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Right Ventricle Function Evaluation by 2D Transthoracic-Echocardiography in Breast Cancer Patients Undergoing Anthracycline Chemotherapy, A Prospective Cohort Study

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ABSTRACT

Background: Breast cancer is one of the most prevalent types of cancers among women in Egypt with incidence rates of 48.8 per 100.000 women. Anthracyclines are the drugs of choice for adjuvant chemotherapy in high-risk patients, however, their use is limited due to their cardiotoxicity. In animal models treated with anthracyclines, right ventricle (RV) dysfunction is thought to be an independent prognostic factor and it's possible that it could be an early indicator of subclinical left ventricle (LV) dysfunction. Therefore, further research is required to study the cardiotoxic effect of anthracycline drugs on the RV using different 2D echocardiographic modalities.

Subjects and Methods: A total number of 40 newly diagnosed breast cancer patients who were planned to receive doxorubicin therapy for 37 of them and epirubicin for 3 patients were prospectively recruited. Serial 2 D echocardiograms including speckle-tracking were done at baseline, 3 months later, and 6 months later.

Results: RV dysfunction was detected more by right ventricle global longitudinal strain (RVGLS) after six months of anthracycline-based chemotherapy (-22.85±1.31 vs. -19.30±2.30, P value 0.001). ROC curve revealed a total anthracycline cumulative dose of 416 mg/m^2 with the highest sensitivity and specificity of RV dysfunction.

Conclusion: RVGLS surpassed other traditional 2D metrics in identifying subclinical RV disease, and the total anthracycline cumulative dose is strongly linked to the incidence of chemotherapy related cardiotoxicity to the right ventricle. 2D speckle-tracking is noninvasive and feasible modality that can be used to detect early anthracycline-induced cardiotoxicity.

Keywords: TAPSE; RVFAC; Chemotherapy induced cardiotoxicity; RVGLS.

INTRODUCTION

Breast cancer is one of the most prevalent types of cancers among women in Egypt with incidence rates of 48.8 per 100.000 women[1]. Anthracyclines are considered a cornerstone of therapy for years because it has a strong impact on breast cancer survival[2]. However, cardiotoxicity from anthracyclines is an early and late cause of death among patients(3).

Left ventricular ejection fraction (LVEF) should be determined before and periodically during anthracycline-based chemotherapy to detect cardiac dysfunction as early as possible. The European association of cardiovascular imaging (EACVI) defined cancer therapy-related cardiac dysfunction (CTRCD) as a reduction in left ventricular ejection fraction (LVEF) of more than 10% to below the lower limit of normal, which is LVEF of 53%, regardless of symptoms. If the situation did not meet the definition, then a reduction more than 15% in global longitudinal strain (GLS) in comparison with a baseline GLS was defined as subclinical left ventricular dysfunction [4].

While the magnitude of anthracyclines on LV function have been well studied, there is no sufficient data regarding their impact on right ventricular (RV) function. In animal models treated with anthracyclines, RV dysfunction is thought to be an independent prognostic factor and it's possible that it could be an early indicator of subclinical LV dysfunction[5].

A complicated geometric structure, smooth muscular input and outflow, and a trabecular apical region are all features of the right ventricle. As a result, no single echocardiographic modality is sufficient for its evaluation. A paramount tool for determining RV myocardial strain and predicting a patient's functional potential and survival is two-dimensional speckle-tracking (2DTSE) [6]. It has been determined that the RV global longitudinal strain (RVGLS) measured by 2DSTE and the RV function measured by cardiac MRI (CMRI), the gold standard for RV assessment, correspond favorably with one another[7]. Recent research revealed that anthracycline-based chemotherapy affects not only LV function but also RV function, and 2D speckle-tracking can identify subclinical impairment. In this study, we examined whether anthracyclines had any effect on Egyptian female breast cancer patients' right ventricle function during the period of follow- up.

SUBJECTS AND METHODS

This prospective cohort study included 40 female patients with newly diagnosed breast cancer who were planned to receive anthracycline chemotherapy after radical/modified radical or conservative surgical mastectomy at Suez Canal University and Ismailia Oncology Hospitals. We included patients who were First time to begin a course of anthracycline according to international standardized protocols. All patients received

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an average of 4-cycle AC agent (doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2) ± cyclophosphamide 600 mg/m^2) with a 21-day inter cycle period. Throughout this trial, none of the patients received any further cardiotoxic medications, radiation treatment, or cardiac safety measures.

Patients who were below the age of 18, patients with previous structural heart disease, patients with chronic illness such as systemic hypertension, diabetes mellitus, and chronic kidney disease were excluded.

All participants were evaluated at baseline, the beginning of the study before starting anthracycline, then after three months and after six months.

