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Usefulness of myocardial strain techniques to assess cardiotoxicity in patients with oncologic diseases undergoing chemotherapy

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ARTICLE INFORMATION

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The authors declare no competing interests.

Abbreviations
2D-ST: two-dimensional speckle-tracking
GLS: global longitudinal strain
LVEF: left ventricle ejection fraction

ABSTRACT

Introduction: Assessment of myocardial function is critical for decision making during the follow-up of patients with oncologic diseases undergoing chemotherapy. Two-dimensional speckle-tracking techniques help to determine the degree of myocardial fiber deformation and provide a more direct measure of systolic function than left ventricular ejection fraction (LVEF).

Objectives: To evaluate myocardial function by means of echocardiography in patients with oncological diseases undergoing chemotherapy.

Method: A prospective longitudinal descriptive study was performed in 21 patients diagnosed with cancer and with indication for chemotherapy with trastuzumab, in the Hospital of Fuerteventura (Spain), between January 2017 and May 2020. All underwent transthoracic echocardiography with speckle-tracking technique (global longitudinal strain) before treatment and during follow-up.

Results: Women (95.2%) with a diagnosis of breast cancer (90.5%) predominated and the mean age was 53.8 years (range 38-75). Left ventricular ejection fraction and global longitudinal strain were normal (100%) before starting chemotherapy. It was necessary to suspend treatment in 3 patients (14.3%); but only in 2 of them (9.5%) due to cardiotoxicity detected by echocardiography. Five patients (23.8%) presented symptoms of heart failure, 1 (4.8%) had cardiotoxicity and in the other 4 (19.0%) the absence of myocardial dysfunction was demonstrated, so that treatment could be continued safely.

Conclusions: Two-dimensional speckle-tracking echocardiography was of vital importance for assessing myocardial performance and guiding chemotherapy in patients with oncologic diseases.

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

Utilidad de las técnicas de deformación miocárdica (strain) para evaluar cardiotoxicidad en pacientes con enfermedades oncológicas y tratamiento quimioterápico

RESUMEN

Introducción: La evaluación de la función miocárdica es fundamental para la toma de decisiones durante el seguimiento de pacientes con enfermedades oncológicas que reciben quimioterapia. Con las técnicas de speckle-tracking bidimensional se puede determinar el grado de deformación de la fibra miocárdica y obte-

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ner una medida más directa de la función sistólica que la que aporta la fracción de eyección del ventrículo izquierdo (FEVI).
Objetivo: Evaluar la función miocárdica, mediante ecocardiografía, en pacientes con enfermedades oncológicas y tratamiento quimioterápico.
Método: Se realizó un estudio descriptivo longitudinal prospectivo en 21 pacientes con diagnóstico de enfermedad oncoproliferativa e indicación de quimioterapia con trastuzumab, en el Hospital de Fuerteventura (España), entre enero de 2017 y mayo de 2020. A todos se les realizó ecocardiograma transtorácico con técnica de speckle-tracking (strain longitudinal global) antes del tratamiento y durante el seguimiento.
Resultados: Predominaron las mujeres (95,2%) con diagnóstico de cáncer de mama (90,5%) y la edad promedio fue de 53,8 años (rango 38-75). La FEVI y el strain longitudinal global fueron normales (100%) antes del inicio de la quimioterapia. Fue necesario suspender el tratamiento en 3 pacientes (14,3%); pero solo en 2 de ellos (9,5%) por cardiotoxicidad detectada por ecocardiografía. Cinco pacientes (23,8%) presentaron síntomas de insuficiencia cardíaca, 1 (4,8%) tenía cardiotoxicidad y en los otros 4 (19,0%) se demostró ausencia de disfunción miocárdica, por lo que se pudo continuar el tratamiento con seguridad.
Conclusiones: El ecocardiograma con técnica de speckle-tracking bidimensional fue de vital importancia para evaluar la función miocárdica y guiar el tratamiento quimioterápico en pacientes con enfermedades oncológicas.
Palabras clave: Ecocardiografía, Cardiotoxicidad inducida por quimioterápicos, Insuficiencia cardíaca, Strain longitudinal global, Quimioterapia

INTRODUCTION

Scientific development has made it possible to detect various types of cancer at increasingly early stages, thus making it possible to apply the most appropriate treatment at an early stage and to achieve greater survival of these patients[1]; but, at the same time, the development of cardiovascular complications related to their treatment has also increased[2].

