Measurement of interatrial dyssynchrony using tissue Doppler imaging predicts functional capacity and cardiac involvement in systemic sclerosis

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ABSTRACT

Objective. We aimed to assess the prevalence of interatrial electromechanical dyssynchrony in systemic sclerosis (SSc) patients, and to study the correlation between interatrial delay and standard follow-up parameters.

Methods. Forty consecutive patients with SSc were studied. Classical echocardiographic measurements were obtained, including indices of left ventricular (LV) systolic and diastolic function, right ventricular function, and pulmonary artery pressure (PAP). Left atrial (LA) function was studied using volume measurements. The interatrial mechanical (IAMD) delay was obtained by measuring the time delay between the peak atrial velocities at the lateral tricuspid and mitral annuli using tissue Doppler imaging. A cut-off value of 35 ms was chosen to define the presence of a significant interatrial delay. The IAMD was compared to NYHA class, six-minute walking test (6MWT), NT proBNP levels, and the carbon monoxide diffusion capacity over alveolar volume ratio (DLCO/VA), as well as to classical echocardiographic parameters.

Results. Forty percent of patients were found to have significant interatrial dyssynchrony with an IAMD of 35 ms or more. Patients with interatrial dyssynchrony were more symptomatic, had a shorter 6MWT, higher NT proBNP levels, and a lower DLCO/VA compared with those without dyssynchrony. Regarding conventional echocardiographic parameters, increased IAMD was associated with more pronounced LV diastolic dysfunction, LA enlargement and dysfunction, altered RV function, and higher PAP.

Conclusion. IAMD correlated with all of the standard follow-up parameters in SSc, and is probably a sensitive marker of LA involvement. This easy to measure parameter should be added to the routine echocardiographic assessment of these patients.

Introduction

Heart involvement is common in systemic sclerosis (SSc), and is one of the leading causes of mortality in this disease. It may remain undiagnosed for a long time while clinically silent. However, the occurrence of overt clinical symptoms is associated with a poor prognosis (1, 2). Early detection is therefore a clinical challenge.

SSc may involve all structures of the heart, including the myocardium, pericardium, valves, and conduction tissue. Myocardial involvement and pulmonary hypertension are among the most serious complications of the disease, and are systematically sought during routine echocardiographic follow-up of SSc patients: left ventricular systolic and diastolic functions, right ventricular dimensions and systolic function, and systolic pulmonary artery pressure may be easily and non-invasively studied using conventional and modern ultrasound modalities. Involvement of the atria has been yet poorly evaluated. A few studies have established that atrial conduction abnormalities are common in SSc, and result in prolonged interatrial electro-mechanical delays (3-5).

In this study, we aimed to assess the prevalence of interatrial electromechanical dyssynchrony in SSc patients using tissue Doppler imaging, and at studying the correlation between interatrial delay and standard follow-up parameters, including exercise capacity, natriuretic peptides, and other echocardiographic parameters of heart involvement.

Material and methods

All consecutive patients with systemic sclerosis were studied over a 6-month period. Patients with atrial fibrillation...
or with a paced atrial rhythm, and those unable to walk, were excluded.

Clinical data were collected, including age, gender, body surface area (BSA), SSc cutaneous subtype, age at diagnosis, and disease duration. Systemic involvement was noted as follows: pulmonary involvement was considered present if the patient had significant interstitial lung disease needing specific immunosuppressive therapy, renal involvement if a scleroderma renal crisis had occurred, and digestive involvement if the patient had either gastro-oesophageal reflux, dysphagia, or malabsorption.

ECG tracings were obtained to measure P-wave duration.

Blood sample were drawn to assess creatinin and Nt proBNP levels.

Functional status was assessed using NYHA classification and 6-minute walking test (6MWT). The 6MWT was performed by a physician blinded to the echocardiographic results.

Pulmonary function tests were performed with the study of carbon monoxide diffusion capacity (DLCO) and the DLCO over alveolar volume ratio (DLCO/VA).

Echocardiographic study

All the echocardiographic examinations were performed by the same cardiologist. A commercially available echocardiography system (IE 33; Philips Medical Systems, Andover, MA, USA) was used with an 5-1 transducer.