Echocardiographic RV parameters that were included in the study:

1. **RV 2D FAC (fractional area change):** It was measured using an RV-focused apical four-chamber view by tracing the RV endocardial boundaries, including the endocardial trabeculae in both systole and diastole**.** It was estimated with the following equation [8].

   RV FAC (%) = 100 × (RV end diastolic area (RV EDA) − RV end systolic area (RV ESA) ÷ RV EDA

2. **TAPSE (tricuspid annular plane systolic excursion):** The amount of longitudinal motion of the tricuspid annulus at peak systole in the typical apical four-chamber view was determined by passing an M-mode cursor through the annulus[8].
3. **Tricuspid annular plane systolic velocity (S'):** pulsed wave Doppler placed in the lateral tricuspid annulus parallel to the free wall (cm/s) [9].
4. **Right ventricular global longitudinal strain:** By tracking the endocardial walls of the right ventricle in an RV-focused apical four-chamber view at around 10 spots in one frame, right ventricular global longitudinal strain was determined offline and then automatically tracked throughout cardiac cycles. Software automatically split the RV into three sections for the free wall and interventricular septum, basal, mid, and apical, and then calculated the RV's GLS. The proportion of systolic shortening of the RV free wall from base to apex was used to calculate longitudinal strain and RVGLS impairment was below -20% [10].

Ethical approval:

Every patient shared in the study gave written consent. Any patient who was contemplating participating in this study was given a thorough explanation of all the test stages, provided in a way that they could comprehend. The Suez Canal University Ethical Committee Council gave their approval to the study. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of the study.

Statistical analysis

Data were analyzed by version 25 of Statistical Package for the Social Sciences (SPSS). Quantitative data were presented as mean, standard deviation (SD), median, and interquartile range (IQR). Qualitative data were presents as frequency and percentage. In order to compare two groups for quantitative variables that weren't regularly distributed, the Mann Whitney test was applied. The Friedman test was used for quantitative variables with abnormal distributions to compare between more than two periods or stages and post hoc test (Wilcoxon signed-rank test) was used for pairwise comparisons. In order to compare qualitative variables between two groups, chi^2 test was applied. The Cochran's *Q* test was used to determine if there were differences in the right ventricular parameters over time. The ROC curve was used to detect the total anthracycline cumulative dose with the most impact on the right ventricle. P value < 0.05 was considered significant.

RESULTS

All studied parameters of RV systolic function were significantly lower after six months of Anthracycline-based chemotherapy, including TAPSE, RVFAC, DTI-derived RV S' velocity, and RVGLS (Table 1).

Table (1): Standard right ventricular echocardiographic parameters in the three periods (N=40 patients)

	Baseline	**POST 3 Months**	**POST 6 Months**	**p**
FAC Mean ± SD	50.24±9.06	42.28±3.64	40.31±3.81	**<0.001***
P0		**<0.001***	**<0.001***	
TAPSE Mean ± SD	24.50±3.21	21.72±4.16	22.62±2.78	**<0.001***
P0		**<0.001***	**0.001***	
S' velocity Mean ± SD	12.98±1.32	12.44±1.65	12.23±1.68	**0.009***
P0		0.243	**0.013***	
RVGLS Mean ± SD	-22.85±1.31	-20.37±1.83	-19.30±2.30	**<0.001***
P0		**0.001***	**0.001***	

P0: p value for comparing between baseline and each measurement. TAPSE: tricuspid annular plane systolic excursion FAC: fractional area change. RVGLS: right ventricle global longitudinal strain.

Despite the significant reduction in RV systolic parameters, RV dysfunction was found more by RVGLS, which was reduced to (-19.30%) after six months of chemotherapy (table 2).

Table (2): Comparison of 3 months and 6 months post chemotherapy right ventricular global longitudinal strain (RVGLS) in breast cancer patients

	RVGLS at base line	RVGLS post 3MO	RVGLS post 6MO	Cochran's	P-Value
Normal	40 (100%)	28 (70%)	21 (52.5%)	29.16	**<0.001***
Impaired	0 (0%)	12 (30%)	19 (47.5%)		

RVGLS: right ventricle global longitudinal strain.

When measuring the possible risk factors of RVGLS reduction, we found that the total anthracycline cumulative dose was the only factor that affected the RVGLS. It is worth mentioning that BMI was not associated with right ventricular cardiotoxicity even though it affected total anthracycline cumulative dose, and this is due to individual dose modification according to the patient's functional capacity and comorbidities (table 3).

