Caspian Journal of Internal Medicine 2025 (Spring); 16(2): 347-354
DOI: 10.22088/cjim.16.2.347

Original Article

Right ventricular echocardiographic function in patients with breast cancer undergoing anthracycline-based chemotherapy: A prospective study

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Abstract

Background: Chemotherapy regimens with anthracyclines, widely used in treating breast cancer and lymphoma, are associated with significant cardiac toxicity. While previous studies have primarily focused on left ventricular (LV) function, limited research exists on right ventricular (RV) function. This study aimed to evaluate RV echocardiographic function in breast cancer patients undergoing anthracycline-based chemotherapy.

Methods: A cohort of 72 breast cancer patients receiving anthracycline treatment at Ghazi Tabatabai and Madani Hospitals from April to March 2022 participated in this study. Echocardiography was performed before treatment initiation, 15 days after the second chemotherapy session, and 15 days after the final session. Cardiotoxicity levels were calculated using SPSS V22 software with inferential statistical methods, including repeated measures analysis and the Friedman test.

Results: RV-free wall strain remained stable 15 days after the second treatment session compared to baseline but showed a statistically significant decrease 15 days after the final session (P = 0.044). The prevalence of abnormal RV-free wall strain increased significantly during the final assessment (P = 0.037). Tumor regression grade (TRG) also demonstrated significant changes over time (P = 0.003). Right ventricular systolic pressure (RVSP) increased significantly throughout the study (P = 0.035), while no significant changes were observed in other parameters such as LVEF, E/E', LAVI, or TAPSE.

Conclusion: Anthracycline-based chemotherapy leads to a decline in RV-free wall strain over time, highlighting the importance of monitoring RV function alongside LV function during treatment. Advanced echocardiographic techniques, including strain imaging, may help detect subclinical RV dysfunction earlier.

Keywords: Anthracycline, Chemotherapy, Cardiotoxicity, Breast cancer, Right ventricular function.

Citation:
Mohammadi K, Gertasi M, Raeisi M, et al. Right ventricular echocardiographic function in patients with breast cancer undergoing anthracycline-based chemotherapy: A prospective study. Caspian J Intern Med 2025; 16(2): 347-354.

The continuous increase of the incidence of cancer could be a developing concern, and it is predicted that its rate may increase 45% by the year 2030 (1). However, it has decreased by 20-30% in recent decades (2). The significant improvement in the survival rate with the introduction of new anti-cancer drugs, but various chemotherapy drugs have shown many manifestations of cardiotoxicity (3). Multiple factors can contribute to cardiac toxicity in these patients, including the type of chemotherapy drug, cumulative drug dosage, age, concurrent or prior radiotherapy treatment, and accompanying diseases. However, the various mechanisms of chemotherapy-induced cardiac toxicity fall into two categories (4). The first category is often irreversible and is predominantly caused by anthracyclines. The second category is more reversible and is initiated by monoclonal antibodies including trastuzumab (4, 5).

Received: 29 Dec 2023
Revised: 10 May 2024
Accepted: 25 May 2024
Published: 21 March 2025

 Publisher: Babol University of Medical Sciences

The accepted mechanism for cardiac toxicity resulting from anthracyclines involves the production of free oxygen species that react with iron, forming highly toxic and reactive hydroxyl radicals, leading to intracellular damage (4, 5). Furthermore, anthracyclines hurt cardiomyocytes by inhibiting topoisomerase II (6). The cardiac changes resulting from anthracyclines are dose-dependent and essentially irreversible, as they lead to the death of myocardial cells. Chemotherapy regimens with anthracyclines, widely used in the treatment of malignancies including lymphoma and breast cancer, have shown efficacy but came with significant side effects, and cardiac toxicity is the most important one (1). These dose-dependent side effects include irreversible right or left ventricular (LV) failure and can lead to severe consequences for the patient (2). Given the widespread use of this therapeutic regimen and its significant cardiac side effects, patients undergoing this treatment require careful monitoring for these effects during therapy, enabling prompt intervention if complications arise. Previous studies have predominantly investigated the LV function after anthracyclines administration, with limited research conducted on right ventricular function (3-5).