Left ventricular mass (LVM) was derived from M-mode measurements according to the recommendations of the American Society of Echocardiography (6).

Left ventricular ejection fraction was measured using the biplane Simpson method. Left ventricular diastolic function was assessed using conventional and tissue Doppler; mitral peak early (E) and peak late (A) velocities, deceleration time of E, mitral E/A ratio were obtained using tissue Doppler. Pulmonary pressures (PAP) were estimated by the pulmonary acceleration time using pulse-wave Doppler at the pulmonary valve, and systolic PAP was calculated by the measurement of the tricuspid regurgitant velocity obtained by continuous wave Doppler.

Left atrial diameter was measured using M-mode. Left atrial volumes were assessed using the Simpson’s method from the apical 4-chamber view: 1) the maximal LA volume (Vmax) or end systolic volume was measured just before the opening of the mitral valve; 2) the pre-atrial contraction LA volume (VpreA) was measured at the onset of P-wave on the ECG; 3) the minimal LA volume (Vmin) or end diastolic volume was measured at the closure of the mitral valve. For the assessment of the LA function three indicators derived from volumes were used: LA expansion index (LA EI) = (Vmax - Vmin) / Vmin x 100; LA passive emptying fraction (LA PEF) = (Vmax - VpreA) / Vmax x 100; and LA active emptying fraction (LA AEF) = (VpreA - Vmin) / VpreA x 100.

The interatrial electromechanical delay (IAMD) was assessed by measuring the time difference between the peak atrial velocities at the lateral tricuspid and mitral annuli using tissue Doppler imaging (Fig. 1). There are very few studies available in the literature that have assessed IAMD in patients with systemic sclerosis: Mizuno et al. used M-mode echocardiography to compare the motion of the right and left ativoventricular rings, and reported a mean IAMD of 37±15 ms in SSc patients versus 25±6 ms in controls (3); Karaahmet et al., using tissue Doppler, found similar results with an IAMD of 32.2±9.2 in SSc patients and of 24.7±9.7 ms in controls (7). Therefore, a cut-off value of 35 ms was chosen in our study to define the presence of significant interatrial delay.

Statistical analysis

Categorical variables were described using percentages. Continuous variables were expressed as means and standard deviations.

Comparisons between the two groups (IAMD with a cut-off value of 35 ms)
were made using Fisher’s exact test for categorical variables and an analysis of variance (ANOVA) for continuous variables. The underlying assumptions of ANOVA (normally distributed populations with equal variances or ‘homo-
scedasticity’) were checked using Bart-
tlett’s test. Linear regression with a robust variance estimator was used to test the relationship between continuous variables. This model was also used in case of violation of the assumptions of ANOVA, with the use of a categorical regressor (dummy coded variable). Linearity was checked using fractional polynomials. All analyses were performed using Stata software version 12 (Stata corporation, College Station, TX, USA). A p-value <0.05 was considered significant.

Results
Forty patients meeting the selection criteria were studied. General characteristics are displayed in Table I. The mean age was 61±15, 87% of them were females. Thirty-two patients had the limited cutaneous subtype compared to 8 with the diffuse subtype; 28% of patients had pulmonary involvement, 61% had gastro-intestinal involvement, 7% had kidney involvement. Most of them were asymptomatic, 12% were in functional class II, 15% in class III, and 1 patient was in class IV. In this population, 40% of patients were found to have significant interatrial dyssynchrony with an interatrial delay of 35 ms or more.

Using the cut-off value of 35 ms for interatrial delay, patients were split into 2 groups. Patients with interatrial dys-
synchrony were significantly older, and were more frequently hypertensive, whereas there was no influence of the scleroderma subtype (Table II). Using age-adjusted analysis (Table III), patients with interatrial dyssynchrony were in higher functional class, had a shorter 6-minute walking distance, and higher NT proBNP levels compared with those without dyssynchrony. Pulmonary involvement was found in 66% of patients with dyssynchrony versus 6% in those without dyssynchrony, and the diffusion capacity for carbon mon-

