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Prevalence and Predictors of Worsening of Diastolic Function in Cancer Patients with Normal Baseline Ejection Fraction undergoing Chemotherapy

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Abstract

Purpose: Chemotherapeutic agents such as anthracyclines and monoclonal antibodies Tyrosine Kinase Inhibitors (TKI) have been associated with systolic and Diastolic Dysfunction (DD). Data from the Middle Eastern region is lacking, and disparities in response to therapy and toxicity profile have been observed among different racial and ethnic groups. We hypothesized that worsening diastolic function proceeded systolic dysfunction among Middle Eastern patients with normal baseline echocardiogram receiving chemotherapy, and sought to assess its incidence and independent predictors.

Methods: Consecutive outpatients presenting for baseline echocardiogram prior to chemotherapy were prospectively enrolled between 7/2013 and 6/2014. Patients with EF <50%, severe valvular disease, or atrial fibrillation were excluded. Diastolic function was graded blindly according to the guidelines by two level III certified cardiologists.

Results: There were 226 patients (age 49.5 ± 14.3 years, 78% female) with LVEF and GLS 59.8 ± 3.9% and -19.8 ± 2.3%, respectively; 135 (59.7%) had normal diastolic function, 82 (36.3%) grade I, and 9 (4%) grade 2 DD. After a mean follow-up time of 93 ± 45 days, 81 patients presented for repeat echocardiogram. There were 49/226 patients (entire cohort) and 35/81 (follow-up) that received anthracyclines or TKI. On follow-up imaging, 14 patients (17.3%) had worsening diastolic function without change in EF; they were all female with breast cancer. On multivariate regression analysis, old age, increased BMI, anthracyclines or TKI, and No ACEi/ARB were independent predictors of worsening diastolic function, while beta-blockers were associated with improved function.

Conclusion: In Middle Eastern patients undergoing chemotherapy, mainly female with breast cancer, worsening diastolic function is not uncommon and could be an early marker of cardiomyopathy. Old age, obesity, anthracyclines or TKI regimens are associated with increased risk, while ACEi/ARB and beta-blockers seems protective. These results should be interpreted with caution given the small sample size, and endpoints limited to female with breast cancer. Larger validation studies are needed.

Keywords: Diastolic dysfunction; Worsening; Chemotherapy; Normal ejection fraction

Introduction

Cancer remains the second leading cause of death after cardiovascular disease in the western world [1,2]. Over the last decade, there have been new chemotherapeutic agents such as monoclonal antibodies that target human epidermal growth factor receptor Tyrosine Kinase (TKI) and new generation of anthracyclines that are showing promising results [3,4]. However, these agents carry potential cardio toxic effect and result in cardiomyopathy [5-7]. Indeed, several studies have shown an association between these agents and a decrease in systolic function on follow-up echocardiography, resulting in heart failure symptoms [8]. Updates in cardiovascular imaging using speckle tracking and strain analysis, have allowed the subclinical detection of systolic dysfunction as evidenced by a decrease in global longitudinal strain before a visual drop in Ejection Fraction (EF) is seen [9,10].

There are increasing data that evaluated the incidence of new or worsening diastolic parameters after the administration of these chemotherapeutic agents; however, data from the Middle Eastern region is vastly lacking [11-15]. Disparities in clinical response to chemotherapy and toxicity profiles have been observed among different racial and ethnic groups [16]. The incidence of cancer, particularly breast cancer, is rising in Lebanon in part due to more screening; therefore, highlighting the need to generate data from such cohort of patients [17]. Also, over the course of previously published studies spanning more than two decades, the assessment of diastolic function has varied considerably with the introduction of new parameters, and with several updates in the guidelines.

Patients with systolic dysfunction often have concomitant Diastolic Dysfunction (DD), but there is little evidence that diastolic dysfunction is an earlier marker for chemotherapy-induced cardiomyopathy [18]. Hence, we hypothesized that DD proceeded early systolic dysfunction, and sought to assess the incidence of new or worsening diastolic function in a standardized blinded fashion among

Lebanese and Middle Eastern outpatients with preserved systolic function presenting for baseline echocardiography prior to chemotherapy.

Methods

Patient selection

Consecutive outpatients presenting to the echocardiographic laboratory at the American University of Beirut Medical Center (AUBMC) were prospectively enrolled into the database after obtaining consent between 7/2013 and 6/2014. The study was approved by the Institutional Review Board (IRB) at AUBMC and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients with ejection fraction <50%, mitral valve surgery, severe valvular disease, atrial fibrillation at the time of image acquisition, or congenital heart disease were excluded. Patient's demographics, co-morbidities, medications, and indication for echocardiographic testing were prospectively collected. Of 1339 outpatients, 226 were having baseline echocardiography prior to initiation of chemotherapy and were included in the final analysis and 81 (36%) had a follow-up echocardiography (mean time 93 ± 45 days) (Figure 1).

