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Journal of Autoimmunity & Research

Research Article

Electrocardiographic and Echocardiographic findings and their Relationships in Patients with Systemic Sclerosis

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Submitted: 24 February 2017

Accepted: 13 March 2017

Published: 14 March 2017

Keywords

- Transthoracic echocardiography
- Systemic scleroderma
- Diastolic dysfunction
- Electrocardiography

Abstract

Objectives: Evaluate electrocardiographic and echocardiographic data in asymptomatic patients affected by Systemic Sclerosis (SSc) compared to healthy subjects, to assess their correlations in a case-control study.

Methods: 71 female patients affected by SSc (Group A) were compared to 60 healthy female subjects (Group B). Both patients and controls were evaluated by electrocardiogram and trans-thoracic echocardiogram.

Results: Patients with the systemic form of disease (dcSSc) showed a longer QT-corrected (QTc) interval (440.58 ± 18.23 msec vs. 427.64 ± 23.12 msec; p = 0.021). The percentage of patients with increased QTc and QTc dispersion (QTcd) values was higher in Group A than in Group B (31.14% vs 14.03%, p = 0.03; 36.06% vs. 1.75%, p <0.001). Left ventricular mass index (LVMI) was higher in group A (80.50 ± 20.59 g/m2 vs. 61.54 ± 11.08 g/m2 ; p<0.0001). Left ventricular ejection fraction (LVEF) was higher in control subjects (63.55 ± 6.58 % vs. 68.42 ± 5.99 %, p <0.001).Left ventricular diastolic dysfunction (LVDD) was more prevalent in group A (70.5% vs. 29.82%, p= 0.001). In Group A, QTc prolongation was associated with LVDD (78.94% vs. 12.5%, p = 0.002). Increased QTc and QTcd were associated with higher LVMI values (p≤ 0.05).

Conclusions: In asymptomatic patients affected by SSc, a P wave duration ≥ 110 msec and/or a QTc ≥450 msec and/or QTcd >60 msec appear to be associated with early myocardial damage. The identification of markers of early cardiac involvement during SSc could allow appropriate prevention strategies against advanced forms of disease.

INTRODUCTION

Systemic Sclerosis (SSc) is an autoimmune chronic disease characterized by chronic and progressive deposition of connective tissue in the skin, small arteries and visceral organs, which leads to irreversible fibrosis [1]. SSc may occur in a wide range of clinical manifestations, depending on the grade of cutaneous fibrosis and on the visceralin volvement (heart, lungs, kidneys, digestive system). It is possible to distinguish two overlapping forms: limited cutaneous scleroderma (lcSSc) and diffuse cutaneous scleroderma (dcSSc). LcSSc is limited to the skin on the face, hands and feet, and Raynaud's phenomenon usually precedes cutaneous involvement and it may remain the only clinical feature for a long period of time. Moreover, this form is frequently associated to anticentromere antibodies. On the other hand, dcSSc is characterized by progressive cutaneous sclerosis developing from limbs to body, and rapid involvement of visceral organs contemporary with Raynaud's phenomenon is also usually observed. The latter form is often associated with anti-topoisomerase I antibodies [2,3].

Cardiac involvement in SSc is common. It can be primary, related to myocardial fibrosis (scleroderma cardiomyopathy) or secondary, when it is associated with pulmonary hypertension or renal crisis [4-8].There is strong evidence showing the connection of a primary cardiac involvement with continuous focal ischemic damage of sub-endocardial arteries, which leads to irreversible myocardial fibrosis. A clinical evident cardiac injury is a bad prognostic factor as it is a cause of higher morbidity and mortality in SSc [9,10]. Several different clinical features can be expressed, from myocardial hypertrophy to left ventricular dysfunction or arrhythmias, depending on the type and severity of damage [4,5,11]. A recent meta-analysis integrated results of several studies, estimating the rate of cardiac involvement in a percentage between 8% and 28% with high risk of mortality. [12]. Pathogenesis of scleroderma cardiomyopathy is still unknown, although the hypothesis of a "cardiac Raynaud's phenomenon" which drives to ischemia, inflammation and fibrosis is commonly accepted. Episodes of cardiac ischemia and subsequent fibrosis and hypertrophy could likely be caused by micro-angiopathy damage [11].

