

# Progression of Left Ventricular Myocardial Dysfunction in Systemic Sclerosis: A Speckle-tracking Strain Echocardiography Study

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**ABSTRACT. Objective.** Cardiac involvement is a main cause of mortality in systemic sclerosis (SSc). Its detection remains challenging using conventional echocardiography and little is known about its potential progression. This study assessed changes in cardiac performance over time in a prospective cohort of patients with SSc, including echocardiographic speckle-tracking strain analysis.

**Methods.** The study included 234 patients with SSc [196 women, age  $52 \pm 14$  yrs, 165 limited SSc, time since diagnosis 5.2 yrs, interquartile range (IQR) 2.9–11.3]. Clinical variables, laboratory tests, pulmonary function tests, and echocardiographic measures were recorded at baseline and followup (median 2.3 yrs, IQR 1.3–3.9). Additionally, left ventricular (LV) systolic function was assessed with global longitudinal strain (GLS) by echocardiographic speckle-tracking analysis.

**Results.** At followup, GLS had significantly worsened ( $-21\% \pm 2$  vs  $-19\% \pm 2$ ,  $p < 0.001$ ) while LV ejection fraction had not changed ( $62\% \pm 7$  vs  $61\% \pm 8$ ,  $p = 0.124$ ). In particular, 39 patients showed a significant deterioration of GLS as defined by a  $\geq 15\%$  decrease, which was accompanied by a concomitant worsening of proximal muscle weakness, lung fibrosis, renal function, LV diastolic function, and right ventricular systolic function. Baseline variables associated with  $\geq 15\%$  deterioration in GLS were proximal muscle weakness (OR 3.437, 95% CI 1.13–10.43,  $p = 0.020$ ), decreased DLCO (OR 3.621, 95% CI 1.25–10.51,  $p = 0.049$ ), and LV diastolic dysfunction (OR 2.378, 95% CI 1.07–5.27,  $p = 0.033$ ).

**Conclusion.** In patients with SSc, progression of LV systolic dysfunction was demonstrated by GLS but not by LV ejection fraction. Proximal muscle weakness, DLCO, and LV diastolic dysfunction may identify patients at risk for progressive LV systolic dysfunction and in need of closer cardiac monitoring. (First Release March 1 2019; J Rheumatol 2019;46:405–15; doi:10.3899/jrheum.171207)

## Key Indexing Terms:

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Systemic sclerosis (SSc) is a connective tissue disease characterized by generalized microangiopathy and fibrosis affecting multiple organs, and is associated with increased mortality<sup>1</sup>. Primary cardiac involvement is common in SSc and can occur in up to 70% of patients as seen in autopsy reports<sup>2</sup>. Particularly, myocardial fibrosis may lead to diastolic and systolic dysfunction and to conduction abnormalities<sup>3,4,5</sup>. When clinically evident, cardiac involvement represents one of the main causes of death in patients with SSc<sup>6,7</sup>. Therefore, identification of myocardial involvement, ideally at a preclinical stage, is of crucial clinical importance for optimal patient management. To date, detection of myocardial dysfunction in patients with SSc has been challenging and no serial echocardiography studies have been performed to evaluate changes in cardiac performance over time. Conventional echocardiographic techniques lack sensitivity for early detection of left ventricular (LV) systolic

dysfunction<sup>8,9</sup>. Yiu, *et al* demonstrated that novel echocardiographic speckle-tracking strain analysis may be a reliable tool to identify subtle myocardial dysfunction<sup>9</sup>. Particularly, a decrease in global longitudinal strain (GLS), as a marker of LV systolic dysfunction, was shown to be associated with lower functional capacity and the occurrence of arrhythmias. However, little is known about how LV systolic and diastolic dysfunction might progress over time and therefore how often, and in which patients, echocardiographic monitoring should be performed<sup>10</sup>.

The objective of our study was to assess changes over time in conventional and advanced echocardiographic parameters using sequential evaluations in a large, prospective cohort of patients with SSc. Additionally, we aimed to identify potential baseline clinical and echocardiographic characteristics associated with progressive LV systolic dysfunction, to help clinicians select patients at risk of myocardial involvement who deserve close followup.

## MATERIALS AND METHODS

**Patient population.** Starting in 2009, consecutive patients with SSc visiting the Department of Rheumatology of the Leiden University Medical Center (Leiden, The Netherlands) were evaluated in a specifically designed healthcare program combining annual organ screening with multidisciplinary team care (The Leiden Systemic Sclerosis Cohort)<sup>11,12</sup>. For our study, patients with at least 2 echocardiographic evaluations were included. Exclusion criteria for the current evaluation were previous myocardial infarction, presence of cardiomyopathy of other causes, and moderate to severe valve stenosis or regurgitation. A baseline echocardiography was selected corresponding to the date of the first visit to the care program. The followup echocardiography was defined as the last one available with a minimum of 1 year after the baseline examination. Patients were diagnosed according to the classification system described by LeRoy and Medsger<sup>13</sup>. Patient written consent and approval by the medical ethics committee was obtained (REU 043).

**Clinical variables.** Disease-related characteristics were reported at baseline and followup visits, including modified Rodnan skin score (mRSS), SSc subtype (diffuse or limited), proximal muscle strength, and arthritis. Laboratory testing included renal function, N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and creatine phosphokinase (CPK). These measures were categorized as elevated or not according to local reference values. To assess functional capacity, 6-min walking distance tests were performed. Pulmonary involvement was assessed by performing spirometry tests according to the recommendations and included percentage of predicted values for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and DLCO. These were categorized as impaired or not according to reference values<sup>14,15</sup>. Presence of lung fibrosis was determined from abnormal findings on thoracic high-resolution computed tomography<sup>16,17</sup>. Patients underwent cardiopulmonary exercise tests on an electrically ramped cycle ergometer according to these guidelines<sup>18</sup>: the peak oxygen consumption (VO<sub>2</sub>max%) was measured and values < 80% of predicted were categorized as decreased. An mRSS increase of ≥ 5 or FVC and DLCO decrease of ≥ 10% were considered increased disease activity<sup>19</sup>. Each patient had a 24-h Holter electrocardiogram (ECG) at baseline. Presence of conduction defects and ventricular and supraventricular arrhythmias was recorded<sup>20,21</sup>.

