

Subclinical Systolic Dysfunction during Chemotherapy for Breast Cancer

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Abstract

Background: Cardiotoxicity is the main complication related to cancer therapy. Studies indicate that global longitudinal strain is an early detector of subclinical dysfunction of the left ventricle, preceding the decline in ejection fraction (EF). However, the reproducibility of such methodology has not been tested outside specialized centers.

Objectives: To assess the frequency of subclinical cardiotoxicity and to compare global longitudinal strain and EF measurements during the clinical course of patients undergoing chemotherapy for breast cancer.

Methods: This was an observational prospective study of 78 adult women who underwent serial echocardiograms (baseline and 1, 3, and 6 months after the beginning of chemotherapy), to evaluate biplane and 3D EF and global longitudinal strain. Cardiotoxicity and subclinical dysfunction were defined according to American Society of Echocardiography/European Association of Cardiovascular Imaging criteria. Statistical significance was set at $p < 0.05$.

Results: The mean age of the patients was 50.1 ± 11.48 years. The frequency of subclinical cardiotoxicity (defined by global longitudinal strain) was 14.9% after 30 days of chemotherapy, 16.7% after 3 months, and 19.7% after 6 months, compared to 4.5%, 3%, and 6.6%, respectively, when clinical cardiotoxicity was determined according to EF. The group that developed subclinical cardiotoxicity by 30 days (group A) had a higher frequency of clinical cardiotoxicity at 3 months ($p=0.028$) and a lower mean biplane EF after 30 days ($p=0.036$) than the group that showed no evidence of subclinical cardiotoxicity (group B).

Conclusion: Subclinical cardiotoxicity was frequent and began early, being associated with a drop in EF during the clinical course.

Keywords: Breast Neoplasms; Drug Therapy; Ventricular Dysfunction; Echocardiography/ methods; Strain.

Introduction

Although most chemotherapy agents have adverse side effects, the most feared, due to its morbidity and mortality, is cardiotoxicity. Its main etiological agents are anthracyclines and trastuzumab, both of which are widely used in breast cancer treatment.¹⁻³

Several methods have been proposed to diagnose and assess cardiotoxicity secondary to cancer treatment. Currently, determining left ventricular ejection fraction

(LVEF) by echocardiography has been recommended.⁴⁻⁹ However, studies have shown that LVEF, despite being a robust predictor of cardiac events in general, has low sensitivity for detecting changes in LV function,⁹ with a detectable drop in LVEF occurring only after damage to a large amount of myocardial tissue.⁵

Large studies have found myocardial strain to be an ideal parameter of myocardial deformation for early detection of subclinical systolic dysfunction, ie, even before cardiotoxicity is diagnosed through a drop in

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LVEF.^{6,7,9} However, despite the concrete evidence of its sensitivity, few studies have used the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) definition of subclinical dysfunction, in which a drop in global longitudinal strain (GLS) is considered a strong predictor of future cardiotoxicity, which is evidenced by LVEF.⁹

Thus, the objectives of the present study were to assess the incidence of subclinical cardiotoxicity according to the ASE/EACVI criterion, identifying the time of occurrence and associated factors, in addition to comparing GLS with LVEF in the clinical course of patients undergoing chemotherapy for breast cancer.

Methods

Study Design and Population

The population of this observational, longitudinal, analytical, and prospective study consisted of women over 18 years of age with breast cancer who were referred from a variety of public and private institutions to the echocardiography service of a reference hospital prior chemotherapy with anthracyclines. The patients underwent four echocardiographic examinations, the first of which was performed before the initiation of chemotherapy, and the others occurred 30 days, 3 months, and 6 months after chemotherapy began. A tolerance of approximately 15 days was allowed for the date of each exam. The aforementioned intervals for the echocardiograms were based on previous studies assessing the effects of anthracyclines on LV function.^{10,11}

Patients who underwent at least two of the four echocardiographic assessments during the study period were included. Exclusion criteria used were: previous structural heart disease, a subnormal baseline LVEF (< 53%),⁹ an inadequate acoustic window, and previous chemotherapy or radiotherapy.

