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**Title:** Pulmonary structure and function analysis in systemic sclerosis: clinical assessment of complicating interstitial lung disease and pulmonary vasculopathy  
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Left ventricular dysfunction assessed by speckle tracking strain analysis in systemic sclerosis patients: relationship with functional capacity and ventricular arrhythmias


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Abstract

Background: Systemic sclerosis is a connective tissue disease characterized by vascular inflammation and fibrosis. Visceral involvement, including cardiac manifestations can lead to severe clinical complications, such as congestive heart failure, arrhythmias and sudden death. Conventional echocardiography parameters have limited sensitivity to detect subtle myocardial dysfunction in patients with systemic sclerosis (SSc). The aim of the study was to assess, using novel speckle tracking strain analysis, the presence of myocardial dysfunction in SSc patients and to investigate its relationship with functional capacity and ventricular arrhythmias.

Methods: A total of 104 SSc patients (age 54±11 yrs, 77% female) were included and underwent cardiopulmonary exercise testing, 24-hour electrocardiography Holter, and transthoracic echocardiography. For comparison purposes, 37 matched healthy controls were included.

Results: The total population consisted of 51 patients with limited SSc and 53 patients with diffuse SSc. Peak VO₂% predicted was 91±20% and 28 patients had abnormal Holter findings (ventricular tachycardia or ventricular ectopics >100/day). Patients with SSc have impaired global longitudinal (-18.2±1.8%) and circumferential strains (-18.2±2.3%) as compared to controls (21.3±1.7%, p<0.01, p<0.01 respectively), but not left ventricular ejection fraction (63.5±7.2% vs 64.6±4.4%, p=0.20). In patients with SSc, global longitudinal (r=-0.46, p<0.01) and circumferential strains (r=-0.41, p<0.01) correlated with peak VO₂% predicted. Multivariate analysis showed that global longitudinal and circumferential strains were independently associated with peak VO₂% predicted. Patients with abnormal Holter findings showed impaired global longitudinal (-18.5±1.5 vs -17.1±2.1%, p<0.01) and circumferential (-18.7±2.0 vs -17.3±2.5%, p=0.01) strains as compared to controls, and were independently associated with abnormal Holter findings.

Conclusion: Speckle tracking strain analysis detected subtle myocardial dysfunction in SSc patients. Importantly, decreased global longitudinal and circumferential strains are associated with lower functional capacity and rhythm disturbances.
Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by deposition of collagen in multiple organs and associated with significant disability and reduced life expectancy (1). Cardiovascular involvement has been shown to be one of the leading causes of mortality in SSc (2) and to occur in up to 70% of patients as autopsic finding (3). Early diagnosis and accurate staging of myocardial involvement are therefore crucial for the management of these patients and for therapeutic strategies.

Conventional echocardiographic assessment of left ventricular (LV) systolic function is based on the measure of LV ejection fraction (EF). This approach however showed limited sensitivity for the assessment of myocardial abnormalities in SSc patients, being able to identify only 5% of patients with cardiac involvement (4). More sophisticated and sensitive techniques for the assessment of LV function are therefore needed to improve the detection of subclinical myocardial dysfunction in SSc patients. Initial studies using tissue Doppler imaging suggested that myocardial velocity and deformation (strain) might be more sensitive than conventional measures in identifying subtle cardiac dysfunction in asymptomatic SSc patients (5-7). However, the clinical implications of this alternative approach for LV function assessment have not been evaluated.

Recently, two-dimensional (2D) speckle tracking 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 in three orthogonal directions (longitudinal, circumferential and radial) (8). The aim of this study was therefore to apply this novel technique to assess the presence of LV systolic dysfunction in a large cohort of SSc patients. Furthermore, the clinical value of the measure of LV global strain by 2D speckle tracking analysis was evaluated in relation with functional capacity and ventricular arrhythmias.

