ORIGINAL ARTICLE

Regional diastolic function by tissue Doppler echocardiography in systemic sclerosis: correlation with clinical variables

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Abstract The incidence of left ventricular (LV) diastolic dysfunction is increased in systemic sclerosis (SSc), while systolic dysfunction is present in a small percentage of patients. The aim of this study was to asses the LV "regional" diastolic abnormalities in SSc patients by the mean of Doppler tissue imaging (DTI). Echocardiographic echo-Doppler (DE) and DTI parameters were analyzed for 67 SSc patients: abnormal E/A ratio at DE was detected in 24, while abnormal *e/a* at DTI was observed in 41. A significant prevalence of DTI diastolic abnormalities in the segments reflecting longitudinal versus those reflecting radial LV motion was found. The segments of the basal regions of LV myocardium were significantly more involved than those of the middle portion. Linear correlation was observed between the extent of the diastolic abnormalities and the duration of disease. Longitudinal myocardial systolic velocities were significantly reduced in patients with abnormal e/a DTI.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease featuring vascular damage, immune activation, and widespread fibrosis of skin and internal organs. Heart involvement is common in SSc patients [1–3] and is one of the main factors shortening survivals [4–6], thus indicating the need of an early diagnosing of cardiac abnormalities.

Several cardiovascular abnormalities (pericardial effusion of various degree, left ventricular (LV) hypertrophy, moderate valvular fibrosis, right ventricular involvement secondary to pulmonary fibrosis and/or pulmonary hypertension) have been reported in SSc patients. However, it has been demonstrated that, while LV systolic dysfunction is present only in a small percentage of SSc patients [7, 8], LV diastolic dysfunction is fairly frequent, thus representing the main feature of the "heart scleroderma". Therefore, an increasing interest has been addressed to the evaluation of the LV diastolic property.

Although it has been supposed [9] that diastolic abnormalities could be secondary to those conditions (systemic and/or pulmonary hypertension, left ventricular hypertrophy, pericardial effusion) that potentially affect LV diastolic function. Almost all the studies have demonstrated that the impaired diastolic function is related to the primary myocardial fibrosis, secondary to both repeated ischemia and immuno-inflammatory damage [10–16]. Particularly, Armstrong [17] reported that LV diastolic alterations can be the unique finding of subclinical myocardial involvement, occurring early as the onset of Raynaud's phenomenon and

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even preceding the eventual and uncommon systolic dysfunction. Fernandes [18], in an endomyocardial biopsy study on SSc patients with no clinical signs or symptoms of heart failure and free from pulmonary or arterial hypertension, LV hypertrophy, and LV systolic dysfunction, demonstrated that an abnormal myocardial collagen deposition occurs in a very high percentage (94%) of patients. In a recent study, performed on 77 SSc patients followed-up for a long time interval, the authors demonstrated that the LV diastolic dysfunction in SSc patients extends progressively and precedes the appearance of LV remodelling [19].

However, in the majority of the previous studies, the diagnosis of left ventricular diastolic dysfunction was made by evaluating the transmitral flow pattern at traditional pulsed Doppler echocardiography (DE). This pattern provides information of global left ventricular dysfunction and is limited by the dependence of the flow velocity of the loading conditions. Doppler tissue echocardiography (DTI) is a recent echocardiographic technique that displays and assesses the velocity of the myocardial structures instead of blood flow, leading to derive measurements of contraction and relaxation velocities directly from the myocardium [20]. Studying myocardial velocities offers the potential for the quantitative regional assessment of both systolic and diastolic function, showing to be more accurate than traditional Doppler echocardiography (DE) in identifying the localization and extension of diastolic and systolic dysfunction.

The current investigation was designed to assess, in our series of SSc patients, the employ of conventional Doppler echocardiography and quantitative DTI of the LV myocardium as diagnostic tools for the detection of early cardiovascular involvement and to evaluate relationships between the detected abnormalities and the epidemiological and clinical features of the disease.

