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Concise report

Early detection of ventricular dysfunction in juvenile systemic sclerosis by speckle tracking echocardiography

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Abstract

Objective. Cardiac involvement is the most important cause of mortality in juvenile systemic sclerosis (JSSc). Recent reports in adult patients underline that traditional techniques of imaging are inadequate to assess the subclinical cardiac involvement, while speckle tracking echocardiography (STE) is able to identify ventricular dysfunctions in the early stages. The aim of our study was to assess the role of STE in JSSc.

Methods. Demographic, clinical and laboratory data were collected from patients with JSSc. Cardiac investigations performed at baseline (T0) and 18 (T18) and 36 months (T36) follow-up included electrocardiography, conventional echocardiography with measurement of the ejection fraction (EF) and STE with assessment of left and right ventricular global longitudinal strain (LV-GLS and RV-GLS). Cardiac parameters have been compared with demographic characteristics and disease severity, assessed by the Juvenile Systemic Sclerosis Severity Score (J4S).

Results. A total of 18 patients, 12 (67%) females, entered the study. At T0, electrocardiography was abnormal in three patients, EF was reduced in one, LV-GLS was abnormal in three (16.7%) and RV-GLS was abnormal in five (27.8%). At T18, EF remained stable while at T36 the result decreased in seven of nine patients. At the same time, LV-GLS also worsened (from −21.6% to −18.2%, $P = 0.01$). LV-GLS and RV-GLS at baseline showed a significant correlation with J4S ($P = 0.012$ and $P = 0.02$, respectively).

Conclusion. STE is more sensitive than standard echocardiography to identify cardiac involvement in JSSc. Over time, we observed a gradual worsening of LV-GLS, a sign of left ventricular dysfunction, that anticipated by several months the decrease of EF.

Key words: scleroderma, juvenile systemic sclerosis, outcome measures, heart, severity score

CLINICAL SCIENCE

Rheumatology key messages

- Cardiac involvement is an important and underdiagnosed cause of mortality in juvenile systemic sclerosis (JSSc).
- Standard echocardiography is often inadequate to assess the subclinical cardiac involvement in paediatric patients.
- Speckle tracking echocardiography is a reliable technique for early detection of subclinical cardiac abnormalities in JSSc.

Introduction

Cardiac complications in juvenile systemic sclerosis (JSSc) can be either primary or secondary to pulmonary arterial hypertension [1]. Clinically evident cardiac involvement in JSSc is reported with a frequency ranging between 5 and 24% [2]; nevertheless, it is the leading cause of morbidity and mortality in JSSc [3].

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While clinically evident myocardial involvement in JSSc seems to have a late onset, histological studies in adult patients show that cardiac abnormalities occur early and are often underdiagnosed [4]. Newer diagnostic techniques are therefore required in order to allow preclinical identification and early treatment of ventricular dysfunction.

Global longitudinal strain (GLS), derived from speckle tracking echocardiography (STE), evaluates myocardial fibre deformation. GLS was reduced in adult SSc patients even though the left ventricular ejection fraction (LVEF), measured by conventional echocardiography (cEcho), was still preserved [5]. It has also been shown that, during a 2 year follow-up, left ventricular GLS (LV-GLS) significantly decreased, with LVEF still preserved [6]. This clearly suggests that cEcho is less appropriate to document subclinical myocardial involvement in SSc.

The aim of our study was to assess whether, in patients with JSSc, STE can identify ventricular dysfunctions more effectively and earlier than traditional echocardiography. Furthermore, we wanted to investigate whether, during the disease course, cardiac involvement was correlated with the global disease severity, measured by the Juvenile Systemic Sclerosis Severity Score (J4S) [7].

Methods

Study population

Unselected consecutive patients with JSSc diagnosed according with the Paediatric Rheumatology European Society/EULAR/ACR criteria [8] were retrospectively evaluated. For every patient we collected demographic, clinical and laboratory data, autoantibody profile and treatment. At each visit the J4S score was calculated in order to quantify the overall disease severity. As part of the J4S, the following clinical instrumental parameters were considered: skin involvement by the modified Rodnan skin score, RP and/or digital lesions, chest X-ray, high-resolution CT (HRCT), diffusing capacity for carbon monoxide, forced vital capacity, musculoskeletal involvement, oesophageal scintiscan or 24 h pH-metry, malabsorption test and glomerular filtration rate. Consent was obtained from the patients and their parents.

