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

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Received on May 3, 2014; accepted in revised form on July 7, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 86): S171-S176.

Key words: systemic sclerosis, Doppler echocardiography, cardiac involvement, heart atria

Competing interests: none declared.

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 S5-1 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 pulse-wave Doppler at the mitral valve in the apical 4-chamber view; tissue Doppler was used to measure the early diastolic myocardial velocity (E') at the septal and lateral mitral annulus; the E/E' ratio was obtained using the average of septal and lateral e' velocities.

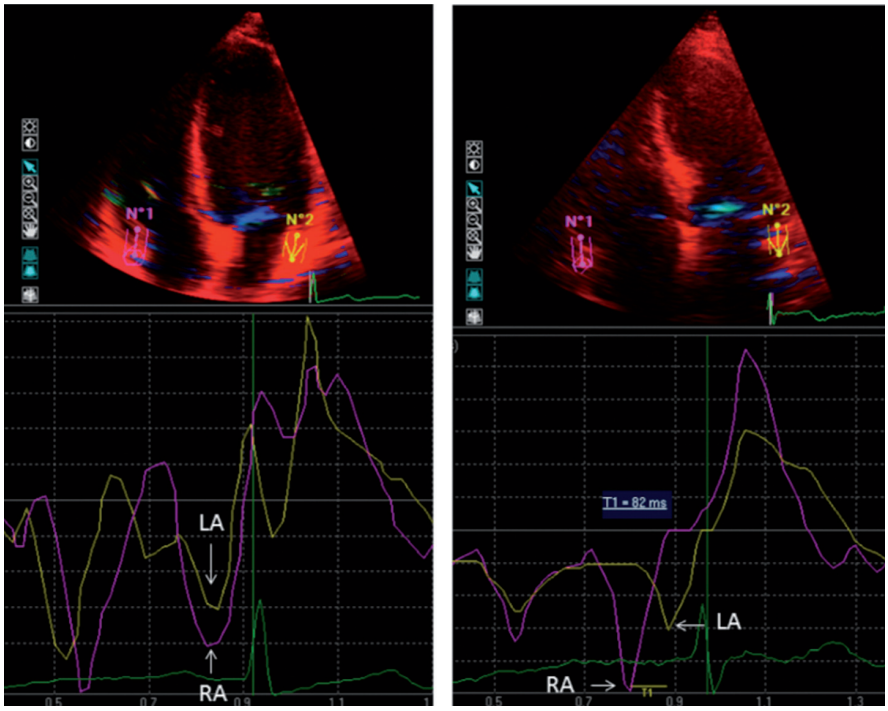

Fig. 1. Two examples of interatrial mechanical delay (IAMD) measurement using tissue Doppler imaging. IAMD is the time delay between peak velocities of right (RA) and left atrium (LA).
Left: patient without delay, with synchronous RA and LA. Right: patient with a severe IAMD of 82 ms.

Right ventricular function was evaluated by the measurement of the tricuspid annulus plane systolic excursion (TAPSE) using M mode imaging of the lateral tricuspid annulus, and by the assessment of the tricuspid annulus velocity using tissue Doppler. Pulmonary artery 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 atrioventricular 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 'homoscedasticity') were checked using Bartlett'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 dyssynchrony 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 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 account partly for the elevated NT proBNP.

We found a good negative correlation between the interatrial delay and the

Table I.

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

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

Table II.

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

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

Table III.

Parameters	IAMD <35 ms	IAMD ≥35 ms	*p*-value (age-adjusted)
NYHA class	1.06 ± 0,24	2.42 ± 1	0.00001
6' walking distance (m)	395.8 ± 46.6	236.1 ± 121.6	0.00003
NT proBNP (pg/ml)	123.6 ± 168,9	1121.7 ± 1800.2	0.049
Pulmonary involvement (%)	5.8	66.6	0.002
DLCO/VA (%)	85.7 ± 10.5	57.7 ± 17.6	0.0003
Renal involvement (%)	0	13	0.10
Serum creatinin (mmol/l)	70 ± 16	118 ± 38	0.0002
Digestive involvement (%)	47	83	0.07
P-wave duration (ms)	84 ± 11.8	109.2 ± 19.3	0.00031
IAMD (ms)	7.3 ± 9.7	55.7 ± 24	<0.0001

Functional parameters, systemic involvement and atrial dyssynchrony. Age adjusted comparative data. DLCO/VA: carbon monoxide diffusion capacity over alveolar volume ratio. IAMD: interatrial mechanical delay.

