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ASSESSMENT OF CARDIAC BIOMARKER WITH MYOCARDIAL 2D STRAIN ECHOCARDIOGRAPHY FOR EARLY DETECTION OF DOXORUBICIN INDUCED CARDIOTOXICITY IN PATIENTS UNDERGOING CHEMOTHERAPY

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ABSTRACT:

BACKGROUND:

One of the highly-effective cancer drug (doxorubicin) are used widely in the treatment of patients with HER2-positive breast cancer, ovarian cancer, leukemia etc.., and have led to important gains in survival. Cancer patients survive longer, the impact of cardiotoxicity associated with the use of cancer treatments escalates. However, these agent carry a significant risk of cardiovascular morbidity. The present study investigates whether early alterations of myocardial strain and blood biomarker predict incident cardiotoxicity in patients treating with doxorubicin chemotherapeutic agent.

METHODS:

A prospective observational study was done in 30 consecutive breast cancer patients who was treated with doxorubicin. Complete clinical details of patients were taken. Blood samples were taken before and after first course of chemotherapy. hs-Trop I were measured and GLS echocardiography were performed. Pearson correlation and Spearman correlation were used to determine before and after first course of chemotherapy using doxorubicin chemotherapeutic agents.

RESULT:

A total of 30 consecutive breast cancer patients were taken up for the study. hs TnI level increased and decline in LVEF were observed from baseline to completion of ($p < 0.05$) Doxorubicin cycle. A greater risk of cardiotoxicity was associated with interval changes in hs TnI and GLS.

CONCLUSION:

Early increases in TnI and decline in LVEF levels offers additive information about the risk of cardiotoxicity in patients undergoing chemotherapy with Doxorubicin chemotherapeutic agent.

INTRODUCTION:

Doxorubicin (DOX), one of the chemotherapeutic agent, has an unpredictable cardiotoxicity profile which restricts its dosage and affects patients' survival and quality of life regardless of their cancer prognosis (1,2). Asymptomatic myocardial injury is the initial dose of DOX-induced cardiotoxicity, which builds up dose-dependently and can cause irreversible symptomatic heart failure (HF) years after treatment (3,4). Doxorubicin alter iron metabolism, produce more reactive oxygen species, and block the enzyme topoisomerase 2ß. These effects result in mitochondrial malfunction and impede DNA replication, repair, and transcription, which ultimately leads to cardiomyocyte mortality (5,6,7). Among cancer survivors in childhood and adolescence, cardiovascular disease is the primary cause of late mortality. Many adult cancer patients in complete remission have a higher risk of cardiovascular death than real cancer recurrence (8,9). In addition, these patients are more likely to develop dyslipidemia, pericardial disease, valvular heart disease, atherosclerosis, and hypertension. In order to accurately identify long-term adverse effects of cancer therapy and begin appropriate treatment before the toxicity becomes irreversible, cancer survivors must have adequate surveillance (10,11). Damage to the cardiomyocytes releases the cardiac-specific isoenzymes of troponins T and I (cTnT, cTnI) into the bloodstream. In patients receiving large dosages of doxorubicin, troponin levels have been used to predict acute LV dysfunction and quantify myocardial damage. Chemotherapy causes troponin levels to rise quickly, which may indicate late cardiac events (12). However, the release of troponins is associated with myocardial cell lysis, which may not occur at first when type II heart damage, chemotherapy is administered. It is difficult to identify cardiotoxicity since it can manifest at any stage of the therapeutic regimen and even in the absence of the previously described conditions. Reducing cardiovascular problems and avoiding the need to stop antitumoural medication depend on early diagnosis of myocardial damage (13). Doxorubicin-induced cardiotoxicity is frequently irreversible and can lead to clinical heart failure, which emphasizes the need for early identification (14). Acute-phase protein C-reactive protein (CRP) is produced during an inflammatory response. Its elevation is associated with several adverse clinical outcomes, including myocardial infarction, congestive heart failure, and stable coronary artery disease, and is prognostic of diastolic dysfunction and lower LVEF (15,16,17). Left ventricular dysfunction caused by doxorubicin, a major class of medication used to treat acute leukemia, lymphoma, and breast cancer, is the hallmark of Cardiotoxicity. Since LVEF has dropped in doxorubicin-treated patients, it might already be too late to stop the disease's progression (18). Early and improved modifications to oncologic and cardiac treatments may be possible with more sensitive and precise markers of cardiac dysfunction or myocardial harm caused by chemotherapy. After doxorubicin-based chemotherapy, reductions in myocardial strain and strain rate have been reported (19,20,21,22,23). The actions of DOX on cardiomyocytes that result in contractile dysfunction are the main focus of DOX-induced cardiotoxicity, new research has also highlighted DOX-induced systemic inflammation and endothelial damage, which may serve as a trigger for the onset and progression of cardiomyopathy (24). In economically developed nations, cancer is the primary cause of death, whereas in underdeveloped nations, it ranks second (25). The main objectives of this study were to assess changes in LVEF by echocardiographic parameters (Simpson’s biplane and GLS) and in biomarkers [high-sensitivity cardiac troponin I (hs cTnI)] extracted before and after first course of chemotherapy and to evaluate their potential for early detection of cardiotoxicity.

