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RESEARCH ARTICLE

ASSESSMENT OF LEFT VENTRICULAR FUNCTION IN PATIENTS UNDERGOING CHEMOTHERAPY BY 2D STRAIN IMAGING.

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Abstract

Introduction: Chemotherapy is one of the largest areas of pharmaceutical development. However, the nature of chemotherapy means that while damaging the cancer cells it also damages healthy cells and myocardium is no exception. Cancer patients usually receive a cocktail of chemotherapy drugs, which can result in myocardial injury and left ventricular dysfunction. Echocardiography is the gold standard for assessment of heart function in these patients before, during and after the treatment. In addition Systolic myocardial strain imaging can theoretically detect cardio toxicity early.

Objective: Assessment of left ventricular function in patients undergoing chemotherapy by 2D Strain imaging

Material & methods: 74 consecutive patients who were subjected for chemotherapy with an age above 18 years were considered for the study. Subjects who had prior structural or functional heart disease, previous history of ischemic heart disease, who underwent percutaneous transluminal angioplasty and/or prior coronary artery bypass grafting, received radiotherapy, LV dysfunction at baseline and with baseline LBBB were excluded from the study. Patients who met the inclusion criteria were subjected for ECHO assessment at baseline and for the second time after completion of the chemotherapy regimen. Data was analyzed by using SPSS software.

Results: Out of 74, 49 were females and 25 were males. 8 (10.8%) out of 74 developed reduction of LVEF > 15% at the end of the chemotherapy regimen. In the 2D strain parameters, mean Global longitudinal strain was significantly reduced in post chemotherapy (-19.33±1.75) individuals when compared to mean pre chemotherapy global longitudinal strain (-23.15±2.4) especially in patients who had more than 15% (n=8) drop in their EF. Global Circumferential Strain reduction was not found to be consistent with reduction of LVEF.

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Conclusion: Strain imaging, Global Longitudinal Strain in particular is ideal for screening and risk profiling of patients undergoing chemotherapy and should be recommended in all patients.

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Introduction:-

Cancer is a major public health concern. It is one of the leading causes of death worldwide and accounts for around 7.6 million deaths annually and is projected to increase to 13.1 million deaths by 2030.[1] It is one of the leading causes of death in India, accounting for close to 650,000 deaths in 2008.[2] The most frequent sites of cancer in India are oral cavity, breast, lung, cervix and esophagus.[2] With improvements in diagnostic as well as treatment modalities the prevalence of patients with a diagnosed cancer is on the rise. Recent technical advances in early detection of cancer and therapeutic strategies have improved cancer survival. The mortality rate has appreciably decreased among patients with over the past 20 to 30 years.[3] However, several treatment related adverse effects have become important issues for cancer survivors.[4]

Chemotherapy has been one of the mainstays of treatment in patients with cancer, and cancer patients receive a cocktail of chemotherapy drugs. Chemotherapy may exert adverse effects on various organs. Cardio toxicity from cancer therapy has become a leading cause of morbidity and mortality in survivors.[5] In patients who develop chemotherapy induced cardio toxicity causing heart failure, the mortality goes up to 60% in 2 years.[6] Cardio toxicity resulting from chemotherapy was first recognized in the 1960s, with the widespread introduction of anthracyclines into the oncological therapeutic armamentarium.[7]

Historically chemotherapy induced LV dysfunction was diagnosed by either end myocardial biopsy or by echocardiography examination. Technical advances in non-invasive imaging modalities have diminished the usage of biopsies. According to the most recent consensus statements, chemotherapy induced cardio toxicity is defined as a decrease in the Left Ventricular Ejection Fraction (LVEF) of more than 10% to a value less than 53%, confirmed by repeated cardiac imaging.[8]

