ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Anthracycline Chemotherapy-Induced Electro-Mechanical Changes: Strain Echocardiography Combined with Repolarization Parameters on Electrocardiography to Predict Early Cardiotoxicity

Antrasiklinlere Bağlı Elektro-Mekanik Değişiklikler: Kardiyotoksisiteyi Erken Dönemde Öngörmede Strain Ekokardiyografinin Repolarizasyon Belirteçleri ile Birlikte Kullanımı

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: The aim of the study was to describe the acute cardiotoxic effects of anthracycline chemotherapy in echocardiographic strain and electrocardiographic repolarization parameters in patients with breast cancer.

Methods: A total of 35 consecutive patients (all females, mean age: 48.9 ± 11.8 years) who received chemotherapy due to breast cancer were prospectively included. Pre-treatment (T0) and third month (T2) 2-dimensional strain echocardiography and electrocardiography were performed. Additionally, within 3 hours of the first dose of chemotherapy (T1), additional electrocardiographic images were obtained. All mechanical and electrical parameters from different time intervals (T0, T1, and T2) were compared with each other.

Results: In the acute period after treatment, electrocardiographic repolarization parameters were prolonged and this prolongation continued to the third month (QT corrected with Bazett formula [440.10 ± 27.63 (T0), 468.00 ± 38.98 (T1), 467.86 ± 35.09 (T2)], QT dispersion [49.85 ± 19.52 (T0), 69.54 ± 16.06 (T1), 57.63 ± 14.42 (T2)], and T-wave peak-to-end interval [94.00 ± 45.46 (T0), 131.20 ± 17.79 (T1), 120.00 ± 18.32 (T2)]; $P < .001$). There was no significant change in global longitudinal strain values before and after treatment (global longitudinal strain avg: −21 ± 7.1%; $P = .8$). However, there were significant reductions in strain parameters including circumferential and radial strain, and torsion (−17.2 ± 3.5 to -13 ± 2.84; $P < .001$, 45.1 ± 8.3 to 35.6 ± 10; $P < .001$, and 12.1 ± 3.5 to 7.7 ± 2.1; $P < .001$, respectively).

Conclusion: Both the electrical and mechanical functions of the heart can be impaired acutely extending to 3 months after anthracycline chemotherapy. Therefore, cardiotoxicity should be evaluated early both electrically and mechanically after chemotherapy.

Keywords: Cardio-oncology, cardiotoxicity, electro-mechanical dysfunction, strain echocardiography

ÖZET

Amaç: Meme kanseri nedeni ile antrasiklin kemoterapisi alan kadınlarda gelişebilecek akut kardiyotoksisiteyi öngörmede strain ekokardiyografi ve EKG'deki repolarizasyon belirteçleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Antrasiklin kemoterapisi alan ardışık 35 meme kanseri kadın hasta (ortalama yaş 48,9 ± 11,8 yıl) çalışmaya dahil edildi. Tedavi öncesi (T0) ve sonrası 3. ay (T2) 2B strain ekokardiyografi ve EKG'leri kaydedildi. Ek olarak kemoterapinin ilk dozu sonrası 3. saatte (T1) EKG'leri de değerlendirildi. EKG repolarizasyon parametreleri ve ekokardiyografik deformasyon belirteçleri analiz edildi. Tüm mekanik ve elektriksel değişkenlerin değerleri zamansal olarak kaydedildi ve birbirleriyle karşılaştırıldı (T0, T1 ve T2).

Bulgular: Akut dönemde EKG repolarizasyon belirteçlerinde uzama olduğu ve bunun geç dönemde de devam ettiği görüldü (QTcB 440,10 ± 27,63 [T0], 468,00 ± 38,98 [T1], 467,86 ± 35,09 [T2]), QT dağılımı (49,85 ± 19,52 [T0], 69,54 ± 16,06 [T1], 57,63 ± 14,42 [T2]) ve Tpe (94,00 ± 45,46 [T0], 131,20 ± 17,79 [T1], 120,00 ± 18,32 [T2]); P < ,001). GLS değerlerinde

Benay Özbay, M.D.[1]
Evrim Şimşek, M.D.[2]
Hatice Kemal, M.D.[3]
Burcu Çakar, M.D.[4]
Oğuz Yavuzgil, M.D.[2]

[1]*Department of Cardiology, İstanbul Çam and Sakura State Hospital, İstanbul, Turkey*
[2]*Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey*
[3]*Department of Cardiology, Near East Faculty of Medicine, Nicosia, Turkish Republic of Northern Cyprus*
[4]*Department of Medical Oncology, Ege University Faculty of Medicine, İzmir, Turkey*

Corresponding author:
Benay Özbay
✉ benayozbay@hotmail.com

Received: February 1, 2022
Accepted: July 15, 2022

Cite this article as: Özbay B, Şimşek E, Kemal H, Çakar B, Yavuzgil O. Anthracycline chemotherapy-induced electro-mechanical changes: Strain echocardiography combined with repolarization parameters on electrocardiography to predict early cardiotoxicity. *Turk Kardiyol Dern Ars.* 2022;50(7):478-484.

