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Breast Cancer

Diastolic Dysfunction Following Anthracycline-Based Chemotherapy in Breast Cancer Patients: Incidence and Predictors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Diastolic dysfunction • Anthracycline chemotherapy • Breast cancer • Cardiac biomarkers

Abstract

Introduction. Cardiotoxicity represents a major limitation for the use of anthracyclines or trastuzumab in breast cancer patients. Data from longitudinal studies of diastolic dysfunction (DD) in this group of patients are scarce. The objective of the present study was to assess the incidence, evolution, and predictors of DD in patients with breast cancer treated with anthracyclines.

Methods. This analytical, observational cohort study comprised 100 consecutive patients receiving anthracycline-based chemotherapy (CHT) for breast cancer. All patients underwent clinical evaluation, echocardiogram, and measurement of cardiac biomarkers at baseline, end of anthracycline-based CHT, and at 3 months and 9 months after anthracycline-based CHT was completed. Fifteen patients receiving trastuzumab were followed with two additional visits at 6 and 12 months after the last dose of anthracycline-based CHT. A multivariate analysis was performed to find variables related to the development of DD. Fifteen of the 100 patients had baseline DD and were excluded from this analysis.

Results. At the end of follow-up (median: 12 months, interquartile range: 11.1–12.8), 49 patients (57.6%) developed DD. DD was persistent in 36 (73%) but reversible in the remaining 13 patients (27%). Four patients developed cardiotoxicity (three patients had left ventricular systolic dysfunction and one suffered a sudden cardiac death). None of the patients with normal diastolic function developed systolic dysfunction during follow-up. In the logistic regression model, body mass index (BMI) and age were independently related to the development of DD, with the following odds ratio values: BMI: 1.19 (95% confidence interval [CI]: 1.04–1.36), and age: 1.12 (95% CI: 1.03–1.19). Neither cardiac biomarkers nor remaining clinical variables were predictors of DD.

Conclusion. Development of diastolic dysfunction after treatment with anthracycline or anthracycline- plus trastuzumab chemotherapy is common. BMI and age were independently associated with DD following anthracycline chemotherapy. ***The Oncologist*** 2015;20:1–9

Implications for Practice: This study characterizes the incidence of diastolic dysfunction in a cohort of patients undergoing anthracycline treatment. The incidence of diastolic dysfunction during follow-up was 57% and persisted at the last follow-up visit in 73% of patients. Age and body mass index were found to be independent predictors of anthracycline-related diastolic dysfunction. These findings may help identify patients at higher risk for developing a clinically relevant anthracycline cardiotoxicity from those at lower risk and to differentiate monitoring programs for breast cancer patients according to their risk.

Introduction

Anthracyclines are broad-spectrum chemotherapeutic drugs used in many adjuvant and metastatic breast cancer treatment regimens. The main limitation for use is the development of cardiotoxicity [1, 2]. A major advance in breast cancer treatment has been the incorporation of trastuzumab, a monoclonal antibody used sequentially following anthracyclines in *HER-2*-positive breast cancers (around 20% of breast cancers) [3]. Incorporation of trastuzumab enhances cardiotoxicity, with published incidences for heart failure ranging from 1.7% to 16% and for asymptomatic left ventricular dysfunction ranging from 6% to 34% [4–7].

Diastolic dysfunction is an important predictor of all-cause mortality in large epidemiologic studies [8] and has been shown to play an essential role in the pathophysiology of other cardiac diseases [9, 10] (e.g., ischemic heart disease,

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hypertensive heart disease, or myocarditis), with pathology similar to anthracycline-related cardiotoxicity [11]. Diastolic dysfunction, in this instance, contributes to the onset of heart failure and has been shown to precede the development of systolic dysfunction.

Some studies have examined the usefulness of several echocardiographic diastolic parameters in detecting anthracycline-related cardiac injury [12, 13]. However, there is limited information from longitudinal studies about the incidence and evolution of diastolic dysfunction in a large and homogeneous cohort of patients treated with anthracyclines or anthracyclines plus trastuzumab.

Troponin T (TnT) and N-terminal pro B-type natriuretic peptide (NTproBNP) are classic biomarkers of cardiomyocyte damage and cardiac overload that have been studied in several settings, including patients undergoing chemotherapy [14]. Heart-type fatty acid binding protein (H-FABP) is also a small cytosolic protein released in the circulation after cardiac damage. It has been studied in chronic heart failure as a marker of ongoing myocardial damage [15] but only evaluated in one small study in the setting of cardiotoxicity [16].

The main objective of this study was to asses the incidence and evolution of diastolic dysfunction, using novel parameters and current recommendations, in a cohort of patients with breast cancer treated with anthracycline or anthracyclines plus trastuzumab. Secondary objectives were to search for clinical predictors of anthracycline-related diastolic dysfunction and to evaluate the role of cardiac biomarkers (high-sensitivity troponin T [hsTnT], NTproBNP, and H-FABP) in this setting.

Materials and Methods

Study Design

This was an analytical observational prospective cohort study carried out in a general hospital.

