Application of Echocardiography in the Early Detection of Cardiotoxicity by Chemotherapy

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Abstract

The cardiotoxicity produced by chemotherapeutic agents, mainly to treat breast cancer, presents a significant incidence, often requiring specific treatment and / or forcing the reduction or suspension of the chemotherapeutic treatment. Cardiotoxicity is characterized by causing cell damage, reversible or not, leading to heart failure. The main indicators of these alterations can be detected by conventional echocardiography, through the left ventricular ejection fraction and techniques that evaluate myocardial deformation, such as the global longitudinal strain, which are now considered essential markers for this analysis. The cardiotoxicity produced by anthracyclines, monoclonal antibodies and their association is analyzed, the latter showing an alarming incidence, mainly in elderly patients.

Description of cardiotoxicity

Over the last three decades, the incidence of new cases of cancer has shown a tendency to decrease, with an increase in the survival of patients. It is not an exception to this malignancy of the breast, considered the greatest cause of death in women including patients of Hispanic origin residing in the USA, with a fall in the mortality rate in the decade of 2003 to 2012, at a rate of 1.3% per year.[1] This has been possible thanks to the dissemination of the self-examination technique, the application of different forms of diagnostic imaging, the support of the media[2] and the implementation of effective treatments.

Unfortunately, different forms of chemotherapy, with or without concomitant radiotherapy, may be caused by undesirable effects, a condition that affects the cardiovascular system and is known as CARDIOTOXICITY (CT).[3] The development of heart failure is an established form of CT, and the drugs that can cause it are used very frequently in the treatment of breast neoplasms. Although the ASE / EACI consensus suggested to define this affection as cardiac dysfunction related to anticancer therapeutics (CTRCD),[4] in the present review we will retain the term CT.

Keywords

Echocardiography; Neoplasms/drug therapy; Cardiotoxicity; Heart Failure.

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Anthracyclines

Anthracyclines used since the 1960s have a known potential for myocardial involvement. Endomyocardial biopsy (EB) was used at the time for CT monitoring, based on the knowledge of ultra-structural changes, (Topoisomerase-11Beta complexes, leading to alterations in DNA transcription and consequent mitochondrial alterations with formation of free oxygen radicals (ROS)[5] and histopathological findings (myofibrils loss and vacuolar degeneration with initial preservation, of the mitochondrial architecture, and then their degeneration along with myocyte death), establishing a scale of affectation from 0 (normal) to 3 (diffuse cellular damage).[6]

Years later, the invasive nature of EB led to the search for less invasive procedures for the early detection of CT, always based on the comparison with EB as a gold standard, using the serial determination of the ejection fraction of the left ventricle (LVEF) in these patients, first using radioisotopes and then echocardiography. This allowed for two fundamental findings for the subsequent development of better cardiac protection strategies: the first was that the greater the dose of anthracycline used, the greater possibility of onset and severity of heart failure, and the second was that structural changes always precedes the appearance of symptomatology and decreased LVEF.[7]

Oncogenes and monoclonal antibodies

The subsequent discovery of the oncogenes (normal genes that when suffering mutations due to inheritance or exposure to substances of the environment, can produce cancer[8] and specifically of the transmembrane receptor HER2 (family of receptors of the Human Epidermal Growth Factor, that being on expressed by the amplification of the ERBB2 gene, will have the potential to stimulate oncogenic cellular processes, so HER2 positive tumors have a particularly aggressive clinical course,[9]) motivated the development of a new line of specific therapy based on monoclonal antibodies such as Trastuzumab with very favorable results, but also with the potential development of heart failure, but in this case with no ultra-structural changes defined so far, absence of dose/toxicity relationship and greater potential for reversibility.[10]

This led to the establishment of two major types of myocardial dysfunction caused by chemotherapy: Type I, characteristic of anthracyclines (Doxorubicin) and Type II, related to monoclonal antibodies, such as Trastuzumab.[4]

Studies on cardiotoxicity

The long-term follow-up of patients with breast cancer has been able to determine the alarming incidence of CT, higher than estimated in controlled clinical studies. In a

retrospective cohort of 12,500 patients, 5% of patients developed clinical heart failure in 4.3% (3.5% to 5.0%) of patients on anthracycline therapy, 12.1% (5.3% to 18.3%) with Trastuzumab and 20.1% (14.0% to 25.6%) in the combination of both.[11]

When analyzed in another publication, a population of 45,500 patients, exclusively older (76 years +/- 6 years), the 3-year follow-up revealed 41.9% incidence of heart failure with the use of the combination of two drugs, establishing that CT is much more frequent in elderly patients.[12]

The ejection fraction of the LV

For many years, the ejection fraction using two-dimensional echocardiography, Simpson's biplanar method (Figure 1), was the primary tool for monitoring patients undergoing chemotherapy with the agents mentioned.

