ORIGINAL ARTICLE

Detection of subclinical left ventricular systolic dysfunction by echocardiography in patients receiving anthracyclines: A prospective cohort study

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ABSTRACT

Objective: Early cardiac structural and functional changes after chemotherapy are significant challenges when treating cancer patients. The aim of this study is the early detection of sub-clinical myocardial systolic depressed functions by echocartography among patients receiving anthracyclines (postoperative chemotherapy).

Methods: Early picking up subclinical left ventricular systolic dysfunction by echocardiography (TTE) among patients who had been treated with anthracycline chemotherapy 18 and 3 months before. The study included eighty patients. We reported measurements of left ventricular ejection fractions (LVEF), fractional shortening (FS), mitral annular plane systolic excursion (MAPSE) and global longitudinal strain (GLS). Pre-chemotherapy 3, 6 and 18 months after complete doses of anthracyclines were mearsured.

Results: This current prospective cohort study included 80 patients: 8 men (10%), 72 women (90%), with a mean age of 51.95 $\pm$ 13.69 years. Number of cycles ranged between 4 and 6 cycles of one of the anthracyclines. Mean heart rate was 76 beats/ minute, mean systolic blood pressure was 118, and mean diastolic blood pressure was 77.5 mmHg. The mean baseline FS was 32.40% $\pm$ 5.11%, which significantly decreased to 29.45% $\pm$ 5.78% and 26.75% $\pm$ 6.85% after 3 and 18 months, respectively. Mean three-dimensional echocardiography measures ejection fraction (3D-EF): Baseline was 61.08% $\pm$ 3.62% which was significantly depressed to 58.30% $\pm$ 5.54% after 3 months. The mean baseline MAPSE was 13.35 $\pm$ 1.35 mm, but it was reduced to 12.69 $\pm$ 1.92 mm and 12.60 $\pm$ 2.46 mm after 3 and 6 months, respectively. Mean baseline GLS was –17.62 $\pm$ 1.32% but reduced to –16.54 $\pm$ 2.42%, –15.35 $\pm$ 2.64% after 3 and 6 months respectively. By univariate analysis, significant parameters that showed abnormal outcome after 18 months were: gender, ejection fraction (EF), end-diastolic volume of the left ventricle (EDV), end-systolic volume of the left ventricle (ESV), 3D-EF (%), but by multivariate analysis, only EF (%) was significantly correlated with the outcome.

Conclusions: Evaluation of myocardial deformation and functional capacity improved early sub-clinical diagnosis of chemotherapy-induced cardiac toxicity. GLS and MAPSE are much more sensitive as predictors for early deterioration of left ventricular functions.

Key Words: Anthracycline chemotherapy, Chemotherapy-induced cardio toxicity, Echocardiographic parameters sensitive to subclinical dysfunction, Subclinical left ventricular systolic dysfunction

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1. INTRODUCTION

Oncologists have begun to decrease the cumulative dose in chemotherapeutic protocols; however, chemotherapy-induced cardiac toxicity is frequently detectable.[1] Cardiotoxicity is defined as a value of ejection fraction < 55%.[2] Prevention is the most effective line of management for chemotherapy-induced cardiotoxicity. Thus, trials for cardioprotection focus on the early detection of left ventricular impairment. Investigators concluded that it is insufficient to clinically detect myocardial injury.[3] Early accurate assessment is essential to improve management and get a better prognosis.

High-risk patients are those who:

- Receive high-dose anthracyclines;
- High-dose radiation therapy;
- Low-dose anthracycline combined with a low-dose radiotherapy;
- Age older than 60 years at cancer diagnosis;
- Compromised cardiac function, multiple cardiovascular risk factors including smoking, hypertension, hyperlipidemia, and/or obesity.[4]

The aim of this study is the early detection of sub-clinical myocardial systolic impairment by echocardiography among patients treated with anthracyclines.

Study question:

What is the additional value of different available echocardiographic parameters for early detection of sub-clinical left ventricular (LV) systolic injury denoting tetracycline-induced cardio-toxicity?

Study hypothesis:

A combination of different echocardiographic patterns (e.g., speckle-tracking echocardiography [STE]) could be beneficial for the early detection of sub-clinical left ventricular impaired functions among tetracycline-treated patients with malignant lesions before evident left ventricular impaired functions. We can detect impaired functions with standard and advanced 2D or 3D echocardiographic techniques. Early detection can be of great benefit as preventive measures and specific lines of treatment can reverse the toxic effects.

