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Right ventricular free wall strain for detection of anthracycline induced cardiac toxicity

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Abstract

Anthracycline agents are routinely used for treatment of many types of malignancy, while imposing the risk for cardiotoxicity (AT-CMP). Although the right ventricle (RV) is more susceptible to cardiotoxicity, most of the studies have focused on left ventricle (LV) function for monitoring AT-CMP. In this study, we have focused on RV function before and after chemotherapy using two-dimensional speckle tracking Echocardiography. In this prospective study, newly diagnosed and untreated cancerous patients without previous cardiovascular diseases were enrolled. For all patients, baseline echocardiography was performed before the initiation of the anthracycline regimen and after 6 months of follow up when the chemotherapy was stopped. Several parameters of LV and RV function were measured using 3D echocardiography and STE techniques. 60 patients were enrolled in the study. There was a significant decrease ($P=0.001$) in RV fractional area change (53.57% ± 4.36 vs. 45.66% ± 6.19), RV Global longitudinal strain (GLS) (− 22.93% ± 1.95 vs. − 18.53 ± 2.75), and RV free wall strain (FWLS) (− 25.75% ± 3.01 VS. − 20.30 ± 3.78). There was a significant decline in LVEF (59.42 ± 6.36% vs. 51.1 ± 6.31%) and LV-GLS (− 21.1 ± 1.8% vs − 18.6 ± 2.6%) (both $P=0.001$) as well. Among the parameters changed following chemotherapy, RV-FWLS was dropped to a pathological level in 25% of patients showing the highest potential for detection of anthracyclines effect on the myocardium. Anthracycline therapy can induce subclinical RV dysfunction. In this clinical setting, RV free wall strain shows a great ability to exhibit deleterious effects of anthracyclines on the myocardium. This finding needs to be confirmed in future and larger studies.

Keywords Anthracycline · Cardiomyopathy · Toxicity · Speckle Tracking · Right ventricle

Abbreviations

AT-CMP	Anthracycline-induced cardiotoxicicity
RV	Right ventricle
LV	Left ventricle
2D-STE	Two-dimensional speckle tracking echocardiography
GLS	Global longitudinal strain
FWLS	Free wall strain
RV-FAC	Right ventricular fractional area change
STE	Speckled tracking echocardiography
2D-TTE	Two-dimensional transthoracic echocardiography
PMI	Point of maximal impulses
AFI	Automated functional imaging
RVFAC	Right ventricular fractional area change
RV LSFW	RV free wall longitudinal strain
ELISA	Enzyme-linked immunosorbent assay
RVEF	RV ejection fraction
CMR	Cardiac magnetic resonance
FAC	Fractional area change
TTE	Transthoracic echocardiography
TAPSE	Tricuspid annular plane systolic excursion
RVGLS	Right ventricular global longitudinal strain
LVEF	Left ventricular ejection fraction
LV-GLS	Left ventricular global longitudinal strain
RV-FWLS	Right ventricular free wall longitudinal strain

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Introduction

Anthracyclines are widely used in the treatment of solid tumors and hematologic malignancies. They can reduce the annual breast cancer mortality rate by 38% for women younger than 50 years and 20% for women aged 50 to 69 years [1]. Patients undergoing chemotherapy with these chemotherapeutic agents are at risk for cardiovascular complications such as cardiac dysfunction, myocardial ischemia, HTN, Thromboembolism, and arrhythmias [2]. With the rise of cancer survivors, the prevalence of chemotherapy-induced cardiotoxicity is growing [3]. Chronic cardiotoxicity event is more prevalent and can arise within the first year of completing treatment (early 1.6 to 2.1%) or several years beyond the first year of treatment (late/delayed—1.6 to 5%); it most frequently presents with a persistent cardiac dysfunction [4].

