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Original Article

Comparison of Conventional and Advanced Echocardiographic Techniques in Early Detection of Cardiotoxicity in Patients Undergoing Cancer Chemotherapy

HN Pradeep, George Rupesh, Thazhath J Anil[1], Krishnan Geethu, TG Jayakumar, S Khadar Abdul

Departments of Cardiology and [1]Medical Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India

Abstract

Context: The assessment of left ventricular ejection fraction (LVEF) is the most important component in prediction and detection of cardiotoxicity in patients undergoing cancer chemotherapy. LVEF may not be sensitive enough to pick the cardiotoxicity early since drop in LVEF occurs in the last and irreversible stage. A 10%–15% early reduction in global longitudinal strain (GLS) by speckle tracking echocardiography proposed to be the earliest indicator of myocardial dysfunction. **Aims:** The aim of this study was to compare the early detection of cardiotoxicity (at 0 and 3 months) using drop in LVEF with two-dimensional echocardiography (2DE), three-dimensional echocardiography (3DE), and GLS techniques. **Settings and Design:** This was a prospective cohort study of patients attending cardiooncology clinic in a tertiary care institute. **Subjects and Methods:** Newly diagnosed 75 cases of cancer of various etiologies, for whom cardiotoxic chemotherapy drugs has to be used, were included from January 2016 to June 2016. **Statistical Analysis Used:** Data were analyzed with Pearson's Chi-square test, mean, standard deviation, and 95% confidence interval. **Results:** A total of 17 (22.6%) subjects out of 75, had drop in LVEF by GLS (<−18.9%) as compared to 5 (6.6%) in 2DE and 7 (9.3%) in 3DE at 3 months with statistically significant *P* values (*P* = 0.0001). In the 17 subjects who had significant fall in GLS at 3 months, the mean GLS was −16.17 ± 1.55% with a significant reduction of 13.48% from baseline. **Conclusion:** Reduction in GLS preceded decrease in ejection fraction. Early detection allows modification of chemotherapeutic regimens and medical intervention preventing the irreversible cardiac damage.

Keywords: *Cardiotoxicity, chemotherapy, global longitudinal strain, left ventricular ejection fraction, speckle tracking echocardiography*

Introduction

The estimated cancer mortality has decreased worldwide over the past 20–30 years.[1,2] However, cardiotoxicity from cancer chemotherapy has become a leading cause of morbidity and mortality in cancer survivors.[3,4] Cardiac dysfunction resulting from exposure to cancer chemotherapeutics was first recognized in the 1960s, with the widespread introduction of anthracyclines.[5] The mortality rate is as high as 60% by 2 years for patients who develop heart failure (HF) from cancer chemotherapy.[6] Hence, careful consideration of potential cardiotoxicity during chemotherapy is necessary, with a focus on early detection and intervention.[7]

Several criteria have been proposed to define cardiotoxicity.[8] According to Cardiac Review and Evaluation Committee, cardiotoxicity is most commonly defined as ≥10% reduction in asymptomatic patients (or ≥ 5% reduction in symptomatic patients) in the left ventricular ejection fraction (LVEF) from baseline to an LVEF <55%.[9]

Modern chemotherapy agents direct against several molecular targets such as antiepidermal growth factor receptor (EGFR) signaling including antihuman epidermal growth factor receptor 2 (HER2), anti-EGFR1, antivascular endothelial growth factor (VEGF), antimammalian target of rapamycin, tyrosine kinase inhibitors, and antimesenchymal–epithelial transition.[10]

Antineoplastic drugs causing cancer therapeutics-related cardiac dysfunction (CTRCD) can be classified into Type I and Type II agents. Type I CTRCD is caused by anthracyclines (doxorubicin),

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Address for correspondence:
Dr. HN Pradeep, Department of Cardiology, Amala Institute of Medical Sciences, Amala Nagar, Thrissur - 680 555, Kerala, India.
E-mail: saipradeepvivek@gmail.com