2. METHODS

2.1 Patient population

This study includes 80 consecutive patients with cancer.

Inclusion criteria:

1) Receiving anthracyclin chemotherapy; 2) At the Chemotherapy Unit in Suez Canal University Hospitals or the Oncology Hospital in Ismailia; 3) Between 1st July 2022 and 30th June 2024.

Exclusion criteria:

1) Patients with ischemic cardiac events; 2) Previous cardiac surgery for coronary revascularization; 3) Patients with heart failure; 4) Patients with cardiomyopathy; 5) Patients with heart block; 6) Those with pacemakers; 7) Patients with attacks of life-threatening arrhythmia.

Sample size: We calculated the sample size according to the following Equation 1:

$$N = (\frac{Z}{D})^{2p(1-p)} \tag{1}$$

Calculated number = 76 patients. We added 4 patients for possible interrupted evaluation of 4 or less patients. Thus, the study included 80 patients.

2.2 Measurement of left ventricular ejection fractions with trans-thoracic echocardiography

M-mode: Teichholz method dividing stroke volume (SV) in the LV outflow tract (LVOT) by LV end-diastolic volume (LVEDV).

American College of Cardiology (ACC) classification: 1) Hyperdynamic: left ventricular ejection fractions (LVEF) > 70%; 2) Normal: LVEF 50% to 70%; 3) Mild; 4) Moderate; 5) Severe impairment of cardiac function: LVEF less than 30%.

Mitral annular plane systolic excursion (MAPSE): M-mode echocardiography in apical 4-chamber view also measures MAPSE. Mean value for MAPSE of > 10 mm is correlated with preserved EF ($\geq$ 55%), and values < 8 mm correlate with reduced EF (< 50%)

Global longitudinal strain (GLS): A measurement of deformation that is used to assess LV systolic function. A measurement of deformation that is used to assess LV systolic function (see Equation 2).

$$Strain = \frac{(Lt - Lo)}{Lo}(\%) \tag{2}$$

Lt is the length at time *T*, Lo is the length at time 0.

GLS is assessed by speckle tracking; the specific methodology varies by vendor. Peak GLS describes the relative length-change between end-diastole and end-systole. Normal LV systolic function was defined as GLS > 18%–20%. Borderline LV systolic function was defined as GLS = 17%–18%; Impaired LV systolic function: GLS < 16 %.[1] GLS < 16% (sic) is abnormal, GLS > 18% (sic) is normal, and GLS 16% to 18% is borderline (see Table 1).

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Table 1. Distribution of the cases studied according to demographic data and Echocardiographic data (n = 80)

	No.	%
Gender		
Male	8	10.0
Female	72	90.0
Age (years)		
Min–Max	32.0–74.0	
Mean ± SD	51.95 ± 13.69	
Type of Ca	**No.**	**%**
Breast Cancer & lung metastasis	66	82.5
Lymphomas	14	17.5

	Univariate		Multivariate
	p	**OR (LL–UL 95% CI)**	***p***
Sex: (male)	< .001*	24.0 (4.125 – 1.640)	.992
Age (years)	.056	0.955 (0.911–1.001)	.997
EF (%)	< .001*	0.687 (0.569–0.828)	.993
EDV (mL)	<.001*	1.106 (1.048–1.168)	1.000
ESV (mL)	.001*	1.114 (1.043–1.190)	.999
FS (%)	.987	–	–
MV peak E (cm/s)	.139	1.070 (0.978–1.171)	–
MV peak A (cm/s)	.314	1.025 (0.977–1.075)	.995
3D-EF (%)	.014*	0.888 (0.808–0.976)	–
MAPSE (mm)	.986	–	
GLS (%)	.992	–	
S wave velocity (cm/s)	.987	–	
LVS/LVPW	.991	–	
No. of cycles			
4 Doxorubicin	.999	–	
5 Doxorubicin	.064	0.226 (0.047–1.092)	
6 Doxorubicin	.921	1.067 (0.297–3.836)	
5 Epirubicin	.824	1.208 (228–6.416)	
6 Epirubicin	< .001*	24.0 (4.125–139.640)	

Note. * = Statistically significant at $p \leqslant .05$; EF = Ejection fraction; EDV = End-diastolic volume of the left ventricle; ESV = End-systolic volume of the left ventricle; FS = Fractional shortening; MV = Mitral valve; 3D-EF = Three-dimensional echocardiography measures ejection fraction; MAPSE = Mitral valve annular prolapse systolic excursion; GLS = Global longitudinal strain; LVS = Left ventricular septum; LVPW = Left ventricular posterior wall

2.3 Ethical considerations

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Suez Canal University, and Hospital of Oncology in Ismailia.