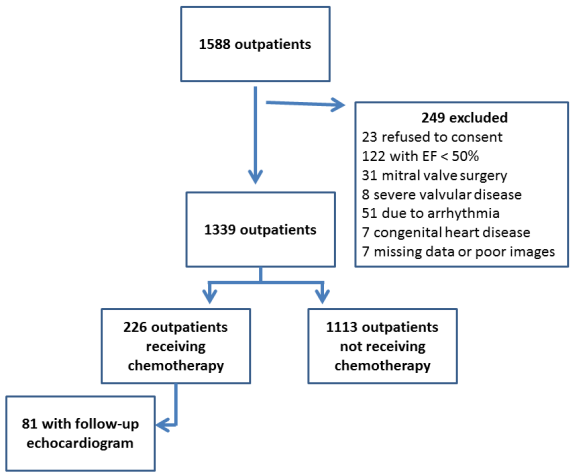

Figure 1: Selection diagram of patients.

Clinical variables

Clinical variables collected at the time of enrollment included demographics (age, gender, height and weight, nationality), co-morbidities (blood pressure, creatinine, history of hypertension, diabetes, revascularization, smoking, sedentary lifestyle, and type of cancer), and medications (angiotensin converting enzyme inhibitor/angiotensin receptor blockers [ACEi/ARB], beta-blockers).

Chemotherapy regimen

The type of chemotherapy regimen that was administed was retrospectively collected from chart review, and were dichotomized as either containing anthracyclines (adriamycine, epirubicin, idarubicin, etc.) or monoclonal antibodies based tyrosine kinase inhibitors (bevacizumab, trastuzumab, etc.) (Most commonly known to cause cardiomyopathy) versus those containing neither of these agents.

Echocardiographic methods and diastolic function

Patients were imaged in the left lateral decubitus position with commercially available systems (Philips Electronics, Andovers, MA, GE Medical Systems, Milwaukee, WI; Siemens Medical Solutions, Mountain View, CA). Diastolic function was assessed in our institution in a standardized method and in accordance with the most recently published guidelines by the European Association of Cardiovascular Imaging using of a combination of echocardiographic variables (transmitral inflow pattern, mitral annular velocities with tissue Doppler imaging, left atrial volume index, and pulmonary venous flow pattern) [19]. Two level III trained echocardiogrpahy certified cardiologists (WA, AA) reviewed all cases and graded the diastolic function (baseline and follow-up) in a blinded manner; in case of a discrepancy, the images were reviewed by a third cardiologist. Diastolic function was labelled as normal or abnormal (DD). DD was then categorized as mild (grade 1, impaired relaxation), moderate (grade 2, pseudo normal), or severe (grade 3, restrictive) [19]. Left ventricular EF was assessed by semi-quantitative manner using the Biplane Simpson method, and left atrial volume index in accordance with published guidelines [20]. Global longitudinal strain was performed on patients imaged on the GE machine that had the automated functional imaging software [21]. No off-line strain analysis package was available at our institution. For patients undergoing follow-up imaging, image acquisition was performed on the same machine that was used for baseline echocardiography. Change in diastolic function was categorized as either improved no change, or worsening. Because of small number of patients, the first two categories were grouped together.

Endpoint

The primary endpoint was worsening of diastolic function on follow-up imaging.

Statistical analysis

Continuous variables were expressed as means ± SD and compared by use of the unpaired Student t test, Wilcoxon rank test, or one way Anova as appropriate. Categorical variables were expressed as percentages and compared by use of the Fisher exact test or Pearson Chi-square test as appropriate. Comparisons between variables at baseline versus follow-up were made with the Paired t test (continuous) or McNemar test (categorical). Multivariate regression analysis model was performed to determine the independent predictors of worsening diastolic function. Significant univariates ($p<0.1$) or clinically relevant ones were entered into the model using stepwise forward selection. Variables with collinearity were entered into the model one at a time. All statistical tests were 2 sided. A p values <0.05 was set a priori and considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences version 19 for Windows (SPSS, Chicago, IL).

Results

Patient characteristics

From a total of 1339 outpatients with EF ≥ 50% presenting to the echocardiography laboratory, 226 (17%) were undergoing baseline

evaluation prior to initiation of chemotherapy and were included in this analysis. Those excluded (i.e. those not receiving chemotherapy) were significantly older (p=0.01), had more hypertension (p<0.001), diabetes mellitus (p=0.001), and diastolic dysfunction (p=0.009) (40.1% vs. 36.3% grade I, and 9.9% vs. 4% for grade ≥2).

The baseline clinical characteristics of the patient cohort (n=226, mean age 49.5 ± 14.3 years, 78% female) are summarized in Table 1 and stratified by baseline diastolic function. History of smoking (36%) and sedentary lifestyle (85%) were particularly high in the cohort, while breast cancer accounted for almost two-third of the cases. There were 49 (21.7%) of patients that received anthracyclines and/or monocolonal based tyrosine kinase inhibitor chemotherapeutic regimen.

