Early impairment of myocardial function in systemic sclerosis: Non-invasive assessment by Doppler myocardial and strain rate imaging

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Abstract  Background: Aim of the present study was to analyze both left (LV) and right ventricular (RV) myocardial function in patients with Systemic Sclerosis (SSc), and their relation to other instrumental features of the disease.

Methods and results: Twenty-five healthy subjects and 23 age- and sex-comparable asymptomatic patients classified as having either diffuse (11 patients) or limited form (12 patients) of SSc underwent clinical examination, serological tests, high-resolution chest-CT, standard Doppler echo, pulsed Doppler myocardial imaging (DMI) and strain rate imaging (SRI) of both LV and RV lateral walls. By chest-CT, 11 patients showed interstitial pulmonary fibrosis. Serological antibodies analysis detected anti-centromere pattern in 8 patients, and anti Scl-70 in 15 patients. LV diameters and ejection fraction were comparable between the two groups, while RV end-diastolic diameter was increased in SSc (p < 0.01). Tricuspid inflow E/A ratio was slightly decreased in SSc (p < 0.01), while systolic pulmonary pressure was increased (p < 0.001). Pulsed DMI detected in SSc impaired myocardial RV early-diastolic (E_m) peak velocity (p < 0.0001), and prolonged myocardial time intervals at tricuspid annulus level. In SSc, peak systolic RV SR and strain were both reduced in basal, middle and apical RV lateral free walls, and in basal and middle LV lateral walls. By multivariate analysis, independent inverse association of RV peak
Em velocity with both Rodnan Skin Score (p < 0.0005) and pulmonary systolic pressure (p < 0.0001), as well as independent inverse correlation of the same RV peak Em velocity with pulmonary fibrosis (<0.0005) in SSc patients were observed. In addition, RV Em was an independent predictor of the anti Scl-70 antibody pattern (p < 0.001).

Conclusions: Pulsed DMI and SRI are valuable non-invasive and easy-repeatable tools for detecting RV and LV myocardial involvement caused by SSc, and may therefore be useful to early identify patients with more diffused and severe form of SSc.

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Systemic sclerosis (SSc) is a multisystem disorder characterized by widespread vascular lesions and fibrosis of skin and distinct internal organs. Cardiac involvement is a common finding in SSc, but often clinically occult. In fact, clinical evidence of myocardial disease may be found in 20–25% of patients with SSc, while at post-mortem examination the heart is affected in up to 80% of patients. Diagnosis of a sub-clinical cardiac impairment may be therefore essential for adequate long-term management of such patients.

Right ventricular (RV) chamber is often involved in systemic pathologies as a consequence of direct injury extension, afterload changes or ventricular interdependence which is mainly due to the close anatomic association between the two ventricles. However, this issue has not been often explored by non-invasive techniques because of RV complex geometry which precludes an accurate assessment of RV internal chamber dimensions and their changes during cardiac cycle.

By use of standard Doppler echocardiography, previous authors have pointed out an impaired RV filling in a significant percentage of SSc patients in whom no other cause of altered diastolic function had been detected. To the best of our knowledge, no report at the present time have described both left ventricular (LV) and RV regional myocardial involvement in such systemic disease.

On these grounds, the aim of the present study was to analyze systolic and diastolic myocardial function in patients with SSc, and their relation to other instrumental features of the disease, by use of Doppler myocardial imaging (DMI), strain and strain rate (SR) imaging. These techniques provide accurate information about segmental myocardial motion and deformation during the cardiac cycle and offer the advantage, with respect to conventional Doppler echocardiography, to assess systolic and diastolic function of both the ventricles at a regional level.

Methods

Study population

Twenty-five healthy subjects and 23 age- and sex-comparable asymptomatic patients classified as having either diffuse (11 patients) or limited form (12 patients) of SSc underwent clinical examination, serological tests, high-resolution chest computed tomography (CT), standard Doppler echocardiography, pulsed DMI and SR imaging (SRI).

