Journal of the Saudi Heart Association

Volume 34 | Issue 1 Article 8

2022

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Recommended Citation

Rasheed, Reham Selmy; El Sokkary, Hatem; El Amrosy, Mahmoud Zaki; El Setiha, Mohammed; and Salama, Mai Mohammed Abd EL Moneim (2022) "Role of Myocardial Strain Imaging by Echocardiography for the Early Detection of Anthracyclines-Induced Cardiotoxicity," *Journal of the Saudi Heart Association*: Vol. 34 : Iss. 1 , Article 8.
Available at: https://doi.org/10.37616/2212-5043.1296

ORIGINAL ARTICLE

Role of Myocardial Strain Imaging by Echocardiography for the Early Detection of Anthracyclines-Induced Cardiotoxicity

Reham Selmy Abo El Magd Rasheed*, Hatem Mohammed Fathy El Sokkary, Mahmoud Zaki El Amrosy, Mohammed El Sayd El Setiha, Mai Mohammed Abd EL Moneim Salama

[a] Cardiology Department, Tanta University Hospital, El Gharbia, Egypt

Summary

Objective: **To investigate the role of myocardial strain imaging by echocardiography is for detecting anthracycline-induced cardiotoxicity early.**

Patients and methods: **Fifty patients had transthoracic echocardiogram before, during, and after taking anthracyclines. GE Vivid E9 Ultrasound System was used for echocardiographic examination and myocardial strain imaging. All patients were assessed three times: on the first visit, before starting anthracycline medication; on the second visit, three months later; and on the third visit, six months later.**

Results: **Cardiotoxicity occurred in 4 patients at the end of the research. There was a statistically significant association between percentage change in global longitudinal strain (GLS) and ejection fraction (EF) at 3 months $p < 0.001$ and 6 months $p < 0.001$. Change in the GLS at 3 months and 6 months had a sensitivity and specificity of 100%, 95.65%, and 100%, 89.13% respectively. Using receiver operating characteristic curve (ROC) for change in GLS showed that Area Under a Curve (AUC) = 1.000, sensitivity, specificity, positive predictive value, and negative predictive value all equals 100%.**

Conclusion: **Strain echocardiographic examination using GLS is a good predictor for early detection of left ventricle dysfunction caused by anthracyclines chemotherapy.**

Keywords: Anthracyclines, Echocardiogram, Cardiotoxicity

1. Introduction

Over the last 20–30 years, the death rate among cancer patients has reduced by 21% and 12% in males and females, respectively, from 1991 [1]. Nonetheless, cancer therapy-induced heart toxicity (cardiotoxicity) has become a prominent survivors' source of morbidity and mortality. Patients who acquire heart failure because of cancer treatment have a death risk of up to 60% after two years [2,3].

The most frequent definition of cardiotoxicity is a 5% decline in symptomatic individuals' LVEF from baseline to LVEF <55% (or a 10% reduction in asymptomatic people). In the early phases of cardiotoxicity, cardiac imaging has been utilized to detect a reduction in LV function without signs or symptoms of the heart toxicity [4–8].

Chemotherapeutic medications including anthracyclines act by disrupting cancer cells' genes and preventing them from reproducing. Breast, gynecologic, sarcoma, and lymphoma are among the cancers

Received 20 January 2022; revised 12 February 2022; accepted 15 February 2022.
Available online 1 July 2022

* Corresponding author.
E-mail address: dr.rehamselmy@gmail.com (R.S. Abo El Magd Rasheed).

https://doi.org/10.37616/2212-5043.1296

treated with anthracyclines, particularly doxorubicin. The negative effects of anthracycline treatment on the cardiac muscle are well documented. Cardiotoxicity is induced by cardiac myocyte necrosis and apoptosis, after which myocardial fibrosis occurs [9].

Cardiotoxicity must be carefully considered during treatment, with an emphasis on early detection and intervention [2,3]. Although an endomyocardial biopsy is the current gold standard for detecting anthracycline-induced cardiomyopathy [10], It is ineffective as a first-line approach for detecting cardiotoxicity or serial monitoring [11]. The measurement of LVSF by echocardiography is the utmost popular non-invasive approach of monitoring myocardial toxicity, although it is insensitive for early diagnosis of subclinical cardiac illness [12].

For evaluating cardiotoxicity, myocardial strain, or the percent of myocardial thickening or distortion during the cardiac cycle, LVEF is less sensitive than strain rate [13,14]. These measurements can be used to assess cardiac mechanics on a multidimensional level (longitudinal, radial, and circumferential function). The longitudinal strain appears to be the most consistent, whereas the radial strain appears to be the most variable, with the added benefit of being able to detect minor regional function defects that do not affect global LVEF [15]. The global strain is defined as the average value of all the strain measurements. All strain parameters are impacted as the disease progresses [14].