Methods

Patient population and protocol

The current study included 113 consecutive patients with SSc referred to the department of Rheumatology, Leiden University Medical Center. The patients were recruited from two studies; a randomized controlled trial evaluating the effectiveness of a multidisciplinary team care program (9) and a study evaluating the outcomes of a two-days diagnostic
multidisciplinary daycare program (10). All patients underwent an extensive screening, including detailed physical examination, a Modified Rodnan Skin Score assessment (11), laboratory testing (including erythrocyte sedimentation rate, anti-nuclear, antitopoisomerase I, anti-RNP and anti-centromere antibodies assessments), chest X-ray and lung function test. Interstitial lung disease was diagnosed by chest X-ray and by lung function test, and with computed tomography scan when indicated. Patients were classified as limited systemic sclerosis (ISSc) or diffuse systemic sclerosis (dSSc), according to the classification system described by LeRoy et al. (12) In addition, cardiopulmonary exercise (CPET) and 24-hour electrocardiography (ECG) Holter monitoring were performed to assess patient functional capacity and potential ventricular arrhythmias, respectively. All patients had no angina pectoris or symptoms attributable to cardiovascular disease and therefore specific tests for microvascular and macrovascular ischemia were not performed. Transthoracic echocardiography was performed to evaluate conventional parameters of cardiac function and to assess subclinical LV systolic dysfunction using novel speckle tracking analysis. The relationship of LV function with functional capacity and ventricular arrhythmias was evaluated.

Seven patients were not able to perform CPET (because of severe pulmonary hypertension in 4 patients, severe aortic valve stenosis in 1 patient and severe SSc disease status in 2 patients) and therefore excluded from the analysis. In addition, 2 patients were excluded because of an incomplete clinical assessment. The final study population consisted of 104 patients.

For comparison purposes, 37 normal individuals (1:3 ratio with SSc patients) matched for age and gender were included as a control group. These subjects were referred for atypical chest pain, palpitations, or syncope without murmur and showed normal structural heart on echocardiography.

The study protocol was approved by the Ethics Committee of the Leiden University Medical Center. All participants provided written informed consent for the studies in which they participated.

**Lung function test**

Lung function test was performed in all SSc patients and included spirometry and single breath diffusion lung capacity for carbon monoxide (DLCO). Spirometry measurements included forced vital capacity (FVC) and total lung capacity (TLC) measured according to
the American Thoracic Society/European Respiratory Society recommendations (13-15) and expressed as percentage predicted.

**Conventional echocardiography**

All SSc patients and controls were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5-MHz transducer and digitally stored in cine-loop format; offline analysis was performed using EchoPAC version 108.1.5 (General Electric – Vingmed, Horten, Norway). LV dimensions, volumes and EF were measured according to the current recommendations (16). Evaluation of LV diastolic function was based on the pulsed-wave Doppler of mitral valve inflow as recommended by the American Society of Echocardiography (17), measuring peak early diastolic velocity (E), peak late (A) diastolic velocity, their ratio (E/A) and the E wave deceleration. Pulmonary venous flow velocities during systole (S) and diastole (D) were also recorded. Using tissue Doppler imaging, the early diastolic velocity (E’) and systolic velocity (S’) was measured at the level of the LV basal lateral segment. In addition, E/E’ ratio was calculated as an estimation of LV filling pressure (18). LV diastolic dysfunction was therefore categorized as previously described: normal; mild, defined as LV impaired relaxation without evidence of increased filling pressure; moderate, defined as LV impaired relaxation associated with moderate elevation of filling pressures or pseudo-normal filling; and severe, defined as restrictive LV filling (17). Pulmonary arterial systolic pressure (PASP) was estimated by right ventricular systolic pressure, which was calculated from the tricuspid regurgitation peak gradient using Bernoulli equation, and adding right atrial pressure estimated by the dimension and the degree of inferior vena cava respiratory collapse (19).