Many factors can increase the risk of Anthracycline-induced cardiotoxicicity (AT-CMP), including cumulative dosage, age, mediastinal irradiation or radiotherapy to the left chest, concomitant cardiovascular diseases, and previous exposure to any anthracycline [5]. Retrospective analysis in clinical trials of patients who had undergone anthracycline agent therapy showed that the incidence of cardiac dysfunction increased to 4.7% at a cumulative dose of 400 mg/m^2, 26% at cumulative doses of 550 mg/m^2, 48% at cumulative dose exceeding 600 mg/m^2, and 100% above 800 mg/m^2. However, subclinical cardiomyopathy may occur at lower cumulative doses [4].

Although several studies have reported the adverse effect of anthracycline agents on the left ventricular (LV) systolic and diastolic function, limited data exists on their effect on the right ventricular (RV) function. However, thinner structure of the RV and fewer myofibrils makes the right ventricle more susceptible to cardiotoxicity [6]. Other cardiovascular diseases with concomitant RV dysfunction are associated with a worse outcomes [7]. Consequently, monitoring RV function during chemotherapy with anthracyclines seems prudent.

Echocardiography is the most appropriate method for repeated evaluation of cardiac function changes because of availability, noninvasive nature, and lack of ionizing radiations [8]. The most commonly used two-dimensional method to assess RV function is the right ventricular fractional area change (RV-FAC) [9]. Speckled tracking echocardiography (STE) is a new method for evaluation of the myocardial strain rate in longitudinal, circumferential, and radial planes which can reveal subclinical abnormalities in the systolic and diastolic function of cardiac chambers [10]. Therefore, we conducted this cohort study to evaluate the RV function in patients undergoing anthracycline-based chemotherapy using echocardiography Speckled tracking echocardiography (STE) to monitor the RV functional changes during chemotherapy.

Methods

Study population

In this cohort study, 60 patients referred to Shahid Faghihi hospital who were supposed to be treated with anthracycline agents were enrolled. These patients were in the range of 30–70 years old and without any cardiovascular problems. The patients with a history of myocardial infarction, COPD, Valvular heart disease, congenital heart disease, previous CABG, pace-maker usage, and LV dysfunction were excluded from the study. All patients gave informed written consent. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences by approval number of IR.SUMS.MED.REC.1399.013 and is based on the declaration of Helsinki.

Study design and protocol

For all the patients, baseline echocardiography was performed before the initiation of the chemotherapeutic regimen and repeated 6 months later when the chemotherapy was stopped. Blood samples were obtained after completing the treatment course for determination of the troponin level. The function of both LV and RV was checked to find the correlation of RV changes with incidence of anthracycline cardiac toxicity (AT-CMP). AT-CMP was defined based on the definition by American society of echocardiography as either more than 10% drop in LVEF, 15% drop in GLS, LVEF drop below 50%, GLS drop below − 19%, or pathological rise in the troponin level [11].

Echocardiographic studies

For all patients, a baseline echocardiography study was done before the initiation of chemotherapy and a follow up after 6 months from first echocardiography when chemotherapy was finished. Two-dimensional transthoracic echocardiography (2D-TTE) was used to evaluate the patient's cardiac structure, LVEF, and Global Longitudinal Strain (GLS). All patients were imaged in the left lateral decubitus position, using the general electric E9 conventional echocardiography machine (GE, USA). The transducer was placed in the left midclavicular line in the 4 to 5th intercostal spaces, where the point of maximal impulses of the heart (PMI) was detected. An echo certified cardiologist blinded to the study analyzed all the echocardiograms. LVEF was calculated by the 2D-TTE probe from the apical 4-chamber view, using an automated 2D protocol method.

Speckle-tracking echocardiography was performed using the same machine; the displacement of the myocardial speckles in each spot was analyzed and tracked frame to frame. The longitudinal strain was assessed using automated functional imaging (AFI). The global longitudinal peak strain was automatically calculated as an averaged value of the peak longitudinal strain in all 3-image planes (apical 2- and 4-chamber and long-axis views) (Fig. 1).

