Evaluation of the Tp-Te interval, Tp-Te/QTc ratio, and QT dispersion in patients with Turner syndrome

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Abstract

Objective: To evaluate ventricular repolarization parameters using the interval from the peak to the end of the T wave (Tp–Te), together with QT and corrected QT (QTc) intervals, QT dispersion (QTd), and Tp-Te/QTc ratio in patients with Turner syndrome (pwTS) and to compare the results with those from healthy controls.

Methods: In total, 38 patients previously diagnosed with Turner syndrome (TS) and 35 healthy girls (controls) were included in our cross-sectional study. Twelve-lead electrocardiography (ECG) and echocardiography after a 30-min rest were performed. The QT, QTc, QTd, Tp-Te interval, and Tp-Te/QTc ratio were determined.

Results: No differences in age or sex were observed between the groups. QT intervals were similar in both groups [pwTS: 354.76±25.33 ms, controls (C): 353.29±17.51 ms, p=0.775]. pwTS had significantly longer QTc and QTd than controls (411.87±22.66 ms vs. 392.06±13.21 ms, p<0.001 and 40.31±2.02 ms vs. 37.54±1.83 ms, p<0.001, respectively). Similarly, the Tp-Te interval and Tp-Te/QTc ratio were significantly longer in pwTS than in controls (71.89±3.39 ms vs. 65.34±2.88 ms, p<0.001 and 0.17±0.01 vs. 0.16±0.01, p=0.01).

Conclusion: As pwTS have longer QTc, QTd, Tp–Te interval, and Tp-Te/QTc ratio, an annual follow-up with ECG can provide awareness and even prevent sudden death in them. Also avoiding the use of drugs that makes repolarization anomaly and having knowledge about the side effects of these drugs are essential in pwTS. *(Anatol J Cardiol 2018; 20: 93-9)*

Keywords: Turner syndrome, sudden cardiac death, QTc, QTd, Tp-Te, Tp-Te/QTc

Introduction

Turner syndrome (TS) is the most common sex chromosome anomaly in the female population caused by partial or total deletion of the X chromosome (1, 2). Mortality and morbidity rates mainly from cardiovascular diseases are higher in patients with TS (pwTS) (3). The most common cardiovascular malformations are aneurysms in the ascending aorta, aortic coarctation, bicuspid aorta, and a partial anomaly in the pulmonary vein connection (4, 5).

Also, electrophysiological anomalies have been also identified in adults with TS other than anatomical anomalies, which include right axis deviation, T-wave abnormalities, short PR in-

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Accepted Date: 11.05.2018 **Available Online Date:** 10.07.2018

DOI:10.14744/AnatolJCardiol.2018.98250

Anatol J Cardiol 2018; 20: 93-9
DOI:10.14744/AnatolJCardiol.2018.98250

terval, increased AV node conduction, prolongation of corrected QT (QTc) interval, and many more. Cardiac conduction and repolarization abnormalities are supposedly caused by intrinsic defects of conduction system in pwTS. The QTc interval prolongs at varying rates in elderly and young pwTS (6-8). Recent studies have shown that the genetic defects causing congenital anomalies in the cardiovascular evolution can be associated with conduction defects and extensive myopathical changes in the adult population (9).

In cardiology practice, Tp-Te interval has emerged as a novel electrocardiography (ECG) marker of increased transmural dispersion of ventricular repolarization. Studies have suggested that the Tp-Te interval and Tp-Te/QTc ratio are associated with malignant ventricular arrhythmias and increased risk for sudden cardiac death (10). We evaluated the ventricular repolarization parameters using the Tp-Te interval together with QT, QTc, QTd, Tp-Te/QTc ratio in pwTS and compared the results with those from healthy control subjects. Identifying patients with increased QTc, QTd, Tp-Te interval, and Tp-Te/QTc ratio during routine follow-up can be life-saving.

Methods

Ethics statement

This study was approved by the Local Medical Ethics Committee of İstanbul University İstanbul Faculty of Medicine. Written informed consent was obtained from all patients before starting the study.

Study subjects

In all, 38 patients who were previously diagnosed with TS and were examined between January 2013 and December 2014 at the Pediatric Medicine Department, İstanbul Faculty of Medicine, İstanbul University and 35 healthy girls (controls) were included. The patients were recruited using the Turner Syndrome Society of the United States website announcements between 2001 and 2005.