Advanced imaging techniques, such as echocardiography and magnetic resonance imaging (MRI), now provide a thorough assessment of the structure, function, and underlying mechanisms affecting LV patients dealing with cancer (7-9). Existing guidelines for assessing cardiac toxicity include parameters of the LV, left ventricular ejection fraction (LVEF) and global longitudinal strain, as well as new mechanical and systolic performance parameters (9-11). Information regarding the impact of chemotherapy on the right ventricular (RV) function is limited and contradictory (12-18). Along with two-dimensional (2D) and three-dimensional (3D) echocardiography and color Doppler, the use of the new Speckle-tracking imaging (STI) method has helped to more accurately identification of RV involvement in patients undergoing chemotherapy (13). Given the mentioned considerations, in addition to LV involvement, there is also damage to the right side, especially the RV of the heart, is implicated, that can serve as a predictor of patient outcomes. However, studies on the evaluation of RV function are very few. This study examined the RV function after initiation of anthracycline chemotherapy.

Methods

The present study was carried out after approval by the Ethics Committee of Tabriz University of Medical Sciences with the ethical code IR.TBZMED.REC.1400.817. The research community of the present study consisted of patients suffering from breast cancer undergoing treatment with anthracyclines who attended the chemotherapy clinic of Shahid Ghazi Tabatabai Hospital (affiliated with Tabriz University of Medical Sciences). These patients received medical care at Shahid Madani Hospital between Aprils to March 2022 and underwent echocardiography. The study enrolled participants based on the following inclusion criteria: age over 18 years, breast cancer diagnosis, receiving anthracycline-based chemotherapy in combination with cyclophosphamide, and signing the consent form to participate. Exclusion criteria consisted of age less than 18 years, any structural or valvular heart disorder of moderate to severe intensity on initial echocardiography, any cardiac arrhythmia that could affect measurements, and the presence of metastatic cardiac involvement and poor acoustic window. Patients meeting the inclusion criteria were selected using a census sampling method. In order not to distort the study due to variable doses of anthracycline treatment regimen, the study population included breast cancer patients. The patients had any evidence of metastasis. During the study period, 72 patients participated in the present study and undergoing the necessary evaluations. All patients signed the informed consent form, and received detailed information about their participation in the study and the reasons for their selection before commencing the study. In general, all patients underwent four cycles of chemotherapy with anthracyclines in combination with cyclophosphamide. All patients underwent echocardiography at three different time points: one session before entering the study (before the initiation of chemotherapy), one session 15 days after completion of the second chemotherapy session, and one session 15 days after completion of the final. Patients underwent echocardiography according guidelines to J Am Soc Echocardiogr (ASE). The following parameters were evaluated during echocardiography: E over É ratio (E/É), left atrial volume index (LAVI), tricuspid annular plane systolic excursion (TAPSE), right ventricular S' velocity (RV S'), right ventricular diastolic diameter (RVDD), right ventricular systolic pressure (RVSP), tricuspid regurgitant gradient (TRG), RV free wall strain, right atrial area (RAA) and inferior vena cava diameter (IVCD), right ventricular fractional area change (RV FAC).

A decrease of more than 10% in fractional area change (FAC) calculated using the formula RVFAC (%) = 'RVEDA - RVESA' / 'RVEDA' compared to FAC before the initiation of chemotherapy, or a decrease in FAC less than 32%, or a decrease in RV- free wall global longitudinal

strain (GLS) less than 20%, was considered significant (23). It is worth mentioning that, to avoid any bias in the study due to variable dosages of anthracycline regimens, the study was conducted exclusively on patients with breast cancer. The analysis was carried out using SPSS Version 22 software (SPSS Inc., Chicago, IL). Quantitative data were reported as means (SD) and qualitative data were presented as frequencies and percentages. The normality of the data distribution was tested using the Shapiro-Wilk test. For data analysis, various inferential statistical methods were utilized, including repeated measures analysis, and the non-parametric Friedman test (given the non-normal nature of the data). P values less than 0.05 were considered statistically significant.