All the patients were enrolled into the study after their informed consent and approval of Ethic Committee of G. Rummo Hospital were obtained. Exclusion criteria were: arterial hypertension, coronary artery disease (angina and/or ECG signs of myocardial ischaemia), severe valvular heart disease, more than 2nd grade of mitral regurgitation, New York Heart Association (NYHA) functional classes II–IV, atrial fibrillation, lung disease and inadequate echocardiograms.

Procedures

Standard Doppler echocardiography and DMI were performed with the subjects in partial left decubitus, by digital ultrasound machine (Vivid 7, GE Medical Systems Inc, Milwaukee, Wis), equipped with DMI and SRI capabilities. A variable frequency phased-array transducer (2.5–3.5–4.0 MHz) was used for two-dimensional, M-mode and Doppler imaging. Doppler echocardiographic, DMI and SRI tracings were recorded on magneto-optical disk. All the measurements were analyzed by 2 experienced readers, by the average of ≥3 cardiac cycles.

M- and B-mode

Two-dimensional measurements of septal and lateral wall thickness were obtained at end-diastole, in parasternal short-axis view. LV mass was calculated
according to the Penn convention by the following formula:

\[
\text{LV mass} (g) = 1.04 \left[ (\text{LVEDD} + \text{IVST} + \text{PWT})^3 - (\text{LVEDD})^3 \right] - 13.6
\]

where \( \text{LVEDD} \) = LV internal end-diastolic diameter, \( \text{LVEDD} = \text{LV} \) internal end-systolic diameter, \( \text{IVST} = \text{Ventricular septal thickness}, \) and \( \text{PWT} = \text{Posterior wall thickness}. \) LV mass was indexed for height\(^2\).\(^{2.7} \) (Cornell adjustment).\(^{15} \) RV ejection fraction was determined as diastolic measurements.\(^{12,13} \)

**Standard Doppler**

Pulsed Doppler assessment of LV inflow was performed in apical 4-chamber view, with the sample volume placed at the level of valve tips. The following measurements of global LV diastolic function were determined: peak velocities of E and A wave (m/s) and their ratio, deceleration time of E wave (ms), isovolumic relaxation time (ms), measured as the time interval occurring between the end of systolic output flow and the transmitral E wave onset, by placing pulsed Doppler sample volume between outflow tract area and LV output velocity integral.\(^{17} \) RV end-diastolic diameter was measured in apical 4-chamber view at basal, middle and apical levels according to the protocol of Foale et al.\(^{8} \)

**Pulsed Doppler myocardial imaging**

Pulsed DMI was performed by spectral pulsed Doppler signal filters, adjusting Nyquist limit until 15–20 cm/s (close to myocardial velocities), and using the minimal optimal gain. In apical 4-chamber view, a 5 mm pulsed Doppler sample volume was placed on both the basal LV and the RV lateral walls, at the level of mitral and tricuspid annulus, respectively. The apical view was chosen to obtain quantitative assessment of regional wall motion almost simultaneous to Doppler inflow and outflow and to minimize the incidence angle between Doppler beam and the longitudinal wall motion. Pulsed DMI is characterized by a myocardial systolic wave (\( S_m \)) and 2 diastolic waves - early (\( E_m \)) and atrial (\( A_m \)). Myocardial peak velocity of \( S_m \) (m/s), myocardial pre-ejection time (\( Q-S_m \)) (from the onset of ECG QRS complex to the beginning of the S wave), ejection time (\( ET_m \)) (from the beginning to the end of S wave) and \( E_m \) and the onset of \( E_m \) - were determined as diastolic measurements.\(^{12,13} \)

**Strain rate imaging**

Strain rate digital data were acquired in real time, with a frame rate > 160 frames/s, and transferred to a magneto-optical disk for off-line analysis, applying the software incorporated in the ultrasound system. This allowed determination of the SR, and strain of a selected sample volume for each instant during 3 cardiac cycles. In the apical 4-chamber view, according to the previous reports, variations in longitudinal SR (1/s) and integrated strain (%) of 3 segments (basal, middle, apical) for both LV and RV free lateral walls were analyzed, simultaneously by off-line analysis of DMI data, and displayed as spectral tracings. To analyze SR variables, the strain rate calculation length was set to 10 mm. The SR corresponded to the local spatial velocity gradient, and the regional strain was obtained from the integration of the SR curves.\(^{14,21} \)
Statistical methods

The analyses were performed by SPSS for Windows release 11.0 (Chicago, Illinois, U.S.A.). Variables are presented as mean ± SD. T test for unpaired data estimated differences between the two groups.