	All patients N=226	**Normal diastolic function N=135**	**Grade I diastolic dysfunction N=82**	**Grade ≥2 diastolic dysfunction N=9**	**P value**
Demographics					
Age, years	49.5 ± 14.3	42.7 ± 12.2	59.6 ± 11.0	59 ± 10	<0.0001
Female gender	177 (78.3%)	104 (77.0%)	67 (82.6%)	6 (66.7%)	0.50
Nationality					0.014
Lebanese	167 (73.8%)	90 (66.7%)	72 (87.8%)	5 (55.6%)	
Iraqi	51 (22.6%)	40 (29.6%)	8 (9.8%)	3 (33.3%)	
Others	8 (3.5%)	5 (3.7%)	2 (2.4%)	1 (11.1%)	
Body mass index, kg/m^2 (n=222)	27.3 ± 5.2	26.9 ± 5.3	28.1 ± 4.9	25.6 ± 4.6	0.16
Body surface area, m^2 (n=222)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.1	1.7 ± 0.2	0.11
Comorbidities					
Systolic blood pressure, mmHg (n=208)	127 ± 17	123 ± 15	133 ± 17	136 ± 22	<0.0001
Hypertension	57 (25.2%)	22 (16.3%)	29 (35.3%)	6 (66.7%)	<0.0001
Diabetes	20 (8.8%)	7 (5.2%)	11 (13.4%)	2 (22.2%)	0.042
Prior revascularization	17 (7.6%)	5 (3.7%)	11 (13.4%)	1 (11.1%)	0.030
Smoking history	81 (35.8%)	44 (32.6%)	34 (41.5%)	3 (33.3%)	0.43
Sedentary lifestyle	190 (84.0%)	109 (80.7%)	74 (90.2%)	7 (77.8%)	0.12
Cancer type					0.17
Breast cancer	147 (65.0%)	87 (64.4%)	55 (67.1%)	5 (55.6%)	
Lymphoma	27 (11.9%)	19 (14.1%)	7 (8.5%)	1 (11.1%)	
Other	52 (23.0%)	29 (21.5%)	20 (24.4%)	3 (33.3%)	
Creatinine, mg/dl (n=202)	0.74 ± 0.4	0.70 ± 0.2	0.75 ± 0.2	1.24 ± 1.4	<0.0001
Glomerular filtration rate, ml/min/1.72 m^2 (n=194)	130 ± 47	144 ± 46	115 ± 39	73 ± 45	<0.0001
Medications					
Beta blockers	48 (21.2%)	15 (11.1%)	29 (35.4%)	4 (44.4%)	<0.0001
ACEi/ARB	40 (17.7%)	15 (11.1%)	21 (25.6%)	4 (44.4%)	0.003
Statins	35 (15.5%)	12 (8.9%)	21 (25.6%)	2 (22.2%)	0.004
Anthracyclines or monoclonal antibodies based tyrosine kinase inhibitors	49 (21.7%)	33 (24.4%)	15 (18.3%)	1 (11.1%)	0.42
Echocardiographic parameters					
LVEDd/height, mm/m (n=221)	28 ± 3	28 ± 4	27 ± 3	29 ± 4	0.22

LVESd/height, mm/m (n=220)	18 ± 2	19 ± 2	18 ± 2	19 ± 3	0.47
LV mass index, g/m^2 (n=212)	46 ± 12	43 ± 9	49 ± 12	61 ± 24	<0.0001
Ejection fraction, %	59.8 ± 3.9	59.6 ± 3.8	60.2 ± 4.2	59.8 ± 2.6	0.54
Global longitudinal strain, % (n=87)	-19.8 ± 2.3	-20 ± 2.3	-19.4 ± 2.3	-19.2 ± 1.9	0.54
LA volume index, ml/m^2 (n=216)	23 ± 5	22 ± 5	24 ± 6	34 ± 3	<0.0001
E, cm/s	74 ± 18	81 ± 17	63 ± 13	83 ± 18	<0.0001
A, cm/s	72 ± 19	65 ± 16	83 ± 17	68 ± 18	<0.0001
E/A	1.14 ± 0.70	1.38 ± 0.82	0.76 ± 0.10	1.25 ± 0.26	<0.0001
Deceleration time, ms	205 ± 35	185 ± 23	238 ± 27	184 ± 24	<0.0001
e' lateral, cm/s	11.4 ± 3.4	13.2 ± 3.0	8.3 ± 1.5	8.4 ± 1.1	<0.0001
E/e'	7.04 ± 2.29	6.4 ± 1.9	7.8 ± 2.2	10 ± 3.9	<0.0001
TAPSE, mm (n=172)	23 ± 12	22 ± 4	24 ± 19	23 ± 4	0.70
Right ventricular S', cm/s (n=198)	14 ± 3	14 ± 3	14 ± 4	14 ± 3	0.76
Systolic PAP, mmHg (n=111)	28 ± 6	28 ± 6	28 ± 5	32 ± 6	0.10

