CARDIO-ONCOLOGY SERIES

GLS – How to/Tips and Tricks/ Limitations – Cardio-Oncology Considerations?

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Introduction

Cardio-oncology is the study of cardiovascular complications of cancer and cancer therapies, including chemotherapy, radiotherapy, immunotherapy and other targeted therapies. Cardiovascular complications include cardiomyopathy, heart failure, arrhythmia, hypertension, thromboembolism, and myocardial ischaemia. With improvement in cancer survival, the importance of long-term cardiovascular side effects of cancer therapies is increasingly recognised.[1]

Heart failure related to cancer therapies, termed cardiotoxicity, is a serious complication impacting cancer patients' prognosis. Early detection and management of cardiotoxicity are important in minimising morbidity and mortality in cancer survivors. This requires close collaboration between oncologists, cardiologists and echocardiographers to monitor cardiac function before, during, and after cancer treatment.

Global longitudinal strain (GLS) is an important parameter to evaluate cardiac function, in particular ventricular performance.[2,3] It is normally assessed by speckle tracking echocardiography. Speckle tracking enables accurate quantification of myocardial strain by measuring the deformation of the myocardium along the longitudinal axis of the heart throughout the cardiac cycle. GLS has emerged as a sensitive indicator of myocardial dysfunction, often detecting abnormalities even when traditional measures like ejection fraction remain unchanged.[4]

Clinical Perspective

The 2022 ESC Guidelines on cardio-oncology give clear recommendations about the use of GLS in cardio-oncology.[5] Baseline left ventricular ejection fraction (LVEF) and GLS are recommended in all patients evaluated with transthoracic echocardiography before potentially cardiotoxic cancer treatment initiation for risk stratification and to assess the significance of any changes during treatment. There is a Class I recommendation that GLS is incorporated into the assessment for all patients with cancer undergoing echocardiography, if available.

The guidelines state: *"A normal LVEF does not exclude cancer related cardiac dysfunction (CTRCD) and deformation parameters can detect early systolic impairment with sufficient test reliability. Determination of GLS using speckle tracking is recommended at baseline, using three apical views, particularly in moderate- and high-risk patients. Baseline GLS can predict left ventricular dysfunction in patients receiving anthracyclines and/or trastuzumab. Strain measurements may be subject to inter-vendor variability and serial GLS measurement for each patient is recommended to be performed using the same machine/software. A median GLS change of 13.6% predicted a future fall in LVEF with a 95% upper limit of GLS reduction of 15%. Using the 15% cut-off improves specificity and is therefore the threshold recommended when monitoring GLS during cancer therapy".*

The definitions for asymptomatic CTRCD also refer to GLS. Moderate CTRCD as defined by a new LVEF reduced by ≥10 percentage points to an LVEF of 40–49% OR new LVEF reduced by <10 percentage points to an LVEF of 40– 49% **AND either new relative decline in GLS by >15% from baseline** OR new rise in cardiac biomarkers. Mild CTRCD is defined as a LVEF ≥ 50% **AND new relative decline in GLS by >15% from baseline** AND/OR new rise in cardiac biomarkers.

1. Standard views

All images used for LV GLS analysis are obtained from the apical window as part of the BSE minimum dataset for an adult transthoracic echocardiogram (TTE).[6] These include the four chamber (A4C), two chamber (A2C) and long axis (APLAX). It is acknowledged that apical images allow for visualisation of all LV walls and segments in the 17-segment model and are more reproducible than parasternal images which are utilised for radial or circumferential assessment.[7]

TIP

1. Speckle tracking works better along the ultrasound beam rather than across the beam, as in standard imaging planes. Therefore, non-standard views or off-axis views are not recommended, even though GLS is less angle dependent than other techniques.[2]

2. Two-dimensional image quality, optimisation, and frame rate

Knowledge and practice of 2D image optimisation is essential when performing GLS. Poor 2D images will produce inaccurate data, but we must be mindful this is often dictated by patient body habitus, no matter how much optimisation we perform. Visualisation of the epicardium and endocardial border for the entire cardiac cycle is essential for robust GLS analysis, as it allows the machine software to track speckles in the reference frame of the 2D image with greater accuracy.

TIPS

1. Use machine settings on all ultrasound machines to maximise myocardial definition, for example, gain, compression, and noise reduction.
2. Breath hold techniques are useful to minimise translation of the heart in and out of the imaging plane and reduce artefact generated by excess noise or rib/lung movement that may confuse the tracking software.