The goal of the study was to analyze how useful myocardial strain imaging by echo is for detecting Anthracyclines-induced cardiotoxicity early.

2. Materials

A prospective observational study was conducted at Cardiology Department, Tanta University, from September 2018 to February 2019 and included Fifty patients who were planned to receive anthracyclines chemotherapy were included in the study.

2.1. Study approval

2.1.1. Ethics

Permission to perform this study and use the hospital facilities was acquired from Tanta University Research Ethics Committee, which is part of the Faculty of Medicine, Quality Assurance Unit.

2.1.2. consent

All patients provided their informed written consent after a thorough explanation of the study's benefits and risks.

Abbreviations list

abGLS	absolute reduction in GLS
BC	Breast cancer
ECG	Electrocardiogram
echo	echocardiogram
EF	Ejection fraction
GLS	Global longitudinal strain
ΔGLS	Percentage change in GLS
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVSF	Left ventricular systolic function
STE	Speckle tracking echocardiography

2.2. Inclusion criteria

All patients were presented with cancer (any type) requiring anthracyclines chemotherapy, with baseline LVEF >55%.

2.3. Exclusion criteria

Pregnant or breastfeeding women, patients who were receiving chemotherapeutic agents other than anthracyclines, patients with baseline LVEF <55%, patients with moderate to severe aortic or mitral valve disease, as well as those with an unstable cardiac condition such pericardial effusion. Also, the poor image quality was excluded.

3. Methods

The following procedures were performed on patients: Full history taking, Laboratory investigations, complete clinical examination, resting 12 leads ECG. Transthoracic echo to detect the underlying cardiac lesion and to assess EF and GLS. The GLS was calculated using apical views (four, two, and three chambers). Myocardial speckles were automatically traced on subsequent frames by tracing the endocardial borders on an end-systolic frame. Adequate tracking was verified and, if necessary, manually adjusted. The average of regional strains was used to calculate GLS. Between baseline and follow-up visits, the percent change in GLS (ΔGLS) and absolute reduction in GLS (abGLS) were computed. Two readers examined the LVEF and GLS data. The readers were blinded to each other's measures as well as the patient visit number.

All patients were assessed three times: on the first visit, before starting anthracycline medication; on the second visit, three months later; and on the third visit, six months later.

Table 1. Comparison between the three studied periods according to EF%.

EF%	Before (n = 50)	3 months (n = 50)	6 months (n = 50)	F	p
Min. – Max.	56.0–74.0	50.0–71.0	48.0–72.0	21.888*	<0.001*
Mean ± SD.	65.70 ± 4.88	64.10 ± 5.46	63.64 ± 6.09		
Median (IQR)	66.50 (62.0–70.0)	65.0 (60.0–70.0)	66.0 (60.0–68.0)		
Sig. bet. periods	$p_1 < 0.001$*,$p_2 < 0.001$*,$p_3 = 0.445$				

Fr: Friedman test, Sig. bet. periods was done using Post Hoc Test (Dunn's).
IQR: Inter quartile range SD: Standard deviation.
p: p value for comparing between the studied periods.
p_1: p value for comparing between before and 3 months.
p_2: p value for comparing between before and 6 months.
p_3: p value for comparing between 3 months and 6 months.
*: Statistically significant at $p \leq 0.05$.

3.1. Statistical analysis of the data

The IBM SPSS software package version 20.0 was used to analyze the data provided into the computer. The significance of the acquired results was determined at a 5% level.

4. Results

4.1. Regarding the demographic data and risk factors

There were 12 (24%) males and 38 (76%) females in the study. The participants ranged in age from 20

Table 2. Comparison between the three studied periods according to GLS%.

GLS%	Before (n = 50)	3 months (n = 50)	6 months (n = 50)	Fr	p
Min. – Max.	−25.0–−17.0	−22.50–−11.0	−22.0–−7.40	71.344*	<0.001*
Mean ± SD.	−19.57 ± 1.66	−18.20 ± 2.42	−17.84 ± 2.94		
Median (IQR)	−19.0 (-20.3–−18.2)	−18.30 (-19.8–−17.5)	−18.20 (-19.2–−17.3)		
Sig. bet. periods	$p_1 < 0.001$*,$p_2 < 0.001$*,$p_3 = 0.147$				

Fr: Friedman test, Sig. bet. periods was done using Post Hoc Test (Dunn's).
IQR: Inter quartile range SD: Standard deviation.
p: p value for comparing between the studied periods.
p_1: p value for comparing between before and 3 months.
p_2: p value for comparing between before and 6 months.
p_3: p value for comparing between 3 months and 6 months.
*: Statistically significant at $p \leq 0.05$.

