Assessment of Inhomogeneities of Repolarization in Patients with Systemic Lupus Erythematosus

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Objectives: Systemic lupus erythematosus (SLE) is a chronic disease that affects many organ systems and manifests a broad spectrum of laboratory and clinical features. SLE patients have an increased risk of developing cardiovascular disease. The aim of this study was to evaluate inhomogeneities of repolarization by using $T_{\text{peak}}-T_{\text{end}}$ (Tp-e) interval and Tp-e/QT ratio were measured from the 12-lead surface electrocardiogram (ECG) in patients with SLE.

Material and method: This study included 69 SLE patients (69 females; mean age 35.8 ± 10.2) and 57 control subjects (57 females; mean age 34.5 ± 8.9). Transthoracic echocardiographic examination was done in all participants. QT parameters, Tp-e intervals and Tp-e/QT ratio were measured from the 12-lead ECG. These parameters were compared between groups.

Results: No statistically significant difference was found between two groups in terms of basic characteristics. Diastolic function parameters were similar between the two groups ($P > 0.05$). In electrocardiographic parameters analysis, QT dispersion (QTd) and corrected QT dispersion (cQTd) were significantly increased in SLE patients compared the control group (49.5 ± 16.4 ms vs. 32.8 ± 11.7 ms and 56.7 ± 19.5 ms vs. 36.4 ± 13.1 ms, all P value < 0.001). Tp-e interval and Tp-e/QT ratio were also significantly higher in SLE patients (82.8 ± 18.9 vs. 72.4 ± 17.6 and 0.22 ± 0.05 vs. 0.19 ± 0.05 , $P = 0.002$ and $P = 0.001$, respectively). Tp-e interval and Tp-e/QT were positively correlated with disease duration ($r = 0.29$, $P = 0.01$ and $r = 0.24$, $P = 0.04$, respectively).

Conclusion: Our study revealed that QTd, cQTd, Tp-e interval and Tp-e/QT ratio increased in patients with SLE. Also, Tp-e interval and Tp-e/QT were positively correlated with disease duration.

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systemic lupus erythematosus; arrhythmia; inhomogeneities of repolarization; Tp-e interval;
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SLE is an autoimmune disease that involves multiple systems.¹ It is a clinically and serologically extremely heterogeneous disease characterized by attacks and remissions, potentially involving any organ and tissue with a broad range of clinical manifestations.² Cardiac manifestations are one of its most important clinical features and all components of the heart can be affected.³ SLE is a chronic inflammation of organism and inflammation is a prominent feature of atherosclerotic lesions.⁴ Investigators

observed the prevalence of clinically manifest ischemic heart disease has ranged between 8% and 16% in patients with SLE in various studies.^{5,6} Decreased myocardial perfusion, even without clinical manifestations, can be a consequence of direct immunologic aggression. Consequently, multiple small areas of fibrosis can affect ventricular repolarization and ventricular dysfunction in patients with SLE.⁷ Abnormalities ventricular repolarization could predispose patients to malignant arrhythmias.⁸

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The $T_{\text{peak}}-T_{\text{end}}$ (Tp-e) interval has been accepted as a measure of global dispersion of repolarization and is one of the risk factors for life-threatening ventricular arrhythmias in adults.^{9,10} Several publications showed that Tp-e is longer in disorders such as long QT syndrome, polymorphic catecholaminergic ventricular tachycardia and Brugada syndrome. It may be also a predicting factor for elevated risk of sudden cardiac death in patients with heart disorders.¹¹⁻¹³ However, It is affected by variations of heart rate and body weight. Tp-e/QT ratio has been suggested to be a more accurate measure for the dispersion of ventricular repolarization compared to others parameters, and to be independent of alterations in heart rate.^{9,14} Ventricular repolarization was previously evaluated by using QT interval measurements in patients with SLE,¹⁵⁻¹⁷ but Tp-e interval and Tp-e/QT ratio have not been studied in SLE patients before.