All-cause mortality data were obtained by retrieval of survival status through the municipal civil registries. Time till death was calculated from date of followup echo until date of death.

**Conventional echocardiography.** All patients underwent echocardiography in the left lateral decubitus position, using a commercially available system (Vivid 7 and E9; General Electric) and 3.5-MHz or 5 MS transducers. Standard M-mode and 2-dimensional, color, pulsed, and continuous wave Doppler images were acquired. Offline analysis was performed using EchoPAC (version 112.0.1; GE Medical Systems).

LV end-diastolic diameter (LVEDd) and volume (LVEDV), end-systolic volume (LVESV) and ejection fraction (EF), and left atrial diameter (LAD) were measured according to current guidelines<sup>22</sup>. LV diastolic function was assessed using a multiparametric approach including (1) peak early (E) and late (A) diastolic velocities and E-wave deceleration time measured on pulsed-wave Doppler recordings of the transmitral flow, (2) E/A ratio, and (3) E-prime measured with tissue Doppler imaging at the lateral side of the mitral annulus in the apical 4-chamber view<sup>23</sup>. According to current guidelines, impaired LV relaxation was defined based on an E-prime value ≤ 10 cm/sec<sup>23</sup>.

Pulmonary arterial systolic pressure (sPAP) was estimated by determining right ventricular systolic pressure, calculated from the tricuspid regurgitation peak gradient, and adding the right atrial pressure estimated by the inferior vena cava diameter and degree of respiratory collapse. Elevated sPAP was defined as > 35 mmHg<sup>24</sup>. Right ventricular systolic function was assessed by the tricuspid annular plane systolic excursion (TAPSE) on M-mode recordings of the tricuspid annulus<sup>25</sup>. Presence of pericardial effusion was also recorded.

**Two-dimensional speckle-tracking echocardiographic (STE) strain analysis.** Two-dimensional STE analysis is an echocardiographic technique that quantifies myocardial deformation (strain) by tracking myocardial acoustic markers (speckles) in every frame within 1 cardiac cycle<sup>22</sup>. LV strain was measured in the longitudinal direction using 3 standard apical views (Figure 1). Each wall is divided into basal, middle, and apical segments and 18 segmental curves were obtained. GLS is automatically calculated as the average value of the peak systolic strain<sup>22</sup> (Figure 1). Reflecting the shortening of LV myocardium, GLS is expressed as negative values and a more negative value represents better myocardial deformation.

**Statistical analyses.** Data analyses were performed using SPSS software 23.0 (IBM). Continuous variables are presented as mean ± SD or median with interquartile ranges (IQR) according to normal distribution. Categorical data are presented as frequencies and percentages. Continuous variables were compared using 1-way ANOVA, applying the Bonferroni posthoc analysis, or the Kruskal-Wallis 1-way ANOVA. Categorical variables were compared with chi-square tests. Changes over time were compared with linear mixed model analysis with unstructured covariance matrix, Wilcoxon signed-rank test for continuous variables, and generalized linear models with binary logistic response for comparing changes in categorical variables between 2 groups. To compare baseline characteristics between groups, ≥ 15% GLS reduction and followup time were incorporated into the models. A GLS reduction of ≥ 15% was chosen arbitrarily because it most likely reflects clinical decline as opposed to minor deviations<sup>26</sup>. Logistic regression analyses were performed to identify baseline variables associated with ≥ 15% GLS reduction at followup. Extracardiac variables significant in the univariate analyses were included in a multivariate baseline model. Limited by the number of events (≥ 15% GLS reduction), the clinically most relevant parameters were chosen. Cardiac variables significant in the univariate analyses were added separately to the multivariate baseline model. A univariate Cox regression analysis and a log-rank test were performed to assess the association of ≥ 15% reduction of GLS and all-cause mortality. A p value < 0.05 was considered statistically significant.

## RESULTS

**Patient characteristics.** Table 1 summarizes the baseline characteristics of the 234 patients with SSc, 165 (70%) of them having limited cutaneous SSc and 69 (30%) having diffuse cutaneous SSc. Ninety-two percent fulfilled American

