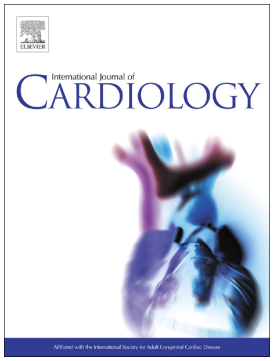

Early and late onset cardiotoxicity following anthracycline-based chemotherapy in breast cancer patients: Incidence and predictors

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Running head: Diastolic Dysfunction Following Chemotherapy in Breast Cancer.

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JMS, RM and JJA conceived of the study. JMS, RM, IG, SC, RJ, CC, PT, CG, CGL, JA and AC performed the echocardiographic exams. JMS, RM and IG performed the analysis of the echocardiographic exams. FM and JAG helped with the study design and implementation and had the first contact with the patients included on the study. LM performed the test of the biomarkers. JM provided statistical expertise in the design and conducted the statistical analysis. MJE helped with the writing of the text in English. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Ethical standards: The protocol was approved by the local institutional review board (ethical committee) and all patients provided informed consent and comply with the current laws of the Spanish legislation.

Abstract

Introduction: Cardiotoxicity represents a major limitation for the use of anthracyclines or trastuzumab in breast cancer patients. Data on longitudinal studies about early and late onset cardiotoxicity in this group of patients is scarce. The objective of the present study was to assess predictors of early and late onset cardiotoxicity in patients with breast cancer treated with A.

Methods: 100 consecutive patients receiving anthracycline-based chemotherapy (CHT) to treat breast cancer were included in this prospective study. All patients underwent evaluation at baseline, at the end of CHT, 3 months after the end of CHT and 1 and 4 years after the beginning of CHT. Clinical data, systolic and diastolic echo parameters and cardiac biomarkers including high sensitivity Troponin T (hsTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and Heart-type fatty acid binding protein (H-FABP) were assessed.

Results: Mean doxorubicin dose was 243 mg/m2. Mean follow-up was 51.8±8.2 months. At one-year incidence of anthracycline related-cardiotoxicity (AR-CT) was 4% and at the end of follow-up was 18% (15 patients asymptomatic left ventricular systolic dysfunction, 1 patients heart failure and 2 patients a sudden cardiac death). Forty-nine patients developed diastolic dysfunction (DD) during first year. In the univariate analysis DD during first year was the only parameter associated with AR-CT (Table1). In the logistic regression model DD was independently related with the development of AR-CT, with an odds ratio value of 7.5 (95% CI 1.59-35.3).

Conclusions: Incidence of late-onset cardiotoxicity is high but mostly subclinical. Diastolic dysfunction early after chemotherapy is a strong predictor of anthracycline cardiotoxicity.

Key Words: Diastolic Dysfunction, Anthracycline Chemotherapy, Breast Cancer, Cardiac Biomarkers.

Body Text

Introduction

Anthracyclines are chemotherapeutic drugs used in many 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]. Early cardiotoxicity defined as that occurring during first year following chemotherapy has been well characterized but there is limited data about late onset cardiotoxicity (1 year or more after chemotherapy) and most of information comes from cohort studies of patients treated during childhood [8]. In breast cancer patients, the available evidence on the incidence of late cardiotoxicity is scarce. So, the main objective of the present study was to assess the incidence and evolution of early and late onset cardiotoxicity in a cohort of patients with breast cancer treated with anthracycline or anthracyclines plus trastuzumab. Secondary objectives were to search for clinical predictors of cardiotoxicity, echocardiographic predictors of cardiotoxicity and to evaluate the role of cardiac biomarkers (high sensitive Troponin T [hsTnT], N-terminal pro B-type natriuretic peptide [NTproBNP] and Heart-type fatty acid binding protein [H-FABP]), in this setting.

Methods

Study Design

Analytical observational prospective cohort study carried out in a General Hospital. The current study is the continuation of the study previously published by the same group with the follow-up data of the cohort of patients at 4 years [9].

Patients

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 one hundred 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 4 years. Exclusion criteria were poor echo window, previous cardiac disease (coronary heart disease, dilated, hypertrophic or restrictive cardiomyopathy, severe valvular heart disease), history of heart failure, ejection fraction under 55%, atrial fibrillation, poor prognosis with an expected survival under 1 year, or previous treatment with anthracyclines. The protocol was approved by the local institutional review board (ethical committee) and all patients provided informed consent. Fifteen patients were treated with Trastuzumab following Anthracyclines.

Patients were evaluated at 5 separate visits: 1) Before the initiation of anthracycline therapy (visit 0); 2) just before the last dose of Anthracycline chemotherapy (visit 1); 3) 3 months after the last dose of anthracycline chemotherapy (visit 2); 4) 9 months after the last dose of Anthracycline chemotherapy (visit 4), 5) Four years after the beginning of chemotherapy (Visit 6). Patients who received Trastuzumab were followed more closely and had 2 extra visits: 1) 6 months after the last dose of anthracycline chemotherapy (visit 3); 2) 12 months after the last dose of anthracycline chemotherapy (visit 5). At each visit, we assessed: clinical status, physical exam, as well as signs and symptoms of heart failure. An ECG and complete echocardiogram were performed. Blood samples were drawn for the measurement of biomarkers at every visit excepting the last one (visit 6).