The aim of this study was to evaluate inhomogeneities of repolarization from a 12-lead surface ECG in patients with SLE.

PATIENTS AND METHODS

Between May 2013 and December 2013, 69 consecutive patients (69 females; mean age 35.8 ± 10.2), who were followed at Selcuk University, diagnosed as SLE according to the revised criteria of the American Collage of Rheumatology for classification of SLE, and the 57 age-matched healthy volunteers (57 females; mean age 34.5 ± 8.9) were included. Clinical characteristics, laboratory findings (C-reactive protein, erythrocyte sedimentation rate, white blood cell, hemoglobin, creatine, fasting blood glucose, low-density lipoprotein cholesterol, triglycerides), echocardiographic findings and medications in current use were recorded. The disease duration was estimated by considering the day of the initial examination, in which the patient fulfilled all the American Rheumatism Association criteria, to be the onset. Patients with coronary artery disease, heart failure, rheumatic valve disease, primary cardiomyopathy, diabetes mellitus, thyroid dysfunction, anemia, hypercholesterolemia, electrolyte imbalance, chronic lung disease, and bundle branch block, atrioventricular conduction abnormalities on ECG and ECGs without clearly analysable QT segment were excluded from the study. None of the participants

Figure 1. Tp-e = QT interval-QT peak.

were taking antiarrhythmic drugs, beta-blockers, digitalis, or nondihydropyridine calcium-channel blockers.

This study complied with the Helsinki declaration of 1975, as revised in 2000, was approved by the Ethics Committee and the institutional review board of Selcuk University Medical School.

ELECTROCARDIOGRAPHY

All standard 12-lead ECGs were obtained simultaneously using a recorder, which was set at a 50 mm/s paper speed and 20 mm/mV standardization. Resting heart rate was measured from the ECG taken during the patient evaluation. ECG measurements of QT and Tp-e intervals were performed by two cardiologists who were blind to the patient data. QT interval was measured from the QRS complex to the end of the T wave in leads DII. The QT interval was corrected by the RR intervals according to the Bazett's Formula (i.e., $QT_c = QT/\sqrt{RR}$). The QTd was defined as the difference between the maximum and minimum QT interval of the 12 leads. QT peak interval was measured from the beginning of the QRS to the apex of the T wave. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave, and was obtained from the difference between QT interval and QT peak interval, measured from the beginning of the QRS to the apex of the T wave (Fig. 1). All

measurements were measured in 12 leads, but V_2 and V_5 leads were used for measurements of Tp-e interval. The Tp-e interval was corrected as heart rate. To improve the reliability of T-wave off set determination, leads with low-amplitude T waves (<0.1 mV) were excluded from analysis. The Tp-e/QT ratio was calculated from these measurements.

ECHOCARDIOGRAPHIC ASSESSMENT

Transthoracic echocardiographic examination was done in all patients with Vivid E9 system using a 1.5–4.6 MHz probe (GE-Vingmed Ultrasound AS, Horten, Norway). Color Doppler, continuous, pulsed and tissue Doppler studies were done to evaluate left ventricular, left atrial and valvular function. The following parameters were recorded by a cardiologist who was blind to the participants' clinical data: ejection fraction (EF), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular mass index (LV mass index), left atrial volume index (LA volume index), peak velocity of early diastolic filling (E wave), late diastolic filling (A wave), deceleration time of the E-wave velocity (DT), isovolemic relaxation time (IVRT). Tissue Doppler parameters were measured: early diastolic mitral annular velocity (Em), and late diastolic mitral annular velocity (Am). The mean of three measurements was used for analysis of the Doppler data. The ratio of mitral peak velocity of early diastolic filling to early diastolic mitral annular velocity (E/Em) was calculated from the lateral annulus. All echocardiographic assessments were performed according to published criteria of the American Society of Echocardiography.

