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Role of Echocardiography in the Assessment of Cancer Therapeutics–Related Cardiac Dysfunction: An Updated State-of-the-Art Review

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Abstract

In the last years, cardiotoxicity in patients treated with chemotherapy became one of the most urgent issues for cardiologists because cancer has become one of the most common diseases of this century. The evidence of significant cardiac side effects of anticancer drugs and the awareness that an early assessment of cardiac damage can substantially reduce the onset of chemotherapy-related heart failure motivated several authors to concentrate their efforts in the study of new tools for sensitive and early detection of Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD). Echocardiography is widely considered the criterion standard technique for the assessment of these patients. The aim of this review is to carefully evaluate strengths and weaknesses of the main echocardiographic parameters commonly used for the detection of CTRCD through a detailed examination of the most relevant and recent papers in literature, while at the same time providing a practical approach to evaluate patients with cardiotoxicity.

Keywords: Cardioncology; Cardiotoxicity; Cancer therapeutics–related cardiac dysfunction; LVEF; 2D speckle tracking strain; Echocardiography

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Introduction

In the last century, cancer became one of the most common diseases of the Western world and chemotherapy one of the most used treatments, with a range of side effects that have been identified only recently. Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD) is one of the most common and dangerous side effects of several agents, especially anthracyclines, trastuzumab and tyrosine-kinase inhibitors [1]. Echocardiography is the most commonly used technique for the evaluation of CTRCD because of its wide availability, easy repeatability, lack of radiation exposure, and accuracy in the assessment of cardiac dysfunction. According to the most recent consensus statements [1,2], CTRCD can be defined as a decrease in the Left Ventricular Ejection Fraction (LVEF) of more than 10% to a value less than 53%, confirmed by repeated cardiac imaging. However, the evaluation of cardiac damage is difficult. Indeed, the entity and the timing of cardiac dysfunction can vary considerably among agents and often is not apparent for several years. Moreover, the assessment of CTRCD must be accurate and done as early as possible. The evidence of cardiac impairment can lead to discontinuation of cancer therapy with the loss of the beneficial anti-cancer effects for the patient, but at the same time, late detection of cardiac injury can lead to irreversible damage with a high risk of heart failure.

Assessment of LV systolic function: the role of LVEF

LVEF has been historically considered the cornerstone for the quantification of LV systolic function. Its importance in the assessment of patients potentially affected by cardiotoxicity is well demonstrated by the definition of CTRCD that the consensus statement from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [2] provides. Reduced LVEF after anthracycline-containing therapy [3-6] and an impaired LVEF before chemotherapy treatment is a good predictor for the onset of heart failure [7]. The main advantages of LVEF for the quantification of LV systolic function are the ease of the calculation and the huge amount of data confirming its effectiveness in every clinical setting. According to the current recommendations [8], LVEF should be quantified using the most accurate echocardiographic

technique available in the echolab, i.e., 3D echocardiography or, if it is not available, 2D echocardiography by the biplane Simpson's method and associated with the analysis of regional function by wall motion score index; moreover, for a more accurate evaluation of changes in patients after chemotherapy, LVEF reduction should be confirmed by comparing baseline and follow-up studies. However, the quantification of LVEF by 2D echocardiography is limited by some technical issues, such as LV geometric assumptions for the calculation of volumes, the frequent foreshortening of LV apex, the difficulties in the tracing of endocardial border in patients with poor image quality, the lack of consideration of subtle regional wall motion abnormalities, and the high dependence from LV shape (less effective if LV is dilated) and loading conditions; the latter is particularly important in patients with cancer because changes in loading conditions are frequent as a result of side effects associated with the chemotherapy like nausea, vomiting, and diarrhea. These limitations could explain the findings of several authors [9-11] who questioned the real effectiveness of LVEF in patients with potential cardiotoxicity, especially in the first months after beginning therapy. Di Lisi et al. [10] reported that inpatients with early breast cancer, after 6 months from the start of chemotherapy with one or more between epirubicin, trastuzumab, fluorouracil, cyclophosphamide, taxotere, and taxolo, significant changes were observed in tissue Doppler systolic parameters but not in LVEF, whereas Jensen et al. [11] showed that LVEF changes frequently occur late, when cardiac damage became irreversible. The issue concerning the timing of LVEF reduction in patients with CTRCD is crucial, because a late change of LVEF only in the advanced stages of cardiac damage makes LVEF poorly effective in the early detection of subtle LV dysfunction and in the prevention of heart failure. There is not a wide consensus about the timing of LVEF impairment in patients with CTRCD. Dodos et al. [4] reported a significant reduction of LVEF immediately after the completion of therapy in patients treated with anthracycline, whereas other authors [5,6] did not find significant LVEF changes in the first months of follow-up, and Cardinale et al. [12] showed that patients with a late detection of cardiotoxicity had a lower rate of LVEF recovery after heart failure treatment and a higher risk of mortality.

