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Research Paper

Evaluation of Right and Left Ventricular Systolic Functions in Breast Cancer Patients on Chemotherapy: A Transthoracic Echo Study

Taher Owaed Shellal [1], Muataz Fawzi Hussein [2], Thamer Imad Al-Jawahiri [3], Wisam Abdul Abbas Alattar [4]

ABSTRACT:

BACKGROUND:

Cardio-toxicity is a major complication of chemotherapy for breast cancer women, and so evaluation of cardiac function is important to protect the heart from harmful drug toxic effects.

OBJECTIVE:

To assess and evaluate the cardio-toxic sequelae of chemotherapy used in the treatment of breast cancer on the left and right ventricular systolic functions by Transthoracic Echocardiography.

PATIENTS AND METHODS:

This is a cross-sectional study that was carried out in Baghdad Teaching Hospital in Baghdad . A sample of 60 women with breast cancer on chemotherapy combination: Endoxan (Cyclophosphamide) + Doxorubicin and Herceptin(Trastuzumab) + Taxol (Paclitaxel) and 30 healthy women without chemotherapy were enrolled in the study Specific echocardiographic parameters for right and left ventricular functions, in addition to hemodynamic measurements, were assessed by the transthoracic echocardiography.

RESULTS:

There were significant differences regarding left ventricular ejection fraction, which was significantly reduced in women receiving chemotherapy (P=0.003). Left ventricular systolic myocardial velocity showed significant reduction in women receiving chemotherapy (P=0.0001). The mitral annular plane systolic excursion was significantly reduced in women receiving chemotherapy (P=0.0002). A significant decline in the fractional area change of the right ventricle among chemotherapy women receivers, P=0.005. Also, the Tricuspid annular plane systolic excursion was statistically with significant reduction (P=0.0001).

CONCLUSION:

This study demonstrated that chemotherapy for Breast cancer causes a decrease in both left ventricular and right ventricular systolic functions.

Moreover, the transthoracic echocardiographic study showed that the effect on left ventricle functions was more evident than on right ventricular functions.

KEYWORDS: Cancer Therapeutics-Related Cardiac Function, LV Ejection Fraction, Myocardial Systolic Tissue Velocity , Tricuspid Annular Plane Systolic Excursion, Fractional area Change

[1] *D. M, Higher Diploma in Echocardiography, Ibn Al-Nafees Teaching Hospital, Baghdad, Iraq.*
[2] *C.A.B.M, F.I.B.M, F.R.C.P (London), College of Medicine, University of Baghdad.*
[3] *Higher Diploma in Echocardiography, Ibn Al-Nafees Teaching Hospital, Baghdad, Iraq.*
[4] *C.A.B.M, D.I.C, Ibn Al-Nafees Teaching Hospital, Baghdad, Iraq.*

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INTRODUCTION:

Cardio-Oncology: Many chemotherapeutic medications lead to ultimate toxicity to the heart. Anthracycline group including Doxorubicin and the monoclonal antibody, namely, Trastuzumab (Herceptin) are the most commonly used and so are the most contributors to cardiotoxicity in the clinical practice .[(1)]

Although the introduction of modest anticancer drugs presents a revolution in the field of oncology, improving survival, they still revealed a huge spectrum of cardiotoxicity and thus increasing morbidity and mortality .[(2)]

Chemotherapy related cardiotoxicity mechanisms could be classified into two groups:

1. Type I is irreversible which results mainly from Anthracyclines.
2. Type II is primarily reversible and triggered by monoclonal antibodies such as Trastuzumab[(1,2)].

Cancer therapeutics–related cardiac dysfunction (CTRCD):

CTRCD is a decline in the left ventricular ejection fraction of more than a tenth percentage point to reach a value of less than 53% (normal reference value for two-dimensional echocardiography (2DE) performed by two to three weeks after the baseline diagnostic study. LVEF reduction can be further categorized as either symptomatic or asymptomatic according to reversibility[1,2].

1- Reversible: Patient improves around 5 % points of baseline.
2- Partially reversible: Improvement of LVEF is nearly 10 % points from the lowest value. However, it is more than 5 % points below baseline.
3- Irreversible: Ejection fraction value is improved by less than 10 % points from the lowest value. Moreover, it is still more than 5 % points below baseline.
4- Indeterminate: Patient is absent at time of re-evaluation[1].

Echocardiographic study of cardiac structure and function in breast cancer patients on chemotherapy:

A-Baseline echocardiographic assessment before initiation of chemotherapy:

Depending on a baseline echocardiographic study, the physician can assess cardiac function, identify whether or not, the patient has a previous cardiovascular disease and thus can modify chemotherapy protocol if needed. This baseline assessment helps to avoid or minimize cardiotoxicity in high risk patients [1,2,3].