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nonanthracyclines, and alkylating agents where dose-dependent irreversible cardiac dysfunction occurs due to generation of reactive oxygen species (ROS). It is mediated by topoisomerase-IIβ in cardiomyocytes through the formation of ternary complexes (topoisomerase-IIβ-ant hracycline-deoxyribonucleic acid). These complexes induce deoxyribonucleic acid double-strand breaks and transcriptome changes responsible for defective mitochondrial biogenesis and ROS formation.[11] Electron microscopy of myocardial biopsies shows varying degrees of myocyte damage, vacuolar swelling progressing to myofibrillar disarray, and ultimately cell death.[12] These agents are now considered to have increased potential for long-term cardiac dysfunction and increased morbidity and mortality.[13,14]

Type II CTRCD is caused by HER2 inhibitors (trastuzumab) and VEGF inhibitors where dose-independent reversible cardiac dysfunction occurs. These agents do not directly cause cell damage in a cumulative dose-dependent fashion. Combined anticancer therapy with Class I and II agents is associated with a higher than expected incidence of cardiac dysfunction.[15]

Echocardiography is the cornerstone in the cardiac imaging evaluation of patients during and after cancer therapy because of its wide availability, easy repeatability, versatility, lack of radiation exposure, and safety in patients with renal disease. It can be used for evaluation of left ventricle (LV), right ventricle dimensions, and systolic and diastolic function.[16]

Potential exposure to cardiotoxic chemotherapeutic agents is a well-recognized indication for baseline and longitudinal evaluation of LV function. The most commonly used parameter for monitoring LV function with echocardiography is LVEF.[17,18]

Historically, fractional shortening using linear measurements from M-mode echocardiography or two-dimensional echocardiography (2DE) was used as a surrogate marker of LVEF in the evaluation of oncological patients. The method of choice for LVEF calculation is the modified biplane Simpson's technique (method of disks) by 2DE as recommended by American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE).[19] The normal reference range for LVEF as recommended by ASE and EAE is ≥55%. LVEF in the range of 53%–73% should be classified as normal.[20] Different methods of LVEF measurements are used in various studies such as Teichholz, Simpson's biplane, and area-length method.[21]

LVEF calculated by conventional 2DE often fails to detect small changes in LV contractility because of factors such as LV geometric assumptions, inadequate visualization of the true LV apex, lack of consideration of subtle wall motion abnormalities, and inherent variability of the measurement.[22] LVEF has low sensitivity for the detection of small changes in LV function. 2DE appears to be reliable in the detection of differences close to 10% in LVEF.[23]

The use of LVEF has important limitations such as technique-related variability, which can be higher than the thresholds used to define cardiotoxicity.[24] Furthermore, the reduction in LVEF is often a late phenomenon, with failure to recover systolic function in up to 58% of patients despite intervention.[25]

Hence, strategies using newer echocardiographic techniques such as three-dimensional echocardiography (3DE) and speckle tracking echocardiography (STE)-derived global longitudinal strain (GLS) imaging is used for the early detection of subclinical LV systolic dysfunction.[26]

3DE is more accurate than 2DE for the measurement of LV volumes with improved accuracy (sensitivity - 53%; false negative rate - 47%) when compared to 2DE (sensitivity - 25%; false negative rate - 75%).[27] 3DE volume measurements are not conditioned by errors induced by geometric assumptions of LV shape, foreshortening of views, or uncontrolled orientation of apical two-chamber and four-chamber views that commonly affect the accuracy of 2DE. 3DE appears to be the technique of choice for monitoring the cardiac effects of chemotherapy.[28]

Markers of early myocardial changes with normal LVEF like the myocardial deformation indices (strain, strain rate [SR], and twist) are used for earlier detection of subclinical LV dysfunction in patients treated for cancer. Myocardial deformation can be measured during routine echocardiography, and its prognostic value has been demonstrated in several clinical trials.[29]