Finally, LVEF assessment by 2D echocardiography is affected by important intra- and inter-observer variability. Its effectiveness has been severely questioned by Thavendiranathan et al. [13] who demonstrated that the quantification of this parameter by 2D echocardiography has an inter-observer variability close to 10%; since the definition of CTRCD is a decrease in LVEF of more than 10% to a value less than 53%, the reliability of this technique appears to be debatable.

Assessment of LV systolic function: What can new myocardial deformation measurements add?

In the last years, the role of myocardial deformation parameters like strain and strain rate in the assessment of LV systolic function became more and more evident; with great results in several clinical settings [14]. Myocardial deformation can be quantified by different techniques, i.e., Doppler strain imaging (DSI) and 2D and 3D Speckle Tracking Echocardiography (STE). DSI is the first method used, and, despite the promising results obtained, it was affected by angle dependency, high intra- and inter-observer variability, limited spatial resolution, and a high sensitivity to signal noise; all these limitations were overcome by 2D STE strain, a method that allows a frame-by-frame tracking of natural acoustic markers (speckles), reducing artifacts due to translational respiration and tethering from the adjacent myocardium and angle-dependency.

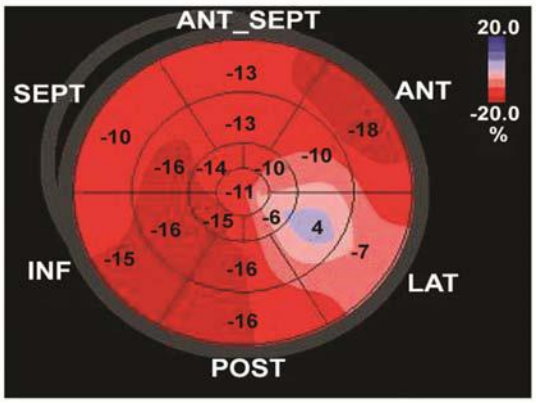

Figure 1: Example of left ventricular (LV) 2D speckle tracking longitudinal strain in a patient with breast cancer treated with anthracyclines. Note the typical pattern of regional dysfunction that involves mid and apical LV segments.

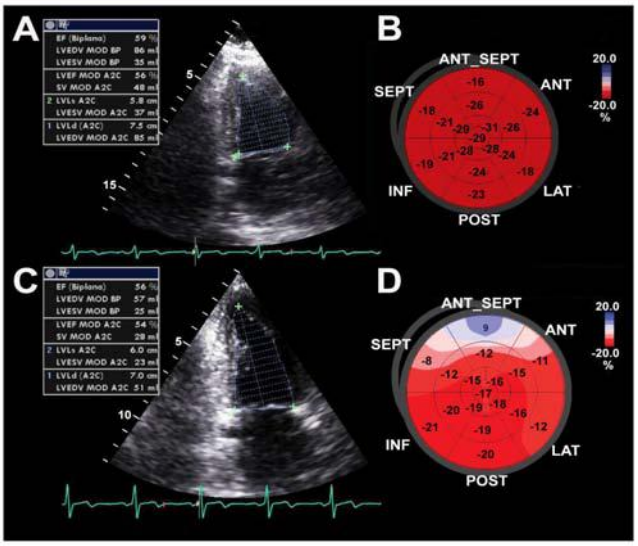

Figure 2: Examples of Left Ventricular (LV) subtle systolic dysfunction in a patient with breast cancer before and after 6 months of anthracyclines treatment. A and C: Left Ventricular Ejection Fraction (LVEF) calculated by the biplane Simpson's method before and after the treatment, respectively. B and D: LV 2D speckle tracking longitudinal strain before and after the treatment, respectively. Note that LV global longitudinal strain is substantially impaired whereas LVEF is not significantly reduced.

