Cardiac Repolarization Abnormalities and Increased Sympathetic Activity in Scleroderma

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Background: Cardiac involvement in scleroderma is a poor prognostic sign and is usually underdiagnosed, particularly in asymptomatic patient. This paper focuses on QT dynamicity and heart rate variability (HRV) in patients with scleroderma and controls in an attempt to investigate the cardiac autonomic system and ventricular repolarization.

Methods: Sixty patients with scleroderma and 30 age- and sex-matched healthy controls who had no cardiovascular risk factors were included in this study. All patients and the controls underwent a 24-hour holter recording as well as a transthoracic echocardiography. HRV and QT dynamicity parameters were calculated.

Results: In HRV analysis, autonomic balance was changed in favor of the sympathetic system in patients with diffuse scleroderma. In QT dynamicity analysis, QT/RR slopes were significantly steeper in patients with diffuse scleroderma compared to patients with limited scleroderma and controls (QTapex/RR: 0.24 ± 0.16, 0.15 ± 0.03, 0.14 ± 0.03 respectively $p<0.001$; QTend/RR: 0.26 ± 0.17, 0.14 ± 0.04, 0.13 ± 0.05, respectively $p<0.001$).

Conclusions: Patients with diffuse scleroderma may have asymptomatic cardiac repolarization abnormalities and autonomic dysfunction. Our results may indicate that QT dynamicity and HRV can be useful noninvasive methods that may detect impaired state of autonomic balance and cardiac repolarization in patients with diffuse scleroderma.

Key words: scleroderma ■ heart ■ QT dynamicity ■ dermatlogy

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INTRODUCTION

Scleroderma is a multisystem connective tissue disorder affecting skin and internal organs mainly by means of fibrosis. Cardiac involvement is a poor prognostic sign, and it may be underdiagnosed particularly in the asymptomatic population.[1,2] Recognition of cardiac dysfunction in affected individuals may be particularly important to influence the overall prognosis favorably.

Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of sinus node and to identify patients at risk for increased cardiac mortality. It has been shown to reflect the sympatho-vagal balance in autonomic control of the cardiovascular system and used previously to define the role of autonomic nervous system (ANS) activity in certain cardiac disorders.[3]

QT dynamicity is a noninvasive and reliable predictor for the development of ventricular arrhythmias, particularly torsade de pointes. It can be measured by the slope of the linear regression line of QT/RR. A steeper slope indicating an excessive shortening of QT interval with faster heart rates and/or excessive lengthening of QT interval with slower heart rates may lead to cardiac arrhythmic events and increased mortality.[4,5]

This paper focuses on QT dynamicity and HRV in scleroderma patients and their age- and sex-matched controls in an attempt to investigate cardiac autonomic system and ventricular repolarization to reveal whether patients with scleroderma show susceptibility to ventricular arrhythmias.

METHODS

Sixty patients with scleroderma who fulfilled the American College of Rheumatology criteria for diagnosis of scleroderma[6] and were admitted to the outpatient clinic of the Hacettepe University Faculty of Medicine, Division of Rheumatology and Department of Cardiology between 2002 and 2004, were enrolled in this study. Patients were classified as having diffuse or limited scleroderma according to the extent of cutaneous involvement (diffuse scleroderma: skin-thickening

proximal to the elbow and/or knee, with or without face and neck involvement; limited scleroderma: skin sclerosis is confined to digits and small areas of the head and the neck). Extent of cutaneous compromise was also evaluated by modified Rodnan method.[7] Immunologic test results for antinuclear antibody, antitopoisomerase I (anti-Scl-70) and anticentromere antibodies, measurements of spirometry and carbon monoxide diffusing capacity (DLCO) of scleroderma patients were obtained from personal patient records. Forced vital capacity (FVC) ≥80% of predicted and DLCO ≥80% of predicted were considered normal pulmonary function.[8] An abnormal value in at least one test defined abnormal pulmonary function. Thirty age- and sex-matched healthy control subjects who had no cardiovascular risk factors were selected for the comparison group.

