International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 6, Issue 8 -2019

Research Article

DOI: http://dx.doi.org/10.22192/ijarbs.2019.06.08.019

Detection of Subclinical Left Ventricular Systolic Dysfunction in Patient Treated with Anthracycline Chemotherapy: A Comparative Analysis Between Different LV Systolic Echocardiographic Parameters

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Abstract

Background: Anthracycline chemotherapeutic agents are undermined by their cardiotoxicity. As life expectancy following treatment is greatly improved, techniques that ensure early detection of cardiotoxicity are essential.
Aims:1. Detection of subclinical left ventricular systolic dysfunction in patient treated with anthracycline chemotherapy.
2. Comparative analysis between different LV systolic parameters measured by echocardiography.
Type of the study: Prospective study.
Methods: Prospective study conducted in Baghdad Teaching Hospital – cardiac department for Six months, from January 2016 to June 2016. Patients referred to echocardiography laboratory from the hematology department for LV function assessment before or during chemotherapy. All patients - being treated with anthracycline chemotherapy - were examined by an echocardiogram at baseline and after three months using 2D, M Mode, Tissue Doppler imaging and speckle tracking imaging. Examination involved LVEF, MAPSE, tissue Doppler septal S' velocity and GLS.
Results: Seventy-eight participants ;46 females (59%) and 32 males (41%) with a mean age of 47 ± 16 years were prospectively studied. Global systolic strain was significantly reduced after three months of anthracyclines chemotherapy (-21.2 ± 2.4% to -19 ± 2.2% ($p < 0.0001$)) with 13% relative reduction.
A non-uniform reduction in strain was observed each time with relative sparing of the LV apex. LVEF remained largely unchanged atbothtime points (64 ± 5% to 62 ± 5% ($p < 0.03$)) with only 3% relative reduction.
A significant reduction in tissue Doppler septal S' velocity (8.2 ± 1.6 to7.3 ± 1.1cm/s ($p = 0.01$)) was seen after anthracycline therapy with 11% relative reduction.

MAPSE was significantly reduced after 3 months of completing anthracycline chemotherapy (11.76 ± 1.9mm) than baseline visit (10.64 ± 1.95mm) (p= 0.016) with 9% relative reduction.

Conclusions: Myocardial strain imaging is the most sensitive technique for the early detection of LV systolic dysfunction following anthracycline chemotherapy.

Also, the use of mitral annular displacement by M-mode echocardiography and/or peak systolic velocity (S') of the mitral annulus by pulsed-wave DTI can be a reliable alternative for quantification of LV longitudinal function.

Keywords: left ventricle, anthracycline.

Introduction

Cardiac dysfunction resulting from exposure to cancer therapeutics was first recognized in the 1960s with the widespread introduction of anthracyclines into the oncologic therapeutic armamentarium[(1)].Several strategies have been used over the past decades to detect it. Two of them evolved over time to be very useful: endomyocardial biopsies and monitoring of left ventricular (LV) ejection fraction (LVEF) by cardiac imaging[(2)].

Examination of endomyocardial biopsies proved to be the most sensitive and specific parameter for the identification of anthracyclineinduced LV dysfunction and became the gold standard in the 1970s.The noninvasive evaluation of LVEF has gained importance and emerged as the most widely used strategy for monitoring the changes in cardiac function; both during and after the administration of potentially cardio toxic cancer treatments[(2)].

The timing of LV dysfunction can vary among agents. In the case of anthracyclines, the damage occurs immediately after the exposure. For others, the time frame between drug administration and detectable cardiac dysfunction appears to be more variable[(3)].

Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD) is defined as a decrease in the LVEF of >10 percentage points, or a decrease in LVEF value <53% (normal reference value for two-dimensional (2D) echocardiography (2DE)) [6]. This decrease should be confirmed by repeated cardiac imaging. The repeat study should be performed 2 to 3 weeks after the baseline diagnostic study showing the initial decrease in LVEF. LVEF decrease may be further categorized as symptomatic or asymptomatic, or with regard to reversibility[(4)]:

• Reversible: within 5 percentage points of baseline.

• Partially reversible: improved by 10 percentage points from the nadir but remaining >5 percentage points below baseline.

• Irreversible: improved by <10 percentage points from the nadir and remaining >5 percentage points below baseline.