Table 3. Agreement (sensitivity, specificity and accuracy) for Δ GLS at 3 and 6 months.

	EF 6 months				Sensitivity	Specificity	PPV	NPV	Accuracy
	Normal (>53) (n = 46)		Abnormal (≤53) (n = 4)						
	No	%	No	%					
Δ GLS 3 months									
Normal (<15)	44	95.7	0	0.0	100.0	95.65	66.67	100.0	96.0
Abnormal (≥15)	2	4.3	4	100.0					
χ^2 (^{FE}p)	31.884*(<0.001*)								
Δ GLS 6 months									
Normal (<15)	41	89.1	0	0.0	100.0	89.13	44.44	100.0	90.0
Abnormal (≥15)	5	10.9	4	100.0					
χ^2 (^{FE}p)	19.807*(<0.001*)								

χ^2: Chi square test FE: Fisher Exact.
p: p value for association between different categories.
*: Statistically significant at $p \leq 0.05$.
PPV: Positive predictive value.
NPV: Negative predictive value.

to 67 years old with a mean ± SD of 45.34 ± 12.11 years. Twelve patients (24%) had hypertension, five patients had diabetes (10%), seven patients were smokers (14%), five patients suffered from obesity (10%); their body mass index (BMI) ≥30kg/m2. The mean cumulative dose of anthracycline at the second visit was 203.50 ± 21.55 mg/m2 and at the third visit was 423.64 ± 32.33 mg/m^2.

The study subjects' oncological diagnosis revealed that 35 of them had breast cancer (BC) (70%), 13 patients had lymphoma (26%), one patient had sarcoma (2%), and one patient had leukemia (2%). The study's patients had never had chemotherapy or radiation before.

4.2. Two-Dimensional Echocardiographic Examination

Using 2D-TTE, cardiotoxicity detected by significant reduction in LVEF in 4 participants at the end of the trial (Table 1).

