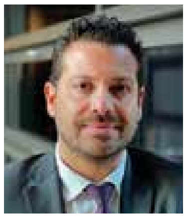
CARDIO-ONCOLOGY SERIES

Three-dimensional echocardiography in cardio-oncology: an increasingly promising field


Ana Ferreira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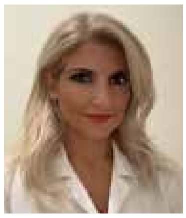
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Echocardiography stands as the recommended primary modality for assessing cardiac function in patients with cancer. It assumes a critical role in baseline cardiotoxicity risk assessment before initiating any cancer treatment and remains indispensable throughout treatment for early detection of cancer therapy-related cardiac dysfunction (CTRCD).[1] Among echocardiographic techniques, three-dimensional (3D) echocardiography (3DE) emerges as the preferred modality for evaluating left ventricular (LV) and right ventricular (RV) volumes and ejection fraction (EF). Expanding beyond CTRCD, both 3D transthoracic (TTE) and transesophageal echocardiography (TOE) serve as invaluable tools for detailed assessment of cardiac masses and valvulopathies associated with cancer, such as carcinoid heart disease (CHD) (Figure 1).

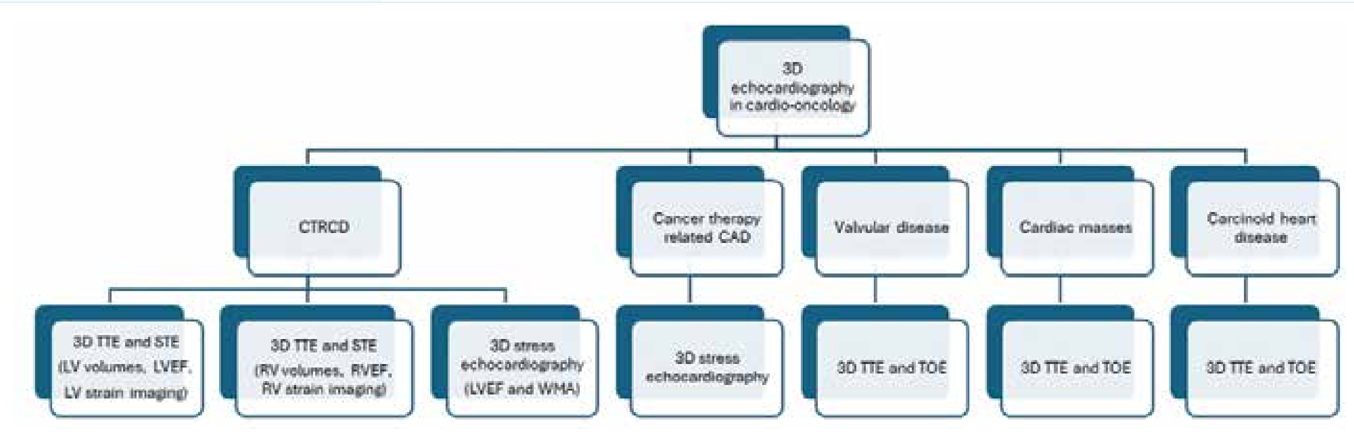

Fig 1. Applications of three-dimensional (3D) echocardiography in cardio-oncology.

CTRCD: cancer therapy-related cardiac dysfunction, CAD: coronary artery disease, TTE: transthoracic echocardiography, TOE: transesophageal echocardiography, LVEF: left ventricular ejection fraction, LV: left ventricular, RV: right ventricular, RVEF: right ventricular ejection fraction, STE: speckle tracking echocardiography, WMA: wall motion abnormalities.

