REVIEWS

Role of new echocardiographic techniques in the detection of cancer treatment-related cardiac dysfunction. Current status and further perspectives

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Abstract: Despite cancer therapeutics-related cardiac dysfunction (CTRCD) can be initially asymptomatic, if not detected and properly managed, it may progress to severe and irreversible heart failure. Therefore, identification of high-risk patients and early detection of subclinical myocardial dysfunction are fundamental tasks for the management of cancer patients undergoing chemo- and/or radiotherapy, involving both cardiologists and oncologists.

Although systematic and periodical assessment of left ventricular ejection fraction (LVEF) by two-dimensional echocardiography (2DE) is conventionally used to monitor LV function during and after chemotherapy, three-dimensional echocardiography (3DE) has been reported to have the best accuracy and reproducibility for LVEF assessment, when compared to cardiac magnetic resonance (CMR). However, LVEF reduction occurs at late and often irreversible stages of CTRCD. Conversely, measurement of LV myocardial deformation by two-dimensional speckle tracking (2DSTE), and particularly measurement of LV global longitudinal strain (GLS) has demonstrated to identify CTRCD at early stages, when LVEF is still normal. Accordingly, baseline and periodical evaluation of GLS have now been introduced by the current recommendations regarding cardiac monitoring of cancer patients.

The purpose of this review is to summarize currently available evidences on the role of the different echocardiographic techniques to monitor LV function in cancer patients treated with potentially cardiotoxic chemotherapeutics with an emphasis on the benefits of novel imaging techniques and on how the latter can be applied in the various clinical settings.

Keywords: cardiotoxicity, cancer treatment-related cardiac dysfunction, three-dimensional echocardiography, three-dimensional speckle tracking, cardio-oncology.

Rezumat: În ciuda faptului că disfuncția cardiacă asociată terapiei cancerului (DCATC) poate fi inițial asimptomatică, neglijată și netratată corespunzător, poate progresa către insuficiență cardiacă (IC) severă si ireversibilă.

În consecință, identificarea pacienților cu risc crescut și detectarea precoce a disfuncției miocardice subclinice sunt obiective fundamentale pentru managementul pacienților cu patologie neoplazică, implicând medicii cardiologi și oncologi.

Deși evaluarea sistematică și periodică a fracției de ejecție a ventriculului stâng (FEVS) prin ecocardiografie bidimensională (E2D) este utilizată în mod convențional pentru monitorizarea funcției ventriculului stâng (VS) în timpul și după chimioterapie, ecocardiografia tridimensională (E3D) s-a dovedit a avea cea mai bună precizie pentru evaluarea FEVS, în comparație cu rezonanța magnetică cardiacă (RMC). Cu toate acestea, reducerea FEVS are loc în stadiile tardive și de multe ori ireversibile ale DCATC.

Pe de altă parte, măsurarea deformării miocardice a VS prin ecocardiografie speckle tracking bidimensională (EST2D) și mai ales, măsurarea strainului longitudinal global al VS (SLG), a demonstrat eficacitate în identificarea DCATC subclinică, atunci când FEVS este încă normală. În consecință, evaluarea inițială și periodică a SLG a fost propusă de recomandările actuale pentru monitorizarea cardiacă a pacienților cu patologie neoplazică.

Scopul acestui articol este de a rezuma dovezile disponibile în prezent referitoare la rolul diferitelor tehnici ecocardiografice pentru monitorizarea funcției VS la pacienții cu patologie neoplazică, accentuând avantajele tehnicilor imagistice noi și modul în care acestea pot fi aplicate clinic.

Cuvinte cheie: cardiotoxicitate, disfuncție cardiacă asociată terapiei cancerului, ecocardiografie tridimensională, ecocardiografie speckle tracking tridimensională, cardio-oncologie.

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INTRODUCTION

Early detection strategies, improved surgical approaches, as well as new drugs and more aggressive treatment protocols have reshaped the prognosis of cancer patients in the last decades. As a result, mortality rates from cancer have dropped by 23% since 1991[1]. However, increased life expectancy, associated with the aging of the cancer patient population, has resulted in a rise of adverse cardiovascular effects, particularly in patients with history of previous cardiovascular diseases[1].

Cancer treatment-related cardiac dysfunction (CTRCD) has a poor prognosis, once it becomes clinically manifested, and it is the leading cause of morbidity and mortality in cancer survivors[2]. Lack of recovery of left ventricular (LV) function after therapy cessation was reported in up to 40–58% of the patients developing CTRCD[3], and treatment has been shown to be more effective when initiated early, before irreversible cardiac damage occurs[4].

Thus, identification of high-risk patients, early detection of CTRCD, and research to identify markers of subclinical myocardial dysfunction are fundamental tasks for the management of cancer patients, involving both cardiologists and oncologists.

CTRCD diagnosis is conventionally based on the calculation of LV ejection fraction (LVEF) using various cardiac imaging modalities. According to current recommendations, LVEF decrease of more than 10% to a value of less than 53%-assessed by two-dimensional echocardiography (2DE) using the biplane Simpson's method and evidenced by repeated studies defines CTRCD[5]. Further characterization of CTRCD relates on presence/absence of symptoms and reversibility.

Among the various cardiac imaging modalities, 2DE is the most frequently use in the cardio-oncological field because of its wide availability, easy repeatability, radiation-free nature, cost-effectiveness and clinical value. The addition of recent echocardiographic techniques, such as contrast, three-dimensional (3DE) and 2D/3D speckle-tracking echocardiography (STE), has fueled the use of echocardiography that has become a cornerstone in the evaluation of patients' before, during and after cancer therapy[5].