Reproducibility of measuring the DMI parameters was determined in 20 subjects (10 SSc and 10 controls), according to the previously reported methods. Inter- and intra-observer variability was examined using Bland–Altman analysis. Ninety-five percent confidence limits of a single estimate of the measurements were calculated as $2 \times SD/\sqrt{2}$, and reported as a percent from the mean value.

Linear regression analyses and partial correlation test by either Pearson’s or Spearman’s method were done to assess univariate relations. Receiver operating characteristic (ROC) curve analysis was performed to select optimal cut-off values of DMI measurements. Stepwise, forwards, multiple either regression analyses or logistic regression analyses were performed to weigh the independent effects of potential determinants on a dependent variable. Differences were significant at $p < 0.05$.

Results

Characteristics of the study population

The two groups were comparable for age (56.3 ± 8.2 in SSc vs. 55 ± 9.3 years in controls), sex (3 M/20 F in SSc vs. 5 M/20 F in controls), mean blood pressure (83.5 ± 4.5 in SSc vs. 80.2 ± 3.3 mmHg in controls), heart rate (HR) (78.1 ± 7.6 in SSc vs. 76.9 ± 10.2 b/m in controls) and body surface area (1.85 ± 0.11 in SSc vs. 1.82 ± 0.08 m² in controls).

Skin thickness was quantified using the modified Rodnan Skin Score (mRSS), according to the Preliminary American College of Rheumatology Criteria.1,22 The SSc was classified into high mRSS (score ≥ 10; 11 patients) and low mRSS (score < 10; 12 patients). By chest-CT, 11 patients showed interstitial pulmonary fibrosis. Immunofluorescence analysis detected anti-centromere antibody pattern in 8 patients, and anti-topoisomerase I (anti Scl-70) in 15 patients (Fig. 1).23–26 Among SSc patients, 12 were taking oral steroids (prednisolone 20 mg/day as the initial dosage) and 7 were undergoing an intermittent continuous therapy with iloprost (for 5 days in the highest tolerated dose of 1–2 ng/kg/min).

Standard Doppler echocardiographic analysis

LV mass index, diameters and ejection fraction as well as RV TAPSE were comparable between the two groups, while RV end-diastolic diameter was increased in SSc (Table 1). Tricuspid inflow $E/A$ ratio was slightly decreased in SSc, while systolic pulmonary pressure was significantly increased. In particular, 10 SSc patients (43.2%) showed pulmonary hypertension (systolic pulmonary artery pressure > 35 mmHg). Of note, among the SSc patients with pulmonary hypertension, 9 showed

Figure 1  SSc patient: chest-CT showing interstitial pulmonary fibrosis (left panel); immunofluorescence analysis detecting anti-topoisomerase antibody pattern (right panel).
also interstitial pulmonary fibrosis by chest-CT, 8 a diffused form of scleroderma, and 9 an anti Scl-70 antibody pattern.

DMI and strain imaging analysis

Pulsed DMI analysis detected in SSc impaired myocardial RV early-diastolic peak velocities, as well as prolonged myocardial RTm, only at tricuspid annulus level, even after correction for age, sex, heart rate and BSA (Tables 2 and 3). As for regional systolic function, with the use of pulsed DMI RV Q−Sm was prolonged in SSc patients, while no significant differences in Sm peak velocities were evidenced between the two groups. Conversely, both peak systolic SR and peak systolic strain in basal, middle and apical RV lateral free walls, as well as in basal and middle LV lateral free walls were significantly reduced in patients with SSc with respect to controls (Fig. 2).

