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Subclinical Ventricular Dysfunction Detected by Speckle Tracking Two Years after Use of Anthracycline

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Abstract

Background: Heart failure is a severe complication associated with doxorubicin (DOX) use. Strain, assessed by two-dimensional speckle tracking (2D-STE), has been shown to be useful in identifying subclinical ventricular dysfunction.

Objectives: a) To investigate the role of strain in the identification of subclinical ventricular dysfunction in patients who used DOX; b) to investigate determinants of strain response in these patients.

Methods: Cross-sectional study with 81 participants: 40 patients who used DOX ±2 years before the study and 41 controls. All participants had left ventricular ejection fraction (LVEF) ≥55%. Total dose of DOX was 396mg (242mg/m²). The systolic function of the LV was evaluated by LVEF (Simpson), as well as by longitudinal (ε_{LL}), circumferential (ε_{CC}), and radial (ε_{RR}) strains. Multivariate linear regression (MLR) analysis was performed using ε_{LL} (model 1) and ε_{CC} (model 2) as dependent variables.

Results: Systolic and diastolic blood pressure values were higher in the control group ($p < 0.05$). ε_{LL} was lower in the DOX group (-12.4 ±2.6%) versus controls (-13.4 ± 1.7%; $p = 0.044$). The same occurred with ε_{CC}: -12.1 ± 2.7% (DOX) versus -16.7 ± 3.6% (controls; $p < 0.001$). The S' wave was shorter in the DOX group ($p = 0.035$). On MLR, DOX was an independent predictor of reduced ε_{CC} (B = -4.429, $p < 0.001$). DOX (B = -1.289, $p = 0.012$) and age (B = -0.057, $p = 0.029$) were independent markers of reduced ε_{LL}.

Conclusions: a) ε_{LL}, ε_{CC} and the S' wave are reduced in patients who used DOX ±2 years prior to the study despite normal LVEF, suggesting the presence of subclinical ventricular dysfunction; b) DOX was an independent predictor of reduced ε_{CC}; c) prior use of DOX and age were independent markers of reduced ε_{LL}. **(Arq Bras Cardiol. 2015; 104(4):274-283)**

Keywords: Heart Failure; Ventricular Dysfunction Left / chemically induced; Echocardiography; Anthracyclines / adverse effects.

Introduction

Cardiovascular and oncologic disorders are the most prevalent diseases and the main global causes of morbidity and mortality. Together they are associated with more than 70% of the death causes worldwide[1]. Treatment of cancer has been conducted with a combination of chemotherapy, radiotherapy and surgery in an attempt, often successful, to benefit the patient. In recent years, it has been observed a marked increase in average survival in patients with cancer due to, among other causes, a greater effectiveness of antineoplastic drugs, in particular the anthracyclines[2]. However, this greater effectiveness occurs at the expense of side effects. Both chemotherapy and radiotherapy are associated with cardiotoxic effects and their cardiovascular complications, which manifest as heart failure, myocardial ischemia, myocardial infarction, hypertension, thromboembolism, pericarditis and cardiac arrhythmias[3].

The combination of increased survival and consequent aging of the population, associated with the cardiotoxicity of the antineoplastic treatment, has led to increased cardiovascular morbidity and mortality in individuals with cancer[4].

In clinical practice, cardiotoxicity has been identified by symptomatic or asymptomatic left ventricular (LV) dysfunction. The LV ejection fraction (LVEF), estimated by echocardiography or myocardial scintigraphy, is generally used to evaluate the LV function[5]. This method presents some limitations, including low sensitivity for detection of initial LV injury. Moreover, the failure to detect changes in LVEF does not exclude subclinical cardiac injury, nor the possibility of cardiac deterioration at a later stage[6].

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Strain, assessed by two-dimensional speckle tracking (2D-STE), is useful in identifying subclinical heart disease in several pathologies[7,8], with the ability to identify early (subclinical) cardiac injury during chemotherapy[9].

The aims of this study are: a) To investigate the role of strain, evaluated by 2D-STE, in identifying subclinical ventricular dysfunction in patients treated with doxorubicin (DOX); b) to investigate determinants of strain response in cancer survivors.

Methods

Research Subjects

Patients who completed treatment with DOX in the oncology unit of our hospital between February 2010 and June 2011 and who lived in our city were invited to participate in this cross-sectional study. Through chart review, we collected demographic data, previous medical history, information about use of adjuvant radiation therapy, doses of anthracycline used (total and indexed to body surface area), as well as the dates of beginning and end of treatment. Members of the administrative staff of the hospital without previous history of neoplasia were invited to participate in the study and composed the control group. In these individuals, we collected demographic data and prior medical history. All participants underwent transthoracic echocardiogram with 2D-STE, as well as clinical evaluation with detailed history and physical examination when the following parameters were obtained: weight, height, heart rate, abdominal circumference (AC), body mass index (BMI), and systolic and diastolic blood pressure (BP). Exclusion criteria were presence of heart failure (HF) by Framingham criteria, history of prior cardiovascular disease (except hypertension), any valvular lesion greater than mild, change in segmental contractile function in transthoracic echocardiogram, LVEF < 55% and/or prior chemotherapy.