3D assessment of the Left Ventricle

Despite its well-established role in assessing LV function, two-dimensional (2D) echocardiography (2DE) comes with notable limitations such as geometric assumptions, foreshortening, malrotation, angulation and inappropriate visualisation of the apex. These drawbacks can result in inaccuracies in volumetric measurements. 3D imaging of the LV provides volume and EF measurements independent of LV shape (Figure 2). Semi-automated evaluation of 3DLVEF has minimised the temporal variations in EF measurements by enhancing both intra- and interobserver consistency, as well as test-retest reliability.[1, 2] Indeed, 3DLVEF, compared to 2DLVEF, has better temporal variation (3% vs. 5%) in stable patients receiving chemotherapy[1] in a 12-month follow-up period. Furthermore, 3DLVEF has demonstrated potential superiority in identifying subclinical cardiotoxicity in cancer patients receiving anticancer treatment earlier than 2DLVEF.[3, 4]

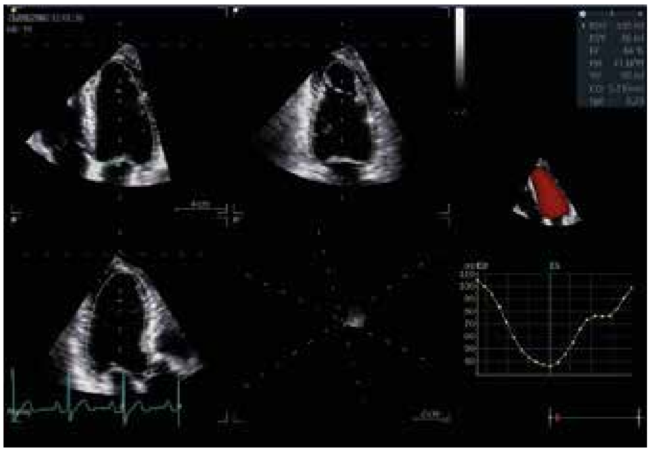

Fig 2. Three-dimensional assessment of left ventricular volumes and ejection fraction.

3D Speckle Tracking Echocardiographic Imaging

3D speckle tracking echocardiographic (STE) imaging can track out-of-plane motion of speckles, has a higher reproducibility of measurements, and allows for a simultaneous evaluation of all strain parameters (longitudinal, circumferential, radial and area strain, twist and torsion) from a single volumetric data set, effectively reducing the time needed[5-8] (Figure 3). 3DSTE can predict changes in 2DLVEF,[9] independently of 2D strain parameters.[3] Coutinho Cruz et al showed that in breast cancer patients receiving anthracyclines, worsening of 3DSTE parameters, with predominant involvement of septal, anterior, and inferior walls, were predictive of CTRCD.[10] This finding is consistent in several other studies confirming the prognostic role of 3D LV strain in CTRCD.[9, 11-15]

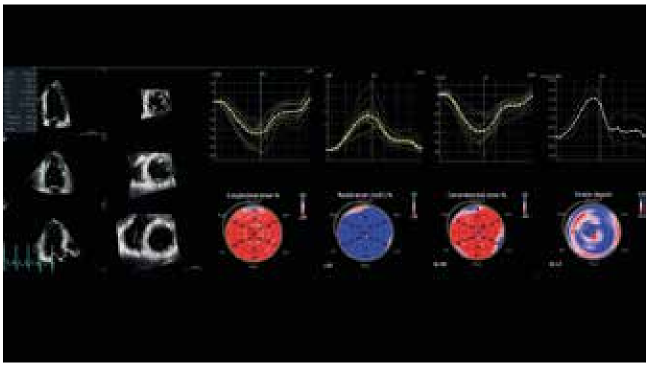

Fig 3. Three-dimensional speckle tracking imaging of the left ventricle.

Real time 3D stress echocardiography

Real time 3D stress echocardiography (RT-3D-SE) has certain advantages compared to two-dimensional stress echocardiography (2DSE). It is faster with reduced operator dependence, requiring only a single acquisition of the entire LV. Compared to the standard 2DSE protocol, which may encounter misalignment of myocardial segments and foreshortening of the LV, RT-3D-SE enables a more accurate assessment of the entire true LV by cropping volumetric datasets along the correct axes. The added value of RT-3D-SE in treadmill exercise SE lies in the ability to acquire peak stress images before the heart rate goes down, which may reduce the sensitivity of the method at detecting ischemia. With RT-3D-SE, this is feasible since a complete dataset can be acquired from a single apical window (Figure 4).[16] SE can have significant applications in cardio-oncology: identification of subclinical cardiotoxicity[17-25] and detection of vascular damage and coronary artery disease in patients receiving fluoropyrimidines, platinum compounds, Vascular Endothelial Growth Factor (VEGF) inhibitors, Tyrosine Kinase Inhibitors (TKIs) and/or radiotherapy.[21]

