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ORIGINAL ARTICLE

QT dispersion increases in patients with systemic lupus erythematosus

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Abstract Although autopsy studies have documented that heart is affected in most of systemic lupus erythematosus (SLE) patients, clinical manifestations occur in less than 10%. QT dispersion, a new parameter that can be used to assess homogeneity of cardiac repolarization and autonomic function, has not been studied in SLE patients. The aim of our study was to evaluate the QT dispersion (QTd) in SLE patients without overt cardiac involvement. Eighty-three patients with a diagnosis of SLE (mean age 41±13) and age- and sex-matched 77 healthy control subjects (mean age 43±10) were enrolled in the study. All subjects had their complete history taken, laboratory examination, and transthoracic echocardiography (ECG). Patients with cardiac disease, hypertension, diabetes, or taking medications that may effect QTd or any ECG abnormalities were excluded. Resting 12-lead ECG were recorded for measurement of QTd. None of the patients and control subjects had overt cardiac involvement. The mean SLE duration was 86.5±15.4 months. QT dispersion was significantly greater in SLE patients than incontrol subjects (55.2±24.7 vs 20.7±5.3 ms, respectively; $p<0.001$). There was no correlation between QTd and duration of SLE, SLEDAI-K score, corticosteroid usage, and presence of anti SS-A antibody. QT dispersion is significantly increased in SLE patients without overt cardiac involvement. Our result suggests that prolonged QT dispersion can be a useful noninvasive and simple method for early detection of cardiac involvement in SLE patients.

Keywords Autoimmune disease · Cardiac involvement · Electrocardiography · QT dispersion · Systemic lupus erythematosus · Ventricular repolarization

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Introduction

Systemic lupus erythematosus (SLE) is a connective tissue disease characterized by the formation of autoantibodies and immune complexes. Cardiovascular involvement is now considered as the third leading cause of death among patients with SLE. Autopsy studies have documented that heart is affected in most patients [1]. Pericarditis and premature coronary atherosclerosis are the most prevalent cardiac manifestations. Other rare associations include myocarditis, coronary arteritis, Libman–Sacks endocarditis, constrictive pericarditis, cardiomyopathy, congenital heart block, and rhythm abnormalities. However, clinical manifestations occur in less than 10% of SLE patients [1, 2].

Interlead variability of the duration of the QT interval in the 12-lead echocardiography (ECG) is defined as QT dispersion (QTd). It is a new parameter that can be used to assess the homogeneity of cardiac repolarization and autonomic function [3]. Increased heterogeneity of repolarization was shown in several heart diseases and also associated with increased risk of ventricular tachyarrhythmias [4]. Prolonged QTd was also shown in rheumatoid arthritis and ankylosing spondylitis [5–7]. However, to our knowledge, QTd has not been studied in SLE patients. The purpose of our study was to examine whether QT dispersion increases in SLE patients without overt cardiac involvement.

Materials and methods

Patients with diagnosis of SLE according to the revised criteria of the American Collage of Rheumatology were selected from the rheumatology outpatient clinic of our university hospital [8]. The healthy control subjects were recruited from our internal medicine and cardiology outpatient clinics. The study patients and control subjects fulfilled all of the following inclusion criteria: (1) no administration of drugs that would potentially influence QT duration except hydroxycholoroquine (HCQ); (2) no history of ischemic heart disease, congestive heart failure, atrial fibrillation, bundle branch block, or abnormal serum electrolytes; (3) normal rest ECG; and (4) a good quality ECG recording for measurement of the QT interval. The exclusion criteria were: (1) moderate or severe valve disease; (2) atrial fibrillation and other ECG abnormalities; (3) systolic LV dysfunction (ejection fraction <50% or an LV end-diastolic dimension >5.5 mm); (4) if the end of the T wave of a patient's ECG could not be determined reliably; and (5) known presence of cardiac disease including hypertension, diabetes, and coronary artery disease. SLE disease activity was detected by erythrocyte sedimentation rate (ESR) and SLEDAI-2K score [9]. All patients gave written informed consent to take part in the study, which was approved by the local ethics committee. All subjects had their complete history taken, laboratory examination, ECG, and transthoracic echocardiography. Treadmill exercise test with Bruce protocol was performed to rule out coronary artery disease.

