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VIEWPOINT

Straining for More Evidence

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Left ventricular (LV) dysfunction is the most well-recognized example of cancer therapy-related cardiac dysfunction (CTRCD). It can directly harm the patient and prevent them from receiving gold standard cancer treatment. In 1 of the early trastuzumab trials, "cardiac dysfunction" occurred in 27% of patients who received trastuzumab and an anthracycline, including NYHA functional class III to IV heart failure in 16%.[1] Accordingly, patients receiving these agents are closely monitored so that heart failure therapy can be promptly initiated and cancer therapy reviewed if required. In addition, it has been hypothesized that monitoring for early or "subclinical" signs of dysfunction may prevent subsequent deterioration. In this Viewpoint, we discuss some of the reasons why the effectiveness of this strategy is yet to be proven and how current-day monitoring could be refined.

Echocardiography remains the most useful method for monitoring patients receiving potentially cardiotoxic cancer therapy. Left ventricular ejection fraction (LVEF) is a well-established measure used in clinical practice and incorporated within the CTRCD definition. One of the main limitations of LVEF is the large coefficient of variation, which limits its sensitivity for detecting small changes in LV function. Prospective studies have reported that declines in global longitudinal strain (GLS) can occur in the absence of significant changes in LVEF and can then predict subsequent LV dysfunction.[2] Identifying an early decline in GLS could provide clinicians the opportunity to alter management and prevent CTRCD. Therefore, significant expectation has been placed on GLS as a monitoring tool in patients receiving cancer therapy. A limitation of the current data supporting GLS is that they are derived from very small patient populations, although meta-analyses have been performed. One of these included 21 different studies and found that both relative and absolute changes in GLS were associated with increased risk of future CTRCD, with adequate sensitivity and specificity.[3] However, all but 4 of the studies included had <100 participants, and significant heterogeneity was identified with regard to inclusion criteria, cancer type and treatment, and the definition of CTRCD. Importantly, a significant potential for publication bias was also noted. These limitations highlight the need for larger prospective studies, which was acknowledged by the authors.

Despite evidence suggesting that changes in GLS have prognostic utility to predict CTRCD, the benefit of changing management based on such a change to prevent CTRCD has not been shown. This was investigated in the pivotal SUCCOUR (Strain surveillance of chemotherapy for improving cardiovascular outcomes) trial, which randomized patients to start cardioprotective therapy based on either an LVEF- or GLS-guided monitoring strategy.[4] Some of the findings were positive, such as a post hoc analysis of those patients who ultimately received cardioprotective therapy having a higher LVEF in the GLS-guided arm. However, the primary outcome of LVEF at 1 year in the overall trial population was no different between the 2 arms nor was the rate of having LVEF <55% at 1 year. This was despite the fact that over twice as many patients in the GLS-guided arm received cardioprotective therapy. The SUCCOUR results were surprising to many given the promising data that formed the basis for conducting the trial. As the authors state in the 3-year follow-up report, 1 reason for the lack of benefit in the GLS-guided arm could be the low event rates.[5] We agree with this and would add that the potential limitations of GLS in a clinical setting could also be a reason.

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ABBREVIATIONS AND ACRONYMS

CTRCD = cancer therapy-related cancer dysfunction

GLS = global longitudinal strain

LV = left ventricular

LVEF = left ventricular ejection fraction

These 2 points are discussed in subsequent sections of this article. Given the SUCCOUR results and a lack of other trial data, at this stage we do not know the best way to proceed when a patient has a significant decline in GLS and whether changing management based on identifying an isolated reduction in GLS can lead to improved outcomes.

There are limitations that could affect the practical utility of GLS both in the setting of a trial and even more so in the real world. Strain imaging requires specialized training and resources, and there is variability in software processing by different vendors. Analysis is also dependent on operator selection of images and the myocardial region of interest for analysis. Strain parameters seem to depend on loading conditions and ventricular volumes,[6] and an early meta-analysis of normal values reported that 1 of the most important causes of variation was blood pressure.[7] The acquisition of optimal images at optimal heart rates is also required. A prospective study of image quality for GLS analysis in patients with breast cancer found that images were suboptimal or inadequate in 48% of echocardiograms.[8] Technology will no doubt improve, and artificial intelligence may reduce the effect of some of these limitations, but for now all these factors limit the practical utilization of GLS in the real-world oncology setting.

Despite the previously discussed points, GLS monitoring has been recommended by many guidelines over the past decade including the inaugural 2022 European Society of Cardiology cardio-oncology guidelines, which gave a Class 1 recommendation for GLS to be used in all patients with cancer when undergoing echocardiography.[9] More specifically, they recommend echocardiographic monitoring including GLS in all patients receiving an anthracycline or trastuzumab regardless of baseline risk. However, the guidelines do limit the practical use of GLS as a tool to diagnose mild asymptomatic LV dysfunction, a diagnosis similar to "subclinical dysfunction." Although the guidelines do not explicitly suggest altering management based solely on GLS changes, a Class 2a recommendation is given to initiating cardioprotective therapy. The 2022 European Society of Cardiology guidelines were a milestone for the field of cardio-oncology and provide a comprehensive overview of all practical aspects in the field, which was certainly needed. Clinicians around the world will take strong guidance from the recommendations, particularly with regard to monitoring for CTRCD. As such, we may see an increase in both the use of GLS and its impact on clinical decisions. Therefore, it is vital we obtain more data on how GLS is being practically used today, especially given its limitations and the lack of evidence for a clinically significant benefit in clinical trials. We need data on how often GLS is being used, its ability to predict CTRCD, and what treatment decisions are being made based on GLS results.