DOI:10.5543/tkda.2022.22359

tedavi öncesi ve sonrası değişim görülmezken (GLS avg: −21 ± %71 P = ,8), diğer strain parametrelerinde bozulma izlendi (CS −172 ± 3,5'ten -13 ± 2,84'e; P <,001, RS 45,1 ± 8,3'ten 35,6 ±10'a; P < ,001, ve torsiyon 12,1 ± 3,5'ten 7,7 ± 2,1'e; P < ,001). Tpe (94,00 ± 45,46 [T0], 131,20 ± 17,79 [T1], 120,00 ± 18,32 [T2]); P < ,001). GLS değerlerinde tedavi öncesi ve sonrası değişim görülmezken (GLS avg: −21 ± %71 P = ,8), diğer strain parametrelerinde bozulma izlendi (CS −172 ± 3,5'ten -13 ± 2,84'e; P <,001, RS 45,1 ± 8,3'ten 35,6 ±10'a; P < ,001, ve torsiyon 12,1 ± 3,5'ten 7,7 ± 2,1'e; P < ,001).

Sonuç: Antrasiklin kemoterapisi sonrası akut dönemde kalbin hem elektriksel hem de mekanik olarak olumsuz etkilendiği ve bu etkinin 3. aya dek uzadığı görülmüştür. Bu nedenle kemoterapi sonrası kardiyotoksisite açısından değerlendirme hem elektriksel hem de mekanik olarak birlikte yapılmalıdır.

Anahtar Kelimeler: Elektro-mekanik disfonksiyon, kardiyoonkoloji, kardiyotoksisite, strain ekokardiyografi

Life expectancy in breast cancer has increased with the use of chemotherapeutic agents. However, most of the chemotherapeutic agents have acute or chronic negative effects on the myocardium.[1] Anthracyclines are the most frequently used agents in the treatment of breast cancer, but they bear the risk of acute, sub-acute, and chronic cardiotoxicity. Cardiotoxicity can emerge as ventricular or atrial arrhythmias and left ventricular (LV) dysfunction. Especially, cumulative doses of anthracyclines >400 mg/m^2 were associated with chronic cardiotoxicity resulting in LV dysfunction.[2]

The major purpose of cardio-oncology is to detect early toxicity and modify medical therapy. Two-dimensional strain echocardiography (2D strain echo) is one of the most valuable tools for the detection of early LV dysfunction. Limited evidence has shown that global longitudinal strain (GLS) is affected before the decline of ejection fraction (EF) following chemotherapy.[3] Therefore, current guidelines recommend the use of GLS in the routine follow-up of patients with breast cancer both during and after chemotherapy.[3,4] However, other strain parameters including circumferential (CS) and radial strain (RS) or torsion imaging are not well studied in the early phase after anthracycline chemotherapy.[5]

Similarly, arrhythmias are mostly seen in the acute period after chemotherapy. Acute anthracycline toxicity may cause sinus tachycardia and ST-segment depression during or days after chemotherapy. Anthracycline chemotherapy can also cause QT-interval prolongation and an increase in QT dispersion. T-wave peak-to-end interval (Tpe) is a marker of ventricular repolarization heterogeneity and it has been associated with increased arrhythmogenic risk in many patient populations including heart failure and coronary artery disease and also has better prediction power than the heart rate corrected QT-interval (QTc) in some special patient populations including hypertrophic cardiomyopathy.[6]

Combined electrical and mechanical monitorization of patients having anthracycline chemotherapy is not comprehensively evaluated. Our aim is to evaluate the cardiotoxic effects of anthracycline chemotherapy in strain echocardiographic and electrocardiographic repolarization parameters in patients with breast cancer.

ABBREVIATIONS

GCS	Global Circumferential Strain
GLS	Global Longitudinal Strain
LVEF	Left Ventricle Ejection Fraction
RS	Radial Strain
Tpe	T peak to end
QT disp	QT dispersion

Material and Methods

Study Population and Design

All consecutive asymptomatic patients who were planned to be treated with chemotherapy due to breast cancer in a single center (Ege University Faculty of Medicine, Department of Medical Oncology) between April 2018 and November 2018 were prospectively evaluated for the study. Patients with a history of structural heart disease, previous chemotherapy, psychiatric and cognitive disease, active infection, severe chronic kidney disease, severe liver insufficiency, pregnant, breastfeeding, and who refused to give informed consent were excluded. All patients were evaluated by echocardiography twice and electrocardiography (ECG) thrice, before chemotherapy (pre-treatment) and 3 months after the first dose of treatment (post-treatment), with an additional ECG in 3 hours of the first dose of chemotherapy for the detection of acute cardiotoxic effects of anthracyclines. The third-month evaluation was also scheduled as it corresponded to the time that chemotherapy was completed. Cumulative anthracycline dose was defined as low if <400 mg/m^2 and high if >400 mg/m^2. Cardiotoxicity was defined as 10% decrease in EF or left ventricular ejection fraction (LVEF) <53% and GLS >15% relative percentage decrease from the baseline. The study was approved by the ethics committee of Ege University Faculty of Medicine (approval number:18-10T/25), and written informed consent was obtained from all participants.

