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Global longitudinal strain value in the early detection of chemotherapy-induced cardiotoxicity

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Abbreviations
2D-ST: two-dimentional speckle-tracking
CMR: cardiac magnetic resonance
CTx: cardiotoxicity
GLS: global longitudinal strain
LVEF: left ventricle ejection fraction

ABSTRACT

Introduction: Advances in early detection and treatment of cancer have significantly reduced mortality. The net result is the emergence of a cohort of patients whose survival is sufficient to evidence the side effects of the used therapies. Cardiotoxicity is the set of cardiovascular diseases resulting from onco-hematological treatments.

Objectives: To evaluate the role of global longitudinal strain in the early detection of cardiotoxicity in patients undergoing chemotherapy.

Method: A quantitative, analytical, prospective, longitudinal study was carried out in 44 patients diagnosed with breast cancer or lymphoma, who started chemotherapy treatment at the Instituto de Oncología y Radiobiología of Cuba, from February 2017 to April 2018. Primary and secondary methods were used for raw data collection and several statistical tests were used for its analysis.

Results: The mean age and treatment period were 47.7 years old and 5.05 months, respectively. The most prevalent risk factor was high blood pressure and cardiotoxicity was higher (27.8%) in patients with previous diastolic dysfunction. Among those who developed cardiotoxicity, the variable that showed the greatest affectation was global longitudinal strain ($p<0.0001$), with a reduction of 19.6% with respect to the basal one.

Conclusions: Global longitudinal strain is an echocardiographic index of myocardial performance, which presented a significant discriminating value with respect to cardiotoxicity in patients who received chemotherapeutic treatment.

Keywords: Echocardiography, Chemotherapy-induced cardiotoxicity, Global longitudinal strain, Chemotherapy

Valor del strain longitudinal global en la detección precoz de cardiotoxicidad inducida por quimioterapia

RESUMEN

Introducción: Los avances en la detección precoz y el tratamiento del cáncer han reducido de manera significativa la mortalidad. El resultado neto es el surgimiento de una cohorte de pacientes cuya supervivencia es suficiente para evidenciar los efectos secundarios de las terapias utilizadas. La cardiotoxicidad es el conjunto de enfermedades cardiovasculares derivadas de los tratamientos onco-hematológicos.

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STG y SHP: Idea and design of the research; data collection, analysis and interpretation as well as manuscript writing.
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Objetivo: Evaluar el papel de la deformación miocárdica (strain) longitudinal global en la detección precoz de cardiotoxicidad en pacientes con tratamiento quimioterápico.
Método: Se realizó un estudio cuantitativo, analítico, longitudinal, prospectivo en 44 pacientes con diagnóstico de cáncer de mama o linfoma, que iniciaron tratamiento con quimioterapia en el Instituto de Oncología y Radiobiología de Cuba, en el período comprendido entre febrero de 2017 y abril de 2018. Se utilizaron métodos primarios y secundarios para la recolección del dato primario y se emplearon varias pruebas estadísticas para su análisis.
Resultados: Las medias de edad y tiempo de tratamiento fueron de 47,7 años y 5,05 meses, respectivamente. Predominó la hipertensión arterial (18,1%) como factor de riesgo y la mayor cardiotoxicidad (27,8%) en pacientes con disfunción diastólica previa. Entre los que desarrollaron cardiotoxicidad, la variable que demostró mayor afectación fue el strain longitudinal global (p<0,0001), con una reducción de 19,6% respecto al basal.
Conclusiones: El strain longitudinal global es un índice ecocardiográfico de deformación miocárdica, que presentó un valor discriminante significativo con respecto a la cardiotoxicidad en pacientes que recibieron tratamiento quimioterápico.
Palabras clave: Ecocardiografía, Cardiotoxicidad inducida por quimioterápicos, Strain longitudinal global, Quimioterapia

INTRODUCTION

Advances in early detection and treatment of cancer have significantly reduced patients' mortality. The introduction of targeted therapies has increased cure and remission rates in some cancers; in others, it has favored their conversion to a chronic disease. The net result is the emergence of a cohort of patients whose survival is sufficient to evidence the side effects of the used therapies[1].

In general, there are three conventional cancer treatments: surgery, radiotherapy and chemotherapy. Unfortunately, chemotherapy drugs do not have tumor specificity and cause damage to healthy cells, including cardiac cells, and it is the organ damage that limits their application and the safety of the therapeutic. The clinical consequences of a cardiac disease influence the survival of these patients, who require a multidisciplinary team to optimize their treatment[2].

Although pharmacological prevention has been a recent strategy, the search for clinical and paraclinical methods for the identification, early detection and prevention of cardiotoxicity (CTx) has had a historical trajectory[3]. This toxic effect was first defined by the National Cancer Institute of United States of America as "the toxicity affecting the heart"[3]; however, this simple concept has adopted many interpretations and has undergone several updates.

Although left ventricular ejection fraction (LVEF) remains the diagnostic parameter of CTx, its prognostic value is currently controversial. This made it necessary to continue the search for new methods based on two-dimensional echocardiography, which would provide additional information, overcome the advantages of LVEF and do not have the disadvantages that limit it[4]. The contraction of the myocardial fibers determines changes in size and shape of left ventricle that are the result of simultaneous longitudinal shortening, circumferential rotation and radial thickening of the myocardium. The LVEF provides a general index of left ventricular chamber function, without taking into account the relative role of the different components of myocardial function (strain in various directions and rotation), which may be affected to varying degrees in different cardiac diseases, even though LVEF remains within normal values[5]. This led to the development of tissue distortion measurements derived from Doppler myocardial imaging, strain and two-dimensional speckle-tracking analysis (2D-ST), capable of detecting myocardial disturbances before the existence of systolic or diastolic dysfunction detectable through other methods[6].