Table 1: Baseline characteristics of all patients stratified by initial diastolic function. P value comparing all 3 groups. ACEi: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; LA: Left Atrial; LV: Left Ventricular; LVEDD: Left Ventricular End-Diastolic Diameter; LVESD: Left Ventricular End-Systolic Diameter; PAP: Pulmonary Artery Pressure; TAPSE: Tricuspid Annular Plane Systolic Excursion

Baseline echocardiographic parameters

There were 135 (59.7%) patients with normal diastolic function, 82 (36.3%) with grade I DD, and 9 (4%) with grade 2 DD. Patients with DD were older, had more hypertension, diabetes, prior revascularization, elevated creatinine, and more use of beta blockers and ACEi/ARB but similar use of cardiotoxic chemotherapeutic agents. The mean LVEF and GLS were 59.8 ± 3.9% and -19.8 ± 2.3%, and were similar across all patients (Table 1). Patients with DD had larger left atrial volume and LV mass indices, lower e' and higher E/e'.

Characteristics stratified by chemotherapeutic agents

There were 49/226 patients (entire cohort) and 35/81 (follow-up) that received anthracycline or monoclonal based TKI, and consisted predominately of female with breast cancer. There was no difference in age, co-morbidities, medication use (ACEi/ARB and beta-blockers), baseline EF, GLS, echocardiographic or diastolic parameters between those who received anthracyclines/monoclonocal based TKI and those that did not (Table 2).

	Anthracyclines or monoclonal antibodies based tyrosine kinase inhibitors (All patients [n=226])			**Anthracyclines or monoclonal antibodies based tyrosine kinase inhibitors (patients with follow-up echo [n=81])**		
	No (n=177)	Yes (n=49)	P value	No (n=46)	Yes (n=35)	P value
Demographics						
Age, yrs	49 ± 15	50 ± 13	0.83	49 ± 17	50 ± 11	0.71
Female gender	129 (72.9%)	48 (98.0%)	<0.0001	33 (71.7%)	34 (97.1%)	0.003
Nationality			0.80			0.70
Lebanese	130 (73.4%)	37 (75.5%)		38 (82.6%)	30 (85.7%)	
Iraqi	41 (23.2%)	10 (20.4%)		8 (17.4%)	4 (11.4%)	
Others	6 (3.4%)	2 (4.1%)		2 (4.3%)	1 (2.9%)	
Body mass index, kg/m^2	27±5	28±5	0.21	27±5	28±6	0.83
Body surface area, m^2	1.8 ± 0.2	1.8 ± 0.1	0.65	1.8 ± 0.2	1.8 ± 0.1	0.70

Comorbidities						
Systolic blood pressure, mm Hg	127 ± 16	126 ± 18	0.56	127 ± 15	127 ± 19	0.88
Hypertension	46 (26.0%)	11 (22.4%)	0.61	13 (28.3%)	7 (20.0%)	0.39
Diabetes	12 (6.8%)	8 (16.3%)	0.037	4 (8.7%)	6 (17.1%)	0.25
Prior revascularization	16 (9.0%)	1 (2.0%)	0.10	8 (17.4%)	1 (2.9%)	0.089
Smoking history	64 (36.2%)	17 (34.7%)	0.83	16 (34.8%)	16 (45.7%)	0.32
Sedentary lifestyle	150 (84.7%)	40 (81.6%)	0.48	40 (87.0%)	30 (85.7%)	0.87
Breast cancer	102 (57.6%)	45 (91.8%)	<0.001	28 (60.9%)	34 (97.1%)	<0.0001
Creatinine, mg/dL	0.76 ± 0.4	0.68 ± 0.2	0.20	0.72 ± 0.2	0.65 ± 0.1	0.10
Glomerular filtration rate, ml/min/1.72 m^2	128 ± 47	138 ± 48	0.27	129 ± 47	142 ± 47	0.19
Medications						
Beta blockers	38 (21.5%)	10 (20.4%)	0.87	12 (26.1%)	8 (22.9%)	0.74
ACEi/ARB	30 (16.9%)	10 (20.4%)	0.57	11 (23.9%)	6 (17.1%)	0.46
Statins	29 (16.4%)	6 (12.2%)	0.48	9 (19.6%)	5 (14.3%)	0.53
Echocardiographic parameters						
LVEDd/height, mm/m	28 ± 3	28 ± 2	0.67	27 ± 3	28 ± 3	0.53
LVESd/height, mm/m	18 ± 2	18 ± 2	0.51	18 ± 2	19 ± 2	0.63
LV mass index, g/m^2	47 ± 12	41 ± 10	0.03	45 ± 9	41 ± 10	0.09
Ejection fraction, %	60 ± 4	59 ± 4	0.090	60 ± 4	59 ± 4	0.19
Global longitudinal strain %	-19.8 ± 2	-19.7 ± 2	0.91	-20.2 ± 3	-19.8 ± 2	0.68
LA volume index, ml/m^2	23 ± 6	22 ± 5	0.15	23 ± 6	22 ± 5	0.13
E, cm/s	75 ± 18	72 ± 18	0.30	76 ± 18	70 ± 16	0.14
A, cm/s	72 ± 19	68 ± 16	0.17	73 ± 22	71 ± 16	0.59
E/A	1.1 ± 0.4	1.3 ± 1.3	0.09	1.1 ± 0.4	1.3 ± 1.5	0.51
Deceleration time, ms	205 ± 37	205 ± 31	0.95	211 ± 39	209 ± 29	0.74
e' lateral, cm/s	11 ± 4	11 ± 3	0.77	11 ± 4	11 ± 3	0.92
E/e'	7.1 ± 2.2	6.8 ± 2.7	0.42	7.1 ± 2.3	6.5 ± 2	0.26
TAPSE, mm	23 ± 13	21 ± 3	0.29	22 ± 3	21 ±4	0.14
Right ventricular S', cm/s	14 ± 3	12 ± 2	0.001	14 ± 2	12 ± 2	0.008
Systolic PAP, mm Hg	28 ± 5	28 ± 7	1.0	29 ± 6	28 ± 6	0.73
Baseline diastolic function			0.42			0.35
Normal	102 (57.6%)	33 (67.3%)		24 (52.2%)	22 (62.9%)	
Grade I DD	67 (37.8%)	15 (30.6%)		20 (43.5%)	13 (37.1%)	
Grade ≥2 DD	8 (4.5%)	1 (2.0%)		2 (4.3%)	0 (0%)	
Worsening of diastolic function				4 (8.7%)	10 (28.6%)	0.023