Materials and methods

Patients

The study group consisted of 67 consecutive patients (60 female and 7 male; mean age 52 ± 11 years) with SSc diagnosed according to the American Rheumatism Association (ACR) criteria [21], admitted to the Clinical Immunology and Allergy Unit of Sapienza University of Rome. All SSc patients fulfilled the ACR criteria for SSc and were subsequently divided into a limited (lcSSc) and a diffuse (dcSSc) cutaneous SSc group according to LeRoy [22]. Table 1 lists the main baseline epidemiological and clinical features of the patients. Disease activity in SSc was measured using the Valentini's Scleroderma Disease Activity Score (SDAS). It consists of ten weighted variables: total

Table 1 Epidemiological and clinical features of the study population (*n*:67)

Sex (female/male)	60/7
Age (mean ± SD)	52.5 ± 10.9
Age at disease onset, mean ± SD years	8.3 ± 9
Raynaud's phenomenon duration, mean ± SD years	15 ± 11
Subset[a] (*n*) dcSSc/lcSSc	30/37
ANA pattern *n* (%)	
Speckled	11 (16.5)
Speckled and nucleolar	5 (7.5)
Nucleolar	25 (37)
Centromere	26 (39)
SSc-specific autoantibody *n* (%)	
Anti–topo I	23 (34)
ACA	26 (39)
None	18 (27)
DAI[b]	4.3 ± 2
DSI[c]	1.7 ± 0.5
Disease features, *n* (%)	
Interstitial lung disease	30 (45)
Scleroderma renal crisis	2 (3)
Myositis	5 (7.2)
Raynaud's phenomenon	66 (98)
Gastroesophageal reflux disease	60 (89)
Digital ulcer	38 (57)

dcSSc Diffuse cutaneous SSc, *lcSSc* limited cutaneous SSc, *ANA* antinuclear antibody, *anti–topo I* anti–topoisomerase I, *ACA* anticentromere antibody

[a] Subset according to Le Roy et al. [22]

[b] Disease Activity Index according to Valentini et al. [23]

[c] Disease Severity Index according to Medsger et al. [24]

skin score > 14, scleredema, digital necrosis, arthritis, total lung capacity < 80%, erythrocyte sedimentation rate (ESR) > 30, hypocomplementemia, and change in cardiopulmonary, skin, and vascular symptoms in the past month. The final score ranges from 0 (no activity) to 10 (very active). Disease severity was measured using a modified Medsger Scleroderma Disease Severity Scale (DSS). The original scale assessed disease severity in nine organ systems, namely general health, peripheral vascular, skin, joint/tendon, muscle, gastrointestinal tract, lungs, heart, and kidneys. Each organ is scored separately from 0 to 4 depending on whether there is no, mild, moderate, severe, or end-stage involvement [23, 24].

Patients with LV hypertrophy secondary to mild or moderate systemic arterial hypertension and/or with those conditions, besides SSc, potentially affecting LV diastolic function were excluded. None of the enrolled patients exhibited cardiac symptoms at the time of the echocardiographic evaluation and all were in the sinus rhythm.

Echocardiographic examinations

2-D and Doppler echocardiography

A conventional transthoracic Doppler echocardiographic examination was performed through commercially available equipment (Toshiba Aplio XG), in order to obtain the standard indexes of cardiac anatomy and of LV systolic and diastolic function.

Standard measurements were obtained with the patients examined in the left recumbent position at 35° with the transducer positioned along the left sternal border; Left ventricular ejection fraction (EF), calculated by apical 2- and 4- chamber views (Simpson's rule) was assumed as index of left ventricular systolic pump function and considered abnormal if <50%. Systolic pulmonary arterial pressure (PAPs) was estimated when a tricuspid regurgitation was detected by continuous wave Doppler echocardiogram. PAPs was measured by adding the estimated right atrial pressure (10 mmHg) to the peak systolic pressure gradient across the tricuspid valve (peak regurgitant velocity). Pulmonary hypertension was defined for mean pulmonary artery pressure (PAPm) >25 mmHg; in absence of tricuspid regurgitation, PAPm was considered normal.