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 dyssynchronic 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.

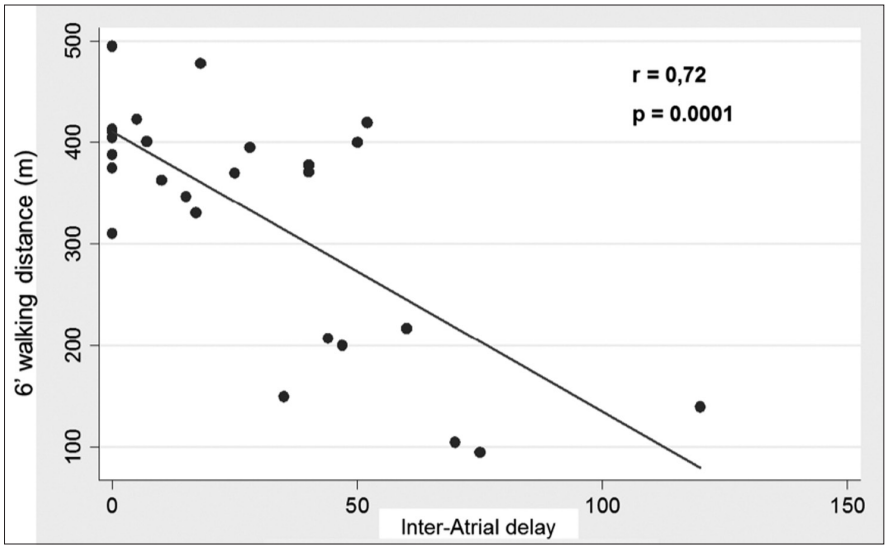

Fig. 2. correlation between 6-minute walking distance and interatrial delay.

Table IV.

Echocardiographic parameters	IAMD <35 ms	IAMD ≥35 ms	*p*-value (age adjusted)
LV end diastolic diameter (mm)	48.5 ± 3.9	50.2 ± 7.4	NS
LV ejection fraction (%)	66.5 ± 6.3	70 ± 10.1	NS
LV mass (g/m²)	82.5 ± 19.9	107.1 ± 21.7	0.0073
E-wave velocity	80.4 ± 17	85.2 ± 22.2	NS
A-wave velocity	68.6 ± 17.8	105.4 ± 18.3	0.00001
E/A ratio	1.26 ± 0.45	0.82 ± 0.23	0.0043
E deceleration time	182.9 ± 32.4	205.5 ± 49.9	NS
E/e' ratio	8.2 ± 1.7	12.8 ± 4.2	0.00032
LA diameter (mm)	36 ± 4.9	44.1 ± 7.4	0.0017
LA end-systolic volume (ml)	43.5 ± 17.3	68.9 ± 25.2	0.0046
LA expansion index (%)	194 ± 93	138 ± 49	NS
LA passive emptying fraction (%)	38.2 ± 13.5	27.7 ± 9.8	0.0370
LA ejection fraction (%)	37.2 ± 12.6	38.6 ± 8	NS
RV diameter (mm)	18.2 ± 4.1	20.6 ± 5.6	NS
TAPSE (mm)	23.7 ± 3.5	19.9 ± 3.7	0.009
Tricuspid annulus S velocity (cm/s)	12.8 ± 2	13.8 ± 1.4	NS
Pulmonary acceleration time (ms)	140.7 ± 13.5	92.7 ± 18.2	<0.0001
Systolic PAP (mmHg)	26.2 ± 6.1	46 ± 17.2	0.00016

Echocardiographic results. Age adjusted comparative data. LA: left atrial; LV: left ventricular; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion.