Clinical and Socio-demographic Variables

The collected data included clinical information, physical examination results, echocardiographic data, and the proposed treatment;

All patients received anthracycline in one of the two chemotherapy regimens chosen by the responsible oncologist:

a) ACT (doxorubicin, cyclophosphamide and paclitaxel) protocol: doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² administered in 4 cycles every 21 days, followed by paclitaxel 80 mg/m² in 12 weekly cycles, both for adjuvant and neoadjuvant treatment.

b) EFC (5-fluoracil, epirubicin and cyclophosphamide) protocol: 5-fluoracil 600 mg/m²; epirubicin 90 mg/m²; cyclophosphamide 600 mg/m² in 4 cycles every 21 days, followed by docetaxel 75 mg/m², also in 4 cycles every 21 days.

Trastuzumab therapy began in eligible patients after the anthracycline cycles ended. However, none of the patients began using the monoclonal antibody in time. Furthermore, the maximum cumulative dose of anthracycline (doxorubicin, 240 mg/m², epirubicin, 360 mg/m²) was not exceeded in any patient.¹²

Doppler echocardiographic procedure

An EPIQ 7 ultrasound system (Philips, Amsterdam, Netherlands) with an X5-1 matrix transducer and Automated Cardiac Motion Quantification (aCMQ) software were used.¹³ The monitoring protocol for chemotherapy treatment was established by the ASE/EACVI.⁹

The sector and depth were adjusted for an optimal view of the entire LV myocardium at the highest possible frame rate. The images were acquired at the end of expiration. Three cardiac cycles from AP3L (Three Chamber Longitudinal Apical), AP4L (Four Chamber Longitudinal Apical), and AP2L (Two Chamber Longitudinal Apical) were acquired and recorded for subsequent analysis.¹⁴

A LVEF > 53% was considered a normal value.⁹ LVEF values were obtained by the following methods:

a) Biplane disc (Simpson's method): aCMQ software was used to determine the AP3L, AP4L, and AP2L strain with automatic delineation of the edge, which was then manually corrected.¹⁵

b) Three-dimensional method: volumetric method of greater accuracy that acquires the entire LV, maximizing the temporal resolution without compromising the spatial resolution using the full-volume.¹⁵

Two-dimensional LV GLS was calculated using speckle tracking. Cardiac cycles were acquired and selected using aCMQ software. The strain was then calculated beginning with the AP3L cycle, followed

by the AP4L and AP2L cycles. The measurements were manually adjusted whenever necessary and, after calculating the myocardial deformation in each cycle, the GLS was graphed in a polar map (bull's eye).¹⁵

Based on the ASE/EACVI consensus,⁹ the following definitions and diagnostic criteria for cardiotoxicity were applied:

a) Subclinical cardiotoxicity: > 15% relative reduction in GLS compared to the baseline value;

b) Clinical cardiotoxicity: an absolute reduction in LVEF > 10% to a value < 53%. As in other studies comparing GLS and LVEF, only biplane EF was considered. Moreover, the acoustic window of some patients was inappropriate for three-dimensional EF acquisition.

Patients who developed subclinical cardiotoxicity during the study period were considered group A, and those who did not were considered group B.

All tests were performed by a single experienced observer and the variables were routinely remeasured, with the means used in the analysis. Each echocardiogram was sent to the patient's oncologist.

Ethical Aspects

This study was approved by the Human Research Ethics Committee of the University Hospital/Federal University of Sergipe (No. 2,659,902, CAAE number 87240718.9.0000.5546) in accordance with Resolution 466/2012 of the National Health Council. All participants provided written informed consent.