The transmitral flow was recorded at the end expiration from the transthoracic 4-chamber view, locating a 0.5 cm pulsed wave Doppler sample volume at a position equidistant between the mitral leaflet tips, at the maximal diastolic excursion point. The following parameters were measured: early diastolic filling peak velocity (*E*), late diastolic filling peak velocity (*A*), *E/A* ratio (*E/A*). Isovolumic relaxation period (IRP) was also evaluated, as time interval elapsing from aortic valve closure to the beginning of the transmitral flow at Doppler echocardiography. An abnormal left ventricular diastolic filling was defined by the presence of an inverted *E/A* ratio (<1) at the transmitral echoDoppler flow profile.

Doppler tissue imaging

Doppler tissue imaging (DTI) was extracted and optimized to improve maximal colour codification of the left ventricular myocardium [20]. Regional myocardial velocity profiles were obtained in pulsed Doppler format, which measures the instantaneous peak velocities from the myocardium, with a pulsed Doppler sample volume of 6–8 mm. For the purpose of segmental analysis of contraction and relaxation, the left ventricle was divided into 12-segment model (Fig. 1): longitudinal myocardial velocities were assumed by sampling by DTI the left ventricular walls in the apical 2 (anterior and inferior walls) and 4 (septal and lateral walls) chamber views; radial myocardial velocities were explored in parasternal long-axis (antero-septal and posterior walls) view. For each segment two levels have been sampled by pulsed wave TDI, i.e. basal and mid level, positioning the sample volume in the center of the segment, equidistant between the endocardial and epicardial borders. We exclude apex from analysis, being in the near field of the echo transducer, with consequent suboptimal image quality and remaining effectively fixed during systolic shortening and diastolic lengthening along the longitudinal axis.

For each myocardial segment, a frozen image of the DTI signals from three consecutive beats was obtained at the end of the data acquisition sequence for off-line data analysis: systolic peak velocity (*s*), regional early diastolic peak velocity (*e*), regional late diastolic peak velocity (*a*), regional *e/a* velocity ratio (*e/a*) were calculated as mean value of the three consecutive measurements.

A DTI low *e*-wave velocity and *a* DTI inverse *e/a* ratio are both sensitive signs of fibrosis; of these two indexes we have preferred to use the *e/a* ratio which is not influenced by the Doppler limitation of angle and thus offers the advantage of being expressed in an adimensional relationship to myocardial velocities [20].

All the echocardiographic parameters were independently calculated by two different experienced observers,
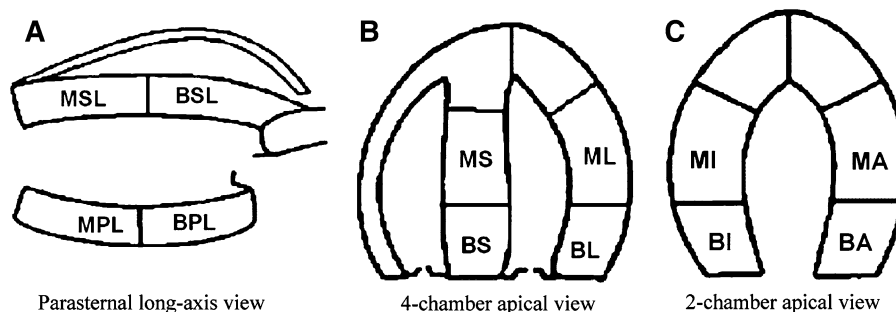

Fig. 1 Left ventricle myocardial segments assessed by Tissue Doppler Echocardiography. *BA* basal anterior, *BI* basal inferior, *BL* basal lateral, *BPL* basal posterior longitudinal, *BS* basal septum, *BSL* basal septum longitudinal, *MA* mid anterior, *MI* mid inferior, *ML* mid lateral, *MPL* mid posterior longitudinal, *MS* mid septum, *MSL* mid septum longitudinal

blinded to clinical information: data reported were the mean of the two independent measurements.

