Abnormal spatial QRS-T angle, a marker of ventricular repolarisation, predicts serious ventricular arrhythmia in systemic sclerosis

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Abstract

Objectives

Cardiac involvement may be under-diagnosed in asymptomatic patients with systemic sclerosis (SSc). Standard electrocardiography-derived spatial QRS-T angle (spQRS-Ta) is an established marker of ventricular repolarisation heterogeneity, and a strong independent predictor of cardiac morbidity and mortality, including sudden death, in the general population. We examined whether spQRS-Ta is abnormal in asymptomatic SSc patients and assessed its predictive value for possibly concurrent, serious ventricular arrhythmia.

Methods

SpQRS-Ta and 24-hour Holter recordings were obtained from 69 SSc patients (aged 51±13 years, 63 women) without clinically evident cardiac involvement and having left ventricular ejection fraction at least 50% by echocardiography. 'Healthy' subjects matched 1:1 with patients for age, gender and body mass index served as controls.

Results

SpQRS-Ta was wider in SSc (median value 15.6°, interquartile range 10.6–24.3°) than controls (10.5°, 7.3–13.5°, p=0.0001) and not associated with skin fibrosis extent or specific clinical manifestations and autoantibodies. Twenty-four-hour Holter recordings revealed couplets of ventricular beats in six (Lown class IVa) and non-sustained ventricular tachycardia in five patients (Lown class IVb); spQRS-Ta was wider in those eleven patients with serious ventricular arrhythmia than the remaining patients (24.9°, 14.9–31.3° vs. 14.4°, 9.6–22.3°; p=0.02). A spQRS-Ta>19.3° demonstrated 80% sensitivity and 68% specificity (area under the curve 0.81, p=0.02) to predict the presence of non-sustained ventricular tachycardia in Holter monitoring.

Conclusion

Ventricular repolarisation heterogeneity, as reflected by wider spQRS-Ta, is common in SSc. Increased spQRS-Ta could serve as a simple screening test for further investigation to identify patients at risk or prone to develop life-threatening ventricular arrhythmia.

Key words

systemic sclerosis, electrocardiography, ventricular arrhythmogeneity, arrhythmia markers

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Introduction

Systemic sclerosis (SSc) is a connective tissue disorder characterised by progressive fibrosis of the skin and internal organs. Myocardial fibrosis involving both ventricles with a patchy distribution is the pathologic hallmark of cardiac involvement (1). Clinical manifestations can range from diastolic dysfunction to life-threatening arrhythmias and are associated with increased cardiovascular morbidity and mortality, whereas sudden cardiac death may occur in about 6% of the general SSc population (2). In asymptomatic patients, however, rhythm disturbances due to early cardiac involvement may be under-diagnosed.

Non-invasive identification of individuals at risk for serious ventricular arrhythmia is mandatory. Spatial QRS-T angle (spQRS-Ta), defined as the angle between the directions of ventricular depolarisation, is an established electrocardiography-derived marker of ventricular repolarisation and an independent predictor for sudden cardiac death (3, 4). Wider spQRS-Ta is associated with classical cardiovascular risk factors and with left ventricular (LV) myocardial dysfunction and hypertrophy, suggesting that it can possibly better identify patients prone to develop malignant arrhythmia and sudden cardiac death events (5).

The present study examined the hypothesis that subclinical myocardial fibrosis in asymptomatic patients with SSc could lead to ventricular repolarisation heterogeneity, as reflected by wider spQRS-Ta in standard 12-lead electrocardiography. Furthermore, we obtained 24-hour Holter recordings from these patients and searched for episodes of serious ventricular arrhythmia (6) and their possible association with wider spQRS-Ta values.