### Table I.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>40</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.7 ± 15.5</td>
</tr>
<tr>
<td>Sex ratio F/M</td>
<td>35/5</td>
</tr>
<tr>
<td>SSc subtype</td>
<td>limited: 32</td>
</tr>
<tr>
<td></td>
<td>diffuse: 8</td>
</tr>
<tr>
<td>Serology</td>
<td>Anti-Scl70: 12</td>
</tr>
<tr>
<td></td>
<td>Anticentromere: 17</td>
</tr>
<tr>
<td></td>
<td>ANA: 10</td>
</tr>
<tr>
<td></td>
<td>Anti-RNP: 2</td>
</tr>
<tr>
<td>Systemic involvement</td>
<td>Pulmonary: 28%</td>
</tr>
<tr>
<td></td>
<td>Gastro-intestinal: 61%</td>
</tr>
<tr>
<td></td>
<td>Renal: 7%</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I: 70%</td>
</tr>
<tr>
<td></td>
<td>II: 12%</td>
</tr>
<tr>
<td></td>
<td>III: 15%</td>
</tr>
<tr>
<td></td>
<td>IV: 4%</td>
</tr>
<tr>
<td>Interatrial dyssynchrony (IAMD &gt; 35 ms)</td>
<td>16/40 (40%)</td>
</tr>
</tbody>
</table>

General characteristics of the study population. SSc: systemic sclerosis. IAMD: interatrial mechanical delay.

### Table II.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IAMD &lt;35 ms</th>
<th>IAMD ≥35 ms</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>n=24</td>
<td>n=16</td>
<td></td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>23/2</td>
<td>12/3</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.2 ± 15.3</td>
<td>69.7 ± 11.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>13.3 ± 13.2</td>
<td>8.9 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>42.5 ± 15.9</td>
<td>60.8 ± 13.7</td>
<td>0.0019</td>
</tr>
<tr>
<td>SSc subtype (L/D)</td>
<td>20/4</td>
<td>12/4</td>
<td>NS</td>
</tr>
<tr>
<td>Serology (anti-Scl70 / anticitromere)</td>
<td>35% / 41%</td>
<td>42% / 17%</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>54%</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity</td>
<td>6%</td>
<td>9%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Comparative clinical data in patients without and with interatrial dyssynchrony. IAMD: interatrial mechanical delay; SSc: systemic sclerosis; D: diffuse; L: limited.

### Table III.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IAMD &lt;35 ms</th>
<th>IAMD ≥35 ms</th>
<th>p-value (age-adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>1.06 ± 0.24</td>
<td>2.42 ± 1</td>
<td>0.00001</td>
</tr>
<tr>
<td>6’ walking distance (m)</td>
<td>395.8 ± 46.6</td>
<td>236.1 ± 121.6</td>
<td>0.00003</td>
</tr>
<tr>
<td>NT proBNP (pg/ml)</td>
<td>123.6 ± 168.9</td>
<td>1121.7 ± 1800.2</td>
<td>0.049</td>
</tr>
<tr>
<td>Pulmonary involvement (%)</td>
<td>5.8</td>
<td>66.6</td>
<td>0.002</td>
</tr>
<tr>
<td>DLCO/VA (%)</td>
<td>85.7 ± 10.5</td>
<td>57.7 ± 17.6</td>
<td>0.0003</td>
</tr>
<tr>
<td>Renal involvement (%)</td>
<td>0</td>
<td>13</td>
<td>0.10</td>
</tr>
<tr>
<td>Serum creatinin (mmol/l)</td>
<td>70 ± 16</td>
<td>118 ± 38</td>
<td>0.0002</td>
</tr>
<tr>
<td>Digestive involvement (%)</td>
<td>47</td>
<td>83</td>
<td>0.07</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>84 ± 11.8</td>
<td>109.2 ± 19.3</td>
<td>0.00031</td>
</tr>
<tr>
<td>IAMD (ms)</td>
<td>7.3 ± 9.7</td>
<td>55.7 ± 24</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


Carbon monoxide was significantly lower (DLCO/VA 57.7±17.6% vs. 85.7±10.5%, p=0.0003). Serum creatinin level was significantly higher, and this could ac-

count partly for the elevated NT proBNP.