The AC was measured at the navel level with a standard tape measure. BMI was obtained by the ratio of the weight to the height squared (Kg/m^2). BP was measured three times with participants in the sitting position. The average of the two last measurements was included in the analysis. All participants had LVEF $\geq$ 55% and showed no clinical manifestations of HF by Framingham criteria. Patients with at least two serum glucose levels > 126mg/dL or in use of oral hypoglycemic drugs and/or insulin were classified as diabetics. Hypertensive were participants in use of antihypertensive medication or who presented systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg on at least two occasions. Patients with dyslipidemia had total cholesterol > 200 mg/dL and/or LDL cholesterol > 130 mg/dL. Smokers were individuals who continued smoking or had left the habit less than 10 years before. Alcohol consumption was categorized in absent, eventual, weekly, or daily. The race of the participants was classified according to self-reported information as white, brown, yellow or black. Physical activity was defined as the practice of exercises at least three times a week, with a minimum duration of 30 minutes per session.

The study was approved by the Ethics Committee for Research Involving Human Subjects of our university and all participants signed an Informed Consent Form.

Conventional Doppler Echocardiography

Echocardiographic images were obtained by experienced echocardiographers (ALCA, VAS, ATSF and VGR) and were interpreted by a single examiner (ALCA). The tests were carried out on the equipment Artida (Toshiba Medical Systems Corp., Tochigi, Japan). All images were digitalized and stored for later analysis. Doppler echocardiographic images were acquired following the recommendations of the American Society of Echocardiography[10]. The LV mass was determined by the diastolic thickening of the septum, the LV posterior wall, and the LV end-diastolic diameter, and indexed to body surface area, generating the variable LV mass index (LVMI)[11]. LVEF was calculated using the modified (biplane) Simpson's rule. The transmitral early diastolic flow velocity (E wave) and late diastolic flow velocity (A wave), as well as the deceleration time were measured using conventional pulsed Doppler. Tissue Doppler evaluates the longitudinal excursion of the mitral ring during systole and diastole. Tissue Doppler velocities were assessed in the four basal segments of the LV in the apical 4-chamber and 2-chamber views, with an angle smaller than 20^0 between the ultrasound beam and the plane of cardiac motion. We measured the peak systolic (S' wave), early diastolic (E' wave) and late diastolic (A´ wave) velocities. The final result of each of these variables consisted on the average of the values found in the four analyzed segments. The volume of the left atrium (LA) was measured by two-dimensional planimetry using the biplane Simpson's rule in the frame that preceded the opening of the mitral valve, and was indexed to body surface generating the variable left atrial volume index (LAVI)[10].

Two-Dimensional Speckle Tracking Echocardiography

The two-dimensional images were acquired in the short axis of the LV, at the level of the insertion of the papillary muscles, and in the apical 4-chamber and 2-chamber views. They were recorded using a sectorial transducer (frequency range 1.7 to 3.5 MHz) with harmonic imaging, pulse repetition frequency between 40 and 80 cycles/second, maintaining a single focus in the central region of the LV, regulating the sector width (narrowest possible), depth (minimum possible) and the gain to optimize the quality of the two-dimensional image.

Longitudinal (ε_{LL}), circumferential (ε_{CC}) and radial (ε_{RR}) strains were analyzed with the two-dimensional speckle tracking software by Toshiba (Toshiba 2D Wall Motion Tracking software, Toshiba Medical Systems). Manual delineation of the endocardial border of the LV at end-systole (determined anti-clockwise) was followed by automatic tracing of the epicardial border (which could be manually adjusted) and of a line in the middle region of the LV wall[12]. A similar approach was made on the apical 4-chamber image, starting the trace on the lateral corner of the mitral valve ring at end-diastole, and in the apical

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2-chamber image (beginning the trace at the junction of the inferior wall with the mitral ring at end-diastole). The software 2D-STE uses the sum of the differences of the squares to find the dot pattern (speckles) most similar to the one obtained in the two-dimensional model in two subsequent cycles (frames)[13]. Strain (ε, %) was calculated as the change in regional length relative to the length at end-diastole: $\varepsilon = (L_{(t)} - L_0) \times 100/_0 L$, in which $L_{(t)}$ is the length at time t and L_0 is the length of the segment at the beginning of the QRS segment. Global ε_{LL} (Figure 1), global ε_{CC} (Figure 2) and global ε_{RR} were represented by the peak of the strain averages, and the values of the longitudinal and circumferential strains were those representative of the middle region of the myocardium. Since ε_{LL} and ε_{CC} reflect shortening of the myocardial segment analyzed, the more negative its value, the greater will be the myocardial deformation relative to the state observed at end-diastole. The regions of the LV short axis and the projections in 4 and 2 chambers were divided according to the recommendations by the American Society of Echocardiography[14]. Segments of the LV with inadequate image quality were excluded from the analysis due to the presence of acoustic shadows, image artifacts, reverberations or poor quality in the trace of the points by manual evaluation.