STATISTICAL ANALYSIS

SPSS 18.0 for Windows was used for statistical analyses (SPSS, Chicago, IL, USA). Quantitative data were expressed as mean $\pm$ SD. Categorical data were presented as frequencies and percentages. Categorical variables were compared using the Student's *t* test. Mann-Whitney *U* test was used for the determination of differences between the two groups. Pearson's correlations analysis was used to examine the strength of relationship between continuous variables and outcomes. A *P*

value less than <0.05 was considered statistically significant.

RESULTS

Clinical characteristics and laboratory findings of the two groups are shown in Table 1. Age, body mass index, body surface area, smoking status, systolic and diastolic blood pressure were similar between the two groups ($P > 0.05$). Erythrocyte sedimentation rate, plasma level of hsCRP, and serum creatinine levels were significantly higher in patients with SLE when compared with controls ($P < 0.001$, $P = 0.001$, and $P = 0.01$, respectively). White blood cell was significantly lower in SLE patients ($P < 0.001$). The mean disease duration was 80.91 ± 56.26 months (Table 1). The echocardiographic parameters of the groups are shown in Table 2. LVEDD, LVESD, EF, LV mass index, aort diameter, LA diameter, LA volume index, and diastolic function parameters were similar between the two groups ($P > 0.05$). Interventricular septum (IVS) and left ventricular posterior wall (PW) thickness were higher in the patients with SLE than in the control group (for both $P < 0.001$).

The electrocardiographic parameters of the groups are shown in Table 3. Heart rate, QT, and cQT intervals were similar in both groups ($P = 0.08$, $P = 0.10$, $P = 0.52$, respectively). QTd and cQTd were significantly increased in SLE patients compared to the controls (for all *P* values < 0.001). Tp-e interval, cTp-e interval, and Tp-e/QT ratio were significantly higher in SLE patients compared to the control group in lead V_2 ($P = 0.002$, $P = 0.001$, and $P = 0.001$, respectively). Also, Tp-e interval, cTp-e interval, and Tp-e/QT ratio were significantly higher in SLE patients compared to the control group in lead V_5 ($P = 0.02$, $P = 0.008$, and $P = 0.001$, respectively). Tp-e interval and Tp-e/QT were positive correlated with disease duration ($r = 0.29$, $P = 0.01$ and $r = 0.24$, $P = 0.04$, respectively; Figs. 2 and 3).

DISCUSSION

SLE patients have an increased risk of developing cardiovascular disease, particularly before the age of 50.¹⁸ Very sensitive methods of cardiovascular investigation have found the prevalence of cardiac involvement in SLE to be higher than 50%.¹⁹

Table 1. Clinical Characteristics of the Study Population at the Time of Examination

	SLE Group (n = 69)	Control Group (n = 57)	P
Age (years)	35.8 ± 10.2	34.5 ± 8.9	0.48
BMI (kg/m ²)	25.9 ± 4.6	26.0 ± 4.7	0.85
BSA (m ²)	1.72 ± 0.15	1.68 ± 0.14	0.17
SBP (mmHg)	107.7 ± 15.1	106.4 ± 13.3	0.64
DBP (mmHg)	68.2 ± 10.8	67.8 ± 8.3	0.81
Hb (mg/dL)	13.1 ± 1.5	13.0 ± 1.0	0.79
WBC (X10 ³ /l)	5.8 ± 1.7	7.1 ± 1.7	<0.001
FBG (mg/dL)	90.2 ± 8.9	91.6 ± 14.0	0.49
LDL-C (mg/dL)	106.1 ± 29.0	115.2 ± 35.0	0.11
TG (mg/dL)	107.9 ± 56.7	97.9 ± 40.1	0.26
Cr (mg/dL)	0.76 ± 0.10	0.72 ± 0.08	0.01
ESR	22.2 ± 17.2	10.6 ± 7.8	<0.001
CRP	5.1 ± 3.7	3.3 ± 0.3	0.001
HT	12	10	1.0
DL	8	4	0.55
Smoking	12	13	0.51
Disease duration (months)	80.91 ± 56.26		
Discoid rash, n (%)	12 (17.4)		
Photosensitivity, n (%)	51 (73.9)		
Oral ulcers, n (%)	24 (34.8)		
Nonerosive arthritis, n (%)	40 (58.0)		
Renal disorder, n (%)	24 (34.8)		
Neurologic disorder, n (%)	13 (18.8)		
Hematologic disorder, n (%)	35 (50.7)		
Medical treatment			
Hydroxychloroquine, n (%)	69 (100)		
Prednisolone, n (%)	22 (31.9)		
Salicylazosulfapyridine, n (%)	2 (2.9)		
Methotrexate, n (%)	6 (8.7)		
Azothioprine, n (%)	8 (11.6)		