• Indeterminate: patient not available for re-evaluation. The damage caused by the anthracyclines occurs in a cumulative dose–dependent fashion. The expression of damage is related to preexisting disease, the state of cardiac reserve at the time of administration, coexisting damage, and individual variability (including genetic variability). Electron microscopy of myocardial biopsies showsvarying degrees of myocyte damage: vacuolar swelling progressing to myofibrillar disarray and ultimately cell death[(5)].

Echocardiography is the cornerstone in the cardiac imaging evaluation of patients in preparation for, during, and after cancer therapy, because of its wide availability, easy repeatability, versatility, lack of radiation exposure, and safety in patients with concomitant renal disease. In addition to the evaluation of LV and right ventricular (RV) dimensions, systolic and diastolic function at rest and during stress; echocardiography also allows a comprehensive evaluation of cardiac valves, the aorta, and the pericardium[(6)].

Exposure to potentially cardio toxic chemotherapeutic agents is a well-recognized indication for baseline and longitudinal evaluation of LV function. The most commonly used parameter for monitoring LV function is LVEF[(7)].

The incorporation of modern techniques such as myocardial contrast echocardiography, three-dimensional (3D) echocardiography (3DE), Doppler tissue imaging (DTI), and speckle-tracking echocardiography (STE), offer a prudent compromise between cost-effectiveness and clinical predictive value[(8)]. Changes in LVEF is an indication of LV damage that can be more appropriately identified when comparisons are made between baseline and follow-up studies. In addition, the calculation of LVEF

should be combined with assessment of the wall motion score index[8]. Resting wall motion score index based on a 16-segment model of the left ventricle has been demonstrated to be a more sensitive marker of anthracycline-induced CTRCD than relying on the LVEF alone[9].

Strategies using newer echocardiographic technology, such as STE derived strain imaging for the early detection of subclinical LV systolic dysfunction, have been actively investigated. When this technology is not available, the quantitation of LV longitudinal function by simple ultrasound tools such as mitral annular plane systolic excursion by M-mode echocardiography, and/or the peak systolic velocity (s′) of the mitral annulus by pulsed-wave DTI, could be useful adjunct information to LVEF in the evaluation of LV systolic function. Mitral annular plane systolic excursion is less dependent on image quality. Although there are no cutoff values that allow the prediction of CTRCD, a progressive decline should raise concern for subclinical LV dysfunction[10].

M-Mode Linear Measurements: The first attempts to quantify left ventricular function involved linear measurements of the minor-axis dimension from a dedicated M-mode echocardiogram:

.These measurements are relatively simple to perform, reproducible with excellent temporal resolution.

.Although the spatial resolution of a dedicated M-mode beam is also superior to that of two-dimensional echocardiography, in practice, the ability to visualize the entire left ventricle and to ensure a true minor-axis dimension mitigates these potential advantages [11].

LV Volumes and Ejection Fraction by M-Mode: The American Society of Echocardiography (ASE) recommends measurement of LV dimensions with the M-mode line perpendicular to the long axis of the heart and immediately distal to the tips of the mitral valve leaflets in the parasternal long axis view [12].

MAPSE (Mitral Annular Plane Systolic Excursion) :M-mode measurement that has been employed is the descent of the base. During ventricular contraction, the base (annulus) of the heart moves toward the apex. In the presence of global left ventricular dysfunction, the magnitude of this motion is directly proportional to systolic function. M-mode interrogation is undertaken of the lateral mitral annulus, and annular excursion toward the transducer is then calculated . There is a relatively linear correlation between the magnitude of systolic annular excursion and global systolic function [11].

Matos J et al proved in their study Cutoff values of MAPSE for normal EF (≥11 mm for women and ≥13 mm for men) and severely reduced EF (<6 mm for men and women) were identified[13].

The widespread availability of Doppler tissue imaging and speckle tracking has afforded a new, more sophisticated window on left ventricular mechanics. Doppler tissue imaging relies on adjustment of Doppler gains and filters to selectively record velocities from within the myocardium itself rather than the blood pool. Speckle tracking relies on identification of unique myocardial ultrasound signatures which can then be tracked. With either technique, either single or multiple regions of interest can be tracked simultaneously. These methodologies can also be applied to three dimensional echocardiographic data sets and global parameters of ventricular performance subsequently extracted [11].