Left ventricular diastolic dysfunction (LVDD)

In patients affected by SSc, the presence of LVDD is common and it is linked with a higher risk of mortality [13-15]. In a study involving 153 patients with SSc the prevalence of LVDD was approximately 23% and it was not related to the duration of the disease [15]. In another multicentric study on 570 patients affected by SSc, the prevalence of left ventricular hypertrophy, left ventricular systolic dysfunction and LVDD were 22.6%, 17.7% and 1.4%, respectively [16].

Strong evidence suggests that myocardial fibrosis may cause progression to cardiac failure with preserved systolic function. Thus, early "pre-clinical" diagnosis of LVDD could be useful. In the majority of published studies, the assessment of LVDD was made by conventional pulsed wave Doppler (PWD). Tissue Doppler Imaging (TDI) is a more recent echocardiographic technique showing higher accuracy and sensitivity [11]. In order to assess LVDD, either European Society of Echocardiography or American Society of Echocardiography (EAE/ASE) recommends an integrated use of both PWD and TDI [17].

Cardiac catheterization is the gold standard for the evaluation of LVDD. However, it is invasive, and not suitable for screening and follow-up. On the other hand, Doppler echocardiography is an easy executable and reproducible procedure, widely used in clinical practice, and well correlated with haemodynamic data [18].

Consequently, the objective of our study was to evaluate echocardiographic data in asymptomatic patients affected by Systemic Sclerosis (SSc) compared to healthy subjects, and to assess their correlations to electrocardiographic parameters.

METHODS

This prospective case-control study involved consecutive patients affected by SSc, enrolled from the ambulatory scleroderma clinic of our Department. All patients fulfilled American Rheumatism Association classification criteria [19]. A control group of volunteer subjects was also evaluated.

Exclusion criteria were: uncontrolled systemic hypertension, heart rate higher than 90 beat per minute, diabetes mellitus, ischemic heart disease, atrial fibrillation/atrial flutter, moderate to severe cardiac valvulopathies, severe pulmonary hypertension, right ventricular dysfunction, treatment with antiarrhythmic drugs or other drugs that can prolong the QT interval, Patients and control subjects treated with systemic vasodilators as calcium antagonists, ACE-inhibitors and angiotensin-receptor antagonists were included in the study.

ECG

All patients underwent 12-lead standard ECG. Tracings were recorded on graph paper using different speeds (25 mm/sec and 50 mm/sec) and analysed by two different physicians not aware of echocardiographic findings. Any discordance was resolved with joint analysis and consensus. The following parameters were evaluated: P wave duration, QT interval, corrected QT (QTc), QT dispersion (QTd) and QTc dispersion (QTCd). QTd and QTCd were calculated by the difference between the maximum and minimum QT and QTc, respectively. QTc was determined using Bazett formula ($QT/\sqrt{RR}$) [20]. In the presence of right bundle branch block, QTc measurement is influenced by the duration of ventricular depolarization. In this case, milliseconds excess to a QRS "standard" of 115 msec were subtracted from QT value [21]. Left ventricular hypertrophy was assessed using Sokolow-Lyon criteria [22]. Criteria for ECG normality were considered: sinus rhythm at a heart rate of 60-90 beat per minute, P- duration < 110 msec, QRS-wave duration < 120 msec, QTc < 450 msec, non-depressed ST segment, absence of complex supraventricular and ventricular arrhythmias [23-26].

Echocardiogram

Both patients and controls underwent trans-thoracic echocardiogram in two-dimensional, Doppler, colour-Doppler and TDI. Cardiac measurements were performed in agreement with ASE/EAE recommendations [27, 28]. All exams were recorded for off-line analysis. For any computation that was not evaluable off-line, an on-line analysis was performed. Left ventricular ejection fraction (LVEF) was calculated using Simpson modified biplane method as average of three consecutive measurements [27]. Left ventricular dysfunction was established at LVEF≤ 50%.