Patients and methods

Study population

Sixty-nine adult outpatients (63 women) with SSc of more than 3 years duration (range 3–25 years) without clinical evidence of cardiac involvement and LV ejection fraction >50% by echocardiography, who fulfilled exclusion criteria described previously (7), participated in this observational study (Table I). All patients underwent complete clinical and laboratory evaluation, standard electrocardiography, 24-hour Holter monitoring, transthoracic echocardiography (Hewlett-Packard, Sonos 5500, Andover, Massachusetts, USA), high-resolution computed tomography (CT) of the chest and lung function tests, including measurements of forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO), as described (7). Medications at the time of the study included calcium-channel blockers (48%), angiotensin-converting enzyme inhibitors (23%), <7.5 mg prednisolone (48%), cyclophosphamide (7%), methotrexate (13%), d-penicillamine (19%), azathioprine (3%) and mucophenolate mofetil (7%). Apparently 'healthy' subjects matched 1:1 with SSc patients for age, gender, and body mass index served as controls. The study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee. All participants provided informed consent.

Electrocardiography, twelve-lead vectorcardiogram and ambulatory electrocardiography recordings

A 12-lead digital electrocardiogram (CardioControl NV, the Netherlands) was recorded in the supine resting position for 5 min. The spatial amplitudes of the maximum T and QRS vectors, and the spQRS-Ta were calculated as previously described (8). Twenty-four-hour recordings started between 11.00 a.m. and 12.00 a.m. using a three-channel recorder (version 3.1 ELA Medical, France). Recordings were categorised according to Lown and Wolf Classification (6), as class 0 (no ventricular ectopic beat); class IA (≤720 ventricular ectopic beats/24h with ≤1 ventricular ectopic beat/min); class IB (≤720 ventricular ectopic beats/24h with ≥2 ventricular ectopic beats/min); class II (≥720 ventricular ectopic beats/24h); class III (multiform ventricular extrasystole or bigeminal or trigeminal extrasystole); class IVA (ventricular extrasystoles in couplets); class IVB (non-sustained ventricular tachycardia); and class V (ventricular extrasystole of the R-on-T type).

Table I. Demographics, clinical and laboratory characteristics of patients with diffuse and limited systemic sclerosis.

	All patients	Diffuse skin involvement	Limited skin involvement
n.	69	42	27
Men / women	6 / 63	4 / 38	2 / 25
Age (years)	50.8 ± 12.5	49.1 ± 11.4	53.5 ± 13.7
Disease duration (years)	8.7 ± 6.3	8.6 ± 4.5	9.3 ± 4.5
BMI (kg/m^2)	24.2 ± 4.16	24.2 ± 4.5	24.3 ± 3.7
Lung fibrosis in CT scan (n)	36	22	14
DLCO <80 % of the predicted (n)	50	30	20
TLC <80 % of the predicted (n)	31	23	8
PASP ≥40 mmHg (n)	14	6	8
LV ejection fraction (%)	59 ± 6	60 ± 7	59 ± 6
Heart rate (beats/min)	72.5 ± 10.6	72.6 ± 10.7	72.2 ± 10.6
QRS amplitude (μV)*	1118.3 (935.7–1311.1)	1100.6 (893.08–1285.8)	1146.6 (1039.2–1388.1)
T amplitude (μV)	334 ± 119	319 ± 122.9	357.5 ± 111
Spatial QRS-T angle (°)*	15.6 (10.7–24.3)	15.8 (10.8–25.6)	15.3 (9.6–24.3)
Systolic arterial pressure (mmHg)	120 ± 20	124 ± 18	113 ± 17
Esophageal involvement (n)	43	27	16
Intestinal involvement (n)	13	8	5
Thyroid disease (n)	17	11	6
anti-Scl-70 Ab positive (n)	40	34	6
anticentromere Ab positive (n)	19	1	18

Data are mean values ±SD; *Median value ±interquatile range; BMI: body mass index; CT: computerised tomography; DLCO: diffusing capacity for carbon monoxide; TLC: total lung capacity; BP: blood pressure; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

Statistical analysis

Two-sample *t*-test, Mann-Whitney U-test, chi-square test and univariate linear regression analysis were used, as appropriate. Receiver operation curves (ROC) were used in order to find the best sensitivity, specificity and discriminate ability of spQRS-Ta to predict Lown class >III arrhythmias. Results are presented as the mean ± standard deviation (SD) or percentage, or as median values (50th quartile) with interquartile ranges (25th to 75th quartiles), as appropriate.