The study patients and control subjects fulfilled all of the following inclusion criteria: 1) no administration of drugs that would potentially influence QT duration; 2) no history of ischemic heart disease, congestive heart failure, atrial fibrillation or complete bundle branch block; and 3) normal serum levels of electrolytes, which may affect myocardial repolarization: potassium: 3.5–5.5 mEq/L; calcium: 8.6–10.2 mg/dl. Exclusion criteria were as follows: 1) moderate-to-severe valvular disease; 2) atrial fibrillation as baseline rhythm; 3) systolic left ventricular (LV) dysfunction (ejection fraction <50% and/or an LV end-diastolic dimension >5.5 mm); and 4) subjects who had cardiovascular disease including hypertension, diabetes mellitus, hypercholesterolemia (total cholesterol>200 mg/dl) and coronary artery disease. All patients and control subjects were in New York Heart Association (NYHA) class I. The local ethics committee approved the study, and patients gave informed consent before entry.

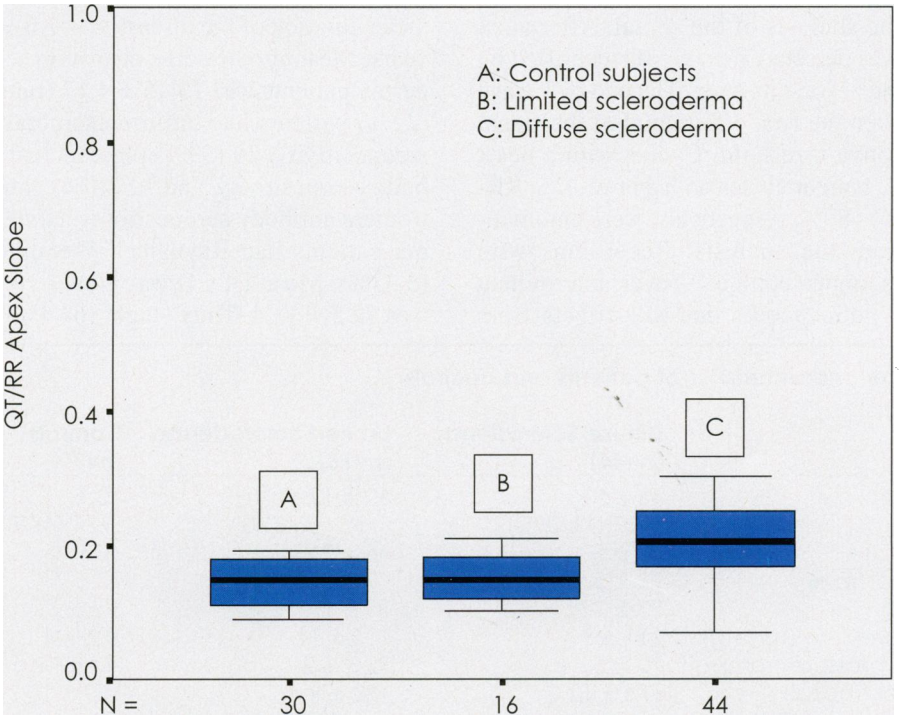
All patients (diffuse scleroderma and limited scleroderma) and controls underwent a 24-hour holter recording. Recordings were obtained using three-channel analog recorders and were analyzed using the ELATEC Holter system. ELATEC Holter software was used to calculate HRV and QT dynamicity parameters. All of the 24-hour recordings were reviewed manually by an experienced physician (Yavuz), and artifacts were deleted before analyzing. A transthoracic echocardiographic examination was performed to all subjects in the three groups.

Analysis of Heart Rate Variability Parameters

All 24-hour periods were used to evaluate HRV parameters. The following standard parameters were calculated from the time series to obtain the time domain analysis of HRV:[9]

1. SDNN (standard deviation of all NN intervals for a selected time period). This gives an impression of the overall circulatory dynamics.