SSc subgroup analysis

We performed a separate subset analysis in SSc patients with (10 patients) or without (13 patients) pulmonary hypertension. By these measurements, patients with pulmonary hypertension showed a more impaired RV myocardial diastolic function (RV Em peak = 0.116 ± 0.04 vs. 0.151 ± 0.03 m/s in pulmonary hypertension vs. normal pulmonary pressure, p < 0.001; RV RTm = 31.6 ± 5.5 in pulmonary hypertension vs. 45.1 ± 6.2 ms in normal pulmonary pressure, p < 0.01), as well as a greater involvement of middle RV lateral wall deformation (RV peak systolic SR: −0.78 ± 0.5 vs. −0.82 ± 0.6; Strain (%): −11 ± 4 vs. −16 ± 5 in pulmonary hypertension vs. normal pulmonary pressure, respectively; both p < 0.01).

Reproducibility of DMI measurements

Inter-observer variability was ±1.8% for Em peak velocity (Fig. 3), 3.2±% for SR, ±2.2% for RTm.
In the SSc group, Univariate relations of DMI indexes

Intra-observer variability was similar: ± 1.9% for 

where SSc Controls p Value

Left ventricular lateral wall

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSc</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm peak (m/s)</td>
<td>0.15 ± 0.02</td>
<td>0.16 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Q−Sm (ms)</td>
<td>77.2 ± 10.7</td>
<td>74.7 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>ETm (ms)</td>
<td>259.7 ± 13.2</td>
<td>250 ± 13.5</td>
<td>NS</td>
</tr>
<tr>
<td>Em peak (m/s)</td>
<td>0.18 ± 0.03</td>
<td>0.20 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Am peak (m/s)</td>
<td>0.10 ± 0.02</td>
<td>0.09 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Em/Am ratio</td>
<td>1.9 ± 0.6</td>
<td>2.2 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RTm (ms)</td>
<td>63.4 ± 12.9</td>
<td>59.2 ± 10.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Right ventricular lateral wall

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSc</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm peak (m/s)</td>
<td>0.11 ± 0.03</td>
<td>0.12 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Q−Sm (ms)</td>
<td>89.2 ± 8.9</td>
<td>75.6 ± 8.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ETm (ms)</td>
<td>243 ± 58</td>
<td>240.6 ± 55.3</td>
<td>NS</td>
</tr>
<tr>
<td>Em peak (m/s)</td>
<td>0.13 ± 0.03</td>
<td>0.20 ± 0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Am peak (m/s)</td>
<td>0.14 ± 0.5</td>
<td>0.09 ± 0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Em/Am ratio</td>
<td>0.9 ± 0.38</td>
<td>2.2 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RTm (ms)</td>
<td>42.8 ± 7.8</td>
<td>18.8 ± 6.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Sm = myocardial systolic peak velocity, Q−Sm = myocardial pre-ejection time, ETm = myocardial ejection time, Em = myocardial early diastolic wave, Am = myocardial atrial diastolic wave, RTm = myocardial relaxation time.

Univariate relations of DMI indexes

In the SSc group, Em peak velocity of tricuspid annulus was inversely related to both Rodnan Skin Score and systolic arterial pulmonary pressure. Conversely, RV RTm appeared to be directly related to the same parameters (Figs. 4 and 5). In addition, close associations were observed between the assessment of interstitial pulmonary fibrosis by CT scan and both RV Em (rho = −0.73; p < 0.0005) and RV RTm (rho = 0.69; p < 0.001), while the same RV peak Em was inversely associated to the presence of serological auto-antitopoisomerase pattern (rho = −0.52; p < 0.005).

Multivariate analysis

Stepwise forward, multiple either linear regression or logistic regression analyses were performed in the SSc group to weigh the independent associations between RV myocardial parameters and other clinical or instrumental features of the disease. By these models, after adjusting for potential determinants as age, sex, body surface area, HR, ventricular diameters and pulmonary artery systolic pressure, the independent inverse association of RV peak Em velocity with both Rodnan Skin Score (β coefficient = −0.62, p < 0.0005) and pulmonary artery systolic pressure (β coefficient = −0.71, p < 0.0001), as well as the independent inverse correlation of the same RV peak Em velocity with interstitial pulmonary fibrosis by CT scan and both RV Em (rho = −0.73; p < 0.0005) and RV RTm (rho = 0.69; p < 0.001), while the same RV peak Em was inversely associated to the presence of serological auto-antitopoisomerase pattern (rho = −0.52; p < 0.005).