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 is followed by Trastuzumab, every 21 days for 9 months.

Echocardiogram

Echocardiographic evaluations were performed utilizing GE Vivid Cardiac Ultrasound (General Electric, Milwaukee, USA), then digitized and analysed using EchoPAC software (GE medical systems, Milwaukee, USA).

Echocardiographic parameters determined at each exam were: 1) Left ventricular diastolic diameter, 2) Left ventricular ejection fraction according to the modified biplane Simpsom´s rule (LVEF), 3) Mitral inflow parameters including early peak diastolic velocity (E wave), late peak diastolic velocity (A wave), deceleration time (DT) and isovolumetric relaxation time (IVRT), 4) Pulmonary venous flow parameters, 5) Pulsed tissue Doppler parameters at septal and lateral mitral annulus, including early diastolic velocity (E´), late diastolic velocity (A´), systolic velocity (S´), 6) Left ventricular deformation parameters including global longitudinal strain (GLS) and 7) Color M-mode propagation velocity.

Two-D echo and Doppler parameters were measured according to recommendations by the American Society of Echocardiography. Interpretation of echocardiogram measurements where blinded to patient identity, chemotherapy regimen and visit number.

Definitions

Anthracycline related cardiotoxicity (AR-CT) was defined as: 1) New onset heart failure, according to Framingham criteria; 2) Symptomatic decline ≥ 5% or asymptomatic decline ≥ 10% to an LVEF < 55%; 3) Onset of sustained ventricular tachycardia, or 4) Sudden cardiac death.

Diastolic function was categorized by previously described and validated criteria [10,11].

Intraobserver variability of LVEF and tissue Doppler parameters was assessed by one reader (J.S) analysing LVEF and Tissue Doppler parameters (S´ and E´ at septal and lateral mitral annulus) in 11 echocardiograms twice. Interobserver variability was assessed by two readers (J.S and I.G) analysing the same 11 echo exams and the same parameters.

Cardiac biomarkers

Blood samples were obtained and NTproBNP, hsTnT and H-FABP were measured at each visit excepting the last one (Visit 6).

Fasting venous blood specimens were drawn according to standard guidelines. Blood samples were centrifuged for 10 min at 3000 g to separate plasma. Plasma samples were stored at -20º C until analysed.

NTproBNP and hsTnT levels were quantified by electrochemiluminescence using a Cobas e411 analyzer (Roche). The upper normal limit for hsTnT was defined as <8.68ng/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, 45-54yo<159, 55-64yo<247, 65-74yo <286, >75yo <738; Men: 18-44yo <62.9, 45-54yo<83.9, 55-64yo<161, 65-74yo <241, >75yo <486. H-FABP levels were measured by immunoturbidimetric method, with a reagent from Randox, and an AU2700 analyser (Beckman Coulter). 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 (SPSS), version 15.0 for Windows. Data are summarized as mean with standard deviation, or proportions, as in the case of discrete variables. Paired Student's t-Test was used for comparisons of continuous variables between follow-up and baseline visits. Univariate comparisons of patient groups who developed anthracycline cardiotoxicity (AR-CT+) or who did not (AR-CT-), were analysed by means of Student´s t-Test or Fisher´s exact test. Univariate logistic regression models were done to identify factors (biomarkers, echocardiographic and clinical variables) potentially related to the development of AR-CT. No potential confounder likely to affect the relationship between the main exposure of interest and risk of AR-CT was identified.

Both intraobserver and interobserver variability were estimated by means of the intraclass correlation coefficient, and absolute differences between measurements using a Bland-Altman 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 septal mitral annulus were 0.67 (95%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 under 10% of the value of each variable.

Results

Clinical characteristics

The study population included 100 consecutive patients with breast cancer scheduled at the Oncology department for anthracycline-based treatment. Fifteen patients received a regimen that included Trastuzumab. Mean Doxorubicin dose was 243 mg per square meter of body surface. In the group of patients receiving Epirubicin we estimated the dose using a conversion factor of 0.55 (50 mg of Doxorubicin=90mg Epirubicin) [12].

Mean age at inclusion was 50.9 years old, with age 42.5 and 55.9 years old representing first and third quartile respectively. Patient characteristics at baseline and chemotherapy schemes are shown in table 1. At one-year follow up, two patients died and at the end of follow-up 8 patients have died (8%). 2 patients suffered sudden cardiac deaths, 1 patient with metastatic breast cancer suffered a pulmonary embolism, 1 patient due to a lung cancer and 4 patients due to progression of underline disease). Ninety out of 100 patients (%) attended all scheduled visits. Only 2 of the living patients missed the last visit because they had moved to another town.