Electrocardiography

All SLE patients and controls had a rest 12-lead ECG recorded at 25 mm/s paper speed. QT intervals were measured manually from the onset of QRS to the end of the T wave defined as a return to the T–P baseline. If U waves were present, the subjects were excluded from the study. Three consecutive cycles in each of the 12 leads were measured. All measurements were made blindly (without knowledge of the subjects' clinical status) by two experienced cardiologist. From the three cycles, QT intervals were calculated. Dispersion parameters were calculated as the difference between maximal and minimal values of QT. The blinded inter- and intra-observer variability of QT measurements were both <5%.

In this study, corrected QTd was not calculated because in previous studies it has been shown that a rate correction of parameters of dispersion of repolarization is probably unnecessary and may even distort the values and predictive value of QTd [10, 11].

Transthoracic echocardiography

Transthoracic echocardiographic examination was performed on all subjects by using a System Five (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner and 2.5–3.5 MHz transducers. Left ventricular end-diastolic and end-systolic diameter (cm), ejection fraction (%) were measured by M-mode echocardiography. Color Doppler and continuous and pulsed Dopler were performed to evaluate LV and valvular functions.

Statistical analysis

The skewed data are expressed as median; min–max and normally distributed data are expressed as mean±SD. As the data of QT dispersion were distributed normally, parametric tests were utilized to evaluate differences among the study groups. Means were compared by analysis of variance. Spearman's correlation rank test was used for the correlation of the parameters. A p value below 0.05 was considered as statistically significant. All analyses were performed by using SPSS 10.0 software.

Results

We studied 83 SLE patients (mean age 41±13) and 77 healthy control subjects (mean age 43±10, p=NS). The baseline characteristics of the patients and of the control group are shown in Table 1. There were no significant differences with respect to sex, age, systolic and diastolic blood pressure, and heart rate. All patients and control subjects had normal ejection fraction (66.9±3.5 vs 65.9±/3.3, respectively). Anti-nuclear antibody was positive in all patients except in one, and anti-ds-DNA was positive in 22 patients. Anti-SS-A antibody was positive in 23 patients. In

Table 1 Clinical characteristics of SLE patients and control subjects

Characteristics	SLE patients (n=83)	Control subjects (n=77)
Age	41±13	43±10
Gender (male/female)	4/79	5/72
Systolic blood pressure (mmHg)	127±14	128±13
Diastolic blood pressure (mmHg)	81±9	83±8
Heart rate (beats/min)	73±2	75±3
Left ventricular ejection fraction (%)	66.9±3.5	65.9±3.3

the patient group, mean disease duration was 86.5± 15.4 months and the mean value of cumulative prednisolone dose was 17.4±1.9 g. Forty patients were receiving hydroxychloroquine, and 22 patients were under corticosteroid treatment (Table 2). The minimum–maximum and median values of ESR in SLE patients were 3–120 and 15.0 mm/h, respectively; those values of SLEDAI-2K score of SLE patients were 0–18 and 2.0, respectively. No subject had significant valvular heart disease and cardiac complaints. Treadmill exercise test result was negative in patients and controls.

We found that QT dispersion value is significantly higher in SLE patients than in control subjects (55.2± 24.7 vs 20.7±5.3 ms, respectively; $p<0.001$) (Fig. 1). The mean QTd of patients receiving corticosteroids or other anti-inflammatory regimens and those who were not at the time of examination was similar. The mean QTd in patients who have not received hydroxychloroquine was 53.7±19.2 ms, and it was 56.6±29.0 ms in patients who have received HCQ (p=NS). Similar to HCQ, corticosteroid did not give statistically significant results. In patients who have not received corticosteroid, mean QTd was 56.1±27.0 ms, and it was 52.5±17.2 ms in patients who have received corticosteroid (p=NS). There was no correlation between the QTd and the baseline characteristics of the subjects including disease duration, ESR, and SLEDAI-2K score, the presence of any of the diagnostic criteria for SLE, and also the presence of anti-SS-A antibody and QTd.