2.4 Statistical analysis of the data

We fed the data to the computer and analyzed it using the IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). We described qualitative data using numbers and percentages. We used the Kolmogorov-Smirnov test to verify the normality of the distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and inter-quartile range (IQR). Significance of the results obtained was judged at the 5% level. We used the following statistical tests:

1) Cochran's test and Post Hoc Test used for pairwise; 2) ANOVA; 3) Paired t-test; 4) Friedman test used for abnormally distributed quantitative variables.

3. Results

This current prospective cohort study included 80 patients: 8 men (10%), 72 women (90%), with a mean age of 51.95 ± 13.69 years. Type of malignancy: breast cancer or lymphomas (see Table 1). Number of cycles: 13% of cases had 4-cycle doxorubicin, 38% had 5-cycle doxorubicin, 27% had 6-cycle doxorubicin, 13% had 5-cycle epirubicin, and 10% had 6-cycle epirubicin.

Mean heart rate was 76.02, and mean systolic/diastolic blood pressure was 118/77.5 mmHg. The mean baseline FS was 32.40% ± 5.11%, which was significantly decreased to 29.45% ± 5.78% and 26.75% ± 6.85% after 3 and 6 months, respectively.

The mean three-dimensional echocardiography measures ejection fraction (3D-EF) baseline was 61.08% ± 3.62%, which was significantly reduced to 58.30% ± 5.54% after 3 months.

The mean baseline MAPSE was 13.35 ± 1.35 mm, which significantly decreased to 12.69 ± 1.92 mm and 12.60 ± 2.46 mm after 3 and 6 months, respectively.

The mean baseline GLS was –17.62% ± 1.32%, which significantly increased to –16.54% ± 2.42% and –15.35% ± 2.64% after 3 and 6 months, respectively (see Table 2).

Table 2. Comparison between the three periods studied according to different parameters

	Baseline (n = 80)	3 months (n = 80)	18 months (n = 80)	p
EF (%)	61.98 ± 3.91	58.75 ± 5.38	55.88 ± 8.29	< .001*
Sig. bet. *p*eriods	p_1 < .001*, p_2 < .001*, p_3 = .002*			
EDV (mL)	83.25 ± 18.22	83.10 ± 17.67	85.25 ± 17.83	< .001*
Sig. bet. *p*eriods	p_1 = .048*, p_2 < .001*, p_3 = .003*			
ESV (mL)	32.73 ± 8.79	33.80 ± 9.0	35.80 ± 9.31	< .001*
Sig. bet. *p*eriods	p_1 = .874, p_2 < .001*, p_3 < .001*			
FS (%)	32.40 ± 5.11	29.45 ± 5.78	26.75 ± 6.85	< .001*
Sig. bet. *p*eriods	p_1 = .001*, p_2 < .001*, p_3 = .001*			
MV *p*eak E (cm/s)	64.23 ± 6.96	60.53 ± 7.61	60.23 ± 6.86	< .001*
Sig. bet. *p*eriods	p_1 < .001*, p_2 < .001*, p_3 = 1.000			
MV *p*eak A (cm/s)	57.98 ± 11.26	64.30 ± 12.25	–	< .001*
MV E/A	0.88 ± 0.15	0.87 ± 0.09	0.87 ± 0.08	.361
3D-EF (%)	61.08 ± 3.62	58.30 ± 5.54	–	< .001*
MA*P*SE (mm)	13.35 ± 1.35	12.69 ± 1.92	12.60 ± 2.46	.026*
GLS (%)	–17.62 ± 1.32	–16.54 ± 2.42	–15.35 ± 2.64	< .001*
LVS/LV*P*W	0.81 ± 0.03	0.82 ± 0.04	0.82 ± 0.05	.009*