Results

Results demonstrated that the patient's age range was from 31 to 68 years, (52.49±8.78). The type of cancer in all study patients was breast cancer without metastatic. All patients received a dosage of 60 mg/m2 for the anthracycline regimen, and the administered dosage of cyclophosphamide was 600 mg/m2. This study revealed that the prevalence of patients with abnormal RV-free wall strain was initially 10 individuals (16.7%), both before treatment and 15 days after completion of the second treatment session. However, this proportion significantly increased to 22 (35.5%) individuals during the echocardiography examination conducted 15 days after the conclusion of the final treatment session. Statistically significant differences were observed in terms of abnormal RV-free wall strain across the different time points of echocardiography. Notably, there was a noteworthy rise in the number of patients exhibiting abnormal RV-free wall strain when the echocardiography was performed 15 days after completion of the final treatment session (P = 0.037).

Significant changes in RV-free wall strain were observed when examining echocardiographic variables at three distinct time points: prior to treatment, 15 days after completion of the second session, and 15 days following the conclusion of the final session. Notably, there was a consistent level of RV-free wall strain measured 15 days after completion of the second treatment session compared to the pre-treatment values. However, a statistically significant increase in RV-free wall strain was detected 15 days after completion of the final treatment session (P = 0.044, figure 1).

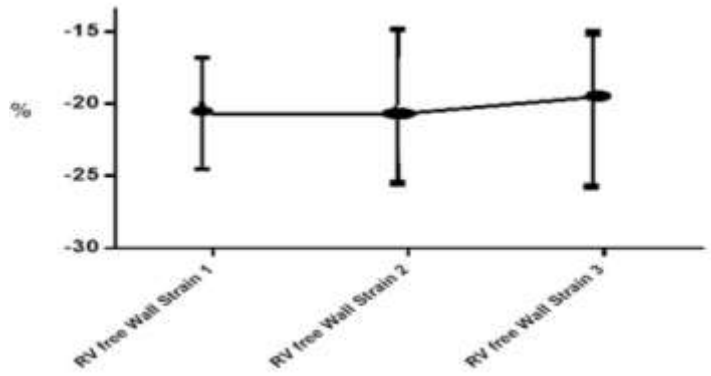

Figure 1. Trend of changes in RV- free wall strain over the different time points of echocardiography

- **RV: Right ventricular**
- **RV- free wall strain 1: Before the start of treatment**
- **RV- free wall strain 2: 15 days after completion of the second session**
- **RV - free wall strain 3: 15 days after completion of the final session**

In the examination of changes observed in echocardiography at three different time points (before the start of treatment, 15 days after the end of the second session, and 15 days after completion of the final session), statistically significant changes in tumor regression grade (TRG) over the different time points of echocardiography were reported. Specifically, there was a statistically significant increase in the measured TRG values 15 days after completion of the second treatment session compared to before treatment and a significant increase was also observed in TRG values 15 days after completion of the final treatment session (P = 0.003, figure 2).

The RVSP changes during echocardiography were reported to be statistically significant over time. Specifically, a significant increase was observed in the measured RVSP values 15 days after completion of the

second treatment session compared to before treatment, and also a significant increase in RVSP values 15 days after completion of the last treatment session was observed (P = 0.035). The number of patients with abnormal TAPSE before treatment was 2 individuals (2.3%). However, 15 days after completion of the second treatment session, none of the patients had abnormal TAPSE, and during the echocardiography performed 15 days after completion of the final treatment session, abnormal TAPSE was reported in 2 (2.3%) cases of the study patients. No statistically significant difference was observed regarding TAPSE (P = 0.112). Other echocardiographic variables examined (LVEF, E/E', LAVI, RVDD, RVS', RV FAC, RA area, and IVC size) were not observed to be abnormal at three different times of echocardiography. The variations in RV-free wall strain values are statistically significant at different measurements (P = 0.037). RV-free wall strain is considered abnormal when the values are less than 20 (table 1).