Electrocardiography

Electrocardiographic findings were recorded with a portable digital electrocardiograph (Nihon Kohden, Shinjuku, Tokyo, Japan) with 10-second recordings at a 25 mm/s speed and a standard voltage of 1.0 mV/10 mm. The QT-interval was measured using the tangent method from the beginning of the QRS complex to the end of the T-wave from lead II.[7] Whenever the end of the T-wave could not be determined in lead II, the QT-interval was measured from V5 or V6. The QTc was calculated using both Bazett's ($QTcB = QT - \text{interval}/\sqrt{RR}$) and Fridericia's formulas ($QTcF = 8.22\sqrt[3]{RR}$). QTc values greater than 450 ms for QTcB and 430 ms for QTcF were considered abnormal.[8,9] QT dispersion was manually calculated by the difference between the longest and the shortest QT intervals measured across the 12 leads. QT dispersion values ≥50 ms were considered abnormal. T-wave peak-to-end interval was measured from the peak of the T wave to the end of the T

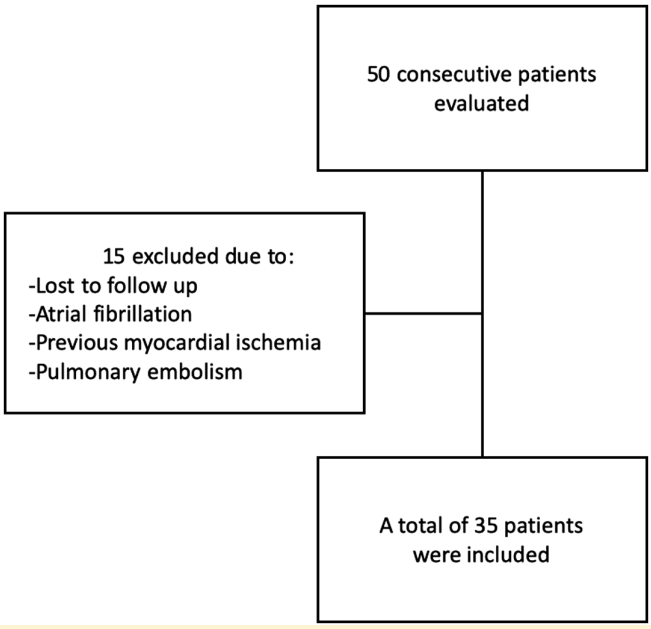

Figure 1. Patient population during the study.

wave in V5, followed by leads V4 and V6, if lead V5 was not appropriate because of artifacts and/or low voltage (<0.15 mV). If the downslope of the T-wave was inconclusive, T-wave was extended by drawing a tangent to the steepest proportion of the downslope until it crosses the isoelectric line. T-wave peak-to-end interval duration was corrected for QTc using Tpe/QTc ratio. All the calculations using QTc were separately conducted for both QTc values obtained by Bazett's and Fridericia's formulations.

Echocardiography

Transthoracic echocardiography was performed in the left decubitus or supine position using commercially available echocardiography systems with a 1.7/3.4 MHz transducer (Vivid 7, GE Vingmed Ultrasound, Horten, Norway) including 2D, color-flow, spectral Doppler and tissue Doppler imaging. All data were acquired in the parasternal, apical, and subcostal views. To obtain an accurate 2D speckle tracking analysis of myocardial deformation, depth, image sector, and frame rate (50-70 frames per second) were adjusted. Three consecutive beats were stored in cine-loop format and analysis of the images was performed offline using dedicated software (EchoPac PC versions 6.0, GE Healthcare, Horten, Norway).

Echocardiography was performed twice, before (pre-treatment) and 3 months after the chemotherapy (post-treatment). Guidelines recommended images were recorded by a single cardiologist (B.O.). Left ventricular ejection fraction was measured by biplane Simpson's method according to the recommendations of the European Association of Echocardiography.[10] Cardiotoxicity was described as 10% decrease in EF or LVEF <53% and GLS >15 % relative percentage reduction from baseline in accordance with the expert consensus from the American Society of Echocardiography and European Association of Cardiovascular Imaging.[11,12] Left ventricular longitudinal strain parameters were measured from the apical 4-chamber, 2-chamber, and 3-chamber views, and the myocardium was divided into 6 segments per view. Care was taken to ensure that the long axis of the ventricle was perpendicular to the plane of the mitral annulus

Table 1. Demographics and Clinical Characteristics

Characteristics	Value
Age, years (SD)	48.9 (11.8)
Female sex, n	35
Body surface area, m^2 (SD)	1.73 (0.13)
Body mass index, kg/m^2 (SD)	28.5 (5.5)
Cumulative dose, mg/m^2 (SD)	415 (32)
Cumulative low dose, mg/m^2 (SD)	376 (8)
Concomitant disease and drugs	
Diabetes mellitus, n (%)	3 (8.6)
Hypertension, n (%)	5 (14.3)
Thyroid hormone replacement, n (%)	3 (8.6)
β-Blocker use, n (%)	3 (8.6)
ACE-I use, n (%)	3 (8.6)

ACE-I, angiotensin-converting enzyme inhibitor; SD, standard deviation; n, number.