Echocardiographic findings

All the patients had normal baseline systolic function, with a mean LVEF of 67.1% and a GLS of -18.9%. The average values of main echocardiographic parameters and blood pressure and heart rate at baseline and follow-up visits are summarized in table 2. We found a significant decrease in LVEF and in GLS from the first visit (visit 1).

Out of 100 patients included in the study, 15 had baseline diastolic dysfunction (DD) and 49 developed diastolic dysfunction within first year (49% of the total population). Forty-six patients developed type I DD and 3 patients developed type II. No patient developed type III DD.

The incidence of DD was similar when we compared the group of patients receiving anthracyclines 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 septal and lateral mitral annulus and an increase in the 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 group of patients AR-CT + and AR-CT - are summarized in table 3. In the univariate analysis, we didn´t found differences in age, weight, body mass index or the incidence of the vascular risk factor. We found a significant difference in the percentage of patients developing DD during first year. As shown in table 3, in the group of patients with AR-CT during follow-up (AR-CT +) 88% of them had developed DD during first year, in comparison only 50% of patients developing DD in the group of patients without AR-CT (AR-CT -).

We found a significant drop in GLS from visit 1 to visit 6. As shown in table 4, when we compared GLS and drop in GLS from baseline between patients AR-CT + and AR-CT - we didn´t found significant differences. Only at visit 6 differences in drop of GLS from baseline was significant and values of the GLS bordered on statistical significance. Figure 1 shows changes in LVEF and GLS, and % of patients developing DD in groups AR-CT+ and AR-CT- throughout the study.

Cardiac Biomarkers.

At baseline, cardiac biomarkers (hsTnT, NTproBNP and H-FABP) were in 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 AR-CT + and AR-CT - are summarized in table 5. There were significant changes in the three tested biomarkers but hsTnT was the only one that showed early changes. As shown in Table 3, there was a significant increase in hsTnT that peaked at visits 1 and 2 and persisted until the last follow-up visit.

Looking at the differences between groups AR-CT + and AR-CT -, there were not significant differences between both groups for any of the biomarkers. In the logistic regression model, none of the biomarkers were independent predictors of AR-CT. Figure 2 shows changes in cardiac biomarkers throughout the study in groups AR-CT + and AR-CT - , from baseline to visit 5. Therefore, unlike what was observed with the echocardiographic parameters, none of the biomarkers was useful with the extraction schedule carried out in our study.

Clinical evolution and Predictors of cardiotoxicity

During the first year 4 patients developed AR-CT (3 patients asymptomatic left ventricular dysfunction and 1 sudden cardiac death) and at the end of follow-up 18 patients had developed AR-CT: one patient had heart failure and left ventricular systolic dysfunction (23 months after the end of CHT), 15 patients asymptomatic left ventricular systolic dysfunction and 2 patients suffered sudden cardiac death. Therefore, 14 of the 18 cases of AR-CT occurred more than 1 year after the beginning of CHT.

The distribution according chemo schemes was: 6 patients of the FEC group (6/30, 20%), 8 patients of the AC-T group (8/55, 14.5%) and 4 patients in AC-TH group (4/15, 26.6%), reflecting a high incidence of AR-CT in patients receiving Trastuzumab plus anthracyclines. Fifteen out of 18 patients with AR-CT during follow-up had developed DD early after chemotherapy and in all cases before development of AR-CT (6 at visit 1, 4 at visit 2, 1 at

visit 3, and 4 at visit 4). One patient developing AR-CT had baseline DD and 2 patients didn´t develop DD.

Then, only two patients with normal diastolic function during follow-up developed AR-CT.

The univariate analysis showed significant differences between groups AR-CT + and AR-CT- regarding development of DD during first year of follow-up (88% in the group AR-CT + vs 50% in the group AR-CT -, p value 0.005, see table 3). We didn't evidence significant early changes in GLS, only a significant drop in GLS in AR-CT + group was evident at visit 6 (last visit), so drop in GLS was not an independent predictor of AR-CT in this study.

Regarding clinical variables, the univariate analysis showed no differences in age (50.3vs 51.0 years-old), BMI (29.1 vs 28.2) or any of the vascular risk factors between groups AR-CT + and AR-CT -, as is shown in table 3. There weren't significant differences in other variables tested as radiotherapy, anthracycline dose or chemo scheme.

In the logistic regression model, neither the traditional vascular risk factors, age, BMI nor other clinical variables such as: radiotherapy of the left hemithorax or mediastinum, total dose of anthracyclines or chemo regimen were independent predictors of AR-CT.

Development of diastolic dysfunction during first year was the only variable independently related with anthracycline cardiotoxicity in the long term, with an odds ratio value of 7.5 (95% CI 1.59-35.3).