López-Fernández *et al.*[1], in the Position Paper and Recommendations on Cardio-Onco-Hematology in clinical practice, published in 2017 in *Revista Española de Cardiología*, renewed the concept of CTx as the set of cardiovascular diseases derived from onco-hematological treatments, with diagnostic criteria similar to those used in the general population. For the first time, myocardial strain rate is taken into

account as a predictor of heart failure and its reference values are indicated[1].

Advances in the early detection and treatment of cancer have improved cancer survival, resulting in more than 16.7 million cancer survivors in the United States of America nowadays; this, in turn, has led to an increased risk of morbidity and mortality from other causes for these individuals, mainly due to cardiovascular diseases[7].

The incidence of CTx secondary to chemotherapy in patients with breast cancer or lymphoma at the Cuban Institute of Oncology is unknown. Cardiovascular diseases, followed by neoplasms, are the leading cause of death in cancer survivors and their treatment poses an enormous challenge. The onco-hematological therapies triple the risk of cardiovascular events in the medium and long terms. Cardiovascular toxicity secondary to chemotherapy treatment is a widely recognized problem, so the focus is no longer directed solely at overcoming the malignancy, but rather on early identification and treatment of possible side effects[8]. However, scientific evidence on the treatment of cardiovascular complications in onco-hematological patients is scarce, since these patients have been systematically excluded from clinical trials and current recommendations are based on expert consensus. There are many studies of cardiotoxicity around the world, but they continue to be scarce in comparison with the accelerated increase in cancer survival and, consequently, the increase in CTx.

In Cuba there is little knowledge about the behavior of such topic in the population with cancer. Historically, health statistics do not contain the causes of death secondary to CTx or due to side effects of the therapy for this oncological disease; likewise, the Cuban Health Statistical Yearbook is not exempt from this deficiency. Cardio-onco-hematology teams around the world bring together the professionals involved in the care of cancer patients, with the aim of optimizing treatment and minimizing cardiovascular toxicity[1]. In our country, it was not until 2018 that the cardio-onco-hematology team was created at the *Instituto Nacional de Oncología y Radiobiología* (INOR by its acronyms in Spanish) for the comprehensive follow-up of cancer patients, so this research was carried out in close interaction with specialists in Oncology to thus optimize patients follow-up; although this modality has not yet been extended to the rest of the country's oncology institutions.

Improving the prognosis of oncology patients is not only about curing the tumor, but also about preventing, diagnosing and effectively treating the complications derived from onco-hematological therapies. We insist that there are very few published studies on cardiotoxicity in Cuba; therefore, it is not known at what point we begin to cause harm pretending a greater benefit. The global longitudinal strain (GLS) allows to early detect CTx before the LVEF measurement is altered. Therefore, the objectives of this study were: to evaluate the role of GLS in the early detection of cardiotoxicity in patients undergoing chemotherapy; to identify its incidence according to clinical and epidemiological variables and treatment regimens; to determine the possible differences in the evolution of echocardiographic variables measured at the beginning, at the end and at one year after cancer treatment according to the occurrence of cardiotoxicity; and to determine the discriminating capacity of GLS in the early detection of CTx.

METHOD

Type of study and patients

A quantitative, analytical, longitudinal, prospective study was carried out at the *Instituto de Cardiología y Cirugía Cardiovascular* (ICCCV by its acronyms in Spanish), with 44 patients (study's population and sample match) from the *Instituto Nacional de Oncología y Radiobiología* (INOR by its acronyms in Spanish) of Cuba, diagnosed with breast cancer or lymphoma who started chemotherapy treatment between February 2017 and April 2018.

Inclusion criteria

Patients over 18 years old, with a diagnosis of *de novo* of breast cancer or lymphoma, who agreed to take part in the research, were able to undergo the planned echocardiographic studies and did not die before the end of the study.

Exclusion criteria

Patients with poor acoustic window for evaluation through transthoracic echocardiogram, previous chemotherapy or radiotherapy, and associated cardiovascular comorbidities: proven coronary artery

disease or heart failure, cardiomyopathies with decreased LVEF, acquired valve diseases, congenital heart diseases, left ventricular hypertrophy secondary to high blood pressure, electrical conduction disorders (atrioventricular or bundle branch blocks, accessory pathways and persistent or chronic tachyarrhythmias).

Echocardiography

A transthoracic echocardiogram was performed to each patient prior to the start of chemotherapy and successively, according to the recommendations of the Cardio-Onco-Hematology consensus published in 2017[1] for the type of drug and the administered doses, and another one at one year after the end of treatment; so that each patient became his or her own controller to evaluate relative changes throughout follow-up.

The echocardiographic studies were carried out in a Philips EPIQ 7 equipment with Quick SAVE function, with 2,5 MHz probe. Measurements were performed according to the American Society of Echocardiography (ASE) recommendations. The studies were carried out in the left lateral decubitus position, with electrocardiographic synchronization.

