Original Article

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Is Electrocardiogram Helpful in Predicting a Rise in Troponin I as a Marker of Anthracycline Cardiotoxicity?

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ABSTRACT

Objective: Screening patients on anthracycline-based chemotherapy regimens for the development of cardiotoxicity can be resource intensive. We therefore studied various traditional electrocardiogram (ECG) parameters to correlate and possibly predict the development of elevated Troponin I as a surrogate marker of anthracycline-induced cardiotoxicity.

Materials and Methods: This was a single-centre prospective cohort study done between January 2014 to January 2016. Baseline ECG was compared with ECG performed after chemotherapy and different parameters were compared. Patients were divided into Troponin I positive and negative groups based on the test performed at the end of chemotherapy, using a cut-off of 0.06 ng/dL.

Results: Of the 160 patients studied, 131 (81.9%) were Troponin I negative (TnI-) and 29 (18.1%) were positive (TnI+). Breast cancer accounted for 79% of all cancers in this study. Many ECG parameters were compared between the TnI- and TnI+ groups. Of them, TP segment and TP/QT showed a significant decrease in the TnI+ group. The mean (95% confidence interval) TP in the TnI- group was 162.9 ms (145.4, 180.4) and in TnI+ groups was 117.9 ms (89, 146.8) (p = 0.03). Corresponding values for TP/QT were 0.47 (0.42, 0.51) and 0.35 (0.27, 0.42) (p = 0.02). These changes were not significant in multivariate analysis and likely reflected the different mean heart rates (HR) in both the groups, as suggested by partial correlation which was run with HR as a confounder.

Conclusion: ECG parameters, such as QTcH, TP and TP/QT do not helpful predicting Troponin I elevations in patients on anthracycline-based chemotherapy. Further studies based on hard endpoints, for example, clinical systolic dysfunction occurring at one year, would give better information on their utility.

Keywords: Anthracyclines; cardiotoxic agents; chemotherapy; ECG; Troponin I

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Key Points

- Little is known regarding the electrocardiogram (ECG) correlates and their role in predicting elevations in Troponin I among patients on anthracyclines.
- This study was an attempt to triage this group of patients who would require closer monitoring and detailed evaluation using advanced imaging modalities.
- Further studies based on more robust endpoints, for example the development of systolic dysfunction, would be needed to clearly understand a role for ECG in this setting.

Introduction

Anthracyclines have been the mainstay in the treatment of many malignancies, especially breast cancer, lymphomas, sarcomas and various childhood malignancies. Anthracycline-induced cardiotoxicity has been well documented at doses exceeding 550 mg/m^2 leading to recommendations not to exceed therapeutic doses above 400–450 mg/m^2 (1, 2). Reducing the cumulative doses brings down the incidence of cardiotoxicity, but the risk persists. The current incidence of clinical heart failure due to anthracycline cardiotoxicity is 1–5%, and asymptomatic cardiac dysfunction is 5–20% (3, 4). The risk increases with mediastinal radiation, advanced age (>65 years), younger age (<4 years), female sex, hypertension, diabetes, peripheral vascular disease, emphysema, bolus dose regimen and pre-existing coronary artery disease (3, 5). However, it still remains impossible to predict if a patient would develop cardiotoxicity with anthracyclines or not.

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The usefulness of Troponin I as a biomarker of cardiotoxicity has been extensively researched in a metanalysis (6). This study analysed Troponin I, Troponin T, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). Of these, only Troponin I, measured at the end of chemotherapy, showed a significant and strong association with future development of cardiotoxicity with 85% positive predictive value and 99% negative predictive value for the development of clinical heart failure at one year. However, the use of Troponin to predict the development of cardiotoxicity merely predicts the inevitable as Troponin itself is a marker of myocardial necrosis (7). Treatment with enalapril and carvedilol has proven to be beneficial in modifying the disease course of cardiotoxicity in high-risk patients identified based on Troponin I (8). A different predictor of cardiotoxicity, based on an electrocardiogram (ECG), would go a long way to better triage such patients.