B- Echocardiographic assessment during chemotherapy :

During cancer chemotherapy, any patient who develops signs and symptoms of heart disease, such as easy fatigability, dyspnea or chest pain, should be referred for echocardiographic study [4,5]. However, echocardiographic surveillance is recommended for some patients without clinical symptoms and signs, especially those patients on specific chemotherapy protocols with significant cardiotoxic potential, such as Anthracyclines and Trastuzumab [6,7,8].

Monitoring of cardiac function should continue until chemotherapy regime is switched off. Further cardiac assessment is needed for patients who need treatment for secondary malignancies. [3,9,10].

Linear measurements: M-mode and two dimensional echocardiographic measurements are important to assess chamber dimensions and cardiac evaluation [11,12].

I-LV Systolic Function :

A-Mitral Annular Plane Systolic Excursion (MAPSE): The magnitude of motion of the mitral annular plane is strongly related to the left ventricular systolic function. So, M-mode measurement of the lateral mitral annulus displacement is a useful tool to assess global systolic function [13].

B-Myocardial Systolic Velocity tissue (s′): Using tissue Doppler Modality, myocardial systolic velocity can be measured. The latter is a powerful marker of global left ventricular systolic function. The above modality can also be used to assess the diastolic function. [11,12,13] See Figure (1).

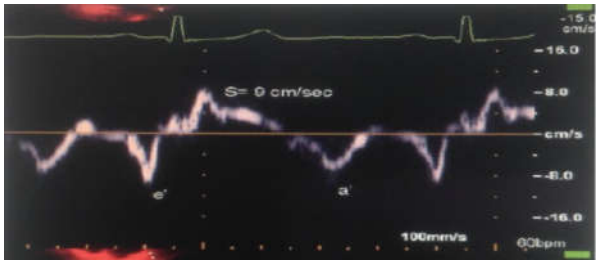

Figure 1: Doppler tissue imaging of the lateral mitral annulus.

C-Modified biplane Simpson's technique: LVEF is the most feasible and widely used echocardiographic parameter for monitoring LV systolic function. [12,13] See Figure (2)

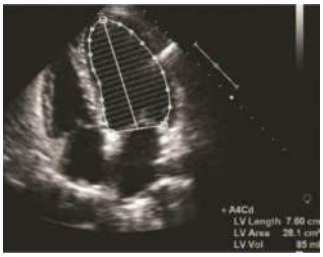

Figure 2: Measurement of LVEF using Simpson's method.

D-Left Ventricular Global Longitudinal Strain (GLS): Measuring left ventricle global longitudinal strain using speckle tracking echocardiography can detect early LV systolic dysfunction after the initiation of cardiotoxic chemotherapy. [14,15,16]

E-4D Echocardiography (4DE): 4D-Echocardiography is more accurate and advanced echo technique for LV function assessment and detection of CTRCD in breast cancer patients on chemotherapy. Although it is image dependant, it is more reproducible, with no geometric assumption and so it is better in LVEF assessment .[12,13].

II-RV systolic function:

A - RV Dimensions : These are RV Basal diameter, RV mid diameter, and RV longitudinal diameter[17].

B- Right ventricular fractional area changes: The RV fractional area change (FAC) estimates global RV systolic function.[18].

C-Tricuspid annular plane systolic excursion (TAPSE) measures the displacement of the base of the RV towards the apex during systole (longitudinal function) .[19]

D-Right ventricular index of myocardial performance (RIMP): It can be obtained by applying tissue Doppler imaging (TDI) to the lateral tricuspid annulus. A RIMP greater than 0.54 is indicative of RV dysfunction[20].

C-DTI-Derived tricuspid lateral annular systolic velocity: Tissue Doppler derived S' correlates well with other global RV systolic function parameters. RV systolic dysfunction is identified when the S' velocity is less than 9.5 cm/sec calculated on the free-wall side [21,22].

Hemodynamic assessment of RV and pulmonary circulation:

Systolic pulmonary artery pressure (SPAP).

Pulmonary artery diastolic pressure (PADP).

C. Mean PA pressure [23,24].

AIM OF STUDY:

To measure the toxic influence of chemotherapy on both left and right ventricular function in breast cancer patients by transthoracic echocardiography.

PATIENTS AND METHODS:

1. Study design & settings: A cross-sectional study was carried out in Baghdad Teaching Hospital from July 1, 2018, to June 30, 2019.