For Doppler tissue imaging, the primary Information extracted is tissue velocity, from which distance or displacement as well as strain and strain rate can be calculated. For speckle tracking, the primary information extracted is tissue motion from which velocity is subsequently calculated. With either technique, assessing the distance between two points allows calculation of myocardial strain and strain rate. This analysis can be expanded to include the entire left ventricle in either apical or short-axis views[11].

Tissue Doppler Imaging (Mitral Annular Peak Systolic Velocity): A sample volume can be placed within the mitral annulus or myocardium and quantitative information extracted regarding tissue velocity. Annular systolic velocity is a marker of global left ventricular function in a uniformly contracting ventricle[11].

Normal values Tissue Doppler Imaging

Doppler tissue peak systolic velocity (cm/s)[14].

Age <65	>8
Age >65	≥5

Today, echocardiography deformation imaging allows measurements based on tissue Doppler imaging and 2D strain measurements based on speckle-tracking

imaging. The amount of deformation (positive or negative strain) is usually expressed in %. Positive strain values describe thickening or lengthening, negative values describe shortening during systole, the ventricular myocardium simultaneously shortens in the longitudinal and circumferential planes and thickens in the radial plane, with reciprocal changes in diastole Longitudinal and circumferential shortening results in negative strain values, whereas radial thickening results in a positive strain value [15].

There are 3 Parameters We can Get on Applying Strain:

1-Peak Systolic Strain: is defined as the maximal shortening or the maximum length change during the entire cardiac cycle, (at any region of the myocardium) during systole (after the onset of the QRS complex and before aortic valve closure occurs)[15].

2-Global Peak Systolic Strain: It is possible to measure strain in individual segments by averaging all segments of the entire ventricle (GPSS)[15].

3- Post Systolic Shortening (PSS): PSS shown as sensitive marker of ischemia but can be seen in healthy individuals as much as 1/3 of all segments at rest however the development or increase in PSS at peak stress might be sensitive marker of inducible ischemia[15].

Aims of the study

1 .Detection of subclinical left ventricular systolic dysfunction in patient treated with anthracycline chemotherapy.
2. Comparative analysis between different LV systolic parameters measured by echocardiography.

Materials and Methods

A prospective study done on seventy-eight patientsattending Baghdad Teaching Hospital – cardiac department from January 2016 to June 2016. Informed consent was obtained from all study patients.

Inclusion criteria:

Patients referred to our echocardiography laboratory from the hematology department for LV function assessment before or during chemotherapy. Patients included have:

1. Normal function in the phase of chemotherapy (anthracycline) that was defined by stability of Ejection Fraction (≥52% in male and ≥54% in female) at two time points (baseline and three months).

2. Good images for EF quantification along with high frame rate 2D acquisitions for speckle strain analysis at each visit.

3. Normal 2D average global systolic longitudinal strain (GLS) at baseline study (defined as GLS greater or equal to -19%).

Exclusion criteria:

1. A GLS value of below -19% at baseline visit.
2. No history of Coronary artery disease, or non-chemotherapy-induced cardiomyopathy.
3. Significant valvular disease.
4. Clinical diagnosis of heart failure.
5. Initiation of cardiac medications such as beta-blockers during the follow-up period.
6. Uncontrolled hypertension
7. Congenital heart disease. 8. A widened QRS complex on surface ECG, arrhythmia.
8. A widened QRS complex on surface ECG, arrhythmia.

LV systolic function was measured in patients referred from the hematology department before anthracycline and after three months (3 courses) of treatment.

Transthoracic echocardiography and ECG were performed simultaneously with a portable echocardiographic equipment (Philips CX-50) that has TDI capabilities and phased array transducer frequency of 2.5 MHz. Measurements were undertaken in the left lateral decubitus position by the researcher.

LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and ejection fraction (EF) were measured by M mode. LV Ejection Fraction (EF) and volumes measured using the following formula:

• Left ventricular volume, Teichholz formula: volume = [7/ (2.4 + LVIDd)] (LVIDd)3

• Ejection fraction= (EDV – ESV)/EDV

Ejection Fraction was considered abnormal if EF<52% in males and EF<54% in females.

