensions, ventricular septum and posterior wall thickness, left atrial volume index, LV mass index, LV outflow tract) were made at baseline prior to the stress test. The LV ejection fraction was obtained from the apical four- and two-chamber views according to Simpson's rule. Pulsed wave Doppler (PWD) was performed in apical four-chamber view with the sample volume placed between the mitral leaflet tips and the early (E) and late (A) diastolic peak velocities were determined and the E/A ratio was derived. Longitudinal function was assessed using Tissue Doppler imaging of mitral annulus, placing the sample volume at the septal and lateral wall corner from the apical four-chamber view. Peak velocities in systole (Sm), and early (Em) and late (Am) diastole were measured. To evaluate LV filling pressure, the ratio of mitral inflow peak velocity E/Em was calculated. Left atrial volume (LAV) was measured by the biplane area length method from the apical four-chamber and two chamber views and indexed for the body surface area (LAVI).

In the apical four-chamber view, the tricuspid regurgitant jet was identified using colour-coded Doppler. Then, using continuous-wave Doppler, the maximum velocity of the regurgitant jet (Vmax) was recorded. Using the simplified Bernoulli equation ($TRPG = 4V^2$), the systolic gradient of pressures between the right ventricle and the right atrium—tricuspid regurgitant peak gradient (TRPG)

Table 1 Clinical and laboratory data

Parameter	Systemic sclerosis	Controls	<i>p</i>
Age (years)	60.4 ± 10.3	60.8 ± 10.8	ns
Male/female	9/36 (1:5)	4/16 (1:5)	ns
BSA (kg/m ²)	1.64 ± 0.18	1.71 ± 0.21	ns
ESR	14.3 ± 7.8	1.2 ± 1.1	<i>P</i> < 0.05
Total cholesterol (mg/dl)	201 ± 13	185 ± 22	ns
Diabetes, n (%)	0 %	0 %	ns
Hypertension no LVH ^a , n (%)	27 %	35 %	ns
<i>SSc disease characteristics</i>			
Years from diagnosis	6.3 ± 5.75		
ANA+, [n (%)]	45/45 (100 %)		
Scl-70 antibodies, [n (%)]	15/45 (33 %)		
Diffuse form, [n (%)]	14/45 (31 %)		
<i>Pulmonary function</i>			
Total lung capacity, % predicted	95 ± 14		
FVC, % predicted	103 ± 16		
FEV1/FVC, % predicted	98 ± 11		
DLCO, % predicted	69 ± 12		
<i>Medication</i>			
Ace inhibitors [n (%)]	5/45 (9 %)		
Ca channel blockers [n (%)]	12/45 (27 %)		
Bosentan [n (%)]	32/45 (71 %)		
Sildenafil [n (%)]	0/45 (0 %)		
Corticoids [n (%)]	4/45 (8 %)		
Immunosuppressors [n (%)]	7/45 (15 %)		

BSA Body surface area, LVH left ventricle hypertrophy, ESR erythrocyte sedimentation rate, ANA+ positive for anti-nuclear antibody, FVC forced vital capacity, DLCO diffusing capacity for carbon monoxide, FEV1/FVC forced expiratory volume 1 and forced vital capacity ratio

^a Hypertension without LV mass >104 g/m² measured with 2D echocardiography

was calculated. PASP was calculated by adding a right atrial pressure estimate to the peak TRV. When inferior vena cava diameter and collapsibility were normal in SS patients and controls, the right atrial estimate was always 5 mmHg, when it was reduced or absent, 10 or 15 mmHg was added accordingly.

Speckle tracking echocardiography

A four-chamber view clip was acquired at each evaluation as well as a two-chamber view clip. Longitudinal ventricular function at baseline and after exercise was calculated offline using raw data. (Toshiba Corp., Tochigi, Japan). Global systolic strain (GLS) and Strain rate (GLSR) were obtained by averaging the relative values of all LV segments at the four-chamber and two-chamber view.

Exercise contractile reserve of the left ventricle (LVCR), that is the capacity of myocardium to improve the contractile activity, was assessed as the difference between peak exercise and baseline GLS values (Δ GLS).