Table 2. Echocardiographic Parameters Before and After Chemotherapy

	Pre-chemotherapy ± SD	Post-chemotherapy ± SD	*P*
LVESD (mm)	23 ± 3.7	25 ± 3.7	**.003**
LVEDD (mm)	41 ± 4.8	44 ± 4	**.009**
LA (mm)	33 ± 4.5	36 ± 4.6	.470
E/e'	7.83 ± 2.3	8.08 ± 2.2	.710
Septal Em	9.3 ± 3.5	9.3 ± 3.6	.854
Lateral Em	13 ± 4.6	12 ± 4.4	.078
TAPSE (mm)	26.9 ± 2.7	26.5 ± 2.5	.498
RV Sm	13.3 ± 2.2	12.7 ± 1.7	.046
TRV (m/s)	1.98 ± 0.3	2.2 ± 0.4	**.003**
LVESV (mL)	32 ± 10	35 ± 11	.364
LVEDV (mL)	89 ± 24	95 ± 24	.309
LVEF (%)	64.1 (4.8)	62.3 (4.4)	**.002**
LV strain echocardiographic parameters			
GLS avg (%)	−18.88 (6.82)	−18.66 (3.50)	.863
CS (%)	−17.2 (3.53)	−13 (2.84)	**<.001**
RS (%)	45.1 (8.32)	35.6 (10)	**<.001**
Torsion (cm)	12.1 (3.54)	7.7 (2.17)	**<.001**

LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; RV Sm, right ventricular systolic motion; TRV, tricuspid regurgitation velocity; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; avg, average; SD, standard deviation; pre, baseline; post, third month after treatment.

in the LV apical views. Segmental and layer analyses were also performed in longitudinal strain analysis. Circumferential and radial parameters were measured using the parasternal short-axis plane at the midventricular level. Torsion motion was measured from basal and apical short-axis planes.

Reproducibility

Intraclass correlation coefficients (ICC) were calculated for the intraindividual and inter-observer variations. Electrocardiographic and echocardiogram findings from 10 randomly assigned patients were reanalyzed by the same observer (B.O.). For inter-observer variability, the same patients and the same images were analyzed by a second observer (E.S.).

Statistical Analysis

The normality of the distributions was evaluated by Kolmogorov–Smirnov test. Continuous parameters which were normally distributed were presented as means and standard deviation and non-normally distributed were presented as median and interquartile range. Continuous parameters were compared with Student's *t*-test or Mann–Whitney *U* test according to distribution. Categorical parameters were presented as percentages and compared between groups using chi-square test or Fisher's exact test. The effect of anthracycline therapy was evaluated with a repeated-measures analysis of variance. A comparison of the repeated measures of 3 ECG parameters at different time periods was performed using Friedman's test. Post hoc analysis with Wilcoxon signed-rank test was conducted with Bonferroni correction, resulting in a significance level set at $P < .016$. Paired *t*-test was used to compare LV segmental strain parameters before and after chemotherapy. Statistical analyses were conducted using the Statistical Package for the Social Sciences 25.0 for Windows (IBM Corp.; Armonk, NY, USA).

Results

Patient Characteristics

A total of 50 consecutive patients were evaluated for the study. Fifteen patients were excluded due to insufficient follow-up data (n=12), history of atrial fibrillation (n=1), previous myocardial infarction (n=1), and previous pulmonary embolism (n=1) (Figure 1). The final study population consisted of 35 patients (mean age 48.9 ± 11.8 years, all females). Table 1 summarizes the baseline characteristics. The mean cumulative doxorubicin