2. Study population: Study populations include the following groups:

Group (1): 60 Women with breast cancer on chemotherapy combination: Endoxan (Cyclophosphamide) + Doxorubicin and Herceptin(Trastuzumab) + Taxol (Paclitaxel).

Group (2): 30 Normal women without risk factors for cardiovascular disease.

Inclusion criteria are Adult women (age ≥29 years), Known cases of breast cancer, on chemotherapy, and Normal (control women).

Exclusion criteria are Valvular heart diseases, Congenital heart disease, Ischemic heart disease, Hypertension, Diabetic mellitus, Pulmonary Hypertension, Chronic obstructive airway disease, Heart failure, Obesity, and Chronic Renal disease.

Transthoracic Echocardiography:

Transthoracic echocardiographic images were acquired by the same echocardiographer at rest with the patient in the left lateral decubitus position. The echocardiography equipment used was G.E. (VIVID E9). Conventional echocardiography images were taken in parasternal and apical views, and the standard LV measurements included the left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD), interventricular septum thickness (IVST), and posterior wall thickness (PWT) using 2D and M-mode measurement. EF%, EDV, and ESV were measured using Simpson's method. MAPSE was measured by M-mode interrogation of the lateral mitral annulus, and the displacement of mitral valve annular plane toward the transducer was then estimated.

Tissue Doppler imaging modality was used to measure Myocardial Systolic Tissue Velocity (s'), Tissue Doppler Velocity of Mitral or

Tricuspid Annulus (E', A'), and Myocardial Performance Index (MPI). The RV fractional area change (FAC) was measured by tracing RV in systole and Diastole using an apical four-chamber view.

Statistical Analysis:

Statistical Package for Social Sciences (SPSS) version 25 was used. Descriptive statistics are presented as (mean ± standard deviation) and frequencies as percentages. The significance level (p-value) is set at ≤ 0.05 in all statistical analyses, and the result is presented as tables.

RESULTS:

The mean BMI of women with breast cancer was 20.6±2.6 Kg/m^2; 18.3% of them were underweight, and 81.6% of them were within the normal range. See Table (1).

Table 1: Sociodemographic properties of women with breast cancer.

Variable	No.	%
Age	**mean±SD (46.1±6.1 years)**	
<40 years	8	13.3
40-49 years	36	60.0
≥50 years	16	26.7
Total	60	100.0
BMI	**mean±SD (20.6±2.6 Kg/m^2)**	
Underweight	11	18.3
Normal	49	81.6
Total	60	100.0

The mean duration of breast cancer therapy was 9.6±3.4 months. Most (86.7%) of women with breast malignancy were treated with Herceptin and Toxol, while 13.3% of them were treated with Endoxan and Doxorubicin. See Table (2)

Table 2: Management history of women with breast cancer.

Variable	No	%
Duration of cancer mean±SD (9.6±3.4 months)		
On chemotherapy		
Yes	60	100.0
No	0	-
Total	60	100.0
Type of chemotherapy		
Endoxan+ Doxorubicin	8	13.3
Herceptin+Taxol	52	86.7
Total	60	100.0
Dose of Endoxan mean±SD (993.8±67.8 mg)		
Dose of Doxorubicin mean±SD (132.5±30 mg)		
Dose of Herceptin mean±SD (531.5±63.5 mg)		
Dose of Taxol mean±SD (306.6±24.3 mg)		
Duration of Endoxan regimen mean±SD (3±0.5 months)		
Duration of Herceptin regimen mean±SD (8.4±2.9 months)		
Number of cycles for Endoxan regimen mean±SD (3.8±0.7)		
Number of cycles for Herceptin regimen mean±SD (11.9±4.2)		

Table (3) illustrates that 13.3% of breast cancer patients had had low EF, 15% had decreased ś, while 13.3 % had decreased MAPSE. Impaired LV diastolic function was observed in 16.6% of women with breast cancer, and 6.6% of them had abnormal left atrial areas.

