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RESEARCH ARTICLE

ROLE OF TWO-DIMENSIONAL SPECKLE TRACKING ECHOCARDIOGRAPHY FOR EVALUATION OF LEFT VENTRICULAR DYSFUNCTION IN ANTHRACYCLINE -INDUCED CARDIOTOXICITY IN BREAST CANCER PATIENTS.

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Key words:-

Chemotherapy, Cardiotoxicity, speckle-tracking Echocardiography.

Abstract

Background: Cardiotoxicity is an important complication of several cancer therapeutic agents such as anthracyclines. Improved cancer survival together with better awareness of the late effects of cardiotoxicity has led to growing recognition of the need for surveillance of anthracycline- treated cancer survivors with early intervention to treat or prevent heart failure. Strain-based imaging techniques and specifically speckle-tracking echocardiography (STE) have been shown to have clinical utility in a variety of settings.

Aim of work: This study aimed to assess the value of 2D speckle-tracking echocardiography for the early detection of left ventricular dysfunction in breast cancer patients on chemotherapeutic treatment with anthracyclines.

Patients and Methods: The study recruited 70 women with newly diagnosed cancer breast. Before start of treatment, they were subjected to careful cardiac and echocardiographic assessment including STE evaluation in addition to the other clinical and laboratory investigations indicated in such situations. After completion of treatment, women had undergone similar cardiological and echocardiographic evaluation.

Results: In the present study, comparison between pretreatment and post treatment echocardiographic data revealed significant changes in both systolic and diastolic functions of the left ventricle. Importantly, the present study found that conventional echocardiographic assessment could identify 12 patients (17.1 %) defined according to reduced LVEF while STE recognized cardiotoxicity in 22 patients (31.4 %) according to reduced GLS. In respect to diastolic dysfunction, the present study reported that 34 patients (48.6 %) had diastolic dysfunction after anthracyclines treatment. Comparative analysis between patients with diastolic dysfunction and patients without in the current study showed that patients with diastolic dysfunction had significantly higher impairment of ejection fraction and GLS.

Conclusions: Speckle-tracking Echocardiography provides a useful tool in the detection of anthracyclines -induced cardiotoxicity.

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Introduction:-

Over the last years the mortality rate among patients with breast cancer has decreased. However, cardiotoxicity from cancer therapy has become a leading cause of morbidity and mortality in survivors. Therefore, contemporary management of patients with cancer should include careful consideration of potential cardiotoxicity during therapy, with a focus on early detection and intervention. Many of the chemotherapeutic agents in use today can have associated cardiovascular side effects, the most common of which are cardiomyopathy and Heart failure. Amongst the various medications, the anthracycline class of drugs (e.g., doxorubicin and epirubicin) and trastuzumab, have been most commonly implicated and best studied. (*Thavendiranathan et al., 2014*).

Echocardiography is a noninvasive, cost-effective, and widely available cardiac imaging tool that is well positioned to serve as the primary screening modality for chemotherapy induced cardiotoxicity. While LVEF is currently the most widely used index to quantify cardiac function in cardio-oncology, there are a number of emerging indices such as Doppler-derived indices, speckle-tracking- derived measures of strain and strain rate, and three-dimensional Echocardiography-derived parameters of myocardial motion that may offer additional sensitivity and prognostic value (*Gulati et al., 2014*).

Global longitudinal strain (GLS) derived from speckle-tracking echocardiography is a novel non-invasive imaging technique that quantitatively measures regional myocardial deformation, a sensitive marker of myocardial function. Strain can identify early pathological changes in myocardial systolic function before any appreciable decline in LVEF becomes apparent, has been demonstrated to be a stronger predictor of outcome than EF, and can accurately predict development of cardiotoxicity (*Nolan, et al., 2016*).

Aim of work:-

The present study aims to assess the value of 2D speckle-tracking echocardiography for the early detection of left ventricular dysfunction in breast cancer patients on chemotherapeutic treatment with anthracyclines.

Subjects and Methods:-

The present study is a clinical cohort study. It was conducted at Mansoura University Hospitals over 2-year period from February, 2017 through October, 2018. The study recruited 70 women with newly diagnosed cancer breast whom indicated for doxorubicin. Patients were excluded from the study if they had ischemic heart disease, systemic hypertension, chronic kidney disease, severe liver disease, COPD, cardiomyopathy or arrhythmia.

