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The impact of elevated cumulative anthracycline dose on cardiac repolarization changes in children with cancer: a prospective study

Artan kümülatif antrasiklin dozunun kanserli çocuklardaki kardiyak repolarizasyon değişiklikleri üzerine etkileri: prospektif bir çalışma

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Abstract

Purpose: We aimed to prospectively interpret the cardiac repolarization changes with 12-lead electrocardiography (ECG) in children with cancer who were treated with anthracycline drugs.

Materials and methods: A total of 53 patients with cancer treated with anthracycline were enrolled in the study. During 6-month follow-up, standard 12-lead ECG was performed at basal, 1st, 4th, and 24th hours after the first dose of anthracycline treatment, at the time of 120 mg/m2 cumulative anthracycline dose and 240 mg/m^2 of cumulative anthracycline dose in the same patients, respectively. P dispersion (PWd), QT dispersion (QTd), corrected QT dispersion (QTcd), Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio were obtained from 12-lead ECG. The patients were classified into three groups according to increasing cumulative anthracycline doses: Group 1: first dose (n=53), Group 2: 120 mg/m^2 (n=53), Group 3: 240 mg/m^2 (n=53).

Results: The median age was 48 months (range 9-192 months). While PWd, QTd, QTcd, and Tp-e interval were significantly increased during first 24 hours of the first dose (p<0.001, p=0.005, p=0.041, p=0.016, respectively), Tp-e/QT and Tp-e/QTc ratios were significantly altered during first 24 hours of 120 mg/m^2 cumulative dose of anthracycline treatment (p<0.001). Any changes in 12-lead ECG were not significantly at 240 mg/m2 cumulative dose. However, it was detected that all variables were affected according to each increased anthracycline cumulative dose despite it was not statistically significant.

Conclusions: ECG parameters such as PWd, QTd, QTcd, Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios are useful for detecting subclinical cardiac abnormality and acute anthracycline toxicity during both uses of single-dose anthracycline and increased anthracycline doses. These parameters may also predict arrhythmias in patients with cancer.

Key words: Childhood cancer, anthracyclines, cardiac toxicity, ECG, dispersion.

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Öz

Amaç: Antrasiklin kemoterapisi ile tedavi edilen kanserli çocuklarda kardiyak repolarizasyon değişikliklerini 12 derivasyonlu elektrokardiyografi (EKG) ile değerlendirmeyi amaçladık.

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Gereç ve yöntem: Antrasiklin ile tedavi edilen kanserli toplam 53 hasta çalışmaya dahil edildi. Bu hastalara 12 derivasyonlu EKG ile antrasiklin tedavisinin ilk dozu, 120 mg/m^2 ve 240 mg/m^2 kümülatif dozu sırasında her doz uygulamasının ilaç verilmeden hemen öncesinde ve ilaç verildikten sonraki 1., 4. ve 24. saatinde EKG'leri çekildi. Bu EKG'lerden P dispersiyonu (PWd), QT dispersiyonu (QTd), düzeltilmiş QT dispersiyonu (QTcd), Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranı hesaplandı. Hastalar artan kümülatif antrasiklin dozlarına göre üç gruba ayrıldı: Grup 1: ilk doz (n=53), Grup 2: 120 mg/m^2 (n=53), Grup 3: 240 mg/m^2 (n=53).
Bulgular: Ortanca yaş 48 ay (aralık 9-192 ay) idi. İlk dozun ilk 24 saatinde PWd, QTd, QTcd ve Tp-e değişkenleri anlamlı olarak artış gösterdiği saptandı. (sırasıyla p<0,001, p=0,005, p=0,041, p=0,016). 120 mg/m^2 kümülatif antrasiklin tedavisinin ilk 24 saatinde ise Tp-e/QT and Tp-e/QTc oranları istatistiksel anlamlı olarak değişiklik gösterdi (p<0,001). 240 mg/m^2 kümülatif antrasiklin dozunda ise herhangi bir anlamlı değişiklik saptanmadı. Ancak istatistiksel olarak anlamlı olmamakla birlikte, artan her antrasiklin kümülatif doza bağlı olarak disperisyon değişkenlerinde uzama, Tp-e/QT ve Tp-e/QTc oranlarında ise azalma olduğu belirlendi.
Sonuç: PWd, QTd, QTcd, Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranları gibi EKG değişkenleri, hem tek doz antrasiklin hem de artan antrasiklin kullanımı sırasında subklinik kardiyak toksisite ve akut antrasiklin toksisitesinin bulgularını saptamada yararlı olduğunu gösterdi. Bu parametreler değerlendirildiğinde kanserli hastalarda aritmileri de belirlemede önemli olacaktır.