Reproducibility

All echocardiographic measurements were performed offline by a single blinded examiner (ALCA). The intraobserver reproducibility for ε_{LL} and ε_{CC} was evaluated by repeating the measurements in 20 randomly selected participants, with a minimum interval of 30 days from the first test.

Statistical Analysis

Quantitative variables were expressed as mean ± standard deviation and compared by Student's t test or Wilcoxon signed-rank test, whereas qualitative variables were expressed by their frequencies and percentages, and compared by the chi-square test or Fisher's exact test. Univariate analysis was used to evaluate the relationship between ε_{CC} and ε_{LL} with the variables of interest. Two stepwise multivariate linear regression (MLR) models were created. The dependent variables in models 1 and 2 were ε_{LL} and ε_{CC}, respectively. We considered as independent those variables with $p < 0.20$ in the univariate analysis and those with biological plausibility of interference with the strain. Intraobserver variability was assessed by the intraclass correlation coefficient. The level of significance was defined as $p < 0.05$. The statistical analyses were processed with the software Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, Illinois).
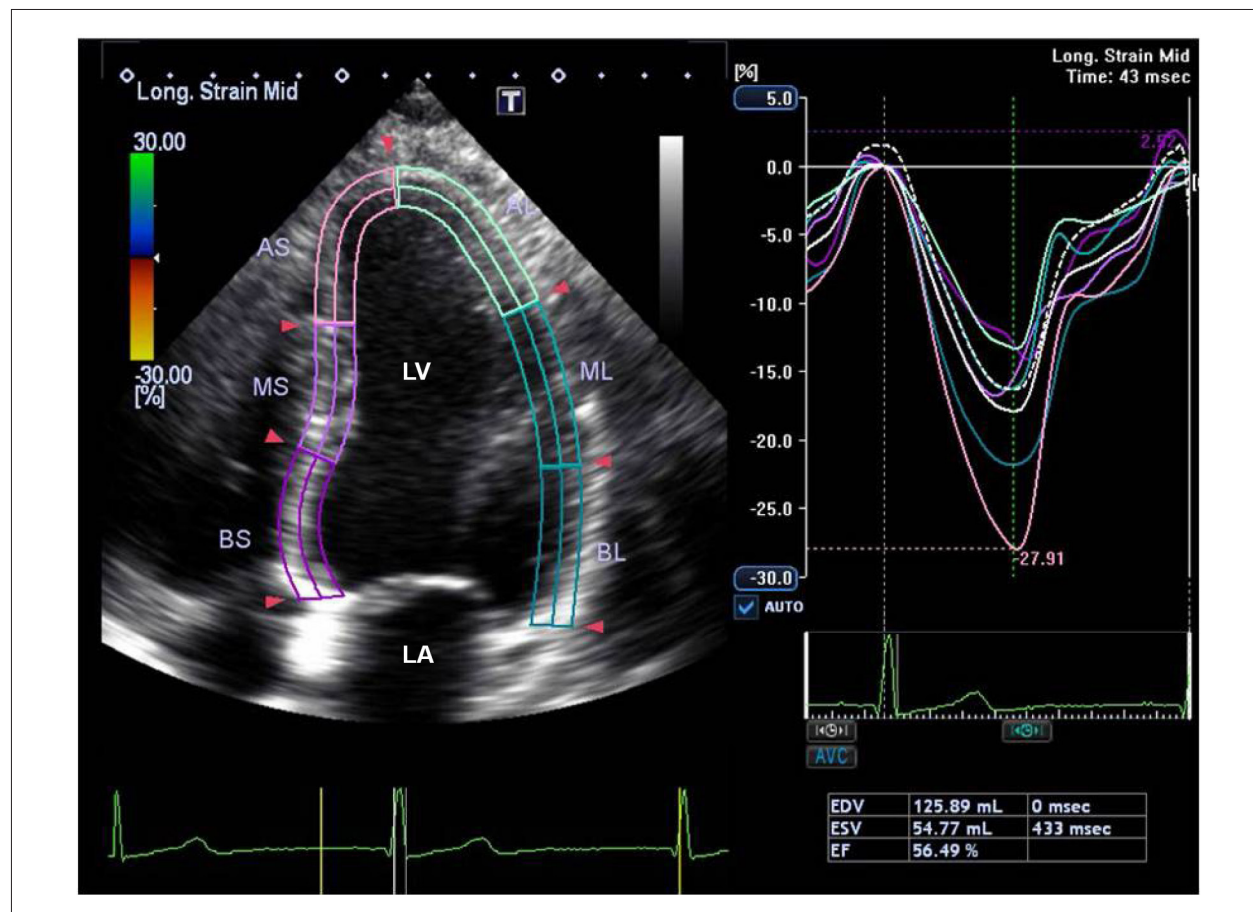