Speckle-tracking echocardiography is a new noninvasive imaging technique of echocardiography that allows an objective and quantitative evaluation of global and regional myocardial function.[9] By tracking the displacement of speckles during the cardiac cycle, speckle-tracking echocardiography allows semi-automated elaboration of myocardial deformation in 3 spatial directions: longitudinal, radial and Circumferential. In addition, speckle-tracking echocardiography offers an evaluation of the occurrence, direction and velocity of left ventricle (LV) rotation.[10] The semi-automated nature of speckle-tracking echocardiography guarantees good intra-observer and inter-observer reproducibility.[11] By convention, depending upon the direction and the lengthening or thickening of segmental deformation gives a positive (+) value, where as a shortening or thinning deformation of the segments gives a negative(-) value. [12] Strain rate (ε′) represents the rate of myocardial deformation. It is expressed as seconds (per second). However, because the strain rate signals are noisier and less reproducible and most clinical studies still use strain measurements.[13] Longitudinal strain represents myocardial deformation directed from the base to the apex. Through longitudinal strain analysis in Apical 4-chamber, Apical 2-chamber, and Apical 3 chamber views, both regional (relative to each of the17 LV segments) and global strain values (global longitudinal strain) can be obtained. Recently Global longitudinal strain has been validated as a quantitative index for global LV function.[14] Circumferential strain represents LV myocardial fiber shortening along the circular perimeter of LV observed on a short-axis view.

Chemotherapy induced cardio toxicity has been studied whereas the evaluation of LV function in chemotherapy patients by 2D speckle tracking based global longitudinal and circumferential strain has not been poorly studied. The present study was designed with a aim to assess the Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Volume (LVESV), Left Ventricular Stroke Volume (SV), Left Ventricular Ejection Fraction (LVEF), Left Ventricular Fractional Area Change by using 2D Speckle-tracking-based left ventricle Global Longitudinal Strain (GLS) and Global Circumferential Strain (GCS) imaging in carcinoma patients before and after chemotherapy.

Methods:-

This prospective observational study was conducted for the period of one year, between December 2016 and November 2017. 74 consecutive patients above 18 years of age who were diagnosed with cancer and advice chemotherapy were included in the study. Patients who had a previous history of ischemic heart disease, underwent percutaneous transluminal angioplasty and/or prior coronary artery bypass grafting, received radiotherapy, with LV dysfunction at baseline and with baseline LBBB (Left Bundle Branch Block) were excluded. Data of the patients who met the inclusion criteria was collected in regards to height, weight, BMI, cancer variant, chemotherapy regimens. Each patient was subjected to a baseline ECG gated echocardiography evaluation, which included 2D speckle tracking transthoracic acquisition. Images of the LV was obtained from apical 2, 3 and 4-chamber view and parasternal short axis view at basal, mid and apical level by real time acquisition. Echocardiography examination was repeated after finishing scheduled cycles of chemotherapy. In patients who had symptoms or signs of heart failure, echocardiography examination was performed as soon as possible even if the patient had not finished all the scheduled cycles of chemotherapy.

The offline analysis was made using automated software installed in EPIQ 7C echo machine on each view of long and short axis views, the left ventricular endocardial borders were manually traced. Longitudinal strain was derived by using apical 2-chamber, 3-chamber, 4-chamber views whereas circumferential by parasternal Short Axis at basal, mid and apical level and finally global strain of longitudinal and circumferential (Bull's eye) with EDV, ESV, EF, SV and FAC were obtained in every patient before and after chemotherapy.

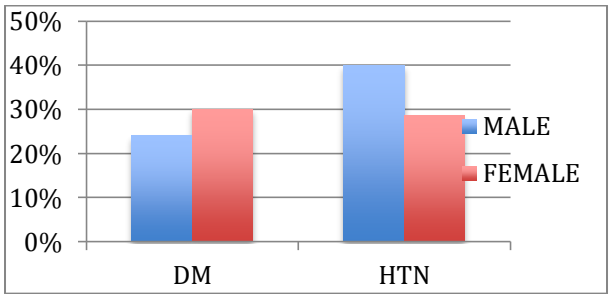
Based on the follow up echocardiography, the study population was divided in to those with LV dysfunction (n=8, 58±10.2) and those with no LV dysfunction (n=67, 53±13.1). Chemotherapy induced LV dysfunction was defined when the EF was < 55% or when there was a drop of ≥15% in LV EF from pre chemotherapy echo (Baseline) on post chemotherapy echo (Follow up)

Statistics:-

The data obtained was entered into Microsoft Excel Worksheet and data was analyzed. Categorical data was presented as in terms of rates, ratios and percentages and continuous data was expressed as mean ± standard deviation (SD). The comparison of those parameters between pre-chemotherapy and post-chemotherapy findings was done using SPSS software. A probability value (p value) of less than or equal to 0.05 was considered as statistically significant.