All measurements were obtained after a light breakfast in a room with a temperature of 20°C-24°C, and we were assured that patients had not smoked cigarettes in the last week, drank alcohol within 1 day, and were not on a strict exercise program. All participants underwent 12-lead ECG and echocardiography after a 30-min rest.

We evaluated the uncorrected QT and the QTc interval with QTd and measured the Tp-Te interval and Tp-Te/QTc ratio of all subjects. Patients with ECG anomalies such as LBBB and RBBB; arrhythmias such as atrial fibrillation, prominent U wave, history of using QT affecting drugs, electrolyte imbalance, cardiovascular anomalies; and patients who smoked cigarettes and/or had alcohol or had any other systemic diseases were excluded (n=17).

Table 1. Reproducibility data for the measurements of electrocardiographic parameters

	Intraobserver (%)	Interobserver (%)
QT	2.6	3.0
QTc	2.6	2.9
QTd	2.6	3.0
Tp-Te interval	2.6	2.9

QT - QT interval; QTc - rate-corrected QT interval; QTd - QT dispersion; Tp–Te - Tp–Te interval

Electrocardiography

All participants underwent 12-lead ECG recorded on a digitized ECG using the on-screen digital caliper software Cardio Calipers ver. 3.3 (Iconico, Inc., New York, NY, USA). All ECGs were recorded at 50 mm/s with an amplitude of 10 mm/mV. Lead DII was selected from all ECG recordings to compare the PR, QRS, QT, and RR intervals. ECG measurements of the QT and Tp-Te intervals were performed manually by one cardiologist two times and by two different cardiologists three times, using calipers and a magnifying glass to decrease measurement errors (Table 1).

The QT interval was measured manually from lead DII as the distance between the beginning of the QRS complex and the downslope of the T wave (intersection with the isoelectric line). The QT interval corrected for heart rate (n) was calculated using Bazett's formula ($QTc=n/\sqrt{RR}$).

QTd was defined as the difference between the maximum (QTmax) and minimum QT (QTmin) intervals of the 12 leads.

The Tp-Te interval (ms) was calculated with the tangent method (11). It was measured from the peak of the T wave (or nadir if a negative or biphasic T wave was obtained) and the intersection between the tangent at the steepest point of the T-wave downslope and the isoelectric line. Previous studies have shown that transmural dispersion of repolarization is better in precordial leads and apical–basal or global spatial dispersion is better in limb leads; thus, the Tp–Te interval was measured from the best available T wave in lead DII (12). Precordial leads V5 and V6 were used when DII was not suitable for analysis. Two subjects had U waves and their T-wave amplitudes were <1.5 mV, so they were excluded. The recorded Tp–Te value was the greatest value obtained by the two observers from the DII precordial lead.

Echocardiographic analysis

All patients underwent an echocardiographic evaluation according to the American Society of Echocardiography recommendations (13). All examinations were performed by one operator using a commercially available echocardiographic machine (IE33; Philips, Andover, MA, USA) with a phased-array probe (X5-1) for the acquisition of M-mode, 2-DE, and Doppler images to study left ventricular dimensions, wall thickness, and functions.

Parasternal and apical views were used with the patient in a left lateral decubitus position. All views were recorded as digital images and then reanalyzed.

Statistical analysis

All statistical analyses were conducted using SPSS 19.0 for Windows software (SPSS Inc., Chicago, IL, USA). The data are presented as mean, standard deviation, median, range, percentage, and number. The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov or Shapiro–Wilk test. Normally distributed data of two independent groups were compared using the independent samples t-test; the Mann–Whitney U test was used if the data were non-normally distributed. Intra- and inter-observer variabilities for QT, QTc, QTd, and Tp–Te interval measurements in all patients were estimated according to the Bland and Altman method. A p-value of <0.05 was considered significant.

Table 2. Baseline characteristics of the study population

	pwTS (n=38)	Control (n=35)	*P*
Age, years	14.39±5.03	13.17±2.85	0.248
Height, cm	138.96±14.92	152.86±15.75	0.002
BMI, kg/m^2	22.62±5.24	19.72±3.47	0.025
SBP, mm Hg	112.28±29.89	97.76±11.38	0.019
DBP, mm Hg	78.00±7.9	67.06±14.73	0.002
ECG			
BPM, beats/min	100.42±19.58	83.55±10.33	<0.001
QT, ms	354.76±25.33	353.29±17.51	0.775
QTc, ms	411.87±22.66	392.06±13.21	<0.001
QTd, ms	40.31±2.02	37.54±1.83	<0.001
Tp-Te, ms	71.89±3.39	65.34±2.88	<0.001
Tp-Te / QTc	0.17±0.01	0.16±0.01	0.01

