Early Diastolic Dysfunction in Breast Cancer Patients Undergoing Chemotherapy

Disfunção Diastólica Precoce em Pacientes com Câncer de Mama Submetidas à Quimioterapia

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Abstract

Background: Chemotherapy for breast cancer is associated with serious cardiovascular complications such as heart failure. The left ventricular ejection fraction is the main parameter used to assess systolic function in these patients. However, the occurrence of diastolic dysfunction may precede that of systolic dysfunction.

Objectives: To evaluate left ventricle diastolic and systolic functions in women with breast cancer undergoing chemotherapy using anthracyclines.

Methods: This observational, longitudinal, analytical, and prospective study included 62 women with breast cancer aged 21–75 years old who underwent echocardiography at baseline and after three months of treatment. Diastolic function parameters were evaluated, and the patients were classified as diastolic dysfunction type 1, 2, or 3. Systolic dysfunction was defined as a left ventricular ejection fraction $\leq 53\%$.

Results: After three months of treatment, 35 patients (56.4%) had type 1 diastolic dysfunction, while one (1.6%) had type 2. Diastolic dysfunction was identified in 26 patients at baseline and developed in 10 patients during treatment. Diastolic function parameters, E wave velocity, and E/A ratio decreased significantly ($p < 0.05$) with chemotherapy; however, the others showed no significant variations. Only three patients had systolic dysfunction, but there was a greater reduction in left ventricular ejection fraction in the group that developed diastolic dysfunction during treatment versus the group with diastolic dysfunction at baseline ($p = 0.04$).

Conclusion: Diastolic dysfunction occurs early in women with breast cancer undergoing chemotherapy. Its onset during the course of treatment is associated with a significantly reduced left ventricular ejection fraction.

Keywords: Breast neoplasms; Cardiotoxicity; Echocardiography; Ventricular dysfunction.

Resumo

Fundamento: A quimioterapia para o câncer de mama está associada a complicações cardiovasculares graves, como a insuficiência cardíaca. A fração de ejeção do ventrículo esquerdo é o principal parâmetro para avaliar a função sistólica nessas pacientes. Todavia, a ocorrência de disfunção diastólica pode preceder à disfunção sistólica.

Objetivos: Avaliar as funções diastólica e sistólica do ventrículo esquerdo de portadoras de câncer de mama em tratamento quimioterápico com antraciclina.

Métodos: Trata-se de estudo observacional, longitudinal, analítico e prospectivo. Estudaram-se 62 mulheres com câncer de mama, com idades de 21 a 75 anos, que realizaram ecocardiogramas basais e após 3 meses de tratamento. Avaliaram-se parâmetros de função diastólica, e as pacientes foram classificadas em disfunção diastólica tipos: 1, 2 ou 3. Definiu-se a disfunção sistólica como fração de ejeção do ventrículo esquerdo $\leq 53\%$.

Resultados: Decorridos 3 meses de tratamento, 35 pacientes (56,4%) apresentavam disfunção diastólica tipo 1, e apenas uma (1,6%) do tipo 2.

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A disfunção diastólica ocorreu em 26 pacientes já na etapa basal e surgiu em dez indivíduos no decorso do tratamento. Os parâmetros de função diastólica velocidade de onda E e relação E/A diminuíram significativamente ($p < 0,05$) com a quimioterapia, todavia, os demais não tiveram variação significativa. Apenas três pacientes apresentaram disfunção sistólica, porém verificou-se maior redução da fração de ejeção do ventrículo esquerdo no grupo que desenvolveu disfunção diastólica durante o tratamento comparativamente ao grupo que apresentava já disfunção diastólica no período basal ($p = 0,04$).

Conclusão: A disfunção diastólica ocorre precocemente em portadoras de câncer de mama submetidas à quimioterapia. O surgimento de disfunção diastólica no decorso do tratamento se associa à redução significativa da fração de ejeção do ventrículo esquerdo.