Exercise stress echocardiography

A stress echo was performed using a symptom-limited, multistage supine stress test with a variable load bicycle

ergometer (Ergoline Inc.). The bed ergometer was rotated to the left by 20°–30°. Briefly, after obtaining the images at rest, patients cycled at a constant speed, starting from a workload of 25 W and adding an incremental workload of 25 W every 2 min. From the apical window, mitral inflow velocities were traced and early mitral peak velocity (E) and late velocity (A) readings were obtained. Mitral annulus velocity was measured by Doppler Tissue imaging. Moreover, from an apical four-chamber view pulmonary pressures were evaluated using the peak velocity of the tricuspid regurgitant wave of the continuous-wave Doppler. Using the simplified Bernoulli equation the TRPG was calculated.

The measurements were accompanied by simultaneous electrocardiography, at a speed of 50 mm/s. Each measurement was performed at basal condition, at 25 W stage, at peak exercise (defined as the maximum work load performed by every patient), and during recovery. Due to the high incidence of fusion of Em and Am during exercise at workloads >50 W, the diastolic function parameters were assessed at baseline and at 50 W. Moreover, the delta Em (Δ Em), defined as the difference from exercise peak to baseline, were calculated.

Also two-dimensional echocardiographic images were recorded at rest at 50 W stage, at peak exercise, and during

recovery, and the raw data was digitally stored for Strain analysis. Patients with more than 2 non-evaluable segments were excluded from the study analysis. Five cycles were acquired and the best (in terms of image quality for the ST analysis) three cardiac cycles was selected for off-line measurements. Longitudinal strain values were averaged over the three cardiac cycles.

To have homogeneous data and image acquisition all echocardiographic examinations were performed by the same operator (C.C.). All off-line measurements were performed by a single investigator, (M.D.), who was blinded to the clinical condition of the study patients. Intra-observer variability of our laboratory has been previously documented [16].

Statistical analysis

With regards the anthropometric and clinical characteristics of the two groups, continuous variables were compared with ANOVA, and categorical variables were compared with the Fisher's exact test. Differences in echocardiographic parameters were also evaluated using ANOVA. Correlations between parameters were assessed using nonparametric Spearman correlation coefficient analysis or Pearson correlation, as appropriate. A p value of <0.05 was considered statistically significant. Data are presented as mean \pm SD.

Receiver operating characteristic (ROC) analysis was used to assess the best cut-off value of Stress GLS. A measure of the area under the ROC curve was calculated. Sensitivity, specificity, and accuracy calculations were performed according to standard definitions. The 95 % CIs were calculated and the individual intervals were compared.

Results

Characteristics of the study population

The anthropometric and laboratory information for both SS patients and healthy matched controls are summarized in Table 1. No differences between the two groups with respect to physical characteristics or in terms of cardiovascular risk factors such as family history, smoking habits, hypertension and dyslipidemia were observed. Resting heart rate (HR) and blood pressure (BP) were within the normal range for both groups.

Eight patients were excluded from the GLS analysis due to suboptimal exercise test LV images (as described above).

Echocardiographic parameters

Normal LV mass and dimensions, as well as normal LV ejection fractions (EF) were observed in all patients and

controls when examined under basal conditions. After observing diastolic function indices, a diastolic impairment in SS patients compared to controls was noticed (E/A 0.89 ± 0.16 vs 1.04 ± 0.21 ; $p < 0.05$ and E/Em 10.9 ± 3.68 vs 8.3 ± 2.01 ; $p < 0.05$; Table 2). Moreover, SS patients showed an increased LAVI and higher PASP compared to controls (Table 2).

Exercise echocardiography

During exercise on the bicycle bed ergometer, HR and BP increased as expected. Workload obtained during exercise was significantly reduced in SS patients compared to controls (Table 3), although all patients and controls reached 85 % of maximal predicted HR. No chest pain or wall motion abnormalities were observed in SS patients or controls.

Some SS patients exhibited repolarization abnormalities, such as not significant (<1 mm) ST depression (17 %), on the exercise ECG. As expected, all controls showed completely normal ECGs during exercise.

Upon exercise echocardiography, Em wave readings increased differently in the 2 groups, showing a significantly reduced exercise Em and Δ Em in SS patients compared to controls (Table 3).

ST echocardiography was used to assess longitudinal function in the 2 groups during exercise, revealing a significantly reduced GLS and GLSR at peak exercise in SS patients compared to controls (Table 3).

Moreover, 46 % of SS patients showed stress PASP > 40 mmHg, significantly higher compared to controls (Table 3).