Table 2: Baseline Characteristics of patients stratified by chemotherapeutic agents. Abbreviations as in Table 1. DD: Diastolic Dysfunction

Follow-up echocardiogram

After a mean follow-up time of 93 ± 45 days, 81 patients that received chemotherapeutic regimen presented for repeat echocardiogram. There was no difference in baseline diastolic function between those who had a follow-up echocardigoram and those that did not (p=0.45). Furthermore, there was no significant change in EF, or GLS (Table 3). There was however 14 patients (17.3%) that had worsening of diastolic function (Table 4, Figure 2). These patients were significantly older, all female, had higher body mass index, more likely to be receiving anthracycline or monocolonal based TKI, and less likely to be receiving ACEi/ARB (Table 4). There was neither difference in baseline nor a change in EF or GLS between those who had worsening of diastolic function and those that did not (Table 5). Patients with worsening of diastolic function had an increase in E/e' and decrease in e'. Finally, there were 11 patients (13.6%) that had improvement in diastolic function that were more likely to be on beta blockers (55% vs. 20%, p=0.014), ACEi/ARB (36.4% vs. 18.6%, p=0.18), and statins (36.4% vs. 14.3%, p=0.072).

	Baseline (n=81)	Follow-up (n=81)	P value (paired t-test or McNemar test)
Echocardiographic parameters			
LVEDd/height, mm/m (n=80)	27.6 ± 2.8	27.7 ± 2.7	0.71
LVESd/height, mm/m (n=79)	18.5 ± 2.2	18.4 ± 1.9	0.74
LV mass index, g/m^2 (n=76)	44 ± 10	45 ± 8	0.59
EF, %	59.8 ± 3.9	59.1 ± 3.9	0.12
LA volume index, ml/m^2 (n=78)	22.8 ± 5.5	23.7 ± 6.3	0.27
E, cm/s	73 ± 17	77 ± 18	0.095
A, cm/s	72 ± 19	77 ± 20	0.003
E/A	1.2 ± 1.1	1.0 ± 0.3	0.17
Deceleration time, ms	210 ± 35	204 ± 42	0.26
e' lateral, cm/s	11.4 ± 3.5	11.2 ± 2.9	0.40
E/e'	6.9 ± 2.2	7.4 ± 2.6	0.029
Systolic PAP (n=36)	30 ± 6	29 ± 6	0.29
TAPSE (n=59)	22 ± 4	21 ± 4	0.80
Right ventricular S'(n=70)	13 ± 2	13 ± 2	0.73
Global longitudinal strain, % (n=76)	-20.1 ± 2.5	-20.1 ± 2.4	0.93
Diastolic function			0.44
Normal	46 (56.8%)	47 (58.0%)	
Grade I DD	33 (40.7%)	28 (34.6%)	
Grade ≥2 DD	2 (2.5%)	6 (7.4%)	

Table 3: Comparison of echocardiographic parameters at baseline and follow-up. Abbreviations as per table 2.