Descritores: Cardiotoxicidade; Disfunção ventricular; Neoplasias da mama; Ecocardiografia

Introduction

Cancer is considered one of the greatest public health problems worldwide, and breast cancer has remained the most prevalent cancer in women for three decades.¹ Most chemotherapy agents are cardiotoxic, with heart failure (HF) being the most common complication.² In fact, mortality rates reach 60% among patients who develop HF during cancer treatment.²

Despite being cardiotoxic, anthracyclines continue to play an important role in the treatment of solid tumors such as breast cancers and lymphomas.³ Proposed mechanisms for anthracycline-mediated cardiotoxicity include increased oxidative stress via redox cycling of the quinone moiety of anthracyclines and through the formation of iron-anthracycline complexes; disruption of mitochondrial and cellular calcium homeostasis; disruption of mitochondrial energetics; deep radiation of ultrastructural proteins including tinin and dystrophin; direct DNA damage via the inhibition of 2-beta topoisomerase; the inhibition of survival pathways such as neuregulin 1 and Erb B2; and direct cytotoxic effects on cardiac progenitor cells, decreasing repair potential after myocardial injury. How exactly these mechanisms interact and lead to cardiac toxicity remains unknown.⁴

The frequency of cardiotoxicity in the population varies among established definitions and tools. The most widely accepted definition by cardiology and cancer communities is a reduction in left ventricular ejection fraction (LVEF) of more than ten percentage points in relation to the baseline value⁵ to a value lower than 53%.⁶ This definition is used as the standard in this study. The assessment of LV diastolic function is an important part of echocardiographic assessment since echocardiographic measurements of diastolic dysfunction (DD) are associated with an increased risk of HF and mortality in the general population⁷ and considered fundamental to the HF pathophysiology.⁸ Isolated DD itself is associated with an increased risk of morbidity and mortality.⁹

The prevention and early detection of cardiotoxicity are paramount in the management of cancer patients¹⁰ since the paradigm shift occurred from cancer as a final disease to a chronic cardiovascular disease condition among survivors after therapy.

Thus, this study aimed to evaluate the LV diastolic and systolic function of women with breast cancer undergoing chemotherapy with anthracyclines.

Methods

Study population

This observational, longitudinal, and prospective study included 62 women with breast cancer aged > 18 years

who were consecutively selected between November 2016 and July 2018 to reduce sampling bias. The clinical variables evaluated included age in years; anthropometric measurements (weight in kilograms and height in meters); body surface in square meters; vital signs (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP]); comorbidities (systemic arterial hypertension [SAH], diabetes mellitus, and dyslipidemia); smoking; family history of coronary artery disease (CAD); and medications used in chemotherapy.

All patients signed an informed consent form, and the Human Ethics Research Committee of the University Hospital of the Federal University of Sergipe and the boards of the participating institutions approved the study.

The study population underwent two echocardiographic tests: the first before the start of chemotherapy and the second three months later.

All patients used anthracyclines according to one of the two chemotherapy regimens defined by the attending oncologist: ACT, which included doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) administered in four cycles every 21 days followed by paclitaxel (80 mg/m^2) in 12 cycles once a week for adjuvant and neoadjuvant treatment; and FEC, which included fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) administered in four cycles every 21 days, followed by docetaxel (75 mg/m^2) in four cycles every 21 days.

No patient exceeded the maximum recommended anthracycline dose of doxorubicin (240 m/m^2) or epirubicin (360 mg/m^2).¹¹ In addition, no patient underwent associated radiotherapy before the three-month evaluation.

Patients who attended the two echocardiography assessments during the study period were included. The exclusion criteria were previous structural heart disease, inadequate acoustic window, and previous chemotherapy or radiotherapy.

Procedures

All patients were examined using a Philips Epiq 7 ultrasound device with an X5-1 transducer and installed Automated Cardiac Motion Quantification (ACMQ;) software. The same ultrasound device was used to obtain all echocardiograms for each patient. Sector and depth were adjusted to acquire an ideal view of the entire LV myocardium at the highest possible frame rate. The acquisition was obtained at the end of expiration. Multiple cardiac cycles from apical longitudinal three-chamber view (AP3L), four-chamber view (AP4L), and

two-chamber view (AP2L) were acquired and recorded for subsequent analysis.