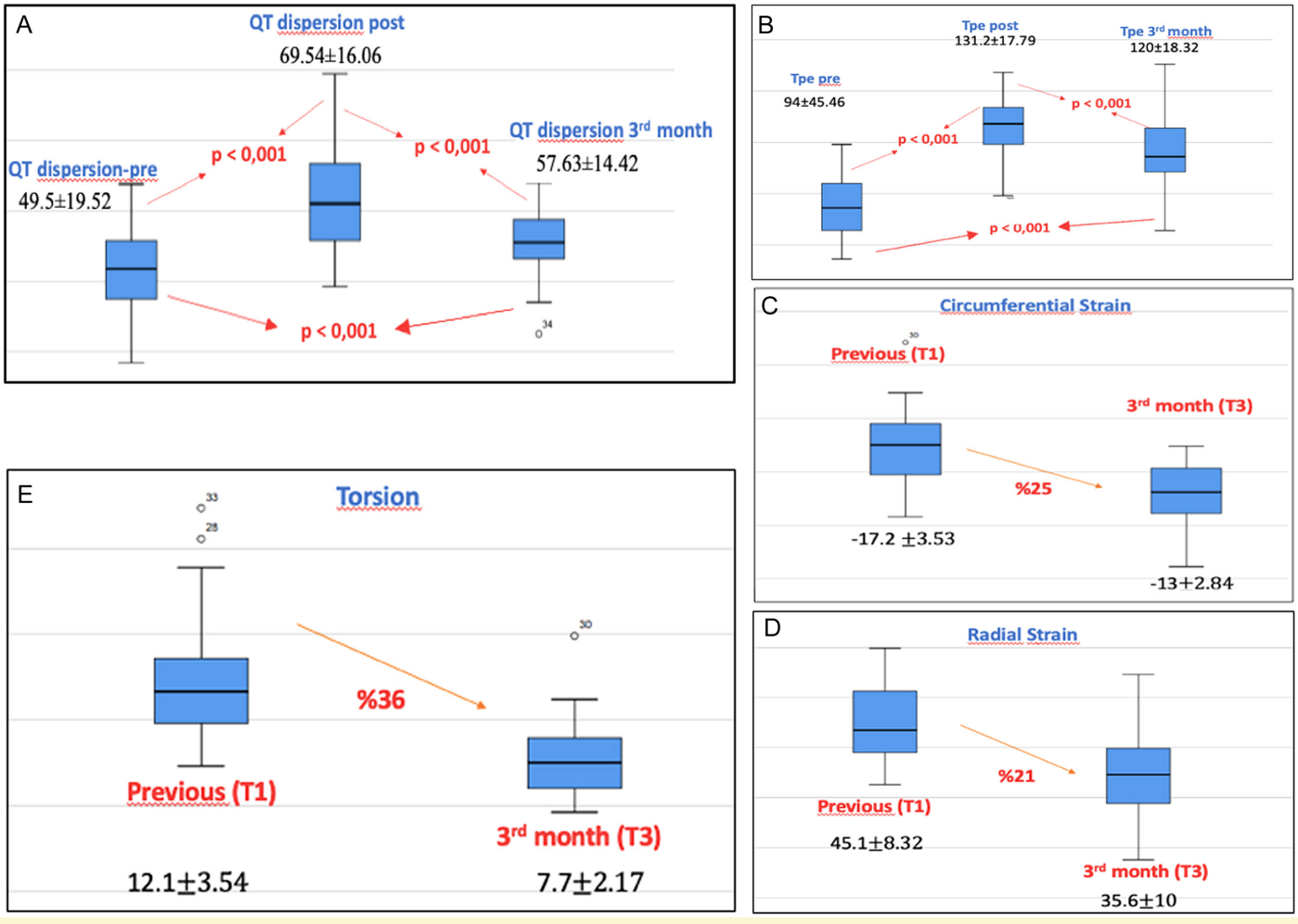

Figure 2. A-E. Electrical and mechanical changes observed early and late after chemotherapy. (A and B) Myocardial repolarization parameters (QT dispersion [A] and Tpe [B]) deteriorated early after and 3 months after chemotherapy. Circumferential strain (C), radial strain (D), and torsion (E) were significantly decreased within the first 3 months of chemotherapy (pre, previous therapy; post, early after therapy).

dose was 415 mg/m^2. Twenty-three patients (65%) had a cumulative dose of more than 400 mg/m^2 (high-dose group). Mean cumulative doxorubicin dose was 376 mg/m^2 in low-dose group.

Echocardiography

The LVEF measured was within normal range for both before and after the treatment; however, mean LVEF was significantly decreased from 64.1% ± 4.8 to 62.3% ± 4.4 (P = .002). None of the patients had classical cardiotoxicity defined as 10% decrease in EF or LVEF <53%. Moreover, none of the patients had significant valvular disease or wall motion abnormalities.

Table 2 and Supplementary Table 1 present the myocardial deformation analyses evaluated by GLS, CS, RS, and regional analysis for 17 myocardial segments and endo, mid, and epicardial layers. All pre-treatment strain, strain rate, and torsion analyses were within normal range. There was no difference between pre- and post-treatment GLS analysis (−18.8% vs −18.6%, respectively; P = .800). However, segmental and layer analyses showed that strain parameters of the endocardial segments of the anterior wall were significantly decreased after treatment. Circumferential and radial strain, and torsion motion were also significantly decreased with treatment (CS: −17.2 ± 3.5 vs −13 ± 2.8, P < .001; RS: 45.1 ± 8.3 vs 35.6 ± 10, P < .001, and torsion 12.1 ± 3.5 vs 7.7 ± 2.1, P < .001, respectively).

There was no significant difference between patients who had low (<400 mg/m^2) and high (>400 mg/m^2) cumulative doxorubicin dose at post-treatment period in all echocardiographic measurements (between low and high cumulative doses of doxorubicin strain values were for GLS average, −19.8 vs −18.2, P = .843; CS, 17.45 vs 17.19, P = .503; RS, 45.86 vs 44.73, P = .99, and torsion, 11.74 vs 12.31, P = .486). There was no significant difference between GLS, CS, and torsion values in low- and high-dose anthracycline groups (Figure 2).

Electrical Changes in Electrocardiogram

Comparison of T0 and T1 showed that heart rate was increased from mean 74.4 ± 9.5 bpm to 77.5 ± 12.6 bpm (P = .001) just after the first dose of chemotherapy. QTc calculations were performed using both Bazett and Fredericia formulas. Changes observed were concordant for both methods. At baseline (T0), one-third (31%) of patients had QT dispersion ≥50 ms. Early after chemotherapy (T1), QTc prolongation was observed in 84% of the patients, whereas compared to the baseline, QTc prolongation was only present in 15% of patients in the third-month evaluation.