**Two-dimensional speckle tracking strain analysis**

Two-dimensional speckle tracking analysis is a novel imaging technique which allows the assessment of LV myocardial deformation by tracking natural acoustic markers (speckles) in a frame-to-frame basis within the cardiac cycle. The speckles are visible in the standard gray-scale 2D images and are equally distributed within the myocardium. As represented in Figure 3.1, LV deformation can be assessed in three orthogonal directions as longitudinal, circumferential and radial strain (20).
Longitudinal strain, evaluating the shortening/lengthening of the myocardial wall, was measured from the 3 apical views: 2-chamber view (including anterior and inferior walls), 4-chamber view (posteroseptal and lateral walls) and long axis view (anteroseptal and posterior walls). Each wall was divided into 3 levels (basal, mid and apical) and subsequently 18 segmental strain curves were obtained. Global longitudinal strain was calculated as the average of peak systolic strain values of the 18 segments (Figure 3.2a).

From LV mid-ventricular short-axis view, circumferential strain (evaluating myocardial shortening/lengthening along LV curvature) and radial strain (evaluating myocardial thickening/thinning) were measured. The global values of circumferential and radial strains were derived from the average of peak systolic strain values of 6 segments, as illustrated in Figure 3.2b and 3.2c, respectively. Global longitudinal and circumferential strains are expressed as negative values, and a lower strain is represented by less negative values. Global radial strain is expressed as positive values, and lower values indicate lower strain.

The intra- and inter-observer agreement for the measurements of longitudinal, circumferential and radial strains have been reported previously (20).
LV dysfunction assessed by speckle-tracking strain analysis in SSc patients

Figure 3.2a illustrates the calculation of global longitudinal strain from the apical 4-chamber, 2-chamber, and the long-axis views. Each color line denotes regional segmental strain (6 segments per views, for a total of 18 segments) and the white dotted line represents the average strain value of each view. The global longitudinal strain (Figure 3.2b) and radial (Figure 3.2c) strains are calculated by averaging the peak strain of six LV segments.

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Cardiopulmonary exercise testing

All SSc patients performed a maximal exercise stress test on an electrically braked stationary cycle ergometer using a ramp protocol according to the American Thoracic Society/ American College of Chest Physician statement on cardiopulmonary testing (21). Briefly, a tight fitting facemask was worn by the patients and allowed ventilation and metabolic gas exchange measurements (Oxycon Pro, Jaeger-Viasys Healthcare, Hoechberg, Germany). The initial work load was 30W, with further increment of 5W every 30 seconds. Patients were encouraged to exercise until exhaustion or until supervising physician stopped the test because of significant symptoms, such as chest pain, dizziness, ST-segment deviations, or marked systolic hypotension or hypertension. Peak VO$_2$ was defined as the highest oxygen consumption during any stage of maximal exercise. Furthermore, peak VO$_2$ was adjusted to age, gender and weight and expressed as percentage predicted.

24-hour electrocardiography Holter monitoring

A 24-hour ECG Holter monitoring was performed in 100 out of 104 patients to detect potential ventricular arrhythmias. Abnormal Holter results were defined as the presence of intermittent bundle branch block, ventricular arrhythmias including frequent monomorphic and/or polymorphic premature ventricular contractions >100 per day, or non-sustained or sustained ventricular tachycardia (22).

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical data are presented as frequencies and percentages. Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test. Statistical comparisons were performed by using Student's t test for continuous variables, and chi square test for binary variables. Univariate linear regression analysis was used to identify potential determinants of peak VO$_2$ % predicted. Correlations were expressed in terms of Pearson's correlation coefficient. Moreover, univariate binary logistic regression was used to determine the factors associated (using odd ratios (OR) and confidence intervals (CI)) with abnormal Holter results. The final multivariate models for peak VO$_2$ % predicted and abnormal Holter results were obtained using the enter method by including parameters that were statistically significant in univariate analysis. To avoid bias from multicollinearity, multi-directional global strains
were entered to the step-wise model individually. ANCOVA tests with covariates to correct for significant different variables of subpopulation characteristics were performed. All statistical analysis were performed using the statistical package SPSS for windows (Version 15.0, SPSS, Chicago, USA). A p-value <0.05 was considered to be statistically significant.