Anahtar kelimeler: Çocukluk çağı kanseri, antrasiklinler, kardiyak toksisite, EKG, dispersiyon.

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Introduction

According to the latest study published by the German Children's cancer registry, the 5-year survival of children under the age of 15 is reported as 85% [1]. Along with increased survival after settled chemotherapy protocols, toxicity findings related to chemotherapy have come to the fore. A potential complication of anticancer treatment is short-term and long-term cardiovascular toxicity [2]. Toxicity related to anthracycline may be encountered in acute or chronic forms. It may occur as asymptomatic (subclinical) or symptomatic cardiac events [3]. The acute form of anthracycline toxicity involves electrocardiography (ECG) changes, rhythm disorders, and immediate ventricular dysfunction. P wave dispersion (PWd), corrected QT interval (QTc), QTc dispersion, and QT dispersion (QTd) were shown to have predictive roles for atrial and ventricular arrhythmia and all mortality linked to these causes. Increasing P-wave dispersion reflects the tendency of the atrial myocardium toward rhythm disorders like atrial flutter and fibrillation. QT, QTd, and QTc are indices of spatial dispersion of ventricular recovery. Previous studies have shown that patients with increased QT and QTd are more prone to ventricular arrhythmia and even sudden cardiac death [4, 5]. In recent years, Tp-e interval and Tp-e/QT ratio have been revealed to be new non-invasive electrocardiographic (ECG) markers of ventricular repolarization dispersion. Researchers have stated that lengthened Tp-e interval and increasing Tp-e/QT and Tp-e/QTc ratios are associated with a tendency toward ventricular arrhythmia and sudden cardiac death [6, 7]. There are higher rates of subclinical heart disease (62%); however, it is frequently reversible. In asymptomatic cardiotoxicity, arrhythmia like ventricular tachycardia and lengthened Q-T interval may be observed. Rarely, arrhythmic and ischemic attacks are observed [8]. Chronic cardiotoxicity linked to anthracyclines is related to cumulative medication dose. Patients receiving increasing cumulative doses of 400, 550, and 700 mg/m^2 doxorubicin were shown to develop clinical heart failure of up to 3%, 7%, and 18%, respectively. Most cardiomyopathy related to cumulative dose is irreversible [9].

In spite of lengthened life expectancy with intense chemotherapy protocols for childhood cancers, cardiac side effects related to treatment are still a problem. One of the most commonly used medications is an anthracycline. The most well-known findings of chronic cardiotoxicity associated with anthracycline are cardiomyopathy, myocardial infarcts, and stroke. Additionally, subclinical but significant acute cardiotoxicity is still not fully explained. In this study, we aimed to assess the subclinical cardiac anomalies and acute anthracycline toxicity with a P wave, QT, QTc dispersion, Tp-e interval, Tp-e/QT, and Tp-e/

QTc ratio using 12-lead ECG in pediatric cancer patients with anthracycline group medication in their treatment protocol during both single-dose anthracycline treatment and with increasing cumulative doses.

Materials and methods

Study population

From 2014 to 2015, children with cancers who were treated with any anthracycline drugs were enrolled in this prospective observational study at the department of oncology. During 6-month follow-up, standard 12-lead ECG was performed at the basal point, 1st, 4th, and 24th hours after the first dose of anthracycline treatment, at the time of 120 mg/m^2 cumulative anthracycline dose and 240 mg/m^2 of cumulative anthracycline dose in the same patients, respectively. P wave dispersion (PWd), QT dispersion (QTd), corrected QT dispersion (QTcd), Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio were evaluated from 12-lead electrocardiography. The patients were classified into three groups according to increasing cumulative anthracycline doses: Group 1: first dose (n=53), Group 2: 120 mg/m^2 (n=53), Group 3: 240 mg/m^2 (n=53). Patients' demographic features were obtained from the patient data system.