All participants were subjected before the doxorubicin to careful history taking, full cardiac examination, ECG and echocardiography using cardiac ultrasound unit device model (VIVID E9 GE) with 2D, M-mode and Doppler, TDI and 2D speckle tracking capabilities. Patients were followed up at end of treatment.

Data were analyzed using SPSS version 25. A two-tailed p value of < 0.05 was considered statistically significant. Qualitative variables were described as numbers and percentage. Quantitative variables were described as mean +/- SD for parametric data and median (min-max) for non-parametric ones. Comparison between pretreatment and post treatment data was achieved using paired t test. Correlation between variables was performed using Pearson's Correlation coefficient. ROC curve analysis was used to identify reliability of independent variables to diagnosis outcome and logistic regression analysis was used to detect independent predictors of binary outcome.

Results:-

Results of the present study are shown in the following tables and figures:

Table-1: Basic data of the studied patients (n=70)

Age (Year)	Range	37.0 – 55.0
	Mean ± SD	45.4 ± 5.4
BMI (Kg/m²)	Range	20.8 – 34.2
	Mean ± SD	27.2 ± 3.4
Cancer staging	I	33 (47.1 %)
	II	18 (25.7 %)
	III	14 (20.0 %)
	IV	5 (7.2 %)

Patients included in the present study had an age of 45.4 ± 5.4 years and BMI of 27.2 ± 3.4 Kg/m². They comprised 33 patients (47.1 %) at stage I, 18 patients (25.7 %) at stage II, 14 patients (20.0 %) at stage III and 5 patients (7.2 %).

Table-2: Comparison between electrocardiographic data throughout the study period (n=70)

	Pretreatment	Post treatment	P value
Arrhythmia	-	1 (1.4 %)	0.32
Low QRS	-	3 (4.3 %)	0.08
Prolonged QT	-	10 (14.3 %)	0.001*
Depressed ST	-	4 (5.7 %)	0.042*
Flattened T	-	4 (5.7 %)	0.042*
Inverted T	-	2 (2.9 %)	0.15

This table shows the ECG changes after chemotherapy.

Table-3: Comparison between echocardiographic data throughout the study period (n=70)

	Pretreatment	Post treatment	P value
LVEF	62.6 ± 2.5	58.5 ± 3.2	0.0001*
E	0.76 ± 0.008	0.77 ± 0.008	0.057
A	0.62 ± 0.07	0.61 ± 0.08	0.3
E/A	1.25 ± 0.021	1.27 ± 0.024	0.23
Septal e'	9.6 ± 0.99	8.0 ± 1.5	0.0001*
Lateral e'	11.9 ± 1.0	10.4 ± 1.5	0.0001*
LA volume index	27.6 ± 2.0	27.5 ± 2.1	0.82
TR velocity	2.45 ± 0.17	2.44 ± 0.19	0.67
GLS	-19.3 ± 0.8	-17.6 ± 1.6	0.0001*

This table shows significantly lower LVEF, septal e', lateral e' and GLS in the post treatment assessment when compared with pretreatment levels.