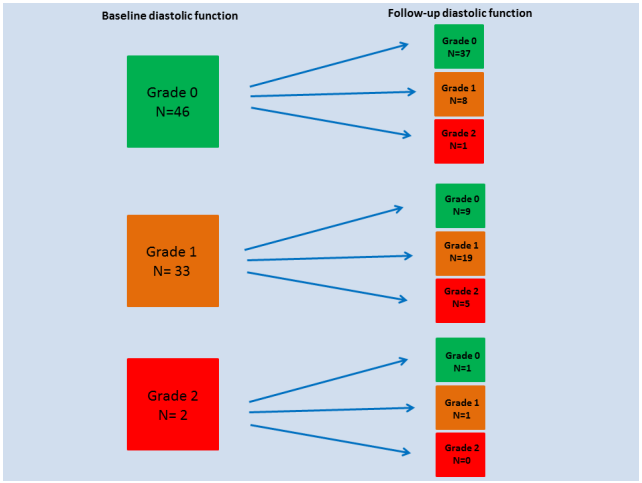

Figure 2: Comparison of diastolic function at baseline versus follow-up echocardiogram

	Improvement or no change in diastolic function (n=67)	Worsening of diastolic function (n=14)	P value
Demographics			
Age, yrs	47.8 ± 15.3	57.1 ± 6.7	0.028
Female gender	53 (79.1%)	14 (100%)	0.060
Nationality			0.49
Lebanese	54 (80.6%)	12 (85.7%)	
Iraqi	11 (16.4%)	1 (7.1%)	
Others	2 (3.0%)	1 (7.1%)	
Body mass index, kg/m^2 (n=80)	26.7 ± 4.8	30.9 ± 7.2	0.008
Body surface area, m^2 (n=80)	1.77 ± 0.17	1.85 ± 0.21	0.11

Comorbidities			
Systolic blood pressure, mm Hg (n=73)	125 ± 16	134 ± 20	0.094
Hypertension	16 (23.9%)	4 (28.6%)	0.71
Diabetes	9 (13.4%)	1 (7.1%)	0.5
Prior revascularization	7 (10.4%)	2 (14.3%)	0.68
Smoking history	26 (38.8%)	6 (42.9%)	0.78
Sedentary lifestyle	56 (83.6%)	14 (100%)	0.10
Cancer type			
Breast cancer	49 (73.1%)	13 (92.9%)	0.11
Lymphoma	7 (10.4%)	0 (0%)	0.34
Other	11 (16.4%)	1 (7.1%)	0.68
Creatinine, mg/dL (n=77)	0.69 ± 0.18	0.70 ± 0.22	0.87
Glomerular filtration rate, ml/min/1.72 m^2 (n=76)	135 ± 49	136 ± 39	0.91
Medications			
Beta blockers	16 (23.9%)	4 (28.6%)	0.71
ACEi/ARB	16 (23.9%)	1 (7.1%)	0.16
Statins	11 (16.4%)	3 (21.4%)	0.65
Anthracyclines or monoclonal antibodies based tyrosine kinase inhibitors	25 (37.3%)	10(71.4%)	0.019

Table 4: Baseline characteristics of patients stratified by worsening of diastolic function

Independent predictors of change in diastolic function

None of the patients with age <50 years had worsening of diastolic function and 13/14 patients with worsening of diastolic parameters were not taking ACEi/ARB (Figure 3). On multivariate regression analysis, old age, increased body mass index, anthracyclines or monoclonal based TKI and No ACEi/ARB were independent predictors of worsening of diastolic function, while beta blockers (odds ratio 0.13 [0.03-0.57], p=0.007) and lower body mass index (odds ratio 0.85 [0.72-0.99], p=0.047]) were independent predictors of improvement in diastolic function (Table 6).

	Improvement or no change in diastolic function (n=67)	**Worsening of diastolic function (n=14)**	**P value**
Baseline Echocardiographic parameters			
LVEDd/height, mm/m (n=80)	27 ± 3	28 ± 3	0.24
LVESd/height, mm/m (n=79)	18 ± 2	18 ± 2	0.57
LV mass index, g/m2 (n=76)	45 ± 9	38 ± 10	0.020
Ejection fraction, %	59.7 ± 4.0	60.4 ± 5.0	0.54
LA volume index, ml/m2 (n=78)	22.9 ± 5.3	22.1 ± 5.2	0.61
E, cm/s	72 ± 17	79 ± 19	0.21
A, cm/s	70 ± 20	80 ± 19	0.095
E/A	1.2 ± 1.1	1.0 ± 0.3	0.49
Deceleration time, ms	209 ± 34	216 ± 38	0.52