Discussion

QT dispersion has been shown to be increased and an important prognostic factor in several cardiovascular conditions such as coronary artery disease, congestive heart failure, and cardiomyopathies [12–16]. Although increased QT dispersion has been shown in various rheumatic diseases [5–7, 17], QTd has not been examined in SLE patients yet. To the best of our knowledge, this is the first study evaluating the QT dispersion in patients with SLE.

Table 2 Medication use in patients with SLE

Drug	Usage of drug (number of patients on drug/ number of patients not on drug; percentage of patients receiving the drug)
Prednisolone	22/66; 26
Azathioprine	28/55; 33
Hydroxychloroquine	43/40; 52
Cyclophospamide	42/41; 50

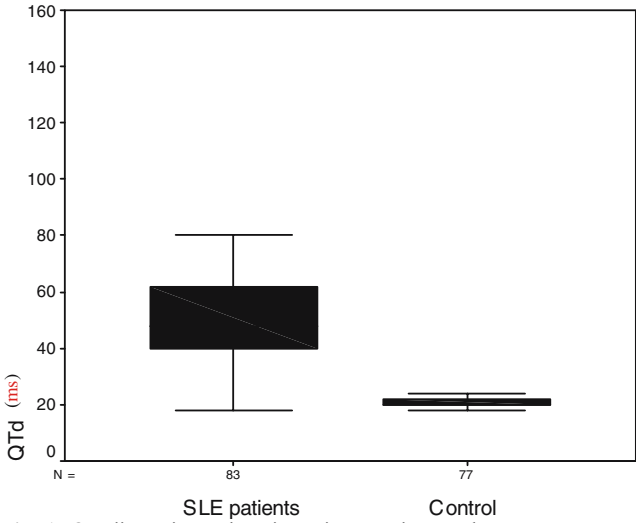

Fig. 1 QT dispersion values in patients and controls

We found that QT dispersion is significantly higher in patients with SLE than in control subjects.

Myocardial involvement can be seen in SLE patients even in the absence of clinical cardiac manifestations. Previous studies using Tc-99 m sestamibi myocardial perfusion single-photon emission computed tomography (SPECT) showed high incidence of myocardial perfusion abnormalities in asymptomatic lupus patients without any clinical signs of cardiac involvement [18–20]. Schillaci et al. found that eight patients with positive SPECT had normal epicardial coronary vessels documented with coronary angiography [18]. In patients without clinical cardiac manifestations, those perfusion defects were probably due to the primary immunological damage and small focal cardiofibrosis of this autoimmune disease. The areas of myocardial fibrosis in SLE may disrupt the course of ventricular repolarization and lead to increase the dispersion of recovery time throughout the ventricle. As QT dispersion proves useful information of heterogeneity of ventricular repolarization, prolonged QTd that we found in our study may reflect silent myocardial involvement in SLE patients. Therefore, QT dispersion may be a useful and simple marker to identify subclinical myocardial involvement in SLE patients.

Heart rate variability (HRV) is one of the methods in evaluating autonomic function which was found to be significantly impaired in patients with SLE than in control subjects [21]. QT dispersion has been shown to increase in patients with autonomic dysfunction [22]. Therefore, another possible explanation of prolonged QTd in SLE patients may be related to the autonomic dysfunction, which can be present in the SLE patients.

The potential limitations of this study should be addressed. HRV measurements and myocardial perfusion SPECT analysis in association with QTd may give more information about the etiology of prolonged QTd in SLE patients, but these tests

are more expensive and complex and may not be necessary in patients without overt heart disease. Therefore, QTd which has not been studied in SLE patients was examined alone in this present study.

Conclusion

QT dispersion is significantly increased in SLE patients without overt cardiac involvement. Our result may indicate that prolonged QT dispersion can be a useful noninvasive and simple method of early detection of subclinical cardiac involvement in SLE patients. Further studies are needed to evaluate the prognostic significance of QT dispersion and to clarify the mechanism of increased QT dispersion in SLE.

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