The consensus led by Juan Carlos Plana,[4] after reviewing the main databases in this regard, adopted the normal lower limit of 53%, being considered as CT the decrease in LVEF by more than 10% below the normal lower value mentioned. This situation should be confirmed in two to three weeks, ideally by the same operator and on the same equipment. The CT would be REVERSIBLE, if the follow-up shows recovery at less than 5% of the baseline value, PARTIALLY REVERSIBLE if the recovery is more than 10% of its lowest registry, but remaining more than 5% below baseline, and IRREVERSIBLE if the recovery is less than 10% of its lowest registry, and remaining more than 5% below baseline. It is called INDETERMINATED when the patient is not available for reevaluation.[4]

The three-dimensional technique (ETT3D) to obtain LVEF showed the best reproducibility in sequential follow-up, comparable to that obtained with cardiac magnetic resonance imaging (MRI), surpassing two-dimensional echocardiography with or without contrast (Figure 2).[13]

In this context, there are recent publications suggesting early changes in left atrial function in patients who develop CT, demonstrable with ETT3D.[14]

Myocardial deformity

The work of Torrent-Guasp allowed to show the ventricular myocardium as a unique helical band rolled in itself and anchored in the aortic and pulmonary rings, allowing an extremely efficient contraction, with fibers disposition in the endocardium almost parallel to the wall, perpendicular to this wall in the epicardium, and variable orientation in the thickness of the intermediate myocardium.[15] Complementing this anatomical model with the inherent properties of the myocardium, especially its INCOMPRESSIBILITY (cardiac tissue changes shape but not volume), motivated research and development of the Strain (deformity), as a new echocardiographic technique, whose detailed description is beyond the scope of this review. Suffice it to say that since its implementation as a diagnostic aid in a variety of cardiac pathologies, important progress has been made, initially with tissue Doppler and for a few years with Speckle Tracking, which has demonstrated interobserver reproducibility lower than 4% and lower intraobserver to 6%,[16] establishing normal values that vary according to the brand of equipment used, which should not be changed in the follow-up of a given patient.[17]

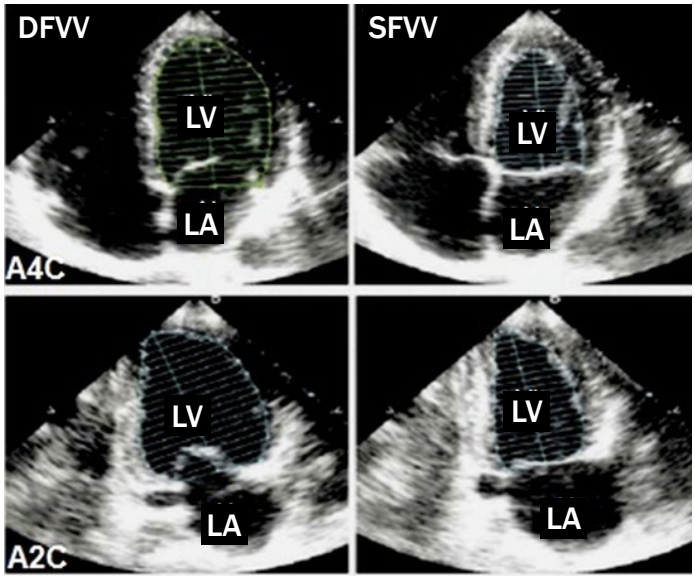

Figure 1 – *Calculation of LVEF by the Simpson method. DFVV: diastolic final ventricular volume; SFVV: systolic final ventricular volume; A4C: apical four chamber view; A2C: apical two chamber view; LV: left ventricle; LA: left atrium.*