ECG could help in predicting cardiotoxicity even before irreversible damage to cardiac myocytes has occurred. Studies done on patients receiving myeloablative chemotherapy have shown that corrected QT interval (QTc) was a predictor of cardiac dysfunction (9). The novel concept of ischemic constellation (10) rather than cascade further supports the fact that ECG could act as a useful tool to predate irreversible myocardial injury. This concept would also hold for myocardial injury due to oxidative stress, as seen during chemotherapy (7). Moreover, there is a paucity of data regarding the diastolic correlates of ECG, such as TP segment and PQ interval, among patients undergoing anthracycline-based chemotherapy, which may show changes corresponding to echocardiography-derived parameters of diastolic dysfunction (11).

An interesting study done to assess the diagnostic accuracy of *TP / (PQ x Age)*, referred to as Decg, showed that a value <0.033 correlated well with the presence of diastolic dysfunction of any grade (11). This parameter (Decg) was validated in the same study and showed a sensitivity and specificity of 83% and 92%, respectively, and a positive and negative predictive value of 92% and 83%. When a combined approach was used in this study incorporating indexed left atrial end-systolic volume (LAESV) with a cut off-of >34 mL/m^2, the sensitivity and specificity only changed marginally to 90% and 92%. At the same time, the positive and negative predictive values were 95% and 86%, respectively. More importantly, the ECG counterpart of increased atrial contribution seen in patients with diastolic dysfunction, that is the PQ interval, predated the actual morphological changes in atria, characterized by left atrial (LA) enlargement denoted by Indexed LAESV. Hence, it would be intuitive to evaluate the discriminatory capacity of this variable in predicting troponin elevation in this group in patients undergoing cardiotoxic chemotherapy.

Cost-effectiveness studies performed on cancer survivors (12-14) suggest that, although newer imaging modalities like global longitudinal strain and speckle tracking, have greater sensitivity in picking up subtle changes in cardiac function, it may not be suitable for mass implementation and may be limited by interobserver variability and operator experience. Therefore there is a need to investigate cheaper, more objective and readily available modalities to help identify patients who would require closer monitoring for the development of chemotherapy-induced cardiotoxicity. The aim of this study was to identify ECG predictors of positive Troponin in patients undergoing anthracycline-based chemotherapy.

Materials and Methods

Study Population

This was a single-centre, prospective, cohort study conducted at Government Medical College Hospital, Kozhikode, Kerala, India, during two years period from January 2014 to January 2016. The study was approved by the Institutional Ethics Committee, reg no: ECR/395/Inst./KL/2013 having approval number GMCKKD/RP 2016/IEC/76. The trial was overseen by the head of the department of cardiology.

All patients who were >18 years of age, with malignancy and were planned to be given a doxorubicin-based chemotherapy regimen, were screened for eligibility. Those who had an ejection fraction of <55%, moderate to severe valvular heart disease based on the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (15) were excluded from the study. The presence of diabetes and hypertension was ascertained based on history. Previous myocardial infarction (MI) was defined as a documented acute coronary syndrome in the past or ECG evidence of pathological Q waves (16). Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Measurement of ECG Parameters

ECG was recorded using the EdanUSA SE-1200 (EdanUSA, San Diego, CA, USA) machine and was scanned to a computer as an image file (.jpeg) at 600 dpi. The various measurements taken were: QT interval; RR interval; TP segment; and PQ interval (Figure 1). These were measured using the Cardio Calipers v3.3 software (Iconico Inc., Philadelphia, PA, USA). Heart rate (HR) was calculated from