BMI = body mass index; BSA = body surface area; Cr = serum creatinine; CRP = C-reactive protein; DBP = diastolic blood pressure; DL = dyslipidemia; ESR = erythrocyte sedimentation rate; FBG = fasting blood glucose; Hb = hemoglobin; HT = hypertension; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TG = triglycerides; WBC = white blood cell.

Statistically significant P values shown in bold.

Mortality rates remain higher in SLE patients compared with the general population. The bimodal distribution of SLE mortality was first described by Urowitz et al. in 1976.²⁰ This model suggests that early death is largely the result of active disease and infections, while a significant portion of late deaths are the result of atherosclerosis and cardiovascular disease. Myocarditis is the most characteristic feature of myocardial involvement in SLE. The risk of developing coronary artery disease (CAD) is four to eight times higher than volunteers. In young women with SLE, the risk of myocardial infarction is increased 50-fold. However, in SLE patients myocardial dysfunction may be the consequence of other features, particularly CAD due to premature atherosclerosis, hypertension, renal failure, valvular disease, and toxicity

from medications, such as cyclophosphamide and chloroquine.^{21,22}

Prior smaller studies have reported LV diastolic dysfunction in SLE patients.²³⁻²⁵ Early myocardial involvement was further confirmed in patients with SLE. Pieretti et al. found that SLE could predict increased LV mass in the absence of valvular and clinical coronary artery disease, possibly due to inflammation-related arterial stiffening, and there was a moderate correlation between LV mass and SLICC/ACR damage index.²⁶ In our study, we also found patients with SLE had increased ventricular wall thickness and LV mass index compared to the controls. We also detected a greater LA diameter and LA volume index, a higher DT and IVRT in the SLE patients, but they were statistically insignificant.

Table 2. Comparison of the Echocardiographic Parameters

	SLE Group (n = 69)	Control Group (n = 57)	P
LVEDD (mm)	43.9 ± 3.6	44.4 ± 3.5	0.46
LVESD (mm)	27.1 ± 4.9	27.2 ± 3.0	0.94
IVS (mm)	8.9 ± 1.0	8.1 ± 1.2	<0.001
PW (mm)	8.6 ± 1.0	7.8 ± 1.3	<0.001
EF (%)	65.9 ± 4.0	66.0 ± 3.7	0.95
LV mass index (g/m ²)	78.5 ± 16.0	77.7 ± 13.5	0.80
Aort diameter (mm)	25.2 ± 2.4	25.2 ± 2.5	0.98
LA diameter (mm)	32.7 ± 3.6	31.7 ± 3.4	0.20
LA volume index (mL/m ²)	28.4 ± 7.1	26.4 ± 6.9	0.20
E/A ratio	1.48 ± 0.37	1.65 ± 0.45	0.06
IVRT (ms)	98.6 ± 19.4	96.2 ± 16.4	0.53
DT (ms)	183.8 ± 43.2	170.5 ± 39.1	0.14
Em/Am (lateral)	1.49 ± 0.48	1.52 ± 0.58	0.72
E/Em (lateral)	6.78 ± 2.01	6.95 ± 2.83	0.74

DT = deceleration time; E/A = early mitral inflow velocity to late mitral inflow velocity ratio; E/Em = early mitral inflow velocity to early diastolic mitral annular velocity ratio; Em/Am = early diastolic mitral annular velocity to late diastolic mitral annular velocity ratio; EF = ejection fraction; IVRT = isovolumetric relaxation time; IVS = interventricular septum; LA = left atrium; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PW = posterior wall. Statistically significant P values are shown in bold.

