

Strain in Monitoring Cancer Therapy-Induced Cardiotoxicity: Where are We After the SUCCOUR Study?

Strain no Monitoramento da Cardiotoxicidade pela Terapia do Câncer: Onde Estamos após o Estudo SUCCOUR?

Cardioeco Cardiovascular Diagnostics Center,¹ Curitiba, PR; Quanta Diagnosis and Therapy,² Curitiba, PR; Brazilian Society of Cardiology,³ Rio de Janeiro - RJ; São Paulo State Cancer Institute,⁴ São Paulo-SP; Heart Institute, School of Medicine, University of São Paulo,⁵ São Paulo, SP, Brazil.



Silvio Henrique Barberato^{1,2,3}



Ludhmila Abrão Hajjar^{4,5}

In recent decades, advances in cancer treatment have led to a significantly increased survival rate for several types of cancer. On the other hand, cancer survival increases patients' vulnerability to cardiovascular complications induced by potentially cardiotoxic cancer therapy.^{1,2} Cardiovascular diseases are currently recognized as a main cause of morbidity and mortality in cancer survivors depending on the type of therapeutic approach used, patient age, and the presence of preexisting cardiovascular risk factors.³ Due to the high incidence of breast cancer in women, anthracyclines and monoclonal antibodies against human epidermal growth factor receptor type 2 (HER2) are the drugs most well-known as potential cardiotoxicity (CTX) inducers.⁴ However, other medications such as vascular endothelial growth factor inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, and immunological checkpoint inhibitors, in addition to mediastinal radiotherapy, are also recognized for having a possible deleterious effect on the cardiovascular system.⁴ It is worth mentioning that CTX can express not only as myocardial dysfunction but also as acute coronary syndrome, arrhythmia, valve disease, pericardial disease, systemic arterial hypertension, and pulmonary hypertension.⁵ Thus, although left ventricular (LV) systolic dysfunction secondary to anticancer therapy is not the only CTX presentation, its development is among the most worrisome in clinical

cardio-oncology practice, and the terms are often used interchangeably.

The diagnosis of LV dysfunction in a CTX setting is traditionally based on the serial evaluation of the LV ejection fraction (LVEF) using the Simpson method on two-dimensional echocardiography.⁶ Despite variation between international guidelines and cancer trials, the most commonly used CTX definition is a decrease of at least ten absolute points for a LVEF below the lower limit of normal after cancer treatment (considered below 53% by the cardiovascular imaging consensus of the European Association of Cardiovascular Imaging/American Society of Echocardiography [EACVI/ASE],⁷ or below 50% by the European Society of Cardiology [ESC]).⁸ However, LVEF measurements have important limitations, which include significant inter- and intra-observer variability, dependence on loading conditions, and low sensitivity to small LV function changes.⁹ Therefore, it was postulated that LVEF changes would occur later, when myocardial damage is severe enough to determine an irreversible cardiomyopathy.

Three-dimensional echocardiography and cardiac magnetic resonance imaging (CMRI) are more reliable and accurate imaging techniques in the assessment of LVEF in cancer patients since they are able to detect more subtle changes in cardiac function than traditional two-dimensional echocardiography.¹⁰ Despite their advantages, neither method is routinely used in daily clinical practice due to a lack of broad access and trained staff and their relatively high cost.¹¹ Thus, an accessible and sensitive tool in the daily routine to detect minor subclinical myocardial function is an unmet need.

Two-dimensional speckle tracking (2D-ST) can assess myocardial deformation as a marker of contractility. It can also estimate the LV global longitudinal strain (GLS), a robust and sensitive parameter to detect subclinical myocardial dysfunction. GLS has better reproducibility than LVEF by traditional 2D echocardiography and a greater correlation

Keywords

Antineoplastic agents; Cardiotoxicity; Echocardiography, Doppler.

Mailing Address: Silvio Henrique Barberato •

Avenida República Argentina, 1.336, sala 215 – Vila Izabel. CEP: 80620-010. Curitiba, PR, Brazil.

E-mail: silviohb@cardiol.br

Manuscript received 7/28/2021; revised 8/1/2021; accepted 8/16/2021

DOI: 10.47593/2675-312X/20213403eabc247

with LVEF calculated by CMRI.¹⁰ In general, a cutoff value $\geq -18\%$ (absolute value without the negative sign) is considered normal. Several studies have shown that an early GLS reduction predicts a subsequent LVEF decrease in patients on chemotherapy with anthracyclines.⁷ The currently most widely accepted definition for CTX diagnosis by GLS was proposed by the EACVI/ASE consensus and considers the relative variation of the parameter over time, comparing the baseline GLS with that obtained after treatment with the potentially cardiotoxicity-inducing drug. Thus, the presence of subclinical LV dysfunction is indicated when there is a relative decrease of more than 15% from the baseline GLS value. A relative decrease between 8% and 15% suggests more frequent patient follow-up, while variation below 8% is consistent with adequate cardiac function maintenance.⁹ GLS also has important limitations, including a strong dependence on image quality, vulnerability to load conditions and arrhythmias, and measurement variability between software from different equipment manufacturers. It is recommended that one always uses the same echocardiography machine brand and the same 2D-ST software version for the serial evaluation of GLS in the follow-up of the same patient.¹²