We found a good negative correlation between the interatrial delay and the
distance walked in 6 minutes (Fig. 2). Regarding quantification of the interatrial delay, ECG analysis logically demonstrated a longer P-wave duration in patients with interatrial mechanical dyssynchrony (109.2±19.3 vs 84±11.8 ms, p=0.00031). The mean interatrial delay measured by tissue Doppler was 56 ms ± 24 in the dyssynchrony group versus 7±9.7 in the other group (p<0.0001).

**Echocardiographic results** (Table IV)

Regarding left ventricular parameters, there was no intergroup difference in terms of left ventricular dimension and systolic function. Left ventricular mass, although in the normal range, was significantly higher in patients with atrial dyssynchrony. Unlike systolic function, diastolic function was significantly altered in dyssynchronous patients, with an E/A ratio significantly lower, and an E/E’ ratio significantly higher.

Regarding left atrial parameters, patients with atrial dyssynchrony had increased left atrial diameter and volumes, and decreased reservoir and conduit functions.

Regarding right heart assessment, interatrial mechanical delay was associated with a significantly lower TAPSE, a shorter pulmonary acceleration time, and higher pulmonary artery pressures.

**Patient outcome**

During a 1-year follow-up, 3 patients died (2 from sepsis, 1 sudden death) and 2 had at least 2 unscheduled hospitalizations for heart failure. All of them were in the dyssynchrony group, with a severely increased mean interatrial delay of 72 ms.

**Discussion**

In this study, we found that the interatrial mechanical delay obtained by TDI is a quick and simple measurement that appears correlated to all standard indices of heart involvement, including classical Doppler echocardiographic measurements, natriuretic peptides, diffusion capacity for carbon monoxide, and 6-minute walking distance. This relatively unexpected finding may have a rather univocal and consistent explanation.

Primary myocardial disease in SSc, i.e. without systemic or pulmonary hypertension and without significant pulmonary or renal disease, is postulated to be due to microvascular injury that progress silently to myocardial fibrosis (1). Myocardial fibrosis can affect both ventricles and can lead to systolic and diastolic dysfunction (8), or may involve the conduction tissue (9, 10). It may also involve atrial tissue and its conduction system (3). Symptoms may manifest without warning and can rapidly lead to arrhythmia and left and right heart dysfunction and failure. Standard recommended follow-up investigations in SSc include 6-minute walking tests, pulmonary function tests with the measurement of DLCO/VA, blood natriuretic peptides measurements, and echocardiography. The 6MWT has been increasingly used as an outcome measure in clinical trials for SSc. Although it lacks specificity, because it reflects the individual combination and severity of cardiac, pulmonary, or other organ involvements, it is easily performed and highly repro-
ducible in SSc patients (11). Both lung diffusion carbon monoxide capacity and NT-pro-BNP levels can be used to identify SSc patients at high risk of the development of pulmonary arterial hypertension (12). NT-pro-BNP correlates with pulmonary arterial pressure and correlates inversely with left ventricular contractility, and detects accurately patients with overall cardiac involvement (13, 14). Importantly, all these markers reflect a least partly the occurrence of pulmonary hypertension, which is often potentially post-capillary in SSc (15).

Doppler-echocardiography is the cornerstone of routine cardiac assessment in SSc, given its availability and its broad spectrum of functional parameters. Left ventricular systolic function may be assessed by measuring LVEF, but the use of tissue Doppler and 2-D strain modalities greatly improves sensitivity in detecting subtle changes in myocardial contractility (16-18). Diastolic function is affected earlier in the course of SSc and may also be studied by conventional and tissue Doppler. Depending on the method used, the prevalence of diastolic dysfunction ranges from 17 to 30% (8, 17, 19). The use of tissue Doppler and the E/E’ ratio rather than the E/A ratio increases sensitivity to detect LV diastolic dysfunction in asymptomatic SSc patients (20).

Right ventricular involvement may be either primary, or secondary to pulmonary hypertension. Right ventricular function may be assessed using simple parameters, including the tricuspid annulus plane systolic excursion (TAPSE) obtained by M-mode (21), or the tricuspid annulus systolic velocity measured by tissue Doppler. 2D-strain modality applied to the right ventricle has recently emerged as a promising tool for the early detection of right ventricular dysfunction and for the prediction of mortality (22).