LVEF was calculated using the biplane disk method or Simpson's method with the ACMQ software from the AP3L, AP4L, and AP2L acquisitions with automatic border detection and subsequently corrected manually. The ventricle was divided into a series of equal-height disks. The volume of each disk was calculated as the area multiplied by the height, and the sum of all disk volumes determined the ventricular volume. An LVEF > 53% was considered normal.⁶

The following parameters were used to calculate the LV diastolic function: mitral diastolic flow with evaluation of E and A wave velocities and E/A ratio with pulsed Doppler; and e' velocities with the tissue Doppler sample positioned in the septal and lateral rings. The mean E/ e' ratio was calculated (normal values: septal $e' > 7$ cm/s, lateral $e' > 10$ cm/s, and mean E/ $e' < 14$); left atrial volume index calculated with acquisition of AP4L and AP2L views starting before the opening of the mitral valve, calculated using the disk method, subsequently indexed by body surface, with the normal value established as < 34 mL/m²; and tricuspid valve regurgitation velocity, whose normal value determined as the cutoff point was < 2.8 cm/s.

LV diastolic function was classified as normal if more than half of the variables were within normal limits and below the cutoff points. In addition, DD was identified if more than half of the parameters met the cutoff points. The study would be inconclusive if half of the parameters met their cutoff points and the other half of the parameters were normal. In patients with a preserved or reduced LVEF, when E wave velocity is ≤ 50 cm/s and E/A ratio is ≤ 0.8 , and the left atrial (LA) pressure is normal or low, then DD is classified as type 1. When the E/A ratio is > 2 and LA pressure is high, the DD is defined as type 3. When the E wave velocity is > 50 cm/s and the E/A ratio ≤ 0.8 (or >0.8 but <2), it is necessary to consider other parameters, such as tricuspid regurgitation (TR) peak velocity with continuous Doppler, E/ e' ratio, and LA volume. The abnormality cutoff points are TR peak velocity > 2.8 cm/s, E/ e' ratio > 14, and indexed LA volume > 34 mL/m². When two of these three parameters meet their cutoff points and the mean LA pressure is high, the DD is classified as type 2. Conversely, if two of these three parameters do not meet the cutoff points, the DD is classified as type 1.¹² For comparative purposes, the sample was divided into three groups: Group 1, patients with DD at baseline; Group 2, patients who developed DD during the three months of treatment; and Group 3, patients who presented no DD at the three-month observation.

All tests were performed by a single examiner, the calculations were repeated, and the mean values of all measurements were analyzed.

Statistical analysis

Qualitative variables are expressed as frequency (percentage), while quantitative variables were subjected to the Shapiro-Wilk test to determine the distribution type. Those that fulfilled the assumption of normality are presented as mean and standard deviation. Non-normally distributed variables are described as median and interquartile ranges or maximum and minimum values.

The chi-square or Fisher's exact test was used to compare qualitative variables as appropriate. Student's t-test was used to compare the two main groups when continuous or discrete variables were normally distributed. Analysis of variance was used to compare patients among groups.

Results

Of the 63 patients eligible for the study, a satisfactory acoustic window for obtaining echocardiographic parameters was not achieved in only one. Thus, 62 patients were evaluated. The mean age of the 21 participants was 48.98 ± 11.3 years (range, 46.11–51.85 years). The clinical and epidemiological characteristics of the study population are shown in Table 1.

Most of the patients (36 [58.1%]) presented with DD at the three-month evaluation. However, 26 patients (41.9%; 95% confidence interval [CI], 29–54.8%) had DD at baseline that persisted at the three-month evaluation, 10 (16.1%; 95% CI, 8.15–25.8%) did not have DD at baseline but developed it by the three-month evaluation; and the remaining 26 patients (41.9%; 95% CI, 29–54.8%) did not present with DD at baseline or the three-month evaluation. As for DD type, only one patient had type 2, while the others had type 1.