Discussion

Despite benefits of anthracyclines in the treatment of cancer, cardiotoxicity and its early diagnosis remain a major concern. This study has shown several interesting findings regarding early and late onset AR-CT. First of all, a significant proportion of patients developed AR-CT during more than 4 years of follow-up, but in most of them presentation was subclinical. Eighteen out of 100 patients developed AR-CT, but only one had clinical heart failure. We also evidence that almost 50% of patients developed DD early in follow-up that precede AR-CT and was the only independent predictor of AR-CT in the logistic regression analysis. We found a strong association between DD during first year and posterior development of AR-CT with an odds ratio value of 7.5. A previous article [9]

reporting evolution of the same cohort of patients during the first year of follow-up showed a high incidence of DD and a low incidence of AR-CT at one year (only 4%). Those 4 patients with overt AR-CT had previously developed DD, suggesting that subclinical diastolic changes might identify patients at risk of developing overt left ventricular systolic dysfunction. However, the small number of patients with overt cardiac toxicity precluded any conclusion regarding DD as a predictor of AR-CT at one year of follow-up. With a longer follow up, we were able to find a higher incidence of AR-CT and to evidence an association between early DD and early and late onset AR-CT.

Some authors have found alterations in diastolic function following CA treatment with different populations and length of follow-up, and with evidence of the relation between DD and AR-CT in some of them.

Stoddard et al [13] in a study with 26 patients and short follow-up (3 months), found that early changes in diastolic function parameters (a prolongation of IVRT) following anthracycline therapy appear before changes in systolic dysfunction parameters are identified. However, another study [14] in paediatric population with acute leukaemia and Wilms´ tumours, treated with anthracyclines and long follow up (6 to 11 years), wasn´t able to find that a reduction of E wave or IVRT prolongation predicted systolic dysfunction at follow-up. Tassan-Mangina et al [15] found an early decrease in E´ velocity at mitral annulus and a late decrease of S´ velocity in a cohort or 20 patients followed for 3 and half years. Similar changes in mitral inflow parameters (reduction in the E/A ratio) and tissue Doppler parameters (reduction of E´ at septal mitral annulus) were reported by Mercuro et al in a study with 16 patients receiving Epirubicin [16]. Finally, a recent study of Upshaw et al [17] in a cohort of 362 patients treated for breast cancer (60% treated with anthracyclines, 23% with Trastuzumab and 17% with anthracyclines plus Trastuzumab) and a median follow-up of 2.1 years found that persistent worsening of diastolic function is associated with a small risk of subsequent systolic dysfunction. Changes in diastolic parameters were of similar magnitude to those found in the present study.

Regarding time of onset of cardiotoxicity, a high proportion of patients in our study (14 out of 18 patients) developed AR-CT after the first year of follow-up, a finding that differs from previous evidence. A large study by Cardinale et al [18] with 2625 patients treated with anthracycline and followed for 5.2 years, found an incidence of anthracycline cardiotoxicity of 9%, with 98% of cases occurring within the first year. Some relevant differences in both cohorts (28% were non-Hodgkin lymphoma patients, 51% breast cancer patients and 2.2% had coronary artery disease in Cardinale et al study) and in anthracycline doses (359/299mg/m2 in Cardinale´s study vs 243mg/m2 in our study) may explain in part the delay in onset of cardiotoxicity in the present study. Finally, a ±14-l large study [19] with 1830 patients treated with A and long follow-up (8 years) evidenced that radionuclide LVEF post anthracycline treatment predicted heart failure at late follow-up. Our study did not reproduce this finding, and we didn´t evidence a significant difference in LVEF between AR-CT + and AR-CT - groups at visit 1 (64.5% in AR-CT + vs 64.3% in AR-CT -, p 0.92) and at visit 2 (62.7% in AR-CT + vs 63.2% in AR-CT-, p 0.92).

GLS is an established echocardiographic parameter used for early detection of AR-CT [20]. In the study there was a greater drop of GLS in AR-CT + vs AR-CT - patients but significant differences were only achieved in last visit and drop in GLS wasn´t an independent predictor of AR-CT.

Regarding cardiac biomarkers, none of them were found to be independent predictors of AR-CT in the regression model. There is well-established evidence of usefulness of troponins in early detection of AR-CT. However, evidence with other biomarkers is much weaker. 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 3 months after the last cycle. The timing of blood sample collection may have influenced our negative results.

Our study has some limitations. It has the common limitations of an observational- single centre study. Analyses of the echocardiographic exams 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 centre 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.

CONCLUSIONS: Incidence of late-onset cardiotoxicity is high but mostly subclinical. Development of diastolic dysfunction during first year was the only variable independently related with anthracycline cardiotoxicity in the long term, with an odds ratio value of 7.5 (95% CI 1.59-35.3).