Although not stated in the definition of CTRCD, integrating LVEF assessment with biomarkers, such as troponin and brain natriuretic peptide (NT-pro BNP) levels, and new parameters obtained with 3DE and STE may increase the detection of CTRCD. Abnormal troponin values next to impaired LV global longitudinal strain (GLS) by STE increases specificity for the prediction of CTRCD from 73% to 93%[6]. If both parameters are abnormal a cardiology consultation is required[4]. Likewise, the high negative predictive value of NT-pro BNP may be useful in the setting of CTRCD as its elevation raises concern for augmented LV filling pressures.

The focus of this review is to summarize currently available evidences on the role of the various echocardiographic techniques to diagnose CTRCD, their advantages, limitations and pitfalls, emphasizing on the benefits of novel imaging techniques and on how the latter can be applied in predicting subsequent development of CTRCD.

Two-dimensional echocardiography left ventricular ejection fraction: pros and cons. Why do we need more?

Both the *American Society of Echocardiography* (ASE) and *European Association of Cardiovascular Imaging* (EACVI) recommend the routine use of bi-plane discs' summation method for measuring LV volumes and calculate LVEF[7]. LV volumes are obtained from manual tracing of the interface between the compacted myocardium and the LV cavity in four- and two-chamber apical views using the end-systolic and end-diastolic frames (Figure 1).

Despite the fact that it is recommended to maximize the LV areas, to avoid view foreshortening, and to reduce the depth of the scan sector to improve endocardial tracing accuracy, 2DE still shows suboptimal accuracy in measuring LV volumes. Wrong view orientation, geometric assumptions about LV shape, and/or errors during manual tracing of endocardial border may explain the relatively low reproducibility of LVEF calculated by 2DE[8]. On average, the reported variability of 2DE LVEF is around 9.5%, failing in accurately detect myocardial dysfunction due to limited extent of regional alterations[9].

The ability to obtain an accurate and reproducible measure of LVEF is of vital importance for patients receiving chemotherapy, since clinical decision relies almost completely on this measurement[10]. Since, cessation or dose reduction of chemotherapy drugs should be considered if LVEF drops more than 10% to below 53%[5], concerns have been raised about erroneously stopping potentially lifesaving therapies due to changes in LVEF that occur only due to the technical variability of the modality in repeat testing.

Indeed, patients at risk for CTRCD require serial evaluation of LVEF at the beginning of cancer therapy, once half of the cumulative dose has been adminis-