Several authors concentrated their efforts in the application of these new tools for the assessment of patients undergoing chemotherapy. Most of studies used Global Longitudinal Strain (GLS), which was more effective than radial and circumferential strains in the evaluation of these patients; however, a reduced circumferential strain was demonstrated in some reports [15].

The importance of GLS in the assessment of cardiac damage was clearly demonstrated. GLS was decreased early in both children [16,17] and adults [18,19] treated with anthracyclines, often in patients with normal LVEF. Poterucha et al. [17] studied a cohort of 19 children treated with anthracycline and found that changes in GLS preceded decreases in LVEF and that a characteristic pattern of regional changes, particularly located in mid and apical LV segments, can be observed (Figure 1). Similarly, Stoodley et al. [19] reported a

significant reduction of GLS after one week of anthracyclines therapy in patients with breast cancer, whereas no reduction in LVEF >10% was registered (Figure 2). According to these data demonstrating the better sensitivity of myocardial deformation measurements in the detection of subtle LV systolic dysfunction, the 2016 ESC position paper on cancer treatments states that the use of strain is preferred, when available, to serve as the basis for clinical decisions whereas the ASA/EACVI consensus statement [2] included 2D STE strain in the protocol for the serial evaluation of these patients, suggesting a comparison of the measurements during chemotherapy with the baseline value; indeed, it has been shown that a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, whereas patients with a reduction >15% from baseline are very likely to be affected by CTRCD [20].

Furthermore, strain showed to have not only a diagnostic but also a prognostic role in this setting. Data reported by several authors [21-23] showing that a decrease in longitudinal strain from baseline predicted the development of cardiotoxicity with high sensitivity have been recently confirmed by Ali et al. [24] who showed that a low pre chemotherapy GLS was a strong predictor of cardiac death and symptomatic heart failure. Interestingly, a GLS <-15.8% quantified at the time of the diagnosis of CTRCD was associated with subsequent recovery of LVEF, underlining the role of this parameter in the risk stratification of these subjects [22]. However, the recovery of LVEF after the end of the chemotherapy does not always indicate a full recovery of LV systolic function. Several authors who studied long-term cancer survivors found that a significant percentage of patients exposed to chemotherapy between 2 and 30 years before had a reduced GLS despite a normal LVEF [16,25-28]. Interestingly, the risk of developing cardiac damage was higher in patients treated with high doses of anthracyclines compared with other anticancer agents [25] and in patients exposed to mediastinal radiotherapy [28]. All these data confirmed the role of myocardial deformation measurements in the lifelong follow-up of patients who underwent chemotherapy. However, it is important to keep in mind several limitations that affect these parameters and the lack of data about its prognostic role. First, 2D STE strain and strain rate need good image quality to obtain reliable results, better than what is needed for the calculation of EF. Moreover, these measurements are very sensitive but poorly specific; they could be reduced in several clinical conditions, and it is not possible to distinguish if chemotherapy is the real cause of the impairment. Furthermore, when doing serial evaluations, similar vendors and algorithms for calculating strain should be used; inter-vendor variability is one of the oldest limitations of strain, and despite the efforts of the EACVI-ASE-Industry Task Force [29] that recently found a good reproducibility of GLS, there is a small but statistically significant variation among vendors that has to be considered. In addition, currently there are not enough data regarding the prognostic role of strain and strain rate in this setting. There is a general consensus that a reduction of LVEF >10% should suggest the discontinuance of chemotherapy; however, the prognostic relevance of a reduced GLS with a normal LVEF is not yet established, and currently, the finding of subnormal strain suggests the need for only closer monitoring of cardiac function. Moreover, not all subtle reductions in LV function will progress to heart failure and studies to define criteria for clinically relevant changes in strain are needed.

Not only the LV systolic function

Echocardiographic evaluation of patients before, during and after chemotherapy treatment should not be limited to the quantification of LV systolic function, but should include the study of LV diastolic function, RV systolic function, heart valves and pericardium.