Mattiuzzi and Lippi[3] state that, according to World Health Organization statistics, cancer represents the greatest global burden of disease and disability in both genders, followed by ischemic heart disease −which is still the leading cause of death− and cerebrovascular disease. In addition, cancer survivors have 15 times more probabilities of developing heart failure[2].

Chemotherapy is a therapeutic strategy that can produce cardiotoxicity, a well-established side effect of several antineoplastic drugs, particularly anthracyclines and trastuzumab[2,4]; and this complication represents the main cause of mortality and morbidity of cardiovascular origin in those who survive oncologic disease[2,5]. For this reason, the evaluation of the myocardial function is essential for decision making during the follow-up of this type of patient[5]. Using two-dimensional speckle-tracking (2D-ST) technique helps to determine the degree of myocardial fiber strain as well as to obtain a more direct measure of systolic function than using left ventricle ejection fraction (LVEF)[4,6], which is based on volumetric measurements and it is an insensitive measure of early myocardial dysfunction[7,8].

The aim of this study was to evaluate myocardial function using 2D-ST strain technique in patients with oncological diseases and chemotherapy treatment.

METHOD

A prospective longitudinal descriptive study was carried out in 21 patients intentionally selected with a diagnosis of oncological disease and indication for chemotherapy with trastuzumab, in *the Hospital General de Fuerteventura Virgen de la Peña*, Spain, between January 2017 and May 2020.

Echocardiography

All patients underwent transthoracic echocardiogram to assess ventricular function before the start of treatment and at the end of chemotherapy. In those with prolonged cycles the second echocardiogram was performed at three months. No patient was excluded from the research. In those with a poor acoustic window, echocardiographic contrast (SonoVue) was used to better define the endocardial

border.

The studies were performed with a Vivid S70 echocardiograph (General Electric, USA) and a 2.5 MHz transducer. The LVEF and the global longitudinal strain (GLS) were measured, using the biplane Simpson's method and the 2D-ST technique in the apical two-, three- and four-chambers views respectively; in addition to the other anatomical and functional measurements performed in a comprehensive transthoracic echocardiogram, according to the recommendations of the American Society of Echocardiography (ASE)[9] and the European Association of Cardiovascular Imaging (EACVI)[10]. Echocardiograms were carried out with naked torso and in the left lateral decubitus position, with electrocardiographic synchronization.

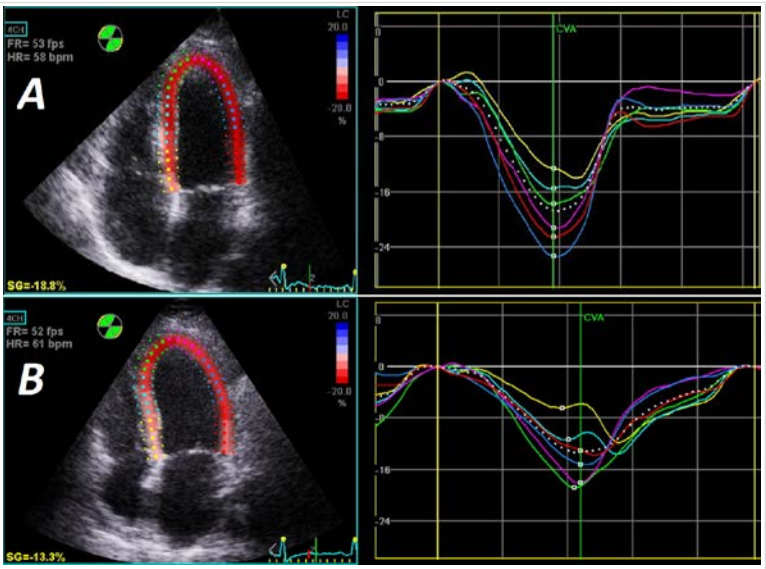

Figure 1. Global longitudinal strain of a patient with cardiotoxicity. **A.** Before starting chemotherapy (-18.8%). **B.** After the administration of trastuzumab (-13.3%, reduction of 29%).