BMI - body mass index; ECG – electrocardiography; SBP - systolic blood pressure; DBP - diastolic blood pressure, BPM - beat per minute; QT - QT interval; QTc - rate-corrected QT interval; QTd - QT dispersion; pwTS - patients with Turner syndrome; Tp–Te - Tp–Te interval

Table 3. Echocardiographic parameters

	pwTS (n=38)	Control (n=35)	*P*
EF (%)	64.85±7.96	69.26±4.56	0.015
E/A	1.40±0.23	1.56±0.32	0.055
IVSd (mm)	7.10±0.16	7.14±0.5	0.131
PWd (mm)	6.88±0.14	6.93±0.19	0.308
LVDD (mm)	39.94±1.32	40.07±1.92	0.767
LVSD (mm)	24.08±1.31	23.60±0.95	0.112
LV mass (g)	91.66±1.74	92.28±1.67	0.156

EF - ejection fraction; E/A - mitral inflow E and A waves ratio; IVSd - interventricular septum diastole; PWd - posterior wall diastole; LVDD - left ventricular end-diastolic diameter; LVSD - left ventricular end-systolic diameter; LV mass - left ventricular mass; pwTS - patients with Turner syndrome

Results

The baseline characteristics of the study population are summarized in Table 2. The mean age of the pwTS group was 14.39±5.03 years and that of controls was 13.17±2.85 years. The mean heights were 138.96±14.92 cm and 152.86±15.75 cm and the mean body mass indexes were 22.62±5.24 kg/m^2 and 19.72±3.47 kg/m^2, respectively. According to multivariate analysis, variables does not effect on Tp-Te interval.

Electrocardiography and echocardiography

No differences in age or sex were observed between the groups, but a significant difference was observed in height. QT intervals were similar between the groups [pwTS: 354.76±25.33 ms, controls (C): 353.29±17.51 ms, p=0.775]. QTc intervals were significantly longer in the pwTS group than in controls (411.87±22.66 ms vs. 392.06±13.21 ms, p<0.001) (Fig. 1); the Tp–Te interval and QTd was also significantly longer in the pwTS group (71.89±3.39 ms vs. 65.34±2.88 ms, p<0.001 and 40.31±2.02 ms vs. 37.54±1.83 ms, p<0.001). The Tp–Te/QTc ratio was significantly higher in pwTS than in controls (0.17±0.01 vs. 0.16±0.01, p=0.01) (Fig. 1).

Although all study participants (pwTS and control group) had normal blood pressure, both systolic and diastolic blood pressures were significantly higher in the pwTS group (pwTS: 112.28±29.89 mm Hg, C: 97.76±11.38 mm Hg, p=0.019 and pwTS: 78.00±7.9 mm Hg, C: 67.06±14.73 mm Hg, respectively, p=0.002). The mean heart rate was higher in the pwTS group (pwTS: 100.42±19.58/min, C: 83.55±10.33/min, p<0.001) (Fig. 1).

Ejection fraction was lower in the pwTS group (pwTS: 64.85±7.96, C: 69.26±4.56, p=0.015), but there was no significant difference in all other echocardiographic parameters between pwTS and control group (Table 3). No bundle branch blocks were detected, and no electrolyte imbalance or drug use that could affect repolarization measurements was present in either group.

Discussion

In this study, we found that the Tp–Te interval, QTc interval, QTd, and Tp–Te/QTc ratio were predominantly longer in pwTS than in controls. TS is caused by partial or total deletion of the X chromosome, which is associated with cardiovascular diseases such as hypertension, aortic dissection, and ventricular arrhythmias. One of the risk factors that can increase ventricular arrhythmia is a prolonged QT interval, which depends on variation