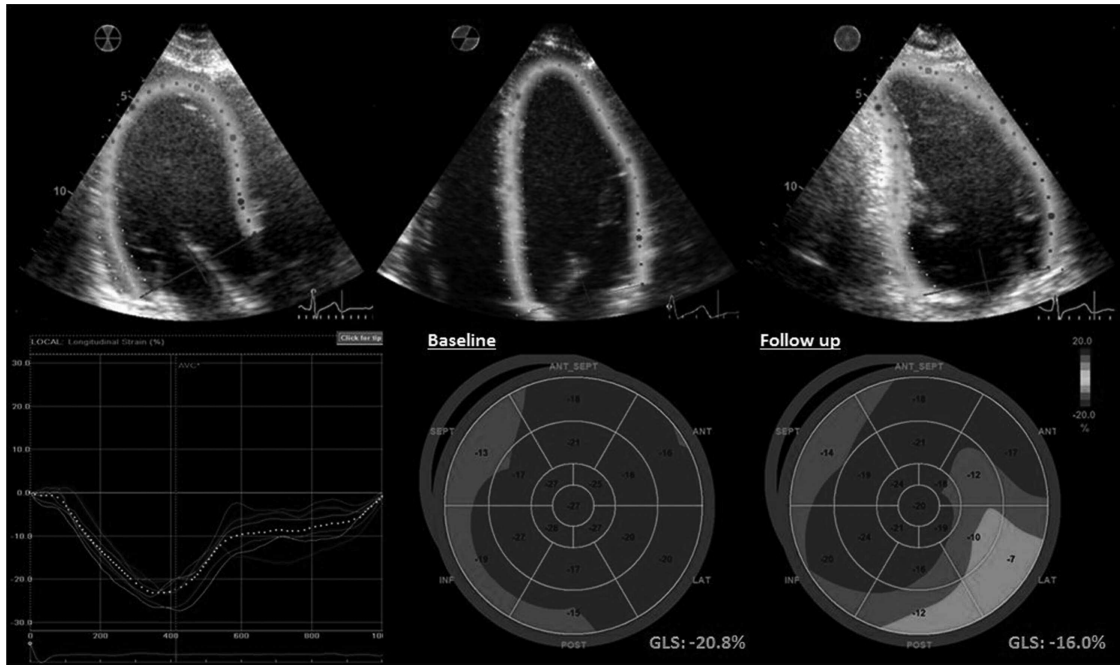


Figure 1. GLS of the left ventricle measured by 2-dimensional speckle-tracking strain analysis applied to 3-chamber (top left), 4-chamber (top middle), and 2-chamber apical views (top right). Bottom left: curves of longitudinal strain per segment and averaged among the segments (dotted line). Bottom middle: bull's-eye display of segmental peak systolic longitudinal strain values at baseline of a patient with SSc; darkest grey representing preserved strain and lighter grey impaired strain. Bottom right: bull's-eye display at followup of the same patient; lightest color indicates even worse contractility (more impaired). GLS is calculated averaging the 17 segments. GLS: global longitudinal strain; SSc: systemic sclerosis.

College of Rheumatology (ACR) 2013 criteria<sup>27</sup>. Patients had a mean age of  $52 \pm 14$  years, and 196 patients (84%) were women. The median time since diagnosis was 5.2 years (IQR 2.9–11.3). Median time since onset of Raynaud symptoms was 9.8 years (IQR 4.5–19.0) and median time since first non-Raynaud manifestation was 4.8 years (IQR 1.9–10.6). The median period between baseline and followup echocardiography was 2.3 years (IQR 1.3–3.9).

**Clinical variables at baseline versus followup evaluation.** No significant changes in median mRSS scores were observed at followup; however, the number of patients with mRSS  $> 15$  was reduced at followup (Table 1), and mRSS increased by  $\geq 5$  in 30 patients (13%). No changes were observed in the presence of arthritis, muscle weakness, 6-min walking distance, laboratory markers (Appendix 1), decreased FEV1, FVC, or DLCO. FVC and DLCO decreased by  $\geq 10\%$  in 45 (19%) and 46 (20%) patients, respectively. Prevalence of lung fibrosis, renal function impairment (defined as estimated glomerular filtration rate  $< 60$  ml/min/1.73 m<sup>2</sup>), and impaired VO<sub>2</sub>max% increased significantly over time.

**Echocardiographic variables.** Although LVEDV slightly decreased at followup, no other changes were detected in LVESV and subsequently in LVEF (Table 1). In addition, LAD increased slightly over time. A relative worsening of LV diastolic function was observed as reflected by a reduction of the E/A ratio and a significant increase in percentage of patients with lateral E-prime  $\leq 10$  cm/sec

(defining LV diastolic dysfunction). Interestingly, 13% of the population had lateral E-prime  $\leq 10$  cm/sec *de novo* at followup. Further, sPAP slightly increased over time, which is also reflected in a significant increase of the proportion of patients having elevated sPAP (from 9% to 12%,  $p < 0.001$ ) defined as sPAP  $> 35$  mmHg. New development of elevated sPAP was observed in 6% of the patients. Further, there was a decline in right ventricular function over time as reflected by a decrease in TAPSE. Occurrence of pericardial effusion increased and new onset at followup was observed in 5% of patients.

**Decrease in LV systolic function as assessed by GLS and its clinical and echocardiographic associates.** Compared to baseline, GLS significantly decreased at followup (Table 1). Particularly, 39 patients (19%) showed a significant decrease in LV systolic function as defined by GLS reduction of  $\geq 15\%$  ( $-20.9\% \pm 2.0$  to  $-16.3\% \pm 2.4$ ,  $p < 0.001$ ), while 165 patients (81%) showed less or no decline in GLS ( $-21.0\% \pm 1.9$  to  $-20.0\% \pm 1.9$ ,  $p < 0.001$ ). The followup period was slightly longer in patients with GLS reduction [median 3.08 yrs (IQR 1.92–4.17) vs 2.25 yrs (IQR 1.17–3.83,  $p = 0.048$ ).

A comparison of baseline extracardiac variables between patients with or without significant GLS reduction is shown in Table 2. There were no differences in age, sex, or time since Raynaud or non-Raynaud manifestations between the 2 groups. No significant difference in SSc type was found, although the percentage of diffuse cutaneous SSc was slightly

Table 1. Clinical characteristics and echocardiographic variables at baseline and followup in the total patient population.