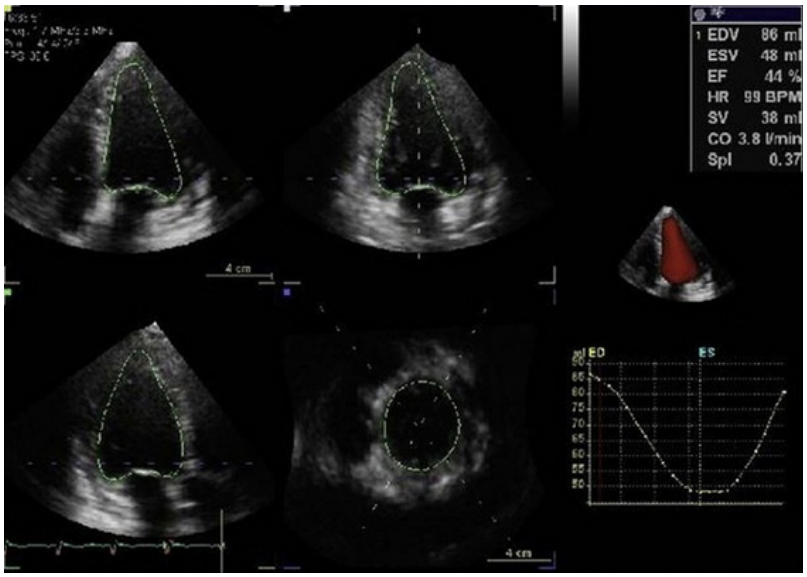

Figure 2 – *Calculation of LVEF with ETT3D.*

In the field of CT, early changes in global left ventricular deformity values have been demonstrated in patients undergoing QT with both Anthracyclines and Trastuzumab, which precede those obtained by conventional two-dimensional echocardiography and ETT3D.[18] Several publications have Established the strength of the Longitudinal Global Strain (SGL) with greater predictive value of CT, alone or combined with biomarkers, establishing a cut point for SGL of -19.7% (CI 95% 20.4% to 18.9%), with greater sensitivity for one reduction of SGL (AUC) 0.84; $p < 0.001$ with a reduction of 11% (95% CI, 8.3% -14.6%) with respect to baseline values established before QT (Figure 3).[19-21]

The ASE / EACVI[4] Consensus and recently the European Society of Cardiology Position Paper[22] agree that the drop of more than 15% of the baseline value in SGL, with no altered LVEF, is suggestive of subclinical ventricular dysfunction, requiring the immediate reference of the patient to the cardiology service. When the decrease is less than 8%, dysfunction is not considered and follow-up can be continued (Figure 4), exams must be serial and on the same equipment.

The usefulness of the deformity study in these patients has also been demonstrated in the long term in the follow-up of survivors of childhood malignancies who received anthracycline QT with or without radiotherapy up to 48 years after treatment, with only 5.8% of patients with LVEF (Calculated by ETT3D) less than 50%, although 28% of patients with LVEF greater than 50% showed SGL suggestive of subclinical left ventricular dysfunction. This increased prevalence of altered GLS was related to the type of treatment administered (combination of Anthracycline with or without Trastuzumab or Radiotherapy) and was able to identify a group of patients at high risk of poor outcome, who would potentially benefit from treatment.[23]

Conclusion

Due to the early diagnosis of imaging methods, dissemination of self-examination techniques and the use of more efficient treatments, cancer mortality in general, breast in particular, has been progressively decreasing.

Echocardiography, because of its accessibility, low cost and reproducibility, plays an important role in the detection of CT produced by chemotherapeutic agents. When using global longitudinal strain, which measures myocardial deformity, subclinical LV dysfunction can be detected, a fact of great importance to initiate the early treatment of myocardial damage and reduce or discontinue treatment with chemotherapeutic agents. For this reason, this method is recommended in the current guidelines.

Anthracyclines, widely used for the treatment of breast neoplasms, can produce, in a significant number of patients, permanent myocardial lesions, characterized by myocyte necrosis. Monoclonal antibodies, in turn, produce less severe, largely reversible, myocardial abnormalities. Importantly, the association of anthracyclines and monoclonal antibodies can cause CT with an incidence of greater than 40%, mainly in elderly patients.

Mortality from cancer is likely to continue to decline and the deleterious effects of chemotherapeutics, among which cardiotoxicity is very important, will also be gradually reduced by progress in research and development of new drugs.