Mitral annular plane systolic excursion (MAPSE) was measured using M-mode imaging in the apical four chamber view. The M-mode cursor was placed on the septal and lateral mitral annulus as much parallel as possible to the LV walls, then both values were averaged. MAPSE < 11 mm was considered abnormal.

Pulsed wave tissue Doppler echocardiography (TDE) was used to measure mitral annular peak systolic velocity (S′) at the lateral site of the mitral annulus. S′ < 8 cm/s was considered abnormal. Global longitudinal peak strain (GLPS) was measured using speckle tracking echocardiography. Apical 3, 2, and 4 chambers high frame rate grayscale acquisitions (40 to 80 frames/s) were obtained with commercially available equipment Philips CX50. GLS was measured for 3, 2, and 4 chamber views separately, and all eighteenmyocardial segments were averaged to obtain the GLS. Segments that were inadequately tracked were excluded from the analysis.

Segmental strain was presented as a bull- eye map and GLPS was automatically calculated.

The strain cutoff -19% was used based on calculation of approximately 2SD from the mean on the basis of known normal strain values from a previous publication.

All measurements were taken along with simultaneous electrocardiogram at a speed of 50 mm/s during three consecutive heart cycles, and the mean values were calculated.

Statistical analysis

All collected patients' data was fed to a computer software; Statistical Package for Social Sciences (SPSS) version 24.

The described statistical results were presented as mean value ± standard deviation and as frequency percentages. Histograms and pie charts were exploited to clarify these statistical results.

Paired (t) tests and Analysis of variance (ANOVA) were used to compare LV segmental strain LPSS parameters before and after chemotherapy.

(p) value of ≤0.05 was considered as level of significance in all statistical analysis.

Results

Seventy-eight patients - 46 females (59%) and 32 males (41%) -with a mean age of 47 ± 16 years were prospectively studied (Table 1). All patients had an echocardiogram (at baseline and after three months of anthracycline chemotherapy treatment) using 2D, M Mode, Tissue Doppler imaging and Speckle Tracking Imaging. Examination involved LVEF, MAPSE, Tissue Doppler Septal S' velocity and GLS.

Table 1: Patients' Characteristics.

No. of Patients	78
Age, years Mean (±SD)	47 ± 16
Male (no., %)	32 (41%)
Female (no., %)	46 (59%)

Limited image quality before and/or after chemotherapy meant that LVEF and strain measurements were not possible in all participants.

No symptoms of cardiac failure were reported during participant follow-up. Also there was no significant difference in the LV dimensions before and after chemotherapy.

Measurement of LVEF before and after anthracycline chemotherapy was possible in 76 of the 78 participants (97%). Mean LVEF at baseline was 64 ± 5% and after three months of completing anthracycline chemotherapy was 62 ± 5% ($p < 0.03$), (Table 2); with a 3% relative reduction (mean LVEF remaining within a clinically normal range), (Figure 1)

Table 2: Left Ventricular Ejection Fraction Before and After Anthracycline Chemotherapy.

	Before Treatment	Post Anthracyclines (3 Mo)	P value
LVEF, % Mean (±SD	64 ± 5%	62 ± 5%	p < 0.03

Results showed that MAPSE was significantly reduced after three months of completing anthracycline chemotherapy (10.64 ± 1.95mm) than baseline visit (11.76 ± 1.9mm); (p= 0.016) ;(Table 3); with a 9% relative reduction (Figure 1).

Table 3: MAPSE Before and After Anthracycline Chemotherapy

	Before Treatment	Post Anthracyclines (3 Mo)	P value
MAPSE, mm, Mean (±SD)	11.76 ± 1.9	10.64 ± 1.95	0.016

A significant reduction in tissue Doppler septal S' velocity (p = 0.01) was seen after anthracycline therapy from 8.2 ± 1.6 cm/s to 7.3 ± 1.1cm/s ;(Table 4); with a 11% relative reduction. (Figure 1)

Table 4: Tissue Doppler Septal S' Velocity Before and After Anthracycline Chemotherapy.

	Before Treatment	Post Anthracyclines (3 Mo)	P value
Septal S' (cm/sec) Mean (±SD)	8.2 ± 1.6	7.3 ± 1.1	p = 0.01

LV LPSS from the apical 4 chamber view was not possible in 9 of 78 (12%). Global biplane LV LPSS (from the apical 3,4 and 2 chamber views) at baseline was -21.2 ± 2.4% and after three months of completing anthracyclines was -19 ± 2.2% (p < 0.0001) ;(Table 5); with a 13% relative reduction (Figure1).