Reproducibility

Intraobserver mean absolute variability of the DTI measurements was 0.1 ± 0.08 for s, 0.1 ± 0.09 for e and 0.2 ± 0.09 for a waves. Interobserver mean absolute variability was 0.3 ± 0.06 cm/s for systolic velocities; 0.2 ± 0.05 cm/s for e and 0.2 ± 0.06 cm/s for a waves.

Statistical analysis

All results are expressed as mean ± standard deviation. Analysis was done for all the 67 patients. Differences in continuous variables were evaluated by one-way ANOVA. Chi-square test was used for categorical variables. Linear regression analysis was employed to determine the role of all the examined variables on the number of DTI abnormalities. P value less than 0.05 was considered significant.

Results

The mean values of the echocardiographic parameters were all within ranges of normality (Table 2). However, in analyzing the individual data, a slight impairment of LVEF was observed in two patients (EF: 48 and 46%, respectively).

Pericardial effusion was detected in 4/67 patients (6%); trivial separation between pericardial layers in other 9/67 patients (13%); fibrosis of cardiac valves, leading to mild valvular incompetence, in 3/67 patients (4%) and pulmonary hypertension in 23/67 patients (34%).

Table 2 Echocardiographic and conventional echoDoppler parameters of the 67 SSc patients

RR (msec)	839.6 ± 100.4
LA (mm)	34.2 ± 5.8
LVIDd (mm)	46.5 ± 3.2
LVIDs (mm)	28.2 ± 3.8
EF (%)	58.3 ± 2.4
IVS (mm)	9.3 ± 1.5
PW (mm)	9.2 ± 1.8
E (cm/sec)	68.5 ± 18.1
A (cm/sec)	61.0 ± 18.2
E/A	1.2 ± 0.49
IRP (msec)	87 ± 11.5

RR interval R–R, *LA* left atrial internal diameter, *LVIDd* left ventricular internal diameter in diastole, *LVIDs* left ventricular internal diameter in systole, *EF* ejection fraction; *IVS* interventricular septum, *PW* posterior wall; *E* peak flow velocity at early diastole, *A* peak flow velocity at late diastole, *E/A E/A* ratio, *IRP* isovolumic relaxation period

At conventional DE we found an inverted transmitral flow pattern (E/A < 1) in the 36% of patients (24/67), while at DTI an inverted *e/a* (<1) was detected in an higher (61%) percentage of patients (41/67). Particularly, eight patients showed an inverted *e/a* ratio in a single segment of the left ventricle, 17 patients in 2 segments, 13 patients in 3 segments and 3 patients in more than 3 segments.

A total number of 492 segments was evaluated in these 41 patients (328 reflecting LV longitudinal and 164 LV radial myocardial velocities): an inverted *e/a* ratio was found in 91 (18%) of these 492 segments, with a significant ($P < 0.001$) prevalence in the segments reflecting the longitudinal (78/328) rather than the radial myocardial velocities (13/164).

It is worth noting that the segments of the basal regions (66/91) were significantly ($P < 0.0001$) more involved than those of the middle portion (25/91). In addition, in patients with a lesser extent of DTI diastolic abnormalities (i.e. 1 or 2 segments), the basal lateral wall was involved in more than 50% of the cases (Table 3).

When we examined the 67 SSc patients considered as a whole, we did not found any correlation between the presence of an inverted *e/a* ratio at DTI and the epidemiological or clinical findings (age, disease duration, onset of Raynaud's phenomenon, SSc subset, score disease index and heart rate) as well as the echocardiographic parameters.

However, stratifying the 67 patients in two subgroups according to the presence ($n = 41$) or absence ($n = 26$) of inverted DTI *e/a* ratio, we found in the 41 patients with diastolic dysfunction a linear correlation between the extent of the diastolic abnormalities (expressed by the number of LV segments with inverted e/a ratio) and both the duration of the SSc disease ($t = 2.21$; $P = 0.04$) and left atrial diameter ($t = 2.25$; $P = 0.038$).