Patients

The study sample size was determined by the number of consecutive patients with breast cancer treated with anthracycline-based chemotherapy for a period of 2 years. From April 2008 to May 2010, 100 consecutive patients with breast cancer who were scheduled to receive anthracycline-based chemotherapy in our hospital and had no exclusion criteria were enrolled in the study and followed for 1 year. Exclusion criteria were as follows: poor echocardiographic window, previous cardiac disease or ejection fraction less than 55%, atrial fibrillation, poor prognosis with an expected survival of less than 1 year, or previous treatment with anthracyclines. The protocol was approved by the local institutional review board (ethics committee) and all patients provided informed consent. Fifteen patients with *HER-2*-positive breast cancers were treated with trastuzumab following anthracycline treatment.

Patients were evaluated at 4 separate visits: (a) before initiation of anthracycline therapy (visit 0); (b) just before the last dose of anthracycline chemotherapy (visit 1); (c) 3 months after the last dose of anthracycline chemotherapy (visit 2); and (d) 9 months after the last dose of anthracycline chemotherapy (visit 4). Patients who received trastuzumab were followed more closely and had 2 extra visits: at 6 months after the last dose of anthracycline chemotherapy (visit 3) and at 12 months after the last dose of anthracycline chemotherapy (visit 5). These patients were evaluated at six separate visits. At each visit, we assessed clinical status and signs and symptoms of heart failure, and performed a physical examination. An ECG and complete echocardiogram were performed. Blood samples were drawn for the measurement of biomarkers.

Therapy

Patients received one of the following regimens:

FECX6: 5-Fluorouracil, epirubicin, and cyclophosphamide administered once every 21 days for a total of 6 cycles.

ACX4-T: Doxorubicin and cyclophosphamide administered once every 21 days for a total of 4 cycles, followed by paclitaxel weekly for 12 weeks.

ACX4-TH: Doxorubicin and cyclophosphamide administered once every 21 days for a total of 4 cycles, followed by paclitaxel and trastuzumab weekly for 12 weeks. This regimen was followed by trastuzumab every 21 days for 9 months. Patients in this regimen received trastuzumab for a full year.

Echocardiogram

Echocardiographic evaluations were performed using GE Vivid Cardiac Ultrasound (GE Healthcare, Milwaukee, WI, http://www3.gehealthcare.com), then digitized and analyzed using EchoPAC software (GE Healthcare, Milwaukee, WI, http://www3.gehealthcare.com). Echocardiographic parameters determined at each examination were as follows: (a) left ventricular diastolic diameter determined from a parasternal, two-dimensional (2D) echocardiogram long-axis view; (b) left ventricular ejection fraction (LVEF) according to the modified biplane Simpson's rule; (c) mitral inflow parameters, including early peak diastolic velocity (E), late peak diastolic velocity (A), deceleration time (DT), and isovolumetric relaxation time (IVRT); (d) pulmonary venous flow, including pulmonary systolic flow velocity, pulmonary diastolic flow velocity, pulmonary reversal flow velocity, and pulmonary venous flow duration; (e) pulsed tissue Doppler parameters at septal and lateral mitral annuli, including early diastolic velocity (E′), late diastolic velocity, and systolic velocity (S′); and (f) color M-mode propagation velocity.

2D echo and Doppler parameters were measured according to recommendations of the American Society of Echocardiography [17]. All Doppler measurements comprised an average of three consecutive cardiac cycles. Interpretation of echocardiogram measurements where blinded to patient identity, chemotherapy regimen, and visit number.

Definitions

Anthracycline cardiotoxicity was defined as follows: (a) new-onset heart failure according to Framingham criteria; (b) symptomatic decline $\geq$5%, or asymptomatic decline $\geq$10% to an LVEF $<$55%; (c) onset of sustained ventricular tachycardia; or (d) sudden cardiac death. Diastolic function was categorized by the following previously described and validated criteria [9, 18]: normal filling pattern (normal diastolic function), grade I

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(delayed relaxation), grade II (pseudonormal pattern), or grade III diastolic dysfunction (restrictive pattern). Diastolic dysfunction was identified when criteria for grade I, grade II, or grade III diastolic dysfunction were met at any follow-up visit. Figure 1 and 2 show examples of mitral inflow parameters, pulsed tissue Doppler parameters at the septal mitral annulus, and color M-mode propagation velocity in a patient not developing (DD−) and developing diastolic dysfunction (DD+), respectively.

Intraobserver variability of LVEF and tissue Doppler parameters was assessed by one reader (J.M.S.) analyzing LVEF and tissue Doppler parameters (S′ and E′ at septal and lateral mitral annuli) in 11 echocardiograms twice. Interobserver variability was assessed by two readers (J.M.S. and I.G.) analyzing the same 11 echocardiograms and the same parameters.