METHODS AND MATERIALS:

The current study was prospective observational study conducted in cardiology and oncology department at CSSH. The IHEC gave their consent to the study. Patients were informed about the trial and given formal consent. In the questionnaire, relevant history was documented. Hospital based prospective observational study was done in Cardiology and Oncology department at CHRI, Kelambakkam. Data was collected in the year of Mar 2022 – Mar 2023 from the department of cardiology and oncology, CARE. This study included a total of 30 female breast cancer patients with main inclusion criteria includes patients who received adjuvant chemotherapy regimen A and AC [A:Adriamycin, C: Cyclophosphamide]. Exclusion criteria includes patients who had a history of Coronary Artery Disease, Valvular Heart Disease, Congenital Heart Disease, LV Dysfunction, and Cardiomyopathies. Venous blood samples for hs-Trop I diagnosis were collected from patients before and after first course of adjuvant chemotherapy with AC regimen chemotherapeutic agents. Samples were processed at the department of biochemistry, CSSH. The serum was separated by centrifugation (2500 rpm for 10 min); aliquots were stored at -20°C for later assay. The serum level of hs-Trop I were measured using particle enhanced Chemiluminescent Immunoassay (CLIA) method for hs-Trop I. Initial and follow-up echocardiographic assessments were performed according to the clinical indications established by the oncologist. Philips Affinity C50 ultrasound systems were used to acquire parasternal long- and short-axis views, as well as apical 4-, 2- and 3-chamber views. Simpson's biplane approach was used to determine LVEF. A semi-automatic approach based on regional assessment of 18 segments—the mean of which was used to calculate GLS—was utilized to examine global longitudinal strain off-line after apical 3-, 2-, and 4-chamber images were acquired for the assessment of longitudinal strain in patients receiving AC regimen of first course of chemotherapy.

STATISTICAL METHODS:

Pearson correlation and Spearman correlation was performed for comparing the pre and post AC regimen of adjuvant chemotherapy. A P-value < 0.05 are regarded as statistically significant

RESULT:

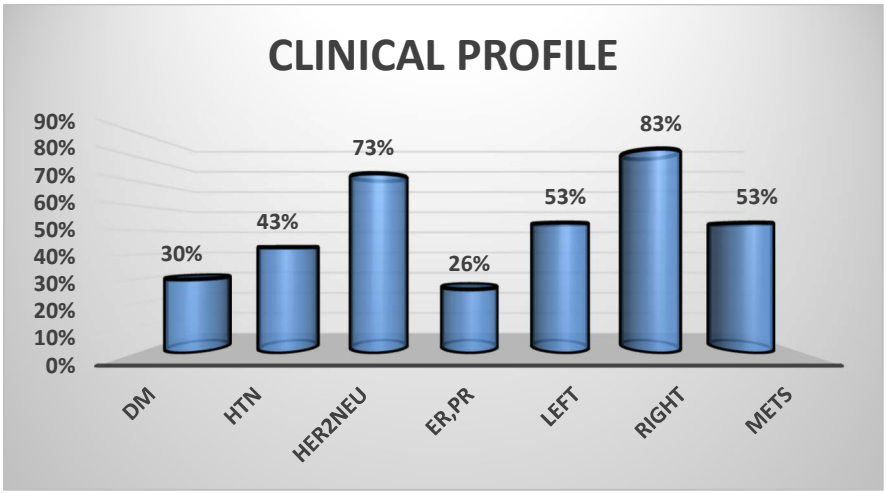
The study participants of 30 consecutive female breast cancer patients who undergoing chemotherapy with AC regimen chemotherapeutic agents. The clinical profile of patients including Age, DM, HTN, etc.., are listed in Table:1. Among 30 consecutive breast cancer patients 30% of patients had DM, 43% of patients had HTN, 73% of patients had HER2NEU positive breast cancer, 26% of patients had ER, PR positive breast cancer, 53% of patients had tumor in left breast, 46% of patients had tumor in right breast, 83% of patients had nodal spread, and 53% of patients had metastatic breast cancer.

TABLE.1: CLINICAL PROFILE OF STUDY POPULATION

AGE	54.5±7.7781
DM	9 (30%)
HTN	13 (43%)

HER2NEU	22 (73%)
ER, PR	8 (26%)
LEFT	16 (53%)
RIGHT	14 (46%)
NODE	25 (83%)
METS	16 (53%)

FIGURE.1: CLINICAL PROFILE OF STUDY POPULATION

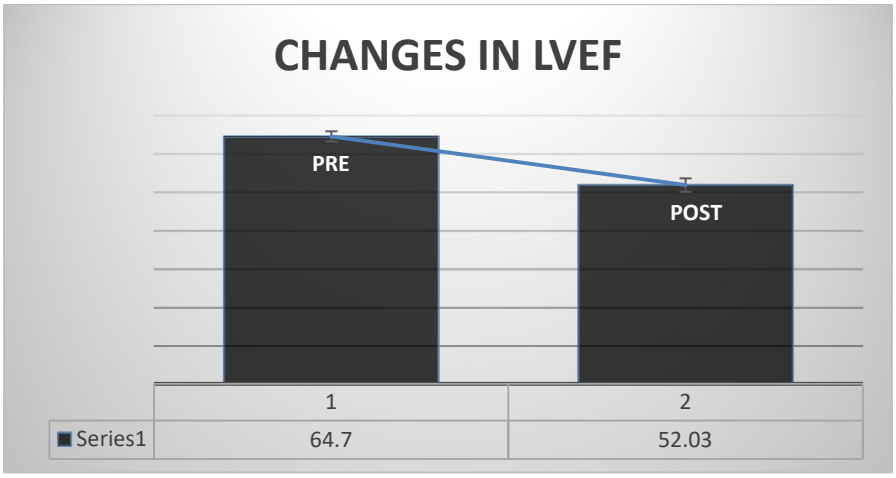


Average LVEF were measured by Simpson biplane method in pre and post chemotherapy patients who was administered with AC regimen chemotherapeutic agents was found to be in range of 64.6 ± 1.302 and 52.13 ± 1.7167 respectively. A p value was calculated by Pearson correlation, and it is 0.05 which is statistically significant.