Strain is a dimensionless index reflecting the total deformation of the ventricular myocardium during a cardiac cycle as a percentage of its initial length (reported as percentage).[30] Negative strain implies shortening of a segment and positive strain as lengthening of a segment.[31] SR is the rate of deformation or stretch.[32] Both strain and SR can be measured in the longitudinal, radial, and circumferential directions.[29,32] A key advantage of strain or SR measurement is its ability to differentiate active versus passive movement within a myocardial segment, allowing for the analysis of regional myocardial deformation independent of the translational motion of the heart.[30]

The decrease in myocardial systolic function induced by anthracyclines appears to be extremely rapid as early as 2 h after the first anthracycline dose.[33] The decrease in myocardial deformation indices preceded the decrease in LVEF and persisted during the subsequent cancer chemotherapy. Early decrease in radial and longitudinal strain using STE has been confirmed with subjects treated with anthracyclines, with or without later decrease in LVEF.[34]

Normal ranges for GLS are defined as mean GLS of −19.7% and 95% confidence interval of −20.4% to −18.9%.[35] An early fall in GLS by STE between 10% and 15% predicts subsequent cardiotoxicity in both asymptomatic and symptomatic LV dysfunction patients.[34,36] This change in GLS between 10% and 15% appears to have the best specificity for predicting future cardiotoxicity.[30,35] The 95% confidence interval for the optimal GLS cutoff extends from 8.3% to 14.6%.[36] Tarr *et al*. believed that detecting myocardial dysfunction by GLS requires >3 months of follow-up.[37]

Subjects and Methods

This was a prospective cohort study of 75 subjects who were newly diagnosed with cancer of various etiologies and planned for cancer chemotherapy from January 2016 to June 2016 were included, after obtaining approval from the Institutional Ethical Committee. Subjects included were those attending the cardiooncology clinic of our hospital. Baseline 0 month and at the end of 3 months, 2DE, 3DE, and GLS were compared. GLS are measured in standard apical two-, three-, and four-chamber views and aortic valve closure is used for timing of end systole [Figure 1]. The same vendor (Philips EPIQ 7C) echocardiography was used for all measurements.

Informed consent was taken from the subjects before being admitted to the study. A detailed clinical examination, including vital parameters and anthropometry, was taken.

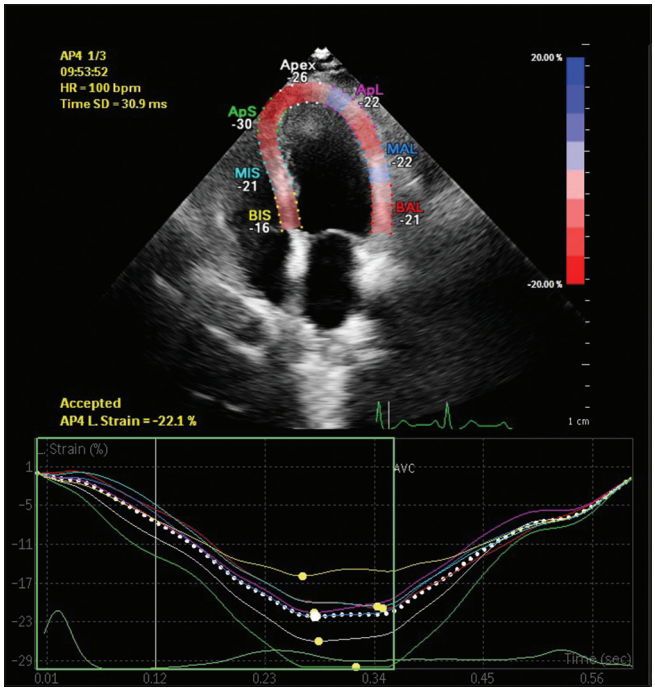


Figure 1: Speckle tracking echocardiography illustrating global longitudinal strain from the apical long-axis four-chamber-view, showing normal left ventricular segmental strain pattern. The color of each trace corresponds to anatomical points on the two-dimensional color image above. The white-dotted line represents average strain

The chemotherapy regimen, route, and dose of drugs were decided by the treating medical oncologist.