Left ventricular mass estimation was based on body surface area, obtaining left ventricular mass index (LVMI). LVMI values ≥ 95 g/m^2 were considered as pathological [28]. An index of right ventricular function was evaluated by the tricuspid annular plane systolic excursion (TAPSE). TAPSE values >18 mm were considered normal, and patients with TAPSE values ≤ 17 mm were excluded from the analysis [28]. Right atrial pressure was estimated by inferior caval vein (IVC) diameter and collapsibility. IVC diameter ≤ 2.1 cm that collapses >50% with a sniff suggests a normal RA pressure of 3 mmHg (range 0-5 mmHg), whereas an IVC diameter > 2.1 cm that collapses < 50% with a sfniff suggests a high RA pressure of 15 mmHg (range 10-20 mmHg); when the IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg (range 5-10 mmHg) might be used [28]. Systolic pulmonary artery pressure (SPAP) was calculated adding right ventricle-to-right atrium pressure gradient. An estimated SPAP ≥ 40 mmHg was considered as pathological [29].

Left atrial diameter was measured using long parasternal axis view at the end of ventricular systole. Left atrial volume was calculated using the four-chamber view and it was indexed by body surface area (LAVI). A LAVI value ≥ 34 mL/ml^2 was considered as pathological [28,30]. Left ventricular diastolic function was assessed using PWD and TDI in the four-chamber view. Transmitral flow envelope was obtained by positioning the sample volume on the free edge of the valve leaflets. Pulsed wave TDI was obtained by pointing the sample volume on the septal edge and the lateral edge of mitral annulus [30].

By using PWD, the following indexes were obtained: early-diastolic filling velocity (E wave), end-diastolic filling velocity (A wave), deceleration time of early filling velocity (DT).Then, using TDI: septal early-diastolic velocity *e'(e'* s*)* and lateral early-diastolic velocity *e' (e'* l). Furthermore E/*e'* m ratio was calculated, where e'm was given by the average of septal e' and lateral e' [17].

It is possible to distinguish four grades of LVDD: grade I is characterized by a reversal of the normal E/A ratio. Grade II is

called „pseudonormal filling dynamics“ and it is characterized by increased left atrial filling pressures. Grade III and IV are called „restrictive filling dynamics” and they are both severe forms characterized by advanced heart failure symptoms [17].

Diagnosis of LVDD was given when *e*'s < 8 cm/s and/or e'l <10 cm/s. Severity of dysfunction was defined using ASE/EAE recommendations [17],as described in Table (1).

Statistical analysis

Results are expressed by mean ± standard deviation for continuous variables and with absolute number and percentage for categorical variables. Comparison between groups was evaluated with Mann-Whitney U-test. Student's T- test was used for quantitative variables whereas $\chi 2$ test or Fisher's exact test were used for dichotomous variables. A p value < 0.05 were considered statistically significant.

RESULTS

General characteristics of patients (Group A) and controls (Group B) are reported in Table (2). Seventy-one SSc patients and 60 control subjects were studied. Ten SSc patients and 3 control subjects were excluded (Group A: 4 patients for increased basal heart rate, 2 patients for TAPSE < 17 mm, 3 patients for valvular disease and 1 patient for severe pulmonary hypertension; Group B: 3 subjects for high basal heart rate). Therefore, 61 patients affected by SSc (Group A) were compared with 57 healthy controls (Group B); Among SSc patients, 22had dcSSc and 39 had lcSSc. Medications taken by patients in Group A are described in Table (3).Control group patients were volunteers from our department. Age and sex were well matched between groups. No statistically significant differences about cardiovascular drugs assumption, smoking habit and hypertension prevalence were found between groups.

ECG findings

The results are reported in Table (4). QT and QTc values were similar between groups. Conversely, QT dispersion (QTd) and QTc dispersion (QTcd) were significant higher in Group A. Patients with dcSSc showed longer QTc values than controls (440.58 ±18.23 vs. 427.64 ± 23.12 msec, p = 0.02, not shown in the Table) while no significant differences were shown between patients with lcSSc and controls. However, QT value, QT dispersion, QTc and P wave duration did not significantly differ between dSSc and lSSc. The percentage of patients with an absolute increase in QTc and QTcd values was higher in Group A vs. Group B. Average P wave duration values were slightly higher in group A than in group B. Similarly, the absolute increment of P wave duration was higher in group A.