Table 5: Left Ventricular Global Strain Measurements Before and After Anthracycline Chemotherapy.

	Before Treatment	Post Anthracyclines (3 Mo)	P value
Longitudinal Strain, % Mean (±SD)	-21.8 ± 2.4%	-19 ± 2.2%	p < 0.0001

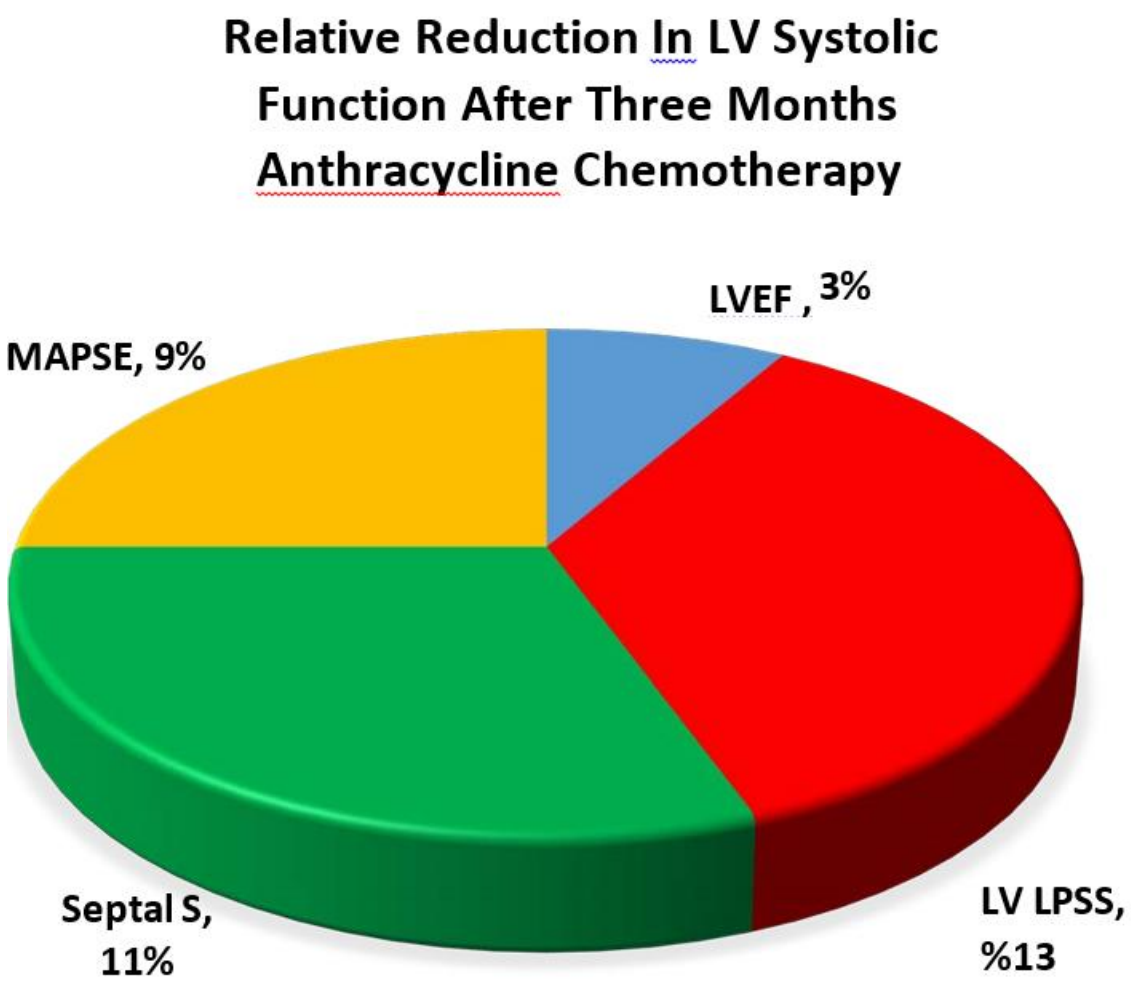

Figure 1: Relative Reduction in LV Systolic Function After Three Months' Anthracycline Chemotherapy.