Of the risk factors, the population that presented with some DD at the three-month evaluation was older. In addition, the most prevalent risk factors of the population were SAH, dyslipidemia, family history of CAD, and obesity, which were present in 33.9%, 32.3%, 12.9%, and 8.1% of patients, respectively. There was a significant difference between SAH and non-SAH patients and dyslipidemic versus non-dyslipidemic patients who presented with DD. The differences in obesity and family history of CAD among groups were insignificant. Data regarding risk factors and their statistical significance by group are shown in Table 2. No intergroup differences in symptoms were observed (Table 3).

The analysis of diastolic function parameters showed intergroup differences in mean variation of the E wave velocity and the E/A ratio, which significantly decreased by three months after treatment. The lateral e' parameter also showed significant intergroup variation during the study period and reductions in Groups 2 and 3. The other parameters did not differ significantly, and the mean values of the parameters, their variation after three months, and their respective statistical

Table 1 – General clinical characteristics of the sample.

Clinical characteristics	Total (n = 62)
Age, years	48.98 ± 11.30
Obesity	5 (8.1)
SAH	21 (33.9)
Diabetes	3 (4.8)
Dyslipidemia	20 (32.3)
Family history of CAD	8 (12.9)
Smoking	3 (4.8)
Hormone replacement	5 (8.1)

Results are expressed as mean $\pm$ standard deviation or n (%). CAD: coronary artery disease; SAH: systemic arterial hypertension.

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significance are shown in Table 4. Furthermore, there was no significant intergroup difference in HR at the time of the echocardiographic assessment at three months after treatment. However, SBP and DBP differed significantly (Table 5).

95% CI: 95% confidence interval; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure

Only three patients had systolic dysfunction according to the biplane method after three months of treatment. However, LVEF showed a greater mean decrease in the group that

developed DD during treatment than in the group with DD at baseline ($p = 0.041$); however, there was no significant intergroup difference at the three-month evaluation ($p = 0.255$) (Tables 6 and 7).

Discussion

The analysis of LV diastolic and systolic function is an essential part of the echocardiographic assessment, especially in cancer patients undergoing breast cancer treatment, as the observation of early echocardiographic changes is important for monitoring and starting cardioprotective medications. The current study presented important findings about early echocardiographic changes. First, there was a significant number of patients in whom DD developed during chemotherapy treatment; of them, 10 (16.1%) developed DD after three months of treatment. Timothy et al.¹⁵ reported a 20% rate of DD similar to that the present study; however, this was after a longer follow-up (12 months of echocardiographic evaluation). Furthermore, this early incidence of DD corroborates the literature since it is known that LV relaxation changes can be detected after one week of anthracycline use.¹³ One of the main pathophysiological mechanisms of DD in the general population may be associated with cardiac oxidative stress,¹⁴ especially in the population being treated for breast cancer with anthracyclines, which are correlated with increased cardiac oxidative stress that can result in mitochondrial dysfunction, apoptosis, and necrosis.¹⁵

As for LV systolic function, after three months of treatment, only three patients (4.8%) had systolic dysfunction according to the biplane method, while 10 developed DD after the three months of treatment, which suggests that LV DD presents earlier than LV systolic dysfunction. A longer follow-up period will be necessary to establish the clinical outcomes of these patients, but DD abnormalities over time are associated with subsequent systolic dysfunction and cardiotoxicity.⁷ It was also possible to observe that patients with baseline DD are less associated with reduced LVEF than those who develop DD throughout treatment, suggesting that baseline DD is not associated with subsequent systolic dysfunction, similarly to what Timóteo et al.¹⁶ and Upshaw et al.⁷ reported when following patients for 12 months and 6.5 years, respectively.

Table 2 - Prevalence of risk factors by study group.