Figure 1 – *Representation of longitudinal strain.*

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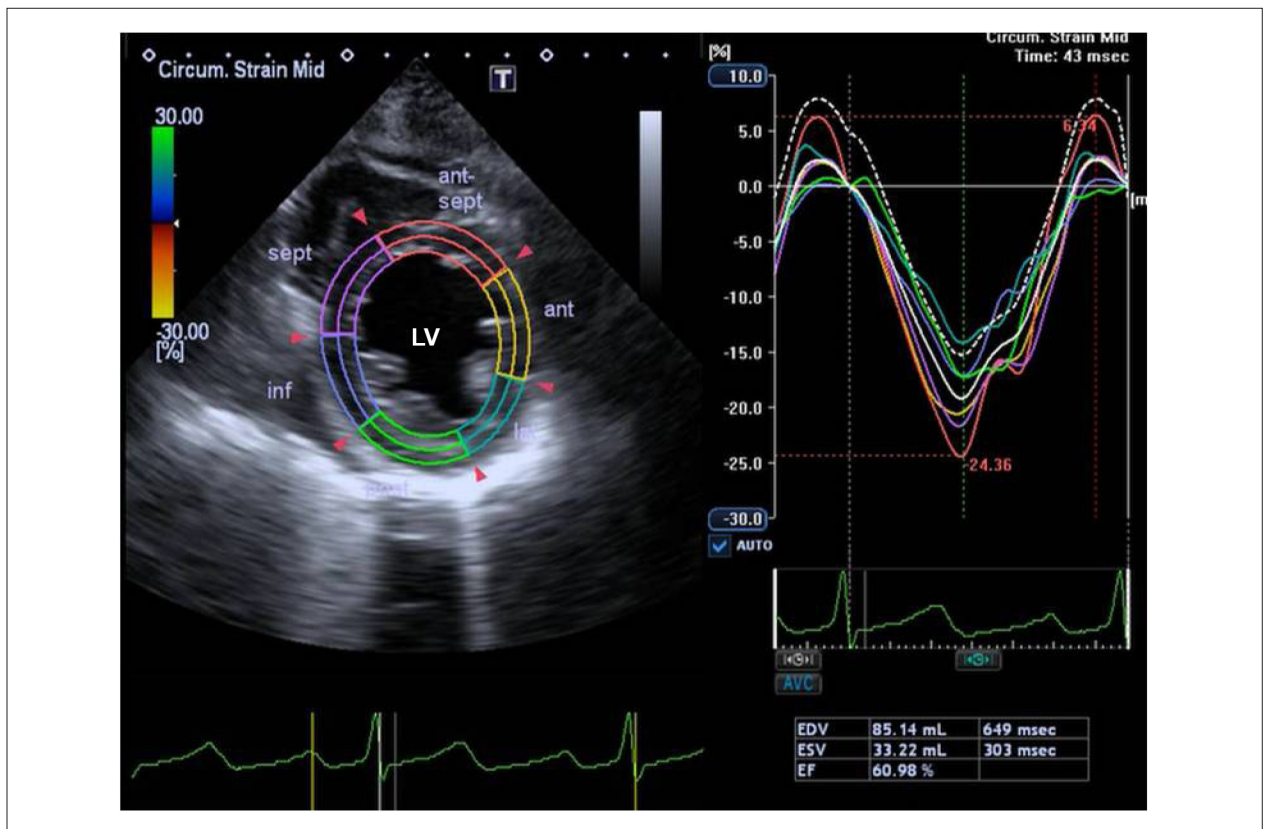
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Figure 2 – *Representation of circumferential strain.*

Results

Cohort Characteristics

The main clinical characteristics of the study population are shown in Table 1.