Figure 1. QT/RR apex slope in patients and controls



2. RMSSD (square root of the mean of the sum of the squares of differences between adjacent RR intervals). Higher values indicate higher vagal activity.
3. pNN50 (the proportion of differences in successive NN intervals >50 ms). This parameter is also a measure of vagal activity.

Spectral analysis of HRV included: total power (TP), which represents variability of the entire signal and is obtained by summing powers of each frequency band; high-frequency (HF) component (0.15–0.40 Hz), which is a measure of parasympathetic limb of autonomic nervous system; low-frequency (LF) component (0.04–0.15 Hz), which is under influence of both parasympathetic and sympathetic systems; and very-low-frequency (VLF) component (0–0.04 Hz), a parameter of unknown origin but considered to reflect the slowly varying changes in the autonomic tone, probably related to processes such as thermoregulation. The normalized high-frequency power (HFnu = 100x HF power/TP), normalized low-frequency power (LFnu = 100 x LF power/TP), and low-/high-frequency power ratio (LF/HF ratio= LF power/HF power) were calculated to give the relative changes in HRV in the frequency domain.

Analysis of QT Dynamicity

Beat-to-beat analyses of QT intervals were done on ELATEC Holter software from a three-lead 24-hour ambulatory ECG. Each RR interval and its QT interval were measured in milliseconds. QRS complexes in each cycle were detected as the starting point. The Q wave was detected by the analysis of the signal. After apex (peak) of T wave was detected, its end was identified by analysis of the slope beyond its apex. The end of T wave was determined when the first differential of the signal fell below an adaptive threshold. Cycles with a heart rate <30 bpm, >160 bpm or cycles with a prevailing RR-interval <66% and >180%, respectively, were automatically excluded from the analysis. Recordings with prominent artifacts, imperceptible T waves, intermittent atrial fibrillation, poor records due to artifacts from excessive sweating and chest movement were also excluded. A minimum of 18 hours of recording and a minimum of 90% consecutive QT intervals were required for a tape to be acceptable. The QT/RR relationship was then analyzed by ELATEC software package. Slopes and correlation coefficients of the linear QT/RR regression were computed for day and nighttime and 24 hours. Recordings were excluded from further analysis if the pooled QT/RR correlation was <0.5.

STATISTICAL ANALYSIS

Distribution of the continuous variables was determined by the Kolmogorov-Smirnov test, and all were found to be distributed normally; therefore, parametric tests were performed. All numeric variables were expressed as mean ± SD, and categorical variables were expressed as percentages. Distribution of the numeric variables between groups was tested by using one-way analyses of variance (ANOVA) method. Means were compared by ANOVA. Tukey was used for post hoc analysis. The significance of correlations was assessed by Pearson correlation analysis. For all statistics, a two-sided p value <0.05 was considered statistically significant. SPSS® for Windows® version 10.0 statistical package was used.

RESULTS

Baseline characteristics of subjects are shown in Table 1. There were no significant differences with respect to age and gender distribution between patients and controls. There were 44 (73.3%) diffuse scleroderma and 16 (26.7%) limited scleroderma patients. The mean duration of the disease was 7.6 ± 7.0 (range 1–40) years. Mean modified Rodnan skin score of the scleroderma patients was 13.15 ± 4.17 (range 8–24). Fifteen (25%) patients had antitopoisomerase I (anti-Scl-70) seropositivity, 20 (33%) patients had antinuclear antibody seropositivity, and 12 (20%) patients had anticentromere antibody seropositivity. None of the scleroderma patients had Raynaud's phenomenon except two (3.33%). Mean DLCO was 84.9 ± 16.4 and mean FVC was 82.5 ± 13.4. Thirty-eight (64.4%) patients had pul-