When the hyperacute period (T1) and late period (T2) were compared, the QT prolongation regressed in 85% of the cases. At the baseline, Tpe measurements were >89 ms in 57% of the patients. Early after chemotherapy, high values persisted in 54% of the study population. However, pathological prolongation observed in the early stage continued only in 10% of patients in the late period. Repolarization parameters including QTc, QTcB/F dispersion, and Tpe intervals were significantly prolonged (Table 3). There were no significant changes in QRS duration and PR intervals at T0, T1, and T2 ECGs. All parameters that were increased at T1 were significantly decreased at T2. However, all repolarization parameters on T2 ECGs were still significantly higher compared to T0 ECGs (Figure 2 and Table 3).

The comparison of the ECG and echocardiography parameters between the high- and low-dose anthracycline groups revealed that there were no differences between the groups (Supplementary Table 2). Correlation analysis between ECG and echocardiography recordings during T0 and T1 intervals showed that there was a statistically significant negative correlation only between CS and QTcB dispersion (r = −0.413, P = .014) (Supplementary Table 3).

The inter-observer correlation coefficients for Tpe and QT dispersion were 0.915 and 0.858 and the inter-observer

Table 3. Electrical Changes in ECG at T0, T1, and T2 Evaluations

ECG Parameter	T0	T1	T2	P*
Heart rate (bpm)	74 ± 9.56	77.51 ± 12.61	80.66 ± 8.98	**.001**
PR interval (ms)	138.14 ± 16.04	137.57 ± 21.01	141.77 ± 16.18	>.05
QRS (ms)	81.91 ± 8.19	84.09 ± 8.44	82.46 ± 6.19	>.05
QTcB (ms)	440.10 ± 27.63	468.00 ± 38.98	467.86 ± 35.09	**<.001**
QTcF (ms)	424.70 ± 24.05	448.30 ± 29.40	445.26 ± 31.87	**<.001**
QT disp (ms)	49.50 ± 19.52	69.54 ± 16.06	57.63 ± 14.42	**<.001**
QTcB disp (ms)	55.48 ± 20.22	78.59 ± 16.15	66.60 ± 14.62	**<.001**
QTcF disp (ms)	53.48 ± 21.21	75.34 ± 17.08	63.37 ± 15.69	**<.001**
Tpe (QT) (ms)	94 ± 45.46	131.20 ± 17.79	120 ± 18.32	**<.001**
Tpe (QTcB) (ms)	104.00 ± 18.52	148.62 ± 19.16	139.77 ± 21.63	**<.001**
Tpe (QTcF) (ms)	100.84 ± 17.32	142.36 ± 20.30	132.50 ± 20.47	**<.001**
Tpe /QTcB	0.213 ± 0.05	0.281 ± 0.08	0.258 ± 0.06	**<.001**
Tpe/QTcF	0.22 ± 0.03	0.29 ± 0.04	0.27 ± 0.04	**<.001**

*P value: between T0-T1, T0-T2, and T1-T2 (all values are expressed as mean ± SD).
T0, baseline; T1, early after first dose of chemotherapy; T2, after third month of chemotherapy; QTcB, corrected with Bazett; QTcF, corrected with Fredericia; disp, dispersion; Tpe: T peak to end; SD, standard deviation; ECG, electrocardiogram.

correlation coefficients were 0.858 and 0.905, respectively. The intra-observer correlation coefficient for strain echo parameters was 0.831 and the inter-observer correlation coefficient was 0.854.

Discussion

Our study shows that despite GLS values obtained by 2D-echocardiography did not change, the CS, RS, and torsion values worsened during the initial 3 months following the anthracycline chemotherapy in women with breast cancer. In addition to the mechanical impairment, repolarization parameters including QTc dispersion and Tpe deteriorated immediately and early after the chemotherapy.

Guidelines recommend GLS as the preferred marker for the assessment of subclinical heart failure for cardiotoxicity.[3,4] However, there is limited information regarding the early changes in strain parameters other than GLS including CS, RS, and torsion.[12,13] Drafts et al[14] have shown that there may be a change in the CS values on cardiac magnetic resonance imaging 6 months after doxorubicin chemotherapy doses at a range of 50-375 mg/m^2 in 53 patients with breast cancer, leukemia, or lymphoma. However, only the CS was evaluated, and no data were presented for GLS, RS, and torsion in their study. Toufan et al[15] evaluated the acute effects of chemotherapy in a small study and showed that longitudinal peak systolic strain deteriorated in 32.4% of 1071 segments. However, only 13% of patients had a significant decrease in GLS. Reduction was more prominent in the basal segments. Our study extends these observations by showing a heterogenic deterioration in segmental layers after cumulative anthracycline doses. Similar to our study, Kang et al[16] showed a deterioration in the subendocardial layer longitudinal strain and CS without impairment of GLS and LVEF. In addition, the current study has shown an impairment in both RS and torsion of LV. Thus, we suggest that anthracycline-caused cardiotoxicity might first affect the most metabolically active subendocardial layer, which also causes CS deterioration.

The electrical effects of anthracyclines were studied in patients receiving either high-dose chemotherapy due to hematological malignancies such as non-Hodgkin lymphoma or who have concomitant diseases.[17] Nousiainen et al[18] have shown dose-dependent deterioration of QTc and QTc dispersion in 28 patients with non-Hodgkin's lymphoma. Dose-dependent late effects were also shown by Uchikoba et al[19] in a small patient population of long-term pediatric cancer survivors. They showed that QT and QT dispersion were more prolonged in patients receiving high-dose doxorubicin (>400 mg/m^2, n=6) compared to low dose (200-400 mg/m^2, n=16). In our study, patients were evaluated according to the doxorubicin dose of 400 mg/m^2 as the cut-off. We did not observe a significant difference between the high- and low-dose groups. The lack of difference might be due to our average cumulative low dose being high.