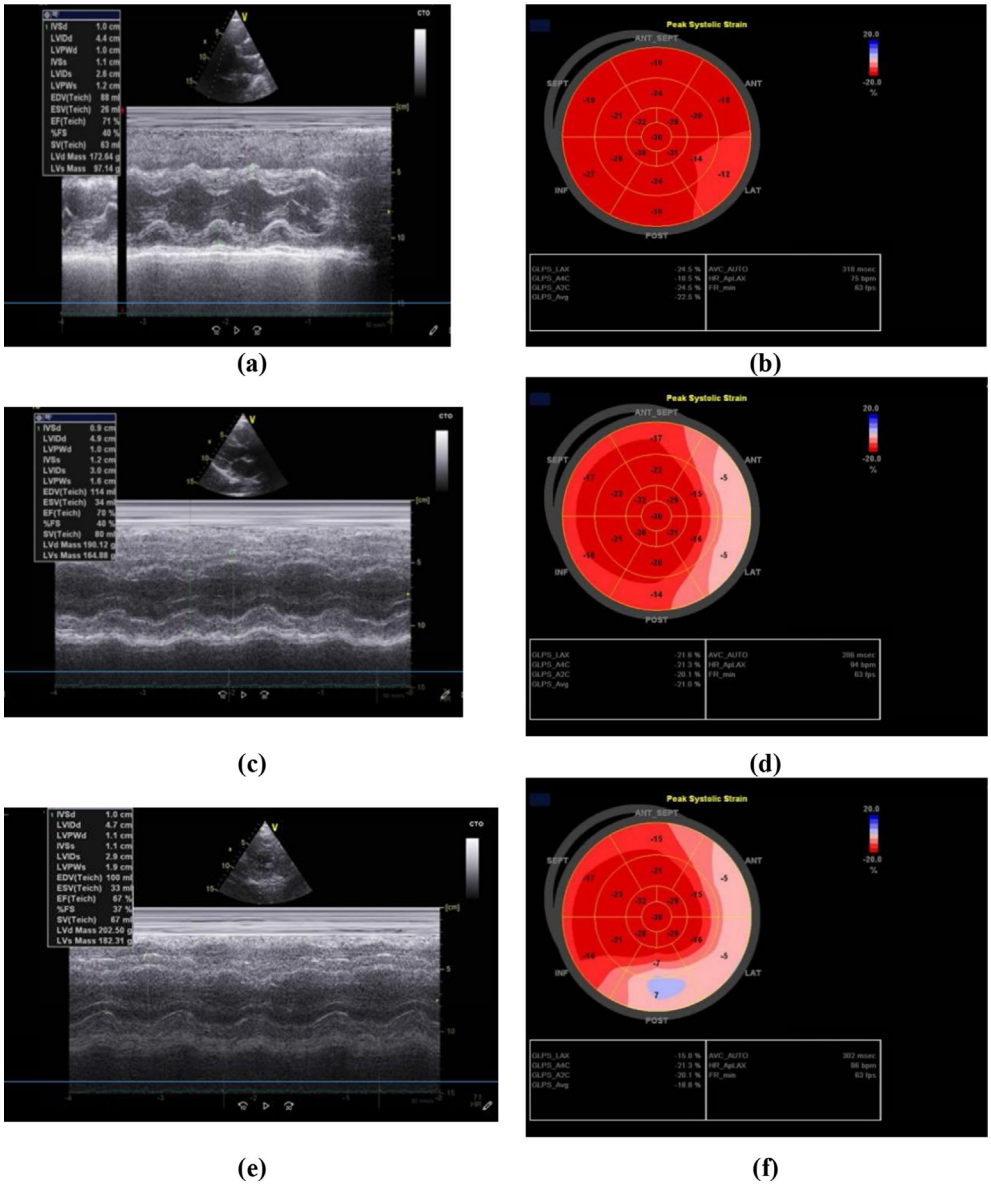

Fig. 1. Female patient aged 36 years, not known to be diabetic, not hypertensive, non-smoker, overweight with BMI=25 kg/m^2, not known to be cardiac, no thyroid or chest diseases, diagnosed as breast cancer. She was planned to receive doxorubicin. On the first visit (V1): ***(a, b):*** *baseline echocardiography showed no significant abnormal echo-doppler data, EF=71% and GLS=-22.5%. On the second visit (V2): she received 215 mg/m^2 of doxorubicin, only complaining of loss of appetite, echocardiographic examination* ***(c, d)*** *showed: EF=70% and GLS=-21% with AbGLS=1.5 and ΔGLS=6.7%. On the third visit (V3): the cumulative dose reached was 427 mg/m^2, echocardiographic examination* ***(e, f)*** *showed: EF=67% and GLS=-18.8%, AbGLS=3.7, ΔGLS=16.4% (Significant reduction in GLS or subclinical cardiotoxicity).* ***(a, c, e):*** *2D echocardiographic examination for assessment of LVEF by M-mode.* ***(B, D, F):*** *Strain echocardiography examination to measure GLS showing Bull's eye.*

Using strain echo, as a baseline, GLS measurements were taken at the first visit. The absolute reduction in GLS (AbGLS) and the percent change in GLS (ΔGLS) were calculated and tabulated during the second and third visits as shown in Table 2. At the second visit, 6 patients had a significant reduction, and 3 more cases had a significant reduction at the third visit. By the end of six months, nine patients had a significant decrease in GLS (Fig. 1), and four of the nine patients had experienced cardiotoxicity (Fig. 2). All of the four cases that progressed to anthracycline-induced cardiotoxicity revealed significantly decreased GLS (GLS≥15%) prior to the detection of significant reduction in EF evaluation by echo.

By Chi-square test, there was a statistically significant association between Δ GLS and EF as Δ GLS at 3 months' values were $\chi 2 = 31.884$ $p < 0.001$ (p-value for the association between different categories and statistically significant at $p \leq 0.05$) and Δ GLS at 6 months values were $\chi 2 = 19.807$ $p < 0.001$.

Calculation of sensitivity and specificity of Δ GLS at 3 and 6 months showed sensitivity and specificity of 100%, 95.6%, and 100%, 89.13%