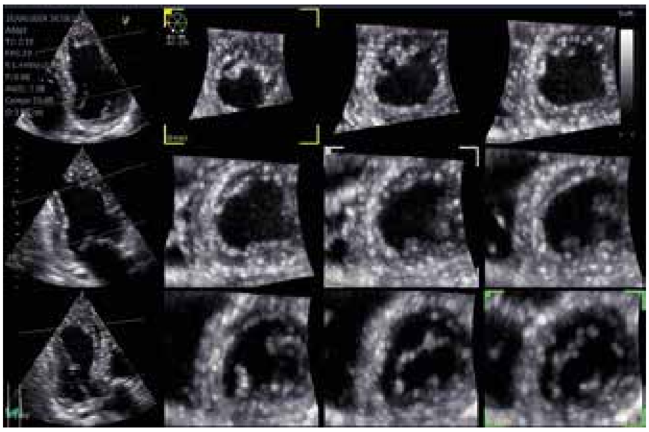

Fig 4. Multislice real-time three-dimensional stress echocardiography for ischemia detection in cancer patients under cancer treatment.

3D assessment of the Right Ventricle

The impact of cancer treatments extends to the right ventricle (RV) as well. Accurate quantification of RV volumes and function by 2D remains challenging, due to the complex shape of the RV, along with prominent endocardial trabeculae, which pose difficulties in identifying the endocardial boundaries in single cut-planes. The ability of 3DE to measure RV volumes without the need for geometric modeling has resulted in improved accuracy[26] and good correlation with CMR findings (Figure 5).[2, 27, 28] Changes in 3D RV strain and volumes are associated with subsequent changes in RVEF,[29] CTRCD[30] and cardiac adverse events.[31] In breast cancer patients, 3DRVEF, 3DLVEF and 3D strain of both ventricles are decreased concomitantly,[32] in correlation with the 2D measured longitudinal strain.[33]

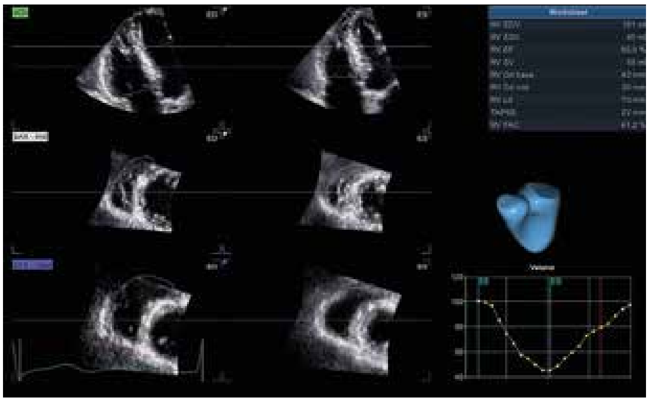

Fig 5. Three-dimensional assessment of right ventricular volumes, ejection fraction and strain.

3D echo in the assessment of Cardiac Masses

Cardiac masses include benign and malignant (primary or secondary) tumors, thrombi, vegetations and normal variants, like displaced papillary muscles and chiari network.[34] 2DE is typically the first diagnostic method used for the differential diagnosis of cardiac masses. However, the reconstruction of 3D masses with irregular shapes by 2D can pose challenges, even when employing multiple planes. On the contrary, 3D is superior to 2D as it enables panoramic and comprehensive views of the masses, facilitating accurate assessment of size, extent, attachment of the mass and evaluation of the anatomical relationships with adjacent structures.[35] Currently, the newest versions of echo machines can potentially provide similar imaging quality between 3D TTE and TOE, so it is always recommended when available, to acquire a complete 2D/3D TTE protocol first before moving to TOE evaluation of masses (Figure 6A-6E).