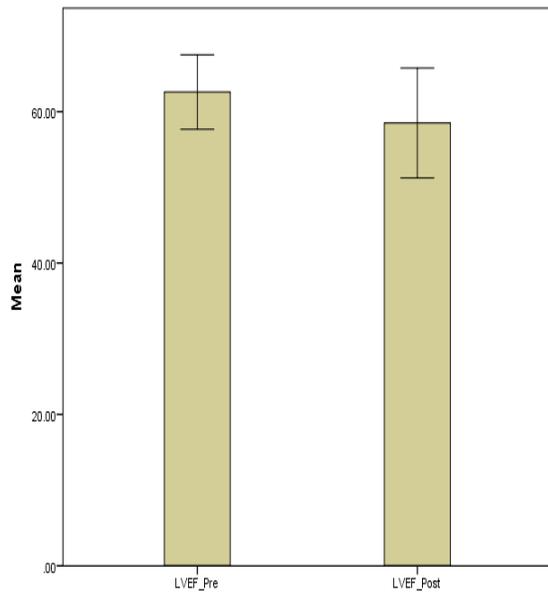


Fig. (1): Pre and post treatment LVEF

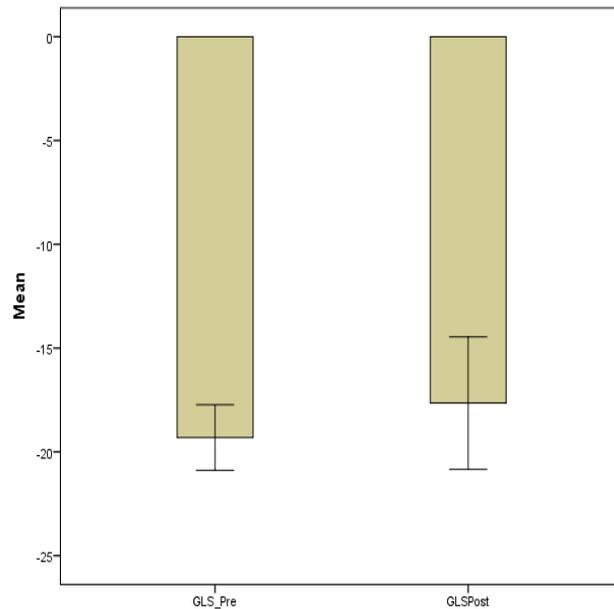


Fig. (2): Pre and post treatment GLS

Table-4: Correlation between GLS and echocardiographic data pre and post treatment

	Pretreatment		Post treatment	
	GLS		GLS	
	r	p	r	p

LVEF	-0.09	0.45	-0.4	0.001*
E	-0.01	0.93	-0.02	0.89
A	0.04	0.72	0.25	0.035*
E/A	-0.06	0.62	-0.25	0.041*
Septal e'	-0.01	-0.91	-0.48	0.0001*
Lateral e'	-0.1	0.38	-0.47	0.0001*
LA volume index	0.13	0.27	0.09	0.45
TR velocity	0.04	0.76	0.1	0.39

This table shows no statistically significant correlations between pretreatment GLS and other pretreatment echocardiographic parameters. But significant inverse correlation between post treatment GLS and LVEF, E/A, septal e' and lateral e'.

Table-5: Prevalence of cardiotoxicity in the studied patients according to ejection fraction and GLS (n=70)

	LVEF	GLS	P value
Cardiotoxicity	12 (17.1 %)	22 (31.4 %)	0.0001*

This table shows significantly higher rate of cardiotoxicity diagnosed by GLS when compared with LVEF.

Table-6: Agreement between LVEF and GLS as measures of cardiotoxicity

		Cardiotoxicity (GLS)		P value
		+ve	-ve	
Cardiotoxicity (LVEF)	+ve	12	0	0.0001
	-ve	10	48	

This table shows that all cases with cardiotoxicity diagnosed according to LVEF were diagnosed using GLS. However, 10 cases with cardiotoxicity according to GLS weren't diagnosed according to LVEF.

Table-7: Comparison between patients with and without cardiotoxicity according to LVEF regarding pre and post treatment echocardiographic data

	Cardiotoxicity +ve =12		Cardiotoxicity -ve n=58		P value	
	pretreatment	post treatment	pretreatment	post treatment	pretreatment	post treatment
E	0.76 ± 0.07	0.76 ± 0.07	0.75 ± 0.06	0.76 ± 0.07	0.69	0.81
A	0.65 ± 0.08	0.64 ± 0.08	0.6 ± 0.07	0.60 ± 0.07	0.07	0.09
E/A	1.19 ± 0.19	1.2 ± 0.19	1.25 ± 0.16	1.28 ± 0.2	0.24	0.23
Septal e'	9.9 ± 0.8	6.45 ± 0.23	9.5 ± 1.0	8.27 ± 1.5	0.16	0.0001*
Lateral e'	12.4 ± 0.7	9.19 ± 0.29	11.7 ± 1.0	10.69 ± 1.47	0.007*	0.0001*
LA volume index	28.1 ± 2.3	27.5 ± 2.1	27.5 ± 2.0	27.6 ± 2.0	0.39	0.93
TR velocity	2.47 ± 0.2	2.47 ± 0.21	2.44 ± 0.16	2.43 ± 0.18	0.55	0.55
GLS	-19.4 ± 0.58	-15.7 ± 0.62	-19.2 ± 0.82	-18.03 ± 1.45	0.58	0.0001*

This table shows that patients with cardiotoxicity had significantly higher lateral e'(pretreatment) and significantly lower septal e', lateral e' and GLS (post treatment) when compared with patients without.