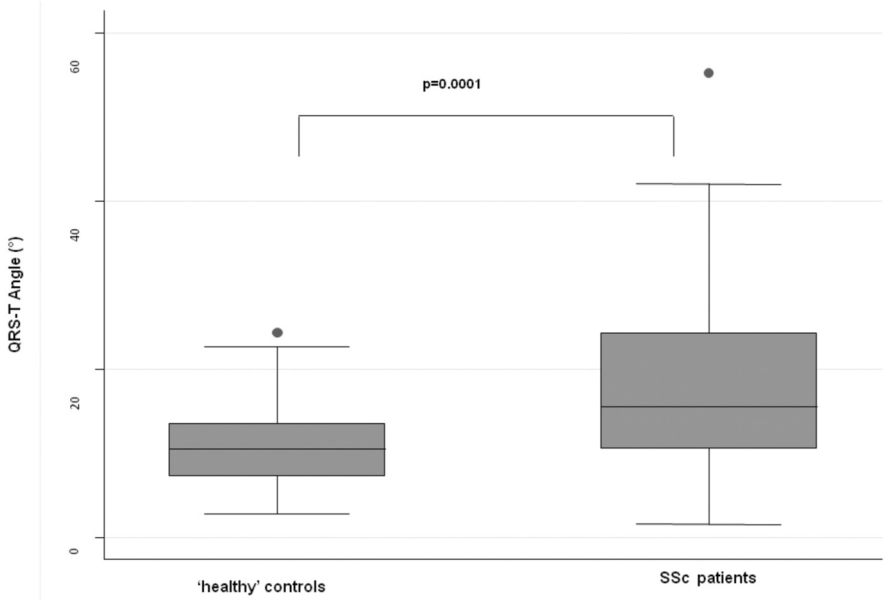

Fig. 1. Box plots representing values of the 12-lead electocardiography derived spatial QRS-T angle in 69 asymptomatic patients with SSc and 'healthy' subjects matched 1:1 with patients for age, gender and body mass index.

Results

Increased spatial QRS-T angle in asymptomatic SSc patients than in controls

Standard 12-lead ECG-recordings revealed sinus rhythm in all patients and control subjects. Among the sixty-nine SSc patients, eight and one had incomplete and complete, respectively, right bundle branch block, four had left bundle branch block (LBBB) and four had left anterior hemiblock. As shown in Figure 1, spQRS-Ta was significantly increased in patients (median 15.6°, interquartile range 10.6–24.3°) than controls (10.5°, 7.3–13.5°, p=0.0001), being comparable between patients with diffuse and limited skin involvement (Table I). There were no significant differences in spQRS-Ta between patients with or without lung CT findings indicative of fibrosis, normal or reduced TLC, normal or reduced DLCO, as well as between patients with pulmonary artery systolic pressure higher or lower than 40 mmHg (echocardiography), LV ejection fraction higher or lower than 60% (echocardiography), with or without esophageal or intestinal involvement and SSc-related autoantibody positivity (Table II).

To detect potential predictors of increased spQRS-Ta, univariate linear regression analysis was performed using alternatively age, duration of SSc disease, body mass index, mean heart rate obtained from the 24-hour Holter recordings, pulmonary function parameters and presence of lung fibrosis in CT, elevated pulmonary artery systolic pressure, presense of esophageal and intestinal involvement and ACA and anti-Scl 70 serologic positivity as dependent variables. Only patient's age (r=0.32, p<0.0001) was associated with wider spQRS-Ta values.