e' lateral, cm/s	11 ± 4	11 ± 3	0.30
E/e'	6.6 ±1.9	8.0 ± 2.9	0.022
Systolic PAP (n=36)	28 ± 5	33 ± 9	0.093
Global longitudinal strain, % (n=76)	-20 ± 2	-19 ± 3	0.35
TAPSE (n=59)	21 ± 4	22 ± 4	0.57
Right ventricular S' (n=70)	13 ± 2	13 ± 2	0.88
Follow-up Echocardiographic parameters			
LVEDd/height, mm/m (n=78)	28 ± 3	27 ± 2	0.49
LVESd/height, mm/m (n=78)	18 ± 2	18 ± 1	0.32
LV mass index, g/m^2 (n=76)	46 ± 8	41 ± 8	0.04
Ejection fraction, %	59.0 ± 4.0	59.5 ± 3.8	0.67
LA volume index, ml/m^2 (n=78)	23 ± 6	25 ± 6	0.40
E, cm/s	75 ± 18	82 ± 22	0.20
A, cm/s	74 ± 18	89 ± 27	0.015
E/A	1.01 ± 0.3	0.96 ± 0.29	0.28
Deceleration time, ms	197 ± 35	233 ± 56	0.04
e' lateral, cm/s	12 ± 3	9 ± 1	0.001
E/e'	6.9 ± 2.1	9.5 ± 3.6	0.001
Systolic PAP (n=43)	28 ± 6	29 ± 7	0.86
Global longitudinal strain, % (n=76)	-19.9 ± 1.9	-18.8 ± 2.0	0.16
TAPSE (n=71)	22 ± 4	21 ± 4	0.73
Right ventricular S' (n=71)	14 ± 2	13 ± 2	0.34
Ejection fraction drop ≥10%	2(3.0%)	1(7.1%)	0.45
Global longitudinal strain drop ≥-2%	2(3.0%)	1(7.1%)	0.45
Change in parameters: follow-baseline (Paired t-test P value)			
Change in global longitudinal strain	-0.15% ± 2.7% (p=0.82)	+0.53% ± 0.16% (p=0.61)	
Change in ejection fraction	+0.69% ± 3.9% (p=0.16)	-0.93% ± 5.2% (p=0.52)	
Change in E/e'	-0.32 ± 2.1(p=0.22)	+1.47 ± 1.9 (p=0.014)	
Change in e'	-0.076 ± 2.3(p=0.79)	-1.6 ± 2.2 (p=0.015)	

Table 5: Echocardiographic parameters stratified by worsening of diastolic function

Discussion

In the current study, we showed that: 1) new onset DD or worsening of baseline diastolic function are not uncommon after the administration of potentially cardiotoxic chemotherapy; 2) DD occurs early post-chemotherapy before notable changes in EF or GLS are seen; 3) anthracyclines and TKI are associated with increased risk for worsening of DD; 4) patients on ACEi/ARB are less likely to develop early diastolic dysfunction and those on beta-blockers more likely to have improvement of DD; 5) old age and obesity are independent predictors of worsening diastolic function; and 6) none of the patients younger than 50 years developed worsening of diastolic function.

Anthracyclines and monoclonal antibodies based TKI among others have been associated with cardiomyopathy, which may result in heart failure symptoms if undetected or left untreated [5,6,8]. Routine echocardiography prior to and after administration of this regimen has become standard of care. While EF is one of the markers of systolic function, early cardiomyopathy occurs before a visual drop in EF is seen or reported [9]. Global longitudinal strain with speckle tracking

imaging is a more sensitive marker of systolic function and detects subtle change, offering additive value to traditional parameters such as EF [9,10]. The role of diastolic parameters as markers for early cardiomyopathy was evaluated several years ago in small studies, and more recently in others [11-15]. Indeed, a recent study showed that worsening of diastolic parameters translated into subsequent worsening of systolic function and were indeed a manifestation of chemotherapy-induced cardiotoxicity [15]. These agents often result in impaired heart relaxation, decreased compliance and elevated filling pressure, hence DD. With the introduction of tissue Doppler imaging, Di Lisi et al. showed a decrease in e' following chemotherapy [14].

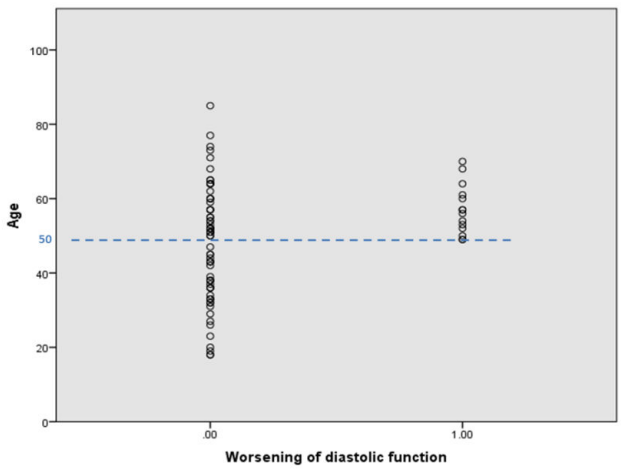

Figure 3: Bar histogram showing distribution of age versus worsening of diastolic function. None of the patients less than 50 years of age had worsening of diastolic function

Variable	Wald	Odds ratio	95% CI	P value
Age, years	0.077	1.080	1.014-1.150	0.016
Body mass index, kg/m^2	0.179	1.196	1.039-1.376	0.012
Anthracyclines or monoclonal antibodies based tyrosine kinase inhibitors	1.733	5.65	1.12-28.4	0.036
No ACEi/ARB	3.20	24.4	1.5-395	0.024

Table 6: Predictors of worsening of diastolic function

Nagelkerke R Square 0.44. ACEi: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker

In the current study, 17% of patients had worsening of diastolic function within 3 months post-chemotherapy. We have previously shown that diastolic function is indeed dynamic and up to 16% of outpatients may have worsening after a mean follow-up over 1 year; however these patients were not receiving chemotherapy which may explain the faster rate of decline in diastolic function in our cohort. The clinical significance of worsening of diastolic function has been previously established as an independent predictor of new onset heart failure and all-cause mortality and that it bears the same prognosis as worsening of systolic function [22,23]. Whether this drop in diastolic function translates into heart failure symptoms needs to be validated on follow-up and in larger studies. It is well accepted that a visual drop in EF is a late manifestation of cardiomyopathy [9]. The fact that a significant percentage of patients had a drop in diastolic function without any change in EF or GLS underlines the importance to DD as early marker of disease. Although GLS has been shown to be a sensitive marker of early cardiomyopathy, the relatively low number of patients that had GLS measured and recorded is perhaps one of the reasons why no statsitically significant change was detected. Furthermore, most patients with DD had mild relaxation abnormality which is not a surprise given the relatively low cardiovascular co-morbidities of the cohort. However, even grade I DD is associated with increased all-cuase mortality after adjusting for traditional cardiac risk factors, and therefore should not be taken for granted [24].

The role of cardio protective medications in patients receiving chemotherapy has been established in several studies. In patients with early manifestation of cardio toxicity, ACEi/ARB and beta blockers have shown promising results in reversing cardiomyopathy and restoring normal systolic function [25-28]. An interesting finding of our study is that patients receiving ACEi/ARB for blood pressure control prior to initiation of chemotherapy and throughout its course were less likely to develop worsening of DD. It is interesting to consider the potential mechanism for this finding. Recent studies showed that renin-angiotensin system activation was associated with c-Src up-regulation, Connexin-43 (Cx43) loss, reduced myocyte coupling, and arrhythmia, while ACEi increased Cx53, prevented left ventricular remodelling, and reduced concentrations of circulating angiotensin II and noradrenaline [29,30]. On the other hand, administration of beta blockers was associated with improvement in diastolic function. This of course is hypothesis generating at best and needs to be evaluated prospectively in large clinical trials. Whether the initiation of such cardio-protective medications in high risk patients (age >50 years, high body mass index, receiving anthracyclines or TKI) at the beginning of the chemotherapy regimen is indeed associated with lower risk of cardiomyopathy (diastolic and systolic) and whether it translated clinically into lower chance of heart failure and cardiovascular death deserves future investigation. Also, until further large clinical trials are conducted to risk stratify patients receiving chemotherapy regarding cardio toxicity, a bisectional collaboration between the oncologist and cardiologist should occur to identify high risk patients, optimize pharmacological therapy prior and during chemotherapy to prevent deterioration of systolic and diastolic function.

Strengths and limitations

The study was performed prospectively and all clinical variables including comorbidities and medications were retrieved and ascertained at enrolment. The same echocardiographic parameters including left atrial volume index and tissue Doppler were acquired for all patients. Furthermore, grading of diastolic function was done by two blinded level III echocardiography board certified cardiologists using standardized updated guidelines, hence minimizing potential error and bias.

However, we acknowledge several limitations. This is a single tertiary referral centre study of small sample size with referral and selection bias. Only 81 (36%) patients had a follow-up echocardiogram; however, there was no significant difference in baseline diastolic function among those who followed-up and those who did not (p=0.45). The global longitudinal strain was not obtained

on many patients because the software was available on one machine (and recently two) only, and an off-line processing workstation was not available. In addition, the cardiac medications were recorded at one time only without the dose and without the knowledge whether patients were compliant with taking them, or whether others started them after enrolment. The cumulative dose of anthracyclines given was also not available. The signs and symptoms of heart failure were not collected nor the NYHA functional classification. The follow-up time between studies was relatively short to notice any significant decrease in systolic performance; yet, there was worsening of diastolic function in a considerable percentage of patients. All patients that developed DD were female with breath cancer, hence narrowing our findings to this subgroup of patients. In addition, the regression model was over fitted given the small number of primary endpoints; a larger study is needed to validate the findings. Finally, there were no hard endpoints collected; this is work in progress and will be prospectively collected at 2 years interval.

Conclusion

In Middle Eastern patients undergoing potentially cardio toxic chemotherapeutic agents, worsening of diastolic function is not uncommon and could be an early marker for developing cardiomyopathy, even before drop in EF or global longitudinal strain. Patients older than 50 years with high body mass index receiving anthracyclines or TKI regimen are at increased risk for worsening DD. Also, the concomitant use of ACEi/ARB and beta blockers seems to have a protective effect. These results however should be interpreted with caution since all patients that developed worsening of diastolic function were female with breast cancer, hence narrowing our findings to this subgroup. Larger validation studies are needed. We believe that diastolic function is an important and integral part of comprehensive LV assessment in patients undergoing chemotherapy, and may identify higher risk groups. A collaborative team consisting of a cardiovascular imaging, heart failure specialists, and an oncologist is needed to establish a multidisciplinary cardio-oncology program to provide optimal patient care.

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