Note. IQR = Inter quartile range; SD = Standard deviation; F = F test (ANOVA) with re*p*eated measures; Sig. bet. *P*eriods were done using Post Hoc Test (Bonferroni); Fr = Friedman test, Sig. bet. Periods were done using Post Hoc Test (Dunn's); p = p value for comparing between the three studied periods; p_1: p value for comparing between Baseline and 3 months; p_2 = p value for comparing between Baseline and 6 months; p_3 = p value for comparing between 3 months and 18 months; * = Statistically significant at $p \leq .05$

Table 3. Univariate and multivariate Logistic regression analysis for the parameters affecting abnormal results at 18 months

	Univariate		Multivariate#	
	p	OR (LL–UL 95% CI)	p	OR (LL–UL 95% CI)
Gender (male)	< .001*	24.0 (4.125–139.640)	.514	0.038 (0.0–696.852)
Age (years)	.056	0.955 (0.911–1.001)		
EF (%)	< .001*	0.687 (0.569–0.828)	.003*	0.679 (0.527–0.874)
EDV (mL)	< .001*	1.106 (1.048–1.168)	.292	1.089 (0.929–1.278)
ESV (mL)	.001*	1.114 (1.043–1.190)	.572	0.947 (0.785–1.143)
FS (%)	.987	–		
MV peak E (cm/s)	.139	1.070 (0.978–1.171)		
MV peak A (cm/s)	.314	1.025 (0.977–1.075)		
3D-EF (%)	.014*	0.888 (0.808–0.976)	.189	1.150 (0.934–1.416)
MAPSE (mm)	.986	–		
GLS (%)	.992	–		
S wave velocity (cm/s)	.987	–		
LVS/LVPW	.991	–		
S.I > 20 PY	.997	–		

Note. OR = Odd's ratio; CI = Confidence interval; LL = Lower limit; UL = Upper limit; EF = Ejection fraction; EDV = End-diastolic volume of the left ventricle; ESV = End-systolic volume of the left ventricle; FS = Fractional shortening; MV = Mitral valve; 3D-EF = Three-dimensional echocardiography measures ejection fraction; MAPSE = Mitral valve annular prolapse systolic excursion; GLS = Global longitudinal strain; LVS = Left ventricular septum; LVPW = Left ventricular posterior wall; #All variables with p < .05 were included in the multivariate; *Statistically significant at $p \leqslant .05$

Univariate analysis revealed a significant abnormal outcome after 18 months, specifically regarding gender, EF, EDV, ESV, and 3D-EF (%). By multivariate analysis, only EF (%) correlates significantly with the outcome (see Table 3).

Significant depression of left ventricular systolic function was evident in 8 patients (10%). During the analysis of the trans-thoracic echocardiographic parameters, the significant reduction in outcome became less evident in the nearly nor-

mal outcome of the remaining 90% of patients.

4. DISCUSSION

Chemotherapy-induced cardio-toxicity and its early diagnosis are the stimuli behind the rapid evolution of cancer therapies and the echocardiographic patterns for assessment of the left ventricular systolic functions.

The mean baseline EF was 61.98 ± 3.91, which significantly decreased to 58.75 ± 5.38 and 55.88 ± 8.29 after 3 and 6 months, respectively. The mean 3D-EF (%) baseline was 61.08 ± 3.62, which significantly decreased to 58.30 ± 5.54 after 3 months. Additionally, we found that the Mean baseline EDV (mL) was 83.25 ± 18.22, which significantly changed after 3 months to 83.10 ± 17.67. However, after 18 months, it increased significantly to 85.25 ± 17.83. The mean baseline ESV (mL) was 32.73 ± 8.79, which did not change significantly after 3 months (33.80 ± 9.0). However, after 6 months, it increased significantly to 35.80 ± 9.31. Similarly, Sadeq IA et al.[5] measured LVEF before and after anthracycline chemotherapy. Mean LVEF before intake of chemotherapy was 64% ± 5% and three months.