Only female patients accepted to participate in the study and reported to the unit for evaluation. Fifty-one women who had used DOX 25.5 ± 4.7 months before the study (median: 24 months; interquartile range [IQR]: 22 to 28 months) comprised the group of patients. Eleven were excluded from the analysis: six due to LVEF < 55%, three had previously undergone chemotherapy and two had echocardiography with inadequate technical quality for analysis. The average age of the patients included in the analysis was 52 ± 11 years. One had history of non-Hodgkin lymphoma and 39 of breast neoplasm. The control group was composed of 42 women from the administrative staff of the hospital, without previous history of neoplasia. One was excluded due to LVEF < 55%. The average age of the patients in the control group was 56 ± 10 years. There was no difference between the two groups regarding the percentage of patients with hypertension, diabetes, blacks, smokers and alcohol consumption. Age, AC, BMI and LVMI were similar (p > 0.05 for all). Systolic and diastolic BP values were higher in the control group (p = 0.028 and 0.027, respectively).

The average total dose of DOX received was 396 ± 85 mg, which corresponded to 242 ± 43 mg/m². None of the patients received trastuzumab. Fifteen patients (37.5%) also used 5-fluorouracil and 31 (77.5%) received cyclophosphamide. Twenty-one patients (52.5%) underwent adjuvant radiation therapy, which was applied to the right side in 13 (32.5%) patients and to the left side in 8 (20%) patients.

Conventional Doppler Echocardiographic Variables

The LVEF was normal and showed no difference between the groups: 65.3 ± 4.8% (patients) versus 66.7 ± 4.3% (controls; p = 0.18). The same occurred with LVMI: 75 ± 15 g/m² (patients) versus 71 ± 16 g/m² (controls; p=0.34). The absolute diameter of the LA was greater in the control group (p = 0.006). However, there was no difference when LA was indexed to body surface area (p = 0.11), nor when we assessed the LAVI (p = 0.58). The average S' wave velocity on tissue Doppler was higher in controls (6.6 ± 0.9cm/s) when compared with patients (6.1 ± 1.0cm/s; p = 0.035). This was mainly due to the increased velocity of the S' wave side corner of the mitral ring (7.1 ± 1.0cm/s versus 6.3cm/s; p = 0.004). The velocity of the E and E' waves, the mitral flow deceleration time, as well as the relationships E/A and E/E´ were similar between the groups, without difference regarding the results of the LV diastolic function. All other conventional echocardiographic variables were similar between groups (Table 2).

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Table 1 – Characteristics of the study cohort

Variable	Doxorubicin (N = 40)	Controls (N = 41)	p value
Total dose of doxorubicin	396 mg (242 mg/m²).	-	-
Age (years)	52 ± 11	56±9	0.11
Hypertension (%)	35	39	0.71
Diabetes (%)	10.0	9.8	1
Dyslipidemia (%)	33	41	0.40
Race - black (%)	77.5	82.1	0.76
Smoking (%)	22.5	29.3	0.22
Alcohol consumption (%)	27.5	19.5	0.34
Abdominal circumference (cm)	93 ± 14	95 ± 9	0.35
BMI (Kg/m²)	25.8 ± 5.3	27.3 ± 3.8	0.15
Body surface area (m²)	1.70 ± 0.21	1.75 ± 0.20	0.30
Systolic BP (mmHg)	130 ± 21	141 ± 22	0.028
Diastolic BP (mmHg)	80 ± 14	87 ± 12	0.027

BMI: body mass index; BP: blood pressure.

Table 2 – Characteristics of conventional Doppler echocardiography

Variable	Doxorubicin (N = 40)	Controls (N = 41)	p value
Aortic root (mm)	30 ± 3	31 ± 3	0.34
LA (mm)	33 ± 3	35 ± 4	0.006
LA/BSA (mm/m²)	19.3 ± 2.2	20.1 ± 2.1	0.11
LVDD (mm)	46 ± 4	47 ± 4	0.87
LVSD (mm)	30 ± 3	30 ± 3	0.94
Septum (mm)	8 ± 1	8 ± 1	0.44
LVPW (mm)	8 ± 1	8 ± 1	0.36
LVEF (%, Simpson)	65 ± 5	67 ± 4	0.18
LVMI (g/m²)	75 ± 15	71 ± 16	0.34
LAVI (mm)	22 ± 5	21 ± 6	0.58
Mitral E wave (cm/s)	67 ± 15	73 ± 14	0.06
Mitral A wave (cm/s)	71 ± 19	73 ± 18	0.52
E/A Ratio	1.0 ± 0.3	1.0 ± 0.3	0.68
DT	181 ± 41	176 ± 31	0.56
Mitral E' wave (cm/s)	8.9 ± 2.5	9.5 ± 2.3	0.30
Mean S' wave (cm/s)	6.1 ± 1.0	6.6 ± 0.9	0.035
E/E' Ratio	8.0 ± 2.7	8.2 ± 2.5	0.78

LA: left atrium; BSA: body surface area; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVPW: left ventricular posterior wall; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LAVI: left atrial volume index; DT: deceleration time.

