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ORIGINAL ARTICLE

# The Assessment of Tp-e Interval and Tp-e/QT Ratio in Patients With Systemic Sclerosis

Çağrı YAYLA,[1] Müçteba Enes YAYLA,[2] Kadriye GAYRETLİ YAYLA,[3]
Ufuk İLGEN,[2] Mehmet Kadri AKBOĞA,[1] Nurşen DÜZGÜN[4]

[1]*Department of Cardiology, Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey*
[2]*Department of Internal Medicine, Medical Faculty of Ankara University, Ankara, Turkey*
[3]*Department of Cardiology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey*
[4]*Department of Rheumatology, Medical Faculty of Ankara University, Ankara, Turkey*

***ABSTRACT***

**Objectives:** This study aims to investigate ventricular repolarization using T-peak to T-end (Tp-e) intervals and Tp-e/QT ratios in patients with systemic sclerosis (SSc).

**Patients and methods:** Totally 65 patients (8 males, 57 females; mean age 49.8 years; range 20 to 77 years) with SSc and 63 control subjects (8 males, 55 females; mean age 49.3 years; range 20 to 77 years) were enrolled. Tp-e intervals, Tp-e/QT, and Tp-e/corrected QT (QTc) ratios were measured from the 12-lead electrocardiogram.

**Results:** Tp-e intervals, QT intervals, QTc intervals, Tp-e/QT, and Tp-e/QTc ratios were significantly higher in patients with SSc than control subjects (all $p<0.01$). There was no difference between patients with diffuse and limited cutaneous SSc in terms of electrocardiogram and echocardiographic findings. Correlation analysis revealed no correlation between Tp-e intervals, Tp-e/QT, and Tp-e/QTc ratios with disease duration and anti-Sjögren's syndrome antigen A antibody levels in patients with SSc (all $p>0.05$).

**Conclusion:** Our study showed that Tp-e intervals, Tp-e/QT, and Tp-e/QTc ratios were increased in patients with SSc than control subjects. The increased frequency of ventricular arrhythmias can be clarified by increased indexes of ventricular repolarization parameters in patients with SSc.

***Keywords:*** Systemic sclerosis; Tp-e interval; Tp-e/QT ratio.

Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by fibrosis of the skin and visceral organs, such as kidneys, lungs, and heart. Varied cardiovascular complications may appear in SSc, most commonly dysrhythmias and pulmonary hypertension.[1-3] Cardiovascular involvement has been demonstrated to be one of the major causes of mortality in SSc and may occur in up to 70% of patients according to autopsy reports.[4,5] The major causes of cardiovascular death in patients with SSc are refractory heart failure and dysrhythmias.[6]

Ventricular repolarization may be defined using QT interval, QT dispersion, and T wave measurements. Prolonged QT interval and increased QT dispersion have been shown in patients with SSc.[7] In recent studies, the Tp-e interval, the interval between the peak and the end of the T wave, has been specified as an index of total dispersion of repolarization.[8,9] Prolonged Tp-e interval may predict ventricular arrhythmias and mortality.[10-12] Thus, Tp-e/QT ratio has been proposed to be a better marker of ventricular repolarization.[13,14]

To our knowledge, no trial has evaluated the Tp-e interval and Tp-e/QT ratio as markers of ventricular arrhythmogenesis in patients with SSc. Therefore, in this study, we aimed to investigate

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**Correspondence:** Çağrı Yayla, MD. Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği, 06230 Sıhhiye, Ankara, Turkey.
Tel: +90 533 - 644 96 43 e-mail: cagriyayla@gmail.com

ventricular repolarization using Tp-e intervals and Tp-e/QT ratios in patients with SSc.

## PATIENTS AND METHODS

Between January 2014 and May 2015, the study included 65 consecutive patients (8 males, 57 females; mean age 49.8 years; range 20 to 77 years) with SSc and 63 age and sex similar control subjects (8 males, 55 females; mean age 49.3 years; range 20 to 77 years). All patients met American Rheumatism Association's preliminary criteria for diagnosis of definite scleroderma and 2013 American College of Rheumatology/European League Against Rheumatism Classification criteria for SSc.[15,16] Patients were classified as having diffuse or limited cutaneous SSc according to LeRoy Classification criteria.[17] Patients with SSc were screened in terms of disease duration (defined as interval between date of diagnosis and inclusion into study) and Raynaud's phenomenon. All patients were examined to be in sinus rhythm and were asymptomatic in terms of cardiac symptoms. Patients and control subjects with diabetes mellitus, hypertension, valvular heart disease, coronary artery disease, wall motion abnormalities with left ventricular ejection fraction below 50%, severe pulmonary disease, malignancy, kidney/hepatic failure, incomplete/complete bundle branch block, atrial fibrillation, and paced rhythm were excluded. Baseline demographic and clinical characteristics were noted. Written informed consent was obtained from each patient. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the Local Ethics Committee.