Table-8: Comparison between patients with and without cardiotoxicity according to GLS regarding pre and post treatment echocardiographic data

	Cardiotoxicity +ve =22		Cardiotoxicity -vet n=48		P value	
	pretreatment	post treatment	pretreatment	post treatment	pretreatment	post treatment
LVEF	62.4 ± 2.6	56.09 ± 4.5	62.6 ± 2.4	59.6 ± 2.5	0.66	0.0001
E	0.75 ± 0.07	0.76 ± 0.07	0.76 ± 0.06	0.77 ± 0.06	0.85	0.74
A	0.64 ± 0.08	0.64 ± 0.07	0.6 ± 0.07	0.59 ± 0.08	0.031	0.018*
E/A	1.18 ± 0.16	1.18 ± 0.16	1.27 ± 0.17	1.3 ± 0.2	0.046	0.024*
Septal e'	9.6 ± 0.94	6.5 ± 0.27	9.58 ± 1.01	8.6 ± 1.4	0.88	0.0001
Lateral e'	12.03 ± 0.94	9.1 ± 0.31	11.79 ± 1.01	11.0 ± 1.37	0.36	0.0001

LA volume index	28.17 ± 2.08	27.8 ± 2.2	27.36 ± 1.97	27.4 ± 2.0	0.12	0.43
TR velocity	2.46 ± 0.18	2.45 ± 0.18	2.43 ± 0.16	2.43 ± 0.2	0.51	0.77

This table shows that patients with cardiotoxicity according to GLS had significantly higher A velocity and lower E/A ratio (pretreatment). And significantly lower septal e', lateral e' and LVEF (post treatment) when compared with patients without toxicity.

Table-9: Logistic regression for predictors of cardiotoxicity according to LVEF

		Univariate analysis			Multivariate analysis		
		OR	P	CI	OR	P	CI
Age		0.96	0.44	0.85-1.07	-	-	-
BMI		0.92	0.37	0.76-1.1	-	-	-
Tumor stage	I	Ref.					
	II	0.0	0.99	0.0-	-	-	-
	III	0.0	0.99	0.0-	-	-	-
	IV	0.0	0.99	0.0-	-	-	-
Pretreatment echocardiography							
E		0.16	0.69	0.0-1354.2	-	-	-
A		0.001	0.086	0.0- 2.86	-	-	-
E/A		9.5	0.24	0.22-425.1	-	-	-
Septal e'		0.63	0.16	0.33-1.2	-	-	-
Lateral e'		0.42	0.026*	0.2-9.0	0.38	0.081	0.13-1.13
LA volume index		0.87	0.39	0.63-1.19	-	-	-
TR velocity		0.32	0.55	0.0-13.7	-	-	-
GLS		1.25	0.58	0.56-2.8	-	-	-
Post treatment echocardiography							
E		0.34	0.81	0.0-2353.0	-	-	-
A		0.001	0.1	0.0-3.9	-	-	-
E/A		8.3	0.23	0.25-272.0	-	-	-
Septal e'		0.26	0.024*	1.52-464.3	13.7	0.074	0.78-241
Lateral e'		3.2	0.009*	1.3-7.6	0.66	0.68	0.09-4.9
LA volume index		1.0	0.93	0.75-1.37	-	-	-
TR velocity		0.36	0.54	0.01-9.7	-	-	-
GLS		0.27	0.0001*	0.13-0.56	0.43	0.039*	0.19-0.96

This table that GLS was the only predictor of cardiotoxicity according to LVEF on univariate and multivariate analyses.

Table-10: Logistic regression for predictors of cardiotoxicity according to GLS

		Univariate analysis			Multivariate analysis		
		OR	P	CI	OR	P	CI
Age		0.98	0.63	0.89-1.1	-	-	-
BMI		0.94	0.43	0.81-1.1	-	-	-
Tumor stage	I	Ref					
	II	1.8	0.41	0.47-6.6	-	-	-
	III	0.67	0.54	0.19-2.4	-	-	-
	IV	2.0	0.56	0.2-20.0	-	-	-
Pretreatment echocardiography							
E		2.0	0.85	0.0-3283.0	-	-	-
A		0.001	0.35	0.01-6.0	-	-	-
E/A		0.24	0.051	0.99-579.1	-	-	-
Septal e'		0.96	0.88	0.58-1.6	-	-	-
Lateral e'		0.79	0.36	0.47-1.3	-	-	-