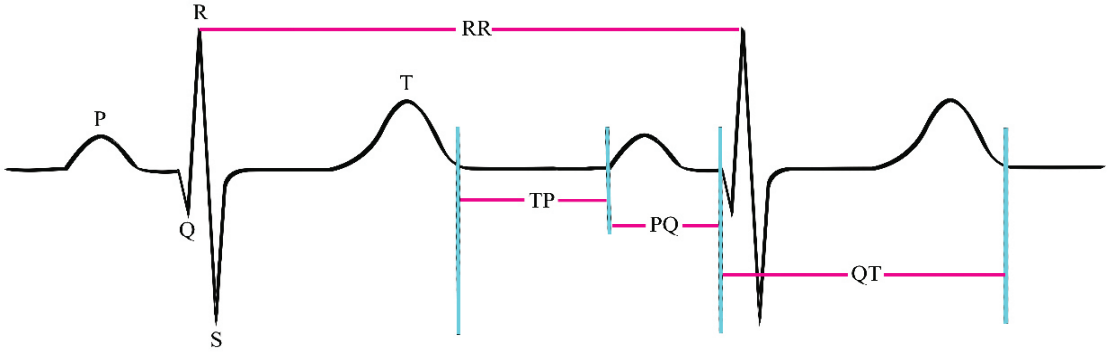

Figure 1. Various measurements of ECG segments and intervals used in this study

ECG: electrocardiogram

the RR interval, measured in milliseconds, by the formula 60,000 ÷ RR. For QT measurement, the lead showing the longest QT was taken. In patients with bundle branch blocks, the QT interval is overestimated due to the widening of the QRS complex and not due to the abnormalities of repolarization. Besides, the formulas used for corrected QT interval calculation are not standardized for use in patients with bundle branch blocks (17). Hence, patients with such ECG abnormalities were excluded from the study to prevent non-uniformity in the study population. QTc was calculated using the Hodges formula (QTcH) (18). Lead II was used to measure TP and PQ as P waves are best delineated in this lead (19). Patients with atrioventricular dissociation will show a beat-to-beat variation in the TP and PQ intervals and therefore were excluded from the study. Decg was measured using the formula *TP / (PQ x Age)*, where TP is the duration of the TP segment measured in milliseconds, PQ is the duration of the PQ interval measured in milliseconds, and age is given in years (11).

Troponin I Assay

Troponin I (TnI) was measured on a Beckman Coulter machine using the Access AccuTnI 3 assay. Based on the validation studies for this assay, the manufacturer claimed 99th percentile of the upper reference level was 0.04 ng/mL. At this cut-off, the total imprecision was <14%. A value of ≥0.06 ng/mL had an imprecision of <10% and was used in this study to define a positive test (20), as previously described (6).

Data Collection

Patients or the public were not directly involved in the design of the study or the collection of data. The patients were asked to report to us at specified intervals, and the institution itself did data collection. Once the patient fulfilled the criteria for enrolment, baseline demographic data collection, and risk factors assessment were done. A baseline ECG was taken, after which the patients were instructed to begin chemotherapy. At the end of their final cycle of chemotherapy, ECG was repeated, and blood samples were collected to test for Troponin I. The study population was then divided into two groups based on their Troponin I results. They were considered Troponin I positive (TnI+) or Troponin I negative (TnI-) based on a cut-off of 0.06 ng/mL. The ECG measurements obtained were then compared between the two groups, as were the change in parameters from baseline to post-chemotherapy.

Chemotherapy Regimens

Two chemotherapy regimens used for breast cancer at our centre during the study were the AC regimen consisting of doxorubicin and cyclophosphamide, and the FAC regimen consisting of 5-fluoro uracil, doxorubicin, and cyclophosphamide. The AC regimen used doxorubicin at a dose of 60 mg/m^2 for four cycles, giving a cumulative dose of 240 mg/m^2. In comparison, the FAC regimen used doxorubicin at a dose of 50 mg/m^2 for six cycles, giving a cumulative dose of 300 mg/m^2. In Non-Hodgkin's lymphoma, doxorubicin was used at a dose of 50 mg/m^2 for six cycles, giving a cumulative dose of 300 mg/m^2. The corresponding dosing regimen for sarcomas and malignant fibrous histiocytomas used doxorubicin at a dose of 75 mg/m^2 for six cycles, giving a cumulative dose of 450 mg/m^2.