Echocardiographic assessment was performed by using a Vivid 7 dimension cardiovascular ultrasound system (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer. Echocardiographic examination was performed in the left lateral decubitus position. Parasternal long- and short-axis views and apical views were used as standard imaging windows. Left atrial diameter, end systolic and end diastolic dimensions were measured from parasternal long-axis view. Ejection fraction was calculated by using modified Simpson method. All echocardiographic examinations were performed by an experienced cardiologist.

The 12-lead electrocardiogram (ECG) was recorded at a paper speed of 50 mm/second (Hewlett Packard, Page-writer, USA) in the supine position. ECGs were performed while the patient was at rest and at 8:00-10:00 AM in the morning. All of the ECGs were scanned and transferred to a personal computer to decrease the error measurements, and then used for x400% magnification by Adobe Photoshop software. ECG measurements of QT and Tp-e intervals were performed by two cardiologists who were blinded to the patient data. Subjects with U waves on their ECGs were excluded from the study. A mean value of three readings was calculated for each lead. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for heart rate using the Bazett's formula: cQT = QT$\sqrt{}$ (R-R interval). The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of the Tp-e interval were performed from precordial leads.[10] The Tp-e/QT ratio was calculated from these measurements. Interobserver and intraobserver coefficients of variation were 2.4% and 2.8%, respectively.

Peripheral venous blood samples were drawn from the antecubital vein after 12-hour of fasting in the morning. Blood samples were taken into standardized tubes containing dipotassium ethylenedinitrilotetraacetic acid for complete blood count. Coulter Counter LH Series (Beckman coulter Inc., Hialeah, Florida) was used for complete blood count. Plasma levels of triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, and creatinine were evaluated using an automated chemistry analyzer (Aeroset, Abbott, USA) with commercially available kits (Abbott, USA). Antinuclear antibodies were analyzed by immunofluorescence (Immunoconcepts, Sacramento, CA, USA). Anticentromere antibodies, anti-topoisomerase I antibodies and anti-Sjögren's syndrome antigen A and B were analyzed by the multiplex immunoassay BioPlex 2200 ANA screen system (Bio-Rad, Hercules, CA, USA).

### Statistical analysis

For statistical analysis, IBM SPSS version 20.0 Statistical Package Program for Windows (IBM Corporation, Armonk, NY, USA) was used. Kolmogorov-Smirnov test was used to test normality of distribution. Quantitative variables with a normal distribution were specified as the mean ± standard deviation. Categorical variables were shown as number and percentage values. Differences between groups were evaluated by using Student's t test. Categorical variables were compared with Chi-square test. Pearson correlation analysis was performed to examine the relationship between Tp-e interval, Tp-e/QT ratio and Tp-e/QTc, and other variations. A p value of <0.05 was accepted as statistically significant.

## RESULTS

Baseline clinical characteristics and laboratory parameters of the study groups were listed in Table 1. There were 12 diffuse and 53 limited cutaneous SSc patients. There was no statistically significant difference between groups in terms of age, sex, and basal laboratory findings (all p>0.05), except for high-density lipoprotein cholesterol level which was significantly lower in patients with SSc than control subjects (p=0.017). Mean disease duration of patients was 8.1±7.5 years.

The ECG and echocardiographic findings were presented in Table 2. There was no difference between the two groups in terms of left ventricular ejection fraction (p=0.108). Tp-e intervals, QT intervals, QTc intervals, Tp-e/QT ratios, and Tp-e/QTc ratios were significantly higher in patients with SSc than control subjects (all p<0.01). Besides, there was no difference between patients with diffuse and limited cutaneous SSc in terms of ECG and echocardiographic findings (Table 3). In correlation analysis, there were no correlations between Tp-e intervals, Tp-e/QT, and Tp-e/QTc ratios with disease duration and anti-Sjögren's syndrome antigen A antibody levels in patients with SSc (p>0.05).

## DISCUSSION

In this study, we demonstrated that Tp-e intervals, Tp-e/QT, and Tp-e/QTc ratios were prolonged in patients with SSc as compared to healthy subjects. To the best of our knowledge, this study was the first clinical trial focusing on the relationship between Tp-e interval, Tp-e/QT, Tp-e/QTc ratios, and SSc.