Systolic function values were obtained through linear methods like Teichholz (Teich); volumetric methods like Simpson and three-dimensional and through 2D-ST strain. The parameters considered normal were classified by the Cardio-Onco-Hematology consensus published in 2017[1]. Using 2D-ST techniques, longitudinal peak systolic strain was quantified and 17 segments were averaged to obtain the GLS. The three apical views (two-, three- and four-chambers) were acquired in gray scales with a high frame rate, between 50-70 frames per second, by averaging two cardiac cycles, using Epic 7.1.1 software; those segments inadequately evaluated through 2D-ST were excluded from the analysis. Normal GLS values were considered to be those recommended by the software provider according to gender and age in healthy populations[1,9,10].

Through three-dimensional echocardiography, complete volumes were obtained from the apical view in real time, where four cardiac cycles were averaged in the acquisition of the images and end-diastolic and end-systolic volumes and LVEF were quantified. Normal values were considered according to the recommendations for cardiac chamber quantification by echocardiography in adults[9] of 2015.

Diastolic function was assessed through pulsed Doppler and early (E) and late (A) transmitral diastolic velocities were determined, and with the tissue Doppler imaging (TDI), early diastolic velocities of the lateral and septal mitral annulus (e'), as well as the E/e' ratio in this annulus. The diastolic function was classified according to the ASE recommendations[11].

Right ventricular (RV) systolic function was also assessed through tricuspid annular plane systolic excursion (TAPSE), and those values recommended in the guidelines for the echocardiographic assessment of the right heart in adults[12] of 2010 were considered normal. Left atrial dimensions were assessed according to the recommendations for cardiac chamber quantification by echocardiography in adults[9,11] of 2015.

Data collection

Primary and secondary methods were used for data collection. The general data of the patients as well as those referring to the chemotherapy treatment were taken from their medical records, which were consulted in the archive department of the INOR of Cuba, as well as in the database of that center. For the collection of echocardiographic data, a form was designed that included the variables under study, which was validated by the opinion of experts from the ICCCV of Cuba.

All the information obtained was emptied and stored in an Excel 2013 data sheet for review, validation and processing. Results are shown in tables and graphs.

Main variables

Clinical variables: Age, treatment period, cardiovascular risk factors, tumor location and chemotherapy regimen.

Echocardiographic variables: LVEF (%) according to the used method, GLS through 2D-ST, TAPSE, mitral flow, mitral annulus TDT and left atrial volume.

Statistical processing

Quantitative variables were described as mean val-

ues and standard deviation, and qualitative or categorical variables as absolute and relative frequencies. The Kolmogorov-Smirnov non-parametric test was used to check compliance with the assumptions of normality. Chi square and Fisher`s exact tests were used to determine the existence of associations among categorical variables. For quantitative variables, the repeated measures analysis of variance was used for the one-factor model in the comparison of echocardiographic measurements at the three time points of the study.

For the comparison between variables from the first echocardiogram and at one year of treatment, the Students` t test for paired observations or the Wilcoxon test were applied, and to classify the discriminating capacity of the GLS diagnostic test in the early detection of chemotherapy-induced cardiotoxicity, the ROC (receiver operating characteristic) curve statistical tool was used. A p value inferior to 0.05 was considered significant. All calculations were made using the SPSS statistical package. 21.0.

Ethical aspects

The research was carried out taking into account the Declaration of Helsinki of 1989 on ethical principles for medical studies on human beings, in accordance with the four basic ethical principles: respect for persons, beneficence, non-maleficence and justice.

The principle of medical confidentiality in the scientific research was respected and the information was properly handled, since it was used only in the research.

In order to carry out this study, prior coordination was made with the involved centers and the approval of the scientific councils of both institutions was obtained. In addition, the informed consent was signed by every patient.

RESULTS

After analyzing the data of the 44 patients included in the study, an overall mean age of 47.7 years old was found, and of 49.1 years old among those who developed cardiotoxicity (**Table 1**), without reaching statistically significant differences (p=0.61). Nevertheless, the mean age of the studied population is relatively low due to the appearance of cancer at increasingly younger ages. The treatment period with chemotherapy was 5.05 months, slightly longer in those patients who presented cardiotoxicity, although also without statistical significance (p=0.74). Regarding risk factors, high blood pressure predom-

Table 1. Clinical-epidemiological distribution of the studied patients.

Variables	Total (n=44)	No cardiotoxicity (n=26)	Cardiotoxicity (n=18)	p
Age	47,7 ± 13,8	46,88 ± 14,9	49,1 ± 12,1	0,613
Months of treatment	5,05 ± 1,81	4,96 ± 1,5	5,17 ± 2,3	0,738
Risk factors				
High blood pressure	8 (18,1%)	5 (19,2%)	3 (16,7%)	0,576
Diabetes mellitus	3 (6,8%)	2 (7,7%)	1 (5,6%)	0,638
Cardiovascular disease	1 (2,3%)	0	1 (5,6%)	0,409
Obesity	2 (4,5%)	1 (3,8%)	1 (5,6%)	0,656
Smoking habit	2 (4,5%)	1 (3,8%)	1 (5,6%)	0,656
Previous diastolic dysfunction	7 (15,9)	2 (7,7%)	5 (27,8%)	0,073
Tumor location*				
Right breast	10 (22,7%)	3 (11,5%)	7 (38,9%)	0,04
Left breast	22 (50%)	14 (53,8%)	8 (44,4%)	0,760
Lymphoma	13 (29,5%)	9 (34,6%)	4 (22,2%)	0,507

Values express media ± standard deviation and n (%).
* One patient had bilateral breast cancer.

inated (18.1%), but it was not representative with respect to the appearance of cardiotoxicity, since only three (16.7%) of the patients who developed cardiotoxicity had it. The highest incidence of CTx was observed in those with previous diastolic dysfunction (27.8%; p=0.07) and cardiovascular disease, since only one patient had the latter one, but developed CTx (p=0.41). Regarding the location of the tumor, there was a predominance of left breast cancer (50%); however, only 36.4% of these patients presented CTx, which constituted 44.4% of the total patients who developed it; however, it was observed that in right breast cancer the incidence of CTx was higher, since it was present in 7 out of the 10 women who suffered from it, representing 38.9% of the total patients with CTx (p=0.04). It is important to point out that there was one patient who presented cancer in both breasts.