Statistical Analysis

Statistical analysis was performed using SPSS, version 26.0 (IBM Inc., Chicago, IL, USA). All variables were evaluated separately in TnI- and TnI+ groups. Categorical variables are presented as frequencies in each group, and their inter-group differences were assessed using the chi-square test or Fisher's Exact test depending on the variable. The normality of data was confirmed using skewness and kurtosis, as well as histograms and Normal Q-Q plots. Continuous variables are presented as mean with their 95% confidence intervals (CI) given in parenthesis. The difference in means of continuous variables between groups was compared using the independent samples t-test. For assessing the difference scores of ECG parameters from baseline to post-chemotherapy, paired t-test was used. For those variables showing statistically significant differences, multivariate analysis using binary logistic regression was done. A cut-off ≤0.05 was used for alpha error. Linear regression was run using Troponin I as a continuous dependent variable and all statistically significant post-chemotherapy variables to predict positive Troponin I, based on the cut-off of ≥0.06 ng/mL. Pearson's correlation was run on Troponin I values with significant post-chemotherapy variables followed by Pearson's partial correlation to eliminate confounders.

Results

A total of 240 patients who were referred to the cardiology department for pre-chemotherapy fitness were screened and found to be eligible. Of them, 32 patients were excluded, and another 48 patients were lost to follow-up. Hence, a total of 160 patients completed the study and were used for this analysis. There were 29 patients (18.1%) who were TnI+ and 131 patients (81.9%) were TnI- (Figure 2). Baseline characteristics (Table 1) were comparable between the two groups. The mean age in both groups was similar, 52.8 (50.7, 54.8) years in the TnI- group and 51.5 (47.4, 55.5) years in the TnI+ group (*p*

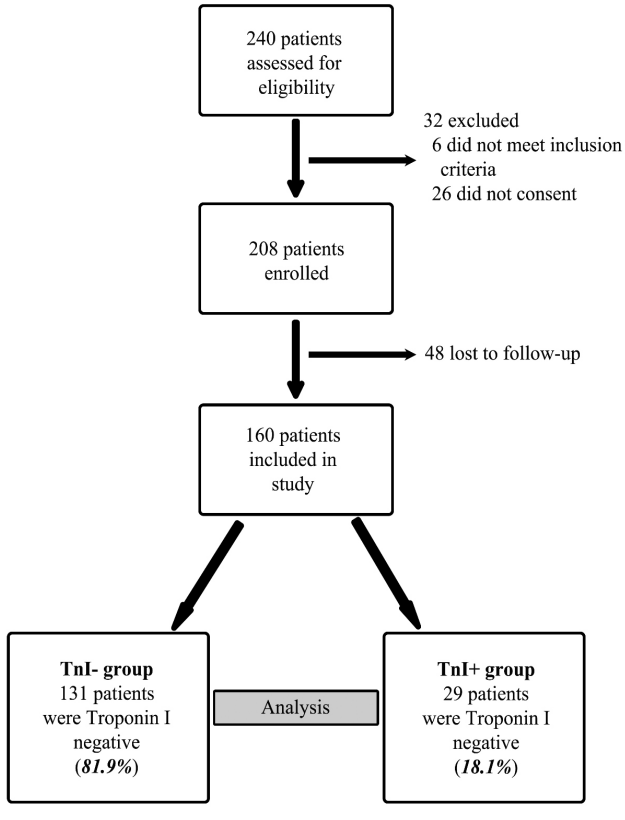

Figure 2. CONSORT diagram

= 0.59). Breast cancer accounted for more than three-quarters of all cancers in both groups, and as expected, females predominated the study population accounting for 86.3% of TnI- group and 93.1% of TnI+ group. Other malignancies in the remainder included bladder cancer, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, sarcoma, and stomach cancer. The risk factors considered were hypertension, diabetes, and previous myocardial infarction, and none of these showed a difference between groups. Baseline ECG parameters were also comparable between groups (Table 2).