3. Image width and depth should be adjusted to ensure focus on the whole chamber of interest. Another advantage of this is temporal resolution will be maximised and thus frame rate, which should be between 40-90 frames per second (fps).
4. For heart rates above 100bpm, greater frame rates will be needed, however, software tracking accuracy is potentially erroneous at higher heart rates.
5. Lower frame rates and temporal resolution may result in erroneously reduced GLS due to myocardial speckle drop out.
6. Avoid apical foreshortening. Often a result of an inadequate echocardiographic window or insufficient sonographer experience, it occurs when the imaging plane does not cut through the true LV apex, therefore producing an abnormally thickened apex and shortened LV length. This has the potential to over-estimate apical strain as the apex appears hypercontractile.

3. Region of interest (ROI)

Selection and accurate plotting of the correct anatomical landmarks are essential for the accurate tracking of the ROI. This can be subjective and performed by the user or automated and selected by the machine software, with the option of post-acquisition editing.

TIPS

1. It is essential to encompass the whole myocardial layer due to the individual role each plays in LV contraction.
2. If the ROI is too thin, encompassing only the endocardial layer, strain values will be too high.
3. Conversely, if the ROI is too thick, encompassing the pericardium, this will result in abnormally low strain.
4. Careful placement of the start and end point of ROI is also important. In the A4C view this should begin at the septal/lateral mitral annulus and extend to the LV apex. In the A2C view it should begin at the inferior/anterior mitral annulus and extend to the LV apex and finally in the APLAX view, it should begin at the posterior MV annulus, LV apex, then to the base of the septal wall taking care not to extend into the LVOT which would reduce strain.
5. Care should be taken not to fall below MV annular level into the LA as this too will reduce strain.
6. Tracking of papillary muscles or trabeculation may increase strain value, therefore attention must be paid to ensure the accurate tracing of the endocardial border.
7. Compare the underlying 2D image to the overlying tracking results. Have any of the above pitfalls occurred? If so, adjust where necessary and reprocess the analysis.

4. Event timing

Correct recognition of end diastole (mitral valve closure) and end systole (aortic valve closure) is imperative for successful and accurate GLS calculation. It is common for software to automatically calculate event timing by recognising aortic valve closure in the APLAX view or peak R-wave on the ECG as a surrogate for MV closure. This may however cause timing inaccuracies in patients with conduction delays.

TIP

1. Study aortic valve closure on the 2-D image and label appropriately before initiating analysis.[8]

5. Results interpretation

The analysis software generates several different outputs when GLS is calculated, namely peak systolic strain, strain rate curves, bull's-eye (BE) plots and colour M-mode. Each method provides clinically relevant information and clues for the user as to whether the analysis has been performed correctly.

TIPS

1. Peak systolic strain is most widely used in clinical practice. It is the average GLS for each anatomical view analysed (A4C, A2C and APLAX) and should be quoted in the echocardiogram report.
2. Strain rate curves allow for direct visualisation of individual segment tracking during each cardiac phase. Here, clear outliers can be easily identified, therefore repeating the process to rectify any tracking inaccuracies should produce a more accurate analysis.
3. Segments that persistently do not track can be excluded from overall strain calculation (method varies with vendor) however it is recommended that this is used cautiously. Excluded segments will display an "X" in the affected apical view and on the corresponding segment in the BE plot.
4. BE plots allow the user to visualise segmental strain based on the 17-segment model. Values are colour coded, with high negative strain values dark red and low strain values light blue or white. BE plots may also provide direct visual information as to the pattern of LV dysfunction or dyssynchrony present e.g. general global reduction in strain values as seen in cardio-toxicity or patterns related to specific pathologies e.g. high apical strain values with low basal-mid LV segment strain values in cardiac amyloidosis.
5. Colour m-mode plots display grading of regional strain using the same colour spectrum as the BE plot.

6. Recommended normal values

The most commonly used LV strain parameter in clinical practice is GLS, which is central to the BSE/BCOS guidance for echocardiography in adult patients receiving anthracyclines and/or trastuzamab.[9]

TIPS

1. This document defines normal GLS as -17% or more negative for males and -18% or more negative for females. It is recognised, however, that defining abnormal GLS is not straightforward as values vary with age, sex, loading conditions, and machine vendor.
2. The document considers a relative change in sequential GLS >15% (e.g. -22% to -18%) to be significant, with each patient acting as their own control.