Table 1. Baseline characteristics of patients and controls

Characteristic	Diffuse Scleroderma (n=44)	Limited Scleroderma (n=16)	Controls (n=30)	P Value
Age (mean ±SD)	46 ± 11	50 ± 12	50 ± 12	NS
Male/female (n/%)	5/39 (11/89%)	3/13 (19/81%)	5/25 (17/83%)	NS
LVEF (mean ± SD)	68 ± 5	68 ± 2	68 ± 4	NS
Heart Rate (beat/min)	75 ± 5	79 ± 6	77 ± 7	NS
ESR (mm/h)	33 ± 22	25 ± 17	5 ± 2	<0.001
Systolic blood pressure (mmHg)	111 ± 9	105 ± 11	108 ± 9	NS
Diastolic blood pressure (mmHg)	70 ± 5.3	72 ± 6.2	70 ± 7.9	NS
Total cholesterol (mg/dl)	176 ± 12.3	182 ± 9.4	179 ± 10.7	NS

LVEF: Left ventricle ejection fraction; ESR: Erythrocyte sedimentation rate

monary involvement that was determined by using FVC and DLCO measurements as described above. Serum creatinine levels were in the normal range in all patients, and none of the patients had proteinuria. Fifty-five patients (92%) were receiving steroids, 53 (88%) cyclophosohamide, two (1%) azathioprine, nine (15%) d-penicillamine; and two patients were on calcium channel blocker therapy due to Raynaud's phenomenon. Left ventricular ejection fraction (LVEF) was not significantly different between patients and controls (68 ± 5 vs. 68 ± 4, p=NS). Systolic blood pressure, diastolic blood pressure, serum potassium, serum calcium and plasma total cholesterol levels were not significantly different in patient and control groups, whereas erythrocyte sedimentation rate (ESR) was significantly different in patients with scleroderma than controls (Table 1).

In HRV analysis, among time domain indices, SDNN showed a statistically significant decrease in diffuse scleroderma patients than limited scleroderma patients and controls, whereas other time domain indices in the patient group did not differ significantly from those in the control group. In contrast, among frequency domain indices, LFnu was statistically higher in diffuse scleroderma patients than limited scleroderma patients and controls, while HFnu was statistically lower in the diffuse scleroderma group than both groups. In addition, the LF/HF ratio was statistically higher in the diffuse scleroderma group than patients with limited form of disease and controls. There was no significant difference in any HRV parameters between patients with limited scleroderma and controls (Table 2).

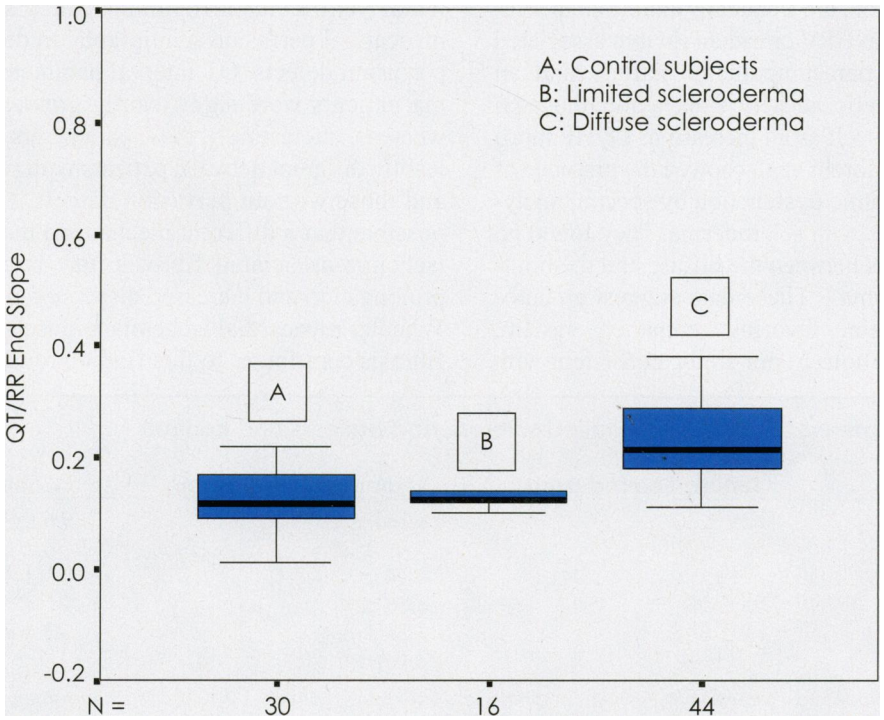
QT/RR slopes over 24 hours were significantly steeper for QT apex and QT end in patients with diffuse scleroderma compared to limited scleroderma and control groups (QTapex/RR: 0.24 ± 0.16, 0.15 ± 0.03, and 0.14 ± 0.03 respectively, $p<0.001$; QTend/RR: 0.26 ± 0.17, 0.14 ± 0.04, and 0.13 ± 0.05 respectively, $p<0.001$). QT dynamicity parameters are shown in Figures 1 and 2.