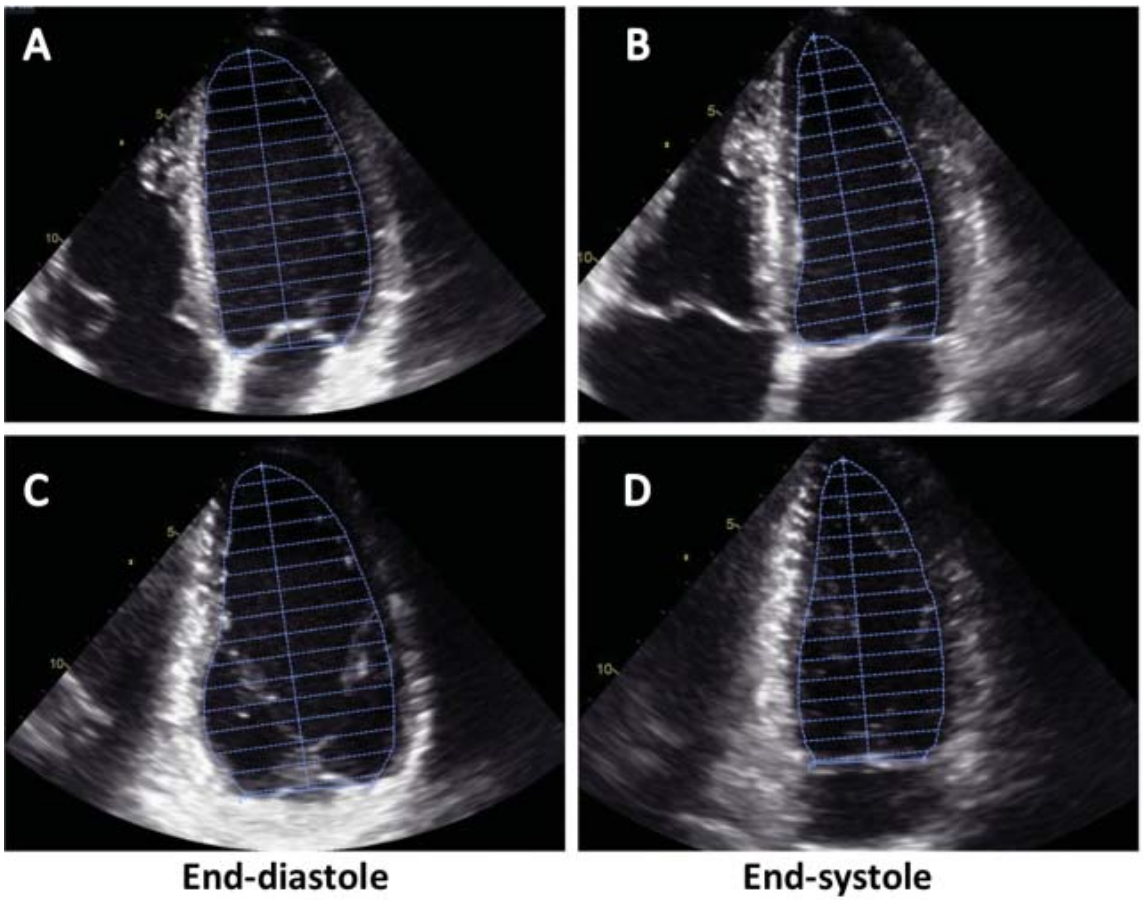

Figure 1. Calculation of left ventricular volumes by two-dimensional echocardiography using the bi-plane discs' summation method (Simpson method). Left ventricular cavity is divided into 20 discs by manually delineating the endocardium in the apical four- (**A** and **B**) and two-chamber views (**C** and **D**).

tered, before every subsequent dose and 3, 6 and 12 months after its completion[5]. Accordingly, in addition to the accuracy, reproducibility and test/re-test repeatability of the imaging technique used to measure LVEF is required to obtain consistent results across the different steps of the therapeutic protocol, and by different observers. Accordingly, ASE/EACVI expert consensus regarding adult cancer patients, recommends to use the best technique available in the echocardiography laboratory (ideally 3DE) for LVEF calculation in patients exposed to potentially cardiotoxic chemotherapy[5].

Left ventricular opacification: to visualize the endocardial border

Some of the inaccuracy of 2DE is due to suboptimal image quality and objective difficulties in identifying the endocardial border to trace. Previous reports have shown that LV opacification using transpulmonary contrast agents (Figure 2) improves endocardial visualization and therefore the accuracy of 2DE LV volume and EF assessment in comparison with computed tomography and cardiac magnetic resonance (CMR) imaging[11-13]. Even more important, LV opacification has been reported to improve inter-observer reproducibility to a level comparable with CMR[14].

However, improved accuracy is not restricted to patients with poor baseline image quality[12]. Therefore, the use of this technique has been suggested to improve accuracy and reproducibility of LVEF measured with 2DE in cancer patients. There is limited data about the use of LV opacification to monitor LVEF during chemotherapy. Thavendiranathan et al.[15], in a comparative study among the different echocardiographic techniques, reported that contrast increased the temporal variability of all tested echocardiographic techniques (2DE, 2D triplane and 3DE). Conversely, interobserver variability of contrast 2DE was significantly better than fundamental 2DE and close to that measured with 3DE.