Table (3): Association of basal characteristics with right ventricular global longitudinal strain (RVGLS) 6 month after chemotherapy

Variables	Group A (N = 21) (patients with normal RV Function)	Group B (N = 19) (patients with impaired RVGLS)	P
Age Median (IQR)	37(32.5-53.5)	57(39-66)	0.33
Metastasis Yes No	9(42.9%) 12(57.14%)	4(21.1) 15(78.9)	0.141
Agent of chemotherapy Doxorubicin Epirubicin	19(90.5%) 2(9.5%)	18(94.7%) 1(5.3%)	0.609
Concomitant agent Cyclo-phosphamide None	10(47.6%) 11(52.4%)	9(47.4%) 10(52.6%)	0.987
Total anthracycline cumulative dose Median (IQR)	408(371- 416)	430(412-456)	**0.001***
BMI Median (IQR)	29.1(25.1-37.9)	32.4(28.9- 40.9)	0.27

RV: right ventricle BMI: body mass index

The ROC curve revealed the cut off value of total anthracycline cumulative dose (doxorubicin) was 416 mg/m^2 with sensitivity of 80% and specificity of 89% for RVGLS impairment. The area under the curve was 0.802 (figure 1).

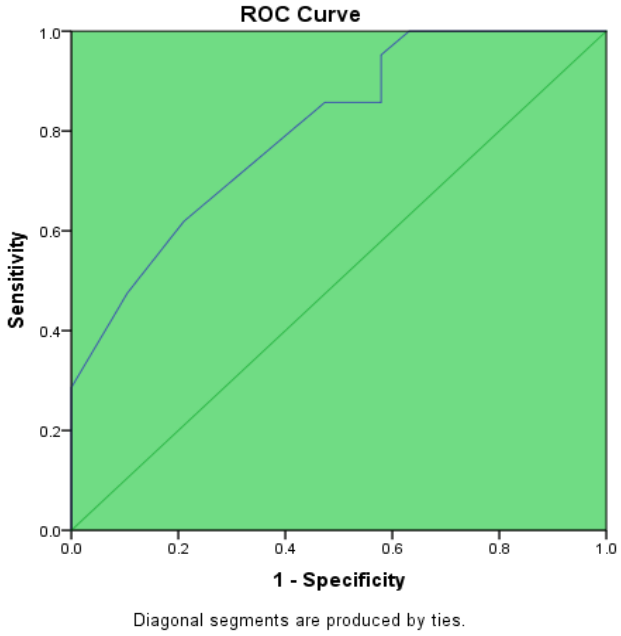

Figure (1): ROC curve test of total anthracycline cumulative dose for prediction of right ventricular subclinical dysfunction

DISCUSSION

More attention was given to the toxic effects of anthracyclines on the right ventricle, given the proven prognostic significance of right ventricular (RV) dysfunction on the prognosis of patients with heart failure with decreased ejection fraction (HFref)[11].

Compared to other echocardiographic techniques, RV speckle-tracking identified RV dysfunction early. This is consistent with **Khairat *et al.*** [12] who discovered increased incidence of RV dysfunction by speckle tracking to 12% after 10 months from anthracycline chemotherapy among children with osteosarcoma. **Xu *et al.*** [13] used three-dimensional echocardiography to assess subclinical right ventricle deterioration among 95 women with breast cancer, who received epirubicin (360 mg/m^2), they also found significant reduction in 3D-RVGLS at the end of the treatment course and at 12 months after it. In **Zhao *et al.*** [14] they evaluated the right ventricle in 74 B-cell lymphoma patients who were receiving anthracycline (AC) using two- and three-dimensional echocardiography. After 4 cycles of doxorubicin 50 to 70 mg/m^2, they discovered a significant reduction in 3D right ventricular longitudinal free wall strain (RVFLS). Moreover, after 6 cycles they found significant reduction in 3D right ventricular global longitudinal strain

(RVGLS) and reduction in right ventricle ejection fraction. The most significant result of this research was RV strain results changed earlier than RVEF. **Boczar *et al.***, involved 49 patients who received anthracycline, and they retrospectively had two echocardiograms 3 months apart. They found that using the deformation technique to evaluate the RV is a crucial way to find subclinical RV systolic dysfunction[3]. In a cohort research involving 40 breast cancer patients who received anthracycline-based chemotherapy, **Laufer-Perl *et al.***, discovered a significant decrease in RVGLS and right ventricular free wall longitudinal strain[15].

We found that the total anthracycline cumulative dose was an independent predictor for right ventricular subclinical cardiotoxicity. This was consistent with the previous studies. For example, **Chang *et al.*,** found that not only total epirubicin cumulative dose was associated with impairment of RVGLS but also the development of dyspnea [16].

CONCLUSION

In this study, two-dimensional right ventricular global longitudinal strain surpassed other traditional 2D metrics in identifying subclinical RV disease, and the total anthracycline cumulative dose was strongly linked to the incidence of chemotherapy related cardiotoxicity to the right ventricle. Further studies with longer follow-up periods are required to detect the appropriate timing to start cardio-protective medications and the correlation between RVGLS and cancer therapy-related cardiac dysfunction.

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