The correlation analysis of electrical changes and echocardiography parameters showed only a weak correlation between CS and electrical changes. This might be due to small sample size, and late electrical changes may only be related to anthracyclines' long-lasting effects on the ion channels and the conduction system of the heart (Supplementary Table 3).

Our study has several limitations, including the small sample size and the lack of long-term follow-up. The lack of the measurements of troponin and brain natriuretic peptide levels might be accepted as a limitation. However, troponin level has no association with clinical significance of cardiotoxicity directly in comparison to strain echocardiography.[20,21]

In conclusion, our study, to the best of our knowledge, is the first to evaluate both the strain echocardiographic parameters and all ECG repolarization parameters concomitantly and systematically. It shows that anthracyclines-induced electrical deterioration could occur early after the first dose of chemotherapy as a hyperacute effect. We also observed that this acute deterioration continued even though it decreases in the late period. Although current guidelines do not recommend the use of CS, RS, and torsion strain and ECG repolarization parameters for the evaluation of cardiotoxicity, we believe that further studies will shed light on the pathology of cardiotoxicity and contribute to the understanding of the importance of these parameters in the future.

Visual summary of the article can be seen in Figure 3.

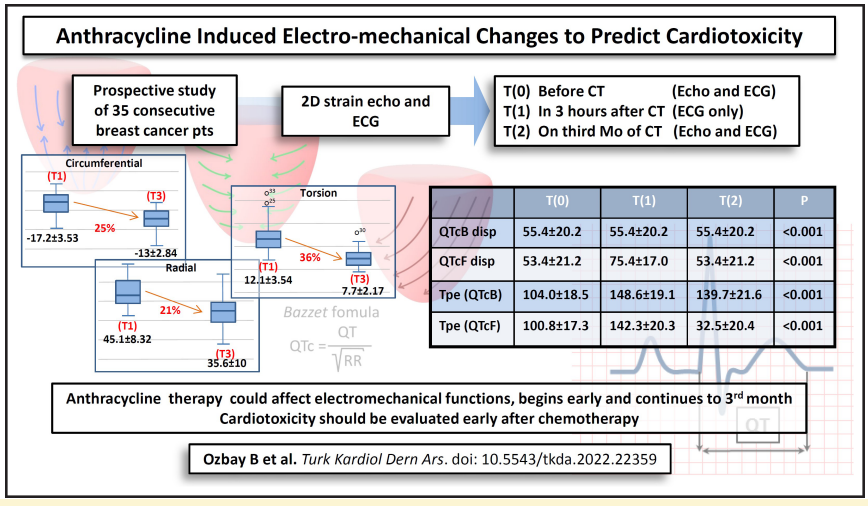

Figure 3. A visual summary of the article.

Availability of Data and Materials: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: The study was approved by the medical ethics committee of Ege University (No: 18-10T/25).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.O., E.S.; Design – B.O., E.S.; Data Collection and/or Processing – B.O., E.S.; Analysis and/or Interpretation – B.O., E.S.; Writing Manuscript – B.O., E.S., H.K., B.C., O.Y.; Critical Review – B.O., E.S., H.K., B.C., O.Y.

Acknowledgments: All authors would like to thank to dear Meral Kayıkçıoğlu, who has reviewed and improved the article before submission.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403. [CrossRef]
2. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2017;35(8):893-911. [CrossRef]
3. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(36): 2768-2801. [CrossRef]
4. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31(2):171-190. [CrossRef]
5. Zito C, Longobardo L, Citro R, et al. Ten years of 2D longitudinal strain for early myocardial dysfunction detection: a clinical overview. *BioMed Res Int*. 2018;2018:8979407. [CrossRef]
6. Castro-Torres Y, Carmona-Puerta R, Katholi RE. Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. *World J Clin Cases*. 2015;3(8):705-720. [CrossRef]
7. Salvi V, Karnad DR, Panicker GK, et al. Comparison of 5 methods of QT interval measurements on electrocardiograms from a thorough QT/QTc study: effect on assay sensitivity and categorical outliers. *J Electrocardiol*. 2011;44(2):96-104. [CrossRef]
8. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *J Am Med Assoc*. 2003;289(16): 2120-2127. [CrossRef]
9. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol*. 2000;36(6):1749-1766. [CrossRef]
10. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-786. [CrossRef]
11. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27(9):911-939. [CrossRef]
12. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;19(1):9-42. [CrossRef]
13. Kavousi M, Leening MJG, Nanchen D, et al. Comparison of application of the ACC/AHA Guidelines, Adult Treatment Panel III Guidelines, and European Society of Cardiology Guidelines for cardiovascular disease prevention in a European cohort [Adult Treatment Panel III guidelines]. *JAMA*. 2014;311(14):1416-1423. [CrossRef]
14. Drafts BC, Twomley KM, D'Agostino R, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging*. 2013;6(8):877-885. [CrossRef]
15. Toufan M, Pourafkari L, Ghahremani Nasab L, et al. Two-dimensional strain echocardiography for detection of cardiotoxicity in breast cancer patients undergoing chemotherapy. *J Cardiovasc Thorac Res*. 2017;9(1):29-34. [CrossRef]
16. Kang Y, Xiao F, Chen H, et al. Subclinical anthracycline-induced cardiotoxicity in the long - term follow-up of lymphoma survivors: a multi-layer speckle tracking analysis. *Arq Bras Cardiol*. 2018; 110(3):219-228. [CrossRef]
17. Chen Z, Lu K, Zhou L, et al. Electrocardiographic characteristics of diffuse large B-cell lymphoma patients treated with anthracycline-based chemotherapy. *J Electrocardiol*. 2020;60:195-199. [CrossRef]
18. Nousiainen T, Vanninen E, Rantala A, Jantunen E, Hartikainen J. QT dispersion and late potentials during doxorubicin therapy for non-Hodgkin's lymphoma. *J Intern Med*. 1999;245(4):359-364. [CrossRef]
19. Uchikoba Y, Fukazawa R, Ohkubo T, Maeda M, Ogawa S. Early detection of subclinical anthracycline cardiotoxicity on the basis of QT dispersion. *J Nippon Med Sch*. 2010;77:234-243.
20. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. *Ann Oncol*. 2002;13(5):710-715. [CrossRef]
21. Sandri MT, Salvatici M, Cardinale D, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? *Clin Chem*. 2005;51(8):1405-1410. [CrossRef]