Table 3. Comparison of the Electrocardiographic Parameters

	SLE Group (n = 69)	Control Group (n = 57)	P
HR (bpm)	78.6 ± 13.9	74.4 ± 11.9	0.07
QT (ms)	358.8 ± 31.2	368.2 ± 33.4	0.10
QTd (ms)	49.5 ± 16.4	32.8 ± 11.7	<0.001
cQT (ms)	406.6 ± 20.8	404.2 ± 22.4	0.52
cQTd (ms)	56.7 ± 19.5	36.4 ± 13.1	<0.001
Tp-eV ₂ (ms)	82.8 ± 18.9	72.4 ± 17.6	0.002
cTp-eV ₂ (ms)	94.4 ± 23.4	80.9 ± 22.3	0.001
Tp-e/QT _{V2}	0.22 ± 0.05	0.19 ± 0.05	0.001
Tp-eV ₅ (ms)	78.1 ± 13.6	72.4 ± 14.0	0.02
cTp-eV ₅ (ms)	88.7 ± 17.0	80.4 ± 17.2	0.008
Tp-e/QT _{V5}	0.21 ± 0.03	0.19 ± 0.03	0.001

HR = heart rate; QT = QT interval; QTd = QT dispersion; cQT = corrected QT interval; cQTd = corrected QT dispersion; Tp-eV₂ = T_{peak} to T_{end} interval in leads V₂; cTp-eV₂ = corrected T_{peak} to T_{end} interval in leads V₂; Tp-e/QT_{V2} = T_{peak} to T_{end} interval to QT interval ratio in leads V₂; Tp-eV₅ = T_{peak} to T_{end} interval in leads V₅; cTp-eV₅ = corrected T_{peak} to T_{end} interval in leads V₅; Tp-e/QT_{V5} = T_{peak} to T_{end} interval to QT interval ratio in leads V₅. Statistically significant P values are shown in bold.

Heart rhythm disorders have been documented in SLE patients and seem to occur in 10% of cases, either alone or in association with other heart conditions.²⁷ Also, conduction disturbances and sudden cardiac death in SLE have higher incidence than expected in the general population.²⁸ Heart rhythm disorders can be related with CAD, myocarditis, or small vessel vasculitis with collagen deposition and fibrosis affecting the conduction system in SLE.^{8,28} Moreover, increased inflammatory activity is proposed to be associated with the pathogenesis of cardiovascular disease and arrhythmia.^{16,17}

In our study, we found significant differences in QTd and cQTd between SLE patients and control group. The QT duration, in particular heart rate-corrected QT interval duration and QT dispersion remain the most common measure for repolarization abnormalities both in clinical and research settings.²⁹ Cardosa et al. reported that QTd was greater in patients with SLE compared with controls.¹⁶ Kojuri et al. reported that QTd was significantly increased in SLE patients with high disease activity compared to patients with low disease activity.¹⁷ Prolonged QTd and cQTd that we found in our study may reflect

Figure 2. Positively correlations between Tp-e interval and disease duration ($r = 0.29$, $P = 0.01$).

silent myocardial involvement in SLE patients. Therefore, QTd may be a useful and simple marker to identify subclinical myocardial involvement in SLE patients.