Anatol J Cardiol 2018; 20: 93-9
DOI:10.14744/AnatolJCardiol.2018.98250

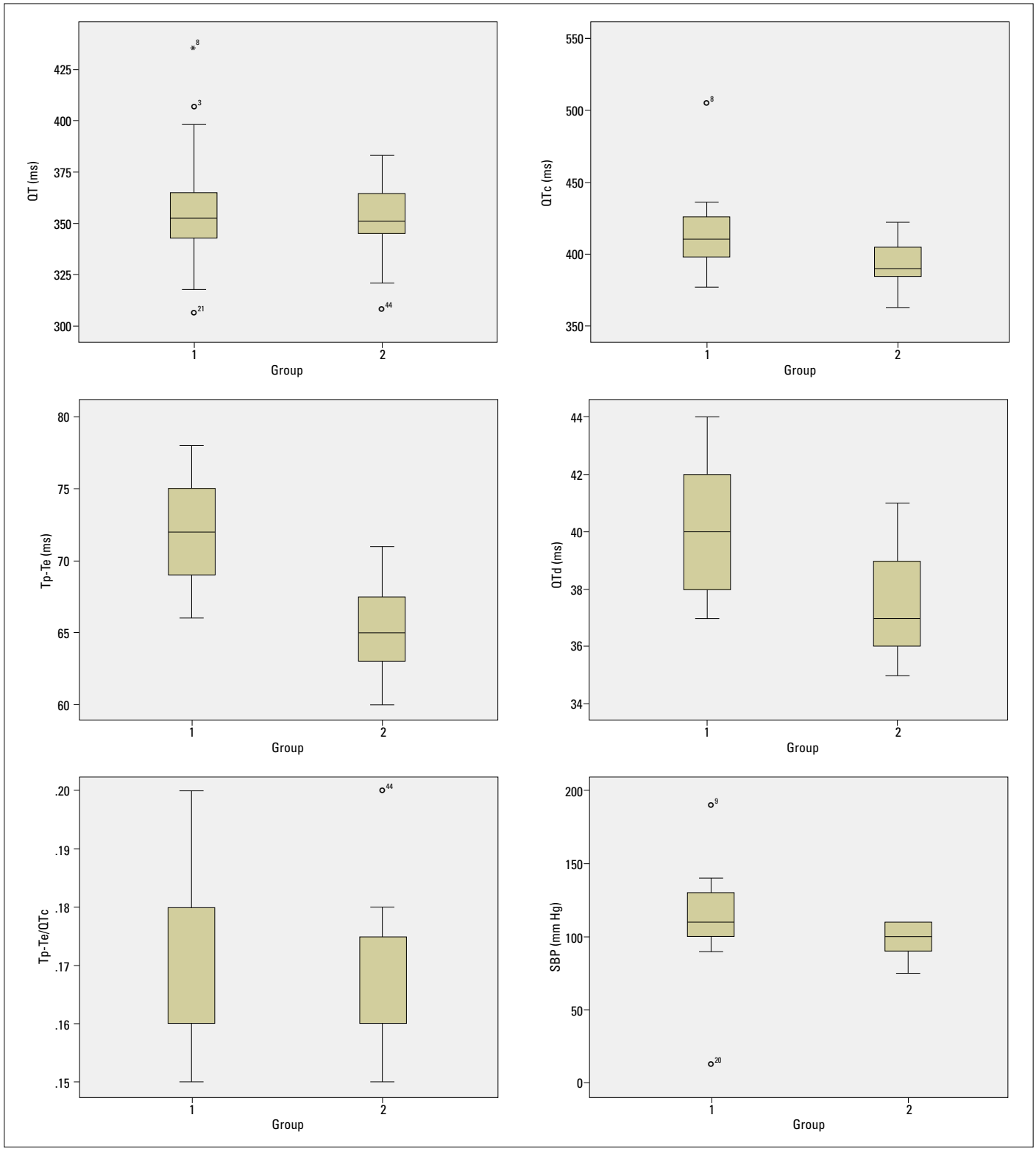

Figure 1. Comparative results of patients with Turner syndrome and control group
QTc - corrected QT; QTd - QT dispersion; SBP - systolic blood pressure; DBP - diastolic blood pressure; HR - heart rate; EF - ejection fraction

in ventricular repolarization (14, 15). Also, some recent studies have reported a prolonged QTc in pwTS than in controls (7, 8, 16). As known, untreated prolonged QTc can be mortal (14). Thus, it is well established that prolonged QTc carries an increased risk for sudden cardiac death and that the underlying mechanism is a repolarization abnormality. New measurement techniques have been developed to help assess this anomaly. One technique is to measure the Tp–Te interval and Tp–Te/QTc ratio. Thus, we mea-