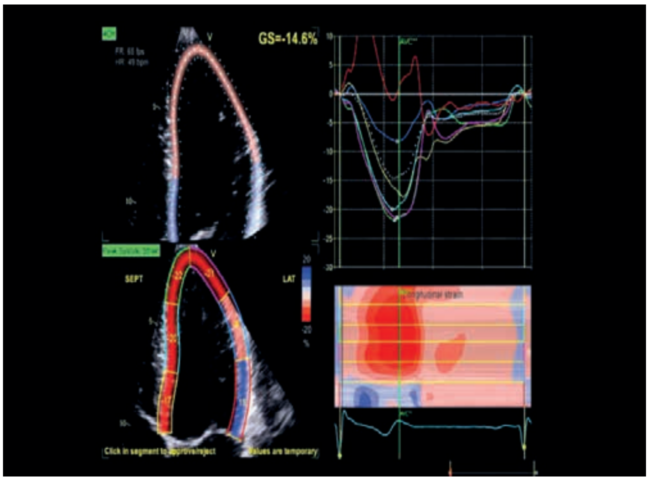

Fig 1. The whole LV epicardium and endocardium is visible during systole and diastole. In this example, the basal and mid anterolateral wall segments leave the scan plane resulting in incorrect strain calculation of +15% and -8% respectively. The strain timing graph is subsequently abnormal.

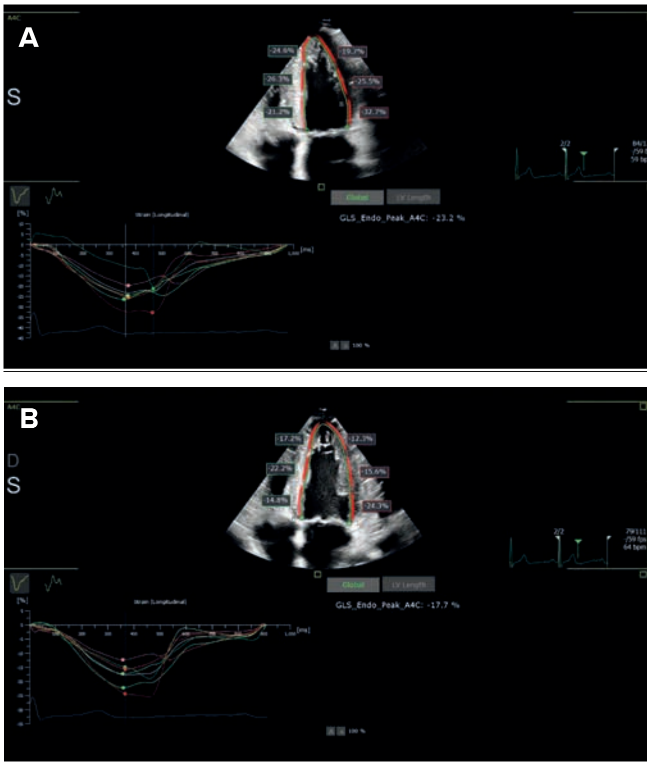

Fig 2. Strain is incorrectly increased for the anterolateral wall in image A due to poor tracking from lung artefact. Image B was recorded with a breath hold to increase image quality and tracking accuracy. Note the difference in the timing on the strain graph between the two examples.

Table 1. Shows an outline of the echo considerations, tips, advantages and inaccuracies when corrections are not performed.

Echo considerations	Tips	Advantages	Challenges if not corrected
1. Standard views	Apical window as per standard adult BSE protocol	Standardised approach	Non-standard imaging planes
2. Two-dimensional image quality, optimisation, and frame rate.	Whole LV epi and endocardium can be seen during systole and diastole	Ensures full myocardial tracking	Segments/walls may be missed and excluded from analysis (Figure 1)
	Adjust gain, compression and noise reductions	Well-defined myocardium and valves	Over or under use of these settings will reduce myocardial definition
	Breath-hold techniques	Image stabilisation	Introduce lung/rib artefact and translation of heart (Figure 2)
	Adjustment of width and depth	Increases frame rate and temporal resolution	Frame rate and temporal resolution insufficient therefore tracking inaccurate.
	Avoid foreshortened LV apex	True apex is tracked	Overestimation of strain in apical segments (Figure 3)
3. Region of interest (ROI)	Correct recognition of landmarks and appropriate inclusion of the whole myocardial layer	Ensures appropriate structures/ myocardial layers are included in analysis	ROI too thin -strain too high ROI too thick-strain too low (Figure 4) Inclusion of LA and LVOT – strain lowered Tracing papillary muscles and trabeculation- strain too high
4. Event timing	Manual recognition of aortic valve closure	Accurate in patients in sinus rhythm and those with conduction delays	Clinically significant variation in strain if end diastole and end systole are wrongly identified
5. Results interpretation	Report peak systolic strain in report. Use strain curves and bull's-eye plot/colour m-mode to inspect tracking and regional LV dysfunction. Exclude poorly tracked segments with caution.	Able to correct poorly tracked segments. Visual outputs give clues to pathology.	Incorrect strain value reported. Too many segments excluded. Poorly tracked segments included in GLS calculation.
6. Recommended normal values	Normal GLS as -17% or more negative for males and -18% or more negative for females. Each patient acts as their own control in serial studies.	Drop in GLS of >15% seen as clinically significant. Recognition of age, gender, blood pressure and using the same machine considered essential.	Loading conditions not considered when change in GLS. Cross-vendor scanning.