Cardiac investigations

Cardiac investigations included at-rest electrocardiography (EKG) and cEcho, performed according with the minimal data set suggested by the British Society of Echocardiography [9]. STE with assessment of LV-GLS and right ventricular GLS (RV-GLS), by analysing two-dimensional images with semiautomatic software Automated Function Imaging (AFI) was also performed. Values were expressed as a negative percentage, as they represent the shortening of a region of interest compared with its original length. An absolute value $<-19\%$ for LV-GLS and $<-25\%$ for RV-GLS were considered pathological [10]. All echocardiographic images were acquired by the same paediatric cardiologist and STE was technically feasible in all patients.

Combined rheumatologic and cardiac assessments were performed at baseline (T0) and after 18 (T18) and 36 (T36) months.

Statistical analysis

The association between categorical variables was investigated with the χ^2 test or Fisher's exact test while the correlation between most relevant variables was investigated with Spearman's test. Wilcoxon's test was used for comparison of the paired observations and the Mann–Whitney test was used for unpaired data. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 18.0 (IBM, Armonk, NY, USA).

Results

Eighteen consecutive Caucasian patients entered the study; 12 (67%) were females. Three patients (17%) suffered from lcSSc and the remainder had dcSSc. The clinical characteristics of the patients and autoantibody profiles are summarized in Table 1.

Baseline assessment

The mean age of the patients who entered the study was 12.3 years (range 4.7–19.3), with a mean disease duration at the first STE assessment of 4.9 years (range 1–12.6). The mean severity of the disease, measured by J4S score, was 6.9 (range 3–11). A total of 16 patients had cutaneous involvement with a mean mRSS of 10.4 (range 0–30), 11 patients had RP, 15 had gastrointestinal involvement and 10 had musculoskeletal symptoms. As for respiratory involvement, nine patients showed functional abnormalities and/or pathological HRCT findings.

Treatments at baseline included DMARDs [13 (72.2%; MTX 7, MMF 6, rituximab 1)], vasoactive drugs [12 (66%)], anti-arrhythmics [2 (11%)] and proton pump inhibitors [12 (66%)].

Four patients had clinically evident cardiac involvement such as non-sustained ventricular tachycardia with ectopic beats, sustained ventricular tachycardia requiring an implanted cardiac device (ICD), pericarditis and ventricular ectopic beats, pulmonary arterial hypertension with right ventricular hypertrophy and arrhythmia.

EKG showed abnormalities in three patients (right ventricular hypertrophy; inferior repolarization abnormalities; abnormal V1–V4 R-wave progression, with low-voltage R-waves).

Standard echocardiography showed normal ejection fraction (EF) in 17/18 patients [mean 66.7% (range 53.8–73.9)]. Two of the four patients with a clinical history of cardiac involvement had pathological Yu index values (Table 2).

Table 1 Clinical characteristics of the patients at baseline

Characteristics	Values
Sex, female:male, *n*:*n*	12:6
Age, years, mean (S.D., range)	12.3 (4.2, 4.7–19.3)
Age at onset, years, mean (S.D., range)	7.8 (3.1, 3.5–13.5)
Disease duration, years, mean (S.D., range)	4.9 (3.7, 1–12.6)
Subtype, diffuse:limited, *n*:*n*	15:3
Autoantibody profile	
ANA	18 (100)
Anti-topoisomerase I (Scl70)	4 (22.2)
Anti-centromere (ACA)	1 (5.6)
Anti-polymyositis-scleroderma (PM-Scl)	2 (11.1)
J4S, mean (S.D., range)	6.9 (2.3, 3–11)
mRSS, mean (S.D., range)	10.4 (9.0, 0–30)
Internal organ involvement, *n* (%)	
RP	11 (61.1)
Respiratory	9 (50.0)
Gastrointestinal	15 (83.3)
Musculoskeletal	10 (55.6)