IMPLICATIONS FOR PRACTICE: In the study we characterize the incidence of late-onset anthracycline cardiotoxicity in a cohort of patients undergoing Anthracycline treatment followed for more than four years. We found that development of diastolic disfunction is a strong predictor of subsequent anthracycline cardiotoxicity. The evaluation of diastolic function is a simple diagnostic measurement and is available in all cardiac imaging departments, and used along with other echocardiographic parameters may help us to discriminate patients at higher risk of developing anthracycline cardiotoxicity from those at lower risk and to set a different monitoring programs for breast cancer patients according to the risk of the patient.

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TABLES AND FIGURES

Table 1- Baseline Characteristics of the Total Population (n=100 patients; results expressed in % unless otherwise stated)	
Age [years, mean (s.d.)]	50.9 (9.0)
Female Gender	98
Weight [kg, mean (s.d.)]	70.3 (11.9)
Height [cm, mean (s.d.)]	157.8 (7)
BMI [kg/cm^2, mean (s.d.)]	28.3±5.1
Distribution	
Normal weight (<25)	26
Overweight (25-29.9)	41
Obesity (30-39.9)	30
Morbid Obesity (≥ 40)	3
Vascular Risk Factors	
Hypertension	27
Smoking status	34
Hypercholesterolemia	14
Diabetes	10
Baseline treatment	
ACE-I/ ARB	14
BB	3
Diuretis	14
HMG CoA reductase inhibitors	11
Antidiabetic drugs	5
CHT regimen	
- FEC	30
- AC-T	55
- AC-TH	15
Anthracycline dose [mg/m^2, mean (s.d.)]	243±4.6 mg/m2
Radiotherapy*	42

Table 1: s.d.: Standard deviation; BMI: Body mass index; ACE-I: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers; BB: beta-blocker; HMG CoA: 3-hidroxy-3-methylglutaryl coenzyme A; CHT: chemotherapy; FEC: 5-Fluorouracil, Epirubicin and Cyclophosphamide; AC-T: Adriamycin (Doxorubicin), Cyclophosphamide and Taxol® (Paclitaxel); AC-TH: Adriamycin (Doxorubicin), Cyclophosphamide, Taxol® (Paclitaxel) and Herceptin® (Trastuzumab);* radiotherapy on left hemithorax or mediastinum.

Table 2- Serial Echocardiographic Parameters at Baseline and During Follow-up							
	Baseline	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
N	100	100	99	15	98	14	90
Heart rate	72±10	73±11	73±11	73±13	71±11	68±10	71±10
SBP	118±17	119±19	118±15	119±21	116±14	117±15	124±16*

DBP	70±10	71±10	71±8	71±13	70±10	73±8*	73±8*
LVEF (%)	67.1±6.0	64.4±5.5*	63.1±4.8*	62.7±4.0*	63.5±5.6*	60.1±4.7*	60.7±6.8*
E/A ratio	1.15±0.3	1.03±0.3*	1.01±0.3*	1.05±0.2*	1.04±0.3*	1.08±0.2	1.01±0.3*
DT (ms)	193±30	205±35*	207±35*	203±27*	208±33*	201±21*	189±41
IVRT (ms)	89±11	94±13*	96±13*	92±13	96±14*	94±10*	89±28*
E´septum(cm/s)	9.4±2.4	8.4±2.3*	7.7±2.2*	8.7±2.6*	7.8±2.3*	8.0±2.7*	7.5±2.3*
E/E´septum	8.9±2.3	9.4±2.4*	9.9±2.7*	9.5±2.2	9.7±2.4*	10.0±2.7	10.4±3.3*
E´lateral(cm/s)	12.3±3.2	11.2±2.9*	10.5±3.1*	11.8±3.1	10.5±3.2*	9.6±3.2*	10.4±3.1*
E/E´lateral	6.8±1.8	7.10±1.9*	7.4±2.3*	7.0±1.7	7.3±2.0*	8.4±2.8*	7.7±2.9*
GLS (%)	-18.9±2.7	-18.1±3.7*	-17.2±3.4*		-17.1±3*		-17.8±3.2*
ΔGLS (%)		4.2	5.9		9.5		8.9
PV (cm/s)	54±10	49±10*	47±10*	44±8.8*	46±10*	47±12*	
LAVI (ml/m2)	24.9±5.7	26.3±5.9*	26.9±5.1*	26.6±5.3*	28.3±6.7*	28.4±6.5*	27.2±5.8*

Table 2: Values are mean ± SD. *denotes p value<0.05 comparing with baseline measurement. Abbreviations: N: number o patients attending each follow-up visit; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; E: early peak diastolic velocity; A: late peak diastolic velocity; DT: deceleration time of the E wave; IVRT: isovolumetric relaxation time; E´: pulsed Tissue-Doppler early diastolic velocity at mitral annulus (septum and lateral wall); GLS: global longitudinal strain; ΔGLS: percentage drop in global longitudinal strain from baseline; PV: Color m-mode propagation velocity; LAVI: Left atrial volume index in ml/m2 body surface area.