There was no significant correlation between HRV and QTd parameters and disease duration, pulmonary involvement, DLCO, FVC, Rodnan index, Raynaud's phenomenon, and medications such as steroids, cyclophosohamide, azathioprine and d-penicillamine.

DISCUSSION

This study showed that diffuse scleroderma is associated with a significant worsening of HRV and QT dynamicity parameters. Our data strongly suggest that diffuse scleroderma patients have cardiac repolarization abnormalities indicated by a steeper QT/RR regression line accompanied by sympathetic overactivity in HRV analysis. Patients with limited scleroderma, however, did not show any significant difference compared to the controls regarding any HRV or QT dynamicity parameter. To our knowledge, our study is the first study evaluating QT dynamicity parameters in patients with scleroderma.

Figure 2. QT/RR end slope in patients and controls



Few studies reported on myocardial repolarization—namely, the QT interval indices—in scleroderma. Increased QTc and QT dispersion have been reported in scleroderma patients.[10] In contrast, in another study, QT interval did not differ significantly between early-stage scleroderma patients and controls.[11] It was reported that QT dynamicity is affected by autonomic nervous system, certain drugs,[12-14] and cardiac electrical milieu.[5] In general, a steeper slope of the QT/RR regression line has been related to an unfavorable prognosis. QT dynamicity has been shown to have a prognostic value in various cardiac pathologies, including CHF,[4] ischemic cardiomyopathy,[15] and ventricular fibrillation without a structural heart disease.[16] It is also associated with an increased risk for ventricular arrhythmias and sudden cardiac death.[4,17] In the present study, we found that slopes for both QTapex and QTend were significantly steeper than controls in diffuse scleroderma but not in limited form.

Steeper QT/RR slopes in our patient population may be explained in two manners. The first possible explanation is the impaired HRV favoring sympathetic nervous system. Autonomic nervous system may modulate cardiac repolarization and cause ventricular tachyarrhytmias. Such an association between ANS and QT interval was found in congenital long QT syndrome.[18] Cardiac autonomic dysfunction in scleroderma has been reported in the literature, the incidence ranging from 0–100%.[19,20] The limited form has also been reported to be involved in some reports, whereas some other reports exclude this finding.[19,21] HRV parameters, an indirect reflection of cardiac autonomic function, are frequently abnormal in scleroderma. A decrease in HRV circadian rhythm associated with a decrease in parasympathetic activity and an increase in sympathetic activity (i.e., sympathovagal imbalance reflecting itself as an increase in LF/HF ratio) has been reported.[22] Morelli et al. showed the presence of cardiovascular autonomic dysfunction by spectral analysis of HRV in patients with scleroderma. They found no significant differences between the diffuse and the limited form of scleroderma.[23] These data suggest an autonomic imbalance, mainly favoring sympathetic system, in this patient population. In our study, consistent with previous reports, we found that frequency domain indices of HRV show dramatic differences between diffuse scleroderma and controls.