Risk factor	Diastolic dysfunction at baseline (n=26)	Diastolic dysfunction at 3-month evaluation (n=10)	No diastolic dysfunction at 3-month evaluation (n=26)	P value
Age, years	57.30 ± 8.28	50.90 ± 6.78	39.92 ± 8.23	0.858
Obesity	3 (11.5)	1 (10)	1 (3.8)	0.576
SAH	12 (46.2)	5 (50)	4 (15.4)	0.03*
Diabetes	3 (11.5)	0	0	0.203
Dyslipidemia	14 (53.8)	2 (20.0)	4 (15.4)	0.01*
Family history of CAD	6 (23.1)	1 (10.0%)	1 (3.8)	0.107
Smoking	1 (3.8)	1 (10)	1 (3.8)	0.708

Results are expressed as mean ± standard deviation or n (%). *Statistically significant. CAD: coronary artery disease; SAH: systemic arterial hypertension.

Table 3 - Signs and symptoms by study group.

Sign or symptom	Diastolic dysfunction at baseline (n=26)	Diastolic dysfunction at 3-month evaluation (n=10)	No diastolic dysfunction at 3-month evaluation (n=26)	P value
Dyspnea	5 (19.2)	1 (10)	1 (3.8)	0.213
Edema	5 (19.2)	3 (30)	1 (3.8)	0.091
Palpitations	2 (7.7)	3 (30)	2 (7.7)	0.124
Precordial pain	1 (3.8)	1 (10.0)	1 (3.8)	0.708
Asthenia	5 (19.2)	3 (30.0)	2 (7.7)	0.226
Asymptomatic	16 (61.5)	7 (70.0)	22 (84.6)	0.172

Results are expressed as n (%).

Table 4 - Mean, standard deviation, and statistical significance of diastolic dysfunction at baseline and the three-month examination.

	Group 1		Group 2		Group 3		P value*
	Baseline	3 months	Baseline	3 months	Baseline	3 months	
E wave velocity	69.67 ± 19.56	65.45 ± 13.02	86.36 ± 12.76	61.17 ± 14.94	93.76 ± 14.83	88.17 ± 13.37	0.001†
A wave velocity	89.44 ± 22.50	89.77 ± 17.9	67.14 ± 17.62	79.48 ± 16.27	59.63 ± 14.1	62.71 ± 13.17	0.147
E/A ratio	0.81 ± 0.32	0.76 ± 0.28	1.34 ± 0.36	0.78 ± 0.08	1.55 ± 0.31	1.48 ± 0.27	0.0002†
Indexed left atrial volume	25.93 ± 6.71	26.55 ± 6.31	23.73 ± 4.83	23.19 ± 4.76	29.21 ± 29.89	23.14 ± 5.25	0.514
E/e' ratio	9.21 ± 2.65	8.63 ± 2.15	8.75 ± 1.91	7.38 ± 1.36	8.63 ± 1.41	8.62 ± 2.02	0.14
Septal e'	6.35 ± 2.11	6.21 ± 2.03	7.75 ± 1.70	6.30 ± 1.45	8.86 ± 2.08	8.51 ± 1.92	0.224
Lateral e'	9.08 ± 3.22	9.61 ± 3.24	12.35 ± 1.81	10.47 ± 2.87	13.69 ± 2.69	12.75 ± 2.76	0.035†

*Statistical significance of the mean variation after three months (analysis of variance). †The tricuspid regurgitation velocity parameter is not in the table because it was not calculated in all patients since its use is only necessary when the other parameters are insufficient for classification.

Table 5 - Mean heart rate and systolic and diastolic blood pressures of the groups on the echocardiographic assessment after three months of treatment with respective p and confidence intervals.

	Group 1		Group 2		Group 3		P value
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
HR	86.04 ± 13.92	80.42-91.66	91.30 ± 14.21	81.13-101.47	81.69 ± 15.01	75.63 ± 87.75	0.191
SBP	142.01 ± 20.80	133.67-150.47	133.90 ± 14.69	123.39-144.41	123.16 ± 19.01	115.47-130.83	0.003*
DBP	77.65 ± 8.89	74.06-81.24	77.30 ± 11.11	69.36-85.24	70.65 ± 10.05	66.60-74.71	0.028*

*Statistically significant. 95% CI: 95% confidence interval; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure.

Table 6 - Mean reduction and standard deviation of the biplane ejection fraction after three months in Groups 1 and 2.