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 independant 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 pathophysiological explanation for heart failure with preserved ejection fraction: patients with severe interatrial dyssynchrony 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 dyssynchrony, we believe that interatrial electromechanical delay is most probably a marker of atrial fibrosis and may summarize 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

to all standard follow-up parameters, including left ventricular diastolic function, left atrial function, right ventricular function, pulmonary pressures, 6' walking distance, Nt proBNP level and carbon monoxide diffusion capacity. We believe that 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.

References

1. KAHAN A, COGHLAN G, MCLAUGHLIN V: Cardiac complications of systemic sclerosis. *Rheumatology* 2009; 48 (Suppl. 3): iii45-8.
2. MEUNE C, VIGNAUX O, KAHAN A, ALLANORE Y: Heart involvement in systemic sclerosis. Evolving concepts and diagnostic methodologies. *Arch Cardiovasc Dis* 2010; 103: 46-52.
3. MIZUNO R, FUJIMOTO S, NAKANO H *et al*.: Atrial conduction abnormalities in patients with systemic progressive sclerosis. *Eur Heart J* 1997; 18: 1995-2001.
4. CAN I, MESUT ONAT A, AYTEMIR K *et al*.: Assessment of atrial conduction in patients with scleroderma by Tissue Doppler Echocardiography and P wave dispersion. *Cardiology* 2007; 108: 317-21.
5. AKTOZ M, YILMAZTEPE M, TATLI E, NESRIN TURAN F, ÜMIT EG, ALTUN A: Assessment of ventricular and left atrial mechanical functions, atrial electromechanical delay and P wave dispersion in patients with scleroderma. *Cardiol J* 2011; 18: 261-9.
6. SAHN DJ, DEMARIA A, KISSLO J, WEYMAN A: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072-83.
7. KARAAHMET T, TIGEN K, GUREL E *et al*.: Impact of systemic sclerosis on electromechanical characteristics of the heart. *Heart Vessels* 2010; 25: 223-8.
8. HINCHCLIFF M, DESAI CS, VARGA J, SHAH SJ: Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. *Clin Exp Rheum* 2012; 30 (Suppl. 71): S30-S37.
9. SEFEROVIĆ PM, RISTIĆ AD, MAKSIMOVIĆ R *et al*.: Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. *Rheumatology* 2006; 45: iv39-42.
10. GIALAFOS E, KONSTANTOPOULO P, VOULGARI C *et al*.: Abnormal spatial QRS-T angle, a marker of ventricular repolarisation, predicts serious ventricular arrhythmia in systemic sclerosis. *Clin Exp Rheumatol* 2012; 30: 327-31.
11. DEUSCHLE K, WEINERT K, BECKER M, BACKHAUS M, HUSCHER D, RIEMEKASTEN G: Six–minute walk distance as a marker for disability and complaints in patients with systemic sclerosis. *Clin Exp Rheum* 2011; 29 (Suppl. 65): S53-9.
12. ALLANORE Y, BORDERIE D, AVOUAC J *et al*.: High N-terminal probrain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum* 2008; 58: 284-91.
13. ALLANORE Y, WAHBI K, BORDERIE D *et al*.: N-terminal brain natriuretic peptide in systemic sclerosis: a new cornerstone of cardiovascular assessment? *Ann Rheum Dis* 2009; 68: 1885-9.
14. CHIGHIZOLA C, MERONI PL, SHREIBER BE, COGHLAN JG, DENTON CP, ONG VH: Role of N-terminal pro-brain natriuretic peptide in detecting significant cardiac involvement in systemic sclerosis patients. *Clin Exp Rheumatol* 2012; 30 (Suppl. 71): S81-S85.
15. COGHLAN JG, SCHRIEBER B: An update on the evaluation and management of pulmonary hypertension in scleroderma. *Curr Rheumatol Rep* 2012; 14: 1-10.
16. MEUNE C, ALLANORE Y, PASCAL O *et al*.: Myocardial contractility is early affected in systemic sclerosis: a tissue Doppler echocardiographic study. *Eur J Echocardiogr* 2005; 6: 351-7.