Table 3- Main clinical variables in groups AR-CT+ and AR-CT-
(Results expressed in % unless otherwise stated)

	AR-CT +	**AR-CT -**	**p-value**
Number of patients	18	82	
Age [years, mean (s.d.)]	50.3 (9.2)	51.0 (9.1)	0.780
BMI [kg/cm^2, mean (s.d.)]	29.1 (5.9)	28.2 (5.0)	0.480

BMI distribution			0.710
Normal weight (<25)	16.6	28.0	
Overweight (25-29.9)	44.4	40.2	
Obesity (≥30)	39.8	31.7	
Cardiovascular risk factors (%)			
-Hypertension	33.3	28.0	0.770
-Diabetes	11.1	9.8	1
-Hyperlipidemia	11.1	14.6	1
-Smoking status (current smoker)	38.9	42.7	0.780
Anthracycline dose (mg/m2)	243±4.8	242±4.5	0.730
Radiotherapy*	38.9	42.7	0.800
Diastolic dysfunction (%)	88.2	50.0	**0.005**
Baseline LVEF (%)	65.9±6.0	67.6±6.0	0.310

Table 3: Abbreviations: s.d.: Standard deviation; BMI: Body mass index; * radiotherapy for left hemithorax or mediastinum; AR-CT C+: group of patients who develop anthracycline cardiotoxicity; AR-CT –: group of patients who do not develop cardiotoxicity; LVEF: left ventricular ejection fraction.

Table 4- Global longitudinal strain/drop in global longitudinal strain in groups AR-CT + and AR-CT -			
	AR-CT +	**AR-CT -**	**p-value**
Number of patients	18	82	
GLS (%) baseline	-18.8±2.8	-18.9±2.9	0.84
GLS (%) visit 1	-17.3±3.9	-18.6±3.5	0.19
GLS (%) visit 2	-16.2±3.8	-17.8±3.6	0.15
GLS (%) visit 4	-16.6±4.2	-17.6±3.1	0.28
GLS (%) visit 6	-16.7±3.1	-18.4±3.2	0.06
ΔGLS from baseline to visit 1 (%)	11.1	4	0.17
ΔGLS visit 2 (%)	17.0	7.4	0.10
ΔGLS visit 4 (%)	17.5	7.9	0.10
ΔGLS visit 6 (%)	15.4	4.2	0.04

Table 4: Values expressed as mean ± standard deviation; Abbreviations: AR-CT+: group of patients who develop anthracycline cardiotoxicity; AR-CT–: group of patients who do not develop cardiotoxicity; GLS: global longitudinal strain; ΔGLS: percentage drop in global longitudinal strain from baseline. Values of P calculated by the Student t-test for the differences between groups AR-CT + and AR-CT -.