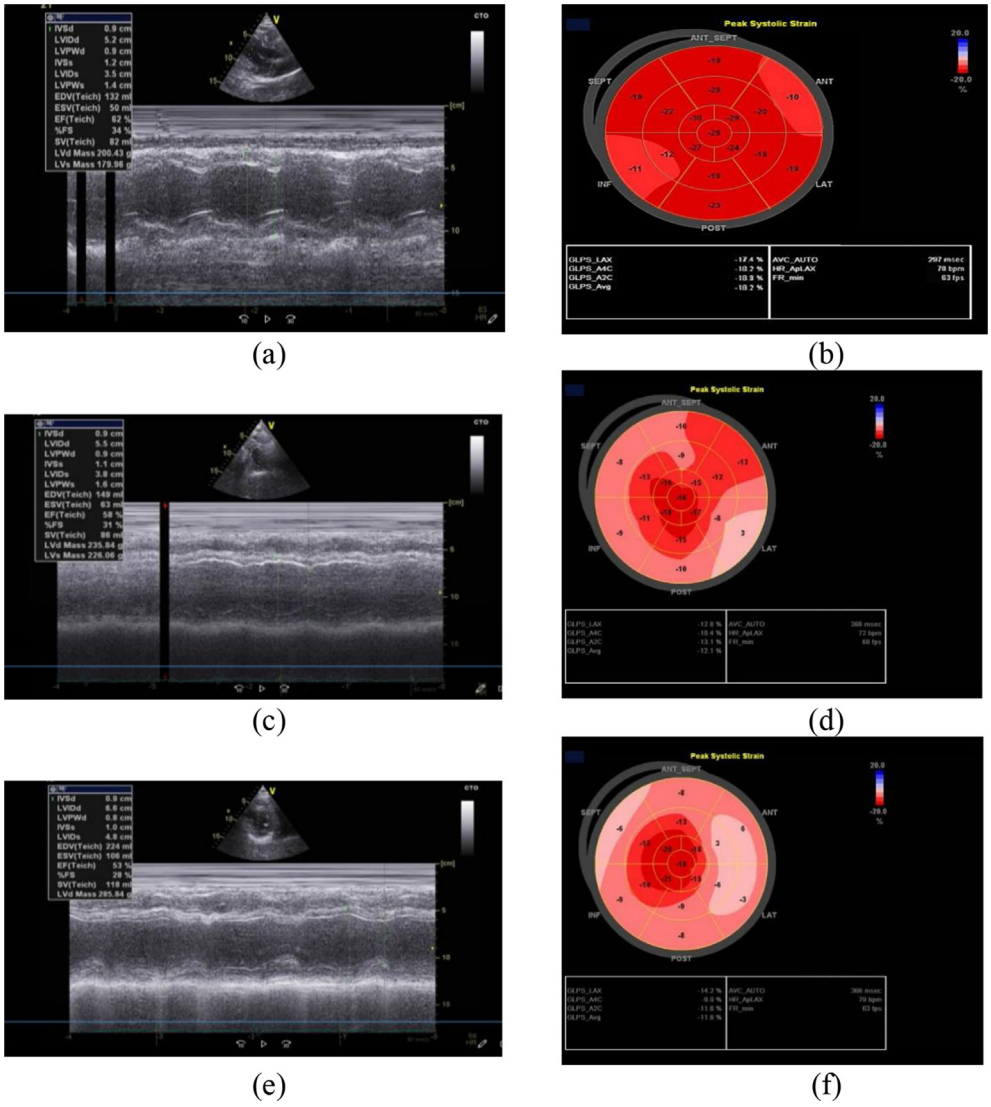

Fig. 2. Male patient aged 58 years, known to be hypertensive and smoker, not known to be diabetic or cardiac before, he denied having any thyroid or chest problems, He had average BMI=23kg/m^2 diagnosed as lymphoma. He was planned to receive doxorubicin. On the first visit (V1): ***(a, b):*** *baseline echocardiography showed no significant abnormal echo-doppler data, EF=62%, and GLS=-18.2%. On the second visit (V2): He received a cumulative dose of 276 mg/m^2, no complaint, Echocardiographic examination* ***(c, d)*** *showed: EF=58%, GLS=-12%, AbGLS= 6.2 and ΔGLS=34% (Subclinical cardiotoxicity). On the third visit (V3): Cumulative dose of doxorubicin= 457mg/m^2, complaining of dyspnea grade III, echocardiographic examination* ***(e, f)*** *showed: , Ef=53%, GLS=-11.6%, AbGLS=6.6 and ΔGLS=36.2% (Cardiotoxicity occurred).* ***(a, c, e):*** *2D echocardiographic examination for assessment of LVEF by M-mode.* ***(B, D, F):*** *Strain echocardiography examination to measure GLS showing Bull's eye.*

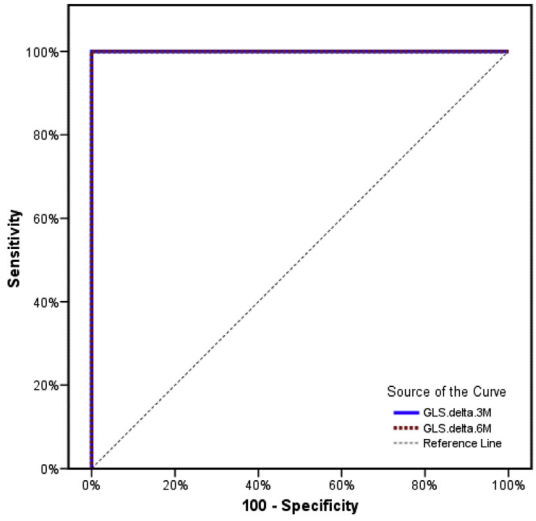

Fig. 3. ROC curve for Δ GLS to diagnose abnormal EF (n= 4).

respectively, suggesting that Δ GLS is a good predictor to diagnose LV affection by anthracyclines (Table 3).

Using receiver operating curve for Δ GLS before diagnosing abnormal EF (Fig. 3) showed that area under a curve = 1.000, sensitivity, specificity, positive predictive value, and negative predictive value all equals 100% (Table 4), proving the high efficiency of Δ GLS to predict Anthracyclines-induced cardiotoxicity.