Table 3 Strain rate and strain analysis of LV and RV lateral free walls

<table>
<thead>
<tr>
<th>Segment</th>
<th>SR (1/s)</th>
<th>Controls</th>
<th>p Value</th>
<th>Strain (%)</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular lateral free wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>−1.4 ± 0.3</td>
<td>−1.8 ± 0.4</td>
<td>&lt;0.05</td>
<td>−15 ± 5</td>
<td>−19 ± 6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Middle</td>
<td>−1.1 ± 0.3</td>
<td>−1.9 ± 0.2</td>
<td>&lt;0.001</td>
<td>−16 ± 4</td>
<td>−24 ± 4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Apical</td>
<td>−1.5 ± 0.4</td>
<td>−1.8 ± 0.3</td>
<td>NS</td>
<td>−22 ± 5</td>
<td>−26 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricular lateral free wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>−0.76 ± 0.3</td>
<td>−2.0 ± 0.4</td>
<td>&lt;0.001</td>
<td>−8.0 ± 5</td>
<td>−19 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Middle</td>
<td>−0.78 ± 0.3</td>
<td>−2.1 ± 0.3</td>
<td>&lt;0.001</td>
<td>−12 ± 4</td>
<td>−25 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apical</td>
<td>−0.81 ± 0.4</td>
<td>−2.2 ± 0.3</td>
<td>&lt;0.001</td>
<td>−14 ± 5</td>
<td>−27 ± 6</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

SR = strain rate.
fibrosis (OR = 0.68; CI: 0.45–0.83; p < 0.0005) and anti-topoisomerase pattern (OR = 0.48; CI: 0.35–0.63; p < 0.001) in SSc patients were confirmed. In addition, pulmonary artery systolic pressure (β coefficient = −0.51, p < 0.001) and pulmonary fibrosis (β = −0.55, p < 0.001) were independent determinants also of peak systolic SR of middle RV lateral wall.

Sensitivity and specificity of standard Doppler and DMI

The sensitivity and specificity of DMI measured $E_m$ peak velocity of tricuspid annulus was determined to compare patients with either diffused or limited cutaneous SSc. A cut-off point of DMI RV $E_m$ peak velocity < 0.11 m/s (ROC curve analyses) well differentiated SSc patients with high Rodnan Skin Score (sensitivity = 89%, specificity = 90%; area under curve: 0.96), interstitial pulmonary fibrosis (sensitivity = 89%, specificity = 92%; area under curve: 0.95) and pulmonary hypertension (sensitivity = 88%, specificity = 82%; area under curve: 0.92). Furthermore, the same cut-off value of RV $E_m$ was able to predict the presence of anti Scl-70 pattern by serological analysis (sensitivity = 78%, specificity = 82%; area under curve: 0.86) (Fig. 6).

Discussion

Cardiac involvement in scleroderma is historically classified into primary and secondary. Primary heart disease depends on the involvement of...
myocardium and microvasculature by SSc disease itself, with impairment of global diastolic function and reduction of coronary flow reserve, even in asymptomatic patients without abnormalities of epicardial coronary arteries.\textsuperscript{10,27} Secondary form of the cardiac disease develops in SSc patients with vascular and/or interstitial lung disease, in which the fibrotic process leads to major reduction in the cross-sectional area of pulmonary vascular bed due to obliteration of alveolar capillaries and/or narrowing of many small arteries.\textsuperscript{28} In both the cases, the pathological hallmark of SSc cardiac impairment is the myocardial fibrosis, which is particularly located in deposits within the interstitium, does not involve the immediate sub-endocardial layer, is equally distributed throughout the right and left ventricle, and is not related to the distribution of the epicardial coronary vessels.\textsuperscript{1–3}

**Myocardial function in SSc**

Although several reports have previously described global diastolic parameters in SSc by standard Doppler echo,\textsuperscript{10,11} myocardial perfusion SPECT\textsuperscript{29} and integrated backscatter,\textsuperscript{30} little is known about DMI and SRI myocardial patterns in such patients.\textsuperscript{4} The present study underscores the usefulness of pulsed DMI and SRI to detect early myocardial dysfunction even in asymptomatic SSc patients without clinically evident cardiac disease and in whom no other cause of either diastolic or systolic

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**Figure 4** Scatter plots of both RV $E_m$ peak velocity and RV $RT_m$ with modified Rodnan Skin Score in the SSc group.