The right ventricular end-diastolic and end-systolic areas were measured from the apical four-chamber view to calculate the right ventricular fractional area change (RVFAC) using following formula (Fig. 1):

$$\text{RVFAC}\ (\%) = (\text{RV end} - \text{diastolic area} - \text{RV end} - \text{systolic area})/\text{RV end} - \text{diastolic area} \times 100$$

RV free wall longitudinal strain (RV LSFW) was assessed by averaging basal, mid, and apical segments of RV lateral wall using Automated Functional Imaging (AFI). Global longitudinal strain was also measured automatically with the same method as the mean of basal, mid, and apical segments of the RV lateral wall and septum in four chamber views.

TAPSE was measured trough M-Mode using the distance between the end-diastolic to end- systolic point in apical four-chamber view by placing the cursor along the tricuspid lateral annulus. The tricuspid annular systolic velocity was measured using tissue Doppler. In this method, the sample volume placed at the tricuspid lateral annulus and Peak systolic (Sa) was calculated. The echocardiography was done by an authorized cardiologist who was blinded to all other parts of the study. The TTE was repeated six months later immediately after completion of chemotherapy course.

Serum biomarkers measurement

All the patients underwent measurement of highly sensitive troponin I measurement at baseline before staring

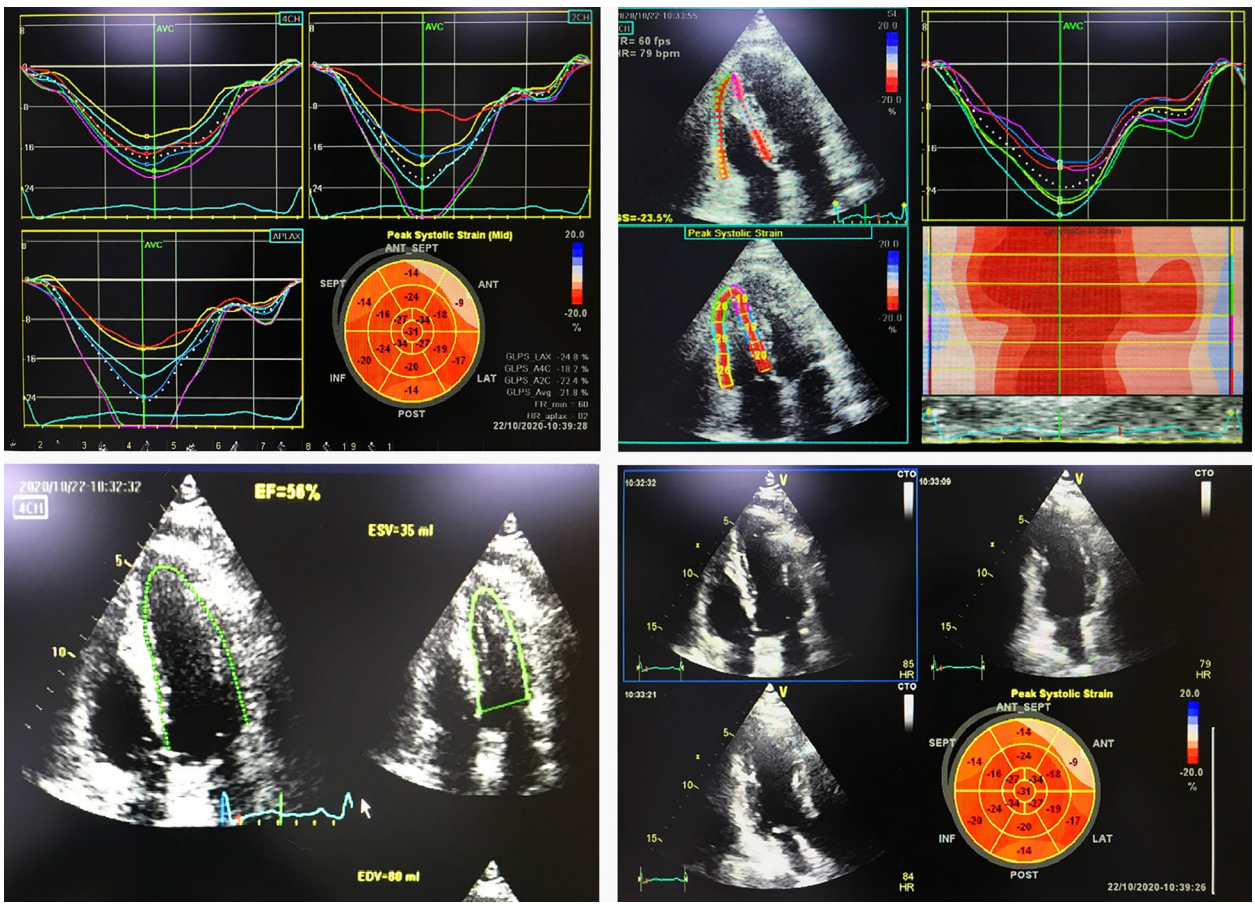

Fig. 1 Demonstration of echocardiographic assessment of the left and right ventricular global longitudinal strain and function

chemotherapy and after 6 months using enzyme-linked immunosorbent assay (ELISA) kits (bioassay technology laboratory, China). Serum samples were taken at the same session that echocardiographic studies are performed.

Statistical analysis