5. Discussion

The use of 2D speckle tracking echo to measure myocardial strain has proven to be a sensitive technique for measuring ventricular function in patients with early myocardial illness [16].

The current study aimed to evaluate the myocardial strain imaging role by echo using GLS (GLS) in the early detection of anthracyclines-induced cardiotoxicity.

A total of 50 adult patients were included in the current study, with 12 males (24%) and 38 females (76%). In this study age range 20–67 years; mean age 45.34 years ± 12.11. Extreme older or younger age (<18 and >65 years) is considered as a risk factor.

In agreement with McGowan et al. [17], who reported that Cardiotoxicity develops over time based on the age of the patient at the time of exposure and the chemotherapy drug's class effect, with childhood cancer survivors facing an exponentially increasing risk of cardiovascular problems. Cardiovascular risk in elderly, on the other hand, appears sooner and is depending on the frequency of classic cardiac risk factors that coexist, particularly hypertension.

In the current study, twelve patients (24%) had hypertension; five patients (10%) had diabetes; seven patients (14%) were smokers; and five patients suffered from obesity (10%) (their BMI ≥30kg/m2). The mean cumulative dose of anthracycline at the second visit was 203.50 ± 21.55 mg/m2 and at the third visit was 423.64 ± 32.33 mg/m2.

This comes in agreement with a study by Ryberg et al. [18], who found that patients with risk factors for heart disease (such as obstructive pulmonary disease, hyperthyroidism, hypertension, diabetes, and obesity) had a three-fold higher incidence of toxicity to the heart, according to a 1097 BC patients' competing risks analysis. Also, Swain et al. [19], retrospective analysis showed that When the cumulative dose of doxorubicin approached 400 mg/m2, the risk of congestive heart failure was 2.25 fold higher in patients above 65 years old than in patients below 65 years old. Also, this study results agreed with Dogru et al. [20], in research that comprised 35 BC and 15 lymphoma patients who received anthracycline-based chemotherapy, the lymphoma cohort had significantly reduced EF and fractional shortening levels. They discovered a link between anthracycline dosage and the development of preclinical heart failure. On the contrary Gripp et al. [21], reported no relation between cardiotoxicity and the conventional risk factors.

In this study, all of the four cases that progressed to anthracycline-induced cardiotoxicity revealed significantly decreased GLS (GLS≥15%) prior to the detection of significant reduction in EF evaluation by echo, indicating that GLS is a good and early predictor of cardiotoxicity.

Similarly, Tang et al. [22] study provided a valuable insight into the value of 2D-speckle tracking

Table 4. Agreement (sensitivity, specificity) for Δ GLS to diagnose abnormal EF (n = 4).

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Δ GLS 3 months	1.000	<0.001*	1.0–1.0	>23	100.0	100.0	100.0	100.0
Δ GLS 6 months	1.000	<0.001*	1.0–1.0	>28.7	100.0	100.0	100.0	100.0

AUC: Area Under a Curve: p value: Probability value.
CI: Confidence Intervals.
NPV: Negative predictive value: PPV: Positive predictive value.
*: Statistically significant at p ≤ 0.05.

echo in the earlier diagnosis of cardiotoxicity caused by anthracycline treatment. Early worsening of LV global longitudinal and circumferential strain is caused by anthracycline therapy. In cancer patients, early changes in the GLS appear to be a good predictor of ventricular dysfunction. Also, Boyd et al. [23] demonstrated that GLS is more sensitive in detecting LV systolic subclinical impairment in the early stages of anthracycline therapy.

Also, in agreement with Santoro et al. [24], 2D GLS is superior to standard echo and presents a good practicability.

Also, Zito et al. [25], Dogru et al. [20], D Mohty et al. [26] and Laufer-Perl et al. [27] Poterucha et al. [28] and Kang et al. [29], concluded that the use of the use of GLS on a regular basis during treatment could lead to an early detection of cardiotoxicity.

This also with Negishi et al. [3] A study involved 159 people who started using anthracyclines, trastuzumab, or their combination as an aspect of their cancer treatment. The findings demonstrate that GLS could be utilized to identify cardiac performance deterioration in patients treated with anthracyclines, trastuzumab, or both.

Also, we agreed with a systematic review and meta-analysis done by Oikonomou et al. [30], the study comprised 1782 patients with cancer, such as BC, hematologic tumors, or sarcomas, who received anthracyclines with or without trastuzumab in 21 studies. Concluded that Deformation analysis using GLS can be utilized to detect early stages of subclinical ventricular dysfunction among cancer patients who are receiving possibly cardiotoxic treatment before progression to chemotherapy-induced cardiotoxicity. The predictive and discriminating performance of an active treatment absolute GLS value or a relative change from baseline seems to be comparable. GLS is now recommended for patients with hematological and solid tumors who are being cured with regimens based on anthracyclines combined or not combined trastuzumab.