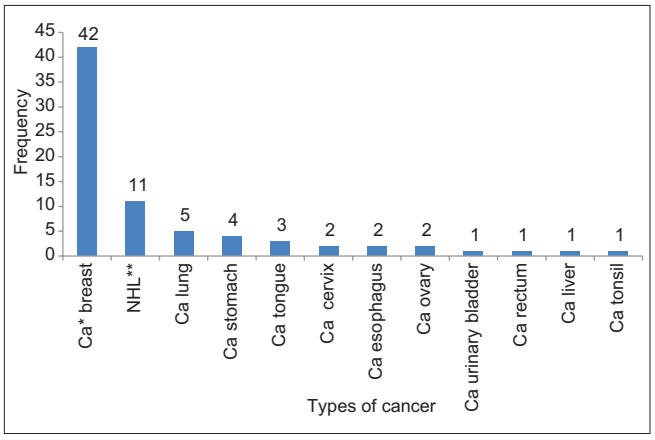
The most commonly used chemotherapy combination was intravenous three cycles of FAC (5 fluorouracil, adriamycin/doxorubicin, cyclophosphamide) and D (docetaxel). The chemotherapeutic doses were adjusted according to body weight and are as follows: 5 fluorouracil - 500 mg/m^2, doxorubicin - 50 mg/m^2, cyclophosphamide - 500 mg/m^2, and docetaxel - 90–100 mg/m^2.

Data were analyzed using Pearson's Chi-square test, mean, standard deviation, and 95% confidence interval. Demographic variables in categories were given in frequencies with their percentages. IBM SPSS Statistics 23 software, IBM Corporation, New York, United States was used to analyze the statistics. $P < 0.05$ was considered statistically significant.

Results

The mean age of the study population was 55.36 (±9.92) years. Of total 75 patients, 55 were female (73.3%) and 20 were male (26.7%). Most common cancer in the study population was breast cancer (n = 42, 56%), followed by non-Hodgkin's lymphoma (n = 11, 14.6%) [Bar Graph 1]. The most common chemotherapeutic agent used was intravenous FAC × 3 (5 fluorouracil, adriamycin/doxorubicin, cyclophosphamide) followed by D × 3 (docetaxel).

Of 75 subjects, 17 (22.6%) had a significant reduction in early myocardial deformation indices as measured by two-dimensional (2D) STE using GLS at the end of 3 months chemotherapy (GLS <−18.9%), when compared to 5 subjects (6.6%) who had decrease in LVEF (≤53%) in 2DE. The above P value was statistically significant (P = 0.0001) with sensitivity of 29%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 82.8%. At 0 month, 6 subjects (8%) of GLS and 1 subject (1.3%) of 2DE had drop in LVEF from the normal baseline values.



Bar Graph 1: Types of cancer (*Ca – Carcinoma; **NHL – Non-Hodgkin's lymphoma)

Furthermore, GLS as compared with 3DE had a significant reduction in GLS in 17 (22.6%) subjects when compared to 7 (9.3%) subjects in 3DE. The above *P* value was statistically significant ($P = 0.0001$), with sensitivity of 41.8%, specificity of 100%, PPV of 100%, and NPV of 85.2%. At 0 month, 6 subjects (8%) of GLS and 4 subjects (5.3%) of 3DE had drop in LVEF from the normal baseline values.

Of 17 subjects who had a significant reduction in GLS at the end of 3 month cancer chemotherapy, 11 subjects (64.7%) had received anthracycline-based chemotherapy.

The mean GLS at the end of 3 months' chemotherapy in the total 75 subjects was −20.60 ± 3.22% when compared to the baseline 0 month GLS of −22.41 ± 2.96% [Table 1]. There was a reduction of 8.07% GLS from the baseline. In the 17 subjects who had a significant fall in GLS at 3 months, the mean GLS was −16.17 ± 1.55% when compared to the 0-month GLS of −18.69 ± 2.25 with a significant reduction of 13.48% from baseline [Table 2]. A "bull's eye" plot of strain values for each of the 17 myocardial segments gives better reproducibility and higher availability for detection of early cardiotoxicity [Figure 2].