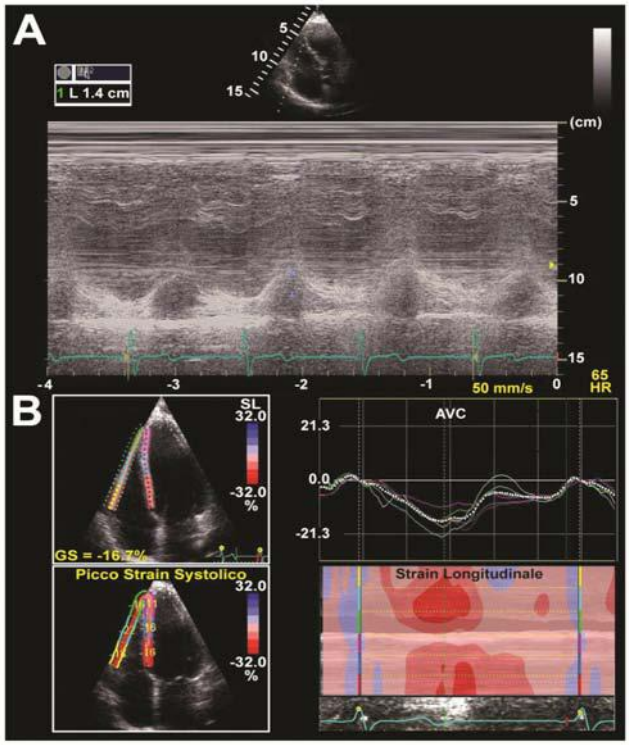

Figure 3: Example of Right Ventricular (RV) systolic dysfunction in a patient with Hodgkin's lymphoma treated with high doses of anthracyclines. A: Tricuspid Annular Plane Systolic Excursion (TAPSE); B: RV 2D speckle tracking longitudinal strain. Note that both the measurements are reduced in this patient.

Diastolic function seems to be reduced in a significant percentage of patients who underwent chemotherapy, but there is little evidence that parameters for the evaluation of diastolic function could be considered effective markers of CTRCD. A prolonged isovolumic relaxation time [30], a reduced E' or E/E' ratio [21,31] and an increased myocardial performance index [32] were indicated as markers of cardiac damage in small studies, but they were not confirmed subsequently [33-34]. Moreover, in a recent study, E/E' ratio at baseline or 3 months after the beginning of the treatment did not show a significant correlation with subsequent LVEF decline [31] and its changes can be strongly influenced by changes in loading conditions due to vomiting and diarrhea, typical side effects of chemotherapy. Therefore, diastolic function should be assessed for a general evaluation of patients but not considered closely related to CTRCD.

On the contrary, the evaluation of RV systolic function is mandatory in these patients. In the last years, the role of RV dysfunction became clearly a strong predictor of mortality and development or worsening of heart failure in several clinical settings [35]. In patients who underwent chemotherapy, RV damage can be due to both the harmful effects of anthracyclines on cardiomyocytes that affect LV and RV myocardium in the same way and the increased left ventricular filling pressures that could lead to increased pulmonary artery pressure and affect RV function through increased after load [36]. RV should be evaluated according to the recent recommendations [8] (Figure 3). In patients with potential

cardiotoxicity, TAPSE [37] and TDI S' wave [38] were effective tools for the evaluation of RV systolic function, which were impaired both in the short-term and long-term follow-up. Interesting results have been obtained with the use of 2D STE strain for the assessment of RV systolic function. RV longitudinal strain were reduced in breast cancer patients after 3 months of anthracycline-based chemotherapy [39] and in long-term adult survivors of lymphoma and acute lymphoblastic leukemia, [36] providing important information for a more accurate risk stratification of these patients. Therefore, RV function should be routinely assessed in patients with potential cardiotoxicity to improve the prognostic relevance of the evaluation.

Anticancer drugs do not seem to directly affect cardiac valves, but valvular diseases can be related to radiation therapy and severe infection that often affect these patients due to the reduction of leukocytes as a side effect of chemotherapy. Moreover, the presence of preexisting valve lesions like mitral prolapse can favor the onset of endocarditis [40]. Radiation therapy can cause a specific damage of valves; known as "radiation-induced heart disease" (RIHD) [41] that usually becomes symptomatic several years after the end of the therapy. Accordingly, the European Association of Cardiovascular Imaging and the American Society of Echocardiography (EACVI/ASE) [41] recommend an echocardiographic evaluation of valves 10 years after the end of radiation therapy and serial exams every 5 years thereafter. In this context, the use of trans-esophageal echocardiography can add important information for a surgeon if surgical treatment is required.