Post-chemotherapy ECG showed a statistically significant difference in three variables between groups (Table 3). These were HR, TP, and TP/QT, which had a significant difference between means. Other parameters (QT, QTcH, PQ, and PQ/QT) were not different between groups. The mean HR in the TnI- group was 97.2 beats per minute (bpm) (94.3, 100) beats and in the TnI+ group this was 106.4 bpm (99.8, 113.1) (p<0.01). The mean TP segment in the TnI- group was 162.9 milliseconds (ms)(145.4, 180.4) and in the TnI+ group was 117.9 ms (89, 146.8) (p = 0.03) and the TP/QT in the respective groups were 0.47 (0.42, 0.51) and 0.35 (0.27, 0.42) (p = 0.02).Change in the baseline values of ECG parameters after chemotherapy were assessed using the paired samples t-test. All parameters, except for HR and PQ/QT, showed a statistically significant change from baseline (Table 4). The mean difference in QT in the TnI- group was 11.5 ms (5.7, 17.2; p<0.01), HR was - 9.2 bpm (-11.8, -6.7, p<0.01), TP was 41.5 ms (26.4, 56.7, p<0.01), TP/QT was 0.1 (0.06, 0.14, p<0.01) and PQ was 6.6 (0.9, 12.2, p = 0.02). In the TnI+ group, the mean HR difference was -12.9 bpm (-18.9, -6.8, p<0.01), QTcH was -14.2 ms (-25.3, -3.1, p<0.01), TP was 52.4 ms (19.5, 85.4, p<0.01) and TP/QT was 0.14 (0.05, 0.23, p<0.01). QT, PQ, and PQ/QT did not show a significant change in the mean. Difference scores of all the ECG parameters were also calculated and compared between groups to see if this change in parameters was significant. To calculate the difference-scores, post-chemotherapy scores were subtracted from the baseline scores and independent samples t-test was performed. It did not show

Table 1. Comparison of baseline categorical variables between Troponin I negative and positive groups

Variable	Subgroups	% in Troponin Negative	% in Troponin Positive	*p*-value
Gender	Male	13.7	6.9	0.53
	Female	86.3	93.1	
Malignancy	Bladder	0.8	0	0.7
	Breast	78.6	82.8	
	Hodgkin's lymphoma	2.3	0	
	Non-Hodgkin's lymphoma	5.3	10.3	
	Sarcoma	4.6	6.9	
	Stomach	6.9	0	
	Others	0.8	0	
Hypertension	Yes	30.5	27.7	0.75
	No	69.5	72.4	
Diabetes	Yes	16	17.2	0.53
	No	84	82.8	
Myocardial infarction	Yes	2.3	3.4	0.55
	No	97.7	96.6	

Table 2. Comparison of baseline continuous variables between Troponin I negative and positive groups

	Troponin Negative		Troponin Positive		
Parameter	Mean	95% CI	Mean	95% CI	*p*-value
Age	52.8	50.7, 54.8	51.5	47.4, 55.5	0.59
QT	352.8	347, 358.6	340.7	329.5, 351.9	0.08
HR	88	85.3, 90.6	93.6	88.2, 98.9	0.07
QTcH	401.7	398, 405.4	399.4	393, 405.8	0.60
TP	204.2	185.7, 223.2	170.3	137.4, 203.3	0.12
TP/QT	0.56	0.52, 0.61	0.49	0.40, 0.58	0.16
PQ	152.5	147.3, 157.7	143.5	133, 153.9	0.14
PQ/QT	0.44	0.42, 0.45	0.43	0.39, 0.46	0.59

CI: confidence interval; HR: heart rates

a statistically significant difference in any of the measured variables (Table 4). Multivariate analysis was performed on the ECG variables QTcH, TP, TP/QT, and PQ, and none of the variables showed a significant association with a positive troponin test.