Cardiotoxicity

According to the recommendations of the guidelines and consensus documents of the EACVI[6], the Spanish Society of Cardiology[7] and the ASE[11], the presence of cardiotoxicity was defined when a reduction in LVEF > 10% was found, with final LVEF < 53%, or a reduction in GLS equal to or greater than 15% with respect to baseline values, regardless the presence or absence of heart failure symptoms.

Data collection and processing

The raw data were obtained from the medical records and echocardiographic reports and they were processed with the 24th version of the Statistical Package for Social Sciences (SPSS). For comparison of the variables between the first and the second echocardiograms, the Student's t test for paired samples was applied.

Ethical aspects

The performance of echocardiogram is part of the protocol for the care and treatment of patients with oncological disease, coordinated between the Departments of Oncology and Cardiology of the hospital where this study was carried out. However, in order to be included in the study, the patients signed the informed consent form. Their data were used only for research purposes and their confidentiality was guaranteed.

This research counts on the approval of the Ethics Committee of the aforementioned hospital.

RESULTS

The vast majority of patients were women (95.2%) and the mean age of the sample at the moment of the diagnosis was 53.8 years old (range between 38 and 75). Breast infiltrating ductal carcinoma predominated (90.5%) and there was a low prevalence of cardiovascular risk factors, the most relevant one being smoking habit (38.1%). The LVEF (63.2 ± 3.4%) and the global longitudinal strain (-19.9 ± 1.3%), generally speaking, were normal (100%) before the start of chemotherapy (**Table**) and showed significant statistical differences compared to post-treatment results (57.4 ± 9.6; p=0.02 and -18.0 ± 3.4; p=0.04; respectively); but, similarly, within normal parameters, except in patients with cardiotoxicity (**Figure 1**).

During the follow-up five patients (23.8%) presented symptoms of heart failure, one (4.8%) had cardiotoxicity and in the other four (19.0%) the absence of myocardial dysfunction was demonstrated, so that treatment could be continued safely (**Figure 2**). Treatment was suspended in three patients (14.3%); but only in two of them (9.5%) due to cardiotoxicity detected by echocardiography, including the one who had symptoms of heart failure (**Figure 3**). In

Table. Patients' basal characteristics (n=21).

Characteristic	Nº	%
Age (years)	53.8 ± 11,4	
Females	20	95.2
CV risk factors		
High blood pressure	5	23.8
Diabetes mellitus	1	4.8
Dyslipidemia	5	23.8
Smoking habit	8	38.1
Obesity	6	28.6
Tumor location		
Left breast	7	33.3
Right breast	12	57.2
Stomach	2	9.5
Initial LVEF (%)	63.2 ± 3.4*	
Post chemotherapy LVEF (%)	57.4 ± 9.6*	
Initial GLS (%)	-19.9 ± 1.3**	
Post chemotherapy GLS (%)	-18.0 ± 3.4**	

Data express n (%) and mean ± standard deviation.
* p=0.02
** p=0.04
CV, cardiovascular; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction.

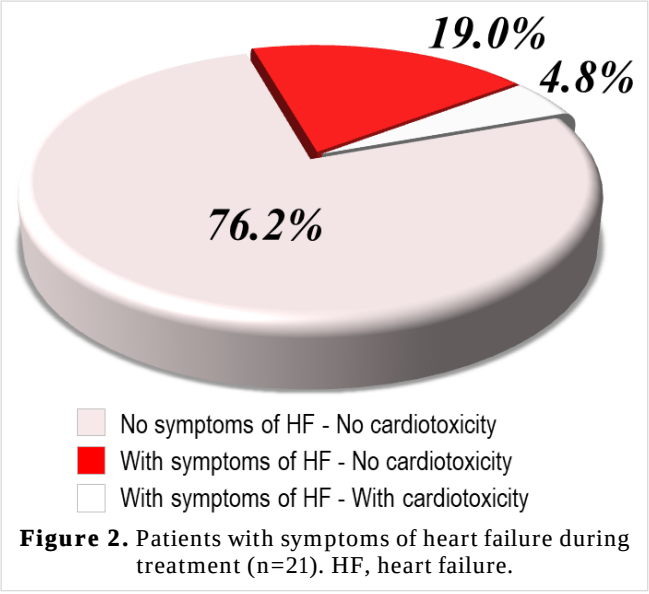

Figure 2. Patients with symptoms of heart failure during treatment (n=21). HF, heart failure.