Table 3: Left ventricular echocardiography parameters of women with breast cancer on chemotherapy and normal (control) women

Group With breast cancer	With breast cancer		Control	Control
Variable	No. %	%	No. %	%
EF * P=0.003	Mean±SD (56±9.7)		Mean±SD(61.5±2.7 %)	
Normal	52	86.7	30	100
Low	8	13.3	0	0
Total	60	100.0	30	100
Ś * P = 0.0001	Mean±SD (9.2±1.7ms)		Mean±SD	10.8±l.lms)
Normal	51	85.0	30	100
Decreased	9	15.0	0	0
Total	60	100.0	30	100
MAPSE * P = 0.0002	Mean±SD (10±1.8mm)		Mean±SD (11.3±0.8mm)	
Normal	52	86.7	30	100
Decreased	8	13.3	0	0
Total	60	100.0	30	100
Diastolic function p.0.323 NS Not Significant				
Normal	50	85.4	28	93.4
Impaired	10	16.6	2	6.06
Total	60	100.0	30	100
Left atrium dimension NS P=0.335	Mean±SD (15.7±5.6cm^2)		Mean±SD (14.7±1.0cm^2)	
Normal	56	93.4	30	100
Dilated	4	6.6	0	0
Total	60	100.0	30	100

** Significant, NS Not Significant*

6.7 % of breast cancer patients had dilated RV base and mid-dimensions, while 3.4% had dilated RV length dimensions. Other echocardiographic findings in breast cancer patients are: 11.7% had impaired Tie index, 10% had impaired FAC, 8.4% had decreased TAPSE, and 11.7% had decreased TD-S' . See Table (4).

Table 4: Right ventricular echocardiography parameters of women with breast cancer on chemotherapy and normal (control) women.

Group	With Breast Cancer		Control	
Variable	**No**	**%**	**No**	**%**
RV dimension (base) NS P=0.897	**Mean±SD (3.0±0.5cm)**		**Mean±SD**	**29.6±2.3cm)**
Normal	56	93.3	30	100
Dilated	4	6.7	0	0
Total	**60**	**100.0**	**30**	**100**
RV dimension (mid) NS P = 0.999	**Mean±SD (2.9±0.6cm)**		**Mean±SD**	**(2.9±0.6cm)**
Normal	56	93.3	30	100
Dilated	4	6.7	0	0
Total	**60**	**100.0**	**30**	**100**
RV dimension (length) NS P = 0.274	**Mean±SD (6.3±0.9cm)**		**Mean±SD**	**(6.1±0.6cm)**
Normal	58	96.6	30	100
Dilated	2	3.4	0	0
Total	**60**	**100.0**	**30**	**100**
Tie index NS P=0.182	**Mean±SD (0.52±0.04)**		**Mean±SD**	**(0.51±0.01)**
Normal	53	88.3	30	100
Impaired	7	11.7	0	0
Total	**60**	**100.0**	**30**	**100**
FAC* P=0.005	**Mean±SD (31.9±5.6%)**		**Mean±SD(37.1±1.3%)**	
Normal	54	90	30	100
Impaired	6	10	0	0
Total	**60**	**100.0**	**30**	**100**
TAPSE * P=0.0001	**Mean±SD (17.4±2.0mm)**		**Mean±SD (19.1±1.8mm)**	
Normal	55	91.6	30	100
Decreased	5	8.4	0	0
Total	**60**	**100**	**30**	**100**
TD-S' NS P=0.154	**Mean±SD (10.5±2.6ms)**		**Mean±SD**	**11.2±0.8ms)**
Normal	53	88.3	30	100
Decreased	7	11.7	0	0
Total	**100**	**100**	**30**	**100**

** Significant, NS Not Significant*

In Table (5), one can see that 8.3% of breast cancer patients had elevated PASP, 5% of them had elevated PADP, and PAMP. Moreover, 3.3% of them had dilated right atrial area.

Table 5: Right ventricular hemodynamic of women with breast cancer on chemotherapy and normal (control) women.

Group	With Breast Cancer		Control	
Variable	**No**	**%**	**No**	**%**
PASP NS P = 0.487	**Mean±SD (15.9±13.2mmHg)**		**Mean±SD(14.2±2.5mmHg)**	
Normal	55	91.7	30	100
Elevated	5	8.3	0	0
Total	**60**	**100.0**	**30**	**100**
PADP NS P = 0.319	**Mean±SD (9.9±5.8mmHg)**		**Mean±SD(8.8±2.2mmHg)**	
Normal	57	95.0	30	100
Elevated	3	5.0	0	0
Total	**60**	**100.0**	**30**	**100**
PAMP NS P = 0.347	**Mean±SD (11.8±6.8mmHg)**		**Mean±SD(10.6±2.0mmHg)**	
Normal	57	95.0	30	100
Elevated	3	5.0	0	0
Total	**60**	**100.0**	**30**	**100**
Right atrium dimension NS P = 0.799	**Mean±SD (14.5±2.0cm^2)**		**Mean±SD(14.4±l.l cm^2)**	
Normal	58	96.7	30	100
Dilated	2	3.3	0	0
Total	**60**	**100.0**	**30**	**100.0**

Table (6) presents a highly significant association between longer cancer duration in women with breast cancer and RV dysfunction ($p<0.001$). No significant relationship between RV dysfunction with type of chemotherapy combination ($p=0.1$).