Cardiac Biomarkers

Blood samples were obtained and NTproBNP, hsTnT, and H-FABP levels were measured at each visit. Venous blood specimens were drawn from fasting patients according to standard guidelines. Blood samples were centrifuged for 10 minutes at 3000*g* to separate plasma. Plasma samples were stored at −20°C until analyzed. NTproBNP and hsTnT levels were quantified by electrochemiluminescence using a Cobas e411 analyzer (Roche Diagnostics, Basel Switzerland, http://www.roche.com). The upper normal limit for hsTnT was defined as <8.68 ng/L. The upper normal limit for NTproBNP was dependent on gender and age, and defined in pg/mL as follows: women: 18–44 years old (yo), <119; 45–54 yo, <169; 55–64 yo, <247; 65–74 yo, <286; and >75 yo, <738; men: 18–44 yo, <62.9; 45–54 yo, <83.9; 55–64 yo, <161; 65–74 yo, <241; and >75 yo, <486.

H-FABP levels were measured by an immunoturbidimetric method, with a reagent from Randox Laboratories Ltd (Crumlin, Country Antrim, Ireland, http://www.randox.com), and an AU2700 analyzer (Beckman Coulter, Inc, Brea, CA, https://www.beckmancoulter.com). The upper normal limit for H-FABP was defined as <3.55 ng/mL.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 15.0 for Windows (IBM Corp., Armonk, NY, http://www.ibm.com). Data are summarized as mean with SD, or as proportions, as in the case of noncontinuous variables. Paired Student's *t* tests were used for comparisons of continuous variables between follow-up and baseline visits. Univariate comparisons between groups DD+ and DD− were done by Student's *t* test or Fisher's exact test. A logistic regression model was constructed in two steps to identify factors (both biomarkers and clinical variables) related to the development of anthracycline-related diastolic dysfunction. Candidate variables first considered were personal and clinical variables (i.e., age, body mass index [BMI], cardiovascular risk factors) and variables related to cancer treatment (i.e., radiotherapy and type of chemotherapy). Variables remained in the model if $p < .1$. In a second step, an individual model was done for every biomarker, adjusting for those variables identified in the first step (i.e., age, hypertension, and body mass index), that remained if $p < .1$.

Intraobserver and interobserver variabilities were estimated by intraclass correlation coefficients, and absolute differences between measurements were determined by using a Bland-Altman plot for each variable. The intraobserver and interobserver intraclass coefficients for LVEF and tissue Doppler parameters were within 0.77 and 0.97, and 0.74 and 0.91, respectively. The intraobserver and interobserver intraclass coefficients for S′ at the septal mitral annulus were 0.67 (95% confidence interval [CI], 0.18–0.90) and 0.64 (95% CI: 0.13–0.88), respectively. The intraobserver and interobserver mean of differences using the method of Bland and Altman for each variable remained <10% of the value of each variable.

Results

Clinical Characteristics

The study population included 100 consecutive patients with breast cancer referred from the Oncology Department at Hospital Universitario de Fuenlabrada for cardiac evaluation preceding anthracycline treatment. Fifteen of the 100 patients had baseline DD and were excluded (none developed heart failure or systolic dysfunction during follow-up).

The remaining 85 patients (all female) were the subjects of the present analysis. Fifteen patients received a regimen that included trastuzumab. Mean doxorubicin dose was 243 mg/m^2 body surface. In the group of patients receiving epirubicin, we estimated the dose with a conversion factor of 0.55 (50 mg of doxorubicin was considered equivalent to 90 mg epirubicin) [19].

The patients' mean age was 49.7 years, with ages 42.5 and 55.9 years representing the first and third quartiles, respectively. Patient characteristics at baseline and the chemotherapy schemes are shown in Table 1. There were no significant differences in the baseline use of antihypertensive, lipid-lowering, or antidiabetic drugs between groups DD+ and DD−.

At 1-year follow up, 2 patients had died. Eighty-three of 85 patients (97.6%) attended all scheduled visits. The remaining two patients missed one visit each.

Echocardiographic Findings

All the patients had normal baseline systolic function, with a mean LVEF of 67.3%. The average values of main echocardiographic parameters at baseline and follow-up visits are summarized in Table 2. We found a significant decrease in LVEF and in a tissue Doppler parameter specifically related to systolic function (S′ at the septal and lateral mitral annuli), detected at visits 1 and 2, respectively.

Of the 85 patients in the study, 49 developed diastolic dysfunction during follow-up (57.6% of the total population). In 36 of the patients, diastolic dysfunction persisted in the last follow-up visit (36 of 49; 73%), whereas in the remaining 13 patients, diastolic dysfunction reversed. Thirty-three patients developed type I dysfunction and three patients developed type II. No patient developed type III dysfunction.