FIGURE 1

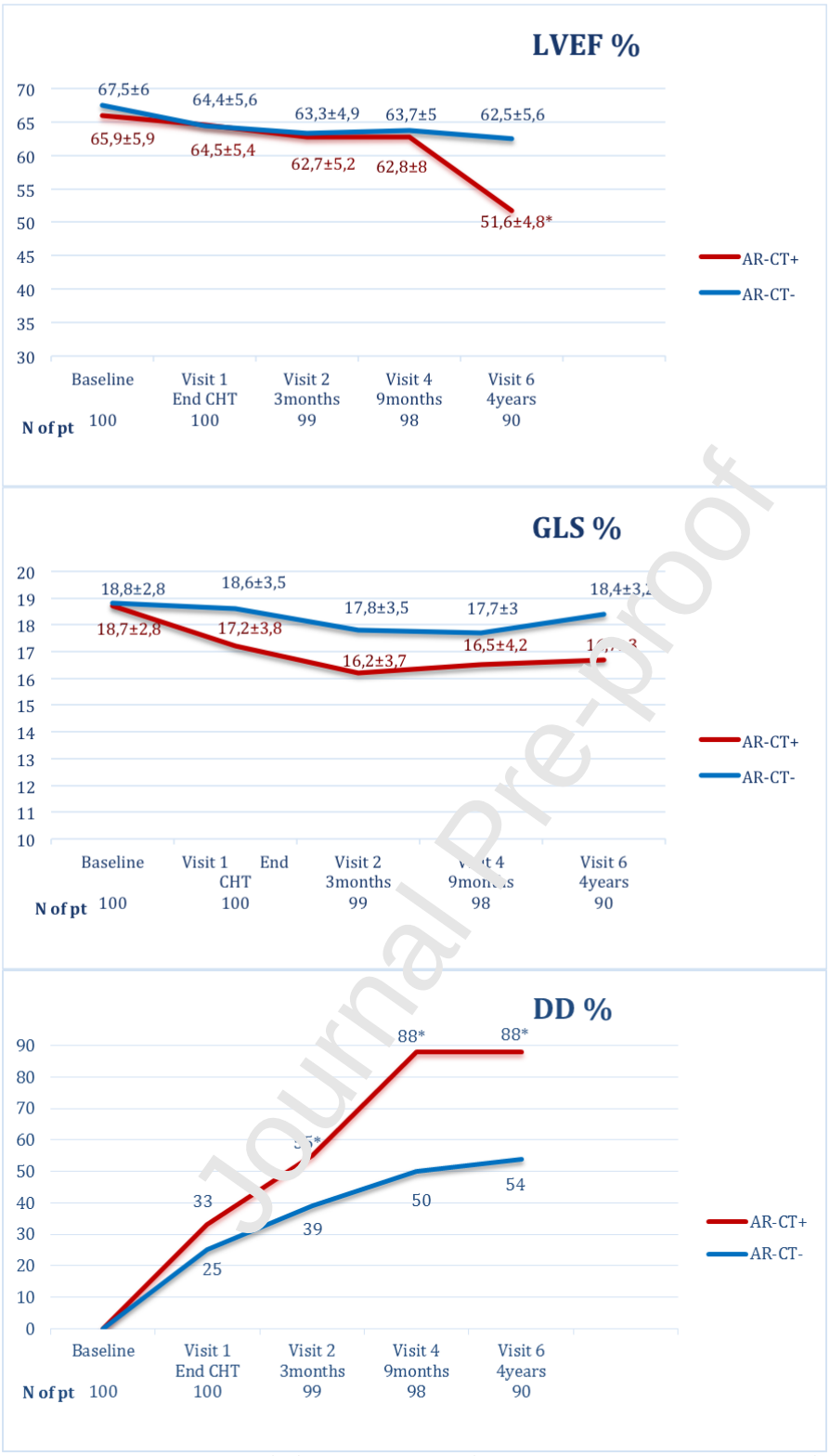

Figure 1-Evolution at each visit of left ventricular ejection fraction, global longitudinal strain and % of patients with diastolic dysfunction in group developing and not developing anthracycline cardiotoxicity. Values expressed as mean ± standard deviation;Abbreviations: AR-CT +: group of patients who develop anthracycline cardiotoxicity. AR-CT –: group of patients who do not develop cardiotoxicity; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain. DD: diastolic dysfunction. *denotes p value<0.05 comparing group AR-CT+ and AR-CT-

Table 5: Values are mean ± SD. *denotes p value<0.05 comparing each visit with baseline measurement in the total population. Abbreviations: AR-CT +: group of patients developing anthracycline cardiotoxicity; AR-CT -: group of patients not developing anthracycline cardiotoxicity; hsTnT: high sensitiveTroponin T; NTproBNP: N-terminal pro-brain natriuretic peptide; H-FABP: Heart-Type fatty acid-binding protein. P values were calculated by Student t test for difference in means between group of patients developing (AR-CT +) and not developing anthracycline cardiotoxicity (AR-CT -).

Table 5 - Biomarkers at each visit (0 to 5) in total population and groups AR-CT + and AR-CT -

	Total Population	AR-CT +	AR-CT -	p-value
Number of patients	100	18	82	
hsTnT (ng/L)				
-Baseline (visit 0)	4.18±3.5	4.3±3.0	4.0±3.6	0.78
-Visit 1	12.2±5.6*	13.2±5.8	12.0±5.6	0.44
-Visit 2	12.5±6.1*	14.1±8.2	12.1±5.5	0.2
-Visit 3	6.9±3.3*	8.2±4.6	6.4±2.8	0.5
-Visit 4	6.6±3.5*	7.3±3.3	6.4±3.5	0.34
-Visit 5	4.7±2.0*	5.2±2.2	4.6±2.0	0.69
NTproBNP(pg/mL)				
-Baseline (visit 0)	63.1±82.5	53.7±70.3	65.2±85.3	0.59
-Visit 1	64.8±61.2	86.0±103.4	60.2±47.1	0.1
-Visit 2	62.4±69.2	78.4±95.2	58.9±62.3	0.28
-Visit 3	41.7±47.8	24.0±17.8	48.0±54.1	0.22
-Visit 4	80.1±71.2*	89.9±108.3	77.8±61.4	0.52
-Visit 5	52.1±47.9	87.9±67.8	42.4±39.7	0.36
H-FABP (ng/mL)				
-Baseline (visit 0)	3.2±2.1	2.9±1.4	3.3±2.2	0.56
-Visit 1	3.1±1.9	2.8±1.4	3.2±2.0	0.43
-Visit 2	3.3±1.9	3.5±2.2	3.3±1.8	0.66
-Visit 3	3.3±1.2*	3.8±2.0	3.1±0.8	0.56
-Visit 4	3.6±1.8*	3.4±1.6	3.7±1.9	0.28
-Visit 5	3.6±1.4*	4.4±2.7	3.3±0.8	0.55