Table 6: Distribution of management properties according to RV function.

Variable	Normal		Dysfunction		P
	No	**%**	**No**	**%**	
Duration of cancer					**<0.001 *S**
Mean±SD (months)	**8.6±3.1**		**11.9±2.3**		
Type of chemotherapy					**0.1** NS**
Endoxan+ Doxorubicin	**7**	**11.66**	**1**	**1.66**	
Herceptin+Taxol	**47**	**78.33**	**5**	**8.33**	

** Independent sample t-test,*

*** Fishers exact test, S=Significant, NS=Not significant.*

Herceptin's mean dose, duration, and cycles were significantly higher among women with low EF. Regarding the dose of Taxol, no significant relationship was observed with the breast cancer women with low EF. See table (7).

Table 7: Distribution of Herceptin regimen characteristics according to LV EF.

Variable	Normal	Low	P
	Mean±SD	Mean±SD	
Dose of Herceptin	521.8±59.8	567.6±66.5	0.03* S
Dose of Taxol	306.9±25.9	305.4±17.8	0.8* NS
Duration of Herceptin (months)	7.6±2.8	11.2±1.4	<0.001* S
Number of Herceptin cycles	10.8±3.9	16.1±1.4	<0.001* S

DISCUSSION:

The present study found that the adult females with breast malignancy had significantly low left ventricular ejection fraction. Consistently, Nowsheen et al. [26] stated that such females who are on breast cancer chemotherapy presented a high risk of left ventricular ejection fraction decline. In our study, 15% of ladies with breast cancer had decreased S´. This finding agrees with the outcome of a study done by Gulati et al. [27] in the USA.

Impaired LV diastolic function was present in 16.6% of studied sample of ladies with breast cancer. Cao et al. [28] reported that impaired LV diastolic function is more sensitive than LV ejection fraction in the diagnosis of cardiotoxicity among such ladies.

On the other hand, the existing study pointed out that ladies on breast cancer chemotherapy had over normal right ventricular dimensions with significantly reduced FAC and TAPSE. These outcomes are approximate to those of the Boczar et al [25] study in Canada, which reported that chemotherapy for ladies with breast cancer had adverse effects on both right atrial size and right ventricular function.

The study shows a highly significant association between longer cancer duration in adult females with breast cancer and RV dysfunction ($p<0.001$). This is consistent with Chen et al. study [29] in the USA.

The mean duration of Herceptin regimen was significantly longer among adult females with RV dysfunction ($p<0.001$). This is consistent with the Tanindi et al. study in Turkey. [30] Moreover, the mean number of cycles for the Herceptin regimen was significantly longer among women with RV dysfunction ($p<0.001$). This is similar to the Tadic et al. [31] study in Serbia.

We found that the Herceptin dose was significantly higher among breast cancer ladies with low EF. This consequence coincides with that of a study done by Yoon et al. [32] in South Korea. Our study also revealed that LVEF was affected by chemotherapy duration and number of cycles. This is similar to Reuvekamp et al.'s [33] study in the Netherlands.

CONCLUSION:

1. Cardiotoxic effect of Breast cancer chemotherapy affects the whole myocardium, and a transthoracic echocardiographic study shows the effect on left ventricle functions more evident than that of right ventricular functions.
2. Right ventricular function of women with breast cancer during chemotherapy is affected by older age, duration of cancer, duration and cycles of Herceptin chemotherapy.
3. The left ventricular function of women with breast cancer during chemotherapy is affected by the dose, duration, and cycles of Herceptin chemotherapy.

Limitations:

1. Poor compliance of some ladies with breast cancer chemotherapy. Those ladies may be absent at the decided time for re-evaluation.
2. Global Longitudinal Strain (GLS) and 4D-Echocardiography modalities could not be applied because the GLS software and the 4D probe were unavailable in the used echocardiography machine. Both modalities may be more informative and reproducible in early detection of the global left and right ventricular systolic dysfunction.

Recommendations:

1. Cardiologists and Echocardiographers should monitor the left and right ventricular function of women with breast cancer at the beginning and during the chemotherapy.
2. Application of left ventricular parameters assessment as the first choice in screening for cardiac function among women with breast cancer during chemotherapy.

Ethical considerations:

1. The ethical approval was taken from hospital authorities.
2. Confidentiality was taken into consideration.
3. The informed consent signed by the patients.

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