The incidence of diastolic dysfunction was similar when we compared the group of patients receiving anthracyclines

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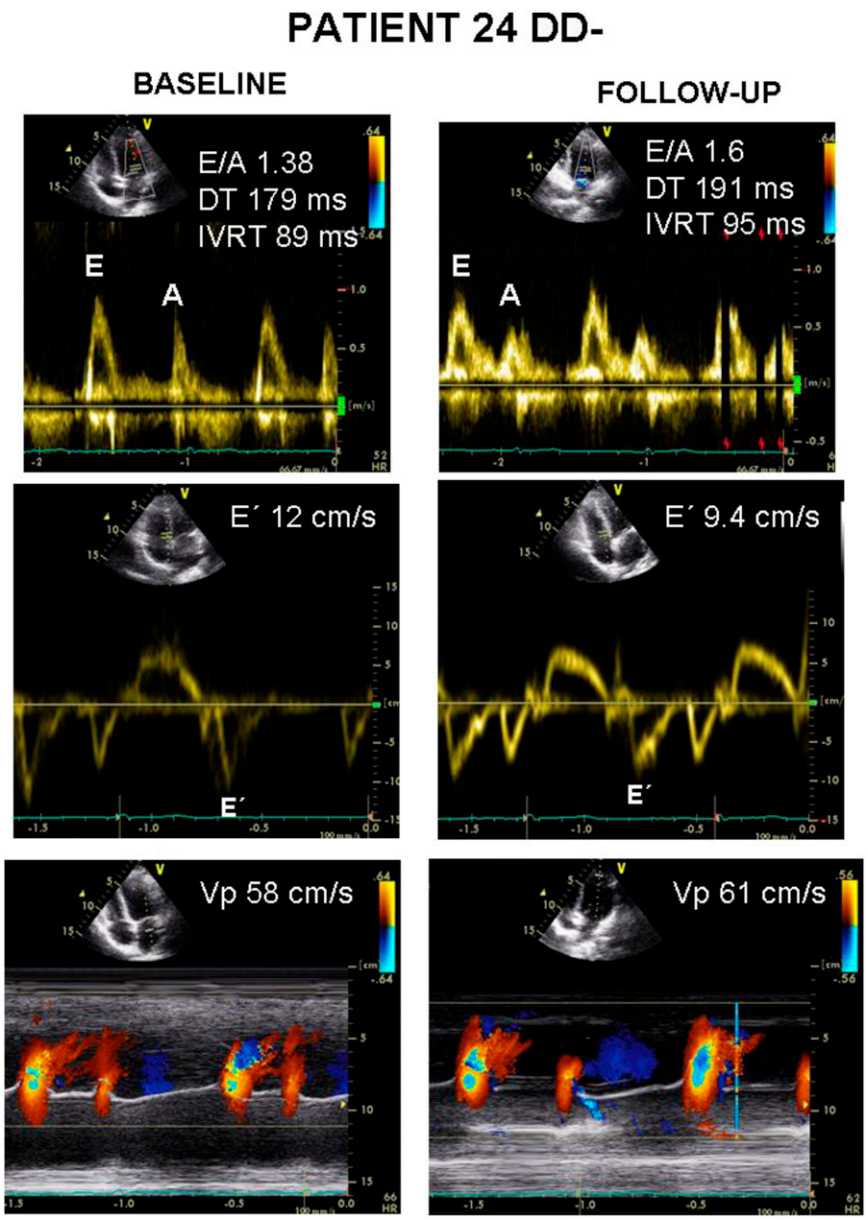

Figure 1. Baseline and follow-up recordings of mitral inflow velocities, pulsed tissue Doppler velocities at the septal mitral annulus and color M-mode propagation velocity in a patient not developing diastolic dysfunction.

Abbreviations: A, late peak diastolic velocity; DD−, no diastolic dysfunction; DT, deceleration time; E, early peak diastolic velocity; E′, pulsed tissue-Doppler early diastolic velocity at the mitral annulus (septum and lateral wall); E/A, ratio of early to late peak diastolic velocity; IVRT, isovolumetric relaxation time; Vp, color M-mode propagation velocity.

plus trastuzumab (60%) with the group receiving only anthracyclines (57%). As shown in Table 2, there were significant changes in main diastolic parameters. There was a significant decrease in E′ at the septal and lateral mitral annuli and an increase in the transmitral Doppler early filling velocity (E)/E′ ratio. We also found significant changes in mitral inflow parameters with an increase in DT and IVRT and a significant decrease in E/A ratio and in color M-mode with a decrease in the propagation velocity of the mitral inflow.

Main clinical variables of groups DD+ and DD− are summarized in Table 3. In the univariate analysis, we found significant differences in age and body mass index between both groups. Three patients developed systolic dysfunction during follow-up; all had previously developed diastolic dysfunction.

Cardiac Biomarkers

At baseline, the measured cardiac biomarkers (hsTnT, NTproBNP, and H-FABP) were within the normal limits for the entire population. The average values of these biomarkers at baseline and follow-up visits in the total population and groups DD+ and DD− are summarized in Table 4.