This also in the same line with Gripp et al. [21] in a prospective and observational study of consecutive cases diagnosed with BC Having no history of anticancer therapy and no ventricular dysfunction, who received anthracycline and/or trastuzumab treatment. The study revealed that the LV GLS was a strong indicator of cardiotoxicity, with a high sensitivity for early detection.

On the other hand, Thavendiranathan et al. [31] stated that reduced myocardial distortion variables on echo are a marker of subclinical myocardial alterations caused by cancer treatment and occur prior to any LVEF decline as measured by standard 2D echo. Notably, early decrease in cardiac distortion seems to predict the occurrence of later cardiac toxicity, and the most reliable indicator being GLS assessed by speckle tracking echo (STE). STE is utilized to predict cardiac toxicity using GLS change criteria ranging from 10% to 15%. The low occurrence of cardiotoxicity in the individuals tested probably explains why these thresholds have a stronger negative predictive value than positive predictive value. Unfortunately, whereas distortion measures tend to discover preclinical myocardial alterations in survivors, their utility in forecasting LV dysfunction or failure of the heart muscle is uncertain.

5.1. Study Limitations

Our follow up period is relatively short.

6. Conclusion

The present study concluded that strain echocardiographic examination using GLS (GLS) is an excellent predictor for early diagnosis of left ventricular impairment caused by anthracycline treatment because GLS values were significantly reduced (ΔGLS $\geq$15%) in all cases before progression to anthracyclines-induced cardiotoxicity (significant reduction in EF values).

Author contribution

Conception and design of Study: RSAEMR, HMFES. Literature review: RSAEMR, HMFES, MZEA, MESES. Acquisition of data: RSAEMR, HMFES, MESES. Analysis and interpretation of data: RSAEMR, HMFES, MZEA. Research investigation and analysis: RSAEMR, HMFES, MESES. Data collection: RSAEMR, MZEA, MESES. Drafting of manuscript: RSAEMR, HMFES, MZEA, MESES. Revising and editing the manuscript critically for important intellectual contents: RSAEMR, HMFES, MZEA, MESES. Data preparation and presentation: RSAEMR, MZEA. Supervision of the research: RSAEMR, MESES. Research coordination and management: RSAEMR, MESES. Funding for the research: RSAEMR. Others: RSAEMR, HMFES, MZEA, MESES, MMAEMS.

Funding

None.

Conflict of interest

None.

References

[1] Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer. PLoS One 2010;5:e9584. https://doi.org/10.1371/journal.pone.0009584.

[2] Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet 2011;377:127–38. https://doi.org/10.1016/s0140-6736(10)62231-3.

[3] Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. Eur Heart J Cardiovasc Imaging 2014;15:324–31. https://doi.org/10.1093/ehjci/jet159.

[4] Khouri MG, Douglas PS, Mackey JR, Martin M, Scott JM, Scherrer-Crosbie M, et al. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues. Circulation 2012;126:2749–63. https://doi.org/10.1161/circulationaha.112.100560.

[5] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239. https://doi.org/10.1016/j.jacc.2013.05.019. 2013.

[6] Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol 2013;61:77–84. https://doi.org/10.1016/j.jacc.2012.09.035.

[7] Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213–20. https://doi.org/10.1016/j.jacc.2009.03.095.

[8] Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 2010;28:3910–6. https://doi.org/10.1200/jco.2009.27.3615.

[9] Csapo M, Lazar L. Chemotherapy-induced cardiotoxicity: pathophysiology and prevention. Clujul Med 2014;87:135–42. https://doi.org/10.15386/cjmed-339.

[10] Friedman MA, Bozdech MJ, Billingham ME, Rider AK. Doxorubicin cardiotoxicity. Serial endomyocardial biopsies and systolic time intervals. JAMA 1978;240:1603–6. https://doi.org/10.1001/jama.240.15.1603.

[11] Ewer MS, Ali MK, Mackay B, Wallace S, Valdivieso M, Legha SS, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol 1984;2:112–7. https://doi.org/10.1200/jco.1984.2.2.112.

[12] Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging 2018;11:260–74. https://doi.org/10.1016/j.jcmg.2017.11.017.

[13] Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst 2010;102:14–25. https://doi.org/10.1093/jnci/djp440.

[14] Biswas M, Sudhakar S, Nanda NC, Buckberg G, Pradhan M, Roomi AU, et al. Two- and three-dimensional speckle tracking echocardiography: clinical applications and future directions. Echocardiography 2013;30:88–105. https://doi.org/10.1111/echo.12079.