Table 1: LVDD assessment.

Diastolic function	*e'** (cm/s)	E/A	E/*e'*m**	DT** (ms)
Normal	*e*'s ≥8			
	e'l ≥10			
Grade ILVDD	*e*'s <8	<0,8	≤ 8	>200
	e'l <10			
Grade II LVDD	*e*'s <8	0,8- 1,5	12-Sep	160-200
	e'l <10			

Table 2: General characteristics of study population.

	Group A	Group B	p
Age ,yrs (SD)	62.59 ± 13.72	57.88 ± 14.66	NS
F, n (%)	58 (95.1)	57 (100)	NS
Height, m (SD)	1.59 ± 0.08	1.61 ± 0.06	NS
Weight, kg (SD)	63.42 ± 11.16)	61.63 ± 9 .03	NS
BSA , m2 (SD)	1.67 ± 0.16)	1.65 ± 0.13	NS
BMI, g/m^2 (SD)	24.90 ± 20.59	23.89 ± 3.08	NS
Hypertension (%)	17 ± 27.9	12 ± 21.1	NS

Abbreviations: F: Female Gender; BSA: Body Surface Index; BMI: Body Mass Index

Table 3: Medications in Group A.

	Daily dosage	dSSc (n=22)	lSSC (n=39)
Prednisone	2,5 mg	3	0
	5 mg	11	14
	6,25 mg	1	0
	12,5 mg	2	1
Azathioprine	100 mg	2	1
Methotrexate	7,5 mg	2	1
	10 mg	8	6
Cyclosporine A	100 mg	1	0
Iloprost	05-2 ng/Kg/min	12	10
Calcium antagonists		19	32
Bosentan	65 mg	1	0
	125 mg	1	0
	250 mg	6	2
Sildenafil	40 mg	1	0
	60 mg	2	0

Table 4: ECG results.

	Group A (n=61) Average ± SD	Group B (n=57) Average ± SD	*p*
P wave (msec)	100.65 ± 17.78	85.96 ± 17.71	<0.0001
QT (msec)	409.18 ± 33.67	401.54 ± 22.90	NS
QTc (msec) *	434.86 ± 28.69	427.64 ± 23.12	NS
QTd (msec)	49.83 ± 32.27	27.85 ± 12.11	<0.0001
QTcd (msec)	51.39 ± 30.63	29.73 ± 13.04	<0.0001
Qtc≥450 msec, n (%)	19 (31.14)	8 (14.03)	0.0303
QTcd> 60 msec, n (%)	22 (36.06)	1 (1.75)	0.0001
P wave ≥110msecn(%)	20 (32.78)	4 (7.01)	0.0005

Echocardiographic findings

The results are reported in Table (5). LVMI and LVEF values were higher and inferior, respectively, in group A compare to group B. No patients with LVEF <55% were found. In addition, LAVI values were higher in-group A than in group B. In particular,

Table 5: Echocardiographic results.

	Group A (n=61) Average ± SD	Group B (n=57) Average ± SD	*p*
LVMI (g/m^2)	80.50 ± 20.59	61.54 ± 11.08	<0.0001
EDLVD (mm)	43.81 ± 4.60	43.44 ± 3.89	NS
IVS (mm)	9.99 ± 1.92	8.01 ± 1.78	<0.0001
PW (mm)	8.55 ± 1.37	7.18 ± 1.07	<0.0001
LVH (n)	12	2	0.0092
LVEF (%)	63.55 ± 6.58	68.42 ± 5.99	0.0001
LAV (mL)	45.80 ± 16.84	31.08 ± 10.53	<0.0001
LAVI (mL/m^2)	27.67 ± 10.83	18.78 ± 6.15	<0.0001
LAVI ≥ 34 (mL/m^2) n(%)	12	1	0.0022
E (cm/sec)	77.00 ± 15.46	76.05 ± 14.96	NS
A (cm/sec)	78.22 ± 20.73	63.15 ± 17.46	0.0001
E/A	1.06 ± 0.43	1.29 ± 0.45	0.0004
DcT (msec)	214.93 ± 45.91	211.12 ± 51.64	NS
E'setptal (cm/sec)	8.060 ± 2.49	10.00 ± 2.44	0.0001
E'lateral (cm/sec)	10.13 ± 3.26	12.39 ± 2.84	<0.0001
E'average (cm/sec)	9.09 ± 2.61	11.19 ± 2.22	<0.0001
E/E' setptal	10.36 ± 3.49	7.94 ± 2.15	<0.0001
E/E' lateral	8.11 ± 2.90	6.33 ± 1.49	<0.0001
E/E' average	8.96 ± 2.58	6.92 ± 1.42	<0.0001
LVDD n(%)	43 (70.50)	17 (29.82)	0.0001