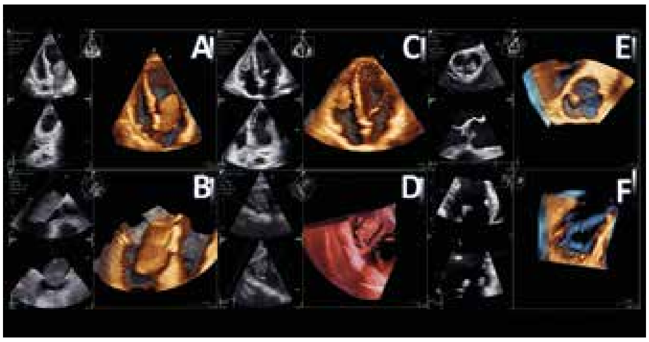

Fig 6 A to F. A) Full volume 3D TTE assessment of a left atrial myxoma attached to the fossa ovalis, B) 3D TOE assessment of a left atrial myxoma attached to the fossa ovalis moving through the mitral valve in diastole, C) full volume 3D TTE assessment of a right ventricular mass, D) 3D TOE transgastric views of a right ventricular mass attached to the RV free wall, E) 3D TOE en face view of aortic valve with papillary fibroelastoma attached to the left coronary cusp, F) 3D TTE en face ventricular view of a tricuspid valve affected by carcinoid syndrome.

3D echocardiography in the assessment of Carcinoid Heart Disease

Echocardiography is the first modality used to diagnose cardiac involvement in carcinoid syndrome. 3DE, has some important advantages over 2D assessment in carcinoid, as it enables better imaging of the right heart structures, which are usually affected. It also allows simultaneous assessment of all leaflets of the affected valves, detailed imaging of the subvalvular apparatus and the surrounding structures (e.g. post-stenotic dilatation of the pulmonary artery) and accurate calculation of RVEF.[36-38] 3D enface views of the right-sided valves are comparable to the surgical ones and 3D imaging may aid in pre-operative planning of patients with carcinoid (Figure 6F).[39] Myocardial metastases, although rare in carcinoid syndrome, may be depicted by 3DE, even though CMR is more sensitive in identifying them.[40]

How to

There are several modalities of acquisition of a 3D dataset: a) simultaneous 2D multiplane (also known as biplane or triplane), b) Real-time-3D (also known as narrow/live 3D, single beat), c) multi-beat electrocardiogram (ECG)-gated full-volume acquisitions, d) 3D colour Doppler, e) focused wide sector ("zoom" mode).[35, 41] RT-3D involves capturing multiple pyramidal datasets per second in a single heartbeat. Although it overcomes limitations posed by rhythm disturbances or respiratory motion, it has drawbacks like poor temporal and spatial resolution especially when the sector width and elevation are wide.[41] Conversely, multiple-beat 3D imaging offers improved temporal resolution by combining multiple acquisitions of narrow data volumes across several heartbeats. 3D TTE and TOE full-volume acquisition mode has the capability to encompass the majority of cardiac structures within a single dataset. However, expanding the volume angle to capture the entire heart from one acoustic window results in a reduction in both spatial-temporal resolution and penetration, making this method inappropriate for correct 3D analysis. To overcome these constraints, it is recommended to acquire images focused on the structure of interest (eg RV or a mass) and store 3DE datasets from multiple positions.[41] For correct post-processing of the images, chambers quantification requires a frame rate (FR) > 20 volumes per second (vps), while valves or masses can nicely be assessed with a lower FR of ≥ 12 vps. The newest generation machines have been designed to achieve a single-beat acquisition with a FR of > 10 vps without compromising the spatial resolution.

Left and Right Ventricle

Acquiring a 3D echocardiographic dataset of the entire ventricle typically takes less than 10 seconds. Although all conventional echocardiography acquisition windows are accessible and valuable for 3D acquisitions, the apical 4-chamber view is typically favoured for obtaining a complete-volume ventricular dataset. Adjusting transducer frequency and overall gain ensures optimal image quality. Full-volume multi-beat (4 or 6 beats) acquisition while holding breath, minimises the risk of stitching artifacts and allows for higher temporal and spatial resolution. When LV is the chamber of interest, contrast opacification may help in poor acoustic windows.[41] Manual corrections to the endocardial border can be made, followed by semiautomated blood endocardial interface detection algorithm, allowing for volume-versus-time curve calculation. Subsequently, in LV assessment, a 3D representation of the chamber is generated (boitel), allowing for the calculation of LV volume based on voxel counts without relying on geometric assumptions.[41, 42] Adequate temporal resolution identifies the true end systole and diastole and allows for correct volumetric calculations.[43]