**Table 1.** Baseline characteristics and laboratory parameters of study population

| Parameters | Systemic sclerosis patients (n=65) | | | Control subjects (n=63) | | | |
|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | n | % | Mean±SD | p |
| Age (years) | | | 49.8±13.2 | | | 49.3±10.5 | 0.832 |
| Female | | 87.6 | | | 87.3 | | 0.947 |
| Smoking | | 3.1 | | | 4.7 | | 0.389 |
| Weight (kg) | | | 65.0±15.4 | | | 67.6±9.5 | 0.469 |
| Height (cm) | | | 162.9±7.8 | | | 163.8±6.3 | 0.634 |
| Body mass index | | | 24.4±5.2 | | | 25.3±4.3 | 0.464 |
| Hemoglobin (g/dL) | | | 12.7±1.3 | | | 13.1±1.0 | 0.159 |
| Creatinine (mg/dL) | | | 0.7±0.2 | | | 0.8±0.1 | 0.065 |
| Glucose (mg/dL) | | | 87.1±16.9 | | | 92.4±12.0 | 0.076 |
| Total-cholesterol (mg/dL) | | | 176.8±37.8 | | | 189.8±42.7 | 0.115 |
| HDL-cholesterol (mg/dL) | | | 48.4±15.2 | | | 54.8±10.7 | 0.017 |
| LDL-cholesterol (mg/dL) | | | 103.8±29.6 | | | 109.3±35.7 | 0.406 |
| Triglyceride (mg/dL) | | | 119.8±47.0 | | | 129.4±76.0 | 0.461 |
| Diffuse/limited | 12/53 | | | – | | | – |
| Raynaud's phenomenon (+/–) | 60/5 | | | – | | | – |
| Anti-centromere antibodies (+/–) | 24/41 | | | – | | | – |
| Anti-Ro/SSA antibodies (+/–) | 15/50 | | | – | | | – |
| Anti-La/SSB antibodies (+/–) | 4/61 | | | – | | | – |
| Anti-Scl-70 antibodies (+/–) | 19/46 | | | – | | | – |
| Antinuclear antibodies (+/–) | 62/3 | | | – | | | – |
| Disease duration (years) | | | 8.1±7.5 | | | – | – |

SD: Standard deviation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Anti-Ro/SSA antibodies: Anti-Sjögren's syndrome antigen A antibody; Anti-La/SSB antibodies: Anti-Sjögren's syndrome antigen A antibody; Anti-Scl-70 antibodies: Anti-scleroderma 70 antibodies.

**Table 2.** Electrocardiographic and echocardiographic characteristics of study population

| Parameters | Systemic sclerosis patients (n=65) | Control subjects (n=63) | *p* |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Heart rate (bpm) | 77.1±15.2 | 75.3±11.4 | 0.503 |
| Tp-e interval (ms) | 70.0±10.8 | 53.2±9.4 | <0.001 |
| QT interval (ms) | 367.1±35.6 | 347.7±26.0 | 0.002 |
| QTc interval (ms) | 410.8±30.2 | 386.9±33.8 | 0.001 |
| Tp-e/QT ratio | 0.19±0.03 | 0.15±0.02 | <0.001 |
| Tp-e/QTc ratio | 0.17±0.02 | 0.14±0.02 | <0.001 |
| Left ventricular ejection fraction | 60.4±2.3 | 61.2±2.5 | 0.108 |
| Left ventricular end diastolic diameter (mm) | 44.9±4.2 | 45.9±3.0 | 0.193 |
| Left ventricular end sistolic diameter (mm) | 26.3±4.9 | 28.0±2.7 | 0.068 |
| Left atrial diameter (mm) | 34.0±6.3 | 33.8±2.7 | 0.918 |

SD: Standard deviation; Tp-e interval: T-peak to T-end interval.

There are some studies investigating the association between SSc, coronary fibrosis, and atherosclerosis.[18-20] Microvascular dysfunction and fibrosis has a major role in the pathogenesis of the SSc, especially in cardiac complications.[2,3] Myocardial fibrosis is characteristic for heart involvement in SSc and observed in 50% to 70% of patients.[4] Fibrosis may be a result of recurrent myocardial ischemia called myocardial Raynaud's phenomenon, similar to primary Raynaud's phenomenon. Researchers showed lesions in microvascular arteries of myocardium like in the peripheral arterioles of primary Raynaud's phenomenon to support this probability.[21,22] Myocardial fibrosis plays a major role in the development of ventricular arrhythmias and makes left ventricle susceptible to by damaging electrical conduction, stimulating the development of re-entry circuits, and augmenting ventricular refractoriness and excitability of myocytes.[23,24]

Symptomatic cardiac involvements such as ventricular arrhythmias, significant conduction disturbances, heart failure, and moderate or severe pericardial effusion were shown in 10.1% of patients with SSc.[25] Nevertheless, asymptomatic and subclinic cardiac involvement are common than estimated, prevalence being approximately 15% to 45%.[1-3,26] Kostis et al.[6] showed a strong correlation between ventricular ectopic beats and total mortality and sudden death in 183 patients with SSc. Ventricular tachycardia was also found in 7% of patients with SSc. In a study, the frequencies of ECG abnormalities such as QT prolongation and ventricular extrasystole were higher in patients with SSc.[27] Sgreccia et al.[7] found that QT dispersion and QT interval were increased significantly in patients with SSc. Also, Gialafos et al.[28] demonstrated that abnormal spatial QRS-T angle, a marker of ventricular repolarization, was wider in patients with SSc.