The most commonly used treatment scheme was adriamycin-cyclophosphamide-docetaxel, which accounted for 20.5% of all patients, followed by those who received adriamycin-cyclophosphamide (**Table 2**). Greater CTx development was observed in those who received adriamycin-cyclophosphamide-docetaxel (22.2%). In patients with radiotherapy associated to chemotherapy, there was a higher incidence of CTx in those who were administered adriamycin-cyclophosphamide-taxanes plus two mono-

Table 2. Distribution of the studied patients according to the chemotherapy regimen used and cardiotoxic response to the treatment.

Treatment scheme	Total (n=44)	No cardiotoxicity (n=26)	Cardiotoxicity (n=18)	p
Chemotherapy				
ABVD	5	4 (15,4%)	1 (5,56%)	0,634
ABVD >	3	3 (11,5%)	0	0,258
AC	8	5 (19,2%)	3 (16,7%)	0,828
CHOP	2	1 (3,85%)	1 (5,56%)	0,656
CHOP >	1	0	1 (5,56%)	0,409
Taxane + Mc-ab	2	1 (3,85%)	1 (5,56%)	0,656
AC + Taxane	11	8 (30,8%)	4 (22,2%)	0,733
AC+ Taxane + Mc-ab	2	0	2 (11,1%)	0,162
AC+ Taxane + 2 Mc-ab	4	1 (3,85%)	3 (16,7%)	0,289
AC + Dctx + Pctx + Cbpl	1	0	1 (5,56%)	0,409
Dctx + Trzb + Cbpl	1	1 (3,85%)	0	0,591
ABVD + CHOP >	2	2 (7,69%)	0	0,505
CHOP + Rtxb	1	0	1 (5,56%)	0,409
Chemo + Radiotherapy	(n=19)	(n=10)	(n=9)	
ABVD	2	2 (20%)	0	0,505
AC	5	3 (30%)	2 (22,2%)	0,675
AC + Taxane	5	3 (30%)	2 (22,2%)	0,675
AC+ Taxane + 2 Mc-ab	4	1 (10%)	3 (33,3%)	0,289
AC + Dctx + Pctx + Cbpl	1	0	1 (11,1%)	0,409
ABVD + CHOP >	1	1 (10%)	0	0,591
CHOP + Rtxb	1	0	1 (11,1%)	0,409

Values express n (%).
>, adriamycin dose greater than 240 mg/m^{2}sc; ABVD, adriamycin-bleomycin-vinblastine-dacarbazine; AC, adriamycin-cyclophosphamide; Cbpl, carboplatin; CHOP, adriamycin-cyclophosphamide-vincristine-prednisone; Dctx, docetaxel Mc-ab, monoclonal antibody; Pctx, paclitaxel; Rtxb, rituximab; Trzb, trastuzumab.

Table 3. Evolution of the echocardiographic variables measured before starting the treatment, after finishing and at one year of treatment in the studied patients.

Variables	Baseline	End of treatment	1 year	p
LVEF - Teich (%)	68,29 ± 5,93	66,84 ± 5,21	65,79 ± 4,60	0,019
LVEF - Simpson (%)	66,27 ± 4,77	65,54 ± 4,83	65,54 ± 4,28	0,315
LVEF - 3D (%)	66,79 ± 5,20	65,79 ± 4,46	64,86 ± 5,28	0,049
LVEF - GLS (%)	65,61 ± 4,83	65,36 ± 5,26	63,57 ± 6,61	0,048
GLS (%)	-21,54 ± 1,45	-20,68 ± 1,72	-19,68 ± 2,45	< 0,0001
TAPSE (cm)	22,84 ± 2,74	22,18 ± 2,38	21,63 ± 2,63	0,021
Mitral E wave (cm/s)	88,63 ± 21,84	86,16 ± 17,50	79,11 ± 27,86	0,044
Lateral e' (cm/s)	14,43 ± 3,73	13,86 ± 3,69	12,09 ± 3,56	< 0,0001
LA volume (ml/m^2)	23,36 ± 6,96	23,48 ± 6,56	23,27 ± 7,02	0,904

Values express media ± standard deviation.
3D, three-dimensional; GLS: global longitudinal strain; LA, left atrium; LVEF, left ventricle ejection fraction; TAPSE, tricuspid annulus plane systolic excursion.

clonal antibodies (33.3%); however, the results were not statistically significant because of the sample size and the variety of treatment combinations, employed in an individualized manner for the optimal benefit of the patients.