There was a significant effect of gender on GLS with lower values seen in males when compared to female subjects at both baseline and 3 months. Mean GLS at 3 months for males and females was −18.57 ± 3.52% and −21.28 ± 2.86%, respectively [Tables 3 and 4].

The cardiotoxicity rate detected by GLS at 3 months was 22.66% when compared 9.3% with 3DE and 6.6% with 2DE.

Discussion

The mean age of study population was 55.36 ± 9.9 years which were comparable with other studies using advanced myocardial mechanics such as strain imaging to study cancer chemotherapy. The studies of Motoki *et al*., Cadeddu *et al*., and Mantovani *et al*. had mean age group of 58 ± 11, 56 ± 13, and 59 ± 14 years, respectively.[38-40] The percentage of women in the study population was 73.3% which was comparable with studies of Cadeddu *et al*. and Mantovani *et al*., where the percentages were 76% and 74%, respectively.[39,40]

The most common cancer chemotherapeutic agent used was anthracycline analogs such as adriamycin (doxorubicin) in 49 subjects (65.3%) of the total 75 subjects, followed by

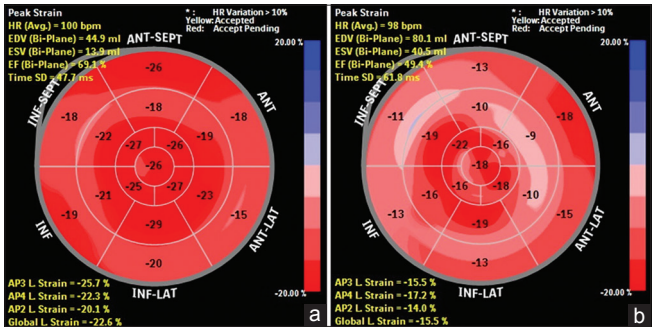


Figure 2: (a) Prechemotherapy bull's eye plot in our patient showing global longitudinal strain values of the 17 myocardial segments with baseline global longitudinal strain of −22.6%, three-dimensional left ventricular ejection fraction of 66%, and two-dimensional left ventricular ejection fraction of 60%. (b) Three months following chemotherapy in the same patient bull's eye plot showed global longitudinal strain of −15.5% (global longitudinal strain fell by 31.4%, indicating significant cardiotoxicity), three-dimensional left ventricular ejection fraction of 50%, and two-dimensional left ventricular ejection fraction of 55% (two-dimensional left ventricular ejection fraction fell by 5% and not significant)

Table 1: Comparison between 0-month and 3-month two-dimensional left ventricular ejection fraction, three-dimensional left ventricular ejection fraction, and global longitudinal strain

	2D mean±2SD (%)	3D mean±2SD (%)	GLS mean±2SD (%)
0 month	67.49±5.43	58.85±7.23	−22.41±2.96
3 month	62.41±7.60	54.93±6.44	−20.60±3.22

2D – Two-dimensional; 3D – Three-dimensional; GLS – Global longitudinal strain; SD – Standard deviation

Table 2: Percentage reduction in global longitudinal strain at 3 months when compared to 0 month

Significant GLS fall	Mean±2SD		Percentage reduction
	0 month GLS (%)	3 month GLS (%)	
Yes (*n*=17)	−18.69±2.25	−16.17±1.55	13.48
No (*n*=58)	−23.51±2.08	−21.90±2.28	6.84
Total (*n*=75)	−22.41±2.96	−20.60±3.22	8.07

GLS – Global longitudinal strain; SD – Standard deviation

Table 3: Comparison between 0-month two-dimensional left ventricular ejection fraction, three-dimensional left ventricular ejection fraction, and global longitudinal strain

	2D mean±2SD (%)	3D mean±2SD (%)	GLS mean±2SD (%)
Female	68.52±4.58	60.25±6.24	−23.18±2.50
Male	64.65±6.92	54.95±8.43	−20.3±3.14
Total	67.49±5.43	58.85±7.23	−22.41±2.96