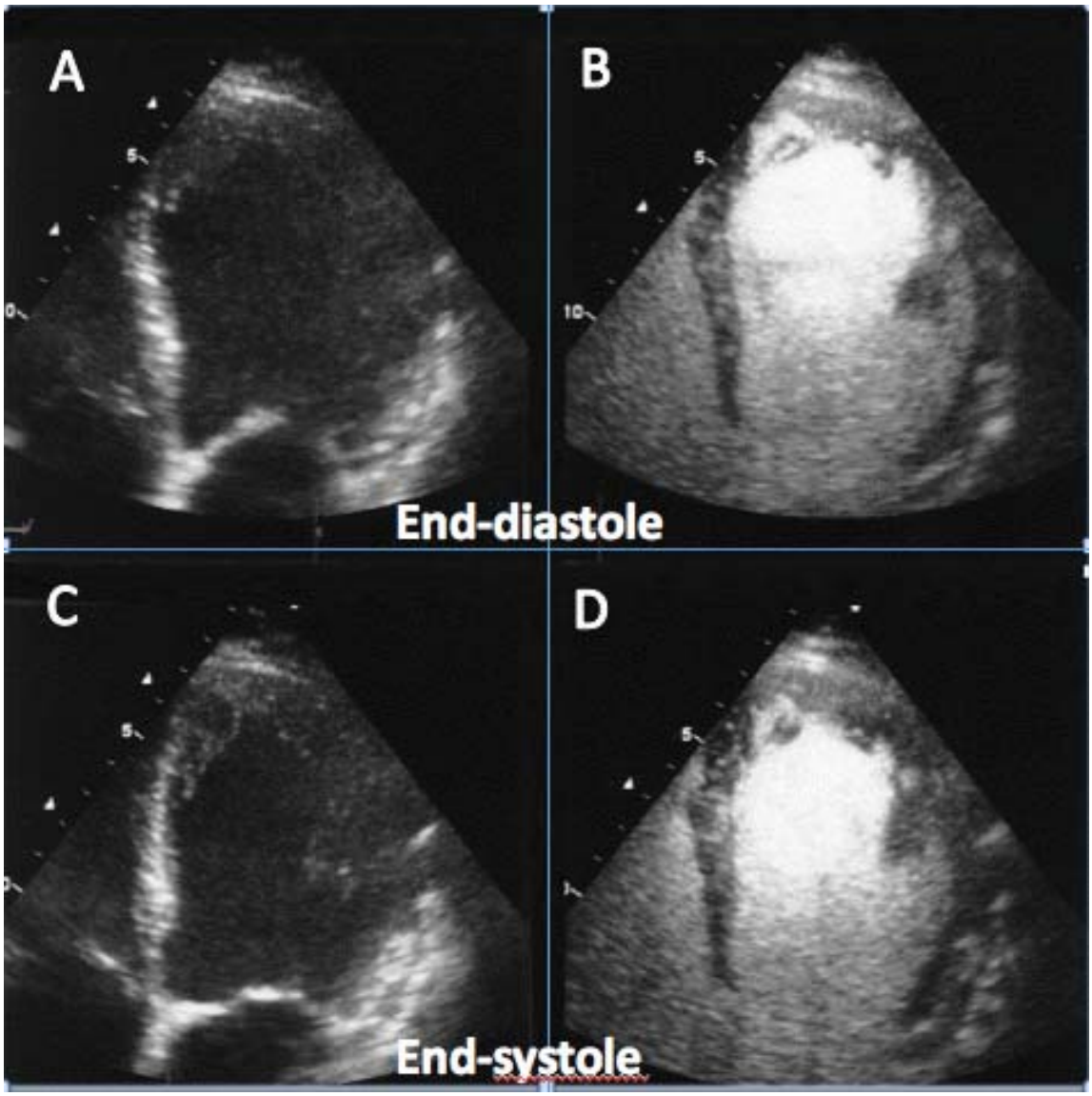

Figure 2. Use of echocardiographic contrast agent (Sonovue, Bracco S.p.A, Italy) to opacify the left ventricular cavity in a patient with sub-optimal endocardial visualization of the lateral wall and the apex in fundamental imaging (panels **A** and **C**). With 1 mL of contrast agent the endocardium of the left ventricle is clearly visualized in all segments (panels **B** and **D**).

Three-dimensional echocardiography left ventricular ejection fraction: beyond geometrical assumptions

The greatest advantage of 3DE in the evaluation of the LV is that, with this technique, the commonest causes of LV volume underestimation with conventional 2DE (i.e., foreshortening of the LV longitudinal axis, plane position errors, and geometrical assumptions about LV shape) are no longer real issues[16,17]. With 3DE, only one acquisition of the LV is required to obtain volumes and ejection fraction (Figure 3). The acquisition is usually performed from the apical approach and requires that the whole LV is included within the 3D data set. LV data set analysis can be performed using computerized automated or semi-automated endocardial surface detection software packages, which do not rely on specific geometric assumptions regarding LV geometry and require only minimal human interaction, therefore improving measurement reproducibility[18]. Transthoracic 3DE has been extensively validated against CMR and has been demonstrated to be more time-saving, reproducible, and accurate than conventional 2DE for LV volumes and ejection fraction measurement[19]. In most publications, transthoracic 3DE has been shown to slightly underestimate both LV end-diastolic and end-systolic volumes in comparison with those measured

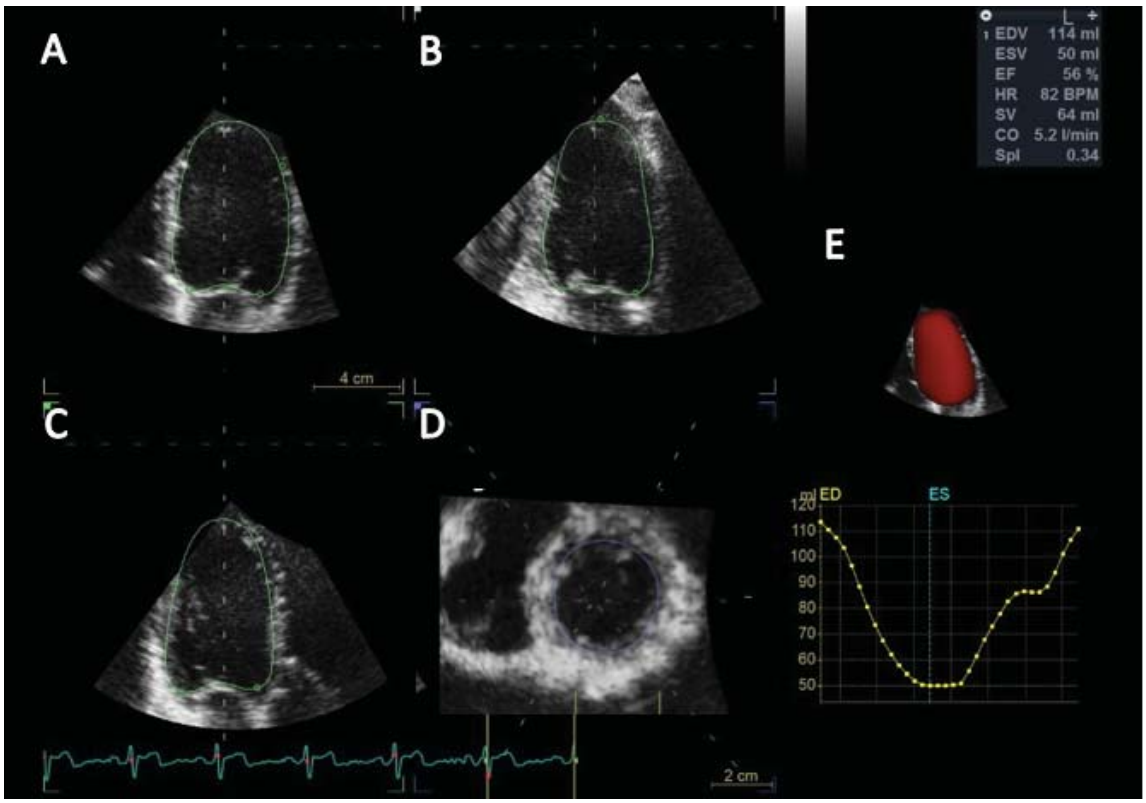

Figure 3. Measurement of left ventricular volumes and ejection fraction using a three-dimensional full-volume data set of the left ventricle. Three longitudinal views and one transversal view obtained by slicing the three-dimensional data set are used to assess the accuracy of the semiautomated endocardial tracking and edited it as needed: apical four chamber view (Panel **A**), apical two chamber view (Panel **B**), apical long axis view (Panel **C**), and short axis view (Panel **D**). The final beutel of the left ventricle and the curve showing the changes of left ventricular volume during the cardiac cycle are displayed in panel **E**.