Table 3 shows the echocardiographic evolution of the patients evaluated before starting treatment, at the end and at one year of finishing it, which made it possible to detect the development of acute and subacute CTx. When applying analysis of variance −with repeated measures for the one-factor model− in the comparison of echocardiographic measurements at the three study moments, greater significance was observed in the values of GLS (p<0.0001) and lateral e' (p<0.0001), both expressions of early ventricular dysfunction.

When comparing echocardiographic variables at the beginning and at one year of treatment (**Table 4**), differences were observed in terms of LVEF variation through different methods, as well as in terms of decrease in GLS (-1.8% decrease; p<0.0001), followed by LVEF per GLS which decreased 2% with respect to the basal value (p=0.05). There was no significant variation in terms of left atrial volume (p= 0.90), but there was significant variation in parameters of right ventricular systolic function (TAPSE p=0.02) and left diastolic function: mitral E waves (p=0.04) and lateral e' (p<0.0001).

These variables, except for lateral e', also showed significant statistical association with the development of CTx when comparing the echocardiographic evolution at the three time points of the research (**Table 5**). The lateral e' wave (p=0.019), despite being one of the diastolic function variables that is usually altered in the early phase of CTx, did not show discriminating diagnostic value, since it also presented significant differences (p=0.001) in patients who did not develop CTx.

The group of patients who did not develop cardiotoxicity showed little differentiation in their echocardiographic values, in contrast to those who did (**Tabla 6**). The LVEF showed little variation; that one estimated through GLS was the most affected one (p<0.0001), but it showed an evolutionary decrease

Table 4. Evolutionary differences of the echocardiographic variables assessed in the studied patients after one year of treatment respect to the basal value in the total sample.

Variables	Mean	SD	p*
LVEF - Teich (%)	2,5	5,58	0,005
LVEF - Simpson (%)	0,727	4,031	0,238
LVEF - 3D (%)	1,932	5,462	0,024
LVEF - GLS (%)	2,045	6,820	0,053
GLS (%)	-1,864	2,474	<0,0001
TAPSE (cm)	1,205	3,366	0,022
Mitral E wave (cm/s)	9,523	29,80	0,040
Lateral e' (cm/s)	2,341	3,027	<0,0001
LA volume (ml/m^2)	0,091	4,783	0,900

* Student's t or Wilcoxon test.
3D, tridimensional; GLS: global longitudinal strain; LA, left atrium; LVEF, left ventricle ejection fraction; TAPSE, tricuspid annulus plane systolic excursion.

at one year of less than 10%, so it did not meet diagnostic criteria. The GLS did show significant variation, with a mean decrease of -4.27%, representing 19.6% with respect to the basal value (p<0.0001) in the group of patients with CTx. The rest of the variables, regardless of their statistical significance, did not show diagnostic values of left ventricular dysfunction.

When analyzing the ROC (receiver operating characteristic) curves to compare the diagnostic accuracy between the different echocardiographic techniques that evaluate disturbances in systolic function (**Figure**), it was observed that GLS had the highest discriminant value (area under the curve [AUC] of 0.94; p<0.0001), followed by LVEF calculated by Simpson's method (AUC 0.50; p=0.962). The remaining echocardiographic techniques have an AUC very close to the baseline and show no significant statistical difference.

Table 5. Evolution of the echocardiographic variables measured before starting the treatment, after finishing and at one year of treatment in specific groups according to the development or not of cardiotoxicity.

Variables	No cardiotoxicity				Cardiotoxicity			
	Basal	Enf of treatment	1 year	p	Basal	Enf of treatment	1 year	p
LVEF - Teich (%)	68,5 ± 6,2	67,2 ± 4,9	66,4 ± 4,4	0,070	68,0 ± 5,7	66,2 ± 5,7	64,9 ± 4,9	0,045
LVEF - Simpson (%)	66,2 ± 5,3	65,5 ± 5,1	65,9 ± 3,8	0,628	66,4 ± 4,0	65,6 ± 4,6	65,0 ± 4,9	0,371
LVEF - 3D (%)	66,9 ± 5,5	65,8 ± 4,4	65,6 ± 4,9	0,202	66,6 ± 4,9	65,8 ± 4,7	63,8 ± 5,8	0,217
LVEF - GLS (%)	64,5 ± 4,9	65,5 ± 4,8	65,6 ± 6,3	0,518	67,2 ± 4,5	65,2 ± 6,0	60,7 ± 6,0	<0,0001
GLS (%)	-21,4 ± 1,7	-21,1 ± 1,6	-21,2 ± 1,6	0,456	-21,8 ±1,1	-20,1 ± 1,8	-17,5 ± 1,7	<0,0001
TAPSE (cm)	22,6 ± 2,6	22,8 ± 2,2	22,6 ± 2,5	0,843	23,2 ± 2,9	21,3 ± 2,5	20,2 ± 2,2	0,004
Mitral E wave (cm/s)	87,8 ± 19,3	89,5 ± 19,6	89,9 ± 19,5	0,741	89,9 ± 25,6	81,3 ± 13	63,6 ± 31,1	0,035
Lateral e' (cm/s)	15,2 ± 3,8	14,7 ± 3,9	13,1 ± 3,6	0,001	13,4 ± 3,5	12,7 ± 2,9	10,6 ± 2,9	0,019
LA volume (ml/m^2)	23,0 ± 7,2	23,5 ± 6,6	23,2 ± 7,8	0,775	23,8 ± 6,7	23,4 ± 6,7	23,4 ± 6,0	0,891

Data express media ± standard deviation.
3D, tridimensional; GLS: global longitudinal strain; LA, left atrium; LVEF, left ventricle ejection fraction; TAPSE, tricuspid annulus plane systolic excursion.