Wider spatial QRS-T angle and serious ventricular arrhythmia during 24-hour Holter monitoring

All patients and controls (n=42) were in sinus rhythm throughout the recording period. Lown class IV ventricular arrhythmia was more frequent in SSc

Table II. Electocardiography-derived spatial QRS-T angle in patients with systemic sclerosis stratified according to specific organ involvement.

	Spatial QRS-T angle (°)	Patients (n)	*p*-value
Lung fibrosis in CT scan			
Yes	15.7 (10.9–24.7)	36	NS
No	15.3 (10.7–19.8)	33	
Diffusing lung capacity for CO			
≥80 % of the predicted	15.3 (10.7–24.9)	19	NS
<80% of the predicted	16.6 (9.6–22.3)	50	
Total lung capacity			
≥80 % of the predicted	16.9 (11.0–24.5)	38	NS
<80% of the predicted	15.3 (9.6–15.3)	31	
PASP			
≥40 mmHg	20.3 (12.3–27.5)	14	NS
<40mmHg	15.3 (9.6–23.4)	55	
LV ejection fraction			
>60%	15.6 (10.7–21.9)	53	NS
50–60%	18.9 (11.8–27.6)	16	
Ventricular arrhythmia (24-hour Holter)			
Lown class IV	24.9 (14.9–31.3)	11	**0.002**
Lown class I-III	14.4 (9.6–22.3)	58	
Esophageal involvement			
Yes	15.6 (11.05–24.5)	43	NS
No	14.9 (9.6–24.3)	26	
Intestinal involvement			
Yes	15.6 (11.05–24.5)	13	NS
No	15.5 (10.2–24.2)	56	
Anti Scl-70 Ab			
Positive	14.4 (10.2–25.2)	40	NS
Negative	15.6 (11.2–23.6)	29	
Anticentromere Ab			
Positive	15.3 (7.9–19.2)	19	NS
Negative	15.6 (10.8–25.6)	50	

Data are median value ±interquatile range; CT: computerised tomography; CO: carbon monoxide; PASP: pulmonary artery systolic pressure; anti-Scl 70: antitopoisomerase I; LV: left ventricular; Lown class I: Lown class IA: ≤720 ventricular ectopic beats/24h with ≤1 ventricular ectopic beat/min, together with Lown class IB: ≤720 ventricular ectopic beats/24h, with ≥2 ventricular ectopic beats/min; Lown class II: ≥720 ventricular ectopic beats/24h; Lown class III: multiform ventricular extrasystole or bigeminal or trigeminal extrasystole; Lown class IV: ventricular extrasystoles in couplets or ventricular tachycardia.

(six patients had couplets of ventricular beats and five patients had non-sustained ventricular tachycardia) than controls (two subjects had couplets of ventricular beats, $p<0.001$). None of the studied subjects presented an R-on-T phenomenon (Lown class V). The spQRS-Ta was significantly wider in those eleven SSc patients with serious ventricular arrhythmia (Lown class >III) than the remaining patients (Table II). The area under the curve of ROC analysis for prediction of serious ventricular arrhythmia was equal to 0.72 (95% C.I. 0.53–0.91) and revealed that a spQRS-Ta value >18° was significantly able to predict serious ventricular arrhythmia events with 73% sensitivity and 67% specificity ($p=0.022$). ROC analysis for the ability of spQRS-Ta to predict episodes of non-sustained ventricular tachycardia (Lown class IVB) revealed an area under the curve equal to 0.81 ($p=0.022$), whereas a spQRS-Ta value >19.3° had 80% sensitivity and 67% specificity (Fig. 2).