In general, repolarization proceeds from epicardium to endocardium, that is, opposite to the direction of ventricular depolarization.³⁰ It is now well recognized that ventricular myocardium is electrically a heterogeneous structure, comprised of three distinct myocardial cell types—epicardial, endocardial, and Masonic Midmyocardial Moe cells (M cells).³¹ Although these cells are histologically similar, they have different electrophysiological properties.³² The action potential duration of epicardial cells is shorter than that of the endocardial and midmyocardial cells.³⁰ The M cells typically have the longest action potential duration followed by endocardial and epicardial cells.⁹ It is known that inhomogeneities of repolarization occur over relatively short distances on the surface of the ventricles and most probably also within the ventricular wall.³⁰ Full repolarization of the epicardial action potential coincides with the peak of the T wave and repolarization of the M cells is coincident with the end of the T wave. It follows

that the duration of the M cell action potential determines the QT interval, whereas the duration of the epicardial action potential determines the QT peak interval, and the Tp-e interval may provide an index of transmural dispersion of repolarization.³²

The clinical value of Tp-e for risk assessment has been previously investigated in several studies involving mainly patients with a known cardiac disease.^{13,29} In most of these studies the difference in action potential duration between epi-/endocardial cells and M cells was suggested to cause lethal arrhythmia.^{11,17,33} So, Tp-e may be useful index for predicting ventricular tachyarrhythmias. In this study, QTc was similar in both groups, but Tp-e was significantly higher in the SLE group. The QTc indicates total repolarization duration, but this may not be the sole determinant of arrhythmia risk. Uniform myocardial repolarization delay may cause increased QT duration. Therefore Tp-e measurements have demonstrated superior discriminatory characteristics when compared with QTc and QTd for predicting adverse arrhythmic events in diverse patient populations.^{34,35} So, both QT and Tp-e

Figure 3. Positively correlations between Tp-e/QT and disease duration ($r = 0.24$, $P = 0.04$).

must also be evaluated to determine the risk of cardiovascular events in patients with SLE.

Tp-e/QT ratio was reported as a more accurate marker for ventricular arrhythmogenesis compared to Tp-e interval and QTd, due to its independence from heart rate. Functional reentry is the underlying mechanism for arrhythmogenesis associated with an increased Tp-e/QT ratio.⁹ This study showed that Tp-e/QT ratio were prolonged in patients with SLE when compared to the controls.

The available data suggest that Tp-e measurements should be limited to precordial leads, because these leads may more accurately reflect transmural dispersion of repolarization.³² Different precordial leads from V₁ to V₆ were used to measurement QT parameters. In some studies QT parameters were measured in right precordial lead (V₂),^{34,36} and QT parameters were measured in left precordial lead (V₅) in other studies.^{37,38} In this study, all parameters were measured in 12 leads. Tp-e and Tp-e/QT measurements were done in leads V₂ and V₅. These values were significantly greater in both right and left precordial leads in the SLE group.

Tp-e and Tp-e/QT ratio were positively correlated with the disease duration. These parameters have not previously been assessed in SLE patients. According to our results, Tp-e and Tp-e/QT ratio may use for predicting an index of transmural dispersion of repolarization in SLE patients. Therefore, our findings may be a pathfinder for further studies.

LIMITATIONS

We did not assess the association between ventricular arrhythmias with Tp-e interval and Tp-e/QT ratio. Also study population could not be followed-up prospectively for ventricular arrhythmic episodes. Large-scale prospective studies are needed to determine the predictive value of Tp-e interval and increased Tp-e/QT ratio in SLE patients.

CONCLUSION

Our study revealed that ventricular repolarization heterogeneity parameters including Tp-e and

Tp-e/QT ratio were increased in patients with SLE. To the best of our knowledge, they might be a useful marker of cardiovascular morbidity and mortality due to ventricular arrhythmias in patients with SLE.

BRIEF SUMMARY

The $T_{\text{peak}}-T_{\text{end}}$ (Tp-e) interval has been accepted as a measure of global dispersion of repolarization and is one of the risk factors for life-threatening ventricular arrhythmias. The aim of this study was to evaluate inhomogeneities of repolarization by using Tp-e interval and Tp-e/QT ratio in patients with SLE. Our study revealed that Tp-e interval and Tp-e/QT ratio increased in patients with SLE. Also, Tp-e interval and Tp-e/QT were positively correlated with disease duration.

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