N = 234	Baseline	Followup	p
Age, mean ± SD	52 ± 14	—	—
Female, n (%)	196 (84)	—	—
Cardiovascular medication, n (%)			
ACEi/ARB	135 (38)	—	—
Beta-blocker	29 (8)	—	—
Ca <sup>2+</sup> channel-blocker	155 (44)	—	—
Diuretics	49 (14)	—	—
Immunosuppressive medication, n (%)			
Corticosteroids	30 (9)	—	—
Cyclophosphamide	4 (1)	—	—
Methotrexate	32 (9)	—	—
Azathioprine	12 (3)	—	—
mRSS, median (IQR)	3 (0–6)	4 (0–6)	0.728
mRSS > 15, n (%)	20 (9)	16 (7)	<0.001
Arthritis, n (%)	23 (10)	15 (6)	0.441
Proximal muscle weakness, n (%)	31 (13)	34 (15)	0.210
Lung fibrosis, n (%)	83 (36)	95 (41)	<0.001
6-min walking distance, m, mean ± SD	513 ± 128	521 ± 118	0.775
eGFR < 60 ml/min/m <sup>2</sup> , n (%)	5 (2)	12 (5)	<0.001
Elevated NT-proBNP, n (%)	34 (15)	32 (14)	0.961
Elevated CRP, n (%)	22 (9)	28 (12)	0.289
Elevated ESR, n (%)	83 (36)	87 (37)	0.520
Elevated CPK, n (%)	152 (65)	137 (59)	0.480
ANA-positive, n (%)	210 (90)	—	—
Decreased FEV1%, n (%)	23 (10)	19 (8)	0.651
Decreased FVC%, n (%)	40 (17)	43 (18)	0.454
Decreased DLCO%, n (%)	159 (68)	158 (68)	0.360
Decreased VO <sub>2</sub> max%, n (%)	53 (23)	40 (29)*	0.045
Holter ECG abnormalities, n (%)	81 (35)**	—	—
Echocardiographic variables			
LVEDd, mm, mean ± SD	47 ± 5	47 ± 5	0.171
LVEDV, ml, mean ± SD	81 ± 25	78 ± 22	0.011
LVESV, ml, mean ± SD	31 ± 12	31 ± 12	0.506
LVEF %, mean ± SD	62 ± 7	61 ± 8	0.124
Left atrial diameter, mm, mean ± SD	34.6 ± 5.0	35.4 ± 4.7	0.010
E mm/s, mean ± SD	78 ± 18	75 ± 20	0.063
E/A ratio, mean ± SD	1.13 ± 0.36	1.08 ± 0.39	0.009
Lateral E' cm/sec, mean ± SD	11.19 ± 2.77	11.03 ± 3.01	0.209
Lateral E' ≤ 10 cm/sec, n (%)	75 (32)	108 (46)	0.002
Lateral E' ≤ 10 cm/sec <i>de novo</i> , n (%)	—	31 (13)	—
sPAP mmHg, mean ± SD	26 ± 8	28 ± 11	0.019
Elevated sPAP, n (%)	18 (9)	27 (12)	<0.001
Elevated sPAP <i>de novo</i> , n (%)	—	13 (6)	—
TAPSE, mm, mean ± SD	23 ± 4	22 ± 4	0.007
Pericardial effusion, n (%)	9 (4)	17 (7)	<0.001
Pericardial effusion <i>de novo</i> , n (%)	—	12 (5)	—
GLS %, mean ± SD***	-20.91 ± 2.01	-19.30 ± 2.46	<0.001

\* 98 patients with missing data. \*\* 8 patients with missing data. \*\*\* Speckle-tracking strain feasible in both baseline and followup echocardiogram in 204 patients. ACEi: angiotensin-converting enzyme inhibitor; ANA: antinuclear antibodies; ARB: angiotensin II receptor blocker; CPK: creatine phosphokinase, cutoff value 145 U/l; CRP: C-reactive protein, cutoff value 10 mg/l; E/A: peak early (E) and late (A) diastolic velocities; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate, cutoff value 20 mm; FEV1: forced expiratory volume in 1 s, percent of predicted value, cutoff value 70%; FVC: forced vital capacity, percent of predicted value, cutoff value 80%; GLS: global longitudinal strain; LV: left ventricular; LVEDd: LV end-diastolic diameter; LVEDV: LV end-diastolic volume; LVESV: LV end-systolic volume; LVEF: LV ejection fraction; mRSS: modified Rodnan skin score; NT-proBNP: N-terminal pro-brain natriuretic peptide, cutoff value 300 ng/l; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; VO<sub>2</sub>max: maximum O<sub>2</sub> uptake during exercise, percent of predicted value, cutoff value 80%; IQR: interquartile range.

higher among patients with GLS reduction of ≥ 15% (36% vs 27% in their counterparts, p = 0.25). The percentage of patients positive for antinuclear antibodies was similar in

both groups (87% vs 92%, p = 0.987). Presence of myositis was similar [3 (2%) vs 2 (5%), p = 0.206]. Clinical variables including mRSS and arthritis were not significantly different

Table 2. Comparison of baseline clinical variables between patients with  $\geq 15\%$  decrease of GLS versus  $< 15\%$  decrease at followup.

N = 204	< 15% Decrease GLS, n = 165	$\geq 15\%$ Decrease GLS, n = 39	p
Age, mean $\pm$ SD	52 $\pm$ 13	55 $\pm$ 14	0.236
Female, n (%)	139 (84)	31 (80)	0.474
Time since Raynaud symptoms, yrs, median (IQR)	9 (4–19)	12 (5–19)	0.538
Time since non-Raynaud symptoms, yrs, median (IQR)	4 (2–10)	5 (1–10)	0.999
Cardiovascular medication, n (%)			
ACEi/ARB	56 (34)	18 (46)	0.083
Beta-blocker	10 (6)	3 (8)	0.636
Ca <sup>2+</sup> channel-blocker	74 (45)	17 (44)	0.867
Diuretics	16 (10)	4 (10)	0.824
Immunosuppressive medication, n (%)			
Corticosteroids	17 (10)	9 (23)	0.020
Cyclophosphamide	2 (1)	2 (5)	0.096
Methotrexate	21 (13)	8 (21)	0.155
Azathioprine	10 (6)	3 (8)	0.126
mRSS, median (IQR)	2 (0.0–5.0)	4 (1.5–9.5)	0.177
mRSS > 15, n (%)	12 (7)	5 (13)	0.265
Arthritis, n (%)	14 (9)	7 (18)	0.080
Proximal muscle weakness, n (%)	13 (8)	10 (26)	0.001
Lung fibrosis, n (%)	58 (35)	17 (44)	0.326
6-min walking distance, m, mean $\pm$ SD	517 $\pm$ 127	515 $\pm$ 132	0.966
eGFR < 60 ml/min/m <sup>2</sup> , n (%)	2 (1)	2 (5)	0.113
Elevated NT-proBNP, n (%)	18 (11)	12 (31)	0.001
Elevated CRP, n (%)	16 (10)	4 (10)	0.916
Elevated ESR, n (%)	59 (36)	16 (41)	0.612
Elevated CPK, n (%)	104 (63)	29 (74)	0.182
ANA-positive, n (%)	151 (92)	34 (87)	0.987
Decreased FEV1%, n (%)	14 (9)	5 (13)	0.409
Decreased FVC%, n (%)	20 (12)	10 (26)	0.035
Decreased DLCO%, n (%)	106 (64)	34 (87)	0.009
Decreased VO <sub>2</sub> max%, n (%)	57 (35)	16 (41)	0.017
Holter ECG abnormalities, n (%)	55 (33)	17 (44)	0.179