There were significant changes in the three tested biomarkers, but only hsTnT showed early changes. As shown in Table 3, there was a significant increase in hsTnT level that

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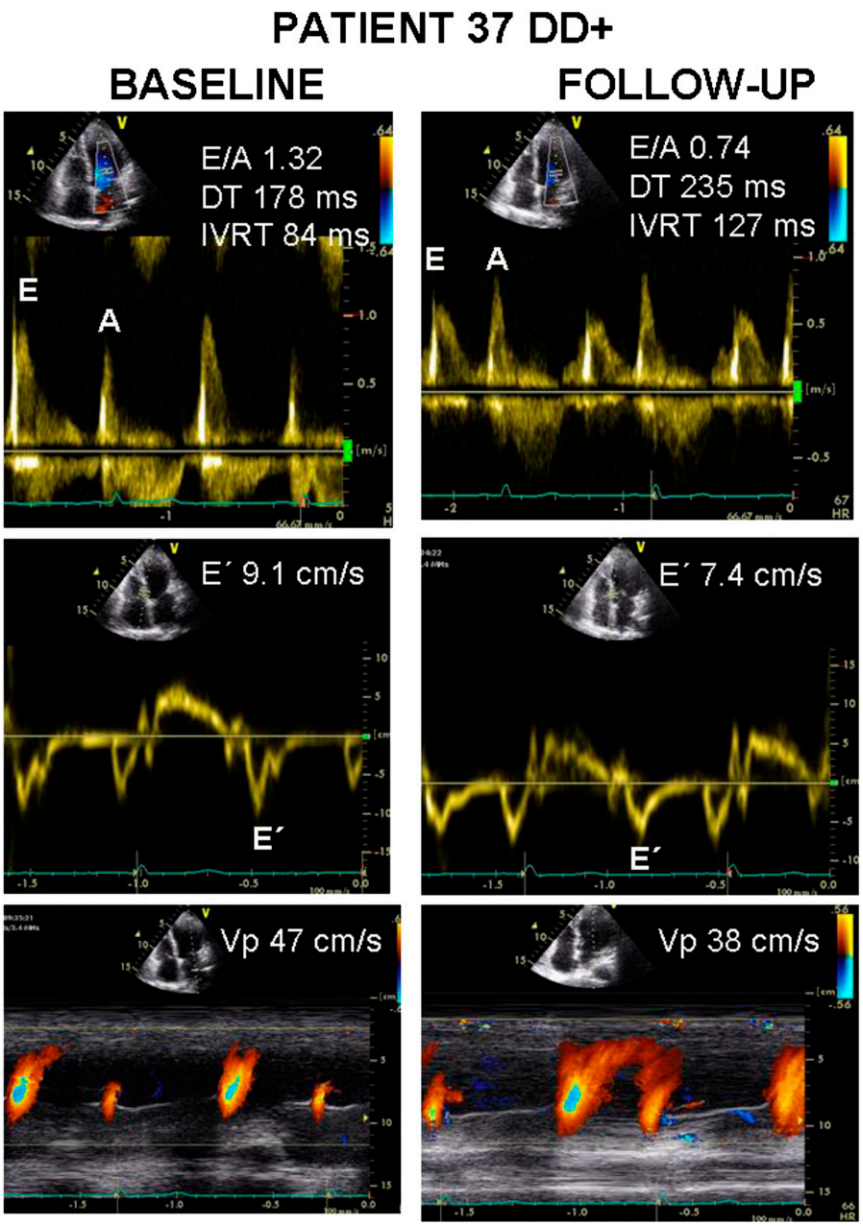

Figure 2. Baseline and follow-up recordings of mitral inflow velocities, pulsed tissue Doppler velocities at the septal mitral annulus, and color M-mode propagation velocity in a patient developing diastolic dysfunction.

Abbreviations: A, late peak diastolic velocity; DD+, patients developing diastolic dysfunction; DT, deceleration time; E, early peak diastolic velocity; E′, pulsed tissue-Doppler early diastolic velocity at the mitral annulus (septum and lateral wall); E/A, ratio of early to late peak diastolic velocity; IVRT, isovolumetric relaxation time; Vp, color M-mode propagation velocity.

peaked at visits 1 and 2 and persisted until the last follow-up visit. We detected a significant elevation in NTproBNP level only at visit 4. H-FABP level was elevated at visit 4, as well as visits 3 and 5, which were specific to the group receiving trastuzumab.

Looking at the differences between groups DD+ and DD−, only hsTnT showed a significant elevation above normal limits and a significant difference between both groups at visit 2.

Clinical Evolution and Predictors of Cardiotoxicity

At the end of follow-up, no patient developed heart failure, but four patients developed anthracycline cardiotoxicity: three of them developed left ventricular systolic dysfunction and one patient suffered sudden cardiac death. The distribution according chemotherapy schemes was as follows: 1 patient of the FECX6 group and 3 patients in ACX4-TH group (3 of 15; 20%), reflecting a high incidence of anthracycline cardiotoxicity in patients receiving trastuzumab plus anthracyclines. One additional patient was dead at the end of follow-up because of progression of underlying disease. None of the patients with normal diastolic function developed anthracycline cardiotoxicity during follow up.