The analysis of the parametric data was shown by the mean and standard deviation. Qualitative and classified data were presented based on the number and percentage. Data were analyzed using SPSS (v.22. IBM Inc. IL). The normality Kolmogorov–Smirnov test was carried out to estimate whether continuous variables were normally distributed. Qualitative and classified data were presented based on the number and percentage and the univariate analysis on quantitative and qualitative data using Independent and paired samples' *t* test and Chi-square tests. The *P* value less than 0.05 was considered significant.

Result

Patients

The results of 60 patients were included in the final analysis. Other patients were excluded as they had a poor echo window, declined to perform the final echo examination, or referred for echocardiographic assessment during therapy with Herceptin, but not within the desired frame time. Baseline demographic data of the patients are presented in Table 1.

Table 1 Baseline demographic data

Variable	Data
Baseline malignancy	
Breast cancer	66.7%
Lymphoma	25%
Other cancers	12.5%
Anthracycline dosage	431.5 ± 125.7 mg
Age (years)	42.6 ± 12.4
Sex (Female)	66.7%
Baseline laboratory Data	
WBC count (n/dl)	8542 ± 4505
Hemoglobin (mg/ml)	12.53 ± 1.06
Platelet count (n/dl)	300,571 ± 103,542
Serum Creatinine.05 (mg/dl)	0.88 ± 0.13
Asparate aminotransferase level (AST)	23.43 ± 9.51
Alanine aminotransferase level (ALT)	25.86 ± 8.47

Serum troponin level

All the patients' baseline troponin level was undetectable (< 0.01 ng/ml). With chemotherapy, only two patients developed a troponin rise to a pathological level (> 0.4 ng/ml).

Development of anthracycline-induced cardiomyopathy

After 6 months of follow up, LVEF was dropped from 59.42 ± 6.36 to 51.1 ± 6.31% (D = 8.31 ± 7.6, $P = 0.001$) and LV-GLS was dropped from − 21.1 ± 1.8 to − 18.6 ± 2.6% (D = 2.4 ± 2.3, $P = 0.001$). In total, 12 patients developed cardiotoxicity during the period of the study.