Results

Clinical characteristics of the patient population

A total of 51 (49%) patients were classified as having lSSc and 53 (51%) patients as having dSSc. Clinical characteristics of the total population and of the 2 subtypes of SSc (limited and diffuse) are shown in Table 3.1. According to the matching criteria, age (54±10 vs. 54±12, p=0.82) and gender (female 77% vs. 73%, p=0.66) were similar between SSc patients and controls. Most of SSc patients were positive for antinuclear antibodies and approximately 50% had underlying interstitial lung disease. In addition, 24 patients (20 dSSc patients and 4 lSSc patients) received a treatment with cyclophosphamide, and 13 patients (all dSSC) stem cell transplantation. A total of 4 patients had mild pulmonary hypertension (2 due to underlying interstitial lung disease and 2 due to pulmonary arterial hypertension), 1 patient had a previous myocardial infarction and 2 patients were known for epicardial coronary artery disease.

Patients with dSSc were associated with a younger age, shorter time since diagnosis and time since onset of Raynaud’s phenomenon and skin manifestation. Moreover, patients with dSSc were more likely to have underlying interstitial lung disease, lower TLC% predicted and to receive angiotensin-converting enzyme inhibitors (mainly to prevent renal crisis) as compared to patients with lSSc. Patients with lSSc had a significantly lower prevalence of anti-topoisomerase antibodies and a lower modified Rodnan skin score.

Echocardiographic characteristics of the patient population

Conventional echocardiographic parameters of LV systolic and diastolic function of SSc patients and controls are shown in Table 3.2. No significant differences were noted in LV volumes and EF between SSc patients and controls (Table 3.2). Moreover, S´ velocity derived from tissue Doppler imaging was similar to controls. However, estimated PASP was significantly higher in SSc patients as compared to controls and E/E´ ratio and LV diastolic
dysfunction grade were significantly worse. When comparing the 2 different subtypes of SSc, both groups showed similar values of conventional echocardiographic parameters.

In order to detect subtle LV dysfunction, myocardial strain values in three orthogonal directions were measured by speckle tracking analysis (Table 3.2). Both global longitudinal and circumferential strains were significantly impaired in SSc patients as compared to controls. However, no difference was noted in global radial strain between SSc patients

### Table 3.1 Clinical characteristics of the 104 patients with systemic sclerosis (SSc) and comparison between patients with limited systemic sclerosis (ISSc) and diffuse systemic sclerosis (dSSc)