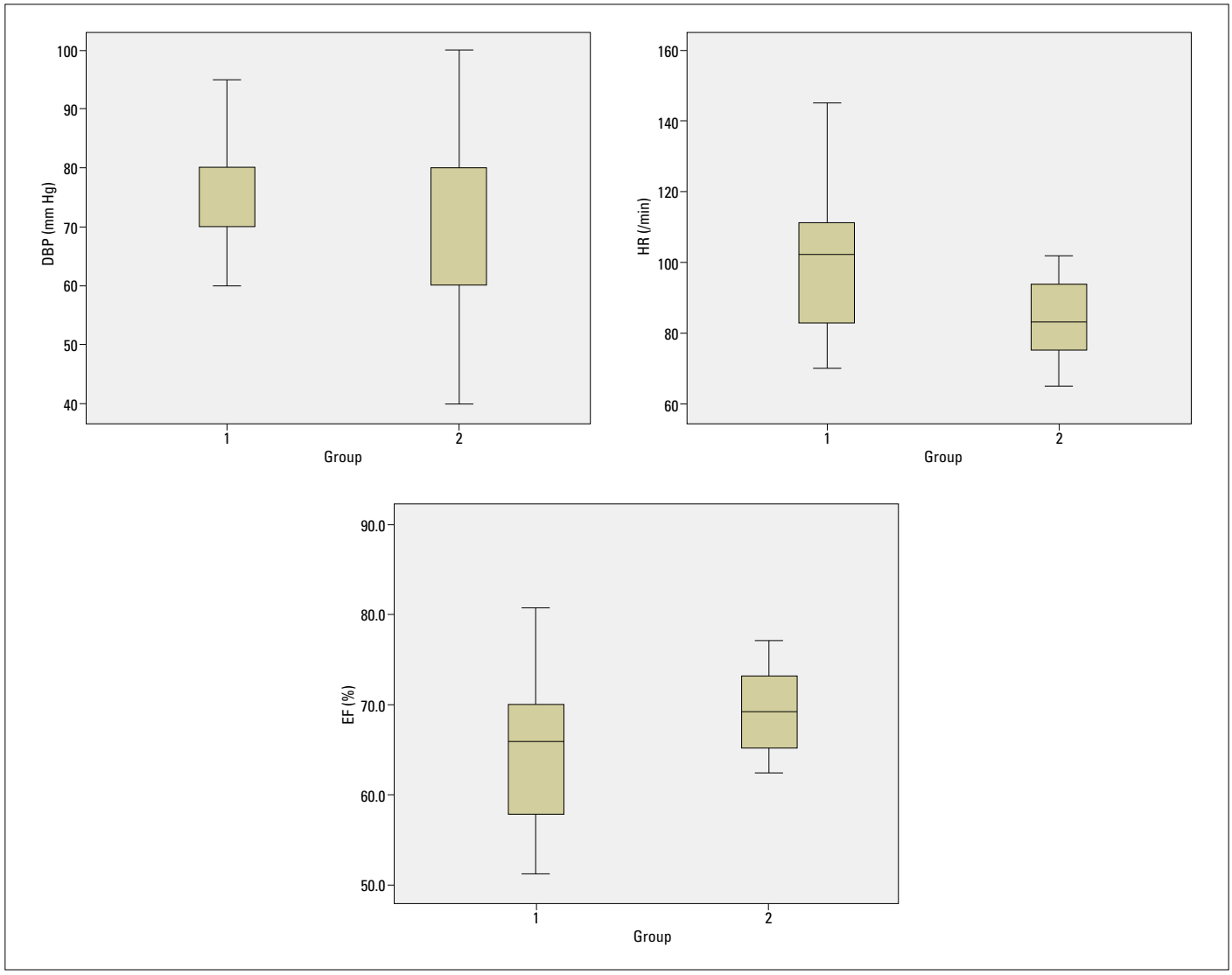

Figure 1. Comparative results of patients with Turner syndrome and control group
QTc - corrected QT; QTd - QT dispersion; SBP - systolic blood pressure; DBP - diastolic blood pressure; HR - heart rate; EF - ejection fraction

sured QTc, QTd, Tp–Te interval, and Tp–Te/QTc ratio together in our study.

Although this study demonstrated that QTc and QTd were longer in pwTS than in controls, as shown in the previous studies (7, 8, 17, 18), having no statistical difference in the QT interval between the groups is attributed to the increased heart rate of pwTS. It is known that prolonged QTd indicates non-homogeneous ventricular depolarization and increases the ventricular arrhythmogenic potential (15). Also, increased QTd and QTc are associated with autonomic neuropathy and heightened cardiovascular mortality (16, 19, 20). Thus, a decrease in QTd and QTc can cause reduced arrhythmia and sudden cardiac death (21, 22).