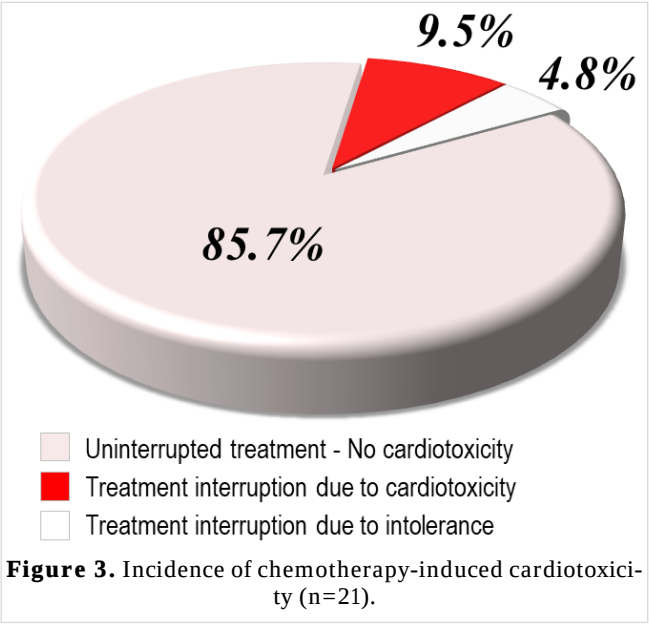

Figure 3. Incidence of chemotherapy-induced cardiotoxicity (n=21).

the third patient the discontinuation was due to intolerance to chemotherapy.

DISCUSSION

Survival after cancer has increased considerably in recent decades thanks, especially, to therapeutic advances (chemotherapy, radiotherapy and surgery)[2]; but the important contribution of diagnostic imaging cannot be forgotten.

Several definitions of cardiotoxicity have been proposed over the years. The most commonly used is a 10% reduction in LVEF from baseline, as long as this second measurement is less than 53-55%[7], depending on the author. However, GLS has emerged as a sensitive marker of subclinical ventricular dysfunction, and its use has gained special interest in the field of cardio-oncology to facilitate early detection of this therapeutic complication[4,7]. A >15% reduction in left ventricular GLS during cancer treatment identifies patients at increased risk for a subsequent reduction in LVEF and the development of heart failure[4].

The results of the presented research are consistent with those of other authors with respect to patients age, cancer incidence and location[3-5,12,13]. In 2018, a total of 18.08 million new cases were diagnosed worldwide, where lung, breast and prostate tumors predominated. In females, breast cancer was, by far, the most frequent one (2.09 million cases); and in males, stomach cancer (0.68 million cases) ranked third[3].

The overall reduction in LVEF and GLS after chemotherapy, found in this research, is explained by the small sample size where the extreme decreases in the values of these variables, in patients with cardiotoxicity, produced a significant reduction in the overall sum. This statistical result, although of little clinical relevance –as it remains within the normal range–, could respond to the depressant effect of chemotherapy on myocardial fiber. In fact, it is recognized that treatment with monoclonal antibodies such as trastuzumab (used in this study) can produce a damage that is usually reversible after withdrawal, transient and regardless to the dose. This in contrast to the dose-dependent and frequently irreversible model of cardiotoxicity generated by anthracyclines, which is often irreversible, and alter myocardial repair gene expression via the neuregulin-1 pathway that promotes myocardiocyte survival and development, which is part of the pathophysiological basis of type 2 cardiotoxicity[2,14-16].

In this regard, our results coincide with those of Portugal *et al.*[17], who observed a significant decrease in GLS for their entire cohort during follow-up (-20.1± 3.5% vs. -18.7±3.4%, p=0.001), although the mean remained within normal parameters; and defined altered myocardial strain as a GLS ≥ -18%, at some point during follow-up, which was more significant in patients who eventually developed cardiotoxicity (GLS -17.2±2.5%, p=0.02).