Table 2 Standard and STE parameters at baseline and during follow-up

Parameters		T0		T18		T36	
		Mean	Range	Mean	Range	Mean	Range
STANDARD	EF-2D, %	66.7	53.8–74	69.1	50–77.1	62.2	39–71
	E, cm/s	91.5	60–115	95.3	81–116	98.1	76–115
	A, cm/s	50.6	32–77	56.6	38–107	53.6	42–74
	E/A	1.9	1–3.1	1.9	0.9–2.6	1.9	1.3–2.6
	E′, cm/s	16.6	11–19	15.2	11–19.2	13.7	8–17.5
	E/E′	5.6	3.8–9.4	6.5	4.9–8.5	7.5	4.9–13.6
STE	LV-GLS, %	−21.7	−16.9/−25	−20.5	−13.7/−23	−18.2	−11.3/−22
	RV-GLS, %	−28.7	−16/−37.3	−29.2	−20.3/−35	−27.2	−15/−36.7

EF-2D: ejection fraction calculated by the Simpson's formula; E: early mitral ventricular filling velocity; A: late mitral ventricular filling velocity; E′: mitral annular early diastolic velocity.

The LV-GLS at baseline had a mean value of −21.7% (S.D. 2.3; range −16.9 to −25), with three patients having an LV-GLS >−19%. All of them suffered from diffuse cutaneous JSSc, but only one had a reduced EF and LV-GLS (53.8% and −16.9%, respectively) and a history of cardiac involvement. The other two patients never had cardiac symptoms, although one showed repolarization abnormalities on an EKG.

As for treatment, none of the patients with abnormal LV-GLS were previously treated with calcium channel blockers (CCBs), while all of those taking CCBs during the follow-up had normal LV-GLS ($P = 0.001$). The mean J4S value of the three patients with abnormal LV-GLS was 9.6, 2.7 points greater than the mean value of all the other patients. A significant correlation between J4S and LV-GLS was found ($R = 0.595$; $P = 0.012$) (Supplementary Fig. S1, available at *Rheumatology* online).

The mean longitudinal strain of the right ventricle (RV-GLS) was −28.7% (S.D. 5.4; range −16 to −37.3) and was abnormal in five patients. In three of the patients, LV-GLS was also reduced, with significant correlation between the two ($R = 0.693$; $P = 0.002$).

No correlation was found between cardiac involvement and other parameters such as sex, age at onset, disease duration, J4S at disease onset, BMI, mRSS and autoantibody profile.

Assessment at 18 months

Nine patients, eight with dcSSc, underwent a cardiac re-evaluation 18 months after the baseline assessment. The cutaneous involvement was significantly decreased as compared with baseline (mRSS from 11.3 to 8.3, $P = 0.03$) and the mean J4S was also slightly decreased,

although not significantly. Conventional EKG in one patient showed an abnormal R-progression from V1 to V4. The mean EF value was 69.1%, slightly increased from the baseline ($P = 0.03$; Table 2). LV-GLS and RV-GLS were unchanged.

Assessment at 36 months

Nine patients underwent cardiac re-evaluation 36 months after the baseline assessment. Six of the patients had already been evaluated at T18, while for three patients, who lived far away from our centre, this was the first re-evaluation after baseline. At T36, the mean J4S value of was 5.8, slightly decreased from the baseline, as was the cutaneous involvement ($P = 0.04$). The LVEF decreased in 7/9 patients, with the mean value (62.2%) slightly decreased, although not significantly, from the baseline ($P = 0.09$). The mean LV-GLS value was −18.2%, significantly worse than baseline (−21.6%, $P = 0.01$). Furthermore, in six patients the LV-GLS decreased >10% and in one it decreased between 5 and 10%. EF decreased by 6.7% from the baseline while LV-GLS decreased by 16.1% (Supplementary Fig. S2, available at *Rheumatology* online). The RV-GLS also showed an overall mild deterioration, decreasing from −28.6 to −27.2% ($P = 0.8$).

Finally, a negative correlation between J4S and LV-GLS at T0–T36 was found, as patients with a greater worsening of J4S presented a greater decrease in LV-GLS ($R = -0.78$; $P = 0.023$).