with CMR[20]. A meta-analysis of 23 studies comparing transthoracic 3DE with CMR volumes and ejection fraction demonstrated biases of -19 ± 34 mL, -10 ± 30 mL, and -1 ± 12% for LV end-diastolic and end-systolic volumes, and ejection fraction, respectively[21]. For years, the usefulness of 3DE in everyday practice was limited by the absence of reference values for LV chamber volumes and ejection fraction. Recently, several publications have addressed this gap in the literature[20-25].

Walker et al[26], in 50 breast cancer patients, showed that LV volumes measured by 3DE were significantly closer to those measured by multiple-gated acquisition and CMR than volumes calculated with 2DE. Armstrong et al[27], in survivors of childhood cancer patients, showed that 3DE was more accurate (sensitivity 53%, false-negative rate 47%) than 2DE (sensitivity 25% and false-negative rate 75%) in detecting LVEF <50% at CMR. In addition, a recent comparative study showed that among 56 cancer patients undergoing chemotherapy with stable LV function, non-contrast 3DE showed significantly lower temporal variability than the other tested echocardiographic techniques (2DE, contrast-2DE, 2D triplane, contrast 2D triplane, contrast 3DE)[15]. Non-contrast 3DE measurement of LVEF provided also the desired level of test/re-test variability of 5.6% (95% confidence interval: 5.0-6.2%), whereas test/re-test variability of 2DE was 9.8% (close to 10% variation that will raise the issue of CTCRD). 3DE appears to be the technique of choice for monitoring LV function during and after chemotherapy[28]. However, it is important to realize that this technique has several limitations as well. 3DE is not as widely available as 2DE because of cost, and it relies heavily on high-quality images and operator expertise to achieve the superior performance mentioned above. Tsang et al.[29], demonstrated the need of the formal standardization of the analytical approach among the readers in the echocardiography laboratory to eliminate the systematic bias and improve the agreement among readers in the measurement of LV volumes.

Two-dimensional speckle tracking echocardiography: available evidences, pros and cons.

Regardless of how it is measured, LVEF measurement remains a relatively insensitive parameter to detect early CTRCD. This is because a decrease in LVEF does

not occur until a critical amount of myocardial damage has occurred and cardiac compensatory mechanisms are exhausted. Accordingly, to overcome the limitations of using parameters like LVEF which are heavily load dependent, the assessment of myocardial function by measuring its deformation during systole (strain) was introduced.

Tissue Doppler Imaging (TDI) was the first echocardiographic technique used for strain analysis, but recently STE has become the preferred technique for clinical practice because it overcomes the technical limitations of TDI[30] (Table 1).

In the LV, the myofibers geometry changes smoothly from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium, such that the helix angle varies continuously from positive at the endocardium to negative at the epicardium. At the equator of the LV, midwall fibers are oriented circumferentially; contraction of these fibers mainly contributes to a decrease in the minor axis of the ventricle (radial contraction) and is responsible for generation of the largest part of the stroke volume. Longitudinally and slightly oblique oriented fibers in the subendocardium contribute to the shortening of the LV long axis by 12 to 15 mm, to LV torsion, and also to LV stroke volume. This intricate arrangement of myocardial fibers results in a complex LV mechanics during the myocardial contraction and relaxation. Myocardial contraction occurs in the longitudinal direction (the base moves towards the apex), the radial direction (walls thickening), and the circumferential direction (cavity size decreases perpendicular to the long axis of the chamber). Since myocardial fibers in the subendocardium are particularly sensitive to chemotherapy damage[31], and GLS being the most robust and reproducible among the myocardial strain parameters[32], this parameter has raised the interest of the investigators to detect early and subclinical myocardial dysfunction in patients at risk of CTCRD[33].

GLS has been reported to decrease earlier than LVEF, at cumulative doses of chemotherapeutic agents that traditionally were not involved in CTRCD development[34-36]. Moreover, GLS has been shown to predict the subsequent occurrence of CTRCD and heart failure (HF)[6,37,38].

Abnormal GLS values before, during, or early after chemotherapy was predictive of long-term all- cause mortality in patients with multiple malignancies[39]. The extent of GLS change among subsequent studies during chemotherapy that could predicts subsequent CTRCD ranged from 10 to 15.9%[33,37], ASE/EACVI expert consensus suggests that in the case of a GLS change of more than 15% from baseline, subclinical CTRCD should be defined and prompt cardiac evaluation along with specific treatment are required[5].

2D STE appears to have a pivotal role in one of the most important scenario in clinical oncology: early detection of CTRCD during cancer treatment (Figure 4). However, the 2DE technique can affect the accuracy of GLS measurement by using foreshortened views or changing the spatial orientation of the apical views from study to study. Moreover, the actual amount of myocardium analyzed using the three 2DE apical views is only a small fraction of total LV myocardial mass. Finally, the myocardium analyzed in the diastolic frame will not necessarily be encompassed in the same systolic frame view due to LV rotation and basal-apical shortening (i.e. limited spatial resolution and the through out-of-plane motion of the tomographic views are known limitations of 2DE GLS)[30].