The second possible mechanism of steeper QT/RR slopes is fibrotic involvement of myocardium with resultant inhomogeneity and dispersion of myocardial repolarization. Fibrotic involvement of myocardium is the hallmark of sclerodermal myocardial involvement and is present in about 50–70% of the patients.[24] It has been hypothesized that this process may be a result of repetitive myocardial ischemia called myocardial Raynaud's phenomenon, similar to primary Raynaud's phenomenon. Supporting this hypothesis, some investigators found lesions in small myocardial arterioles similar to those in the peripheral arterioles of primary Raynaud's phenomenon.[25,26] Some, on the other hand, did not confirm this finding.[27,28] Hence, the mechanism responsible for myocardial ischemia in scleroderma may be different than that of primary Raynaud's phenomenon. The fibrotic involvement of the myocardium may be present in both forms of the disease—namely, the diffuse scleroderma and the limited scleroderma, and the widespread myocardial fibrosis is associated with the degree of cardiac dysfunction.[24] Although fibrosis is such a common finding, whether it causes prolongation and increased dispersion of ventricular repolarization in scleroderma patients remains controversial. Patchy myocardial fibrosis and contraction band necrosis might lead to electrical inhomogeneity throughout the myocardial cells, thereby causing distortion of repolarization and making patients prone to lethal ventricular arrhythmias. In a study that used myocardial perfusion scintigraphy to detect myocardial perfusion defects, QT interval parameters in scleroderma patients were significantly greater than controls, whereas, interestingly, these parameters were not significantly different between patients with perfusion defects and those without perfusion defects.[10] Therefore, it is possible that a different mechanism than ischemia and ischemia-associated fibrosis may be responsible for prolongation and increased dispersion of repolarization. Whether myocardial ischemia and ischemia-associated fibrosis contributes to this finding remains unknown in

Table 2. HRV parameters in diffuse and limited scleroderma patients and controls

	Diffuse Scleroderma	Limited Scleroderma	Control Subjects
SDNN (ms)	125 ± 30*	161 ± 38	163 ± 41
RMSSD (ms)	34 ± 30#	43 ± 25	38 ± 22
PNN50 (%)	7 ± 1α	14 ± 4	11 ± 10
24-hour LFnu	55 ± 15**	38 ± 7	35 ± 7
24-hour HFnu	12 ± 8†	24 ± 6	23 ± 7
LF/HF ratio	7.1 ± 6.6‡	1.6 ± 0.6	1.7 ± 0.9

* P=0.01 for diffuse scleroderma vs. controls; ** P <0.001 for diffuse scleroderma vs. controls; ‡ P <0.001 for diffuse scleroderma vs. controls; ‡ P=0.001 for diffuse scleroderma vs. controls; # P=NS for diffuse scleroderma vs.limited scleroderma and controls; α=NS for diffuse scleroderma vs.limited scleroderma and controls

our study, as we did not apply myocardial perfusion scan to detect myocardial ischemia, and we did not perform myocardial biopsy, either. Future studies on QT dynamicity and myocardial ischemia may answer this question.

Study Limitations

There are some limitations of our study. First, as mentioned above, we did not perform myocardial perfusion scintigraphy to address the relationship between perfusion defects and QT dynamicity parameters. As the number of patients with Raynaud's phenomenon is too small, we could not perform correlation analysis between QT dynamicity, and HRV parameters and peripheral Raynaud's phenomenon, a myocardial form of which is considered responsible in myocardial fibrosis and repolarization abnormalities.

CONCLUSION

Patients with diffuse scleroderma may have asymptomatic cardiac repolarization abnormalities and ANS dysfunction. Our results may indicate that QT dynamicity and HRV can be useful noninvasive methods that may detect impaired state of autonomic balance and cardiac repolarization in patients with diffuse scleroderma.

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