	Group 1	Group 2	P value
Mean reduction and standard deviation in BPEF after three months	0.59 ± 10.1	8.21 ± 8.31	0.041

BPEF: biplane ejection fraction.

Table 7 - Mean reduction and standard in biplane ejection fraction after three months in Groups 2 and 3.

	Group 1	Group 2	P value
Mean reduction and standard deviation in BPEF after three months	8.21 ± 8.31	4.62 ± 8.23	0.255

FEBP: fração de ejeção pelo método biplanar.

Figure 1 – Evaluation of a patient's E wave, A wave, and E/A ratio during the study. (A) Basic parameters: E wave velocity of 89.1 cm/s, A wave velocity of 56.6 cm/s, E/A ratio of 1.6. (B) Parameters after three months of chemotherapy: E wave velocity of 51.4 cm/s, A wave velocity of 79.3 cm/s, and E/A ratio of 0.6. Note the decreased E wave and E/A ratio after three months of treatment.

Figure 2 – Razão E/e' de uma paciente durante o estudo. (A) E/e' de 6,0 basal. (B) E/e' de 8,2 da mesma paciente após 3 meses de tratamento. Ambos os valores dentro do limite da normalidade.

Other important findings were related to diastolic function parameters. A significantly reduced E wave velocity and E/A ratio were noted early on, while AE and E/e' indexed volume parameters showed no significant variation. Similar changes in mitral inflow (reduced E/A ratio) were reported in other studies, such as those by Serrano et al.¹⁷ and Ho et al.,¹⁸ the latter also reporting a significantly reduced E wave velocity. Despite being an important tool to assess remodeling and, indirectly, LA function, the indexed LA volume has low sensitivity in the early stages.¹⁹ In turn, variations in the E/e' parameter are also linked to chronic conditions,^{13,20} which justifies the absence of changes in both parameters in the present study. Timóteo et al.¹⁶ showed significant indexed LA volume changes, but not until later – on 12-month echocardiography follow-up.

Factors such as HR and systemic blood pressure should be considered in the context of assessing diastolic function.¹² The present investigation showed no significantly different intergroup mean HR, suggesting that the observed changes in mitral inflow were not directly impacted by this parameter. On the other hand, SBP and DBP differed among the three groups, with higher mean echocardiographic evaluation values in Groups 1 and 2 after treatment due to the greater number of chronic hypertensive patients within them.

One of the limitations of the study was the evaluation time, which, despite having demonstrated early echocardiographic changes in the studied population, did not allow the objective assessment of the long-term behaviors of the systolic and diastolic function parameters correlated with the occurrence of cardiovascular outcomes. It would also be interesting to evaluate the behavior of diastolic and systolic parameters in patients undergoing additional chemotherapy treatment with trastuzumab after anthracycline since the patients did not undergo the former due to the short evaluation time. Another important limitation stems from the dependence of mitral inflow parameters on hemodynamic conditions, such as volume depletion, a side effect related to chemotherapy

that does not allow the conclusion that the E wave and E/A ratio changes observed result directly from its cardiotoxicity. However, it is known that the situations mentioned here are inherent to the study population and methodology.

Conclusion

The study data demonstrated that DD occurs early in breast cancer patients undergoing chemotherapy and that its development during treatment is associated with a significant LVEF reduction compared to patients with DD at baseline. The significantly changed early diastolic function parameters include a reduced E wave velocity, lateral e', and E/A ratio. Further longer-term follow-up studies are needed to assess intergroup differences in cardiovascular outcomes and identify which myocardial function parameters would be chronically changed.

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Authors' contributions

Research conception and design: Barroso GMHM; manuscript writing: Barroso GMHM; data analysis and interpretation: Silva PVJ; data collection: Aragão VAS, Fonsêca KYS, Aquino MM, and Albuquerque UMLAC; statistical analysis: Melo EV and Silva PVJ; critical review of the manuscript for important intellectual content: Sousa ACS and Oliveira JLM.

Conflict of interest

The authors have declared that they have no conflict of interest.

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