ACEi: angiotensin-converting enzyme inhibitor; ANA: antinuclear antibodies; ARB: angiotensin II receptor blocker; CPK: creatine phosphokinase, cutoff value 145 U/l; CRP: C-reactive protein, cutoff value 10 mg/l; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate, cutoff value 20 mm; FEV1: forced expiratory volume in 1 s, percent of predicted value, cutoff value 70%; FVC: forced vital capacity, percent of predicted value, cutoff value 80%; GLS: global longitudinal strain; mRSS: modified Rodnan skin score; NT-proBNP: N-terminal pro-brain natriuretic peptide, cutoff value 300 ng/l; VO<sub>2</sub>max: maximum O<sub>2</sub> uptake during exercise, percent of predicted value, cutoff value 80%; IQR: interquartile range.

between the groups, although they were numerically worse among patients with GLS reduction. Patients with GLS reduction had a significantly higher frequency of muscle weakness compared to patients without GLS reduction. Additionally, elevated NT-proBNP, decreased FVC, DLCO, and VO<sub>2</sub>max% were significantly more prevalent in patients with significant GLS reduction. No differences were observed in the prevalence of elevated CRP, ESR, CPK, and Holter-ECG abnormalities at baseline, although the latter occurred numerically more often in patients with GLS reduction.

Over time, in patients with GLS reduction, various concomitant increases were observed: of proximal muscle weakness, lung fibrosis, and impairment of renal function, in comparison to their counterparts (Figure 2A). Additionally, mRSS increase  $\geq 5$  and FVC decrease  $\geq 10\%$  occurred significantly more often (Figure 2B) in patients with GLS reduction and DLCO decrease  $\geq 10\%$  showed a trend toward a higher prevalence in this group (28% vs 19%,  $p = 0.191$ ).

*Echocardiographic variables.* As for LA and LV dimensions, volumes, and systolic function, no differences were seen at baseline between the 2 groups (Table 3). However, patients with GLS reduction had a significantly lower E/A ratio and lateral E-prime and a higher prevalence of lateral E-prime  $\leq 10$  cm/sec, suggesting worse LV diastolic function compared to those with less reduction of GLS. At baseline, the GLS reduction group also had a significantly higher sPAP and a worse right ventricular function reflected by a lower TAPSE.

Over time, no significant changes were seen in LVEF in patients with and without GLS reduction ( $p = 0.066$  and  $p = 0.246$ ), although the  $p$  value was almost significant in patients with GLS reduction. Patients with GLS reduction showed a significant deterioration in E-prime (10.2  $\pm$  2.5 cm/sec to 9.1  $\pm$  2.6 cm/sec,  $p = 0.014$ ) and TAPSE (22  $\pm$  4 to 20  $\pm$  4 mm,  $p = 0.003$ ) in contrast to their counterparts ( $p = 0.564$  and  $p = 0.150$ , respectively). Moreover, patients classified as having LV diastolic dysfunction increased significantly in