ε_{LL}, ε_{CC} and ε_{RR} Obtained by Two-Dimensional Speckle Tracking

Even though the LVEF was normal and showed no difference between groups, the ε_{LL} in the patients' group was -12.4 ± 2.6%, representing values 7.5% lower than the corresponding values for the controls (-13.4 ± 1.7%; $p = 0.04$; Table 3). ε_{CC} was -12.1 ± 2.7% in patients, representing a reduction of 27.5% compared with controls (-16.7 ± 3.6%; $p < 0.001$). There was no difference between the groups with respect to ε_{RR} ($p = 0.89$).

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There was no correlation between the dose of DOX and the strain (DOX versus ε_{LL}: p = 0.89; DOX versus ε_{CC}: p = 0.95).

Intraobserver intraclass correlation coefficient was 0.89 (p < 0.01) for ε_{LL} and 0.83 (p = 0.01) for ε_{CC}.

Determinants of Longitudinal Strain

In model 1 of the MLR analysis, previous use of DOX (B = -1.289; 95% confidence interval [CI]: -2.282 to -0.296; p = 0.012) and the age in years (B = -0.057; 95% CI: -0.108 to -0.006; p = 0.029) were the only independent predictors of ε_{LL} (Table 4).

Determinants of Circumferential Strain

In model 2 of the MLR, previous use of DOX was the only independent predictor of reduction in ε_{CC} after adjustments for LVMI, presence of dyslipidemia, age, prior radiotherapy and systolic BP (B = -4.429; 95% CI: -5.907 to -2.952; p < 0.001; Table 5).

Discussion

The results of this study show that ε_{LL} and ε_{CC}, evaluated by 2D-STE, are reduced in patients who used DOX 2 years before when compared with healthy controls. This occurred even though the LVEF was normal and did not differ between the groups, suggesting the presence of subclinical ventricular dysfunction in a group considered at high risk for cardiovascular events. Our results also showed that previous use of DOX was an independent predictor of reduction of ε_{CC} in cancer survivors, and that previous use of DOX and age were independent markers of reduced ε_{LL} in this population. The S' wave, another echocardiographic variable able to identify preclinical changes in LV systolic function, was also reduced in patients who used the anthracycline.

With the global trend of population aging, the risk factors for cardiovascular disease will become more prevalent. It is therefore expected that there will be an increase in the occurrence of heart disease. Likewise, there is an increase

Table 3 – Strain results in the study population

Variable	Doxorubicin (N = 40)	Controls (N = 41)	p value
ε_{LL} (%)	-12.4 ± 2.6	-13.4 ± 1.7	0.04
ε_{CC} (%)	-12.1 ± 2.7	-16.7 ± 3.6	< 0.001
ε_{RR} (%)	30.9 ± 10.4	31.2 ± 10.4	0.89

ε_{LL}: longitudinal strain; ε_{CC}: circumferential strain; ε_{RR}: radial strain

Table 4 – Determinants of longitudinal strain

Independent Variables	Dependent Variable: ε_{LL}					
	Univariate Analysis			Multivariate Analysis (p = 0.011)		
	B Coef (%)	95% CI	p value	B Coef (%)	95% CI	p value
Doxorubicin (Yes)	-1.02	(-2.006;-0.038)	0.042	-1.289	(-2.282;-0.296)	0.012
Age (years)	-0.052	(-0.102;0.002)	0.044	-0.057	(-0.108;-0.006)	0.029
LV mass index (g/m²)	-0.008	(-0.041;0.025)	0.616	-	-	0.867
Diabetes (Yes)	-0.561	(-2.232;1.110)	0.506	-	-	0.65
Obesity (Yes)	-0.775	(-1.945;0.395)	0.191	-	-	0.246
Systolic BP (mmHg)	0.004	(-0.019;0.028)	0.716	-	-	0.842
Prior radiotherapy (Yes)	-0.401	(-1.560;0.758)	0.493	-	-	0.953
Alcohol (Yes)	0.424	(-0.662;1.512)	0.440	-	-	-
Smoking (Yes)	0.350	(-0.599;1.298)	0.465	-	-	-
Race (Black)	0.583	(-0.827;1.994)	0.412	-	-	-
Physical activity (Yes)	0.230	(-0.914;1.373)	0.690	-	-	-
Abdominal circumference (cm)	-0.021	(-0.064;0.022)	0.340	-	-	-
BMI (Kg/m²)	-0.051	(-0.159;0.057)	0.347	-	-	-
Hypertension (Yes)	-0.501	(-1.552;0.550)	0.345	-	-	-

LV: left ventricle; BP: blood pressure; BMI: body mass index; Coef: coefficient; CI: confidence interval.