Regarding diastolic dysfunction, hsTnT was the only marker with significant elevation in early visits, but this elevation of hsTnT and development of diastolic dysfunction occurred simultaneously. In the logistic regression model, none of the biomarkers were independent predictors of anthracycline-related diastolic dysfunction.

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Table 1. Baseline characteristics of the total population ($N = 85$)

Characteristic	Data
Age, mean (SD), years	49.7 (9.0)
Female gender	100
Weight, mean (SD), kg	69.8 (12.3)
Height, mean (SD), cm	157.9 (7)
BMI, mean (SD), kg/m^2	28.1 ± 5.2
BMI distribution	
Normal weight (<25)	28.2
Overweight (25–29.9)	42.4
Obesity (30–39.9)	25.9
Morbid obesity (≥40)	3.5
Vascular risk factors	
Hypertension	22.4
Smoking status	35.3
Hypercholesterolemia	10.6
Diabetes	7.1
CHT regimen	
FEC	28
AC-T	54
AC-TH	18
Anthracycline dose, mean (SD), mg/m^2	242 ± 4.5
Radiotherapy[a]	42.4

Data given as % unless otherwise indicated.
[a]Radiotherapy on left hemithorax or mediastinum.
Abbreviations: BMI, body mass index; CHT, chemotherapy; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; AC-T, doxorubicin, cyclophosphamide, and paclitaxel; AC-TH, doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab.

Regarding clinical variables, the univariate analysis showed significant differences in age (52.7 vs. 44.8 years) and BMI (29.6 vs. 25.7 kg/m^2) between group DD+ and group DD− (Table 3). The odds ratios (ORs) for the development of diastolic dysfunction in overweight and obese patients were, respectively, 2.8 (95% CI: 0.95–8.217.30; $p = .004$) and 7.6 (95% CI: 2.1–26.9; $p = .001$); and the OR for patients more than 50 years old versus less than 50 years old was 4.1 (95% CI: 1.62–10.38; $p = .001$). The regression model controlling for main clinical variables confirmed that both age and BMI were independent predictors of anthracycline-related diastolic dysfunction with the following odds ratio values: BMI, 1.21 (95% CI: 1.05–1.39); age, 1.15 (95% CI: 1.05–1.25). Neither the traditional vascular risk factors nor other clinical variables such as radiotherapy of the left hemithorax or mediastinum, total dose of anthracyclines, or chemotherapy regimen were independent predictors of diastolic dysfunction.

Discussion

Despite benefits of anthracyclines in the treatment of cancer, cardiotoxicity and its early diagnosis remain major concerns. This study has shown several interesting findings regarding early changes in the myocardium of patients treated with anthracyclines.

First, we found that a significant number of patients ($n = 49$; 57% of our population) developed diastolic dysfunction. Of the 49 patients, diastolic dysfunction persisted in 36 at the last follow-up visit (73%). The subclinical changes detected on echocardiogram may represent ultrastructural changes that appear early after exposure to anthracyclines, as previously reported [11]. These subclinical diastolic changes might identify patients at risk for developing overt left ventricular systolic dysfunction. However, the small number of patients with overt cardiac toxicity ($n = 4$) precludes any conclusion at this time, although it is noteworthy that all of them had previously developed diastolic dysfunction. This should be addressed in a larger study with longer follow up.

Stoddard et al. [12], in a study with 26 patients, found that early changes in a diastolic function parameter (i.e., a prolongation of isovolumetric relaxation time) following anthracycline therapy appeared before changes in systolic dysfunction parameters were identified. Additional studies have found changes in tissue Doppler parameters. Lotrionte et al. [20] and Fallah-Rad et al. [21] found a decrease of S′ velocity at the mitral annulus in patients exposed to anthracyclines and anthracyclines plus trastuzumab, respectively, and Tassan-Mangina et al. [22] found a decrease in E′ velocity at the mitral annulus in a cohort of 20 patients. Similar changes in mitral inflow parameters (reduction in the E/A ratio) and tissue Doppler parameters (reduction of E′ at the septal mitral annulus) were reported by Mercuro et al. in a study with 16 patients receiving epirubicin [13]. Our study is the first to characterize the incidence of DD in a cohort of numerous patients receiving anthracyclines in a systematic and prospective way.

Data on the relationship between biomarkers and diastolic dysfunction are scarce. Killickap et al. [23], in a study with 41 patients receiving anthracyclines, observed elevations in troponin T levels in the first 3 to 5 days after chemotherapy in 34% of their patients. The elevation in Troponin T levels correlated to diastolic dysfunction as measured by mitral inflow parameters (i.e., decrease in E/A ratio and prolongation in IVRT). We found an elevation of hsTnT levels over upper normal limits in visit 1 and 2 and a significant difference between groups DD+ and DD− at visit 2 that was consistent with evidence of cardiac damage. Ky et al. [24], in an multicenter study in 78 breast cancer patients treated with doxorubicin and trastuzumab, found increases in troponin I levels at patients' 3-month visits that were associated with an elevated risk for cardiotoxicity. With a sampling protocol similar to our study, they found an increase in levels of troponins of identical magnitude to those found in our study (3.2 times the levels between baseline and first follow-up visit).