Results:-

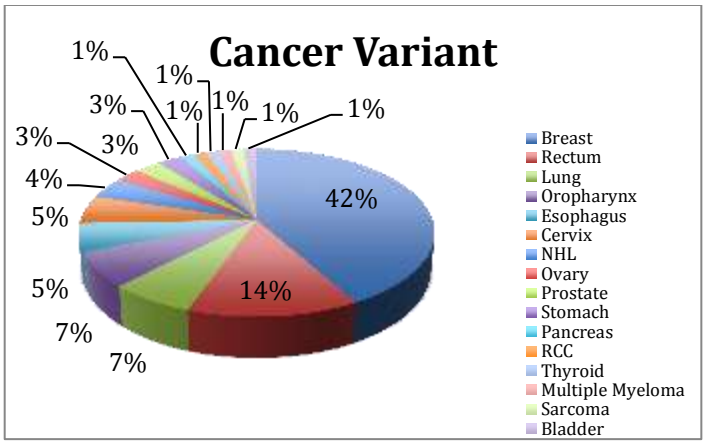
A total of 74 patients who met the inclusion criteria were enrolled in the study. The mean age of 54±15 years which comprised of 49 (66%) females and 25 (34%) males comprised of the study population. Graph 1 shows the gender wise distribution of diabetes and hypertension. Mean BMI in individuals who had >15% drop (19.68) in EF was significantly lower than those with <15% Drop (22.45) ($p<0.01$)



Graph 1:- Gender wise Distribution of Diabetes and hypertension

Cancer Variant:-

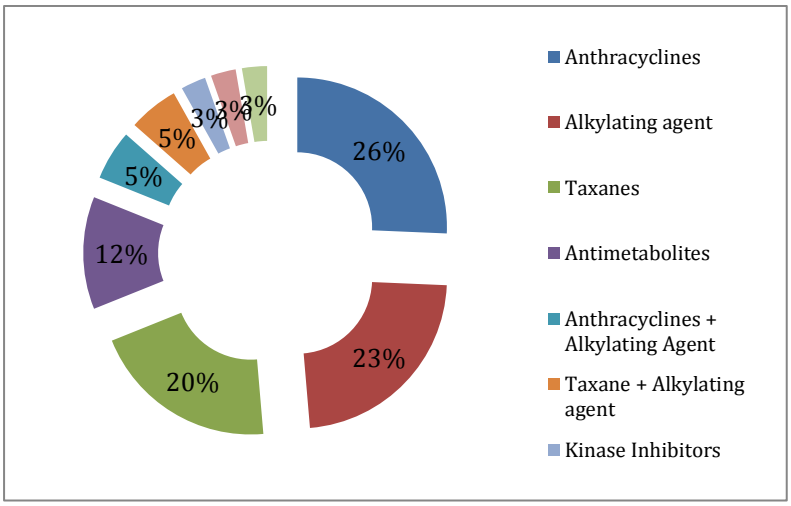
Breast cancer was the most common primary cancer variant in our study, followed by carcinoma of the rectum, lung and oropharynx. Graph 2 shows the cancer variants among the study group



Graph 2:- Primary Cancer Variants

Type of Chemotherapy:-

Most common class of chemotherapy used was anthracyclines, followed by alkylating agent and taxanes. Graph 3 shows the type of chemotherapeutic agent used