RV function assessment

During the 6 months of therapy, the average RV fractional area change (RVFAC) decreased from 53.57% ± 4.36 at the first echocardiogram to 45.66% ± 6.19) on the follow-up echocardiogram ($P = 0.000$). The mean RV global strain decreased from − 22.93% ± 1.95 to − 18.53% ± 2.75 on the follow-up ($P = 0.000$). RV free wall longitudinal strain worsened from − 25.75% ± 3.01 to − 20.30% ± 3.78 ($P = 0.000$).

TAPSE significantly decreased after therapy ($P = 0.001$). Accordingly, it decreased from 24.66 ± 2.33 prior to the treatment course to 20.57 ± 2.11 after that. However, no significant changes were observed in the tricuspid systolic annular velocity after treatment (0.1195 ± 0.0.0149 to 0.1186 ± 0.0142 with a $P = 0.649$) (Table 2).

These variables were also assessed in patients who were in AT-CMP category according to the LV dysfunction and troponin rising (12 patients) that showed a significant decrease in FAC (54.33 to 44.91), RV GLS (− 23.11 to − 18.84), RVFWLS (− 25.69 to − 20.77), and TAPSE (25.16 to 20.25); however, RVs did not show a significant change (Table 2). Similarly, among the other patients who did not have AT-CMP, the variables were calculated for them, showing a significant decrease in all variables at the follow up echocardiography compared to baseline echocardiography except RVs (Table 2). Also, comparison of parameter changes before and after chemotherapy in patients with and without AT-CMP indicated no significant differences in RV FAC change, RVGLS change, RVFWLS change, TAPSE change and RV s' change (Table 2). Based on the global longitudinal strain change, before and after chemotherapy, 13 participants had pathological change in GLS and 15 of them had pathologic level in FWLS; while no patient's TAPSE, Sa' became under the cutoffs predetermined in the literature. (Table 3).

Table 2 Comparison of Echocardiography RV function parameters before and after chemotherapy

Parameter	Groups	Baseline	Follow up	Change	*P* Value
RV FAC	AT-CMP	54.33 ± 5.12	44.91 ± 7.68	9.41 ± 7.77	0.001
	No AT-CMP	52.55 ± 3.08	46.66 ± 3.60	5.88 ± 4.31	0.003
	P value			0.202	N/A
	Total	53.57 ± 4.36	45.66 ± 6.19	9.41 ± 7.77	0.000
RVGLS	AT-CMP	− 23.11 ± 1.92	− 18.84 ± 2.62	− 4.27 ± 2.28	0.000
	No AT-CMP	− 22.68 ± 2.09	18.13 ± 3.04	− 4.55 ± 4.10	0.010
	P value			0.843	N/A
	Total	− 22.93% ± 1.95	− 18.53 ± 2.75	− 4.27 ± 2.28	0.000
RVFWLS	AT-CMP	− 25.69 ± 3.32	− 20.77 ± 3.94	− 4.91 ± 2.96	0.000
	No AT-CMP	25.84 ± 2.71	19.66 ± 3.69	− 6.17 ± 4.84	0.005
	P value			0.503	N/A
	Total	− 25.75% ± 3.01	− 20.30 ± 3.78	− 4.91 ± 2.96	0.000
TAPSE	AT-CMP	25.16 ± 2.97	20.25 ± 2.22	4.91 ± 2.46	0.000
	No AT-CMP	24.00 ± 0.70	21.00 ± 2.00	3.00 ± 2.29	0.004
	P value			0.843	N/A
	Total	24.66 ± 2.33	20.57 ± 2.11	4.91 ± 2.46	0.000
RV s'	AT-CMP	0.11 ± 0.01	0.12 ± 0.01	0.001 ± 0.010	0.586
	No AT-CMP	0.12 ± 0.19	0.11 ± 0.15	0.004 ± 0.007	0.104
	P value			0.128	N/A
	Total	0.11 ± 0.01	0.11 ± 0.01	0.001 ± 0.010	0.649