Statistical analysis

The study had an initial non-random sample of 82 consecutively selected patients to minimize sampling bias. The Kolmogorov-Smirnov test was used to assess data normality. Numerical variables were described as mean \pm standard deviation. Categorical variables and simple and relative frequencies were used with their respective 95% confidence intervals. Pearson's chi-square test or Fisher's exact test was used for categorical variables. A paired Student's *t*-test was used to compare groups with and without cardiotoxicity. Statistical significance was defined as $p < 0.05$. In addition, the internal consistency of GLS measurements was analyzed using Cronbach's α . SPSS 23.0 was used for the statistical calculations.

Results

Study population

Of the 82 patients eligible for the study, 3 did not return for any subsequent evaluations and 1 had an inadequate echocardiographic window for baseline values. Thus, 78 patients with breast cancer were included, whose general characteristics are shown in Table 1.

Only 49 of the patients returned for all 3 subsequent assessments (30 days, 3 months, and 6 months). A total of 67, 64, and 61 patients attended the 30-day, 3-month, and 6-month evaluations, respectively.

The mean age of the patients was 50.1 (SD, 11.48) years with a minimum of 21 and a maximum of 77 years. Five (6.4%) patients died between 30 days and 3 months after the start of treatment.

The behavior of echocardiographic parameters that define cardiotoxicity

Each patient was assessed for cardiotoxicity over time in each of the 3 recommended echocardiographic parameters (Table 2). It was observed that subclinical cardiotoxicity occurred earlier and more frequently when defined according to GLS than when defined according to EF, with the 95% CI demonstrating the statistical power of this difference. Furthermore, after an initial peak, the prevalence of cardiotoxicity remained similar over time in all 3 methods (GLS, biplane EF, and 3D EF). The behavior of these echocardiographic parameters over the four periods can be seen in Figure 1.

In addition, the internal reliability of the GLS measurements (baseline, 30 days, 3 months, and 6 months) was assessed, showing a Cronbach's α value of 0.855, which indicates high internal reliability.

Assessment of subclinical cardiotoxicity and GLS

During the first month of treatment, 10 (14.9%) of the 67 patients already met the criteria for subclinical cardiotoxicity (group A), and two also met the criteria for clinical cardiotoxicity. As shown in Table 3, there was no difference in the baseline characteristics between the two groups. However, clinical cardiotoxicity within

Table 1 – General characteristics of the sample

Characteristic	N = 78 (%)
Age (years)	50.1 ± 11.48
Asymptomatic at the 1 st evaluation	76 (97.4)
SAH	30 (38.5)
Diabetes Mellitus	4 (5.1)
Hypercholesterolemia	22 (28.2)
Obesity	10 (12.8)
Smoking	4 (5.1)
Family history of CAD	10 (12.8)
ACEI or ARB	24 (30.8)

Values expressed as a percentage (%).

SAH: systemic arterial hypertension; CAD: coronary artery disease; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Table 2 – Frequency of cardiotoxicity according to echocardiographic parameters, measured before and during chemotherapy

	Cardiotoxicity at 30 days	Cardiotoxicity at 3 months	Cardiotoxicity at 6 months
GLS	14.9% (10/67) CI: 9-22.4%	16.7% (11/66) CI: 10.1-25.8%	19.7% (12/61) CI: 11.5-27.9%
Biplane EF	4.5% (3/67) CI: 0-10.4%	3% (2/66) CI: 0-7.6%	6.6% (4/61) CI: 1.6-13.1%
3D EF	4.9% (3/61) CI: 1.6-8.2%	7% (4/57) CI: 3.5-10.5%	5.9% (3/51) CI: 0-13.7%

CI: 95% confidence interval; EF: Ejection Fraction; GLS: Global Longitudinal Strain.