The main issues which limited the routine clinical use of 2D STE were the lack of reference values to distinguish between normal and abnormal GLS and the reported significant intervendor variability of strain measurements obtained using different echocardiographic systems[40-44]. Normal values for the different strain components have been reported in both adults[7,45,46]

Table 1. Differences between strain parameters obtained from Tissue Doppler Imaging and Speckle Tracking Echocardiography

TDI STRAIN	STE STRAIN
One-dimensional	Two-dimensional
Angle-dependent	Angle-independent
Limited spatial resolution	Better spatial resolution
High temporal resolution	Lower temporal resolution
Less dependent on image quality	Dependent on image quality
Requires expert readers to ensure reliability of results	Semi-automated analysis for less experienced observer
Time consuming	Rapid
Lower interobserver reproducibility	Better reproducibility

Abbreviations: TDI-Tissue Doppler Imaging; STE-Speckle Tracking Echocardiography.

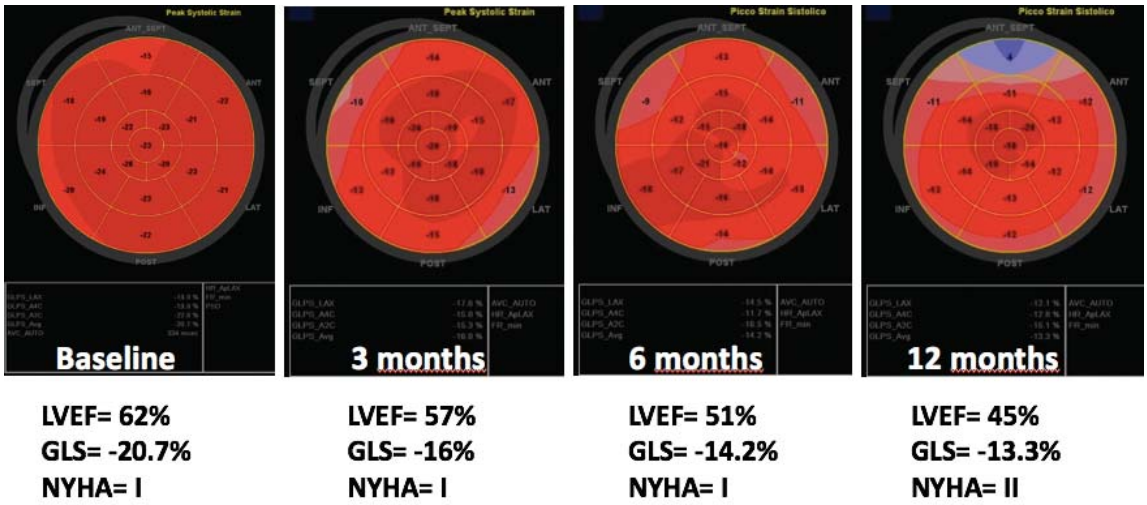

Figure 4. Example showing the role of global longitudinal strain (GLS) in the early detection of cancer treatment-related cardiac dysfunction in a patient with mantle cell lymphoma treated with anthracyclines. At baseline study, both GLS and left ventricular ejection fraction (LVEF) were within normal limits. At 3-month follow-up study: LVEF slightly decreased, though remaining in the normal range. Conversely, GLS was definitely abnormal (-28% compared to baseline values). The patient has no symptoms. At 6-month follow-up study: LVEF was significantly decreased (-18% compared to baseline and below 53%) along with a further reduction of GLS compared to the 3-month study. The patient is still asymptomatic. At 12-month follow-up study a further reduction of both LVEF and GLS were detected and the patient complained with fatigue and dyspnea on efforts.
Abbreviations GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

and children[47]. To address the issue of intervendor variability of the strain measurements, the EACVI, the ASE and all the companies manufacturing echocardiographic systems and/or developing software packages to analyze echocardiographic images have joined in a Task Force to standardize myocardial strain imaging[48]. Application of the standardized criteria set by the EACVI/ASE-Industry Task Force has proven to be effective in reducing both the intervendor[49] and the test/re-test[50] variability of GLS measured by STE to clinically acceptable values which were below the variability of LVEF in the same patients.

Three-dimensional speckle tracking echocardiography: a tool with great potentialities to monitor myocardial function!

The recently developed 3D STE holds promises to represent a further advance in LV myocardial deformation imaging. Theoretically, it should overcome the main technical limitations of 2DE STE by allowing to analyze the whole LV myocardial mass and to follow myocardial speckle motion in the 3D space[51,52]. As a result, provided that 3DE data set have reasonable spatial and temporal resolution, 3DSTE has the ability to estimate true 3D myocardial deformation (Table 2).