GLSL – Global longitudinal strain; SD – Standard deviation; 2D – Two-dimensional; 3D – Three-dimensional

Table 4: Comparison between 3-month two-dimensional, left ventricular ejection fraction, three-dimensional left ventricular ejection fraction, and global longitudinal strain

	2D mean±2SD (%)	3D mean±2SD (%)	GLS mean±2SD (%)
Female	63.63±6.87	56.23±5.79	−21.28±2.86
Male	59.05±8.64	51.35±6.93	−18.57±3.52
Total	62.41±7.60	54.93±6.44	−20.57±3.26

2D – Two-dimensional; 3D – Three-dimensional; GLS – Global longitudinal strain; SD – Standard deviation

epirubicin in 6 (8%) subjects and the HER 2 monoclonal antibody, trastuzumab in 5 (6.6%) subjects, respectively. Furthermore, the study of cancer chemotherapy done by Baratta *et al*. had doxorubicin in 58% and trastuzumab in 22% subjects.[41] Another study done by Stoodley *et al*. had doxorubicin in 77% and epirubicin in 23% subjects.[42]

The pre- and post-chemotherapy GLS at 0 month and 3 months were −22.41 ± 2.96% and −20.60 ± 3.22%, respectively. Similarly, studies done by Baratta *et al*. and Sawaya *et al*. had pre- and post-chemotherapy GLS at 0 month (−20.3 ± 2.7%, −21 ± 2%) and 3 months (−18.9 ± 2.5%, −19.2 ± 2%), respectively.[41,43]

The percentage reduction of GLS was 8.07% from baseline at 3 months in the total 75 study subjects. While the percentage reduction was 13.48% in 17 subjects (22.6%) who had a significant reduction in GLS at 3 months when compared to the baseline. Negishi *et al*. have proposed the strongest predictor of CTRCD was GLS at 6 months. An 11% reduction of GLS was the optimal cutoff, with sensitivity of 65%, specificity of 94%, and 95% confidence interval of 8.3%–14.6%, respectively. In the same study, it was concluded that reduction of GLS <8% compared with the baseline appears not to be clinically meaningful, whereas >15% reduction appears to be of clinical significance.[36] Reductions in myocardial deformation parameters such as GLS are a sign of subclinical myocardial changes from cancer therapy and occur before any change in LVEF as assessed by conventional 2DE.[30]

The cardiotoxicity rate was 22.66% which was seen in 17 subjects by GLS method at 3 months following chemotherapy. Similarly, the cardiotoxicity rate was 19.4% and 21% in the studies conducted by Baratta *et al*. and Sawaya *et al*., respectively.[41,43]

The mean normal GLS at baseline was lower in men when compared to women with values being −20.3 ± 3.14% and −23.18 ± 2.50%, respectively. The study of Kocabay *et al*. reported a mean GLS of −20.7 ± 2% for men and −22.1 ± 1.8% for women, respectively.[44] These values were comparable with our study results. Furthermore, the Japanese Ultrasound Speckle Tracking of the Left Ventricle study showed lower GLS values for men when compared to women.[45]

Limitations of the study include the small sample size and shorter follow-up period. The 2D LVEF was measured by Teichholz method while the recommended method was Simpson's method which could have still predicted better drop in LVEF. Biomarkers such as troponins and N-terminal pro brain type natriuretic peptide which could detect subclincal LV dysfunction was not used in our study.

Conclusion

Myocardial deformation indices such as GLS are the optimal parameter to be used for early detection of subclinical LV dysfunction in cancer chemotherapy subjects. GLS is favored because of a lack of angle dependency and better reproducibility. The GLS measurements during chemotherapy should be compared with the baseline value. A relative percentage reduction of GLS >15% from the baseline is very likely to be abnormal and predicts subsequent cardiotoxicity including asymptomatic and symptomatic LV dysfunction. Early detection of decline in GLS helps subjects to be benefitted from cardioprotective therapy and modification of chemotherapeutic regimen.

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Conflicts of interest

There are no conflicts of interest.

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