Patients were excluded if they were using any medication which lengthens the QT duration or if they had any electrolyte imbalance causing lengthened QT (hypopotassemia, hypocalcemia, hypomagnesemia). Additionally, patients with hypothermia, congenital heart disease, or a history of dysrhythmia were excluded.

The study was conducted in accordance with the Declaration of Helsinki. Izmir Dokuz Eylül University Ethics Committee approval under protocol number 225-SBKAEK (date: 30.10.2014), was granted and consent informed was obtained from the patients and their parents.

Electrocardiography

The standard 12-lead ECG (Cardiofax GEM, Model 9022 K; Nihon Kohden Tokyo, Japan) was recorded at a speed of 25 mm/s and an amplitude of 1 mV/cm while the patients were lying in a supine position right after the diagnoses were made. P wave dispersion (PWd), QT dispersion (QTd), corrected QT dispersion (QTcd), Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio were calculated from 12-lead electrocardiography. To increase the accuracy of the measurements, ECG recordings were scanned and transferred to a personal computer. After usingx400 zoom in Adobe Photoshop software, assessments were made directly from the ECG tracing by one pediatric cardiologist who was blind to the data. No significant discrepancy was present between investigators. The interobserver variance for each measurement ranged between 5% and 12%.

P-wave dispersion: We defined the onset of the P-wave as the junction between the isoelectric line and the beginning of the P-wave deflection, and the offset of the P-wave as the junction between the end of the P-wave deflection and the isoelectric line. We calculated the dispersion of the P-wave as the difference between the maximum and minimum P-wave duration (P-wave dispersion: maximum P-wave duration–minimum P-wave duration) [10]. P waves from all 12 leads were measured and used for calculations.

QT dispersion: We measured the QT interval from the beginning of the QRS complex to the end of the T-wave, but did not measure the QT interval if the T-wave was absent. If T-waves had two peaks and the second was <50% of the first one, then the point where the first peak reached the isoelectric line was assumed to be the end of the T-wave. For every patient, we calculated the corrected QT (QTc) interval regarding the previous cardiac cycle length according to the Bazzet formula [11]. In the presence of a U wave, the end-point of the T wave was accepted as the lowest point between the T and U waves. Both the QT (QTd) and QTc (QTcd) dispersions were calculated as the difference between the maximum and minimum QT and QTc intervals [12].

Tp-e interval: Tp-e was measured from Tp (highest point of the T-wave, T-wave with maximum amplitude) to Te. We defined Te as the intersection point of the tangent to the downslope of the T-wave and isoelectric line. If a lead contained inverted T-waves, the measurement was taken from the lowest point of the inverted T-wave to Te. The U-wave was not taken into consideration [13]. The Tp-e/QT ratio was calculated from these measurements [14].

Echocardiography

All the echocardiographic images were acquired using an EPIQ 7 ultrasound system (IE5x Matrix System, Phillips Medical Systems, Andover, MA). All measurements were taken according to the methods recommended by the American Society of Echocardiography [15]. Images were recorded at end-expiratory phase using a 5 MHz centre frequency phased-array probe with second-harmonic imaging. Two-dimensional (2D) greyscale images at a frame rate of 60 and 90 frames/s were obtained from the apical four-chamber view.

Statistical analysis

SPSS 18.0 was used (SPSS Inc., Chicago, IL, USA) for statistical analysis. The distribution pattern of the data was evaluated via the Kolmogorov–Smirnov test. Values are expressed as mean ± SD or median (interquartile range) where appropriate. According to the distribution type of the variable, comparison of independent means was performed with the Mann Whitney U test or Student's t test, whereas comparison of dependent means was performed with the paired Student's t test or Wilcoxon test. Chi-square analysis was used for the comparison of categorical variables. The associations between parameters were assessed using Spearman's correlation test for normally distributed data and Pearson's test for abnormally distributed data. A *p*-value <0.05 was considered statistically significant.

Results

The data were collected from 53 patients with cancer. There were 32 males (60.4%) and 21 females (39.6%) patients in the baseline study group. The median age in our study was 48 months with a range from 9 to 192 months. Table 1 shows the type of cancer in our study. All types of cancer were distributed as 38 patients (71.7%) with acute leukemia, 2 patients (3.8%) with T lymphoblastic lymphoma, and 13 patients (24.5%) with other childhood cancers who treated with anthracycline during chemotherapy protocols (Table 1).