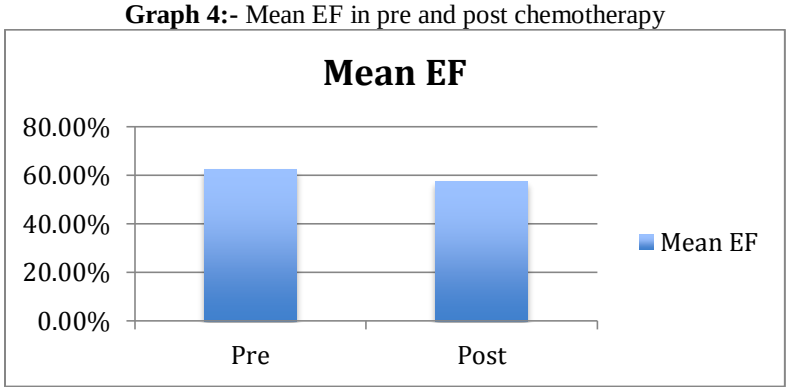
Graph 3:- Type of chemotherapeutic agent

Among the chemotherapy agents that were used, anthracyclines (26%) was the most commonly used followed by alkylating agents (23%). In patients who developed chemotherapy induced LV dysfunction, 50% (n=4) was because of anthracyclines, 25% (n=2) was because of alkylating agents.

Evaluation of EF:-

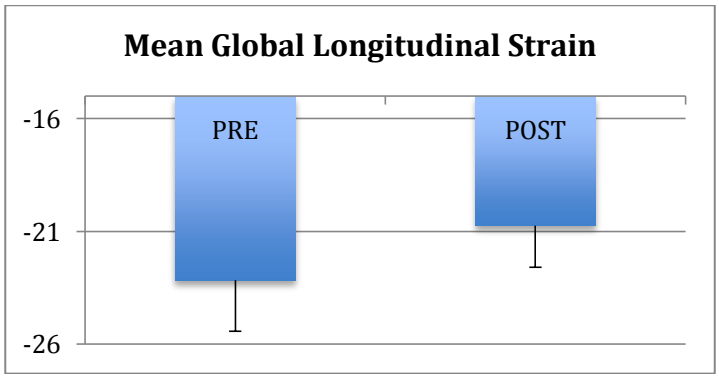
Although there was a drop in Mean EF in pre chemotherapy (61.3%) and post chemotherapy (58.4%), it was not statistically significant ($p<0.2$) depicted in graph 4 & also the absolute value of the mean EF post chemotherapy was within the normal range.

Graph 4:- Mean EF in pre and post chemotherapy



Global Longitudinal Strain:-

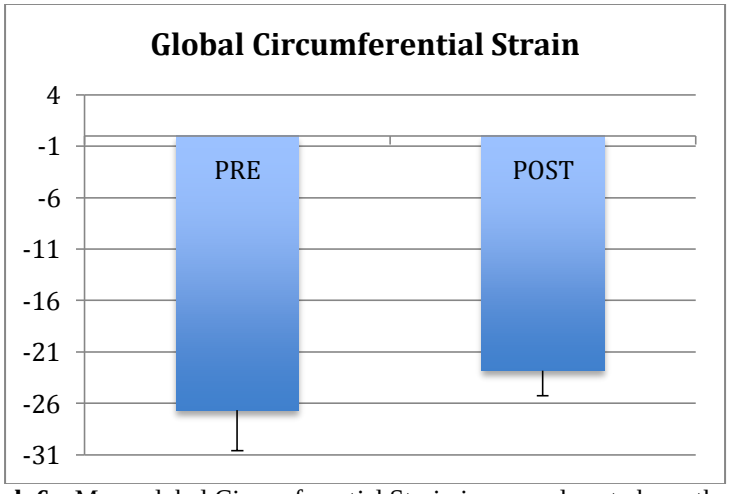
The mean global longitudinal strain was significantly reduced in post chemotherapy (-19.33±1.75) individuals when compared to mean pre chemotherapy global longitudinal strain (-23.15±2.4) especially in patients who had a more than 15% drop in their EF, even though their absolute value of EF was more than 55%, their global longitudinal strain parameters were less (< -17). (graph 5)



Graph 5:- Mean Global Longitudinal strain in pre and post chemotherapy

Global Circumferential Strain:-

The mean global circumferential strain was significantly reduced in post chemotherapy (-22.832±2.4) individuals when compared to mean pre chemotherapy global circumferential strain (-26.67±3.9), however global circumferential strain was not significantly reduced when compared between those with more than 15% drop and those with less than 15% drop. (graph 6)



Graph 6:- Mean global Circumferential Strain in pre and post chemotherapy

Chemotherapy induced LV dysfunction was found in 10.8% (n=8) of the study group. It was defined as a drop in LV EF of more than 15% when compared between baselines to post chemotherapy.