Pericardial involvement is very common in patients who underwent chemotherapy, especially anthracyclines and radiotherapy, whereas damage due to cancer itself is quite rare. Pericarditis can be acute or delayed, with the onset of symptoms and pericardial effusion from 2 months to 15 years after the treatment [1,41] Echocardiography is the first line tool for the assessment and quantification of pericardial effusion; more rarely, constrictive pericarditis with the typical signs of constriction can be found, particularly in patients who underwent high-doses of radiotherapy. Finally, echocardiography is the technique of choice to guide pericardiocentesis, when needed.

Advanced assessment of CTRCD: 3D echocardiography and cardiac magnetic resonance

As previously discussed, the quantification of LVEF by 2D echocardiography is limited by several issues, including the LV geometric assumptions for the calculation of volumes, the foreshortening of LV apex, the difficult tracing of endocardial border in patients with poor image quality, and the high dependence from LV shape and loading conditions. Most of these limits can be overcome by 3D echocardiography, which allows an assessment of LV volumes and EF not based on geometrical assumption, unaffected by apical foreshortening and improved by the use of an automated or semi-automated method for the identification of LV endocardium. Accordingly, 3D echocardiography was the most reliable echocardiographic technique for the assessment of LV volumes and EF and should be considered the method of choice, when available [8]. These recommendations are confirmed by several studies in patients with potential cardiotoxicity that showed that 3D echocardiography has the highest sensitivity in identifying subjects with CMR-derived EF <55% [42,43]. Indeed, Toro-Salazar et al. [42] reported that in pediatric cancer survivors exposed to high doses of anthracycline, 3D echocardiographic measurement of EF had a sensitivity of 68% in identifying subjects with CMR-derived EFs <55%, compared with 50% and 46% for quantitative analysis of 2D images by the area-length and Simpson's biplane methods. Moreover, they found that 3D speckle-tracking echocardiographic peak global longitudinal strain magnitude <-17.5% best identified subjects with abnormal longitudinal strain magnitude by CMR. Furthermore, 3D echocardiography can provide better evaluation of RV function and allows a better estimation of valve disease severity, giving additional information for the management of these patients. However, 3D echocardiography is affected by high cost, need for good image quality data for analysis, time-consuming processing, inter vendor software variability, need for a regular cardiac rhythm, and a relatively low temporal resolution, all of which limited its spread and use in recent years. When 3D echocardiography is not available and 2D assessment does not provide satisfactory information, Cardiac Magnetic Resonance (CMR) can be considered for the detection of CTRCD. CMR is the criterion standard technique for the assessment of LV and RV systolic function and has a greater accuracy than echocardiography in the detection of cardiac diseases in all clinical settings [44]. This evidence has been widely confirmed in patients with potential cardiotoxicity [45-47]. Ylänen et al. [47] showed that LV and RV dysfunction were detectable in most of anthracycline-exposed, long-term survivors of childhood cancer and that both LV and RV end-systolic and LV end-diastolic volumes were increased compared with controls, whereas several other authors [48,49] found that global circumferential and longitudinal strains were reduced in these patients. However, the high costs, claustrophobia and hazards associated with ferromagnetic devices limited CMR use in clinical routine. Accordingly, the current recommendation is to consider the use of CMR only in situations in which the estimation of LVEF by echocardiography is thought to be unreliable and discontinuation of chemotherapeutic regimens secondary to CTRCD is being entertained [2].

Conclusion

Early assessment for CTRCD is fundamental in patients with potential cardiotoxicity and echocardiography is the diagnostic technique of choice. A comprehensive assessment of LV and RV systolic function, LV diastolic function, heart valves and pericardium is mandatory before the beginning of the therapy, during the treatment, and after the discontinuation, often with a lifelong follow-up. LV systolic function and LVEF should be evaluated by 3D echocardiography and, when it is not available, by 2D. LVEF is considered the benchmark for the detection of CTRCD, but it should be associated with myocardial deformation measurements that appear to be more sensitive and accurate compared with LVEF. LV diastolic function should be assessed but, so far, is not considered closely related with the onset of cardiac damage. RV function must be detected to better stratify the risk of developing heart failure. Heart valve diseases and pericardial effusion should be detected simultaneously.

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