Simultaneous assessment of the various components myocardial wall motion together with LV volu-

Table 2. Comparison of technical characteristics of two- and three- dimensional speckle tracking technologies

2D strain	3D strain
2-dimensional segmental slice	3-dimensional segmental slice
50-80 fps	>25 fps (40% of HR)
Regular HR (consecutive 2D LV views)	Regular HR (gated LV full-volumes)
Peak and end-systolic strain	Frame-by-frame strain values
Only single direction strain	Both single direction and area strains
Single bull's eye view	Frame-by-frame bull's eye view
Non-simultaneous segmental peaks	Both simultaneous and peak segmental values
Positive peak rule (>75% of peak negative)	No positive peak rule
Drift compensation	No drift compensation
Tracking quality: automated algorithm	Tracking quality: more user expertise

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; fps, frames per second; HR, heart rate.

mes is one of the advantages of 3DSTE. Global and regional longitudinal, circumferential and radial strains together with LV volumes, EF calculation, LV mass and stroke volume assessment, can be obtained from the same data set reducing both the acquisition and the analysis time[53].

All these unique characteristics are likely to propel 3DSTE strain parameters as a future diagnostic tool to assess myocardial mechanics. However, for an effective clinical and research application, we need the normative values of 3DSTE parameters. Accordingly, reference values for 3DSTE strain components and the effects of demographic, hemodynamic and technical factors on these values, have been recently reported by Muraru et al[54].

In addition to conventional strain parameters (i.e. longitudinal, radial and circumferential strain values), 3DSTE provides a composite deformation parameter (e.g. area strain), an area tracking-based parameter, measured at mid myocardial wall, which takes into account both longitudinal and circumferential myocardial deformation. 3DSTE global AS was reported to detect subclinical LV myocardial damage in adults after aortic coarctation repair[55], and demonstrated accuracy and reproducibility as a regional wall motion abnormality parameter[56].

3DSTE deformation parameters have been reported to be sensitive markers of subclinical LV impairment after surgery for aortic coartaction[55] or percutaneous coronary interventions[56], in patients with aortic valve disease[57] and in hypertensive patients[58].

There are few studies which applied 3DSTE to detect myocardial dysfuction in cancer patients who received potentially cardiotoxic chemotherapy.

Yu et al.[59] demonstrated that childhood cancer survivors had significantly reduced 3DSTE GLS and torsion ($p<0.001$) in comparison to healthy controls. Another study showed that GLS evaluated with 3DSTE was superior to biomarkers and LVEF in predicting future development of CTRCD[60].

A recent study compared 2D and 3D echocardiographic measurements of LV function parameters with those measured with CMR in 57 oncological survivors[61]. They found that LVEF by 3DE below 55%, 3D end-systolic volume indexed larger than 29 mL/m^2 and 3DE GLS higher than -17.5% were the most sensitive echocardiographic parameters to identify subclinical myocardial dysfunction at CMR defined as LVEF lower than 55% and/or abnormal values of peak global longitudinal strain. Finally, 3DSTE area strain was found useful for early detection of cardiac dysfunction associated with the use of anthracycline, and may thus prove to be clinically useful for predicting CTRCD in cancer patients[62].

However, despite the fact that 3DSTE parameters may have an important role in detecting subclinical myocardial dysfunction and better understanding CTRCDs pathophysiology (Figure 5), studies on oncological patients cardiac function are limited and included small number of patients.

Intervendor and intersoftware variability, dependence on the image quality and the need of trained operators, are currently the most important limitations of this promising method[54,63].

Clinical and research implications. What do we need to expand our knowledge about CTRCD detection and its management?

It is widely acknowledged that LV myocardial strain assessment now represents an integral part of the evaluation of cardiac function of cancer patients treated with chemotherapy. Despite the significant progresses in reducing the intervendor differences in strain measurements, for an optimal management of cancer patients it is recommended to measure the strain relative change, comparing pretreatment values to measurements obtained during treatment using the same echocardiographic system[5]. The best approach seems to be the use of individualized baseline strain value, as a reference for further follow up and ideally, each laboratory should produce its own baseline reference values to compare normalcy and pathology in dedicated studies.

Moreover, whether or not cardiac intervention or modification to cancer therapy based on strain changes will have a favorable impact on cardiac outcomes in these patients remains to be clarified. EACVI/HFA *Cardiac Oncology Toxicity* (COT) registry[64] is an ongoing multinational, multicenter, randomized controlled study that will specifically address this issue.

According to the most recent literature, it seems that 3DSTE popularity is increasing and research studies continue to explore its clinical added value over conventional 2DSTE. 3DSTE global strain parameters seem to have good test-retest measurements reproducibility[65], which together with physiological sound measurements and time efficiency, make 3DSTE very attractive for researchers, as well as for clinicians. However, unlike 3DE volume quantification, which is ready for daily clinical use, the current 3DSTE technology is still not developed enough for routine clinical