The changes in NTproBNP and H-FABP levels were delayed on follow-up. None of the cardiac biomarkers measured were found to be independent predictors of DD in the regression model, aside from the elevation in hsTnT level that occurred simultaneously to changes in diastolic function. It is not possible, therefore, to draw conclusions on the role of cardiac biomarkers in anthracycline-related diastolic dysfunction. In our study, blood samples were obtained at the scheduled visits just before the last cycle (at least 21 days after the previous dose of anthracyclines) and at 3 months after the last cycle. The timing of blood sample collection may have influenced our results.

Regarding clinical variables, neither classical vascular risk factors nor radiotherapy of the mediastinum or left hemithorax were found to be independently related with the

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Table 2. Serial echocardiographic parameters at baseline and during follow-up

Parameter	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
No.	85	85	84	15	83	14
LVEF, %	67.3 ± 5.7	64.6 ± 5.6[a]	63.2 ± 4.9[a]	62.7 ± 4.0[a]	63.3 ± 5.9[a]	60.1 ± 4.7[a]
E/A ratio	1.22 ± 0.3	1.08 ± 0.3[a]	1.06 ± 0.3[a]	1.05 ± 0.2[a]	1.11 ± 0.3[a]	1.08 ± 0.2
E/A ratio, DD+	1.11 ± 0.2	0.92 ± 0.2[a]	0.88 ± 0.2[a]	0.93 ± 0.2[a]	0.93 ± 0.2[a]	1.01 ± 0.2
DT, ms	186 ± 24	200 ± 32[a]	202 ± 34[a]	203 ± 27[a]	202 ± 33[a]	201 ± 21[a]
IVRT, ms	86 ± 8	92 ± 12[a]	95 ± 14[a]	92 ± 13	93 ± 13[a]	94 ± 10[a]
S′ septum, cm/s	7.3 ± 1.1	7.1 ± 1.0	7.0 ± 1.1[a]	7.1 ± 0.7	6.8 ± 1.0[a]	6.6 ± 0.8
E′ septum, cm/s	10.1 ± 2.2	8.8 ± 2.2[a]	8.2 ± 2.1[a]	8.7 ± 2.6[a]	8.2 ± 2.3[a]	8.0 ± 2.7[a]
E/E′ septum	8.6 ± 2.3	9.3 ± 2.2[a]	9.7 ± 2.7[a]	9.5 ± 2.2	9.6 ± 2.6[a]	10.0 ± 2.7
S′ lateral, cm/s	9.2 ± 2.0	8.8 ± 1.8	8.7 ± 1.9[a]	8.5 ± 1.3	8.3 ± 2.1[a]	7.7 ± 1.5[a]
E′ lateral, cm/s	13.1 ± 2.9	11.7 ± 2.8[a]	11.1 ± 3.0[a]	11.8 ± 3.1	11.1 ± 3.1[a]	9.6 ± 3.2[a]
E/E′ lateral	6.6 ± 1.7	7.0 ± 1.9[a]	7.2 ± 2.4[a]	7.0 ± 1.7	7.1 ± 2.0[a]	8.4 ± 2.8[a]
PV, cm/s	58 ± 10	51 ± 9[a]	48 ± 10[a]	44 ± 8.8[a]	48 ± 11[a]	47 ± 12[a]

Data given as mean ± SD.
[a]$p < .05$ compared with baseline measurement.
Abbreviations: A, late peak diastolic velocity; DT, deceleration time of the early peak diastolic velocity wave; E, early peak diastolic velocity; E′, pulsed tissue Doppler early diastolic velocity at the mitral annulus (septum and lateral wall); E/A, ratio of early to late peak diastolic velocity; IVRT, isovolumetric relaxation time; LVEF, left ventricular ejection fraction; PV, color M-mode propagation velocity; S′: pulsed tissue Doppler systolic velocity at the mitral annulus (septum and lateral wall).

Table 3. Main clinical variables in groups DD+ and DD− (Results expressed in % unless otherwise stated)

Variable	DD+	DD−	*p* value
Patients, No.	49	36	
Age, mean (SD), years	52.8 (7.90)	45.4 (8.83)	<.001
BMI, mean ± SD, kg/m^2	29.9 ± 5.2	25.7 ± 4.3	<.001
BMI distribution			.0045
Normal weight (<25)	16.3	44.4	
Overweight (25–29.9)	42.9	41.7	
Obesity (≥30)	40.8	13.8	
Cardiovascular risk factors			
Hypertension	24.5	19.4	.611
Diabetes	8.2	5.6	1
Hyperlipidemia	12.2	8.3	.727
Smoking status (current smoker)	38.8	30.6	.496
Anthracycline dose, mean ± SD, mg/m^2	242 ± 4.3	243 ± 4.7	.384
Radiotherapy[a]	42.9	41.7	1.000
Anthracycline cardiotoxicity, no.	4	0	.134
Baseline LVEF	65.9 ± 5.3	68.8 ± 6.3	.024