Segmental strain analysis showed regional differences in the left ventricle following anthracycline chemotherapy.

The basal and mid left ventricular segments were significantly reduced, whereas the LV apex was largely unchanged.

A base to apex gradient was observed in LV LPSS, with maximal strain values at the LV apex. A modest increase in this gradient was observed following anthracyclines (Table 6 and Figure 1).

Table 6: Longitudinal Peak Systolic Strain (LPSS) Values in The Basal, Mid and Apical Left Ventricle Before and After Chemotherapy.

	Before Treatment	Post Anthracyclines (3 Mo)	P value
Basal LV	-20.5 ± 2.4% [32%]	-18.9 ± 2.6% [31%]	$p < 0.01$
Mid LV	-21.0 ± 2.7% [33%]	-19.4 ± 2.4% [32%]	$p < 0.01$
Apical LV	-21.9 ± 4.1% [35%]	-22.2 ± 3.5% [37%]	$P > 0.5$

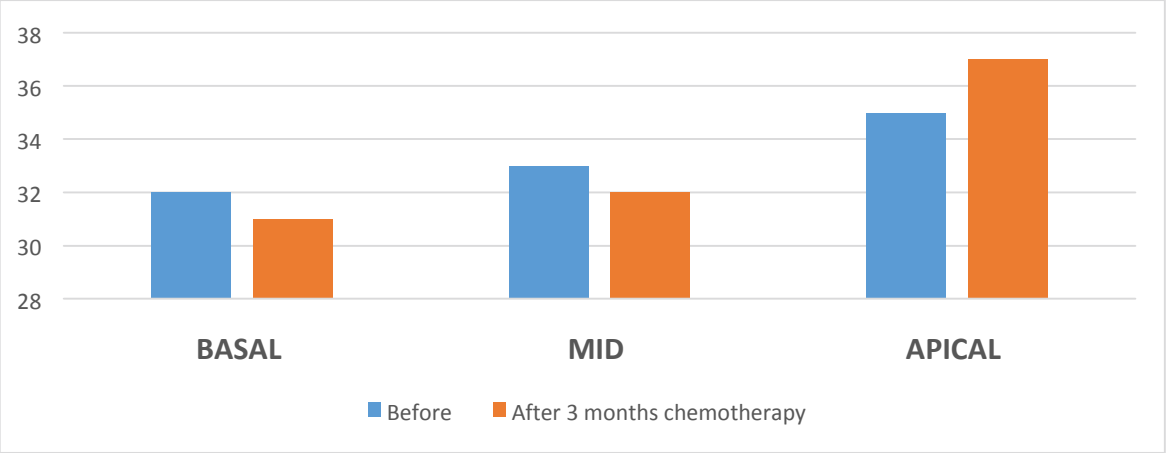

Figure 2: Percentage of Relative Reduction in Global LV LPSS in the Basal, Mid and Apical Left Ventricle; Before and Three Months After Anthracyclines.

Discussion

To evaluate LV systolic function in seventy-eight patients treated with anthracycline chemotherapy, four parameters (LVEF, tissue Doppler septal S' velocity, MAPSE and myocardial strain imaging) were measured at two time points; before anthracycline chemotherapy and after three months of anthracycline chemotherapy.

In similar with two previous studies (Yu Kang et al.,2013) [16].and (AlBiltagi M et al.,2012) [17].which demonstrate that LVEF did not change after anthracycline chemotherapy, a decrease of only 3% in LVEF was found in patients receiving anthracycline chemotherapy for three months in this study.

Furthermore, a similar reduction in LVEF was observed in other previous studies as in (Stoodley et al.,2013) [18].and (Poterucha, Kutty, Lindquist, Li, & Eidem, 2012) [19].

MAPSE is one of the parameters used to quantify long-axis LV systolic function and to predict subclinical changes in LV systolic function in anthracycline chemotherapy's patients.

Study results highlight the sensitivity of MAPSE to early changes in LV systolic function with 9% relative reduction in MAPSE.

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 (Joanna Luszczak et al., 2013) [20].

MAPSE can become sensitive to LV systolic dysfunction as showed 9% relative reduction compared to 13% relative reduction in global LPSS observed after chemotherapy similar to previous report demonstrated that in patients with heart failure and preserved ejection fraction MAPSE correlates with longitudinal strain at rest and during exercise (Wenzelburger et al.,2011) [21].