On the basis of the univariate analysis of the stress echo data stress GLS, GLSR and Em have been selected and

Table 2 Transthoracic conventional echocardiographic and TDI parameters

Parameter	Systemic sclerosis	Controls	p
LVEF(%)	64 ± 4.2	66 ± 4.4	ns
EDV (ml)	80.62 ± 20.20	70.65 ± 4.26	ns
LVM (g/m^2)	83.66 ± 13.9	77.46 ± 12.2	ns
E/A ratio	0.89 ± 0.16	1.04 ± 0.21	<0.05
Sm (cm/sec)	6.4 ± 7.1	6.9 ± 6.2	ns
Em (m/sec)	7.1 ± 1.8	8.2 ± 1.6	ns
E/Em	10.9 ± 3.68	8.3 ± 2.01	<0.05
LAVI (mL/m^2)	28.4 ± 8.74	19.32 ± 4.6	<0.05
PASP (mmHg) <i>Basal</i>	25.4 ± 8.7	20.2 ± 3.4	<0.05

EDD, end diastolic diameter; EDV, end diastolic volume; LAA, left atrium area; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; E/A, early and late diastolic peak velocity ratio; S_m , TD systolic peak velocity; E_m , TD early diastolic peak velocity; E/E, early PWD and TD diastolic peak velocity ratio

Table 3 TDI and speckle tracking echocardiographic evaluations at rest and peak exercise

	Controls	Systemic sclerosis	<i>p</i>
Work (watt ± SD)	122.8 ± 22	98.5 ± 18	< 0.05
<i>Tissue Doppler imaging</i>			
Basal			
Em (cm/sec)	7.1 ± 1.8	8.2 ± 1.6	n.s.
Exercise			
Em (cm/sec)	9.2 ± 3.5	12.3 ± 2.1	<0.01
ΔEm	2.1 ± 2.6	4.1 ± 1.4	<0.05
<i>2D Speckle tracking echocardiography</i>			
Basal			
GLS (%)	-13.6 ± 2.65	-12.24 ± 2.85	n.s.
GLSR (sec ⁻¹)	0.68 ± 0.10	0.62 ± 0.17	n.s.
Peak exercise			
GLS (%)	-18.15 ± 2.15	-15.74 ± 3.57	<0.005
GLSR (sec ⁻¹)	1.13 ± 0.12	0.98 ± 0.22	<0.005
PASP			
B-PASP (mmHg)	20.2 ± 3.4	25.4 ± 8.7	<0.05
S-PASP (mmHg)	30.6 ± 4.3	44.7 ± 16.5	<0.001

Em, early diastolic peak TD velocity; ΔEm, difference from Em exercise peak to baseline; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; B-PASP, basal pulmonary systolic pressures; S-PASP, stress pulmonary systolic pressures

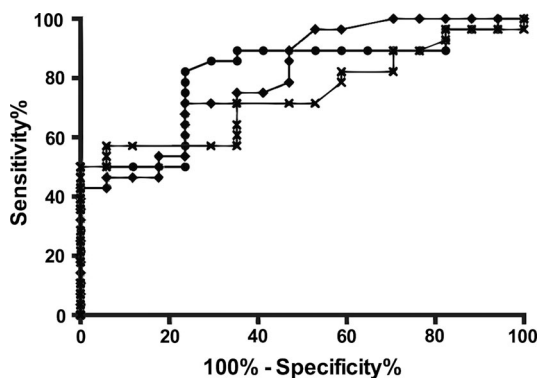


Fig. 1 ROC analysis of stress GLS (filled circle) [Area under the curve 0.81 (95 % CI 0.67–0.94)], stress GLSR (cross) [Area under the curve 0.74 (95 % CI 0.60–0.88)] and stress Em (filled diamond) [Area under the curve 0.79 (95 % CI 0.67–0.91)]

then compared using a ROC analysis. GLS resulted having the higher area under the curve 0.81 (95 % CI 0.67–0.94; Fig. 1).

A stress GLS value of 18 % was obtained as the best cut-off value to identify reduced myocardial contractile reserve [sensitivity 82 % (95 % CI 63–94) and specificity 76 % (95 % CI 50–93; Fig. 1)].

The patients were then divided into two groups: patients with stress GLS ≤ 18 % and patients with stress GLS > 18 % (Table 4).