Recent data suggest the incident rate and prognosis of CTRCD secondary to anthracyclines and trastuzumab may in fact be improving. A meta-analysis of modern trials of cardioprotective medications in anthracycline patients found that the mean decrease in LVEF was only 5.4% in the placebo arms.[10] This will impact both the clinical effectiveness and cost-effectiveness of certain monitoring strategies, such as those evaluated in SUCCOUR. If the incidence and outcomes of CTRCD are now more favorable, then monitoring strategies may need to adapt, and intensely monitoring all patients may not be necessary. A strategy that aims to identify subclinical dysfunction could theoretically even cause harm (especially if the real-world specificity is low). Making clinical decisions based on the results of a test that does not have high positive predictive value could lead to increased patient anxiety, unnecessary heart failure therapy, or, worse, unnecessary cessation of cancer therapy. The intensity of a monitoring strategy must depend on the incidence and severity of the condition being detected. We need more contemporary data regarding the rates and prognosis of CTRCD to guide the development of practical and safe monitoring strategies.

Now may be the time to refine monitoring by investigating strategies beyond isolated GLS-based assessment for subclinical dysfunction in all patients. Biomarkers such as troponin and B-type natriuretic peptide have shown promise but have not been adopted into widespread use, and although cardiac magnetic resonance imaging offers many advantages, it may not be practical. Therefore, echocardiography is likely to remain the core monitoring tool given its accessibility and extent of information provided. A targeted echocardiographic strategy using baseline stratification of risk could be 1 way to improve current-day monitoring. How would we identify high-risk patients though? The SUCCOUR trial did attempt to enroll only high-risk patients based on cancer treatment and demographic factors, but there were difficulties with this approach. Almost all participants had breast cancer and were included

TABLE 1 Future Research Goals to Help Improve Cardiotoxicity Monitoring

Goals	Approaches	Rationale
Acquire data on real-world use of GLS monitoring.	Descriptive studies: 1. Frequency of use of GLS monitoring 2. Rates of subclinical dysfunction and subsequent clinically overt LV dysfunction 3. Management of subclinical dysfunction identified by GLS	GLS monitoring is recommended by major guidelines despite a lack of trial data supporting a clinically useful benefit. We need to understand how this monitoring strategy is currently being used.
Confirm contemporary rates and outcomes of CTRCD.	Observational studies on rates of CTRCD using trial, registry, or retrospective data.	If rates and outcomes are improving, then monitoring strategies should adapt. The benefit of monitoring all patients for subclinical dysfunction with GLS may not outweigh the cost and potential harms.
Identify baseline risk predictors of CTRCD.	Retrospective analyses of association between baseline cancer, clinical, and echocardiographic variables and CTRCD. Development of risk scores. Prospective assessment of rates of CTRCD stratified according to baseline risk.	May enable accurate baseline risk stratification to inform targeted monitoring strategies.
Test the utility of targeted monitoring strategies.	Feasibility of risk stratifying and selectively monitoring high-risk patients (requiring effective collaboration between cardiologists and oncologists). Clinical trials assessing the safety and efficacy of targeted monitoring.	Possible benefits: 1. Reduced cost 2. Reduced inconvenience to patients 3. Reduced potential harms of a nontargeted strategy.

CTRCD = cancer therapy-related cardiac dysfunction; GLS = global longitudinal strain; LV = left ventricular.

based on the need for trastuzumab therapy in addition to anthracycline chemotherapy rather than the presence of cardiovascular risk factors, the rates of which were low. Other groups that often receive anthracycline chemotherapy with recommendations to undergo echocardiographic monitoring were under-represented in the trial. This includes patients with HER2-negative cancers (who account for approximately 80% of breast cancer patients) and patients with hematologic malignancies. These groups accounted for only 12% and 9% of the SUCCOUR trial population, respectively. The lessons are that there are limitations to stratifying risk using cancer treatment and demographic factors alone, and this approach may not actually be effective at identifying high-risk patients because the event rates in the SUCCOUR trial were low.

A patient's pretreatment echocardiogram could also enhance baseline risk stratification, but this has been relatively understudied. There are some data that suggest a low-normal ejection fraction or reduced average GLS at baseline is associated with an elevated risk of subsequent LV dysfunction.[11] We need more data to confirm this and to elucidate other echocardiographic predictors. Although not currently recommended or practiced, a targeted monitoring strategy in only higher-risk patients using a combination of cancer treatment, demographic, and baseline echocardiographic factors merits consideration. We agree with the SUCCOUR authors who concluded the paper reporting their 3-year follow-up by stating a "more selective imaging strategy for surveillance is warranted."[5] The standard 3-monthly frequency of monitoring may also need to change in this setting. Furthermore, whether a targeted monitoring strategy would rely on traditional LVEF assessment alone or in combination with GLS is unclear, and this should be tested. Although some of the concerns and limitations regarding GLS monitoring raised in this article would still be applicable, it is possible it may be of clinical benefit in a more selective group of patients undergoing more frequent testing.

In this Viewpoint, we highlight issues regarding how we currently monitor for CTRCD, which has remained relatively unchanged for the past 2 decades, and suggest areas where further research is needed, which are summarized in Table 1. GLS has shown great promise as a tool to enhance monitoring, and although guidelines support its use, there is still a lack of evidence for a clinically significant benefit. Therefore, we should aim to improve monitoring by considering other, more targeted strategies.

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