**Table 3.** Electrocardiographic and echocardiographic characteristics of patients with systemic sclerosis

| Parameters | Diffuse cutaneous systemic sclerosis (n=12) | Limited cutaneous systemic sclerosis (n=53) | *p* |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Heart rate, bpm | 73.7±5.8 | 78.0±16.8 | 0.485 |
| Tp-e interval, ms | 67.8±9.5 | 70.6±11.2 | 0.530 |
| QT interval, ms | 370.6±21.3 | 366.2±38.9 | 0.763 |
| QTc interval, ms | 409.8±19.3 | 411.1±32.9 | 0.921 |
| Tp-e/QT ratio | 0.18±0.02 | 0.19±0.02 | 0.346 |
| Tp-e/QTc ratio | 0.16±0.02 | 0.17±0.03 | 0.520 |
| Left ventricular ejection fraction | 59.5±1.3 | 60.6±2.4 | 0.144 |
| Left ventricular end diastolic diameter (mm) | 46.3±1.9 | 44.5±4.5 | 0.246 |
| Left ventricular end systolic diameter (mm) | 27.3±3.9 | 26.1±5.2 | 0.515 |
| Left atrial diameter, mm | 36.6±3.5 | 33.2±6.8 | 0.252 |

SD: Standard deviation; Tp-e interval: T-peak to T-end interval.

QT dispersion was described as a sign of increased dispersion of repolarization but finally lost its importance as a faulty concept.[8,29] Recently, the Tp-e interval and Tp-e/QT ratio have been used as novel markers of increased dispersion of ventricular repolarization.[13,14,30] Prolonged Tp-e interval was related with increased mortality in long QT syndrome, Brugada syndrome and in patients with acute ST-segment elevation myocardial infarction.[14] Nevertheless, Tp-e interval is affected by alterations in heart rate and body weight.[9] In recent studies, the Tp-e/QT ratio was suggested to be a more precise measure for the dispersion of ventricular repolarization than QT dispersion, QTc dispersion and Tp-e intervals, and to be independent of variations in heart rate.[9,13] The literature indicates the applicability of Tp-e/QT ratio as a potency significant index of arrhythmogenesis, under the conditions of short, normal, and long QT intervals.[14] Also, several studies have demonstrated the relationship between Tp-e/QT ratio and rheumatic diseases such as rheumatoid arthritis and ankylosing spondylitis.[31,32] Myocardial fibrosis is well known result of SSc. Therefore, alterations in myocardial tissue may cause heterogeneity in ventricular repolarization and this may also result in significant ventricular arrhythmias in patients with SSc. Similarly, we have found significant differences in Tp-e interval, QT interval, QTc interval, Tp-e/QT and Tp-e/QTc ratios between patients with SSc and the control group. Tp-e interval, QT interval, QTc interval, Tp-e/QT and Tp-e/QTc ratios were significantly higher in patients with SSc.

These results may contribute to the pathophysiological mechanisms of the increased prevalence of arrhythmias by specifying increased ventricular repolarization heterogeneity in patients with SSc. Increased incidence of ventricular arrhythmias may be clarified by prolonged transmural dispersion in these patients.

Our study has some limitations. First is its relatively small sample size. Second, it has a cross-sectional design and lacks follow-up of patients. Also, since we had no data on Rodnan skin scores, disease activity index, and disease severity scale, we were unable to evaluate the association between ECG findings and these indexes. Additionally, due to diurnal variation of ECG parameters in a day, 24-hour Holter ECG recording may be more valuable for evaluating dispersion of ventricular repolarization. We were unable to evaluate the relationship between ventricular arrhythmias and Tp-e interval and Tp-e/QT ratio. Therefore, long-term follow-up and large-scale prospective studies are needed to investigate the predictive value of the Tp-e interval and Tp-e/QT ratio in patients with SSc.

In conclusion, our study demonstrated that Tp-e interval, QT interval, QTc interval, Tp-e/QT and Tp-e/QTc ratios were increased in patients with SSc. Further and large-scale prospective studies are required to clarify the prognostic importance of Tp-e interval and Tp-e/QT ratio in predicting arrhythmias in patients with SSc.

**Declaration of conflicting interests**

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