As regards the regional systolic function, the measured systolic velocities were all in the normal reference range [25]. However, stratifying the 67 patients in two subgroups according to the presence ($n = 41$) or absence ($n = 26$) of inverted DTI *e/a* ratio too (Table 4), the systolic velocities reflecting longitudinal (but not the radial) LV myocardial motion were significantly lower in the subgroup of patients with inverted regional e/a ratio.

Discussion

Systemic sclerosis is a multisystem disorder characterized by connective tissue fibrosis of skin and internal organs. As expected, in the present study, the prevalence of pericardial effusion, pulmonary hypertension, and fibrosis of the cardiac valves, commonly found in SSc patients, was very close to that previously reported [1–3, 7–11, 13, 15].

Table 3 DTI parameters of the 67 SSc patients

			e/a ratio < 1	e/a ratio > 1
SSc Patients (n = 67)			41 (61%)	26 (39%)
	1 segment	8 (12%)		
	2 segments	17 (25%)		
	3 segments	13 (19%)		
	> 3 segments	3 (4%)		
Segments reflecting the longitudinal velocities (n = 328)			78 (23%)	250 (77%)
Segments reflecting the radial velocities (n = 164)			13 (8%)	151 (92%)
Segments of the basal regions (n = 246)			66 (27%)	180 (73%)
Segments of the middle portion (n = 246)			25 (10%)	221 (90%)

Table 4 Comparison of DTI peak systolic longitudinal velocities in the two subgroups of patients with (n = 41) an without (n = 18) inverted DTI e/a ratio

	Overall (n = 67)	e/a < 1 (n = 41)	e/a > 1 (n = 18)	P
BS (cm/s)	8.0 ± 1.7	7.7 ± 1.6	8.6 ± 1.7	0.07
BL (cm/s)	9.2 ± 2.1	8.8 ± 2.0	10.1 ± 1.9	0.03
MS (cm/s)	6.7 ± 1.6	6.5 ± 1.6	7.2 ± 1.7	0.10
ML (cm/s)	7.7 ± 1.8	7.4 ± 1.8	8.4 ± 1.8	0.04
BI (cm/s)	7.6 ± 1.6	7.2 ± 1.5	8.3 ± 1.6	0.002
MI (cm/s)	6.3 ± 1.5	5.9 ± 1.4	7.1 ± 1.4	0.008
BA (cm/s)	8.8 ± 2.0	8.4 ± 1.9	9.7 ± 1.9	0.02
MA (cm/s)	7.2 ± 1.8	6.9 ± 1.7	8.0 ± 1.7	0.02

BS basal septum, *BL* basal lateral, *MS* mid septum, *ML* mid lateral, *BI* basal inferior, *MI* mid inferior, *BA* basal anterior, *MA* mid anterior
Significatively is referred to the comparison between the subgroups. *P* value less than 0.05 was considered significant

As regards LV diastolic function, even if the myocardial fibrosis has been indicated as the pathological hallmark of myocardial disease in SSc [1, 14], a substantial discrepancy has been noted between the prevalence (81%) of the myocardial fibrosis at autopsy and the prevalence (30–40%) of diastolic dysfunction, as evaluated by conventional Doppler echocardiography [9, 10, 14, 18].

In the present study the prevalence of an inverted *E/A* ratio at conventional Doppler was similar (36%) to that observed by others authors [9, 10, 14, 18] who have utilized traditional pulsed Doppler echocardiography too. Conversely, when we employed DTI, we found a considerably higher incidence (61%) of the regional diastolic abnormalities, more close to that reported in autopsy studies. This finding suggests that the DTI is more reliable in the early detecting the cardiac damage in SSc than conventional DE [26–28], which provides only an indirect and hampered by pre-load dependency assessment of global LV diastolic function. Moreover, SSc myocardial fibrosis is known to be patchy distributed in both ventricles, this accounting for the rational of the employ of a peculiar tool, as DTI, able to perform a regional quantitative analysis. The better overall accuracy of DTI had been already reported by Coucelo [29], who examined by DTI a large number of LV segments and demonstrated a good correlation between the

extent of the damage of the myocardial texture and the absolute value of the regional systolic and diastolic velocities. These results were further supported by Di Bello [30] who employed videodensitometry in a selected population of SSc patients with normal LV systolic function, demonstrating a significant reduction of the cyclic variation index amplitude, strongly related to myocardial fibrosis.