Table 6. Evolutionary differences of the echocardiographic variables assessed in the studied patients after one year of treatment respect to the basal value in specific groups according to the development of cardiotoxicity.

Variables	No cardiotoxicity			Cardiotoxicity		
	Mean	SD	p	Mean	SD	p
LVEF - Teich (%)	2,077	5,513	0,066	3,111	5,759	0,035
LVEF - Simpson (%)	0,231	3,204	0,717	1,444	5,008	0,238
LVEF - 3D (%)	1,385	4,158	0,102	2,722	6,994	0,117
LVEF - GLS (%)	-1,038	5,667	0,359	6,5	5,9	<0,0001
GLS (%)	-0,192	1,415	0,495	-4,278	1,447	<0,0001
TAPSE (cm)	-0,038	3,000	0,948	3,000	3,106	0,001
Mitral E wave (cm/s)	-2,115	15,042	0,480	26,333	37,512	0,008
Lateral e' (cm/s)	2,038	2,600	<0,0001	2,778	3,590	0,004
LA volume (ml/m^2)	-0,115	4,828	0,904	0,389	4,840	0,737

3D, tridimensional; GLS: global longitudinal strain; LA, left atrium; LVEF, left ventricle ejection fraction; TAPSE, tricuspid annulus plane systolic excursion; SD, standard deviation

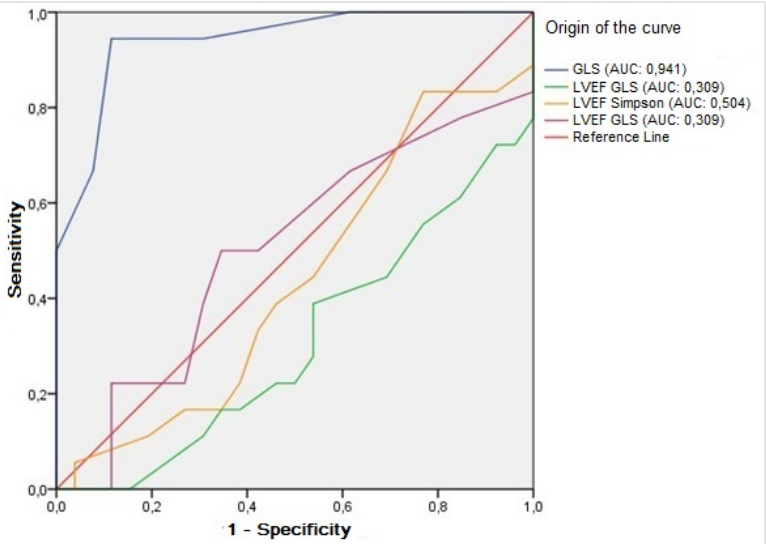

Figure. ROC curve which assess the diagnostic accuracy of the different echocardiographic techniques used to assess cardiotoxicity. AUC, area under the curve.

DISCUSSION

Most of the measures applied to reduce cardiotoxicity focus on early diagnosis and treatment of left ventricular dysfunction. When analyzing the results of the study, alarming data are observed regarding early detection of cardiotoxicity through 2D-ST, not detected by other echocardiographic measurements such as LVEF, when this technique is not commonly used in Cuba for this purpose.

Regarding the development of CTx according to age, this is in agreement with studies published nationally and internationally[1,8,13], which explain an increase in risk with age, which may be caused by pre-existing subclinical myocardial damage. This result corresponds with some studies such as that of Fallah-Rad *et al.*[8] who found a mean age of 47 years old in patients with CTx, while it contrasts with others –referenced by this same author– where age was higher and others who propose age >65 years old as a risk factor for CTx. This result may be influenced by the exclusion criteria of the studied sample (although age itself is not an exclusion criterion, elderly persons have a higher prevalence of comorbidities excluded in the sample under study), or due to the fact that in Cuba the incidence of cancer is higher in younger populations[13].

Skin color was not evaluated in this research because no data were found to highlight the influence of this variable on the development of CTx. Gender was not taken into account either since all breast cancers took place in women, and patients with lymphoma belong to both genders, which would produce a bias due to the predominance of females in the sample.

High blood pressure and dyslipidemia are the risk factors that internationally show the highest prevalence in studies of cardiotoxicity, but they do not show any influence on their subsequent development, as occurred in the current study. However, none of the consulted publications evaluated previous diastolic dysfunction as a risk factor for developing cardiotoxicity; it was included in the current study because of its high prevalence in the studied population when analyzing the basal echocardiogram data, and its significant association with this outcome[14].

Our results coincide with international studies that show a greater development of cardiotoxicity among patients with right breast cancer, and they also contrast with others that show a greater association with left breast cancer[8.14].

There are no international studies that specify the variety of treatment scheme included in this research. Precisely one of our objectives was to directly associate them with the development of cardiotoxicity, but no statistically significant data were obtained.