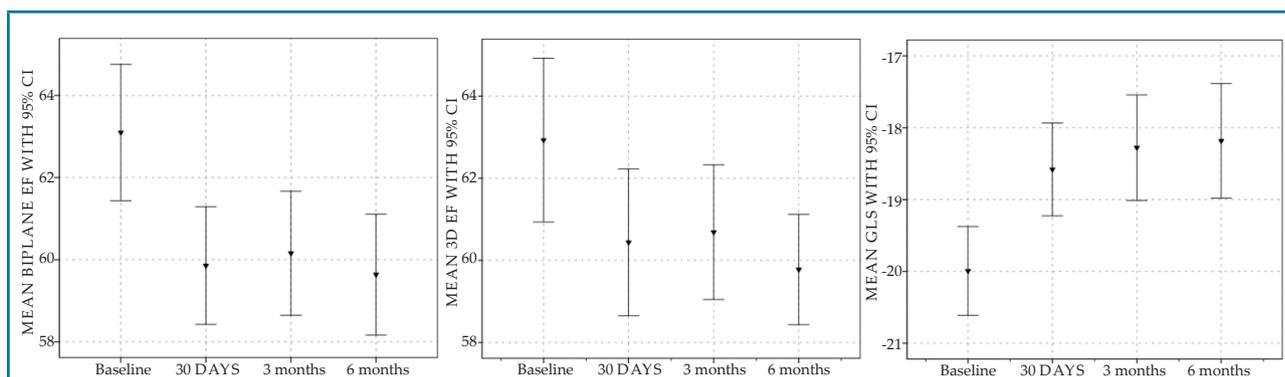


Figure 1 – Graphic representation of the clinical course of global longitudinal strain, 3D ejection fraction, and biplane ejection fraction measurements over six months.

Table 3 – Comparison of variables between patients who did and did not develop subclinical cardiotoxicity after 30 days of chemotherapy

Characteristics	Group A: WITH subclinical cardiotoxicity at 30 days (N = 10)	Group B: WITHOUT subclinical cardiotoxicity at 30 days (N = 57)	p-value
Age (years)	53.4±11.58	49.73±11.82	0.368
Baseline BP EF	63.92±5.65	62.95±5.61	0.617
30-day BP EF	57.41±4.18	60.55±4.93	0.048
3-month BP EF	58.81±4.56	60.91±5.27	0.248
6-month BP EF	58.31±4.62	59.85±5.15	0.389
Clinical cardiotoxicity at 30 days	10% (1/10)	3.5% (2/57)	0.389
Clinical cardiotoxicity at 3 months	20% (2/10)	0% (0/47)	0.028
Clinical cardiotoxicity at 6 months	20% (2/10)	4.8% (2/42)	0.163
SAH	60% (6/10)	33.3% (19/57)	0.157
Diabetes	0% (0/10)	7% (4/57)	1
Hypercholesterolemia	40% (4/10)	26.3% (15/57)	0.452
Obesity	10% (1/10)	12.3% (7/57)	1
Smoking	10% (1/10)	3.5% (2/57)	0.389
Previous CAD	0% (0/10)	15.8% (9/57)	0.335
ACEI or ARB	20% (2/10)	31.6% (18/57)	0.711
Asymptomatic	70% (7/10)	78.9% (45/57)	0.681
Dyspnea	0% (0/10)	12.3% (7/56)	0.583
Edema	0% (0/10)	5.3% (3/57)	1
Palpitations	10% (1/10)	5.3% (3/57)	0.485
Chest pain	0% (0/10)	1.8% (1/57)	1
Asthenia	30% (3/10)	10.5% (6/57)	0.125

values expressed as a percentage (%); bold font indicates significant values; BP EF: biplane ejection fraction; SAH: Systemic Arterial Hypertension; CAD: coronary artery disease; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

3 months was more frequent in group A. It should also be pointed out that the mean biplane EF after 30 days of treatment was also considerably lower in group A, although most of the group did not yet meet the criteria for clinical cardiotoxicity.

At the 6-month evaluation, group A had a higher mean age, as well as a lower mean biplane EF, allowing clinical cardiotoxicity to be more clearly determined at this stage. The only clinical characteristic that differed between the two groups was the prevalence of hypercholesterolemia, which was higher in group A. Table 4.