No significant correlation between LV-GLS progression and other clinical variables, such as non-cardiac organ involvement or age at disease onset, was found.

Discussion

Myocardial damage in patients with SSc is more frequent than clinically suspected [6] and, being a leading cause of death in JSSc [3, 4], it is crucial to find new techniques for its early detection. In adult patients with SSc, EF was found within the normal range for a long time after the diagnosis [11]. Conversely, by using STE for strain analysis, it was possible to detect myocardial abnormalities early in a preclinical stage, much earlier than the reduction of LVEF [11–13].

The results of our study are similar to those reported in adult SSc. At baseline, only one patient (5.5%) had a reduced LVEF, although five (27.8%) had abnormal myocardial contractility, measured by STE, in the right and/or left ventricle. The only patient with reduced LVEF also had a reduced LV-GLS, while the other patients had just mild EKG alterations, such as repolarization abnormalities or signs of ventricle hypertrophy. In general, combining clinical signs and symptoms of myocardial dysfunction with cEcho and EKG, we were able to detect cardiac involvement in 22.2% of the patients, a frequency quite close to what is reported in adults [2]. By adding STE, we almost doubled this (38.8%), confirming that STE is much more sensitive to detect subtle cardiac abnormalities early in JSSc.

As for the cardiac involvement over time, our study shows that at the 18 month follow-up, LVEF remained relatively stable, while at 36 months it slightly decreased, although with a pathological value only in the patient in whom it was already reduced at baseline.

In the same period of time, LV-GLS significantly worsened (from −21.6% to −18.2%; $P = 0.01$). A similar study in adult patients also showed that while EF remained stable during a 2 year follow-up period, LV-GLS underwent a significant reduction [8]. These results further confirm that LV-GLS is more appropriate than traditional LVEF measurement to study the cardiac involvement in JSSc.

A possible explanation for this discrepancy may be related to the fact that compensatory mechanisms, coming from ventricular remodelling and the increased activity of meso- and subepicardial fibres, allow preservation of the LVEF, even in cases of reduced subendocardial function. Conversely, as coronary microvascular dysfunction of SSc mainly affects the subendocardial layers, which are more sensitive to ischaemia, LV-GLS, mirroring the subendocardial fibers' state, allows identification of cardiac involvement in earlier stages of the disease [14].

Similar results have also been reported in paediatric patients treated with myocardiotoxic drugs for leukaemia [15, 16]. While LVEF often remains normal, LV-GLS reveals signs of cardiotoxicity earlier. Indeed, a retrospective study showed that in JSSc patients both longitudinal circumferential STE and LVEF were impaired while the right ventricular strain was inversely correlated with skin involvement [17].

As for the role of treatment, we observed that, at baseline, none of the patients with pathological LV-GLS was using CCBs while, conversely, all those taking CCBs had normal longitudinal STE. These results are consistent with another recent study showing a protective role of CCBs on the myocardium [17].

Both LV-GLS and RV-GLS at baseline showed a significant correlation with disease severity measured by the J4S. This underlines the nature of JSSc as a systemic condition in which organ damage develops, especially in the diffuse subtype. Of interest, this correlation was less strong during the follow-up observation, as J4S improved while LV-GLS underwent a general worsening. This discrepancy might be due to immunosuppressive therapy, which is likely effective for organs other than the heart.

In general, the pathogenesis of JSSc and cardiac damage is still controversial [18]. Most likely, ischaemia due to microvascular changes and concomitant chronic inflammation result in two different patterns of tissue fibrosis: replacement fibrosis and interstitial/perivascular fibrosis [19, 20]. Our study seems to support the first mechanism more, as STE is more sensitive to subendocardial ischaemia while the reduction of EF is more related to the combined process.

Our study has some limitations. STE was not performed at disease onset in every patient because ours, being an Italian referral centre, often admits patients previously followed by peripheral hospitals where STE is not available. Indeed, the number of patients completing the follow-up assessment was half of the initial one. Nevertheless, we decided to describe these preliminary data as a proof-of-concept study in order to promote and stimulate larger studies on this topic in the future.