<table>
<thead>
<tr>
<th></th>
<th>SSc (n=104)</th>
<th>ISSc (n=51)</th>
<th>dSSc (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>54±12</td>
<td>58±12</td>
<td>50±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>80 (77)</td>
<td>43 (84)</td>
<td>37 (70)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Time since diagnosis, yrs</strong></td>
<td>5.1±2.3</td>
<td>7.1±3.5</td>
<td>4.1±2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Time since onset of Raynaud’s, yrs</strong></td>
<td>8.6±6.3</td>
<td>15.0±5.8</td>
<td>5.8±4.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Time since onset of skin manifestation, yrs</strong></td>
<td>5.6±3.5</td>
<td>7.1±6.2</td>
<td>4.7±2.8</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Modified Rodnan Skin Score</strong></td>
<td>5.6±6.1</td>
<td>2.8±2.2</td>
<td>8.3±7.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122±18</td>
<td>125±18</td>
<td>119±18</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>71±9</td>
<td>70±8</td>
<td>72±11</td>
<td>0.23</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>11 (11)</td>
<td>2 (18)</td>
<td>9 (82)</td>
<td>0.03</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
<td>20.5±17.6</td>
<td>20.7±19.8</td>
<td>20.3±15.4</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Immune markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-nuclear, n (%)</td>
<td>94 (90)</td>
<td>46 (90)</td>
<td>48 (91)</td>
<td>0.61</td>
</tr>
<tr>
<td>Anti-topoisomerase, n (%)</td>
<td>36 (35)</td>
<td>7 (14)</td>
<td>29 (58)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anti-centromere, n (%)</td>
<td>25 (24)</td>
<td>21 (41)</td>
<td>4 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anti-RNP, n (%)</td>
<td>7 (7)</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Interstitial lung disease, n (%)</td>
<td>49 (47)</td>
<td>15 (28)</td>
<td>34 (64)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>4 (4)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>0.62</td>
</tr>
<tr>
<td>*Chronic kidney disease</td>
<td>10 (10)</td>
<td>6 (12)</td>
<td>4 (8)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>94.4±14.4</td>
<td>94.9±12.4</td>
<td>93.9±15.9</td>
<td>0.73</td>
</tr>
<tr>
<td>TLC% predicted</td>
<td>86.9±18.1</td>
<td>92.7±17.2</td>
<td>82.1±17.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DLCO% predicted</td>
<td>63.3±16.8</td>
<td>65.4±17.5</td>
<td>61.2±16.1</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Current immunosuppressive medication (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids, n (%)</td>
<td>15 (14)</td>
<td>6 (12)</td>
<td>9 (17)</td>
<td>0.45</td>
</tr>
<tr>
<td>Methotrexate, n (%)</td>
<td>4 (8)</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td>0.52</td>
</tr>
<tr>
<td>Azathioprine, n (%)</td>
<td>2 (4)</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Current cardiovascular medications (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists, n (%)</td>
<td>46 (44)</td>
<td>17 (33)</td>
<td>29 (55)</td>
<td>0.03</td>
</tr>
<tr>
<td>ACE inhibitors, n (%)</td>
<td>42 (40)</td>
<td>12 (24)</td>
<td>30 (57)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ACE, Angiotensin converting-enzyme; dSSc, Diffuse systemic sclerosis; DLCO, Diffusion lung capacity for carbon monoxide; ESR, Erythrocyte sedimentation rate; FVC, Forced vital capacity; TLC, Total lung capacity.

* Chronic kidney disease defined as an estimated glomerular filtration clearance rate <60 ml/min/1.73m² for more than 3 months.
and normal subjects. Of note, dSSc patients showed worse values of global longitudinal and circumferential strain as compared to lSSc patients.

Table 3.2 Conventional echocardiographic parameters and two-dimensional speckle tracking strain measurements in patients with systemic sclerosis (SSc) versus controls and in patients with limited (lSSc) versus diffuse (dSSc) systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=37)</th>
<th>SSc (n=104) p-value</th>
<th>lSSc (n=51)</th>
<th>dSSc (n=53) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional echocardiographic parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end diastolic volume (ml)</td>
<td>70.6±20.6</td>
<td>67.0±25.4</td>
<td>0.21</td>
<td>72.9±22.4</td>
</tr>
<tr>
<td>LV end systolic volume (ml)</td>
<td>26.6±5.7</td>
<td>29.1±13.1</td>
<td>0.13</td>
<td>28.8±13.9</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>64.6±4.4</td>
<td>63.5±7.2</td>
<td>0.20</td>
<td>64.6±7.9</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>21.7±6.3</td>
<td>28.9±8.7</td>
<td>&lt;0.01</td>
<td>29.5±8.3</td>
</tr>
<tr>
<td>LV diastolic function, n (%)</td>
<td>Normal 21 (62)</td>
<td>35 (34)</td>
<td>&lt;0.01</td>
<td>18 (35)</td>
</tr>
<tr>
<td></td>
<td>Mild 9 (24)</td>
<td>24 (23)</td>
<td></td>
<td>12 (24)</td>
</tr>
<tr>
<td></td>
<td>Moderate 5 (14)</td>
<td>30 (29)</td>
<td></td>
<td>16 (31)</td>
</tr>
<tr>
<td></td>
<td>Severe 0 (0)</td>
<td>15 (14)</td>
<td></td>
<td>5 (10)</td>
</tr>
<tr>
<td>E` velocity (cm/s)</td>
<td>9.8±2.0</td>
<td>8.5±2.8</td>
<td>0.03</td>
<td>8.8±2.7</td>
</tr>
<tr>
<td>E/E` ratio</td>
<td>7.7±1.9</td>
<td>10.1±3.8</td>
<td>&lt;0.01</td>
<td>10.2±3.8</td>
</tr>
<tr>
<td>S` velocity (cm/s)</td>
<td>6.4±1.4</td>
<td>6.3±2.1</td>
<td>0.81</td>
<td>6.8±2.0</td>
</tr>
<tr>
<td><strong>Speckle tracking analysis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>-21.3±1.7</td>
<td>-18.2±1.8</td>
<td>&lt;0.01</td>
<td>-18.6±1.6</td>
</tr>
<tr>
<td>Global circumferential strain (%)</td>
<td>-21.3±2.1</td>
<td>-18.2±2.3</td>
<td>&lt;0.01</td>
<td>-19.0±2.0</td>
</tr>
<tr>
<td>Global radial strain (%)</td>
<td>40.3±12.4</td>
<td>37.0±13.9</td>
<td>0.18</td>
<td>37.6±13.1</td>
</tr>
</tbody>
</table>