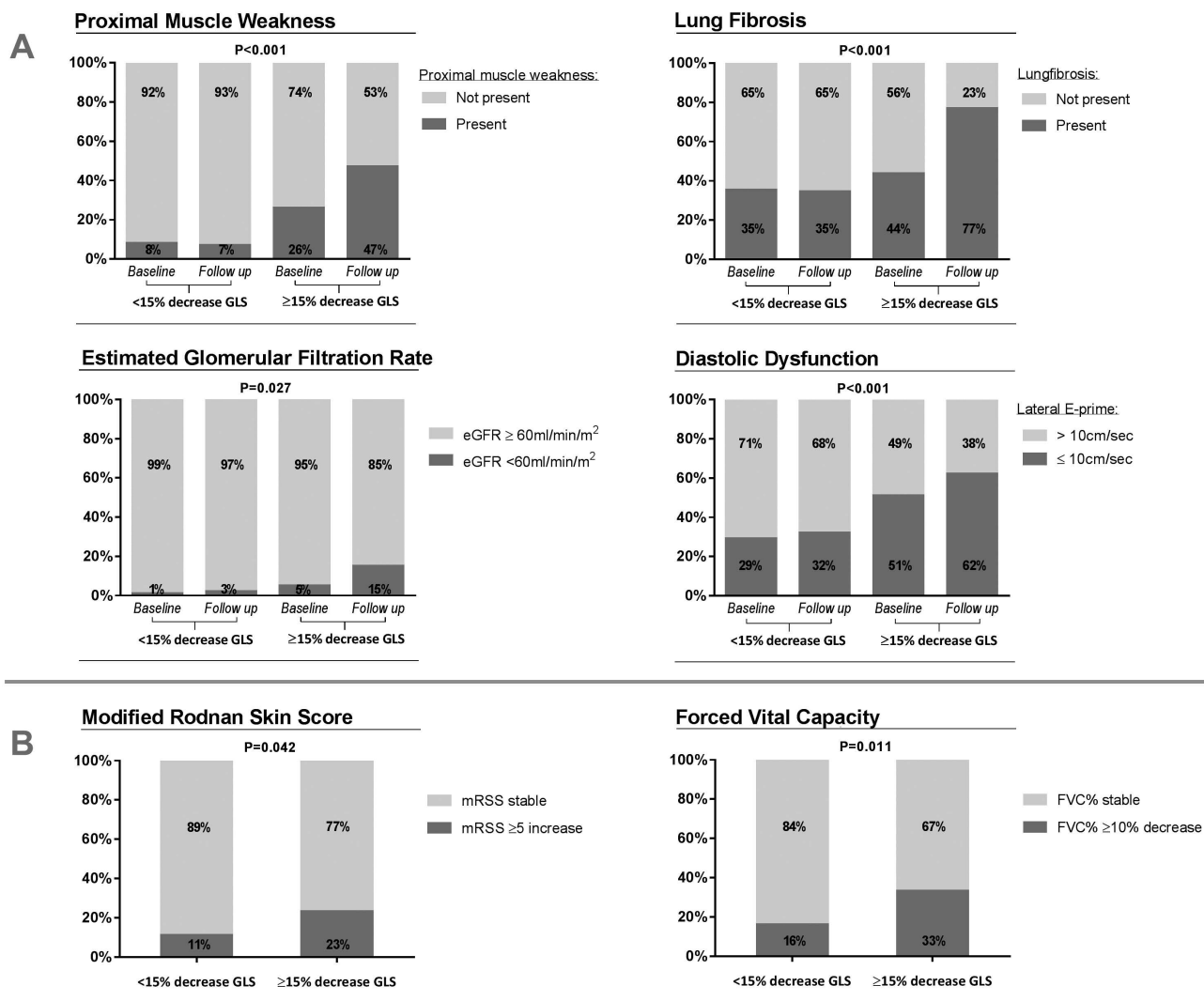


Figure 2. A. Baseline and followup prevalence of clinical variables and lateral E-prime  $\leq 10$  cm/sec (a marker for left ventricular diastolic dysfunction) compared between patients with  $\geq 15\%$  decrease of GLS versus  $< 15\%$  decrease. B. Prevalence of clinical variables at followup considered as signs of increased disease activity compared between the latter 2 groups. GLS: global longitudinal strain; eGFR: estimated glomerular filtration rate; mRSS: modified Rodnan skin score; FVC: forced vital capacity.

patients with GLS reduction (Figure 2A). Over time, sPAP did not change significantly in both groups. However, more patients developed elevated sPAP at followup among those with GLS reduction (6% vs 2%,  $p < 0.001$ ). Patients with GLS reduction were at increased risk for developing elevated sPAP at followup (OR 2.575, 95% CI 0.999–6.635,  $p = 0.050$ ).

The prevalence of pericardial effusion increased similarly in both groups (3% to 8%,  $p = 0.077$ , and 4% to 7%,  $p < 0.001$ , respectively).

*Univariate and multivariate analyses to identify associates of GLS reduction at followup.* According to logistic regression analyses (Table 4), baseline extracardiac variables significantly associated with GLS reduction were use of corticosteroids, proximal muscle weakness, elevated NT-proBNP,

decreased FVC, DLCO, and  $VO_{2max}\%$ . Cardiac variables significantly associated with GLS reduction were E/A ratio, lateral E-prime, lateral E-prime  $\leq 10$  cm/s, sPAP, elevated sPAP, and TAPSE. Indicated by the number of patients with GLS reduction (39 patients), first a baseline model was created for multivariate analysis that included 4 extracardiac variables that were significant in the univariate analysis (corticosteroid use, proximal muscle weakness, decreased DLCO, and elevated NT-proBNP). In the baseline model, proximal muscle weakness and decreased DLCO remained independently associated with GLS reduction. Together with elevated NT-proBNP, these variables were used as a baseline model for further multivariate analyses. When lateral E-prime  $\leq 10$  cm/sec was added to the model, proximal muscle weakness, decreased DLCO, and lateral E-prime  $\leq 10$  cm/sec

Table 3. Comparison of baseline echocardiographic measures between patients with  $\geq 15\%$  decrease of GLS versus  $< 15\%$  decrease at followup.

N = 204	< 15% Decrease GLS, n = 165	$\geq 15\%$ Decrease GLS, n = 39	p
LVEDd mm, mean $\pm$ SD	47 $\pm$ 5	47 $\pm$ 7	0.719
LVEDV ml, mean $\pm$ SD	81 $\pm$ 24	80 $\pm$ 24	0.795
LVESV ml, mean $\pm$ SD	31 $\pm$ 12	32 $\pm$ 13	0.667
LVEF %, mean $\pm$ SD	62 $\pm$ 7	60 $\pm$ 8	0.106
Left atrial diameter mm, mean $\pm$ SD	36 $\pm$ 6	35 $\pm$ 5	0.093
E mm/s, mean $\pm$ SD	77 $\pm$ 17	77 $\pm$ 21	0.114
E/A ratio, mean $\pm$ SD	1.16 $\pm$ 0.36	1.03 $\pm$ 0.32	0.008
Lateral E' cm/sec, mean $\pm$ SD	11.49 $\pm$ 2.68	10.15 $\pm$ 2.49	0.005
Lateral E' $\leq 10$ cm/s, n (%)	45 (27)	20 (51)	0.005
sPAP mmHg, mean $\pm$ SD	25 $\pm$ 8	30 $\pm$ 8	0.004
Elevated sPAP, n (%)	10 (6)	6 (15)	0.036
TAPSE mm, mean $\pm$ SD	23 $\pm$ 4	22 $\pm$ 4	0.031
Pericardial effusion, n (%)	7 (4)	1 (3)	0.627

GLS: global longitudinal strain; LV: left ventricular; LVEDd: LV end-diastolic diameter; LVEDV: LV end-diastolic volume; LVESV: LV end-systolic volume; LVEF: LV ejection fraction; E/A: peak early (E) and late (A) diastolic velocities; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion.

remained independently associated with GLS reduction. When elevated sPAP was added to the baseline model, proximal muscle weakness and decreased DLCO remained significant. When TAPSE was added to the baseline model, proximal muscle weakness and decreased DLCO remained independently associated with GLS reduction.