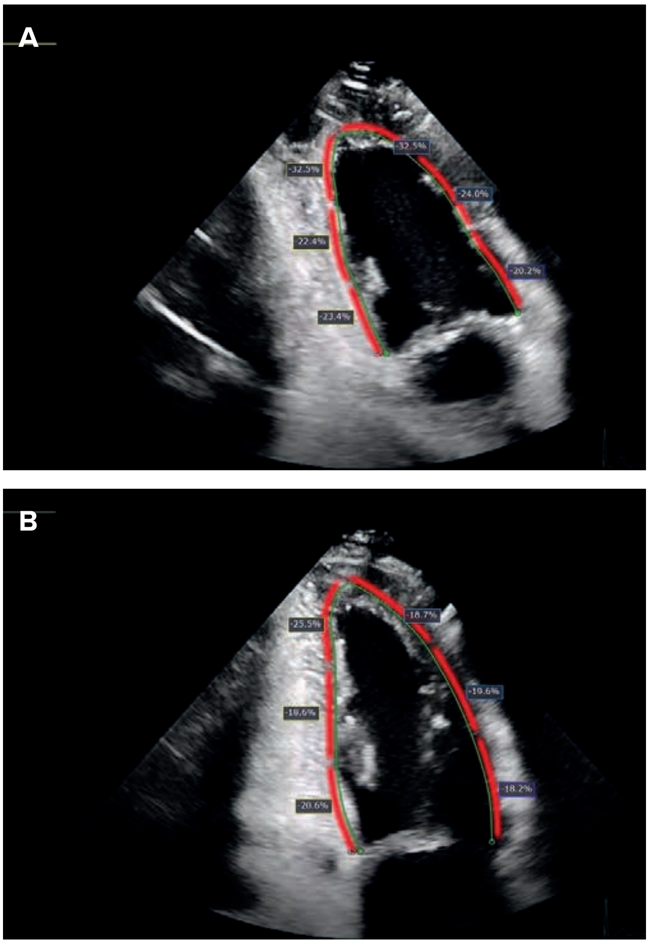

Fig 3. LV apex is foreshortened in image A which over-estimates apical strain. Image B is on axis with the correct strain values calculated.

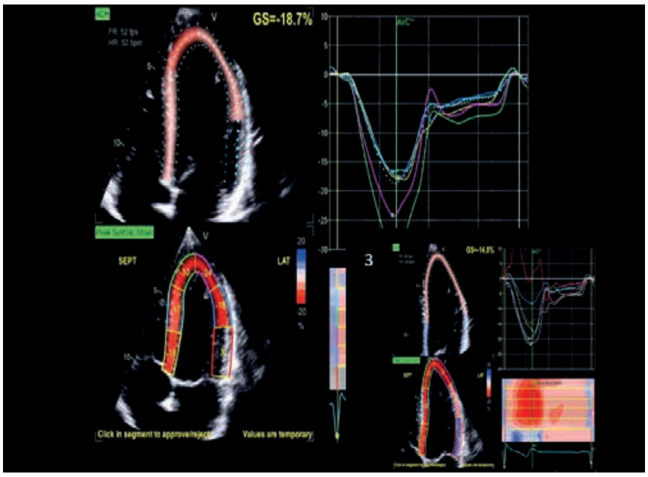

Fig 4. Sector width for the basal anterolateral segment is incorrectly too broad which will reduce accuracy of calculated GLS.

Conclusion

GLS is a key component of the cardio-oncology echocardiogram and following the 2022 ESC Guidelines should be incorporated when feasible. Care is required for accurate measurement. GLS is an early marker of cardiac dysfunction related to cancer therapies and can help to optimise cancer and heart failure management for patients.

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