LA volume index	0.81	0.12	0.63-1.1	-	-	-
TR velocity	0.36	0.51	0.02-7.5	-	-	-
LVEF	1.0	0.66	0.85-1.3	-	-	-
Post treatment echocardiography						
E	3.5	0.73	0.0-4613.0	-	-	-
A	0.0	0.22	0.01-0.32	-	-	-
E/A	28.1	0.29	0.4-56.0	-	-	-
Septal e'	28.8	0.007*	2.5-333.8	0.3	0.04	1.2-807.0
Lateral e'	6.5	0.0001*	2.3-18.7	1.2	0.85	0.17-8.6
LA volume index	0.9	0.42	0.7-1.2	-	-	-
TR velocity	0.66	0.76	0.05-9.4	-	-	-
LVEF	1.4	0.001*	1.1-1.6	1.2	0.24	0.9-1.6

This table shows that septal e' was the only significant predictor of cardiotoxicity according to GLS on univariate and multivariate analysis.

Table-11: Reliability of post treatment GLS in diagnosis of cardiotoxicity

Cut-off	-16.9
AUC	0.89
P value	0.0001
Sensitivity	100.0 %
Specificity	81.0 %

At a cut-off of -16.9, GLS had n AUC of 0.89 with a sensitivity of 100.0 % and a specificity of 81.0 %.

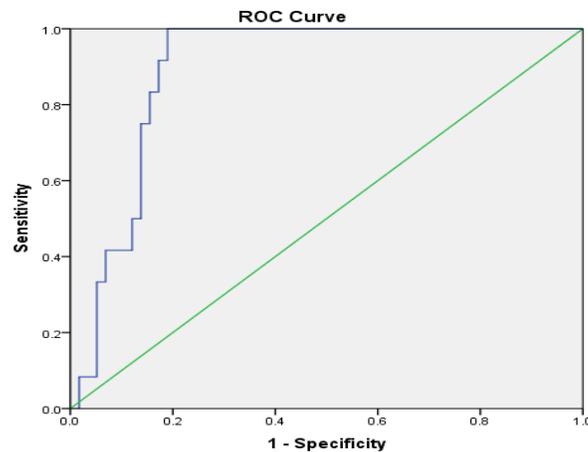


Fig. (3): ROC curve analysis for GLS in diagnosis of cardiotoxicity

Table-12: Prevalence of diastolic dysfunction in the studied patients

	n	%
Diastolic dysfunction +ve	34	48.6
Diastolic dysfunction -ve	36	51.4

In the studied patients, diastolic dysfunction was reported in 34 patients (48.6 %).

Table-13: Comparison between patients with and without diastolic dysfunction regarding the pretreatment echocardiographic data

	Diastolic dysfunction +ve n=34	Diastolic dysfunction -ve n=36	P value
LVEF	62.1 ± 2.4	63.0 ± 2.4	0.13
E	0.76 ± 0.07	0.75 ± 0.06	0.96
A	0.63 ± 0.08	0.6 ± 0.07	0.11
E/A	1.21 ± 0.17	1.28 ± 0.17	0.17
Septal e'	9.65 ± 0.9	9.53 ± 1.02	0.62

Lateral e'	12.05 ± 0.94	11.69 ± 1.01	0.12
LA volume index	27.6 ± 2.3	27.6 ± 1.8	0.97
TR velocity	2.4 ± 0.17	2.5 ± 0.16	0.94
GLS	-19.4 ± 0.7	-19.2 ± 0.84	0.24

This table shows no statistically significant differences between patients with and without DD regarding the pretreatment echocardiographic data.

Table-14: Comparison between patients with and without diastolic dysfunction regarding the post treatment echocardiographic data

	Diastolic dysfunction +ve n=34	Diastolic dysfunction -ve n=36	P value
LVEF	56.9 ± 4.0	59.9 ± 2.5	0.001*
E	0.76 ± 0.08	0.76 ± 0.07	0.9
A	0.62 ± 0.07	0.6 ± 0.08	0.14
E/A	1.23 ± 0.19	1.29 ± 0.2	0.24
Septal e'	6.56 ± 0.25	9.28 ± 0.95	0.0001*
Lateral e'	9.08 ± 0.32	11.7 ± 0.82	0.0001*
LA volume index	27.5 ± 2.3	27.6 ± 1.8	0.95
TR velocity	2.4 ± 0.18	2.44 ± 0.2	0.9
GLS	-16.8 ± 1.71	-18.4 ± 0.94	0.0001*

This table shows significantly lower LVEF, Septal e', Lateral e' and GLS in patients with DD when compared with patients without.