Table 5 – Determinants of circumferential strain

Independent Variables	Dependent Variable: ε_{CC}					
	Univariate Analysis			Multivariate Analysis (p < 0.001)		
	B Coef (%)	95% CI	p value	B Coef (%)	95% CI	p value
Doxorubicin (Yes)	-4.539	(-6.010;-3.067)	< 0.001	-4.429	(-5.907;-2.952)	< 0.001
Dyslipidemia (Yes)	-1.077	(-2.921;0.767)	0.248	-	-	0.065
LV mass index (g/m²)	0.012	(-0.047;0.071)	0.688	-	-	0.206
Prior radiotherapy (Yes)	-3.237	(-5.119;-1.354)	0.001	-	-	0.851
Age (years)	0.04	(-0.05;0.14)	0.349	-	-	0.928
BMI (Kg/m²)	-0.056	(-0.265;0.152)	0.591			0.124
Systolic BP (mmHg)	0.026	(-0.017;0.069)	0.235	-	-	0.651
Diabetes (Yes)	0.703	(-2.247;3.653)	0.636	-	-	-
Smoking (Yes)	0.157	(-1.510;1.823)	0.852	-	-	-
Alcohol (Yes)	-0.168	(-2.126;1.790)	0.865	-	-	-
Physical activity (Yes)	0.464	(-1.558;2.485)	0.649	-	-	-
Abdominal circumference (cm)	-0.011	(-0.095;0.072)	0.787	-	-	-
Race (Black)	0.958	(-1.412;3.327)	0.422	-	-	-
Hypertension (Yes)	0.0412	(-1.46;2.248)	0.662	-	-	-

LV: left ventricle; BP: blood pressure; BMI: body mass index; Coef: coefficient; CI: confidence interval.

in cancer incidence in older populations[15]. The effectiveness of antineoplastic treatment has significantly reduced the mortality due to cancer[2]. These same drugs, however, are associated with increased morbidity and mortality due to cardiovascular causes. Patients treated with DOX who develop signs of HF have a mortality rate at 2 years of 60%, a 3.5 times higher risk than those with idiopathic dilated cardiomyopathy[16]. Monitoring of myocardial function in patients using chemotherapeutic agents is usually based on clinical findings and on LVEF. These parameters, however, only change in the later stages of cardiovascular disease, usually when there is already structural apoptosis of myocytes and therefore, little likelihood of reversion of the clinical picture[3,4]. The identification of cardiac injury in the early stages has proven beneficial in patients undergoing cancer treatment[17], and the reduction in ε_{LL} emerging as an independent predictor of late reduction in LVEF in patients treated with anthracyclines justify early therapy with drugs with cardioprotective effect in these patients[18].

Sawaya et al[18] showed that unlike the longitudinal strain, LVEF and information from LV diastolic function are unable to predict cardiotoxicity, and that LVEF is not sensitive enough to detect early LV injury[19]. In other words, when the dysfunction is detected, heart injury has already occurred for some time, preventing use of prophylactic strategies. Moreover, the failure to detect changes in LVEF does not exclude subclinical cardiac damage, nor the possibility of later cardiac deterioration[6,20]. Our results showed that more sensitive markers related to subclinical myocardial injury, such as ε_{LL}, ε_{CC} and S' wave, are reduced in patients who used the anthracycline, despite normal LVEF which did not differ

between groups. Similar results were obtained by other authors, signaling that the use of these new technologies can be useful in the evaluation of cardiotoxicity in patients undergoing chemotherapy[17,21-23].

The differences observed in the absolute value of the strain tend to be small when we deal with subclinical ventricular dysfunction[8,17]. In our study, the relative difference observed in ε_{LL} was 7.5% and in ε_{CC} of 27.5%, similar to the results obtained in other studies[21,24].

Even though the qualitative analysis (DOX: yes versus no) have influenced the results of the ε_{CC} and the ε_{LL}, the variation in DOX dose used in our study was very low (median = 240 mg/m²; IQR: 231-286 mg/m²), justifying the absence of correlation observed between the dose of DOX and the strain.

The participants in the control group in this study cannot be considered normal. Although they were included as controls, none of them underwent a stress test and, therefore, did not have potential incipient heart diseases excluded. Additionally, the prevalences of dyslipidemia, diabetes, hypertension, smoking and alcohol consumption in both groups bring our cohort very close to the "real world", which, in our view, reinforce even more the results of the study. In an article from the MESA (Multi-Ethnic Study of Atherosclerosis) trial[8], the characteristics of the control group were very similar to those in our control group, and the software used for the analysis of strain was the same used in our study. In that article, longitudinal strain between controls was -13.9 ± 2.3%, a result close to that found in our study (-13.4 ± 1.7%). It is also possible that these values may be slightly lower when compared with truly normal individuals.