Abbreviations: LVMI: Left Ventricular Mass Index; LVEDD: Left Ventricular End-Diastolic Diameter; IVST: Interventricular Septum Thickness; LVPWT: Left Ventricular Posterior Wall Thickness: LVH: Left Ventricular Hypertrophy; LVEF: Left Ventricular Ejection Fraction; LAV: Left Atrial Volume; LAVI: Left Atrial Volume Indexed For Body Surface; DCT: Deceleration Time of E Wave; LVDD: Left Ventricular Diastolic Dysfunction.

among patients with abnormal LAVI, 11 had LVDD dysfunction. PWD showed higher average levels A in patients with SSc as well as a significant reduction of E/A ratio.By TDI study, a reduction of *e*' s wave values, *e*'l, *e*'m value and an increase of E/*e*'s, E/*e*'l, and E/*e*'m ratio in Group A patients were shown.

The percentage of patients with LVDD was higher in group A compared with group B (70.5% and 21.8%, respectively; p<0.001). Within group A, 13 patents had a grade-I LVDD, 27 a grade-II and 3 a grade-III. Within group B, 7 subjects displayed a grade-I LVDD and 10 subjects a grade-II. . A correlation between the presence of LVDD and duration of the disease has not been shown in our study. No statistically significant evidence was found comparing echocardiographic parameters between dcSSc and lcSSc patients, as well as between single forms of disease versus control subjects

Electrocardiographic and echocardiographic correlations

The results are reported in Table (6). In Group A, an absolute increase of QTc duration was associated with the presence of LVDD, and this association was not shown in control subjects. Increased values of QTcd and P wave duration were also associated with the presence of LVDD. Mean wall thickness and LVMI values were increased in SSc patients with LVDD. Compared with patients with normal left ventricular diastolic function, QTc values were significantly higher in patients with LVDD. Mean QTd, QTcd and P wave values were similar between groups. Increased QTc and QTc dispersion values were associated with higher LVMI. An absolute increase of P wave duration was associated with higher values of LAVI. Neither electrocardiographic nor echocardiographic findings nor the presence of LVDD were associated with the disease form or its duration, as well as with the history of arterial hypertension.

DISCUSSION

In this study, we identified several electrocardiographic and echocardiographic parameters in asymptomatic patients affected by SSc. In particular, we observed a higher QTd value and a statistically significant increase in the number of patients showing increased QTc and QTcd values. Subgroup analysis underlined a significant difference in QTc value between patients with dcSSc and controls. This finding is supported by a previous paper of our group, which showed a higher percentage of perfusion myocardial abnormalities in patients with dcSSc compared with patients affected by IcSSc, together with a higher prevalence of ventricular late potentials in dcSSc subgroup [31]. QTc interval prolongation is an independent risk factor for cardiac mortality and sudden death [32]. Cut-off QTc values considered in various studies are variable from >440 to 470 msec [23,25,26,32]. In patients with a previous myocardial infarction a QTc value > 400 msec was associated with a higher risk for sudden cardiac death [32]. In the Strong Heart Study (1839 patients aged between 45 and 74 years, with a 2.5 years follow-up) a QTC value ≥460 msec was associated with doubled risk for any cause of mortality (HR 2.6; 95% CI, 1.8-3.7) and cardiac mortality (HR 2.3; 95% CI, 1.2-4.6) [23].