The European Society of Cardiology and the Canadian Cardiovascular Consensus Statement recommend serial imaging for calculating LVEF, with 3D-echocardiography being the best approach for assessing LVEF after chemotherapy.[6]

We also found that the Mean baseline FS (%) was 32.40 ± 5.11, which significantly decreased to 29.45 ± 5.78, 26.75 ± 6.85 after 3, 6, and 18 months, respectively. Regarding tissue Doppler imaging, the mean baseline MV peak E (cm/s) was 64.23 ± 6.96, which significantly decreased to 60.53 ± 7.61 and 60.23 ± 6.86 after 3 and 6 months, respectively. Mean baseline MV peak A (cm/s) was 57.98 ± 11.26, which significantly increased to 64.30 ± 12.25 after 3 months. The mean baseline MV E/A was 0.88 ± 0.15, which changed to 0.87 ± 0.09 and 0.87 ± 0.08 after 3 and 6 months, respectively, with insignificant differences.

Puzzovivo A et al.[7] observed a significant increase in the LV-end diastolic volume, LV-end systolic volume, and SV. This result may reflect an effective compensatory mechanism to anthracycline-induced cardiotoxicity. In these patients, the administration of anthracycline may represent the trigger for stimulating compensatory mechanisms to maintain SV.

Regarding the mean baseline MAPSE (mm), it was 13.35 ± 1.35, which significantly decreased to 12.69 ± 1.92 and 12.60 ± 2.46 after 3 and 6 months, respectively. MAPSE is one of the parameters used to quantify long-axis LV systolic function and to predict sub-clinical changes in LV systolic function in patients receiving anthracycline chemotherapy. Sadeq IA et al.[5] highlight the sensitivity of MAPSE to early changes in LV systolic function with 9% relative reduction in MAPSE.[8] A similar study showed the same result that mitral annular plane systolic excursion can be used as a sensitive tool to detect early longitudinal LV systolic dysfunction.

The mean baseline GLS (%) was –17.62 ± 1.32, which significantly increased to –16.54 ± 2.42 and –15.35 ± 2.64 after 3 and 18 months, respectively. In agreement with our result. Planek MI et al.[9] showed that during the mean follow-up period from pre- to post-doxorubicin therapy, there was a significant reduction in mean GLS ($p \leq .01$).

By univariate analysis, significant parameters showing abnormal outcome after 6 months were gender, EF, end-diastolic volume of the left ventricle (EDV), end-systolic folume of the left ventricle (ESV) and 3D-EF%, but by multivariate analysis, only EF (%) is significantly correlated with the outcome.

Pre-chemotherapy GLS is an effective parameter for risk stratification of cardio-toxicity in patients with a baseline LVEF between 50% and 59%.[10] Additionally, circumferential strain has been shown to be a strong predictor of cardiac toxicity.[11]

GLS is able to pick up sub-clinical myocardial dysfunction. The advantage of GLS over LVEF may be its sensitivity in detecting early sub-clinical cardiotoxicity before LVEF reductions.

These studies open new approaches of noninvasive assessment to identify patients at high risk for heart failure before initiation of cancer chemotherapy.[12]

4.1 Limitations of this study

1) Short follow-up period: We will continue the follow-up for a period of 5 years.
2) One tool to assess cardio-toxicity. We studied the TTE parameters. This is because another team of researchers at the same institute began evaluating changes in cardiac enzymes as a method to detect cases of cardiotoxicity.
3) One center study.

5. CONCLUSIONS

Resting ejection fraction and fractional shortening are insensitive to early changes in cardiotoxicity. Parameters that assess myocardial deformation and functional capacity raised sensitivity for early detection. Myocardial strain assessed by speckle tracking echocardiography can detect minimal cardiac systolic dysfunction and predict early changes in left ventricular systolic function. GLS and MAPSE are much more sensitive as predictors for early deterioration of LV functions among patients having cancer and receiving anthra-

cyclines.

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AUTHORS CONTRIBUTIONS

All Authors contributed equally to finalizing this article. All authors contributed to the study conception and design. Material preparation, data collection and analysis. The first draft of the manuscript was written by A.H. Elayouty and all authors commented on previous versions of the manuscript. All authors read and approved the final report. All authors have read and agreed to the content and are accountable for all aspects of the content. This article is an original one and has not been submitted anywhere else.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

INFORMED CONSENT

Informed consent for conducting special investigations has be obtained from patients participating in this study.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

DATA SHARING STATEMENT

No additional data are available.

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