LV, Left ventricular; PASP, Pulmonary arterial systolic pressure; E, Early; A, Late; E’, Early diastolic velocity at basal mitral annulus; for other abbreviations, see Table 3.1.

**Cardiopulmonary exercise testing**

All SSc patients completed the CPET with at least 50W exercise level and reached anaerobic threshold, the heart rate recovery (HRR) was >12 beats/minute and a respiratory exchange ratio >1.00, suggesting a satisfactory exercise capacity in the study population. The mean peak VO2% predicted was 90.6±20.4% and the maximum exercise time was 9.9±3.6 min suggesting a relatively preserved functional capacity in the population. Patients with dSSc had a significantly lower peak VO2% predicted compared to those with lSSc (83.2±21.1 vs. 99.7±24.7%, p<0.01).

According to Pearson’s correlation analysis, peak VO2% predicted was not related to conventional echocardiographic parameters including LV dimensions, LVEF and LV
diastolic function (p>0.05). However, peak VO₂% predicted was significantly related to global longitudinal (r=-0.46, p<0.01), circumferential (r=-0.41, p<0.01) and radial (r=0.20, p=0.05) strains (Figure 3.3).

Univariate analysis revealed that among all the clinical and echocardiographic characteristics, age (β=0.24, Confidence interval [CI] = 0.09–0.83, p=0.02), subtype dSSc (β=0.40, CI=0.30–0.79, p<0.01), underlying interstitial lung disease (β=0.24, CI=2.23–20.6, p=0.02), TLC% predicted (β=0.40, CI=0.30–0.79, p<0.01) and DLCO% predicted (β=0.49, CI=0.46–0.96, p<0.01) were significantly associated with peak VO₂% predicted. Strain measurements were adjusted with the aforementioned parameters in a multivariate analysis, which demonstrated that global longitudinal (β=-0.36, CI=-2.72–-7.25, p<0.01) and circumferential (β=-0.34, CI=-1.77–-5.47, p<0.01) strains were independently associated with peak VO₂% predicted, together with age and DLCO%.

24-hour ECG Holter monitoring

Among the 100 SSc patients who underwent 24-hour ECG Holter monitoring, 28 (28%) patients had abnormal results. In particular, 9 patients presented with non-sustained ventricular tachycardia and 19 patients had ventricular ectopic >100 per day.