Table 5 shows the behavior of GLS in both groups. Although the mean baseline GLS was equal between the groups, patients who developed clinical cardiotoxicity at 6 months had a lower mean GLS in the 30-day and 3-month assessments. At 3 months there was a relevant difference in GLS reduction between patients who had developed clinical cardiotoxicity by 6 months and those who had not. This difference did not occur for biplane EF. Of note, in the patient with the greatest relative decrease in GLS, this reduction occurred between the third and sixth month, while EF remained at normal levels (Figure 2).

Table 4 – Comparison of variables between patients who did and did not develop subclinical cardiotoxicity after 6 months of chemotherapy

Characteristics	Group A: WITH subclinical cardiotoxicity in 6 months	Group B: WITHOUT subclinical cardiotoxicity in 6 months	p-value
Age (years)	55.91±9.63	47.83±10.86	0.022
Baseline BP EF	61.70±5.73	62.89±5.80	0.525
30 day BP EF	59.05±4.05	60.15±5.09	0.527
3 month BP EF	59.22±5.07	60.15±5.36	0.601
6 month BP EF	56.15±4.97	60.55±5.00	0.008
Clinical cardiotoxicity at 30 days	0% (0/10)	4.8% (2/42)	1
Clinical cardiotoxicity at 30 days	9.1% (1/11)	2.2% (1/44)	0.357
Clinical cardiotoxicity at 6 months	25% (3/12)	2% (1/49)	0.022
Asymptomatic	41.7% (5/12)	61.2% (30/49)	0.330
SAH	58.3% (7/12)	30.6% (15/49)	0.098
Diabetes	16.7% (2/12)	2% (1/49)	0.096
Hypercholesterolemia	58.3% (7/12)	24.5% (12/49)	0.036
Obesity	8.3% (1/12)	12.2% (6/49)	1
Smoking	16.7% (2/12)	4.1% (2/49)	0.170
Previous CAD	8.3% (1/12)	12.2 (6/49)	1
ACEI or ARB	25% (3/12)	28.6% (14/49)	1
Asthenia at 30 days	30% (3/10)	7.1% (3/42)	0.077
Asthenia at 6 months	33.3% (4/12)	12.2% (6/49)	0.096

Values expressed as a percentage (%); bold font indicates significant values; BP EF: biplane ejection fraction; SAH: systemic arterial hypertension; CAD: coronary artery disease; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Discussion

In the present study, the frequency of subclinical cardiotoxicity was high from the first month of anthracycline chemotherapy, unlike the results of myocardial dysfunction analysis based exclusively on EF (biplane and 3D). Furthermore, the general cardiotoxicity assessment showed a peak frequency in the first month of treatment, which remained approximately constant until the sixth month.

Population and risk factors

The only risk factors associated with cardiotoxicity were age and hypercholesterolemia. It should be pointed out that the prevalence of SAH was higher at all assessments in the group that developed cardiotoxicity

(subclinical or clinical). Among studies assessing the risk factors for myocardial failure after chemotherapy, SAH was the factor most consistently associated with this outcome.^{12,16} A major review by the American Society of Clinical Oncology lists other important risk factors, such as: a radiotherapy field that includes the cardiac area, a history of structural heart disease, high doses of anthracyclines, trastuzumab therapy, diabetes, smoking, and obesity.¹² In our study, radiotherapy was not analyzed because many patients could not undergo it in time; this was also the case with those eligible for trastuzumab therapy. No patient received high doses of anthracyclines. Although a history of structural cardiac disease was an exclusion criterion in the present investigation,¹⁷ its prevalence was relatively low in the population, which could explain the lack of associations.