Supplementary Table 1. Longitudinal 2D Strain Echocardiography Segmental and Layer Analysis for Pre and Post Chemotherapy

	Pre-treatment	Post-treatment	*P*
Anterior epicardium	-18.0±5.6	-17.6±5.9	.745
Anterior mid-cardium	-19.3±5.4	-17.7±6.6	.128
Anterior endocardium	-23.8±6.2	-19.4±7.8	**.004**
Lateral epicardium	-17.7±3.54	-16.8±4.07	.284
Lateral mid-cardium	-20.8±4.06	-20.6±4.53	.757
Lateral endocardium	-22.3±6.53	-22.6±5.56	.796
Posterior epicardium	-19.6±4.17	-17.4±6.42	.202
Posterior mid-cardium	-19.3±4.03	-17.5±6.13	.110
Posterior endocardium	-22.7±5.75	-21.0±5.39	.132
Inferior epicardium	-18.1±4.01	-18.3±4.19	.849
Inferior mid-cardium	-20.3±4.24	-19.8±5.03	.604
Inferior endocardium	-21.5±5.07	-19±5.95	.031
Septum epicardium	-19.8±3.63	-17.4±4.99	.016
Septum mid-cardium	-19.4±4.03	-17.9±4.68	.124
Septum endocardium	-21.0±7.15	-21.1±4.88	.988
Anterior septum epicardium	-15±3.57	-14.4±4.46	.422
Anterior septum midcardium	18.8-±4.46	-17.7±4.46	.263
Anterior septum endocardium	-15±3.57	-14.4±4.46	.162

Pre, previous chemotherapy; post, after chemotherapy (all values are expressed as mean ± SD).

Supplementary Table 2. ECG and Echocardiography Parameters Compared According to the Anthracycline Dose Before and After Chemotherapy

	Low-Dose Group		High-Dose Group		
	Baseline (T0)	Post (T2)	Baseline (T0)	Post (T2)	*P*
GLS (-%)	-19.87±2.44	-19.98±3.40	-18.29±8.42	-17.89±3.39	.843
CS (-%)	-17.45±2.91	-13.53±2.28	-17.19±3.92	-12.70±3.13	.458
RS (%)	45.86±6.70	36.39±9.58	44.73±9.27	35.25±10.53	.707
Torsion (cm)	11.74±2.72	7.93±2.03	12.31±3.98	7.69±2.28	.728
QTcB disp	50.78±15.15	58.25±25.42	72.06±15.89	82.45±18.77	.746
Tpe	105.08±14.42	148.20±25.89	104.32±21.31	148.86±21.19	.994

GLS, global longitudinal strain; CS, circumferential strain; RS, radial strain; QTc disp, QT dispersion; Tpe, T peak to end (all values are expressed as mean ± SD).

Supplementary Table 3. Correlation Between Increased ECG Parameters and Impaired Strain Echocardiography Parameters

	GLS	CS	RS	Torsion
QTcB				
Rho	0.019	-0.234	0.055	0.020
P	.913	.176	.754	.910
QTc disp				
Rho	-0.097	**-0.413**	0.305	0.137
P	.577	**.014**	.074	.432
Tpe				
Rho	-0.325	0.332	-0.032	-0.279
P	.057	.052	.854	.105
Tpe				
Rho	-0.166	0.281	-0.033	-0.246
P	.339	.102	.852	.154
Tpe (QTc)				
Rho	0.144	**0.373**	-0.015	-0.270
P	.409	**.028**	.934	.116

Rho, correlation coefficient; GLS, global longitudinal strain; CS, circumferential strain; RS, radial strain; QTcB, corrected with Bazzet QT; Tpe, T peak to end.