Clinical and echocardiographic parameters differences between patients with or without abnormal Holter results are shown in Table 3.3. Patients with abnormal Holter results were more likely to be male and with underlying interstitial lung disease. Conventional LV systolic function, LV diastolic dysfunction grade, and S’ velocity were similar between patients with or without abnormal Holter results. However, E/E’ ratio was significantly higher in patients with abnormal Holter results. Moreover, global longitudinal and circumferential strains, but not global radial strain, were significantly impaired in patients with abnormal Holter results.

Univariate analysis demonstrated that the presence of abnormal Holter results was associated with male gender (OR=2.94, CI=1.12–7.69, p<0.01), interstitial lung disease (OR=3.32, CI=1.32–8.36, p<0.01), higher E/E’ ratio (OR=1.15, CI=1.02–1.32, p=0.04), and lower values of global longitudinal (OR=1.71, CI=1.24–2.38, p<0.01) and circumferential strains (OR=1.55, CI=1.18–2.03, p<0.01). After multivariate adjustment, both global longitudinal (OR=1.47, CI=1.05–2.07, p=0.03) and circumferential (OR=1.35, CI=1.01–1.82, p=0.04) strains remained the only independent predictors of abnormal Holter results in SSc patients.
Figure 3.3 Correlation between peak VO₂% predicted and global longitudinal (Panel A), circumferential (Panel B) and radial (Panel C) strain measured by two-dimensional speckle tracking analysis. Dashed lines correspond to 95% confidence interval.
The results of the current study demonstrated that patients with SSc present subtle LV systolic dysfunction, as assessed by 2D speckle tracking strain analysis, despite normal LVEF and dimensions. More importantly, LV global longitudinal and circumferential strains, but not...
conventional echocardiographic parameters, were independently associated with functional capacity assessed by CPET, and ventricular arrhythmias detected by 24-hour ECG Holter monitoring.

Cardiac involvement in patients with SSc has been mainly described by the presence of elevated PASP and LV diastolic dysfunction (5;6). Recent studies (5-7) using tissue Doppler imaging in relatively small groups of SSc patients, have also suggested an impairment in myocardial systolic deformation (strain), despite preserved LVEF and dimensions (4;23). However, strain analysis by tissue Doppler imaging is significantly limited by angle dependency (the measure changes with the insonation angle) and does not allow for the evaluation of all LV segments and of different directions of myocardial deformation. The advent of 2D speckle tracking analysis overcomes these limitations and allows angle-independent, direct evaluation of LV global strain in all three orthogonal directions, providing more accurate assessment of LV function (8).

The current study applied this novel analysis in a large cohort of SSc patients and found that both LV global longitudinal and circumferential strains were modestly but significantly impaired in SSc patients as compared to controls. The relatively small difference of strain values noted between the 2 groups could be explained by the fact that SSc patients in the present cohort were asymptomatic and had a relatively preserved functional capacity, suggestive of mild and subclinical cardiovascular involvement. Furthermore, dSSc patients showed worse values of global longitudinal and circumferential strains as compared to lSSc patients, confirming a more common and severe cardiac involvement in the diffuse form of the disease (5;24). Therefore, the use of more sensitive echocardiographic parameters may enable the detection of subtle LV systolic dysfunction before clinical manifestation, not identified by conventional approaches. Of note, both the present result and the studies from Mele and Kepez et al. (5;6) failed to show a significant difference in myocardial function by using tissue Doppler imaging derived S’ velocity between SSc patients and controls. These findings therefore suggest that 2D speckle tracking derived strain analysis, which allows angle-independent and global LV functional assessment, is superior to tissue Doppler imaging derived S’ velocity to detect subtle myocardial dysfunction in SSc patients.