AT-CMP anthracycline induce cardiomyopathy, *RV* Right ventricle, *TAPSE* tricuspid annular plane systolic excursion, *FAC* fractional area change, *GLS* global longitudinal strain, *FWLS* free wall strain

Table 3 Number of patients who developed with a pathological level of LV or RV function assessment parameters following anthracycline induced chemotherapy

	Number	Percent
RV FAC change into pathological level from baseline	1	1.7
RV GLS change into pathological level from baseline	13	21.6
RV free wall strain change into pathological level from baseline	15	25
TAPSE change into pathological level from baseline	0	0
RV s' change into pathological level from baseline	0	0
LV EF dropped below 50%	8	13.3
LV EF dropped more than 10%	9	15
LV GLS dropped below − 19%	9	15
LV GLS dropped more than 15%	4	6.6

RV right ventricle, *TAPSE* tricuspid annular plane systolic excursion, *FAC* fractional area change, *GLS* global longitudinal strain, *LV* left ventricle, *EF* ejection fraction

Discussion

In this prospective study, we demonstrated that anthracycline agents can cause an adverse effect on the right ventricular function, and the sensitivity of FAC and other conventional parameters such as TAPSE and Sa for the distinction of RV systolic dysfunction, based on the cutoffs predetermined in the literature, was significantly lower than using strain methods. We found that anthracycline-induced cardiac toxicity can be detected via the STE method in subclinical phase of RV dysfunction, and strain technique is the best diagnostic value in assessing the RV function in this setting.

Anthracyclines alter the ultrastructural configuration of the cardiomyocytes and may cause cellular apoptosis and necrosis. Invasive animal studies have indicated that anthracyclines impose global injuries extending to both left and right ventricles [12]. AT-CMP is characterized by impairment of both systolic and diastolic functions secondary to thinning of the ventricular walls with or without a dilated LV cavity. As development of advanced

heart failure has a very poor prognosis, early detection of cardiac injury has attracted the attention of many investigators as it might facilitate timely therapeutic measures to prevent cardiac injury. However, most of these studies have focused on LV function. Nevertheless, the incremental value of RV function over clinical risk factors and other parameters of LV dysfunction for predicting the outcome in patients with various cardiovascular pathologies has been shown in many studies [13]. Despite this fact, there have been few investigations into the effects of cancer chemotherapy on RV function, and remodeling and right ventricular (RV) dysfunction has not been considered in the definition of cardiotoxicity.

Echocardiography is the most appropriate method for the evaluation of cardiotoxicity because of availability, noninvasive nature, and lack of ionizing radiations [8]. Due to technical challenges of routine 2D echocardiography for accurate assessment of the complex crescent-shaped right ventricle, until recently, focused assessment of the right ventricular functions has been ignored. Among the conventional method of echocardiography, RV FAC is the most commonly used method to assess RV function [9]. It seems to be a strong predictor of heart failure, sudden death, stroke and mortality [14]. A study by Tanandi et al. on newly diagnosed breast cancer patients receiving cyclophosphamide + Adriamycin ± 5-fluorouracil revealed significant impairment in the RV systolic function even after the first chemotherapy cycle. RV diameter increased, whereas FAC decreased after the second chemotherapy cycle [15]. On the contrary, Belham et al. in their study on 23 patients, using Tei index, suggested that Low-dose Anthracycline administration was significantly associated with an adverse effect on LV function but does not affect the RV function [16]. However, RVFAC change might be the late manifestation of RV dysfunction [17], whereas early detection of subclinical cardiotoxicity is desirable for the optimization of timing of medical interventions to prevent frank cardiomyopathy. There are other indices of RV function such as TAPSE and RVs'. Both TAPSE and RVS are measured at the base of the RV free wall. These two echocardiographic indices are easy to perform and does not require complex calculation; also, evaluation is not complicated and time-consuming. These predictors also widely used in RV function evaluation. However, in our study, none of these parameters could identify subclinical RV dysfunction.