Table 5 – Comparison of variables between patients who did and did not develop clinical cardiotoxicity after 6 months of chemotherapy

	WITH apparent cardiotoxicity	WITHOUT apparent cardiotoxicity	p-value
Age	48.5±5.56	49.49±11.35	0.864
Baseline GLS	-19.15±1.96 (N = 4)	-20.03±2.24 (N = 57)	0.444
30-day GLS	-16.42±2.10 (N = 4)	-18.87±2.19 (N = 48)	0.037
3-month GLS	-15.70±1.92 (N = 4)	-18.65±2.40 (N = 52)	0.020
6-month GLS	-15.45±1.04 (N = 4)	-18.38±2.75 (N = 57)	0.039
GLS reduction at 30 days	12.98±17.96 (N=4)	5.57±9.94 (N=48)	0.186
GLS reduction at 3 months	17.71±9.68 (N=4)	6.99±9.66 (N=52)	0.037
BP EF reduction at 30 days	3.91±11.88 (N=4)	4.72±8.78 (N=45)	0.864
BP EF reduction at 3 months	7.13±7.58 (N=4)	4.01±8.66 (N=45)	0.491
SAH	75% (3/4)	33.3% (19/57)	0.129
Diabetes	0% (0/0)	5.3% (3/57)	1
Hypercholesterolemia	50% (2/4)	29.8% (17/57)	0.582
Obesity	0% (0/0)	12.3% (7/57)	1
Smoking	25% (1/4)	5.3% (3/57)	0.243
Previous CAD	0% (0/4)	12.3% (7/57)	1
ACEI or ARB	0% (0/4)	29.8% (17/57)	0.322
Asymptomatic	75% (3/4)	56.1% (32/57)	0.629
Edema	25% (1/4)	24.6% (14/57)	1

GLS: Strain Longitudinal Global; BP EF: biplane ejection fraction. SAH: systemic arterial hypertension; CAD: coronary artery disease; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

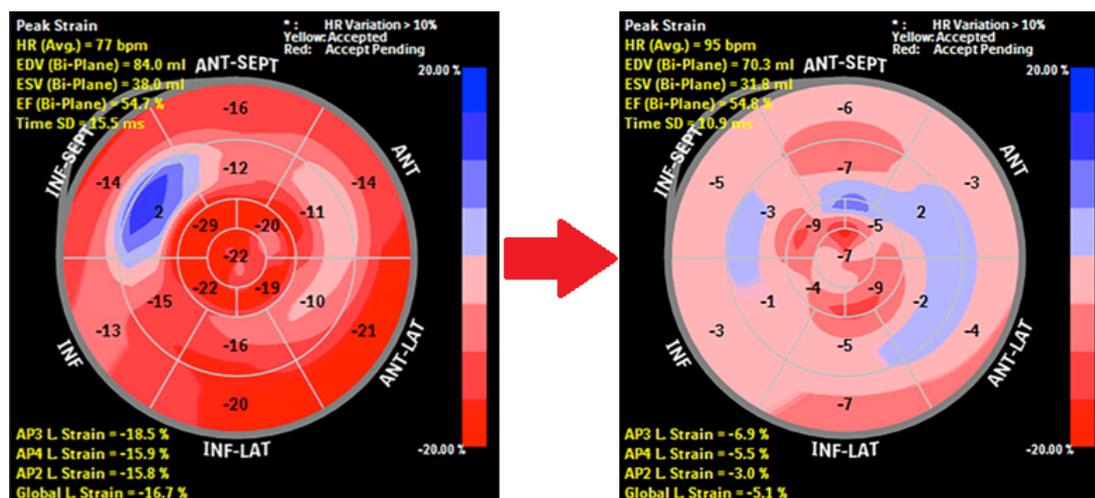


Figure 2 – Polar map of the clinical course of a patient from the third to the sixth month of follow-up.

A further analysis involved the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, drugs known to provide protection against early decline in global LV function.¹⁸ Interestingly, in this study, baseline treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers did not decrease the occurrence of cardiotoxicity. As shown by Laufer-Perl et al.,¹⁹ this is due to the fact that the treatment was not administered to prevent LV dysfunction, but as a therapy for SAH, which would put these patients at greater risk of LV dysfunction.