There was a linear correlation between HR, TP, TP/QT, and Troponin I values. However, when Pearson's partial correlation was run to control for HR as a confounder, the relationship of both TP and TP/QT with Troponin I ceased to be statistically significant ($p = 0.35$).

Discussion and Conclusion

This is the largest single centre data available on ECG and Troponin I elevations in patients on anthracyclines. Breast cancer was the predominant malignancy for which doxorubicin was used. Our study demonstrates that HR, TP, and TP/QT showed a significant difference in the Troponin positive group in univariate analysis, but this did not hold in multivariate analysis. Besides, the changes in TP and TP/QT were likely related to the changes in mean HR between groups. Other ECG parameters did not show any difference between groups, nor was a change from baseline significant in any of the parameters assessed.

Ever since animal models demonstrated a prolongation of QT interval with the use of anthracyclines (21), QTc assessment had attracted a lot of attention for its putative role in predicting not only arrhythmias but also heart failure. Association with heart failure was suggested by a study done in 2003 in patients undergoing myeloablative chemotherapy (9). Since then, numerous small studies (22-24) in patients on anthracyclines have documented a prolongation of QTc, but the clinical significance or the association with cardiotoxicity has not been ascertained. The present study also showed a significant change in QTcH (δQTcH) from baseline in the TnI+ group compared to the TnI- group but this difference was not statistically different between groups. Also, the mean δQTcH in the TnI+ group was -14.2 (-25.3, -3.1) msec, which is too small a change to have any practical application. This makes δQTcH a weak parameter to identify TnI+ patients.

The diastolic ECG parameters measured in this study (PQ, PQ/QT, TP and TP/QT) have never been previously studied in the context of anthracycline cardiotoxicity, to the best of our knowledge. PQ and PQ/QT did not show any difference between groups, but both TP and TP/QT showed a significant difference. There was an average drop of approximately 50 ms in the TnI+ group, which was significant ($p = 0.03$). With the development of diastolic dysfunction, the TP segment was expected to prolong but in the present study, a reduction in TP and TP/QT was observed among those with positive Troponin I. This might be because diastolic dysfunction might not have been present and direct subclinical oxidative damage could have released Troponin I into the blood. This was indeed confirmed in studies that evaluated diastolic function on echocardiography. In a study that evaluated changes in echocardiographic measurements of diastolic dysfunction like E/A ratio (which is the ratio of the velocity of mitral

Table 3. Comparison of post-chemotherapy ECG characteristics between Troponin I negative and positive groups

	Troponin Negative		Troponin Positive		p-value
Parameter	Mean	95% CI	Mean	95% CI	
QT	341.4	336.2, 346.6	332.4	322, 342.9	0.15
HR	97.2	94.3, 100	106.4	99.8, 113.1	<0.01
QTcH	405.9	401.9, 409.9	413.7	404.9, 422.4	0.11
TP	162.9	145.4, 180.4	117.9	89, 146.8	0.03
TP/QT	0.47	0.42, 0.51	0.35	0.27, 0.42	0.02
PQ	146	140.7, 151.2	144.1	134.7, 153.5	0.85
PQ/QT	0.44	0.41, 0.46	0.44	0.40, 0.47	0.72

CI: confidence interval; HR: heart rates; ECG: electrocardiogram

Table 4. Change in ECG parameters from baseline to post-chemo in Troponin negative and positive groups

	Troponin Negative			Troponin Positive			p-value for diff between groups
Parameter	Mean diff	95% CI	*p*-value	Mean diff	95% CI	*p*-value	
QT	11.5	5.7, 17.2	<0.01	8.3	-3.1, 19.6	0.15	0.64
HR	-9.2	-11.8, -6.7	<0.01	-12.9	-18.9, -6.8	<0.01	0.24
QTcH	-4.2	-9.1, 0.7	0.09	-14.2	-25.3, -3.1	<0.01	0.09
TP	41.5	26.4, 56.7	<0.01	52.4	19.5, 85.4	<0.01	0.55
TP/QT	0.1	0.06, 0.14	<0.01	0.14	0.05, 0.23	<0.01	0.34
PQ	6.6	0.9, 12.2	0.02	-0.7	-13, 11.6	0.91	0.28
PQ/QT	-0.01	-0.02, 0.02	0.98	-0.1	-0.05, 0.03	0.57	0.46