TABLE.2: LVEF IN PRE AND POST CHEMOTHERAPY

	PRE CHEMO	POST CHEMO	T- VALUE	P- VALUE
LVEF MEAN±STD	64.7±1.342925	52.03±1.751518	2.017392	0.053332

FIGURE.2: LVEF IN PRE AND POST CHEMOTHERAPY

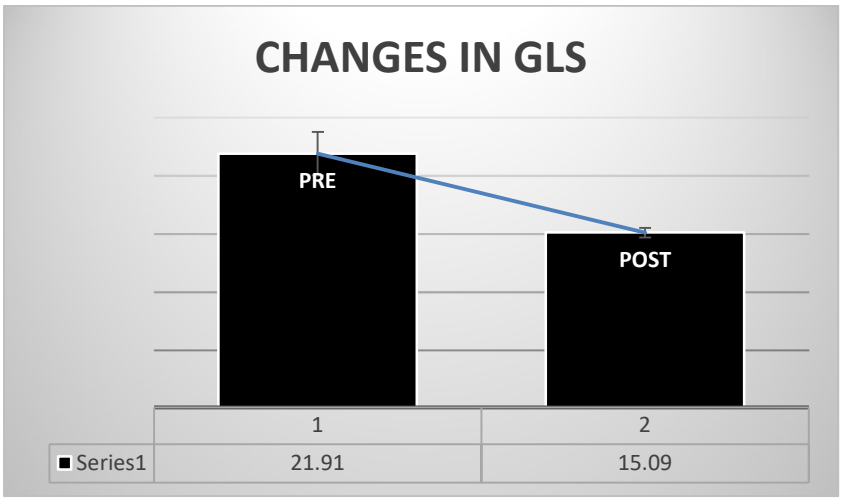


Average LVEF were measured by Global Longitudinal Strain in pre and post chemotherapy patients who was administered with AC regimen chemotherapeutic agents was found to be in range of 21.91 ± 1.8702 and 15.09 ± 0.414 respectively. P- value was calculated by Pearson correlation , and it is <0.05, regarded as statistically significant.

TABLE.3: GLS IN PRE AND POST CHEMOTHERAPY

	PRE CHEMO	POST CHEMO	T- VALUE	P-VALUE
GLS MEAN±STD	21.91 ± 1.8702	15.09 ± 0.4147	2.09786	0.04506

FIGURE.3: GLS IN PRE AND POST CHEMOTHERAPY

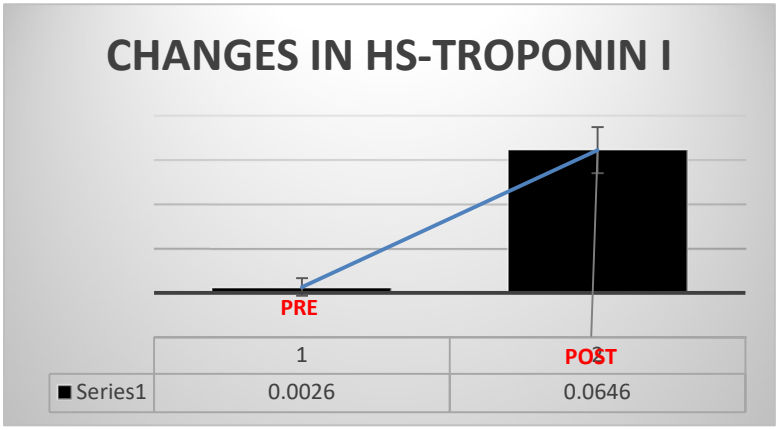


Average hs-TROPONIN I were measured by Chemiluminescent Immunoassay (CLIA) method in pre and post chemotherapy patients who was administered with AC regimen chemotherapeutic agents was found to be in range of 0.0026 ± 0.004 and 0.0646 ± 0.0104 respectively. A P-value was calculated by Spearman correlation and it is <0.05 which is statistically significant.

TABLE.4: hs-TROPONIN I IN PRE AND POST CHEMOTHERAPY

	PRE CHEMO	POST CHEMO	T- VALUE	P-VALUE
Hs-TnI MEAN±STD	0.0026 ± 0.004	0.0646 ± 0.0104	2.274993	0.030761

FIGURE.4: hs-TROPONIN I IN PRE AND POST CHEMOTHERAPY



DISCUSSION:

In this prospective study of women with breast cancer treated with doxorubicin, peak systolic longitudinal myocardial strain and hsTnI measured at the completion of doxorubicin therapy were predictive of the development of cardiotoxicity (3months after the completion of doxorubicin). A significant decrease of LVEF was detected at the completion of doxorubicin In contrast, changes in more sensitive markers of myocardial injury or dysfunction such as troponin or strain were detected at completion of the doxorubicin, developing subsequent cardiotoxicity. The primary mechanism by which anthracyclines cause cardiotoxicity is the production of reactive oxygen species. Increased cardiomyocyte calcium overload and irreversible apoptosis are also associated with this effect (26). Conversely, myofibrillar structure is disrupted by human epidermal growth factor receptor 2 inhibitors, although significant cardiomyocyte mortality does not appear to be the result (27). Remarkably, the LVEF declines during the course of the treatment period but, when averaged over the entire group, stays within normal bounds; large-scale investigations have also reported this result (28). In the present study, the changes of hs-troponin I and Global longitudinal strain detected before and after the doxorubicin treatment, which emphasize the critical part doxorubicin play in the development of cardiotoxicity. According to Cardinale et al., in patients receiving large dosages of anthracyclines, the measurement of troponin I indicated the occurrence of subsequent cardiac events (29). However, peak longitudinal myocardial strain was also predictive with LVEF declines to less than 50% and of cardiotoxicity as assessed by CREC. Such a drop in LVEF has significant clinical implications; among 4257 participants in the Framingham research, those with an asymptomatic LVEF between 40% and 50% had a 3.9 risk of heart failure and a 1.9 chance of death, relative to those with an LVEF >50%

(30). Age, a history of heart disease, prior mediastinal irradiation, and the use of other medications such trastuzumab are among the medical and demographic characteristics that may indicate the development of cardiac toxicity (31-35). Prior research indicates that there is a regional pattern to the heart damage caused by chemotherapy. Certain regions might involve, while others might make up for the segments that are involved. As a result, cardiac cells sustain damage while LVEF either stays the same or slightly changes (36). Predictive value for cardiac toxicity was highest for inferoseptal SLS. Some research recommend using the difference in volume between the systolic and diastolic phases as a predictor (37,38). hs-cTnI baseline levels were greater in the group that later displayed cardiac damage. Baseline is another significant determinant in the greatest level of these biomarkers degree. Therefore, it could be more appropriate to calculate the hs-cTnI increment from the baseline to the maximum level (39). The hs-cTnI increment's specificity and sensitivity are then computed from the baseline to three weeks later. This index's sensitivity and specificity were both lower at the first and second evaluations than the absolute level of hs-cTnI. Our evaluation of cTnI was extremely sensitive; it was demonstrated to be able to predict cardiac toxicity and was more sensitive than the previous approach [39,40,4142]. Particularly in the leukemia population, cTnI seems to have a somewhat higher predictive value than cTnT and a higher sensitivity for identifying cardiac alterations brought on by anthracycline poisoning (43). Previous research has addressed the prevention of cardiotoxicity. The risk of CHF may be reduced by using less cardiotoxic analogs, extending the infusion period, and using cardioprotective medications like dexrazoxane (44,45). There are several restrictions on this research. The tiny sample size is the first problem. A small sample size may mean that the results cannot be applied to the entire patient group. This study may have less power because of the small number of events that are classified as cardiac toxicity. Identifying the period for changes in markers may need more frequent blood sample, which is the second constraint. Since each patient only had their blood drawn twice, the trend of the change in cardiac biomarkers may not be perfectly depicted. Only acute cardiac toxicity was assessed; more monitoring is required to identify cardiac damage with a late onset. Throughout the two groups in our study—one with and one without cardiac toxicity—we were able to account for demographics and other health issues.

CONCLUSION:

Women with breast cancer treated with doxorubicin can predict the early occurrence of subsequent cardiotoxicity by measuring peak systolic Global longitudinal myocardial strain and hs-troponin before and after treatment. This research has demonstrated that in patients receiving doxorubicin treatment, hs-cTnI can accurately predict cardiac damage. The primary aim of this investigation was to ascertain the predictive significance of cardiac biomarkers and echocardiographic parameters in the timely identification of cardiac toxicity associated with doxorubicin. This information can also help a clinician make decisions about the appropriateness of cardiovascular therapy, closer monitoring of cardiac function, and therapy adjustments for the next course of treatment.

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