In 5812 patients with mean follow-up 4 years from the Rotterdam Study, a QTc value > 400 msec was associated to higher risk for both every cause of mortality and cardiovascular mortality, and a QTc value > 460 msec doubled the risk [26]. QT interval was strictly related to heart rate and women had longer QTc compared to men. It has been suggested that, according with QTc interval distribution, the threshold to define an increase of

Table 6: Relationship between ECG findings and LVDD.

	LVDD N (%)	Normal diastolic function N (%)	N Tot
Group A			
QTc ≥ 450 (msec)	15 (78.94)	4 (21.05)	19
Group B	1 (12.5)	7 (87. 5)	8
QTc ≥ 450 (msec)			
Group A	16 (72.72)	6 (27.27)	22
QTcd> 60 (msec)			
Group B	0	1 (100)	1
QTcd> 60 (msec)			
Group A	15 (75)	5 (25)	20
P wave ≥110 (msec)			
Group B	1 (25)	3 (75)	4
P wave ≥110 (msec)			

QTc value should be higher for woman then for men. In our female patients with SSc, we defined as pathological a QTc interval ≥450 msec.

Several studies suggested that QTd is useful to identify patients with higher risk for ventricular arrhythmias. Still, QTd value in risk stratification is not homogeneous. The pathological substrate of myocardial involvement in SScis characterized by an abnormality of coronary microcirculation without epicardial vessels disease and by the presence of fibrosis areas, probably related to a coronary microcirculation disorder. These fibrosis areas can influence ventricular repolarization and increase the dispersion of recovery time through the ventricle [33].

SSc has been reported to be associated with a neuropathic autonomic disease, possibly involved in the pathogenesis of Raynaud's phenomenon and gastrointestinal symptoms. This dysautonomia represents another possible mechanism involved in the change of ventricular refractory period, as suggested by the presence of an abnormal 24-hour heart rate variability [34-36].

As regards the QTc interval in patients with SSc, limited data have been reported [33,37-40]. In particular, a case-control study on 38 patients with SSc showed QTc, QTd, and QTcd values significantly increased in SSc patients compared to healthy subjects [33].

In our study, the prevalence of LVDD was higher in SSc patients with prolonged QTc interval. Among patients with SSc, both QTc and LVMi mean values were significantly increased when LVDD was present. Moreover, an absolute increase of the value of QTc and QTcd was associated with increased LVMI values.

An association between QTc prolongation and LVDD has already been described among patients with arterial hypertension [21] and it has been attributed to the left ventricular hypertrophy elicited by pressure overload [36,37]. In our study, patients with SSc showed a high prevalence of left ventricular hypertrophy. Notwithstanding, no differences were shown in the prevalence of systemic hypertension. This discordance suggests that the increase of ventricular wall thickness during SSc could not be due to a true hypertrophy of myocardial cells, but to extracellular fibrosis, a process that should not increase voltages of the QRS interval. Furthermore, the prevalence of P wave duration ≥ 110 ms and of increased LAVI was higher in SSc patients versus control subjects. A previous study on 270 patients showed that the P wave duration and its dispersion were associated with LAVI values and with the presence of LVDD [40]. Enlargement of left atrium may be a marker of severity and chronicity of LVDD and its linked to an increased left atrial pressure. Moreover, a LAVI value ≥ 34 ml m/m^2 was an independent risk factor for death, heart failure, atrial fibrillation and an additional criterion of LVDD [17,26,27].

CONCLUSIONS

This study suggests that ECG and echocardiogram may be able to assess early cardiac involvement in asymptomatic patients affected by SSc. A P value ≥ 110 msec and/or a QTc value ≥ 450 msec and/or a QTcd >60 msec appear to be linked with early myocardial damage. Therefore we recommend to perform a 12-lead standard ECG once a year to every patient affected by SSC, considering to include an echocardiographic study to patients with the above electrocardiographic features.

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Cite this article

Rubini G, Vinci F, Farina L, Riccieri V, Sciarra I, et al. (2017) Electrocardiographic and Echocardiographic findings and their Relationships in Patients with Systemic Sclerosis. J Autoimmun Res 4(1): 1017.