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The algorithm used by Toshiba's equipment allows measurement of circumferential and longitudinal strain in the endocardial, mid-myocardial and epicardial regions. In the absence of ischemia, strain is greater in the endocardium than in the epicardium, with intermediate values in the middle region of the myocardium[12]. Experimental data validated by sonomicrometry show that while the circumferential strain in the mid-myocardial region was -13.3 ± 4.7%, the results in the endocardium and epicardium were -25.2 ± 8.7% and -9.4 ± 9.3%, respectively[12]. In our study, the results of longitudinal and circumferential strains were those representing the middle region of the myocardium, as described in the methodology.

According to Feigenbaum et al[25], one of the limitations for propagation of the method of strain analysis by speckle tracking is the fact that many manufacturers have not yet presented interchangeable results between different software applications for strain analysis. That is, the results obtained with the Toshiba software, used in our study, are unlikely to be the same results obtained by another manufacturer.

Participants in the control group had levels of systolic and diastolic BP higher in the initial clinical evaluation, although there was no difference between groups in the percentage of participants labeled hypertensive. This finding seems contradictory, but it was probably due to greater adherence to antihypertensive therapy among patients who were undergoing medical follow-up after chemotherapy. The increase in BP levels tend to influence the results of ε_{LL} and ε_{CC}. Marwick et al[26] showed that the higher the diastolic BP, the greater will be the impact on the strain. Our results showed that patients who underwent chemotherapy presented lower ε_{LL} and ε_{CC}, despite presenting lower levels of systolic and diastolic BP when compared with healthy controls. Although this contradicts the results reported by Marwick et al[26], this information can reinforce the importance of prior use of DOX as an independent predictor of reduced ε_{LL} and ε_{CC} in our patients.

Although the absolute dimension of the LA was higher in controls, there was no difference when it was indexed to body surface area. Similarly, there was no difference in the values of LAVI, which is a more robust index to represent the dimensions of the LA and has a higher correlation with cardiovascular disease[10,27].

Side effects of mediastinal radiotherapy on the heart can be expressed in the form of cardiomyopathy, valvular injury, coronary artery disease (CAD), and mainly pericardial disease[3,28]. Pericardial effusion has been reported in earlier phases after radiation. However, constrictive pericarditis, CAD, valvular heart disease and cardiomyopathy usually appear after longer follow-up[3], with higher incidence when the radiation is directed towards the left side of the chest[29]. In our sample, 52.5% of the patients received adjuvant radiotherapy. However, only 20% had it performed on the left side of the chest. In addition, the average time after chemotherapy was only two years, which may justify the absence of signs of pericardial disease in our sample.

Cyclophosphamide and 5-fluorouracil were used by 77.5% and 37.5% of our patients, respectively. Both are also associated with cardiotoxicity, but with a frequency much lower than that associated with use of anthracyclines[3].

Limitations

This is a cross-sectional study and as such, is unable to establish a precise causal relationship between the use of anthracyclines and the findings of reduced ε_{LL} and ε_{CC}. However, the reduction in the values of ε_{LL} and ε_{CC} in patients who used DOX was observed even in the absence of HF by Framingham's criteria, history of illness, prior cardiovascular disease, valvular lesion greater than mild, change in segmental contractile function in the transthoracic echocardiogram and LVEF <55%. In addition, the participants were examined under stable conditions to prevent changes secondary to the effects of hemodynamic instability. However, larger prospective studies will be necessary to assess the possible effects of confounding variables. Even though the patients had no prior angina or myocardial infarction, they did not undergo stress test. The sample was composed only by women, therefore these results cannot be extrapolated to male patients. The analysis of the echocardiographic findings variables was performed by only one examiner.

Conclusions

ε_{LL}, the ε_{CC} and the S' wave are reduced in patients who used DOX ± 2 years prior to the study, despite normal LVEF, suggesting the presence of subclinical ventricular dysfunction in a group considered at high risk of cardiovascular events. Previous use of DOX was an independent predictor of ε_{CC} reduction in cancer survivors. Previous use of DOX and age were independent markers of ε_{LL} reduction.

Author contributions

Conception and design of the research: Almeida ALC, Silva VA, Souza Filho AT, Rios VG, Lopes JRP, Afonseca SO, Santos Júnior EG; Acquisition of data and Critical revision of the manuscript for intellectual content: Almeida ALC, Silva VA, Souza Filho AT, Rios VG, Lopes JRP, Afonseca SO, Cunha DCA, Mendes MOC, Miranda DL, Santos Júnior EG; Analysis and interpretation of the data: Almeida ALC, Santos Júnior EG; Statistical analysis and Obtaining financing: Almeida ALC; Writing of the manuscript: Almeida ALC, Santos Júnior EG.

Original Article

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