At the time of diagnosis 53 patients did not have malnutrition. None of our patients had received radiotherapy. Aortic coarctation, tricuspid insufficiency, patent foramen ovale (PFO), atrial septal defect (ASD), mitral insufficiency, and decreased apical function, and left shift of intraventricular septum in mid septal region were detected with echocardiography in 7 of 53 patients.

The comparison of the electrocardiographic features of the basal, 1st, 4th, and 24th hours after the first dose of anthracycline treatment is given in Table 2. Table 2 shows that QT and QTc dispersions were found to be significantly higher at the first hour, and the PW and Tp-e dispersions at the first, fourth and twenty-fourth hours. There were no differences in Tp–e/QT ratios, and Tp–e/QTc ratios 24 hours after the first dose of anthracycline chemotherapy.

The comparison of the electrocardiographic features of the basal, 1st, 4th, and 24th hours after the 120 mg/m^2 cumulative dose of anthracycline chemotherapy is given in Table 3. There were no differences in PW, QT, and QTc dispersions during 24 hours after the first dose of anthracycline chemotherapy. The Tp–e/QT and Tp–e/QTc ratios at the first, fourth, and twenty-fourth hours and Tp–e dispersions at the first hour were found to be significantly higher at 120 mg/m^2 cumulative dose of anthracycline treatment. According to the comparison of the electrocardiographic features of the basal, 1st, 4th, and 24th hours after the 240 mg/m^2 cumulative dose of anthracycline chemotherapy, no significant difference was found in all of the parameters.

When the increasing cumulative anthracycline dose is compared with the first dose, PW dispersion was identified to have a statistically significant increase with 120 mg/m^2 and 240 mg/m^2 cumulative dose compared to the first dose (p=0.025, p=0.025, respectively). Though not statistically significant, with increasing cumulative anthracycline dose, QT, QTc, and Tp-e dispersions were identified to lengthen. There was a statistically significant reduction identified for Tp-e/QT ratio and Tp-e/QTc ratio between the first dose and 120 mg/m^2 cumulative dose (p=0.001, p<0.001, respectively) (Table 4).

Table 1. Baseline characteristics of cancer types

Type of cancer	Frequency	Percent
Acute leukemia (ALL+ AML)	38	71.7
Lymphoma (HL+ T cell lymphoblastic lymphoma+ Burkitt lymphoma)	7	13.2
Solid tumor	8	15.1
Total	53	100.0

ALL=acute lymphoblastic leukemia
AML=acute myeloid leukemia
HL= Hodgkin Lymphoma
Solid tumor included Neuroblastoma+Hepatoblastoma+Ewing sarcoma+Wilms tumor+Osteosarcoma

Table 2. Comparison of electrocardiographic characteristics between the groups at the first dose of anthracycline (n=53)

	Basal (A) (mean±SD)	**1st hour (B) (mean±SD)**	**4th hour (C) (mean±SD)**	**24th hour (D) (mean±SD)**	***p* (A-B)**	***p* (A-C)**	***p* (A-D)**
PW dispersion (ms)	12.6±6.78	18.3±7.59	15.56±6.55	18.86±11.91	**0.001**	**0.032**	**0.002**
QT dispersion (ms)	27.07±13.4	34.71±17.1	29.90±13.21	30.94±13.19	**0.005**	0.288	0.193
QTc dispersion (ms)	33.50±16.6	41.37±22.2	37.5±19.39	40.32±19.73	**0.041**	0.223	0.091
Tp-e dispersion (ms)	17.54±9.98	22.7±11.79	24.33±11.18	22.26±10.07	**0.016**	**0.001**	**0.025**
Tp-e/QT ratio	0.23±0.06	0.24±0.05	0.24±0.054	0.24±0.089	0.507	0.375	0.420
Tp-e/QTc ratio	0.18±0.04	0.19±0.04	0.18±0.038	0.18±0.08	0.137	0.431	0.598

Table 3. The evaluation of electrocardiographic data at 120 mg/m^2 cumulative dose of anthracycline (n=53)