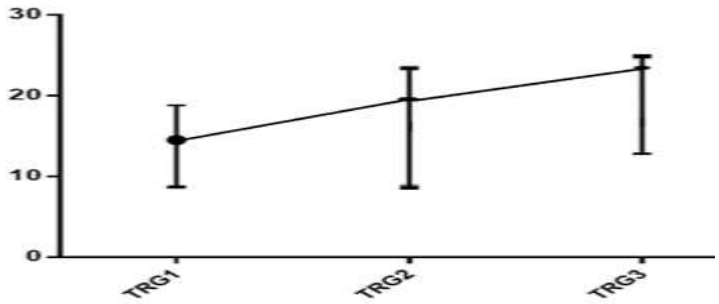

Figure 2. Trend of changes in TRG over the different time points of echocardiography

- **TRG: Tumor regression grade**
- **TRG1: Before the start of treatment**
- **TRG2: 15 days after completion of the second session**
- **TRG3: 15 days after completion of the final session**

Table 1. Changes in echocardiographic parameters at different measurements

Variables		Before the initiation of treatment	15 days after the end of the second session	15 days after the end of the final session	P-value
LVEF		60 (60-55)	60 (60-55)	60 (60-55)	*0.301
E/e'		1.2± 6.31	1.09±6.13	1.05±6.30	**0.461
LAVI		23 (26-19)	24 (25-20)	23 (24-20)	*0.762
TRG		15 (8-18)	20 (8-24)	26 (25-12)	*0.003
RVSP		20 (13-23)	25 (13-29)	29 (17-30)	*0.035
RVDD		32 (27-35)	34 (24-38)	32 (25-39)	*0.223
TAPSE		21 (23-15)	21 (23-19)	21 (23-15)	*0.112
RVS'		12 (13-9)	11 (12-10)	11 (13-11)	*0.091
RV FAC		51.22±6.61	50.19±7.37	8.04±50.03	**0.065
IVC size		10 (13-6)	13 (15-8)	15 (18-12)	*0.765
RA area		13 (15-11)	12 (14-11)	12 (13-12)	*0.249
RV- free Wall strain	Abnormal	10 (16.7)	10 (16.7)	22 (35.5)	***0.037
	Normal	62 (83.3)	62 (83.3)	50 (64.5)	

*Friedman Test ** Repeated Measures Method *** Cochran's Q Test

LVEF: Left ventricular ejection fraction, E/e: E over É ratio, LAV1: Left atrial volume index, TRG: Tricuspid regurgitate gradient, RVSP: Right ventricular systolic pressure, RVDD: Right ventricular diastolic diameter, TAPSE: Tricuspid annular plane systolic excursion, RVS: Right ventricular S' velocity, RV FAC: Right ventricular fractional area changes, IVC: Inferior vena cava, RV: Right ventricular

Correlation analysis between LVEF and RV- free wall strain did not reveal a statistically significant relationship between these two variables at any time point (P = 0.256, r = 0.03). The results of the correlation between LVEF and RV Free Wall Strain at different time points are presented in figure 3.