All-cause mortality occurred in 25 patients. Significantly more patients with GLS reduction died [9 (23.1%) vs 11 (7%),  $p = 0.002$ , respectively]. GLS reduction was associated with increased risk of all-cause mortality (HR 2.771, 95% CI 1.002–7.666,  $p = 0.050$ ; log-rank 4.330,  $p = 0.037$ ).

## DISCUSSION

Our study is the first, to our knowledge, to assess serial echocardiography in a relatively large group of patients with SSc reflecting the whole spectrum of disease severity. Our study showed that advanced STE can detect a decline in LV systolic function over a relatively short period of time. A reduction of  $\geq 15\%$  in GLS was found in 19% of the patients at followup. Patients with  $\geq 15\%$  GLS reduction were more likely to have proximal muscle weakness, lung fibrosis, renal impairment, and elevated NT-proBNP at followup. Additionally,  $\geq 15\%$  GLS reduction was associated with all-cause mortality.

Identified as independent associates of  $\geq 15\%$  GLS reduction at followup were proximal muscle weakness, decreased DLCO, and lateral E-prime  $\leq 10$  cm/sec (as a marker of LV diastolic dysfunction) at baseline. Studies in large SSc patient populations demonstrated that cardiac involvement is the most or the second-most prevalent cause of mortality<sup>6,7</sup>. However, identification of cardiac involvement remains challenging and recommendations are usually based on clinical symptoms or conventional echocardiography. Cardiac involvement is frequently described as presence of arrhythmias and/or LV dysfunction, and/or

pericardial effusion<sup>9,28,29,30</sup>. Particularly, LV diastolic dysfunction is often observed in patients with SSc, even at young ages<sup>28,29,30</sup>. In turn, impaired LV systolic function, as measured by LVEF, is not frequently observed in patients with SSc, mainly owing to the low sensitivity for detecting subtle myocardial systolic dysfunction<sup>8</sup>. One study demonstrated that advanced echocardiographic strain analysis is more sensitive for detecting LV systolic dysfunction<sup>9</sup>, which is more prevalent than initially described and is associated with reduced functional capacity and DLCO. However, little is known about when LV systolic dysfunction may occur or whether it may progress, because we lack sequential echocardiographic studies.

Our current study offers a unique description of the typical course of the disease, because it is the first, to our knowledge, to assess changes in SSc-related clinical and echocardiographic characteristics over time. Although conventional echocardiography could assess a relative progression in LV diastolic dysfunction and a mild impairment in right ventricular systolic function, LVEF did not change over time. When using GLS as a more sensitive marker of LV systolic function, progressive impairment in LV systolic function could be detected, which was substantial in almost 20% of the cases. Interestingly, next to increases of proximal muscle weakness, lung fibrosis, renal dysfunction, and elevated NT-proBNP, clinical deterioration of mRSS and FVC were more frequent in patients with GLS reduction. These findings suggest that STE echocardiography can detect subtle changes in LV systolic myocardial function and may reflect disease activity and cardiac involvement, and is significantly associated with all-cause mortality. It may therefore be a useful tool in a preclinical stage and thus contribute to risk stratification in SSc.

*Potential associates to LV systolic dysfunction.* Manifestation of proximal muscle weakness, potentially reflecting

Table 4. Univariate and multivariate logistic regression analyses to identify baseline associates of  $\geq 15\%$  decrease of GLS at followup.

	Univariate Analysis			Baseline model			Multivariate Analysis		
	OR (95% CI)	p		OR (95% CI)	p		OR (95% CI)	p	
N = 204									
Age, yrs, mean $\pm$ SD	1.016 (0.99–1.04)	0.236							
Female, n (%)	0.725 (0.300–1.75)	0.475							
Time since Raynaud symptoms, yrs	1.006 (0.977–1.036)	0.674							
Time since non-Raynaud's symptoms, yrs	0.999 (0.943–1.058)	0.969							
Cardiovascular medication									
ACEi/ARB	1.893 (0.913–3.925)	0.086							
Beta-blocker	1.382 (0.360–5.298)	0.637							
Ca <sup>2+</sup> channel-blocker	1.064 (0.516–2.194)	0.867							
Diuretics	1.141 (0.357–3.640)	0.824							
Immunosuppressive medication									
Corticosteroids	2.843 (1.149–7.038)	0.024	1.543 (0.501–4.755)	0.450					
Cyclophosphamide	4.706 (0.640–34.585)	0.128							
Methotrexate	1.918 (0.772–4.764)	0.160							
Azathioprine	1.000 (0.500–1.434)	0.998							
mRSS	1.020 (0.98–1.06)	0.346							
mRSS > 15	1.863 (0.62–5.64)	0.271							
Arthritis	2.359 (0.88–6.31)	0.087							
Proximal muscle weakness	4.176 (1.67–10.45)	0.002	3.688 (1.33–10.24)	0.012	3.437 (1.13–10.43)	0.020	4.033 (1.42–11.43)	0.009	3.641 (1.31–10.12)
Lung fibrosis	1.426 (0.70–2.89)	0.327							
eGFR < 60 ml/min/m <sup>2</sup>	0.227 (0.03–1.66)	0.227							
Elevated NT-proBNP	3.840 (1.65–8.94)	0.002	1.924 (0.76–4.88)	0.168	1.563 (0.57–4.30)	0.388	1.989 (0.77–5.10)	0.153	1.735 (0.67–4.47)
Decreased FEV1 %	1.576 (0.53–4.67)	0.412							
Decreased FVC %	2.466 (1.05–5.81)	0.039							
Decreased DLCO %	4.750 (1.89–11.95)	0.001	3.617 (1.36–9.64)	0.010	3.621 (1.25–10.51)	0.049	3.088 (1.14–8.38)	0.027	3.377 (1.24–9.19)
Decreased VO2max %	2.588 (1.19–5.65)	0.017							
E/A ratio	0.319 (0.10–0.98)	0.047							
Lateral E' $\leq$ 10 cm/s	2.807 (1.37–5.74)	0.005							
Elevated sPAP	3.064 (1.03–9.12)	0.044							
TAPSE, mm	0.899 (0.81–0.99)	0.037							
							2.521 (0.78–8.16)	0.123	0.897 (0.80–1.00)
									0.060