Discussion

Acknowledging the relatively small sample size of this study, the three main novel findings confirmed our hypothesis. Firstly, spQRS-Ta is increased in patients with SSc in the absence of clinical evidence of cardiac involvement. Secondly, of all SSc disease-related parameters evaluated, only the presence of serious ventricular arrhythmia in 24-hour Holter recordings could be associated with wider spQRS-Ta. Thirdly, an optimal cut-off value for the clinical utilisation of the spQRS-Ta as a surrogate marker for non-sustained ventricular tachycardia, the most serious form of arrhythmia found in our patients, was identified. Notably, a cut-off value of 18° was able to predict 7 out of 11 SSc patients having serious arrhythmia in 24-hour Holter monitoring, whereas a cut-off spQRS-Ta value of 14.7° demonstrated 100% sensitivity to predict the presence of non-sustained ventricular tachycardia. To the best of our knowledge, this is the first study that found a link between abnormalities in spQRS-Ta and ventricular arrhythmia in an asymptomatic population, which, albeit, is at risk of increased cardiac mortality.

An abnormal spQRS-Ta is considered to reflect subclinically damaged myocardial areas due to ischaemia and/or microvascular disease which could distort the normal spread of electrical forces through the myocardial wall (9). Since fibroblast proliferation, collagen accumulation, and microvascular dysfunction, are thought to play a primary role in the pathogenesis of cardiac involvement in SSc (1), an abnormally wide spQRS-Ta in our patients can be electrophysiologically explained and etiological attributed to all possible causes of an interruption or even a fragmentation of the usually smooth path of excitation in the ventricular wall. On the other hand, spQRS-Ta can be also affected by autonomic nervous system dysfunction (10) which may occur in SSc (11).

In the larger study to date, 183 SSc patients underwent 24-hour Holter recording; ventricular ectopy occurred in 67% of patients, while episodes of ventricular tachycardia were also observed in 7% of patients. Importantly, the presence of ventricular ectopy was strongly correlated with total mortality and with sudden cardiac death (12). Another study revealed ventricular tachy-

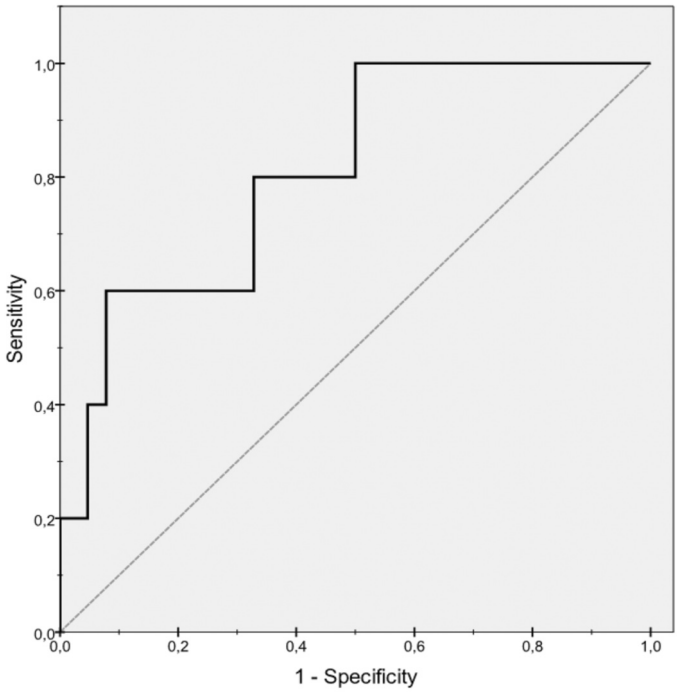

Fig. 2. Receiver operator curve analysis showing the ability of the 12-lead electrocardiography derived spatial QRS-T angle to predict the presence of non-sustained ventricular tachycardia in 24-hour electrocardiography recordings in asymptomatic patients with SSc (area under the curve 0.81, 95% confidence interval 0.63–0.99, p=0.022)

cardia runs in 8% of SSc patients (13), consistent with our findings (7.2%) presented herein. Of all clinical characteristics of SSc, only the presence of ventricular arrhythmia episodes Lown class IV in 24-hour Holter monitoring was significantly associated with wider spQRS-Ta. These types of arrhythmias are considered serious since they increase the risk for sustained ventricular tachycardia, ventricular fibrillation and sudden cardiac death even in apparently healthy individuals (14, 15).