In conclusion, STE is more sensitive than cEcho to evaluate the cardiac involvement in patients with JSSc. Over time, we observed a gradual worsening of LV-GLS, a sign of a progressive left ventricular dysfunction, that anticipated by several months a decrease in the EF.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Zulian F. Scleroderma in children. Best Pract Res Clin Rheumatol 2017;31:576–95.

2 Martini G, Foeldvari I, Russo R *et al*. Systemic sclerosis in childhood: clinical and immunologic features of 153 patients in an international database. Arthritis Rheum 2006;54:3971–8.

3 Martini G, Vittadello F, Kasapçopur Ö *et al*. Factors affecting survival in juvenile systemic sclerosis. Rheumatology 2009;48:119–22.

4 Champion HC. The heart in scleroderma. Rheum Dis Clin North Am 2008;34:181–90.

5 Spethmann S, Dreger H, Schattke S *et al*. Two-dimensional speckle tracking of the left ventricle in patients with systemic sclerosis for an early detection of myocardial involvement. Eur Heart J Cardiovasc Imaging 2012;13:863–70.

6 Spethmann S, Rieper K, Riemekasten G *et al*. Echocardiographic follow-up of patients with systemic sclerosis by 2D speckle tracking echocardiography of the left ventricle. Cardiovasc Ultrasound 2014;12:13.

7 La Torre F, Martini G, Russo R *et al*. A preliminary disease severity score for juvenile systemic sclerosis. Arthritis Rheum 2012;64:4143–50.

8 Zulian F, Woo P, Athreya BH *et al*. The Pediatric Rheumatology European Society/American College of Rheumatology/European League Against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum 2007;57:203–12.

9 Wharton G, Steeds R, Allen J *et al*. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo Res Pract 2015;2:G9–G24.

10 Castaldi B, Baldini L, Di Salvo G *et al*. New echocardiographic techniques in congenital heart disease. In: G Santoro, G Pacileo, MG Russo, eds. New insight in pediatric cardiology: from basic to therapeutics. Sarjah, UAE: Bentham Books, 2013: 87–122.

11 Cusmà Piccione M, Zito C, Bagnato G *et al*. Role of 2D strain in the early identification of left ventricular dysfunction and in the risk stratification of systemic sclerosis patients. Cardiovasc Ultrasound 2013;11:6.

12 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 2011;63:3969–78.

13 Guerra F, Stronati G, Fischietti C *et al*. Global longitudinal strain measured by speckle tracking identifies subclinical heart involvement in patients with systemic sclerosis. Eur J Prev Cardiol 2018;25:1598–606.

14 Hsiao J-F, Chung C-M, Chu C-M *et al*. Two-dimensional speckle tracking echocardiography predict left ventricular remodeling after acute myocardial infarction in patients with preserved ejection fraction. PLoS One 2016;11:e0168109.

15 Yu AF, Raikhelkar J, Zabor EC *et al*. Two-dimensional speckle tracking echocardiography detects subclinical left ventricular systolic dysfunction among adult survivors of childhood, adolescent, and young adult cancer. Biomed Res Int 2016;2016:9363951.

16 Poterucha JT, Kutty S, Lindquist RK, Li L, Eidem BW. Changes in left ventricular longitudinal strain with anthracycline chemotherapy in adolescents precede subsequent decreased left ventricular ejection fraction. J Am Soc Echocardiogr 2012;25:733–40.

17 Dedeoglu R, Adroviç A, Oztunç F *et al*. New insights into cardiac involvement in juvenile scleroderma: a three-dimensional echocardiographic assessment unveils subclinical ventricle dysfunction. Pediatr Cardiol 2017;38:1686–95.

18 Stevens AM, Torok KS, Li SC *et al*. Immunopathogenesis of juvenile systemic sclerosis. Front Immunol 2019;10:1352.

19 Pieroni M, De Santis M, Zizzo G *et al*. Recognizing and treating myocarditis in recent-onset systemic sclerosis heart disease: potential utility of immunosuppressive therapy in cardiac damage progression. Semin Arthritis Rheum 2014;43:526–35.

20 Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest 2007;117: 557–67.