	Basal (A) (mean±SD)	1st hour (B) (mean±SD)	4th hour (C) (mean±SD)	24th hour (D) (mean±SD)	*p* (A-B)	*p* (A-C)	*p* (A-D)
PW dispersion (ms)	17.3±8.49	18.21±8.32	17.09±7.77	19.04±7.98	0.588	0.871	0.362
QT dispersion (ms)	31.42±12.79	33.33±12.23	32.73±19.19	28.09±11.94	0.421	0.755	0.218
QTc dispersion (ms)	41.80±19.23	40.97±17.95	40.85±23.2	37.0±16.2	0.842	0.833	0.273
Tp-e dispersion (ms)	20.47±9.29	24.4±11.69	22.97±12.25	20.59±7.82	**0.038**	0.184	0.927
Tp-e/QT Ratio	0.20±0.054	0.25±0.047	0.25±0.12	0.23±0.048	**<0.001**	**0.003**	**0.029**
Tp-e/QTc Ratio	0.15±0.035	0.19±0.050	0.20±0.11	0.17±0.038	**<0.001**	**<0.001**	**0.008**

Table 4. ECG characteristics of elevated cumulative anthracycline dose

	First dose 0 hour ECG (A) (n=53) (mean±SD)	120 mg/m^2 0 hour ECG (B) (n=53) (mean±SD)	240 mg/m^2 0 hour ECG (C) (n=53) (mean±SD)	*p* (A-B)	*p* (A-C)	*p* (B-C)
PW dispersion (ms)	12.6±6.78	17.3±8.49	17.38±8.49	**0.025**	**0.025**	1.000
QT dispersion (ms)	27.0±13.4	31.4±12.79	32.89±15.75	0.136	0.208	0.427
QTc dispersion (ms)	33.6±17.51	41.8±19.23	42.6±22.3	0.071	0.117	0.162
Tp-e dispersion (ms)	17.54±9.98	20.4±9.29	18.6±9.25	0.152	0.613	0.906
Tp-e/QT ratio	0.24±0.062	0.20±0.054	0.21±0.024	**0.002**	0.149	0.539
Tp-e/QTc ratio	0.18±0.047	0.15±0.035	0.16±0.030	**<0.001**	0.137	0.219

Discussion

Anthracycline group medications comprise the basic foundation of chemotherapy protocols. Multiple medication protocols clearly lengthen the survival after cancer in the childhood age group. This means that side effects related to treatment become an important topic. Cardiotoxicity related to anthracycline, forming the basis of chemotherapy protocols, is an important problem. Cardiotoxicity may occur in the acute (hours immediately after treatment), subacute (days or weeks after treatment, up to 30 weeks), and late periods (years after treatment is completed, 1-20 years). At the same time, the cardiotoxic effect may be clinical or subclinical. When it occurs clinically, the patient displays findings of heart failure. Subclinical cardiotoxicity is the identification of disruption in left ventricular functions on echocardiographic assessment without observing findings of heart failure or cardiomyopathy clinically or in the laboratory of the patient. Many echocardiographic parameters are used for the early diagnosis of subclinical cardiotoxicity [16, 17].

Clinical studies in recent years have shown the P wave dispersion, QT interval, QTc, QTd, and QTcd on 12-lead ECG are sensitive for arrhythmia of the myocardium and show the risk of sudden cardiac death. P wave dispersion is characterized by heterogeneity in conduction of interatrial sinus impulses and carries a risk of lengthened atrial arrhythmia. Lengthened QTd and QTcd values have the risk of ventricular arrhythmia due to heterogeneity of myocardial repolarization and myocardial instability, which may lead to sudden cardiac death [18, 19]. Gülen H et al. [20] report that there was no significant difference in QTc values between patients taking active treatment and those who completed the therapy and between the patients given a cumulative dose of anthracycline lower and higher than 250 mg/m^2. But Qtcd values were found to be higher in patients than controls.

Tp-e interval is a new marker of relative transmural repolarization dispersion. It is also associated with risk of sudden cardiac death (SCD) [21]. The duration between the peak point of the T wave with the end point (Tp-e) can be used as a marker of total repolarization dispersion and was shown to also be an important marker for prediction of increased mortality linked to cardiovascular causes and ventricular arrhythmia. The new index of Tp-e/QT ratio is not affected by heart rate variation and is reported to be more reliable for assessment of ventricular repolarization compared to QT duration, QT dispersion and Tp-e duration [22]. Panikkath et al. [23] suggested that a prolonged Tp-e interval and high Tp-e/QT ratio were associated with SCD. Previously studies have reported a prolonged Tp-e interval and increased Tp-e/QT ratio in patients with myocardial infarction [24].-