**Figure 5** Scatter plots of both RV $E_m$ peak velocity and RV $RT_m$ with Doppler-measured pulmonary systolic pressure in the SSc group.
impairment was detected. To the best of our knowledge, this is the first attempt to assess myocardial involvement in SSc by both these techniques.

**Pulsed DMI analysis**

Experimental studies have reported that in normal conditions the right ventricle, unlike the left ventricle, begins to eject after a minimal isovolumic systolic contraction time, and starts its diastolic filling without an isovolumic relaxation interval, since it works against lower vascular impedance. However, the present study emphasizes early RV diastolic dysfunction in patients with SSc since significantly lower early diastolic peak velocities and prolonged relaxation time intervals were observed at tricuspid annulus level, despite slightly reduced Doppler measurements. Conversely, LV regional diastolic peak velocities were comparable between the two groups, and only a significant reduction of LV $E_m/A_m$ ratio was observed.

As for regional systolic function, by pulsed DMI SSc patients showed normal both RV and LV systolic peak velocities, while a prolongation of pre-ejection times at the level of tricuspid annulus was evidenced, even after correction for age and HR.

Previous report demonstrated that both systolic and early diastolic regional velocities evaluated by DMI are directly dependent on myocardial structure, characterized by the percent of interstitial fibrosis and the myocardial beta-adrenergic receptor density assessed by endomyocardial biopsy. In particular, in our experience we have already detected by DMI a prolongation of myocardial relaxation times and a reduction of RV myocardial peak velocities in several pathologic conditions involving the right ventricle, in relation to either increasing pulmonary load or RV intrinsic myocardial dysfunction.
Strain rate imaging analysis

Strain rate imaging has been recently developed to measure regional velocity gradients. This has been validated in both phantom and animal studies. Using this method, a spatial map of longitudinal deformation within the myocardium can be obtained, which can be used for a rapid visual evaluation of local myocardial function and to obtain quantitative information. In addition, this technique overcomes several limitations inherent in measuring regional velocity profiles, because it is not influenced by global cardiac displacement and the tethering effects of adjacent segments.

In our SSc population, despite normal TAPSE, LV ejection fraction and DMI systolic peak velocities, a significant reduction of strain and SR indexes at the level of both RV and LV lateral free walls was detected. Even if the reduction of peak systolic strain may be the consequence of change in ventricular afterload or preload, the concomitant reduction of peak SR points out an early impairment also of RV and LV myocardial contractile function in SSc patients, at a time when other global and regional systolic parameters remain normal. Therefore, our findings demonstrate that SRI is a feasible technique that allows evaluation of bi-ventricular regional wall motion in patients with SSc with higher sensitivity than DMI and conventional ultrasound technique.

Relations of myocardial function with skin and pulmonary involvement in SSc

In our population of SSc patients, multivariate analyses provided useful information about associations of DMI and SRI data with other instrumental features of the disease, by adjusting for several confounders, chosen according to the heart physiology. By these models, RV peak $E_m$ velocity was the only independent predictor of Rodnan Skin Score, pulmonary systolic pressure and pulmonary fibrosis, and an RV $E_m$ peak velocity < 0.11 m/s well selected SSc patients with larger skin and pulmonary involvement, with high sensitivity and specificity (Fig. 6). Similarly, pulmonary systolic pressure and pulmonary fibrosis were the only independent determinants of RV peak strain rate. These correlations indicate how the impairment of RV myocardial systolic and diastolic function in SSc occurs simultaneously with the skin involvement and the progressive increase in systolic pulmonary pressure.