Table 4 Global longitudinal function in systemic sclerosis patients

Stress GLS	<18 %	>18 %	<i>p</i>
E/E'	10.9 ± 3.68	8.3 ± 2.01	<0.05
LAVI (mL/m ²)	28.4 ± 8.74	19.32 ± 4.6	<0.05
6MWT	377 ± 8.7	434 ± 3.4	<0.05
S-PASP (mmHg)	43.4 ± 14.6	32.3 ± 4.5	<0.05
Δ PASP	25.4 ± 8.7	20.2 ± 3.4	<0.05

E/E', early PWD and TD diastolic peak velocity ratio; LAVI, left atrial volume indexed for body surface area; 6MWT, six minute walking test; S-PASP, stress pulmonary artery systolic pressures

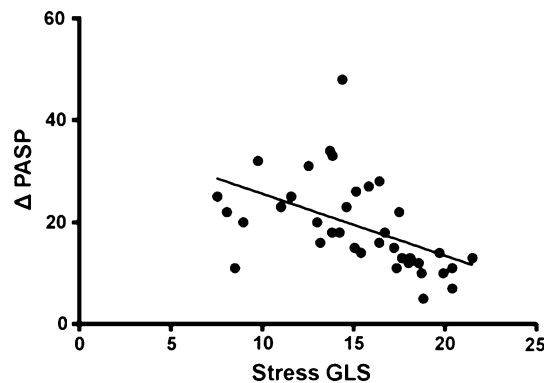


Fig. 2 Correlation of stress GLS versus Δ PASP [$r = -0.4990$ (95 % CI -0.71 to -0.21); $p = 0.0017$]

Patients with GLS ≤ 18 % at peak exercise, compared with patients with stress GLS > 18 %, showed worst diastolic function at rest, with higher E/Em, larger left atrial volumes, higher pulmonary pressures and a reduced physical capacity evaluated with the 6MWT (Table 4).

Furthermore significant correlations between stress GLS and delta PASP [Pearson $r = -0.4990$ (95 % CI -0.71 to -0.21); $p = 0.0017$] (Fig. 2) and 6MWT [Pearson $r = 0.6609$ (95 % CI 0.43–0.81); $p < 0.0001$] (Fig. 3) were evidenced.

The intra-observer variability for the stress GLS reported as the mean error of 10 measurements was 0.91 (CI 0.80–0.97). Furthermore the Coefficient of Variation was 0.23 both for basal GLS and for stress GLS.

Discussion

The present study examined the contractile function at rest and at peak exercise in SSc patients compared to healthy, matched controls. It was found that SSc patients: (1) have diastolic dysfunction, mild at basal rest, but appreciably increased by exercise; (2) show greater atrial dimensions and higher PASP at rest and at peak exercise; (3) show a normal global contractile function at baseline rest, but a

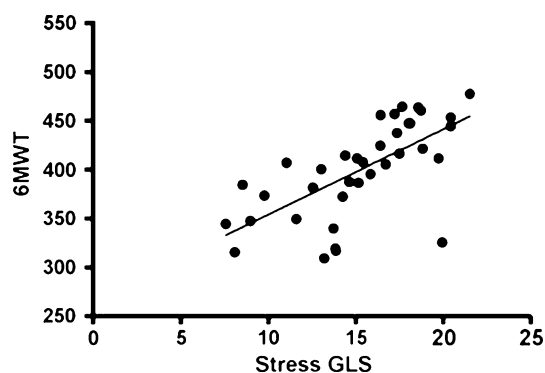


Fig. 3 Correlation of stress GLS versus 6MWT [$r = 0.6609$ (95 % CI 0.43–0.81); $p < 0.0001$]

significant reduction in GLS and GLSR at peak exercise; (4) show a stress GLS strict correlation with physical tolerance, as well as change in pulmonary pressure during exercise (Δ PASP); (5) we identified a stress GLS cut off (<18 %) which discriminates SSc patients with a poorer diastolic function, higher atrial dimensions, higher PASP at rest and during exercise and a poorer physical tolerance.

The left ventricular involvement in patients with SSc was previously directly attributed to myocardial fibrosis, especially for evidence of fibrotic lesions with scattered distribution in both ventricles, in the later stages of the disease [17, 18]. In fact, even if a myocardial fibrosis can lead to heart failure in the final stages of SSc, an early diastolic impairment was highlighted in these patients several years before it became clinically apparent.