Figures 1-4 show examples of 2D strain imaging in apical 4 chamber, apical 3 chamber and apical 2 chamber with a bull's eye plot of global longitudinal strain

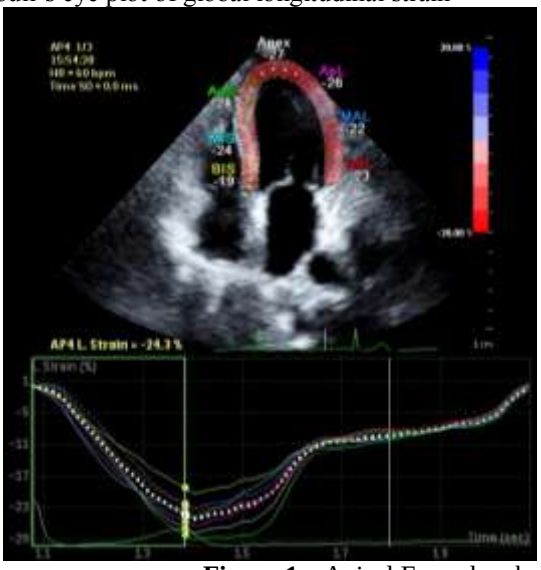


Figure 1:- Apical Four chamber

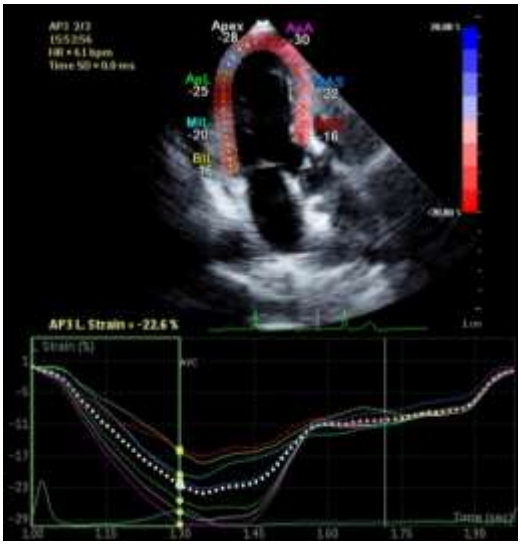


Figure 2:-Apical Three chamber

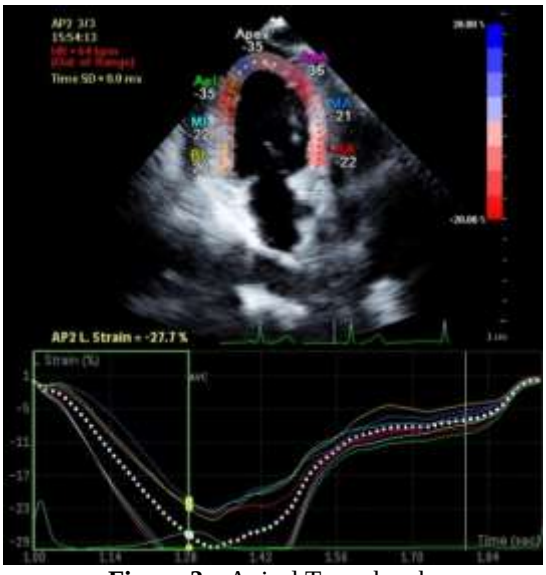


Figure 3:- Apical Two chamber

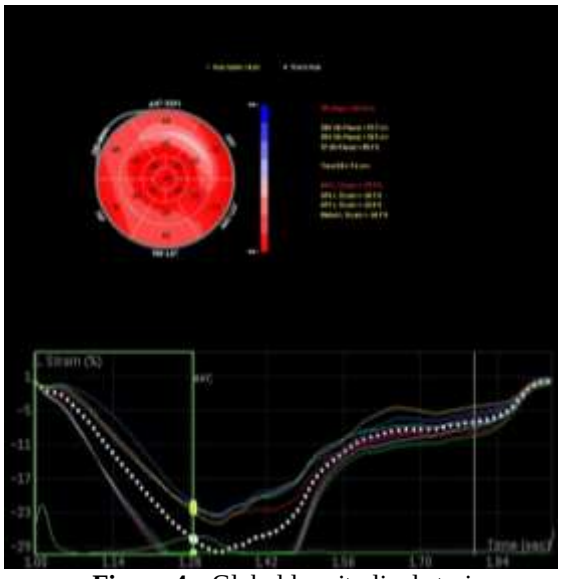


Figure 4:- Global longitudinal strain

Discussion:-

Cancer is a leading cause of morbidity and mortality worldwide. Recent technical advances in early detection of cancer and developments in therapeutic strategies have improved cancer survival. Chemotherapy remains one of the mainstays of treatment in patients with cancer. Historically chemotherapy induced LV dysfunction is done by either end myocardial biopsy or by echocardiography examination. Endomyocardial biopsies have proven to be the most sensitive and specific investigation for detecting cardio toxicity, but their usage has taken a back seat off late as the total cumulative dosage of chemotherapy has decreased and also because of the invasive nature of the procedure. The timing of cardiac dysfunction can vary considerably among agents and may not be apparent for several years. Diagnosis of cardiac impairment should be done accurately and as early as possible, because continuing

chemotherapeutic agent can cause irreparable damage, where as on the other hand, if chemotherapeutic agent is inadvertently stopped then the beneficial effects of the same will be lost.

The present study was designed to study the effect of chemotherapy induced LV dysfunction in Indian patients by various Echo modalities including 2D speckle tracking. 74 patients who were undergoing chemotherapy were included for baseline and post chemotherapy evaluation of LV function with various 2D echo modalities. In our study group we had a higher female population (66%), owing to the higher cases of Ca breast that were included in the study.