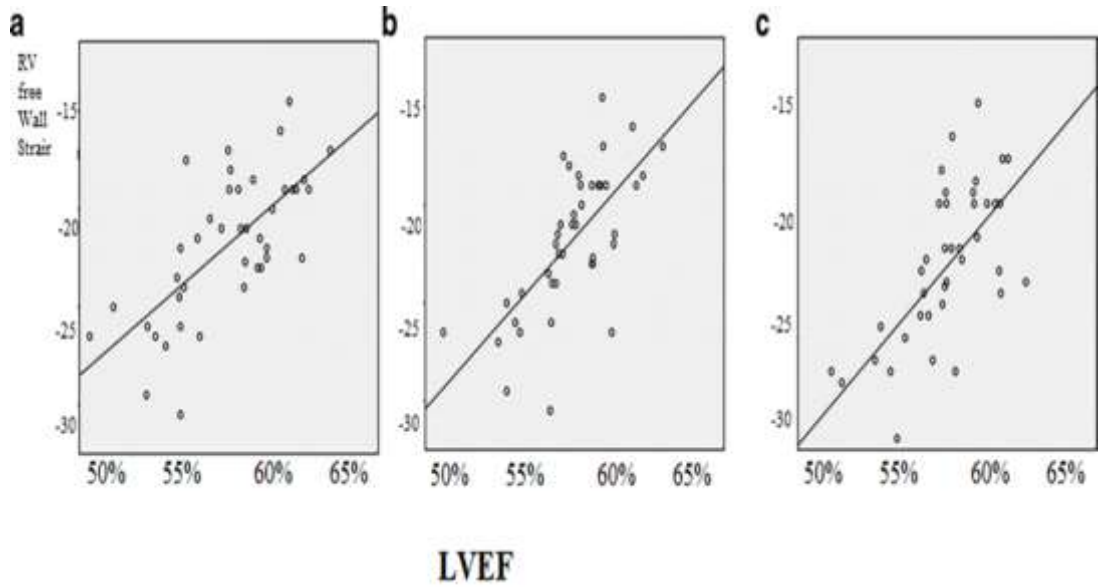

Figure 3. The relationship between LVEF and RV- free wall strain
LVEF: Left ventricular ejection fraction, RV: Right ventricular

Discussion

The aim of the investigation of this study was to evaluate the echocardiographic characteristics of the RV after administration of anthracycline-based chemotherapy. The results indicated that the measured values for RV-free wall strain were relatively stable 15 days after completion of the second session compared to the before treatment. However, a statistically significant decrease in RV-free wall strain was observed 15 days after completion of the final treatment session. The justification for abnormal strain in echocardiography before the start of chemotherapy may be related to the toxic effects and oxidative reactions resulting from cancer in the pulmonary circulation, ultimately leading to RV remodeling. Additionally, the measured value of the TRG variable increased at a 15-day interval from the completion of the second treatment session compared to before treatment. Furthermore, a statistically significant increase in the TRG value was observed 15 days after completion of the final treatment session. The justification for the elevated TRG may be associated with anemia, increased pulmonary pressure, loading conditions, and other factors. Chemotherapy with anthracyclines can cause heart failure years after treatment. This hidden toxicity can have significant clinical consequences. Previous researches have established the negative impact of anthracycline-based drugs on LV systolic and diastolic function. However, there is insufficient understanding regarding their effects on RV function (16-21). It is important to note that RV function is a robust prognostic indicator in patients with impaired LV systolic function and various LV pathologies. Assessment of RV function using conventional echocardiographic methods, as recommended in current multidisciplinary guidelines for diagnosing subclinical LV dysfunction, may provide evidence of RV cardiac toxicity (22). The results of previous studies show that anthracycline-based chemotherapy has demonstrated clinical and subclinical LV dysfunction in breast cancer patients. Our study reveals that anthracycline-based chemotherapy impairs both LV and RV functions in breast cancer patients (23). Studies have consistently reported the negative effects of anthracycline-based agents on LV systolic and diastolic function. However, the impact of these agents on RV function remains relatively understudied, and there is limited knowledge regarding their specific effects on the RV. More research is required to enhance our comprehension of the potential detrimental effects of anthracyclines on RV function and its clinical implications. Evaluating the LV using standard 2D echocardiography continues to be problematic due to its complex shape and dynamic function (24). The clinical significance of RA enlargement is that it may reflect RV dysfunction, and a significant association between right atrial enlargement and adverse clinical