The presence of diastolic dysfunction in patients with SSc, detected by the majority of previous studies [19–21], was commonly demonstrated by pulsed wave Doppler-derived transmitral inflow patterns. However, the use of TDI, less influenced by loading conditions, suggests that the Em determined by pulsed TDI is more reliable than conventional transmitral Doppler flow [22]. A previous study showed that impaired LV diastolic relaxation worsens with exercise and that the dysfunction is correlated with the severity of the skin lesions [23].

In the present study, we confirmed these findings, showing in SSc impaired diastolic function at rest, worsened by exercise. In contrast to diastolic dysfunction, systolic impairment is underestimated in most investigations of patients with SSc. Some studies showed wall motion abnormalities with a reduced functional reserve correlated with the disease duration in small populations of patients with SSc [24]. On the other hand, several studies showed that LV impairment is linked not only to the myocardial fibrosis, but also to an extensive involvement of the coronary microcirculation [5, 6]; recurrent vasospasm with poor vasodilator reserve, focal ischemia and repeated ischemia–reperfusion injury may lead to diastolic and systolic dysfunction and extensive fibrosis [6, 7].

Researchers, using the TDI technique and more recently 2D Strain, showed an early reduction in longitudinal function in patients with SSc, where the parameters of conventional echocardiography were not suitable to highlight the systolic function impairment [25–27]. This is because the involvement of the myocardial subendocardial layer, mainly responsible for the longitudinal function and more susceptible to phenomena of ischemia and fibrosis, occurs before that of the subepicardial layer.

Longitudinal function measured with GLS and functional capacity evaluated with the 6MWT also proved to be strictly related to diastolic function [9, 28]. In our study, GLS and GLSR measured at rest in SSc were slightly reduced in comparison with controls albeit not significantly. Although, exercise echocardiography was able to unmask a significant longitudinal impairment in SSc patients compared to controls.

Recent studies in SSc patients showed an excessive increase in PAP during physical exercise, associated not only with increase in pulmonary vascular resistance, but also with left ventricle diastolic dysfunction [11, 12]. In previous studies, stress echocardiography has been used mainly to verify whether an exercise echocardiogram could identify SSc patients who may develop PH [29, 30].

Our findings underline the usefulness of this method to unmask a subtle diastolic and systolic impairment, even before a significant dysfunction at baseline, and confirm its close relationship with pulmonary pressures, as well as with the patient's functional capacity.

Furthermore, in our study, we identified a stress GLS cutoff of 18 % that characterized the subgroup of patients with the worst diastolic function at rest, larger left atrial volumes, higher pulmonary pressures and a poorest functional capacity evaluated with the 6MWT.

The importance of having a new tool as the stress GLS to identify the patients with more extensive myocardial involvement, is related to the existing evidence of the association between LV longitudinal function and increased risk of death and cardiovascular events in SSc [27, 31]. More recently, it has been confirmed that the pulmonary pressures measured with the tricuspid regurgitation velocity, a non-specific marker that may be increased in PAH as well as in left ventricular dysfunction, is an independent predictor of mortality in SSc [32].

In this regard, the early identification of the patients with a more extensive cardiovascular involvement may be particularly valuable in order to provide a more adequate therapeutic management.

Limitations

As a limitation of our study, we enrolled a relatively small number of patients related to the low prevalence of SSc; the

size of our population, however, doesn't differ from that reported in many previous studies on this topic.

Moreover, there are some limitations of the LV evaluation under exercise. They are related to image quality during the stress test, which resulted in a feasibility of 82 % in our population. Moreover the inter-observer variability could be increased in this setting. Additionally, under exercise our analysis has been limited to the longitudinal function, having the circumferential and radial measurements an even lower feasibility limiting their utility.

Conclusion

Early impairment of LV function, even though associated to a worse clinical course of SSc, is, frequently, sub-clinical and hardly detectable by means of standard echocardiography.

Exercise echocardiography has proved to be an effective tool to unmask subtle LV impairment before their evidence at rest. Moreover, stress GLS appears to be a sensible and specific index, which can be helpful in the identification of SSc patients with a more extensive LV involvement, strictly related to patient's functional capacity. In addition to standard echocardiography, exercise echocardiography with the evaluation of the stress GLS might have a role augmenting the efficacy of screening algorithms identifying a group at increased risk. A prospective longitudinal study is needed to identify the prognostic value of this parameter.

Conflict of interest All authors have no conflict of interest to disclose.

Ethical standard The study was approved by the Ethics Committee of the University Hospital, University of Cagliari. Written informed consent was obtained from all patients involved. The study was carried out in accordance with the Declaration of Helsinki.

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