The most difficult to predict and manage clinically is the development of cardiomyopathy and ultimately congestive heart failure. The incidence of DOX cardiomyopathy depends on the cumulative lifetime dose, increasing to 36% when the dose exceeds 600 mg/m^2 [25]. Heart failure incidence affects 26% of the patients receiving DOX when the cumulative dose exceeds 550 mg/m^2 [26]. Early-onset and progressive anthracycline cardiotoxicity can occur within a year or may not become apparent until years after cessation of treatment and can manifest as chronic dilated cardiomyopathy in adult patients or as restrictive cardiomyopathy in younger patients, associated with decreased left ventricular ejection fraction, occasionally leading to fatal events [27, 28]. Early detection of subclinical cardiovascular alterations within the first year post-treatment can lead to a total or partial recovery of cardiac function, as demonstrated by Cardinale et al. [29]. Our study may be a guide for both how evaluating early cardiotoxicity and how detecting early cardiac repolarization change by increasing cumulative dose. As a result, cardiomyopathy or heart failure can be prevented by taking early measures in patients with early detected cardiac repolarization change.

Although we observed some subclinical cardiac effects between the first dose and 120 mg/m^2 doses, we thought that the reason we did not find a difference at the 240 mg/m^2 dose was related to the interval time. The time between the first dose and 120 mg/m^2 is approximately 1 month, while the period between 120 mg/m^2 and 240 mg/m^2 is approximately 3 months. Therefore, we thought that some subclinical cardiotoxicity findings might have improved during this long interval.

Conclusion, ECG parameters like P wave, QT, QTc dispersion, Tp-e interval, Tp-e/QT

and Tp-e/QTc ratio may be beneficial for identification of subclinical cardiac anomalies and anthracycline acute toxicity during single-dose anthracycline treatment and with increasing cumulative doses. We identified the variation in these ECG parameters within the first 24 hours of anthracycline treatment developed with arrhythmia risk. Again, with increasing cumulative dose, there was increased risk of development of atrial and ventricular arrhythmia, though this was not statistically significant. At the same time, these parameters can identify arrhythmia in pediatric patients with cancer. As a result, during treatment and with increasing cumulative doses of anthracycline group chemotherapy, it will be important to assess cancer patients with ECG. But it's a difficult application to obtain ECG parameters according to cumulative dose and at the basal, 1st, 4th, and 24th hour.

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References

1. Scholz Kreisel P, Kaatsch P, Spix C, et al. Second malignancies following childhood cancer treatment in Germany from 1980 to 2014 – a registry-based analysis. Dtsch Arztebl Int 2018;115:385-392. https://doi.org/10.3238/arztebl.2018.0385
2. Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular disease in survivors of childhood cancer: insights into epidemiology, pathophysiology, and prevention. J Clin Oncol 2018;36:2135-2144. https://doi.org/10.1200/JCO.2017.76.3920
3. Van der Pal HJ, van Dalen EC, van Delden E, et al. High risk of symptomatic cardiac events in childhood cancer survivors. J Clin Oncol 2012;30:1429-1437. https://doi.org/10.1200/JCO.2010.33.4730
4. Christensen PK, Gall MA, Major Pedersen A, et al. QTc interval length and QT dispersion as predictors of mortality in patients with non-insulin-dependent diabetes. Scand J Clin Lab Invest 2000;60:323-332. https://doi.org/10.1080/003655100750046486
5. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008;41:575-580. https://doi.org/10.1016/j.jelectrocard.2008.07.030
6. Gupta P, Patel C, Patel H, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008;41:567-574. https://doi.org/10.1016/j.jelectrocard.2008.07.016
7. Bieganowska K, Sawicka Parobczyk M, Bieganowski M, Piskorski J. Tpeak-tend interval in 12-lead electrocardiogram of healthy children and adolescents in childhood. Ann Noninvasive Electrocardiol 2013;18:344-351. https://doi: 10.1111/anec.12035
8. Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voûte PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol 2002;13:819-829. https://doi.org/10.1093/annonc/mdf167
9. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2015;16:123-136. https://doi.org/10.1016/S1470-2045(14)70409-7
10. Dilaveris PE, Gialafos EJ, Sideris SK, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998;135:733-738. https://doi.org/10.1016/s0002-8703(98)70030-4
11. Bazett HC. An analysis of the time relations of electrocardiograms. Heart 1920;7:353-370. https://doi.org/10.1111/j.1542-474X.1997.tb00325.x
12. Sap F, Karatas Z, Altin H, et al. Dispersion durations of P-wave and QT interval in children with congenital heart disease and pulmonary arterial hypertension. Pediatr Cardiol 2013;34:591-596. https://doi.org/10.1007/s00246-012-0503-5
13. Bieganowska K, Sawicka Parobczyk M, Bieganowski M, et al. Tpeak -tend interval in 12-lead electrocardiogram of healthy children and adolescents tpeak -tend interval in childhood. Ann Noninvasive Electrocardiol 2013;18:344-351. https://doi.org/10.1111/anec.12035
14. Kılıcaslan F, Tokatli A, Ozdag F, et al. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are prolonged in patients with moderate and severe obstructive sleep apnea. Pacing Clin Electrophysiol 2012;35:966-972. https://doi.org/10.1111/j.1540-8159.2012.03439.x
15. Lang RM, Badano LP, Mor Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:14-39. https://doi.org/10.1016/j.echo.2014.10.003
16. Kremer LC, Caron HN. Anthracycline cardiotoxicity in children. N Engl J Med 2004;351:120-121. https://doi.org/10.1056/NEJMp048113
17. Outomuro D, Grana DR, Azzato F, Milei J. Adriamycine–induced myocardial toxicity: new solutions for an old problem? Int J Cardiol 2007;117:6-15. https://doi.org/10.1016/j.ijcard.2006.05.005