Although it is internationally recognized that the risk of CTx increases with the dose of adriamycin, of the five patients exposed to doses higher than 240 mg/m^2 of body surface area, only two of them developed cardiotoxicity. This finding contrasts with most of the consulted literature, but corresponds to the study performed by Chibuzor *et al.*[13] at the *Hospital Hermanos Ameijeiras* (Havana, Cuba), which did not show a higher incidence of CTx in the group exposed to high doses of adriamycin (only 31%). This study –in spite of evaluating myocardial strain by means of tissue Doppler imaging– is the one that has come closest in Cuba to the objectives of the current investigation. It leads to think that, in the Cuban patients suffering from oncologic diseases, measures were adopted for the prevention of damage caused by high doses of adriamycin, so that no significant incidence of CTx is obtained in the patients exposed to it. As for the exposure to radiotherapy associated to chemotherapy, there are also

international reports that state that this factor may increase the incidence of CTx. This association was not proved in the current study and it is consistent with the results of Fallah-Rad *et al.*[8] and Sawaya *et al.*[14].

The LVEF is a poorly sensitive measure of early myocardial dysfunction. When a patient has left ventricular dysfunction detectable by decreased LVEF, especially with the use of anthracyclines, myocardial injury is already established, and the likelihood of recovery, even with optimal medical treatment, decreases over time. Data continue to emerge indicating that cardiac biomarkers and new echocardiographic techniques may be more sensitive for early detection of cardiotoxicity[14,15].

The relative independence of angle and the ability to assess strain in two dimensions make of 2D-ST an attractive technique compared to tissue Doppler-based strain. The 2D-ST is the current imaging tool of choice for the detection of the subclinical cardiac dysfunction. In the JUSTICE study[16] a standardized value of normality was not achieved for three different equipment, so ranges were established according to the used software. Cheng *et al.*[17] observed an excellent reproducibility of 2D-ST when performed by trained operators, therefore a learning curve and training as well as quality monitoring (i.e., intra- and inter observer variability) are required to obtain good and reliable results. The most important limitation of 2D-ST in clinical practice is the variability between different manufacturers.

Farsalinos *et al.*[18] compared GLS measurements with nine different manufacturers' equipment and reported an absolute mean GLS value of -18.0% to -21.5%; with a maximum difference between the different manufacturers of 3.7 strain units, showing a strong correlation. The different societies and the most recent guidelines still recommend using the same equipment and the same software version for serial evaluation of GLS, since the differences are moderate but statistically significant. In the current study, a single device was used (described in the Method) and the patient's own baseline value was taken as a reference[16-18].

The change in myocardial strain value at the different times of analysis was superior to LVEF in the detection of subclinical cardiac dysfunction. Eighteen patients presented a decrease of more than 15% in GLS with respect to the basal value, the limit used as a diagnosis of CTx based on this parameter, while only three patients reached this limit in relation to LVEF (less than 53%), and only one presented clinical symptoms developing a supraventricular arrhythmia without hemodynamic repercussions. Fallah-Rad *et al.*[8] evaluated 42 patients with breast cancer and −using global longitudinal and longitudinal peak systolic strain− detected, over a three-month period, preclinical changes in left ventricular systolic function before a decrease in LVEF was observed. Kang *et al.*[19] found a significantly reduced GLS, while LVEF remained within normal limits until the end of chemotherapy. Narayan *et al.*[20] prospectively analyzed echocardiographic changes in left ventricular structure and function in 277 women with breast cancer treated with doxorubicin or trastuzumab, and detected early variations in GLS; while Tang *et al.*[21], in the follow-up of 86 patients, obtained a significant decrease in GLS at six months of treatment to a mean of -13.84%; as did Sawaya *et al.*[14] who found a marked decrease in GLS, with little variation in LVEF and other parameters related to diastolic function, among the 45 studied patients. The findings of these studies coincided with the results obtained in the current work[8,14,19-21].

Left ventricular diastolic dysfunction, as occurs in ischemic heart disease, usually precedes systolic dysfunction; however, the consulted studies[8,19-21] did not demonstrate significant changes, in correspondence with the data obtained in the current study.

Although cardiac magnetic resonance (CMR) is the reference test for the quantification of LVEF, López-Fernández *et al.*[1] in the Position Paper and Recommendations suggest using it only in patients with doubts in the echocardiographic assessment. Velásquez *et al.*[22] recognize the importance of CMR as an eligible method, although endomyocardial biopsy is considered a more reliable method for assessing myocardial injury; however, due to the high cost and low availability of the former, and the invasiveness of the latter, where small portions of the myocardium are obtained without providing functional information −which is why it is little used−, it was decided not to include these diagnostic techniques in the study of these patients; for this reason, traditional LVEF and, recently, GLS, are the techniques recommended for the diagnosis and follow-up of cardiotoxicity. Therefore, in this study, the ROC curve was used to classify the discriminant capacity of GLS in the early detection of chemotherapy-induced cardiotoxicity.

Negishi *et al.*[23] also evaluated the diagnostic accuracy of GLS, compared to other echocardiographic techniques, by means of ROC curves, without using the aforementioned reference techniques. In

addition, at the beginning of this study, the *Instituto de Cardiología y Cirugía Cardiovascular* did not have CMR, but a research project will soon be launched to evaluate CTx as a starting point for echocardiography, using CMR and nuclear ventriculography as reference techniques.

LIMITATIONS

The results should be interpreted with caution since the small sample size limits its statistical power and may not represent the reality of large population groups. This small sample size is due to the scarce existing casuistry free of comorbidities, which is necessary in order not to falsify the incidence of chemotherapy in the development of CTx.

CONCLUSIONS

Diagnosis of breast cancer, age under 50 years old and the presence of cardiovascular risk factors were frequent. The incidence of cardiotoxicity was not influenced by sociodemographic or clinical variables nor by oncologic treatment schemes. Global longitudinal strain and lateral e' values showed the greatest variability among the three performed echocardiograms. The global longitudinal strain presented a significant discriminating value regarding the detection of cardiotoxicity.