As it has been reported in previous studies, in SSc patients the appearance of the cardiac involvement is probably independent from disease's severity, subsets and antibody profile.

In our 41 patients with diastolic abnormalities at DTI, we found a good correlation between the extent of the myocardial involvement (expressed by the number of the segments with inverted *e/a* ratio) and the duration of the disease, this suggesting that in SSc patients, the appearance of the cardiac involvement, although independent from disease's severity, subsets and antibody profile, once it occurs, become progressive, mainly affecting the diastolic properties of relaxation in an increasing number of left ventricular myocardial segments. A linear correlation was also found between the extent of segment with inverted *e/a* ratio at DTI and the left atrial internal dimension, this confirming the results of an our previous (2005) longitudinal study, performed by conventional DE in a series of SSc patients,

in some of them a progressive LV filling dysfunction was observed at the end of the follow-up, with a significant increase of the left atrial diameter.

Physiological LV fibers orientation of the normal hearts is complex: in fact, in the subendo-and subepicardial layer the principal fibers orientation is longitudinal, while in the mid-myocardial layer the fibers are mostly oriented in the circumferential direction**. I**n our SSc patients we found a prevalence of regional diastolic dysfunction in the segments reflecting longitudinal motion (23%) respect to those reflecting radial motion (8%). Also Plazak [16], employing DTI in a small group of SSc patents and in a matched control group, showed a significant decrease of the early diastolic myocardial velocity in SSc respect to controls and found that this feature was present only at the level of the longitudinal fibers. Since both contraction and relaxation of the left ventricle are mainly caused by subendocandial fibers in the longitudinal axis and by the radially oriented fibers in the short axis, the subendocardial layer seems to be firstly involved in SSc cardiomyopathy. It can be supposed that the subendocardial regions of the left ventricular myocardium are more sensitive to the peculiar aspects of the ischemic damage in SSc, characterized by an impairment of the microcirculation, including vasospasm.

In our SSc patients, observing the distribution of the segments with regional diastolic abnormalities along the plane base-apex, we found a significant reduction in the velocities of the basal ($n = 66$) rather than of the middle ($n = 25$) LV segments, with a prevalence in the patients showing DTI inverted e/a ratio in one or two segments only. This finding suggests that probably the myocardial damage firstly involves the basal segments of the left ventricle and then extends to the other portions. It has been demonstrated that substantial heterogeneity of velocities exists within individual myocardial segments, being in normal subjects regional contraction and relaxation velocities more vigorous at the basal level than in the other regions [31, 32]. It is difficult to explain the early impairment of relaxation in the basal segments of the left ventricle in our patients, since previous necropsy studies in scleroderma hearts have not reported a peculiar prevalence of anatomic alterations. SSc myocardial fibrosis is known to be patchy distributed throughout the right and left ventricle, is not related to the distribution of the epicardial coronary vessels and is associated with a normal wall thickness. However, these istological findings arise from autopsy studies of SSc patients who were affected by cardiomyopathy of advanced degree and thus showing a more severe and diffuse anatomic damage.

LV systolic function (EF at DE) was found normal in all except two the examined patients, this confirming that LV function is generally well preserved in SSc patients [6, 7, 17]. In the subgroup of 41 patients with "regional" diastolic alterations, the "systolic" longitudinal velocities were significantly reduced respect to those of patients without DTI abnormalities.

Abnormalities of "regional" systolic left ventricular longitudinal function in SSc patients have already been reported [33, 34]. Our study seems to demonstrate that regional systolic and diastolic impairment coexists and that both early affects the subendocardial fibres of the myocardium, longitudinally oriented.

DTI may early identify those SSc patients in the preclinical stage, prone to develop a diastolic dysfunction, in order to early start a specific medical treatment and to delay the progression of the myocardial damage.

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