Although the mechanism underlying LV systolic dysfunction is unknown, previous studies have demonstrated the presence of significant myocardial fibrosis in SSc patients, using delayed gadolinium enhanced magnetic resonance imaging (25;26). These structural alterations, mainly caused by repeated focal ischemia due to abnormal vasoreactivity, may be
responsible for myocardial dysfunction. Interestingly in the current study, multi-directional strain analysis demonstrated significant impairment of longitudinal and circumferential strains (shortening), but not of radial strain (thickening). This finding may suggest that myocardial involvement of the subendocardial layer (responsible for longitudinal and circumferential shortening) occurs earlier as compared to the subepicardial layer (responsible for radial deformation), since the subendocardium is more susceptible to ischemia and fibrosis phenomena. Nevertheless, the exact mechanism of myocardial dysfunction requires further studies.

Patients with SSc were shown to have reduced cardiopulmonary exercise capacity measured by VO₂% predicted, which could be caused by multiple factors (27-30). Previous studies have suggested that lung pathology is one of the main determinants of impaired functional capacity in these patients (28;31). Similarly, the present study also showed the important role of lung function assessed by DLCO% predicted, which was independently associated with VO₂% predicted (31). In addition, a recent study by Walkey and colleagues has also suggested that exercise induced LV diastolic dysfunction, undetected by resting echocardiography, was a cause of impaired exercise capacity (29). However, the potential role of LV systolic dysfunction as an important contributing factor to functional capacity, has not been demonstrated before. Importantly, the present study demonstrated that LV global longitudinal and circumferential strains were significantly related with VO₂% predicted, independently of age, SSc subtype and lung function. This observation thus provided direct evidence that LV systolic dysfunction significantly contributes to impaired functional capacity in patients with SSc. Therefore, novel 2D speckle tracking strain analysis may be used in conjunction with lung function testing in order to provide a global assessment and monitoring of the cardiopulmonary status in SSc patients.

Ventricular arrhythmias commonly occur in patients with SSc (32) and, are responsible for up to 6% of the deaths, as demonstrated by a recent study (2). In particular, the presence of non-sustained ventricular tachycardias has been reported in 6–10% of patients with SSc and showed to be significantly associated with total mortality and sudden death (31;32). In the current study, 24-hour ECG Holter monitoring was systematically performed in a large group of SSc patients and identified non-sustained ventricular tachycardias in 9% of the cases. Importantly at the multivariate analysis, LV systolic dysfunction, assessed by LV global longitudinal and circumferential strains, was the only independent predictor of ventricular arrhythmias (ventricular ectopics and non-sustained ventricular tachycardia). These results suggest that subtle LV systolic dysfunction is per se an important factor associated with
ventricular arrhythmias and may also reflect the extent of myocardial fibrosis, which is a well-known arrhythmogenic substrate (25). These novel echocardiographic parameters therefore represent a valuable tool to improve risk stratification of SSc patients. The current study underscores the need for implementing speckle tracking strain analysis in larger systemic sclerosis cohort studies, investigating risk stratification and potential protective effects of anti-arrhythmic strategies.

The current study was a cross-sectional analysis and therefore a causal relationship between impaired 2D speckle tracking derived strain and impaired functional capacity and ventricular arrhythmias in SSc patients could not be established. Moreover, the current population included SSc patients with preserved functional capacity and low prevalence of pulmonary hypertension and the results of the present study can not be extrapolated to SSc patients with severe cardiopulmonary involvement. Lastly, microvascular and macrovascular ischemia were not fully documented, since all patients had no clinical evidence of myocardial ischemia (neither during CPET) and invasive evaluations and/or vasoreactivity tests were therefore not performed. Future studies are required to evaluate the impact of both microvascular or macrovascular ischemia on 2D speckle tracking derived multi-directional strain in SSc patients.

In conclusion, patients with SSc are associated with LV systolic dysfunction measured by 2D speckle tracking strain analysis. Importantly, LV global longitudinal and circumferential strains independently predicted impaired functional capacity measured by CPET and ventricular arrhythmias detected by 24-hour ECG Holter monitoring. The use of this novel imaging technique may therefore improve risk stratification and monitoring of the cardiovascular involvement in patients with SSc.
Chapter 3

References


LV dysfunction assessed by speckle-tracking strain analysis in SSc patients


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