Furthermore, we also investigated the Tp–Te interval and Tp–Te/QTc ratio unlike previous studies. The Tp–Te interval and Tp–Te/QTc ratio, a novel ECG marker, was significantly longer in the pwTS group than in the control group. This marker has not been studied before to assess repolarization abnormalities in pwTS. Our results indicate that a repolarization abnormality should be considered in pwTS.

The Tp–Te interval and Tp–Te/QTc ratio have been revealed as novel electrocardiographic markers of increased irregular distribution of ventricular repolarization (12, 23). These parameters can be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death (11, 12). Previous studies have shown increased mortality in patients with a high Tp–Te interval and Tp–Te/QTc ratio and Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy, stimulated ventricular tachycardia, myocardial infarction (after the infarction) (11, 24, 25). The main mechanism of Tp–Te interval elongation and ventricular repolarization anomaly is the ion transport problem of the cells in the different layers of ventricular myocardium (26). The Tp–Te interval corresponds to the transmural distribution of the repolarization in the ventricular myocardium, which is a pe-

Anatol J Cardiol 2018; 20: 93-9
DOI:10.14744/AnatolJCardiol.2018.98250

riod wherein the epicardium is repolarized and fully excitable, but the M cells in the subendocardium are still in the repolarization process and are vulnerable to the possibility of early afterdepolarization (27-29). In the appropriate situations, a critical early afterdepolarization starts the re-entrant circuit and continues until it turns into VT or VF.

It appears that cardiac conduction and repolarization anomalies are intrinsic features of TS. The X chromosome has genes that synthesize proteins associated with membrane repolarization. Normally, genes such as KCNE1 (KCNEIL; Xq22.3) code potassium channel proteins but when a mutation or defect occurs in the X chromosome, it can cause long QT syndrome (30). Additionally anomalies in the autonomous nervous system can be another cause of increased Tp–Te interval and Tp–Te/QTc ratio in pwTS.

The pulse rate was also higher in pwTS than in controls, as reported previously (31). Heart rate variability is considered an autonomous nervous system abnormality in pwTS (18). The increased heart rate is due to the dominant sympathetic activity in the autonomous nervous system, which affects repolarization in pwTS. This leads to a longer QTc but a normal QT in pwTS.

In addition, some noncardiac drugs affect repolarization channels. Several drugs have been withdrawn because of the increased risk of sudden cardiac death (1, 32), which warrants a special awareness of this issue in this patient group.

The QTc interval, QTd (15, 33), Tp–Te interval, and Tp–Te/QTc ratio (10, 11), all of which are correlated with an increased risk for ventricular tachycardia and sudden cardiac death, were significantly higher in pwTS than in controls. pwTS also had lower ejection fractions, higher systolic and diastolic blood pressures, and higher heart rates. Increased mortality in pwTS may be associated with these differences, particularly QTc, QTd, Tp–Te interval, and Tp–Te/QTc ratio. This should be considered during the cardiovascular screening of these patients. Another crucial point is not to prescribe or administer any drugs that can lead to dysrhythmias in pwTS. Larger studies are warranted to determine whether repolarization abnormalities significantly contribute to life-threatening risk in pwTS.

Study limitations

This study was a single-center trial performed on 38 pwTS. The arrhythmia potential of patients was evaluated using ECG, so it is unclear if we would have obtained similar results based on long-term rhythm data in this patient group. This repolarization problem may be a characteristic of TS or a result of sex hormone-related gene effects on myocardial ion channels (8, 34, 35). We do not have sufficient data to clarify this issue, as we did not measure the hormone levels in our subjects. Nevertheless, as the subjects were of similar ages and physical condition and were not taking any hormonal drugs, it is likely that a genetic issue is responsible for this discrepancy. Genetic problems, such as canalopathy and/or protein synthesis defects, can be the reason in patients with a long QT interval.

Conclusion

Studies using a larger number of patients in the future will undoubtedly help determine the significance of repolarization parameters (QT, QTc, QTd, Tp–Te interval, Tp–Te/QTc ratio) in pwTS. The effects of androgen and estrogen levels in pwTS should be investigated. Annual follow-up by ECG can provide awareness and even prevent sudden death in pwTS. Avoiding the use of drugs that makes repolarization anomaly is essential in pwTS.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – A.A., A.D.; Design – C.P.; Supervision – E.B.K., A.K.B.; Fundings – None; Materials – O.K.; Data collection &/or processing – K.K., E.K., L.S., Z.N.A.S.; Analysis &/or interpretation – A.A., E.B.K., A.K.B.; Literature search – A.A., A.D.; Writing – A.A., E.B.K.; Critical review – C.P., A.D.

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