outcomes. Among the various echocardiographic indices of RV function, RVFAC is the most common 2D method for evaluating RV performance. In patients with biventricular disease, this factor significantly increases the risk for heart failure (HF), sudden cardiac death (SCD), stroke, and mortality. However, changes in RVFAC might indicate late-stage RV dysfunction, similar to LVEF. In the context of cardiac toxicity resulting from cancer treatment, timely clinical detection of cardiac toxicity is paramount. It enables prompt adjustments in cancer treatment or optimization of cardiac function to mitigate potential adverse effects (25). Strain imaging was originally used to measure LV function. Studies in recent years have shown that it is appropriate to assess RV when RV function may be impaired. The strain has the potential to detect early and subclinical stages of myocardial dysfunction. In patients undergoing chemotherapy who are prone to changes in fluid status and weight during treatment, pressure assessment is less influenced by loading conditions (26). Echocardiography-based strain imaging of the RV is a potential method for clinical identification of cardiac toxicity during cancer therapy (27). Our study demonstrated that RVFAC and RV strain (in addition to LVEF) were affected by anthracycline-based chemotherapy. Previous histopathological studies have indicated that cardiac tends to be more conspicuous in the subendocardial region of the ventricular walls. Although data are limited, there is a suggestion that chemotherapy might exert a more significant impact on a thinner RV as opposed to a thicker LV. Future non-human studies with histopathological analysis, are needed to explore whether the RV is affected earlier than the LV, thereby supporting this hypothesis (26-35).

Boczar et al. utilized echocardiographic methods to follow 49 patients suffering from breast cancer undergoing anthracycline-based chemotherapy. They demonstrated a significant worsening of RV-free Wall Strain three months after the start of treatment (11). The study on 30 breast cancer patients showed significantly lower RV-free wall strain in patients treated with trastuzumab anthracycline compared to who had cancer before chemotherapy (36). Chang et al. recently reported that RV-free Wall Strain is an independent predictor of dyspnea in patients suffering from cancer undergoing chemotherapy, independent of LV and RV systolic and diastolic function (37). In this study, we selected patients only from two hospitals, therefore the results could only be generalized within this geographical range and population. In this study, the sample size was small and patients were not followed-up long-term, so analysis of data with risk factors was not possible. It is better to check Cardiac troponin I (CTNI) and B-type natriuretic peptide (BNP) besides echocardiography to confirm toxicity, which was not checked in this study due to high cost. Large prospective and long-term studies are required to validate the results. The future studies consider these limitations to obtain better results. In this study, it is concluded that the expected involvement of isolated RV by chemotherapy is noteworthy, and it is recommended that, during echocardiography, RV function should be assessed alongside LV function. This assessment should include advanced echocardiography techniques, including strain study, to detect RV dysfunction at the subclinical stage. Because there is currently a lack of sufficient information regarding treatment strategies for isolated RV failure in patients undergoing chemotherapy, it is suggested that these patients be jointly evaluated by a cardiologist and an oncologist for ongoing care. Additionally, considering the increasing proportion of patients treated with chemotherapy, clinics termed Cardio-Oncology clinics should be established to provide better service to these patients.

Acknowledgments

The authors would like to thank the authorities of Tabriz University of Medical Sciences and to all the patients who participated in this study.

Funding: This study was funded by the Tabriz University of Medical Sciences (IR>TBZMED>REC>1400.817).
Ethics approval: None declared.
Conflict of interests: None declared.
Authors' contribution: Kamran Mohammadi: Designed, directed the study and visiting patients. Mohammad Gertasi: Gathering data of patients, Data curation and performing echocardiography. Mortaza Raiise: Investigation, supervising and visiting patients. Asma Yosefzadeh: Contributed to leading study, writing manuscript and performing echocardiography. Haleh Bodagh: Contributed to performing echocardiography. Razieh Parizad: Performing statistical analyses, writing the manuscript. Writing–review and editing.

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