The incidence of this therapeutic complication in the current research (9.5%) is similar to that found in other studies, but lower than the mean. Oikonomou *et al.*[5], in a meta-analysis that included 21 studies and 1782 cancer patients treated with anthracyclines with or without trastuzumab, found an incidence of cardiotoxicity between 9.3% and 43.8% (mean 21%), with a mean follow-up of 4.2 to 23 months; and for Portugal *et al.*[17] this incidence was 18.9% in 158 breast cancer patients, same therapeutic scheme and a mean follow-up of 5.4 months (1-48 months).

The prevalence of cardiovascular risk factors and cardiotoxicity was not relevant, except for smoking habit; however, the small number of cases in this investigation does not allow inferences to be made or the results to be extrapolated to other populations. In contrast, our approach to patients with symptoms of heart failure coincides with that proposed by Fei *et al.*[18], who consider GLS to be useful for risk stratification, predicting subsequent recovery of myocardial function and guiding treatment with anthracyclines and trastuzumab; because this echocardiographic technique also has a high negative predictive value[7].

Gripp *et al.*[4] found that a GLS reduction of 14% –or an absolute value of -16.6% as a cut-off point– allowed early identification of patients who could develop anthracycline- and trastuzumab-induced cardiotoxicity. Oikonomou *et al.*[5] suggest that GLS measurement after initiation of potentially cardiotoxic chemotherapy is of great prognostic value for the detection of cancer treatment-related myocardial dysfunction; however, the limited data on its optimal cutoff values highlight the need for larger prospective multicenter studies[5,19]. Other authors indicate that myocardial dysfunction, even in the subclinical phase, secondary to chemotherapy-induced cardiotoxicity can be early detected using GLS by 2D-ST[20] and that early alteration of this variable is a good predictor of a subsequent development of cardiotoxicity related to these drugs[13]. Therefore, the application of this echocardiographic technique allows early initiation of timely treatment[7,20], which favors the possibility of more rapid recovery of ventricular function and the resumption of the necessary chemotherapy in many patients[16,18].

Portugal *et al.*[17] state that worsening of GLS by 2D-ST is common in breast cancer patients after chemotherapy, with predominant involvement of the interventricular septum and the anterior wall of the left ventricle; they also found that this impairment of myocardial function was independently associated with an increased incidence of cardiotoxicity and those who presented it had a 4.9-fold increased risk of developing it (OR 4.88; CI 1.32-18.0; p=0.017). Charbonnel *et al.*[21] demonstrated that an GLS greater than -17.45%, obtained after chemotherapy, is an independent predictor of future cardiotoxicity, a finding that should encourage physicians to perform early echocardiographic evaluations during treatment with anthracyclines. These authors suggest that from this cutoff value (GLS > -17.45%) cardioprotective treatment with beta-blockers and angiotensin-converting enzyme inhibitors should be initiated, and a personalized echocardiographic follow-up should be established for each patient.

It is evident that advances in imaging techniques, especially in echocardiography, have demonstrated the superiority of GLS by 2D-ST, based on the three apical views, for the early detection of cardiotoxicity[22,23]. Thavendiranathan *et al.*[23] consider it their favorite technique.

The prognosis of the World Health Organization for the year 2060 –as described by Mattiuzzi and Lippi[3]– is that deaths due to cancer will increase 2.08

times and will surpass those caused by ischemic heart disease, which will have a smaller increase (1.76 times); therefore, from 2030 on, malignant neoplasms will become the leading causes of mortality in the world. More than enough reason to spare no effort in the early detection of the cardiovascular complications of their treatment. During and even after cancer therapy, adequate cardiovascular care should be guaranteed to be able to early detect and treat a possible cardiotoxicity[2,4-8], which will favor the survival of these patients with a better life quality.

CONCLUSIONS

The measurement of global longitudinal strain by echocardiography with two-dimensional speckle-tracking was of vital importance for assessing myocardial performance, detecting early alterations suggestive of cardiotoxicity, and guiding chemotherapy in patients with oncologic diseases.

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