18. Higham PD, Campell RW. QT dispersion. Br Heart J 1994;71:508-510. https://doi.org/10.1136/hrt.71.6.508
19. Tutar HE, Ocal B, İmamoglu A, Atalay S. Dispersion of QT and QTc interval in healthy children, and effects of sinus arrhythmia on QT dispersion. Heart 1998;80:77-79. https://doi.org/10.1136/hrt.80.1.77
20. Gulen H, Kazanci E, Mese T, et al. Cardiac functions by myocardial performance index and QT dispersion in survivors of childhood lymphoblastic leukaemia. Minerva Pediatr 2007;59:107-113.
21. Tasolar H, Ballı M, Cetin M, Otlu YO, Altun B, Bayramoglu A. Effects of the coronary collateral circulation on the Tp-e interval and Tp-e/QT ratio in patients with stable coronary artery disease. Ann Noninvasive Electrocardiol 2015;20:53-61. https://doi.org/10.1111/anec.12173
22. Zhao X, Xie Z, Chu Y, et al. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 2012;35:559-564. https://doi.org/10.1002/clc.22022
23. Panikkath R, Reinier K, Uy Evanado A, et al. Prolonged Tpeak-toTend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011;4:441-447. https://doi.org/10.1161/CIRCEP.110.960658
24. Haarmark C, Hansen PR, Vedel Larsen E, et al. The prognostic value of the Tpeak–Tend interval in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. J Electrocardiol 2009;42:555-560. https://doi.org/10.1016/j.jelectrocard.2009.06.009
25. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302-314. https://doi.org/10.1002/1097-0142(197308)32:2<302::aid-cncr2820320205>3.0.co;2-2
26. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869-2879. https://doi.org/10.1002/cncr.11407
27. Buzdar AU, Marcus C, Smith TL, Blumenschein GR. Early and delayed clinical cardiotoxicity of doxorubicin. Cancer 1985;55:2761-2765. https://doi.org/10.1002/1097-0142(19850615)55:12<2761::aid-cncr2820551206>3.0.co;2-p
28. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991;266:1672-1677.
29. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981-1988. https://doi.org/10.1161/CIRCULATIONAHA.114.013777

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Authors' contributions to the article

D.İ., R.C.V. and T.M.:They set up the main idea and hypothesis of the study.

S.A.K., Y.O. and R.Ö.: They developed the theory and edited the material method section. The evaluation of the data in the results section

M.M.Y., B.D., R.Ö.: The evaluation of the data in the results section

The discussion section of the article was written by S.A.K.

Y.O., D.İ. and T.H.K.: They reviewed manuscript, made the necessary corrections and approved. In addition, all authors discussed the entire study and approved its final version.