Data given as % unless otherwise indicated.
[a]Radiotherapy on left hemithorax or mediastinum.
Abbreviations: BMI, body mass index; DD+, patients developing diastolic dysfunction; DD−, no diastolic dysfunction; LVEF, left ventricular ejection fraction.

development of DD. Previous studies have found high blood pressure [25] and radiotherapy [26] to be independent predictors of anthracycline cardiotoxicity. Age is another established clinical risk factor [2, 25] for anthracycline cardiotoxicity. We confirmed in our study the association of age with the development of DD, with an OR of 1.12 (95% CI: 1.03–1.19) in the regression model. The other interesting finding was that BMI was a strong predictor of the development of anthracycline-related diastolic dysfunction, with an OR of 1.19 (95%: CI: 1.04–1.36). Some authors have also found this association. Fumoleau et al. [27] found that BMI more than 27 kg/m^2 significantly correlated with the occurrence of left ventricular dysfunction after epirubicin treatment in 3,778 breast cancer patients included in the French Adjuvant Study Group, with a incidence of 1.8% versus 0.9% in patients with BMI less than 27 kg/m^2. Dranitsaris et al. [28] identified weight more than 70 kg as a predictive factor of cardiotoxicity in 509 patients with metastatic breast cancer who were included in a prospective trial comparing doxorubicin with liposomal doxorubicin.

Our study has some limitations, including the common limitation of being an observational single-center study.

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Table 4. Biomarkers at each visit in total population and groups DD+ and DD−

Parameter	Total Population	DD+	DD−	*p* value[a]
Patients, No.	85	49	36	
hsTnT, ng/L				
Baseline (visit 0)	3.8 ± 3.5	4.6 ± 4.0	2.7 ± 2.3	.014
Visit 1	12.3 ± 5.7[b]	13.0 ± 8.9	11.3 ± 5.3	.178
Visit 2	12.5 ± 6.1[b]	13.7 ± 7.0	10.8 ± 4.1	.030
Visit 3	6.9 ± 3.3[b]	7.1 ± 4.0	6.7 ± 2.3	.831
Visit 4	6.6 ± 3.5[b]	7.2 ± 4.2	5.7 ± 1.7	.071
Visit 5	4.6 ± 2.0[b]	4.9 ± 2.6	4.3 ± 0.8	.608
NTproBNP, pg/mL				
Baseline (visit 0)	65.1 ± 88.1	68.2 ± 110.3	61.0 ± 44.2	.715
Visit 1	66.2 ± 64.2	74.9 ± 77.8	54.5 ± 37.0	.149
Visit 2	63.9 ± 73.7	75.3 ± 87.4	48.6 ± 46.9	.101
Visit 3	41.7 ± 47.8	30.0 ± 21.9	59.1 ± 70.9	.369
Visit 4	82.6 ± 75.7[b]	86.6 ± 88.4	76.8 ± 53.0	.572
Visit 5	52.2 ± 47.9	52.6 ± 51.3	51.6 ± 47.8	.968
H-FABP, ng/mL				
Baseline (visit 0)	3.1 ± 2.2	3.5 ± 2.6	2.6 ± 1.1	.053
Visit 1	3.0 ± 2.0	3.6 ± 2.2	2.7 ± 0.9	.076
Visit 2	3.2 ± 1.8	3.6 ± 2.2	2.7 ± 0.9	.025
Visit 3	3.3 ± 1.2[b]	3.7 ± 1.3	2.7 ± 0.5	.076
Visit 4	3.6 ± 1.9[b]	3.9 ± 2.1	3.1 ± 1.2	.047
Visit 5	3.6 ± 1.4[b]	4.1 ± 1.6	2.8 ± 0.4	.047

Data given as mean ± SD unless otherwise indicated.
[a]*p* values were calculated by Student *t* test for difference in means between DD+ and DD− groups.
[b]$p < 0.05$; each visit compared with baseline measurement in the total population.
Abbreviations: DD+, patients developing diastolic dysfunction; DD−, no diastolic dysfunction; H-FABP, heart-type fatty acid-binding protein; hsTnT, high-sensitivity troponin T; NTproBNP, N-terminal pro B-type natriuretic peptide.

Analyses of the echocardiographic examinations were assessed off-line in a blinded manner and in random order. We checked intra- and interobserver variability and agreement with comparable results to other single-center studies; however, we cannot exclude some degree of bias. We tried to limit the number of patient visits by scheduling study visits and blood sampling at the same time. As a result, blood samples were collected at least 21 days after the previous anthracycline dose. This may have limited our ability to detect elevations in cardiac biomarkers such as hsTnT and H-FABP.

The follow-up was only 12 months long and this may account for the low incidence of overt anthracycline cardiotoxicity identified in this study.

Conclusion

Development of diastolic dysfunction after anthracycline or anthracycline plus trastuzumab chemotherapy was common in this study. Body mass index and age were independently associated with diastolic dysfunction following anthracycline chemotherapy.

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Disclosures

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