To conclude, ventricular repolarisation heterogeneity, as reflected by wider spQRS-Ta, is common in asymptomatic patients with SSc. These results further support the importance of spQRS-Ta as a tool for cardiovascular risk stratification in vulnerable populations and suggest that represents a simple screening test for further investigation with 24-hour Holter monitoring to identify SSc patients at risk or prone to develop life-threatening ventricular arrhythmia. Cardiac magnetic resonance studies or radionuclide imaging could further confirm that wider spQRS-Ta represents a surrogate marker of subclinical myocardial fibrosis. Prospective studies to establish associations between spQRS-Ta and clinical outcome in SSc are warranted.

References

1. ALLANORE Y, MEUNE C: Primary myocardial involvement in systemic sclerosis: evidence for a microvascular origin. *Clin Exp Rheumatol* 2010; 28 (Suppl. 62): S48-53
2. TYNDALL AJ, BANNERT B, VONK M *et al*.: Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69: 1809-15.
3. KARDYS I, KORS JA, VAN DER MEER IM *et al*.: Spatial QRS-T angle predicts cardiac death in a general population. *Eur Heart J* 2003; 24: 1357-64.
4. TRIOLA B, OLSON MB, REIS SE *et al*.: Electrocardiographic predictors of cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol* 2005; 46: 51-6.
5. BORLEFFS CJ, SCHERPTONG RW, MAN SC *et al*.: Predicting ventricular arrhythmias in patients with ischemic heart disease: clinical application of the ECG-derived QRS-T angle. *Circ Arrhythm Electrophysiol* 2009; 2: 548-54.
6. LOWN B, WOLF M: Approaches to sudden death from coronary heart disease. *Circulation* 1971; 44: 130-42.
7. MOYSSAKIS I, GIALAFOS E, VASSILIOU V *et al*.: Aortic stiffness in systemic sclerosis is increased independently of the extent of skin involvement. *Rheumatology* 2005; 44: 251-4.
8. DILAVERIS P, PANTAZIS A, GIALAFOS E *et al*.: Determinants of electrocardiographic and spatial vectorcardiographic descriptors of ventricular repolarization in normal subjects. *Am J Cardiol* 2001; 88: 912-4.
9. ANTZELEVITCH C: Heterogeneity and cardiac arrhythmias: an overview. *Heart Rhythm* 2007; 4: 964-72.
10. VOULGARI C, MOYSSAKIS I, PERREA D *et al*.: The association between the spatial QRS-T angle with cardiac autonomic neuropathy in subjects with Type 2 diabetes mellitus. *Diabet Med* 2010; 27: 1420-9.
11. CIFTCI O, ONAT AM, YAVUZ B *et al*.: Cardiac repolarization abnormalities and increased sympathetic activity in scleroderma. *J Natl Med Assoc* 2007; 99: 232-7.
12. KOSTIS JB, SEIBOLD JR, TURKEVICH D *et al*.: Prognostic importance of cardiac arrhythmias in systemic sclerosis. *Am J Med* 1988; 84: 1007-15.
13. MORELLI S, PICCIRILLO G, FIMOGNARI F *et al*.: Twenty-four hour heart period variability in systemic sclerosis. *J Rheumatol* 1996; 23: 643-5.
14. MORSHEDI-MEIBODI A, EVANS JC, LEVY D *et al*.: Clinical correlates and prognostic significance of exercise-induced ventricular premature beats in the community: the Framingham Heart Study. *Circulation* 2004; 109: 2417-22.
15. KATRITSIS DG, CAMM AJ: Nonsustained ventricular tachycardia: where do we stand? *Eur Heart J* 2004; 25: 1093-9.