Table-15: Comparison between patients with and without diastolic dysfunction regarding the prevalence of cardiotoxicity

	Diastolic dysfunction +ve n=34	Diastolic dysfunction -ve n=36	P value
Cardiac toxicity (LVED)	12	0	0.0001
Cardiac toxicity (GLS)	22	0	0.0001

This table shows significantly higher rate of cardiotoxicity in patients with DD as compared to patients without DD.

Discussion:-

The current study provides a valuable insight into the utility of 2D STE in the detection of left ventricular dysfunction in breast cancer patients subjected to anthracycline-based chemotherapy.

The study recruited 70 women with newly diagnosed cancer breast. Before start of treatment, they were subjected to careful cardiac and echocardiographic assessment including STE evaluation in addition to the other clinical and laboratory investigations indicated in such situations. After completion of treatment, women had undergone similar cardiological and echocardiographic evaluation.

In the present study, comparison between pretreatment and post treatment echocardiographic data revealed significant changes in both systolic and diastolic functions of the left ventricle. Importantly, the present study found that conventional echocardiographic assessment could identify 12 patients (17.1 %) defined according to reduced LVEF while STE recognized cardiotoxicity in 22 patients (31.4 %) according to reduced GLS. This showed the superior performance of STE over conventional echocardiography.

The current study results are in agreement with *Sawaya et al., (2011)* who found (21%) of 43 breast cancer patients who received anthracyclines and trastuzumab developed a decrease in LV GLS, *Guerra et al., (2016)* who found a decrease of LV GLS in 27 % of 69 breast carcinoma patients undergoing adjuvant and/or neo-adjuvant chemotherapy, *Arciniegas Calle et al., (2018)* who found that GLS was the strongest indicator of cardiotoxicity detected in 20% of the 66 breast cancer patients who received anthracycline-trastuzumab treatment and the study of *Barros et al., (2019)* on 112 patients with breast cancer treated with doxorubicin and trastuzumab showed that (16.1%) had cardiotoxicity, In the multivariate analysis using the logistic regression model, those global longitudinal strain by speckle tracking were strongly associated with cardiotoxicity.

In respect to diastolic dysfunction, the present study reported that 34 patients (48.6 %) had diastolic dysfunction after anthracyclines treatment. But according to the latest ASE/EACVI guidelines for diastolic dysfunction no patient had fulfilled the criteria of diastolic dysfunction after chemotherapy.

Our data are in agreement with the conclusions of *Serrano et al., (2017)* who aimed to assess the incidence, evolution, and predictors of diastolic dysfunction in patients with breast cancer treated with anthracyclines. The study found that at the end of follow-up (median: 12 months, interquartile range: 11.1-12.8), 49 patients (57.6%) developed diastolic dysfunction. Diastolic dysfunction was persistent in 36 (73%) but reversible in the remaining 13 patients (27%).

The prevalence of diastolic dysfunction in breast cancer patients under anthracycline treatment was also reported by the study of *Mahfouz et al., (2018)* who identified diastolic dysfunction in 94.7 % of patients.

Comparative analysis between patients with diastolic dysfunction and patients without in the current study showed that patients with diastolic dysfunction had significantly higher impairment of ejection fraction and GLS. These data are in line with those obtained from the study of *Stoodley et al., (2013)* who utilized two-dimensional speckle tracking echocardiography (2DSTE) at baseline and immediately after anthracycline chemotherapy to investigate whether patients with significant changes in systolic function after anthracycline therapy would also develop alterations in diastolic parameters. They found that altered LV diastolic function was observed in the entire cohort after chemotherapy, with a differential reduction in participants with a post therapy LVEF < 55%. Univariate predictors of diastolic dysfunction were LVEF post therapy and systolic strain post-therapy. In a multivariate analysis, systolic strain after chemotherapy was the strongest independent predictor.

Conclusion:-

The present study confirmed the value STE in the detection of anthracyclines -induced cardiotoxicity and the superior performance of STE over conventional echocardiography in this situation.

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