A decrease of tissue Doppler septal S' velocity (index of LV longitudinal function in anthracycline chemotherapy patients) was detected with an 11% relative reduction compares to a 13% relative reduction in global LPSS and a 3% relative reduction in LVEF after chemotherapy .

The above results are similar to previous experimental and clinical studies using Eco-TDI in patients treated with anthracyclines that showed that early alterations in diastolic function and longitudinal left ventricular contractile function are detected earlier than changes in LVEF (Ines Monte et al.,2013) [22] and (Lotriionte M et al.2007) [23].

A relative reduction in global LPSS of 13% was observed after three months of completing anthracycline chemotherapy which provides confirmation of observations reported previously (Stoodley et al., 2011) [24]and similar to another study that stated the ability of longitudinal systolic strain to detect pre-clinical changes in LV systolic function in patients receiving anthracycline chemotherapy (Yu Kang et al.,2013) [16].The results of this study highlight the sensitivity of strain to detect early changes in LV systolic function as a 13% relative reduction in global LPSS was observed after chemotherapy.

These results are consistent with previous findings of early fall in GLS by STE between 10% and 15% that predicts subsequent cardiotoxicity (including both asymptomatic and symptomatic LV dysfunction) (Baratta S.et al.,2013) [25].and (Mornos C, Petrescu L,2013) [26].and also compatible with (Sawaya H, Sebag IA, Plana JC, et al,2012) [27]. and (Sawaya H, Sebag IA, Plana JC, et al,2011) [28].(Negishi K et al.,2013) [29].and (Fallah-Rad N et al.,2011) [30].

Strain cutoff -19% was chosen based on normal strain values from a previous publication and considered abnormal if GLS value of below 19%.

(Sawaya H et al.,2012) [27].and (Negishi K et al.,2013) [29] stated that in patients where a relative change in GLS was unavailable, absolute levels of GLS less than -19% during early therapy have been associated with cardiotoxicity.

After the administration of anthracycline chemotherapy, characteristic pattern in the regional LV myocardial systolic strain values was observed in which strain was not significantly reduced in the apical segments after anthracycline therapy.

In fact, a greater difference between basal and apical strain values was evident indicating a non-uniform disruption of LV myocardial systolic function .While normally regional LV myocardial systolic strain valuesincrease modestly along the longitudinal axis from base to apex (Sengupta et al., 2007) [31].

Conclusion

1. Reduction in myocardial deformation parameters (LV LPSS) is a sign of subclinical myocardial changes from anthracycline chemotherapy which occur prior to any change in LVEF assessed by conventional 2D echocardiography.

2. Parameters -such as tissue Doppler septal S' velocity and MAPSE- can be used to detect myocardial systolic dysfunction in patients treated with anthracycline chemotherapy.

3. Myocardial deformation (LV LPSS) is the most sensitive measurement to detect subclinical myocardial changes (resulting from anthracycline chemotherapy). The second important measurement is tissue Doppler septal S' velocity and finally MAPSE.

4. LV systolic dysfunction occurs non-uniformly in the LV with relative sparing of the apical segments.

5. Calculation of GLS should be avoided if regional tracking is suboptimal in more than two myocardial segments in a single view.

6. In the absence of global longitudinal strain (GLS) by STE, the use of mitral annular displacement by M-mode echocardiography and/or peak systolic velocity (S') of the mitral annulus by pulsed-wave DTI can be a reliable alternative for quantification of LV longitudinal function.

7. LVEF is not accurate for measuring subtle segmental LV dysfunction.

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DOI:10.22192/ijarbs.2019.06.08.019	

How to cite this article:
Israa Ali Sadeq, Maitham Qasim Mohammed, Akram Kdiar Abass AL-Timimi, Alaa Abdul Hussein Al Enbari. (2019). Detection of Subclinical Left Ventricular Systolic Dysfunction in Patient Treated with Anthracycline Chemotherapy: A Comparative Analysis Between Different LV Systolic Echocardiographic Parameters. Int. J. Adv. Res. Biol. Sci. 6(8): 137-147.
DOI: http://dx.doi.org/10.22192/ijarbs.2019.06.08.019