[15] Voigt JU, Arnold MF, Karlsson M, Hübbert L, Kukulski T, Hatle L, et al. Assessment of regional longitudinal myocardial strain rate derived from Doppler myocardial imaging indexes in normal and infarcted myocardium. J Am Soc Echocardiogr 2000;13:588–98. https://doi.org/10.1067/mje.2000.105631.

[16] Fine NM, Shah AA, Han IY, Yu Y, Hsiao JF, Koshino Y, et al. Left and right ventricular strain and strain rate measurement in normal adults using velocity vector imaging: an assessment of reference values and intersystem agreement. Int J Cardiovasc Imag 2013;29:571–80. https://doi.org/10.1007/s10554-012-0120-7.

[17] McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther 2017;31:63–75. https://doi.org/10.1007/s10557-016-6711-0.

[18] Ryberg M, Nielsen D, Cortese G, Nielsen G, Skovsgaard T, Andersen PK. New insight into epirubicin cardiac toxicity: competing risks analysis of 1097 breast cancer patients. J Natl Cancer Inst 2008;100:1058–67. https://doi.org/10.1093/jnci/djn206.

[19] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–79. https://doi.org/10.1002/cncr.11407.

[20] Dogru A, Cabuk D, Sahin T, Dolasik I, Temiz S, Uygun K. Evaluation of cardiotoxicity via speckle-tracking echocardiography in patients treated with anthracyclines. Onkologie 2013;36:712–6. https://doi.org/10.1159/000356850.

[21] Gripp EA, Oliveira GE, Feijó LA, Garcia MI, Xavier SS, Sousa AS. Global longitudinal strain accuracy for cardiotoxicity prediction in a cohort of breast cancer patients during anthracycline and/or trastuzumab treatment. Arq Bras Cardiol 2018;110:140–50. https://doi.org/10.5935/abc.20180021.

[22] Tang Q, Jiang Y, Xu Y, Xia H. Speckle tracking echocardiography predicts early subclinical anthracycline cardiotoxicity in patients with breast cancer. J Clin Ultrasound 2017;45:222–30. https://doi.org/10.1002/jcu.22434.

[23] Boyd A, Stoodley P, Richards D, Hui R, Harnett P, Vo K, et al. Anthracyclines induce early changes in left ventricular systolic and diastolic function: a single centre study. PLoS One 2017;12:e0175544. https://doi.org/10.1371/journal.pone.0175544.

[24] Santoro C, Arpino G, Esposito R, Lembo M, Paciolla I, Cardalesi C, et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. Eur Heart J Cardiovasc Imaging 2017;18:930–6. https://doi.org/10.1093/ehjci/jex033.

[25] Zito C, Manganaro R, Cusmà Piccione M, Madonna R, Monte I, Novo G, et al. Anthracyclines and regional myocardial damage in breast cancer patients. A multicentre study from the Working Group on Drug Cardiotoxicity and Cardioprotection, Italian Society of Cardiology (SIC). Eur Heart J Cardiovasc Imaging 2021;22:406–15. https://doi.org/10.1093/ehjci/jeaa339.

[26] Mohty D, Magne J, Aboyans V. Global longitudinal strain: mature for early detection of anthracyclines-induced cardiotoxicity? Eur Heart J Cardiovasc Imaging 2017;18:402–3. https://doi.org/10.1093/ehjci/jew310.

[27] Laufer-Perl M, Derakhshesh M, Milwidsky A, Mor L, Ravid D, Amrami N, et al. Usefulness of global longitudinal strain for early identification of subclinical left ventricular dysfunction in patients with active cancer. Am J Cardiol 2018;122:1784–9. https://doi.org/10.1016/j.amjcard.2018.08.019.

[28] Poterucha JT, Kutty S, Lindquist RK, Li L, Eidem BW. Changes in left ventricular longitudinal strain with anthracycline chemotherapy in adolescents precede subsequent decreased left ventricular ejection fraction. J Am Soc Echocardiogr 2012;25:733–40. https://doi.org/10.1016/j.echo.2012.04.007.

[29] Kang Y, Xiao F, Chen H, Wang W, Shen L, Zhao H, et al. Subclinical anthracycline-induced cardiotoxicity in the long - term follow-up of lymphoma survivors: a multi-layer speckle tracking analysis. Arq Bras Cardiol 2018;110:219–28. https://doi.org/10.5935/abc.20180042.

[30] Oikonomou EK, Kokkinidis DG, Kampaktsis PN, Amir EA, Marwick TH, Gupta D, et al. Assessment of prognostic value

of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. JAMA Cardiol 2019;4:1007−18. https://doi.org/10.1001/jamacardio.2019.2952.

[31] Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63:2751−68. https://doi.org/10.1016/j.jacc.2014.01.073.