For obtaining the 3D RV pyramidal dataset, either a single-beat or multi-beat approach from the RV-focused apical 4-chamber view can be employed. RV volumes and EF derived from 3D datasets show strong correlation with measurements from the RV-focused view, given the entire RV can be captured.[2, 28] Despite incremental enhancements in accuracy and reproducibility over 2DE, volumes from 3DE still tend to underestimate compared to CMR.[2, 43]

Tips and tricks for Optimal 3D Imaging

- Ensure proper patient positioning to optimise imaging quality. Adjustments may be needed to accommodate patient comfort and facilitate accurate imaging acquisition.
- Capture images with the probe consistently positioned and during end-expiration for stability.
- A high-quality ECG trace with a clear R-wave is essential for an accurate 3D full-volume triggering.
- Optimise the sector size (azimuth and elevation level) and depth of the image according to the structure that will be analysed.
- Chambers are ideally evaluated with full-volume images while masses and valves need a "zoom" acquisition.
- Calibrate gain levels effectively, as insufficient gain may lead to echo "dropout artifacts", while excessive gain compromises resolution and diminishes the 3D perspective or depth in the dataset. The optimal gain set includes the elimination of the static noises, with preservation of anatomic structures. It is however widely recommended for all 3D acquisitions to be slightly over-gained.
- Optimise FR and adjust number of sub-volumes based on patient's breath-holding capability. A multi-beat acquisition of 4-6 cardiac cycles usually provides adequate FR and spatial resolution for post-processing.
- Crop the images with caution to remove redundant tissues and expose the structure of interest.
- Consider the use of contrast agents to improve endocardial border delineation and enhance visualisation of cardiac structures, particularly in patients with suboptimal image quality or difficult acoustic windows. Contrast agents are necessary for the evaluation of cardiac masses and differentiation from thrombus. Full-volume images with LV opacification are of low spatial and temporal resolution with the current vendors and 3D contrast echo is recommended in biplane and triplane imaging.
- Develop standardised image acquisition protocols to maintain consistency across studies and facilitate comparison of serial imaging assessments.

Limitations of 3D echocardiography

The limitations of 3DE primarily stem from challenges in achieving optimal image quality, particularly evident in certain patient groups, such as those who have undergone left mastectomy for cancer, with or without a prosthesis, as well as in elderly or obese individuals. Additionally, deterioration of image quality over time can significantly hinder the feasibility of 3DE during follow-up assessments.[6] While 3DE offers the advantage of simultaneously assessing ventricular volume, EF, and 3D strain, it lags behind 2DE in both temporal and spatial resolution and requires the acquisition of multiple consecutive beats. Furthermore, in cases of severe LV dilatation, capturing the entire LV myocardium presents challenges due to conflicting requirements for adequate image quality, FR, and sector width. Variations in 3D LVEF calculation between different equipment vendors must also be considered, particularly in the serial assessment of cancer patients.[46] Ideally, consistent use of the same machine and analysis software should be employed for a given patient across different time points.[47] The presence of arrhythmias such as atrial fibrillation, supraventricular, and ventricular ectopic beats introduce significant beat-to-beat variability, rendering STE precarious.

Finally, patient or respiratory motion, as well as irregular cardiac rhythms make it prone to imaging stitching artifacts.

Conclusion

The evolution of 3DE from a complex research tool to a rapid and accessible imaging technique has transformed everyday clinical practice with specific applications in cardio-oncology. Accurate assessment of biventricular volumes, EF and STE imaging, enables the prediction or diagnosis of CTRCD, even at subclinical stages. Moreover, due to its superior visualisation, it plays a pivotal role in the evaluation of valvular disease and cardiac masses. Overall, the widespread adoption of 3DE has revolutionised the practice of cardio-oncology, offering clinicians a powerful tool for the early detection, accurate diagnosis, and comprehensive management of cardiovascular complications associated with cancer therapy.

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