CI: confidence interval; HR: heart rates; ECG: electrocardiogram

vale opening in the early rapid filling phase vs the same in late rapid filling phase), Isovolumetric Relaxation Time (IVRT; which is the time between the closure of the aortic valve at the end of systole to the opening of the mitral valve at the beginning of diastole), and deceleration time (time from the peak of E wave to the equalization of pressures between left ventricle and left atrium before the onset of A wave) in patients undergoing chemotherapy with anthracyclines, it was not found to be associated with the future development of cardiotoxicity (25). Another small study of 51 patients showed that diastolic dysfunction on echocardiography developed during chemotherapy with a significant reduction in e' and E/e'. This change was not correlated with Troponin I or ejection fraction, and thus it had limited ability to identify patients at risk of developing cardiotoxicity (26). Such heterogeneity in studies suggest that diastolic dysfunction may not necessarily be part of the spectrum of chemotherapy-induced cardiotoxicity. This could be explained by the fact that diastolic dysfunction parameters are heavily dependent on the loading conditions of the heart, meaning, when intravascular volume is high, the load borne by the left ventricle could strain it enough to worsen the diastolic properties of the heart and vice-versa. This makes echocardiographic diastolic parameters quite unreliable and for this reason, load independent variables, such as global longitudinal strain imaging, have gained importance.

TP interval is known to be inversely correlated with HR. It is likely, in our study, that the change in the TP segment duration and TP/QT observed is merely a function of the different mean HR values in each group. Both groups showed a significant decrease in mean HR from baseline with a significant reduction of 9.2 bpm in the TnI- group and 12.9 bpm in the TnI+ group. Although there was a numerically greater reduction in HR in those with positive Troponin I, this difference was not significant. This association was conclusively proven by Pearson's partial correlation controlling for HR. This further demonstrates that TP/QT is not a reliable way to control the TP segment duration for HR.

Although a Troponin I test done at the end of chemotherapy has a high negative predictive value, it is only a marker in high-risk patients. Elevation of Troponin I does not always predict the development of clinically significant left ventricular dysfunction, with only 85% positive predictive value (6). Our study was conducted to find ways to predict the development of elevated Troponin I. Testing ECG against hard endpoints, like systolic dysfunction, over a year's follow-up would have provided more conclusive evidence regarding a correlation. An interim analysis of ECG would have helped in understanding the temporal changes occurring in these parameters and would have identified subtle changes that predate the occurrence of positive Troponin I itself.

In conclusion, none of the studied ECG parameters used in this study are useful to identify patients at risk of developing anthracycline-induced cardiotoxicity. HR, TP, and TP/QT showed a significant reduction in Troponin I positive patients on univariate analysis, but it did not prove significant in multivariate analysis. Also, the differences observed in TP and TP/QT between groups were merely a reflection of different mean HRs in the two Troponin I groups.

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee, Government Medical College, Kozhikode, Institutional Ethics Committee, Government Medical College, Kozhikode, reg no: ECR/395/Inst./KL/2013 having approval number GMCKKD/RP 2016/IEC/76.

Informed Consent: Consent was obtained from the study participants prior to inclusion.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.M., B.J.; Concept: K.M., B.J., S.C.G., K.M.N.; Design: K.M., B.J., A.T., S.C.G., K.M.N.; Data Collection and/or Processing: K.M., B.J.; Analysis and/or Interpretation: K.M., B.J., G.D.; Literature Search: K.M., B.J., G.D.; Writing: K.M., B.J., G.D.

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