Another interesting association found in our SSc population is the one between impaired RV early diastolic function and prevalence of auto-antitopoisoerase pattern. One of the most characteristic serologic features of SSc is the occurrence of autoantibodies against nuclear and nucleolar antigens. Although scleroderma is a heterogeneous disorder in terms of disease symptoms and clinical course, SSc-specific auto-antibody profiles associate strongly with distinct clinical phenotypes, making serologic testing of great diagnostic aid. In particular, antibodies targeting DNA topoisomerase (found in 65% of our SSc patients) have been correlated to diffuse form of the disease, greater lung and skin involvement, pulmonary hypertension, right heart failure and therefore to a worse long-term prognosis.

Therefore, the main impairment of RV both velocity and deformation indexes, as well as the close relationship of RV regional dysfunction with pulmonary hypertension and with a more aggressive auto-antibody subset suggest that cardiac involvement in SSc may be mainly secondary to pulmonary pressure overload, that may determine RV myocyte hypoxia, consequent impairment of intracellular calcium transport and sufferance in diastolic regional relaxation. Of note, in our previous reports we have already assessed by DMI an RV myocardial dysfunction in patients with chronic obstructive lung disease or late after repair of Tetralogy of Fallot.

On the other hand, the concomitant impairment of LV myocardial systolic deformation indexes in our SSc patients, accurately identified only by SRI, could suggest also a direct involvement of LV ventricular walls by the myopathic process. These results are in accordance with several recent reports showing either fixed or reversible LV thallium defects as well as LV small coronary intramyocardial involvement, with reduced flow reserve of left anterior descending coronary artery, even in asymptomatic patients with SSc.

Study limitations

Our study has some limitations. The first one, intrinsic to Doppler technique, is the angle dependence of pulsed DMI and the possible presence of artefacts. However, we used the same angle incidence of transmural Doppler and our DMI reproducibility was good.

We have also to point out that cardiac overall motion in the space influences DMI regional velocities, thus limiting the myocardial heterogeneity evaluation. In our study, however, we performed also SRI analysis which is not influenced by overall
heart motion, rotation and contraction of adjacent myocardial segments.\textsuperscript{40}

Another problem with the SRI technique is the evaluation of apical segments. With SRI, longitudinal systolic shortening at the apex should be subtracted to myocardial thickening at this level: these 2 phenomena, in fact, move in opposite directions. This can potentially affect SR measurement.\textsuperscript{41}

Then, the gold standard techniques devoted to assess diastolic function and pulmonary artery pressure are those based on invasive methods. An assessment of systolic pulmonary arterial pressure by heart catheterization might have been provided more accurate information about RV and right atrial pressures in our patients.\textsuperscript{28} However, a number of studies have pointed out that pulmonary hypertension may be accurately detected by Doppler-measured tricuspid regurgitation.\textsuperscript{9,20}

Next, our SSc population includes a small number of male patients. However, this is in accordance with the general epidemiological features of the disease.\textsuperscript{1} What’s more, the control group was sex-comparable, and excluding 3 male patients from the analysis did not change the results.

Finally, the data of the present study may not be extrapolated to the overall population of SSc because of the exclusion of severe heart failure classes which may have eliminated from statistical analyses patients with advanced systolic impairment. However, we intentionally selected a small group of asymptomatic patients to examine early changes of regional diastolic and systolic properties in scleroderma.

Clinical implications

The present study proposes that pulsed DMI and SRI are valuable non-invasive and easy-repeatable tools for detecting both RV and LV early myocardial involvement in SSc. The relationships of myocardial systolic and diastolic dysfunction with both skin and pulmonary involvement as well as with serological antibodies pattern emphasizes the ability of DMI and SRI to identify patients with more diffused and severe form of SSc.

Further longitudinal studies by DMI and SRI will be needed to follow the progression from early myocardial impairment until the appearance of chamber dysfunction and the development of overt congestive heart failure. This issue may be critical to early identify SSc patients at higher risk of cardiac and pulmonary impairment, ideally in asymptomatic cases prior to the development of severe vasculopathy, when it may be most feasible to modify the disease process by new potential therapies.

Acknowledgements

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References