RECOMMENDATIONS

It is recommended to carry out a research at the institution to evaluate the long-term follow-up of patients exposed to chemotherapy through similar variables, to materialize the detection of cardiotoxicity through different imaging techniques and to establish a treatment protocol to prevent the progression of CTx after its early detection in subclinical stages, which can be evaluated in future studies as an intervention study.

REFERENCES

1. López-Fernández T, Martín García A, Santaballa Beltrán A, Montero Luis A, García Sanz R, Mazón Ramos P. Cardio-Onco-Hematología en la práctica clínica. Documento de consenso y recomendaciones. Rev Esp Cardiol. 2017;70(6):474-86. [DOI]
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30. [DOI]
3. Villasmil Camacho JK, Escudero E. Evaluación ecocardiográfica de la función ventricular derecha para la detección temprana de la cardiotoxicidad inducida por antraciclinas. Insuf Card. 2017; 12(2):62-90.
4. Caro Codón J, Rosillo Rodríguez SO, López Fernández T. Cardiotoxicity from the cardiologist's perspective. Future Cardiol. 2015;11(4):425-32. [DOI]
5. Kocabay G, Muraru D, Peluso D, Cucchini U, Mihaila S, Padayattil-Jose S, *et al*. Mecánica ventricular izquierda normal mediante ecocardiografía speckle tracking bidimensional. Valores de referencia para adultos sanos. Rev Esp Cardiol. 2014;67(8):651-8. [DOI]
6. Mele D, Rizzo P, Pollina AV, Fiorencis A, Ferrari R. Cancer therapy-induced cardiotoxicity: role of ultrasound deformation imaging as an aid to early diagnosis. Ultrasound Med Biol. 2015;41(3):627-43. [DOI]
7. Gilchrist SC, Barac A, Ades PA, Alfano CM, Franklin BA, Jones LW, *et al*. Cardio-Oncology Rehabilitation to Manage Cardiovascular Outcomes in Cancer Patients and Survivors: A Scientific Statement From the American Heart Association. Circulation. 2019;139(21):e997-e1012. [DOI]
8. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, *et al*. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol. 2011;57(22): 2263-70. [DOI]
9. Lang RM, Badano LP, Mor-Avi V, Spencer KT, Tsang W, Voigt JU, *et al*. Recommendations for cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association Of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39. [DOI]
10. Menting ME, McGhie JS, Koopman LP, Vletter WB, Helbing WA, van den Bosch AE, *et al*. Normal myocardial strain values using 2D speckle tracking echocardiography in healthy adults aged 20 to 72 years. Echocardiography. 2016;33(11): 1665-75. [DOI]
11. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF,

Dokainish H, Edvardsen T, *et al*. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314. [DOI]

12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, *et al*. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713;quiz786-8. [DOI]
13. Chibuzor Nwuruku G, Prohías Martínez J, Castro Arca Á, Mérida Álvarez O, Brooks Tamayo J, García Hernández R. Detección precoz de cardiotoxicidad inducida por antraciclinas. CorSalud [Internet]. 2014 [cited Sep 16, 2020];6(3):229-34. Available at: http://www.revcorsalud.sld.cu/index.php/cors/article/view/159/371
14. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, *et al*. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375-80. [DOI]
15. López-Fernández T, Thavendiranathan P. Nuevas técnicas de imagen cardiaca en la detección precoz de cardiotoxicidad secundaria a tratamientos oncológicos. Rev Esp Cardiol. 2017;70(6):487-95. [DOI]
16. Takigiku K, Takeuchi M, Izumi C, Yuda S, Sakata K, Ohte N, *et al*. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. Circ J. 2012;76(11):2623-32. [DOI]
17. Cheng S, Larson MG, McCabe EL, Osypiuk E, Lehman BT, Stanchev P, *et al*. Reproducibility of speckle-tracking-based strain measures of left ventricular function in a community-based study. J Am Soc Echocardiogr. 2013;26(11):1258-66.e2. [DOI]
18. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt JU. Head-to-Head comparison of global longitudinal strain measurements among nine different vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr. 2015;28(10):1171-81.e2. [DOI]
19. Kang Y, Xu X, Cheng L, Li L, Sun M, Chen H, *et al*. Two-dimensional speckle tracking echocardiography combined with high-sensitive cardiac troponin T in early detection and prediction of cardiotoxicity during epirubicine-based chemotherapy. Eur J Heart Fail. 2014;16(3):300-8. [DOI]
20. Narayan HK, Finkelman B, French B, Plappert T, Hyman D, Smith AM, *et al*. Detailed echocardiographic phenotyping in breast cancer patients: Associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. Circulation. 2017;135(15):1397-412. [DOI]
21. Tang Q, Jiang Y, Xu Y, Xia H. Speckle tracking echocardiography predicts early subclinical anthracycline cardiotoxicity in patients with breast cancer. J Clin Ultrasound. 2017;45(4):222-30. [DOI]
22. Velásquez CA, González M, Berrouet MC, Jaramillo N. Cardiotoxicidad inducida por la quimioterapia desde las bases moleculares hasta la perspectiva clínica. Rev Colomb Cardiol. 2016;23(2):104-11. [DOI]
23. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013;26(5):493-8. [DOI]