GLS: global longitudinal strain; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; mRSS: modified Rodnan skin score; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide, cutoff value 300 ng/l; FEV1: forced expiratory volume in 1 s, percent of predicted value, cutoff value 70%; FVC: forced vital capacity, percent of predicted value, cutoff value 80%; E/A: peak early (E) and late (A) diastolic velocities; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion.



involvement of the skeletal muscles, has been associated with increased risk of myocardial involvement such as congestive heart failure, myositis, arrhythmias, or conduction defects<sup>31,32,33,34</sup>. Allano and colleagues reported proximal muscle weakness to be independently associated with a decreased LV systolic function, which occurred in 5.4% of the population<sup>8</sup>. Additionally, the current study emphasizes the clinical importance of detecting proximal muscle weakness for identifying patients at high risk of developing LV dysfunction.

Impaired DLCO is also known to be associated with reduced functional capacity and as a predictor of interstitial lung disease<sup>35,36,37</sup>. Therefore, as our current study suggests, decreased DLCO may indicate both primary and secondary (to pulmonary involvement) cardiac involvement, and may be considered as a marker of potential progression in LV systolic dysfunction over time.

Although elevated NT-proBNP was more prevalent in patients with GLS reduction, no significant association was found. This may be because NT-proBNP is elevated by more overt LV dysfunction and also reflects noncardiac abnormalities (e.g., renal dysfunction).

In addition, the presence of LV diastolic dysfunction has been shown to be associated with disease duration and an increased risk of mortality<sup>10</sup>. Therefore, it is not surprising that the current study suggests a concomitant worsening in LV systolic and diastolic function and that the presence of LV diastolic dysfunction is independently associated with decline of LV systolic function over time.

**Clinical implications.** The ability to detect progression in myocardial dysfunction offers the opportunity to start appropriate therapeutic measures at an earlier stage of the disease, to prevent further impairment in cardiac performance. Because myocardial involvement has been suggested as an important factor in treatment-related mortality in patients with SSc undergoing autologous stem cell transplantation<sup>38</sup>, speckle-tracking strain analysis may contribute to better risk stratification and selection for this treatment. Further, identification of potential associates of development of LV systolic dysfunction over time may help physicians identify which patients with SSc would benefit from a closer echocardiographic followup. Currently, it is unclear how frequently patients with SSc should be followed up for screening of cardiac involvement<sup>39</sup>. The specific healthcare program developed in our institution, which includes yearly examinations by the cardiologist including echocardiography, enabled us to robustly assess the changes in cardiac performance over time, irrespective of disease duration or SSc subtype. Although significant progression in LV systolic dysfunction could be detected in almost 20%, up to 80% showed normal or stable LV systolic function. This suggests that a standard yearly echocardiographic screening in all patients with SSc is redundant. The current study identified proximal muscle weakness, DLCO, and LV diastolic dysfunction as potential

measures that can be used in deciding whether to perform a closer echocardiographic followup.

**Limitations.** Specific analyses to assess microvascular or macrovascular myocardial ischemia were not systematically performed. However, all patients were routinely seen by a cardiologist and underwent ECG and cardiopulmonary exercise testing, which makes significant ischemia unlikely. The population of our study is representative of patients with SSc referred for screening in a specific healthcare program in a tertiary care center, and 92.3% fulfilled the ACR 2013 criteria. Certain characteristics (e.g., the relatively low mRSS) reflect that the majority of the population consists of patients with longstanding disease. Additionally, the design of this followup study may introduce selection bias, because standard evaluations are not always possible owing to illness or death in the most severely ill patients. However, to evaluate echocardiographic changes over time, this study design was inevitable. Further, changes in (medical) treatment were not taken into account, and potential associations with changes in cardiac function remain unclear. Results of our current study should be confirmed in larger, prospective, multicenter studies with longer followup.

Development and progression of LV systolic dysfunction could be detected using 2-dimensional speckle-tracking strain (GLS) and not by conventional echocardiography. This decrease in GLS was associated with concomitant deterioration of variables reflecting SSc disease activity, indicating that speckle-tracking analysis can detect subclinical myocardial involvement in patients with SSc. As independent associates, decreased DLCO, muscle weakness, and LV diastolic dysfunction at baseline may help identify patients at risk for myocardial involvement and can guide clinical followup.

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**APPENDIX 1.** Course of inflammation measures between patients with and without GLS reduction at followup.

N = 204	< 15% Decrease GLS, n = 165			≥ 15% Decrease GLS, n = 39		
	Baseline	Followup	p	Baseline	Followup	p
Elevated CRP	16 (10)	14 (9)	0.016	4 (10)	7 (18)	0.002
Elevated ESR	57 (34)	59 (36)	< 0.001	16 (41)	18 (46)	< 0.001
Elevated CK	104 (63)	93 (56)	< 0.001	29 (74)	27 (69)	0.037
Pericardial effusion	7 (4)	12 (7)	< 0.001	1 (3)	3 (8)	< 0.001

Data are n (%). CK: creatine kinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GLS: global longitudinal strain.