17. MEUNE C, AVOUAC J, WAHBI K *et al*.: Cardiac involvement in systemic sclerosis assessed by tissue Doppler echocardiography during routine care: A controlled study of 100 consecutive patients. *Arthritis Rheum* 2008; 58: 1803-9.
18. YIU KH, SCHOUFFOER AA, MARSAN NA *et al*.: Left ventricular dysfunction assessed by speckle tracking strain analysis in patients with systemic sclerosis: relationship to functional capacity and ventricular arrhythmias. *Arthritis Rheum* 2001; 63: 3969-78.
19. DE GROOTE P, GRESSIN V, HACHULLA E *et al*.: Evaluation of cardiac abnormalities by Doppler echocardiography in a large national multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 31-6.
20. LEE SW, CHOI EY, JUNG SY, CHOI ST, LEE SK, PARK YB: E/E' ratio is more sensitive than E/A ratio for detection of left ventricular diastolic dysfunction in patients with systemic sclerosis. *Clin Exp Rheumatol* 2010; 28 (Suppl. 58): S12-17.
21. MATHAI SC, SIBLEY CT, FORFIA PR *et al*.: Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. *J Rheumatol* 2001; 38: 2410-8.
22. MATIAS C, ISLA LP, VASCONCELOS M *et al*.: Speckle-tracking-derived strain and strain-rate analysis: a technique for the evaluation of early alterations in right ventricle function in patients with systemic sclerosis and normal pulmonary artery pressure. *J Cardiovasc Med* 2009; 10: 129-34.
23. DIMITROULAS T, GIANNAKOULAS G, PAPADOPOULOU K *et al*.: Left atrial volume and N-terminal pro-B type natriuretic peptide are associated with elevated pulmonary artery pressure in patients with systemic sclerosis. *Clin Rheumatol* 2010; 29: 957-64.
24. ABHAYARATNA WP, SEWARD JB, APPLETON CP *et al*.: Left atrial size. Physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006; 47: 2357-63.
25. MIZUNO R, FUJIMOTO S, NAKANO H *et al*.: *Cardiology* 1999; 91: 134-9.
26. ARIYARAJAH V, SPODICK DH: The Bachmann bundle and interatrial conduction. *Cardiol Rev* 2006; 14: 194-9.
27. SPODICK DH: Effects of interatrial block on left atrial function. *J Cardiol* 2001; 38: 169-71.
28. ARIYARAJAH V, MERCADO K, APIYASAWAT S, PURI P, SPODICK DH: Correlation of left atrial size with P-wave duration in interatrial block. *Chest* 2005; 128: 2615-8.
29. GOYAL SB, SPODICK DH: Electromechanical dysfunction of the left atrium associated with interatrial block. *Am Heart J* 2001; 142: 823-7.
30. LEIER CV, MEACHAM JA, SCHAAL SF: Prolonged atrial conduction. A major predisposing factor for the development of atrial flutter. *Circulation* 1978; 57: 213-6.
31. AGARWAL YK, ARONOW WS, LEVY JA, SPODICK DH: Association of interatrial block with development of atrial fibrillation. *Am J Cardiol* 2003; 91: 882.
32. SAURA D, MARTIN F, CLIMENT V *et al*.: Left atrial remodelling in hypertrophic cardiomyopathy: relation with exercise capacity and biochemical markers of tissue strain and remodelling. *Int J Clin Pract* 2009; 63: 1465-71.
33. PARK S, HA JW, KO YG *et al*.: Magnitude of left atrial V wave is the determinant of exercise capacity in patients with mitral stenosis. *Am J Cardiol* 2004; 94: 243-5.
34. HA JW, CHUNG N, JANG Y *et al*.: Is the left atrial V wave the determinant of peak pulmonary artery pressure in patients with pure mitral stenosis? *Am J Cardiol* 2000; 85: 986-91.
35. WONG RC, YEO TC: Left atrial volume is an independent predictor of exercise capacity in patients with isolated left ventricular diastolic dysfunction. *Int J Cardiol* 2010; 144: 425-7.
36. KURT M, WANG, JW, TORRE-AMIONE G, NAGUEH SF: Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009; 2: 10-5.
37. EICHER JC, LAURENT G, MATHÉ A *et al*.: Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of 'diastolic' heart failure. *Eur J Heart Fail* 2012; 14: 248-58.