Definitions and incidence of cardiotoxicity

Several definitions of cardiotoxicity have been developed, making it difficult to standardize and estimate its incidence as an outcome. The present study was based on ASE/EACVI guidelines.⁹

The incidence of clinical cardiotoxicity in our sample was relatively low, which can be explained, in part, by the fact that our definition was more specific than that of most publications.^{20,21} Another possible explanation is that our study only included patients treated with anthracycline, while other studies have investigated associations with multiple cardiotoxic drugs.^{10,21} Such hypotheses are corroborated by the results of studies with designs similar to ours, which obtained similar results regarding the incidence of clinical cardiotoxicity.^{22,23}

In our study, echocardiographic parameters of systolic function during chemotherapy behaved similarly to those of other studies that performed this analysis. The early drop (by 30 days) in GLS and EF (3D and biplane) and their subsequent lower mean values has also been demonstrated in other cohorts that evaluated the cardiotoxicity of chemotherapy.^{19,21,22}

GLS and Subclinical Cardiotoxicity

As for the occurrence of subclinical cardiotoxicity, few studies have evaluated it as a categorical variable (mostly investigating only the behavior of the GLS values themselves) and fewer still have done so according to the ASE/EACVI definition. The frequency of subclinical cardiotoxicity was relatively high in this study, being 15.2% 30 days after the start of chemotherapy and unaccompanied by a significant reduction in EF (biplane or 3D). This agrees with the results of other studies, such as Laufer-Perl et al.,¹⁹ and Santoro et al.,²² in which the mean frequency of subclinical cardiotoxicity was approximately 20% at the end of 3 and 12 months of follow-up, respectively.

Another pertinent analysis concerns the relative reduction of GLS and EF. When divided into groups, it was observed that the GLS reduction after 3 months compared to baseline was greater in those who developed clinical cardiotoxicity at 6 months. However, EF did not also drop during the same period, which suggests that this echocardiographic parameter has a lower sensitivity. Similar results were also found in a cohort of 49 Brazilian patients.²⁴ Moreover, between patients with and without clinical cardiotoxicity at 6 months, GLS differed significantly 30 days after the beginning of the chemotherapy and continued to do so in all subsequent assessments, which reinforces the fact that GLS changes are early when myocardial aggression occurs.⁶

In general, this behavior can be explained by the fact that GLS reductions precede EF reductions, making the former a more sensitive method.^{6,7,9} Several factors explain why GLS is a better early indicator of cardiotoxicity. In dysfunction related to cancer therapy, certain segments of the myocardium may be more affected than others, leading to early changes in GLS. The unaffected areas of the myocardium can then compensate for the damaged segments, thus preserving LVEF.²¹ However, GLS, which assesses myocardial deformation, can be measured more accurately.¹¹

Study limitations

One limitation of this study was the short and non-homogeneous follow-up. Thus, an objective assessment of long-term LVEF behavior in relation to the occurrence of subclinical cardiotoxicity was not possible. Furthermore, the low number of patients who appeared for all assessments reduced the statistical power of the results. However, such scenarios are inherent to the study population. Another limitation was the fact that the study was conducted by a single researcher. Nevertheless, the Cronbach's α analysis indicated high internal reliability, which minimized the possibility of measurement bias.

Conclusion

Subclinical cardiotoxicity had a high frequency and began early in this sample. It was associated with a significant drop in EF during the course of treatment but was not associated with known risk factors. The value of assessing GLS at early stages of exposure to anthracyclines was also apparent, which is in line with the ASE/EACVI definition of subclinical cardiotoxicity. It is expected that identifying subclinical cardiotoxicity

will be of great value in daily clinical practice, identifying patients at higher risk of overt cardiotoxicity.

Author contributions

Conception and design of the research: Barroso GMHM, Teles JCOC. Acquisition of data: Barroso GMHM, Teles JCOC, Silva PVJ, Ferreira KO, Assis RJF, Alves MFS, Aragão VAS, Fonsêca KYS, Aquino MM. Analysis and interpretation of the data: Teles JCOC, Melo EV, Oliveira, JLM. Statistical analysis: Teles JCOC, Melo EV. Writing of the manuscript: Barroso GMHM, Teles JCOC. Critical revision of the manuscript for intellectual content: Sousa ACS, Oliveira, JLM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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