FIGURE 2

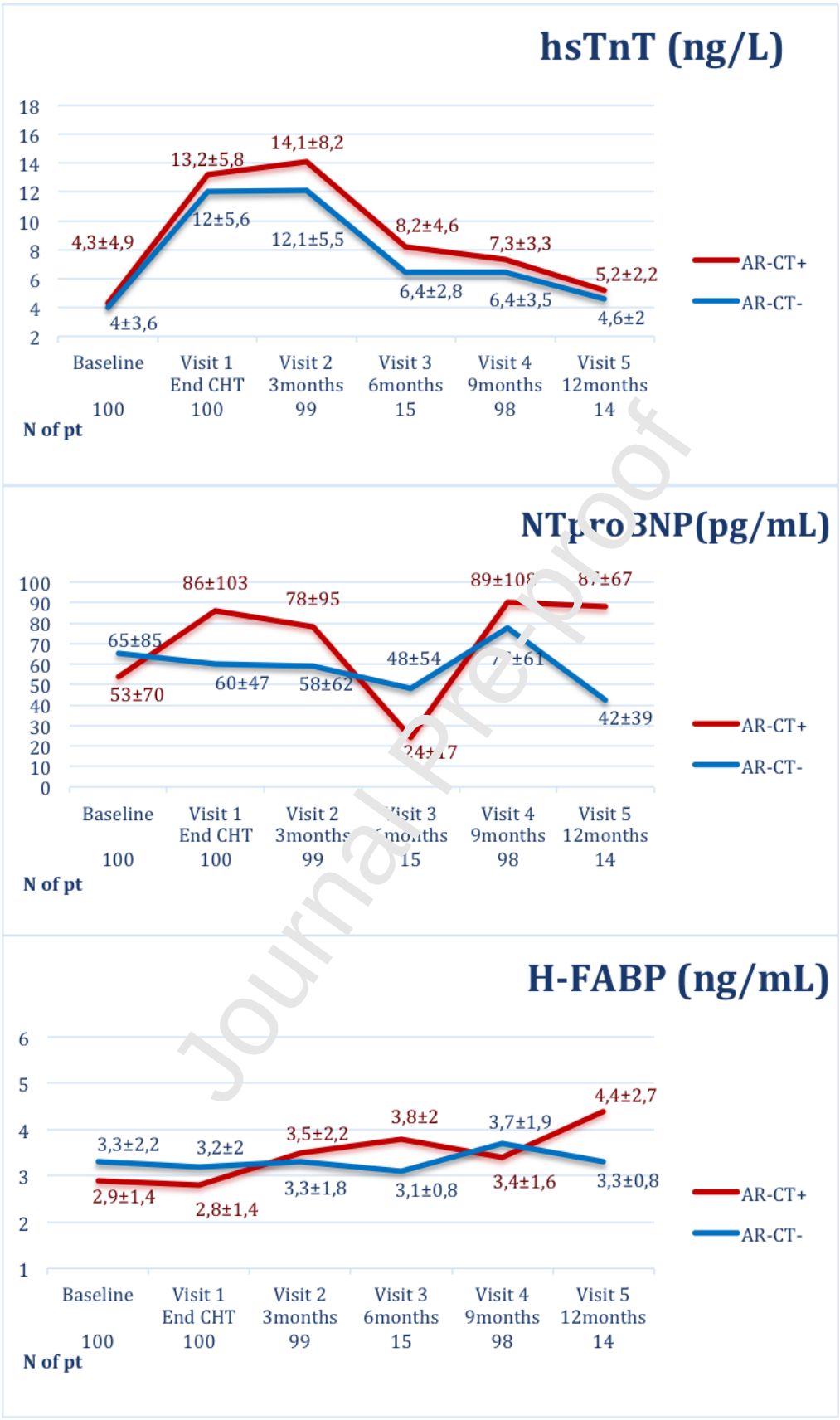

Figure 2: Changes in cardiac biomarkers throughout the study in groups developing and not developing anthracycline cardiotoxicity. Values expressed as mean ± standard deviation .Abbreviations: AR-CT +: group of patients developing anthracycline cardiotoxicity; AR-CT -: group of patients not developing anthracycline cardiotoxicity; hsTnT: high sensitiveTroponin T; NTproBNP: N-terminal pro-brain natriuretic peptide; H-FABP: Heart-Type fatty acid-binding protein.

Highlights

What is already known about this subject?

Some studies with small number of patients have found early changes in several diastolic function parameters in patients exposed to Anthracycline therapy. Data regarding late-onset cardiotoxicity comes from cohort studies of patients treated during childhood but information of incidence of late-onset cardiotoxicity in adult population with breast cancer is scarce.

What does this study add?

In this study we characterize the incidence of late-onset cardiotoxicity (clinical and subclinical) in a cohort of consecutive breast-cancer patients undergoing Anthracycline treatment. We also found that development of diastolic dysfunction early after chemotherapy is a strong predictor of subsequent anthracycline cardiotoxicity.

How might this impact on clinical practice?

The evaluation of diastolic function is a simple diagnostic measurement, available in all cardiac imaging departments, and may help us to discriminate patients at higher risk of developing anthracycline cardiotoxicity from those at lower risk and to set a different monitoring programs for breast cancer patients according to the risk of the patient.