Introduction of advanced echocardiographic techniques such as three-dimensional TTE and strain imaging have improved our ability for accurate assessment of RV anatomy and function [18]. In a study, Zhao et al. used 3D TTE to describe the sequence of changes in RV size and function in lymphoma patients with lymphoma treated by doxorubicin-based chemotherapy. They found an increase in the RV end systolic and diastolic volumes, which was followed by a decrease in RV ejection fraction (RVEF). They noticed a simultaneous worsening in LV GLS, while there were no changes in the LV volume or EF, indicating that RV remodeling and functional impairment occurs before any changes in LVEF or LV volume. In other words, the right ventricle may be affected earlier than the left ventricle during chemotherapy with anthracyclines and this was not previously reported [19]. Our findings add the new data that more patients on anthracyclines develop with a decline in RV-FWLS than LV-GLS or an increase in the RV volume and reduction in the RV function. This raises the possibility of the RV strain imaging being more sensitive to detect myocardial injury with anthracyclines. In agreement with our findings, Boczar et al.'s study demonstrated that anthracycline-based chemotherapy decreased both FAC and RVFWLS. They also suggested that RVFWLS could be used as a marker in the diagnosis of subclinical dysfunction for the left ventricle [17]. It seems that STE echocardiography and strain imaging can reveal early stages of myocardial deterioration which are not evident on routine RV indices.

RV may conceivably be more prone to cytotoxic effect of anthracyclines than LV due to its morphological features and myofiber architecture. It is comprehensible that a thinner wall with fewer myocytes would be more susceptible to cytotoxicity anthracyclines than a thicker more muscular wall. In addition, the structure of the RV free wall is constructed predominantly by longitudinally arranged apex to base subendocardial fibers [20], and histological studies have revealed that the subendocardial myocardial fibers which produce the longitudinal shortening of the ventricles are among the most vulnerable parts of the ventricle to the toxic effects of chemotherapeutic agents [21]. Furthermore, contrary to the LV, RV lacks the mid-layer of circumferential fibers and, thus, cannot compensate for the loss of longitudinal shortening of the subendocardial fibers. Consequently, STE which can assess the longitudinal shortening of the myocardium may detect early alterations in the RV function. Our study provided new data to confirm such presumptions.

Our study had some limitations. First of all, longer follow ups are needed to see if these subclinical RV changes are going to change into a clinical problem in future and should be used as a screening method or not. In addition, this was a small single-center study. Consequently, the reproducibility and accuracy of our findings must be confirmed in larger and multicenter studies. Furthermore, our study was a single center investigation which limits its generalization ability. Also lacking a control group limited our ability to exclude confounding factors such as age, gender etc. Finally, it would be ideal to add cardiac magnetic resonance imaging (CMR), the reference standard for RV volume and function assessment to future studies. CMR can add information

about tissue characterization such as myocardial edema and inflammation and this may provide further insight into the underlying histopathological myocardial changes [22].

Conclusions

Our study confirms that anthracycline agents can affect the RV function. Speckle-tracking echocardiography is an appropriate technique to evaluate the RV function in patients undergoing anthracycline-based chemotherapy. In this clinical setting, RV free wall strain shows a great ability to exhibit deleterious effects of anthracyclines on the myocardium. Further studies are needed to confirm if our observed changes in the RV function would persist over time and can predict development of declines in the LVEF or incidence of heart failure more accurately than the current standard methods.

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Authors contributions AA and FA designed and conducted the study. FA and MK gathered the sample and made the follow ups and examinations. All authors helped providing the draft of manuscript and made critical revision on it. Also all accept the full responsibility for data and manuscript.

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Data availability Data are however available from the authors upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate This study was approved by the Ethics Committee of Shiraz University of Medical Sciences by approval number of IR.SUMS.MED.REC.1399.013 and is based on the declaration of Helsinki. All patients gave informed written consent.

Consent for publication Not applicable.

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