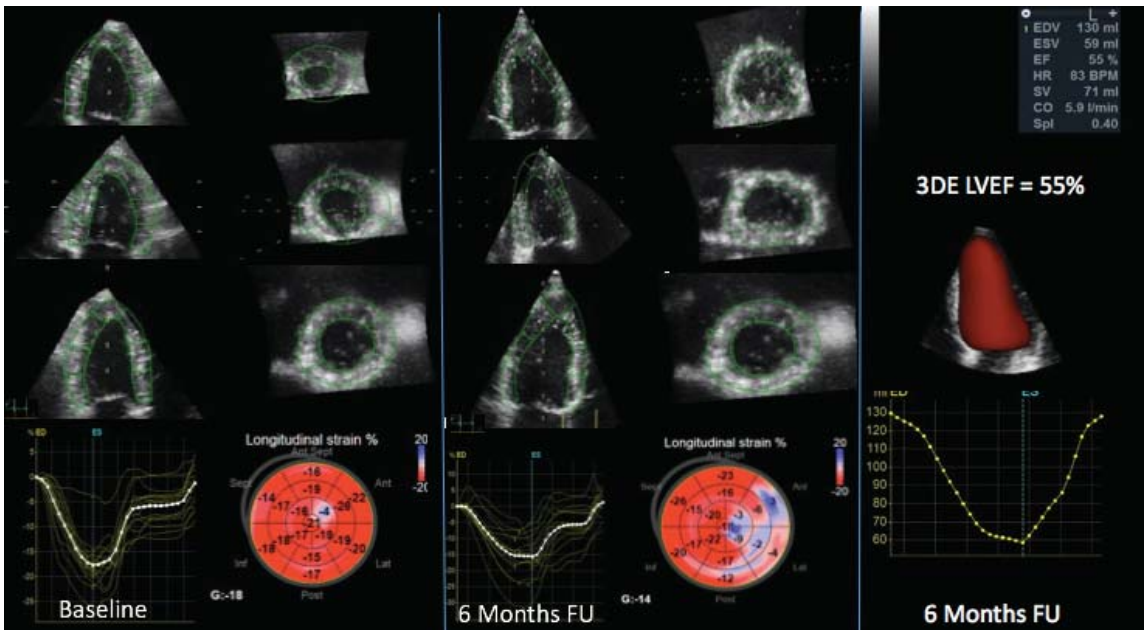

Figure 5. Detection of subclinical cancer treatment-related cardiac dysfunction by three-dimensional global longitudinal strain (GLS) in a patient with non-Hodgkin lymphoma. Compared to the measurements performed at baseline (GLS= -18%, left panel), the study performed at 6 months after anthracycline regimen start showed impairment of GLS (-14%) despite a preserved left ventricular ejection fraction. The patient was asymptomatic. 3DE, three-dimensional echocardiography; FU, follow-up; LVEF, left ventricular ejection fraction.

applications[30,32]. Given its higher feasibility and larger body of evidence, 2DSTE should be used for routine clinical purposes when assessing LV function in patients treated with potentially cardiotoxic regimes[5].

3D analysis requires training and experience, which adds the need of specific expertise in acquiring adequate LV 3D data sets, both playing an important role in the reliability of inter-observer reproducibility for 3D measurements, including strain[66]. The clinical role of fully automated algorithms to obtain LV volumes and strain parameters from both 2DE[67] and 3DE[18,68] data sets of the LV remain to be established with properly designed outcome studies.

Although various preliminary studies have reported the usefulness of 3DSTE strain parameters, a systematic comparison of 3DE and 2DE strain parameters feasibility, reproducibility and accuracy to detect subclinical CTRCD has never been carried out. A multicenter study, with an adequate sample size to compare 3DSTE to 2DSTE in cancer patients should be designed to provide clinical evidence. The results may impact the clinical use of 3DSTE and may be useful in the design of future chemotherapeutic safety test trials.

At present, recommendations concerning cardiac function monitoring of cancer patients are based on expert consensus statements. Prospective controlled outcome studies are urgently required to provide data, which can support recommendations.

Finally, including new echocardiographic parameters (e.g. GLS) and echocardiographic techniques (STE and 3DE) into clinical cardio-oncology trials may ultimately prove useful in defining the cardiotoxic profile of new and existing chemotherapeutic agents. Being able to identify subclinical CTRCD may support the identification of patients who can benefit by closer surveillance during and after exposure to potentially cardiotoxic chemotherapy, decreasing the number of cardiac complications and further increase the life expectancy of patients suffering from cancer.

CONCLUSIONS

Although 2DE LVEF is widely used for cardiac function monitoring in clinical practice, it has sown low sensitivity and suboptimal reproducibility in detecting subclinical CTRCD.

3DE has overcome many limitations of 2DE and has significantly improved the accuracy of LV volumes and function measurements to become the method of choice to measure LVEF.

The detection of early myocardial impairment (e.g. when LVEF is still preserved) is crucial to start early treatment and improve the patients prognosis. 2DSTE GLS measure the extent of longitudinal myocardial deformation, this myocardial function can be impaired at early stages of CTRCD, when LVEF is still normal. Since it is highly feasible and there is a large body of evidence

showing its predictive power for subsequent LV dysfunction and heart failure, 2DSTE should be used together with LVEF to monitor LV function, especially in patients treated with potentially cardiotoxic regimes.

3DSTE strain has potentialities to become the imaging technique of the future to assess LV function. However, to translate the use of 3DSTE from research to clinical routine in the cardio-oncological field, we need more outcome studies to show its added value compared to 2DSTE to predict CTRCD.

Finally, current recommendations concerning cardiac function monitoring of cancer patients are largely based on expert consensus statements. Prospective controlled trials are urgently required to provide references to support dedicated guidelines for the early detection, prevention and treatment of CTRCD.

Abbreviations

2DE	two-dimensional echocardiography
2DSTE	two-dimensional speckle tracking
3DE	three-dimensional echocardiography
3DSTE	three-dimensional speckle tracking
ASE	American Society of Echocardiography
CMR	cardiac magnetic resonance
CTRCD	cancer-therapeutic related cardiac dysfunction
EACVI	European Association of Cardiovascular Imaging
GLS	global longitudinal strain
HF	heart failure
LV	left ventricle
NT-pro BNP	brain natriuretic peptide
LVEF	left ventricle ejection fraction
STE	speckle tracking echocardiography
TDI	tissue Doppler imaging

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