It is well known that the prevalence of cancer increases with increasing age, in the present study, the prevalence of cancer was highest in the age group of >60years (33%). The incidence of chemotherapy induced LV dysfunction was 10.8% in the present study, which is comparable to 11% in a study conducted by Hyun Ju Yoon et al.[15] Hershman et al had a incidence of chemotherapy induced LV dysfunction of 8.5%.[16] In the present study LVEF reduced not only in those with >15% EF group but also in the <15% EF drop group on completion of chemotherapy. This may suggest that subclinical LV dysfunction is more frequent and more often than not is not recognized. Therefore early recognition is very important to prevent further progression of LV dysfunction from subclinical to clinically significant heart failure

Patients who had a lower BMI and those who had received a higher cumulative dose were more likely to develop chemotherapy induced LV dysfunction. In patients who developed Chemotherapy induced LV dysfunction, Global Longitudinal strain and Global circumferential strain was significantly reduced in post chemotherapy evaluation. However reduction in global longitudinal strain was more attributable to LV dysfunction than Global circumferential strain. Hence, 2D strain imaging by speckle tracking, especially Global Longitudinal Strain is an excellent imaging modality for screening and follow-up of individuals who are candidates for chemotherapy.

In the present study, large number of patients who were undergoing chemotherapy were included and it is a first of its kind that is done to assess chemotherapy induced LV dysfunction by 2D speckle tracking in various malignancies.

Conclusion and Clinical Implications:-

Assessment of LV function by 2D speckle tracking strain imaging is ideal in patients undergoing Chemotherapy as it is noninvasive and can potentially assess early onset of LV dysfunction. Early detection is pertinent as the chemotherapeutic agent can be stopped and helps in better survival. The clinical implications of reversibility of chemotherapy induced LV dysfunction have to be studied further for better cardiovascular outcomes.

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