Left atrium is a less studied heart chamber. However, left atrial volume has been shown to be an independent predictor of pulmonary hypertension in SSc patients (23). Aktoz et al. demonstrated that left atrial mechanical function, particularly LA passive emptying fraction, was impaired in asymptomatic scleroderma patients (5). Left atrial enlargement and dysfunction may be the consequence of left ventricular diastolic dysfunction, as the LA volume has been compared to the “glycated haemoglobin” of left ventricular filling pressures (24). However, in SSc, LA tissue may be primarily involved by the collagen deposition process, with 2 major consequences: increased stiffness, and prolonged intra-atrial conduction time.

In 1997, Mizuno et al. compared mechanical phenomena at the right lateral, septal and left lateral sites of the atrioventricular rings using M-mode echocardiography, and demonstrated that intra-atrial electromechanical coupling intervals were delayed in patients with progressive systemic sclerosis, with a mean interatrial delay of 37±15 ms vs. 25±6 ms in healthy controls (3). Using ultrasonic tissue characterisation, they also found that interatrial electromechanical conduction time correlated well with atrial tissue damage (25). In 2006, Can et al. measured atrial electromechanical delays between P-wave on ECG and A’-wave at the tricuspid and mitral annuli using tissue Doppler, and showed that interatrial conduction time was delayed in patients with scleroderma compared with controls; this mechanical delay was correlated to the P-wave duration on ECG (4). More recently, Karaahmet et al. reported similar results, with increased electrocardiographic P-wave dispersion, and a mean interatrial electromechanical delay of 32.2±9.2 ms in asymptomatic SSc patients vs. 24.7±9.7 in healthy controls; they suggested that the evaluation of atrial dyssynchrony using tissue Doppler echocardiography could be useful for the detection of subclinical cardiac involvement in SSc patients with normal conventional echocardiographic findings (7).

Our results have shown that interatrial dyssynchrony is common in systemic sclerosis: using a cut-off value of 35 ms for the IAMD measured by tissue Doppler, 40% of patients were found to have dyssynchrony, with a mean IAMD of 55.7±24 ms compared to 7.3±9.7 ms in the other group. Although this delay may be due to a specific involvement of the Bachmann’s bundle (26), in our opinion it is rather a marker of left atrial fibrosis. This left atrial involvement could have important haemodynamic consequences, due to impaired left atrial compliance and increased stiffness which account for increased filling pressures, post-capillary pulmonary hypertension, and decreased exercise capacity.

Interatrial block has been shown to be associated with left atrial enlargement and dysfunction (27-29), and with an increased risk of atrial arrhythmias (30, 31). Importantly, left atrial size and compliance are powerful predictors of exercise capacity and correlate to pulmonary artery pressure in various heart diseases, including hypertrophic cardiomyopathy (32), mitral stenosis (33, 34), and diastolic dysfunction (35, 36).

Our group has recently established that atrial dyssynchrony could be one pathological explanation for heart failure with preserved ejection fraction: patients with severe interatrial dysynchrony have delayed and shortened left atrial emptying, decreased LA reservoir function, and severe post-capillary pulmonary hypertension due to increased LA stiffness (37).

Therefore, we could postulate the following paradigm: atrial involvement by the fibrosing process of SSc translates into decreased LA compliance, increased left ventricular filling pressures, post-capillary pulmonary hypertension, right ventricular dysfunction, increased natriuretic peptides, decreased DLCO/VA, and decreased exercise capacities. Although we cannot exclude a role of systemic hypertension, which was more prevalent in our patients with atrial dysynchrony, we believe that interatrial electromechanical delay is most probably a marker of atrial fibrosis and may summarise all the echocardiographic and functional indices of heart involvement in SSc.

Conclusion
Measurement of the interatrial mechanical delay using tissue Doppler imaging is quick and simple to do, and should be added to the routine echocardiographic evaluation of scleroderma patients. Despite limitations due to the small number of patients, our study indicates that this parameter is correlated...
Interatrial dyssynchrony in systemic sclerosis / J.-C. Eicher et al.

Interatrial dyssynchrony may be a sensitive marker of heart involvement, and even more of multisystemic involvement. It may have intrinsic haemodynamic consequences if the delayed left atrial emptying is compromised by the closing mitral valve. Finally, this parameter may have a prognostic value which deserves further investigation.

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