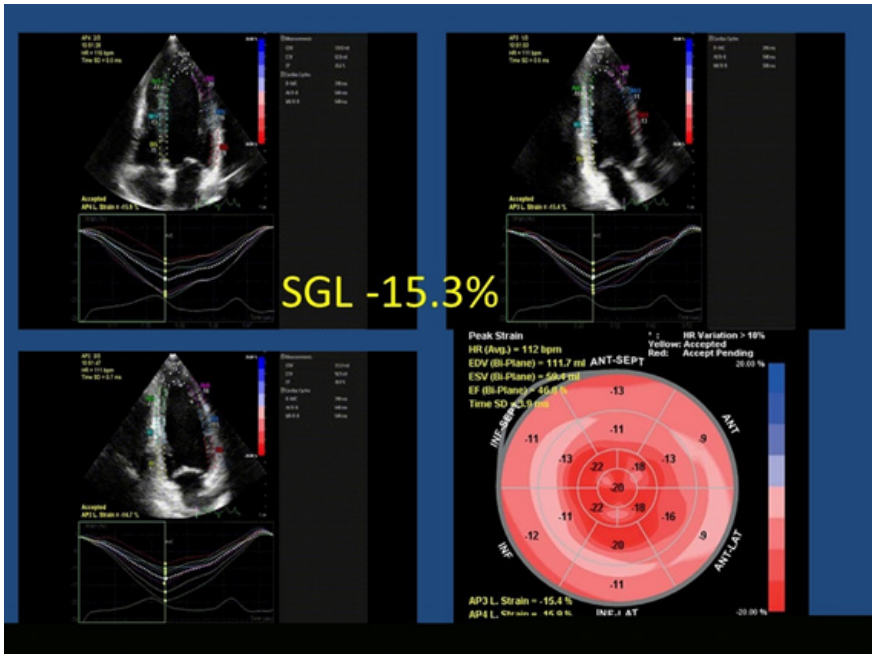

Figure 3 – *Reduced SGL in 48 year old patient, with LVEF of 55%, 18 months after completing treatment with anthracyclines.*

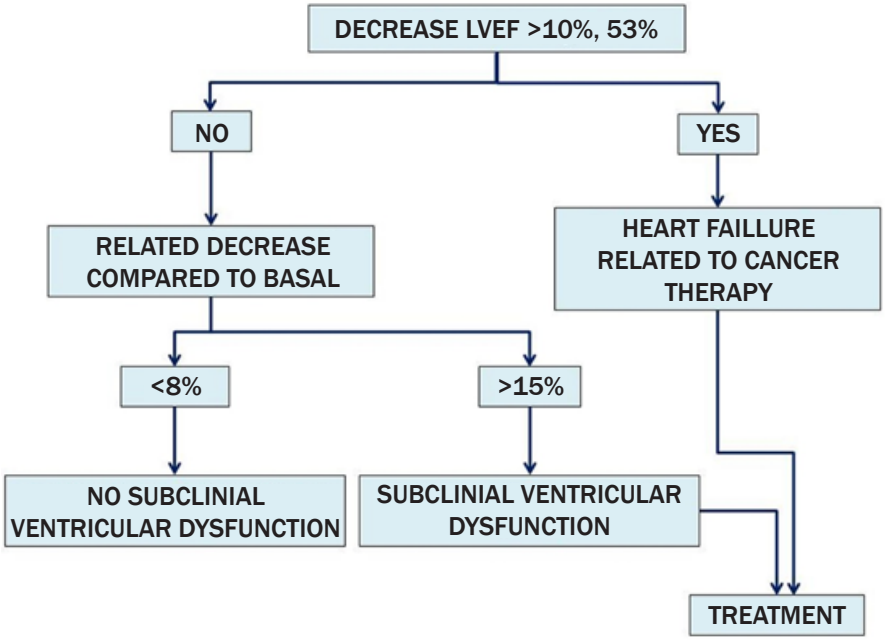

Figure 4 – *Detection of sub-clinical left ventricular dysfunction during and after chemotherapy, starting from a baseline examination before starting treatment.*

Authors' contributions

Concept and design of the research: Castilla RC; Data collection: Castilla RC; Data analysis and interpretation: Castilla RC; Writing the manuscript: Castilla RC; Critical review of the manuscript regarding the important intellectual content: Castilla RC, Del Castillo JM.

Potential Conflict of Interest

I declare there is no relevant conflict of interest.

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Academic Linkage

There is no linkage of this study to graduate programs.

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