Despite intense research and the body of publications generated, consensus is still lacking on which echocardiographic parameter of LV systolic function should be used throughout cancer treatment to monitor CTX and appropriately indicate cardioprotective intervention. Several studies have described the relative variation and/or absolute value of GLS as predictors of LV dysfunction and worse prognosis, but there is little evidence to support the initiation of drug therapy with renin-angiotensin system inhibitors and/or beta-blockers guided by GLS changes.¹³ A study of HER2-positive breast cancer patients under adjuvant therapy suggested that the early detection of cardiac injury guided by GLS reduction can lead to total or partial recovery of LV function through appropriate interventions, such as the initiation of cardioprotective treatment and/or cancer therapy adjustment.¹⁴ However, the lack of a direct comparison between the two surveillance approaches (GLS versus LVEF) prevented the confirmation of the superiority of one method over the other to initiate drug treatment in asymptomatic patients with LV systolic dysfunction (stage B heart failure).

The randomized multicenter Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) study was designed to provide this answer by comparing two distinct CTX monitoring strategies for initiating cardioprotective therapy - the traditional one guided by LVEF and the new one guided by GLS. A total of 307 patients (91% with breast cancer, of which almost 88% were the HER2 type) treated with anthracyclines and stratified as at high risk for heart failure were followed up for one year. Beta-blockers and/or renin-angiotensin system inhibitors were administered when there was an LVEF decrease greater than ten points to an absolute value $< 55\%$ (or a decrease greater than 5% associated with symptoms) in any of the study arms or when there was a GLS relative decrease $\geq 12\%$ in the strain guided arm.

The primary outcome was the comparison of LVEF changes between the two groups over the course of the study. Secondary outcomes were the comparison of CTX incidence

(declining LVEF) and symptomatic heart failure in addition to chemotherapy completion rates. LVEF was obtained by three-dimensional echocardiography in most patients (in only 8% LVEF was obtained from 2D echocardiography). GLS was feasible in 100% of the sample at baseline and in 81% of patients at the end of the study. A worsening in the quality of thoracic acoustic window during cancer treatment impairs the use of the three apical planes necessary to calculate GLS and reflects a series of factors, such as left mastectomy, prosthesis or breast expander insertion, concomitant radiotherapy, and cachexia. After a one-year follow-up, there was no significant intergroup difference in LVEF changes, but fewer patients were diagnosed with CTX in the GLS-guided group (5.8% versus 13.7%, $p = 0.02$).¹⁵ Although the authors concluded that these results support the use of GLS for the early initiation of cardioprotective therapy, the editorial that accompanied the study was quite harsh in questioning such assumptions.¹⁶

Attention should be drawn to some important SUCCOUR limitations. The main point is that the study did not reach its primary outcome (the mean LVEF difference after a one-year follow-up was -3% for the LVEF arm and -2.7% for the GLS arm, $p = 0.69$). In addition, the finding of LVEF $< 55\%$ after one year did not differ between groups (21% versus 22%). The cutoff values used to define significantly decreased LVEF and GLS were not the ones most currently used, as the study design was established before the publication of the EACVI/ASE consensus. Thus, the sensitivity level for GLS change was higher than the one currently recommended. Furthermore, the short-term clinical impact can be questioned, as the outcome of hospitalization for heart failure was rare (only one patient in each group).

Another concern was that the incorporation of the concept of myocardial dysfunction by GLS led to therapy discontinuation in nine patients versus only five in the LVEF-guided group. Although these numbers reached no statistically significant difference, the tendency to interfere more with cancer therapy can be critical in the clinical outcome of individual cases. Finally, the GLS-based strategy resulted in the prescription of cardiac medications for more than twice the patients in this group versus the LVEF group. This fact should not be ignored in clinical practice due to the potential of causing side effects and financial impact on patients. Although a decreased GLS appears to be a predictor of further LVEF decline, the number of patients in the GLS arm that would develop CTX if untreated is unknown.

On the other hand, the results of the study published to date are limited to the temporal observation window of one year. It is known that doxorubicin and trastuzumab can lead to a modest but persistent LVEF decline up to three years after treatment.¹⁷ Further studies should determine whether an asymptomatic cardiac function decline will have a long-term impact on the development of heart failure symptoms, the need for hospitalizations, and mortality for cancer survivors. It is reasonable to assume that the heart subjected to subclinical cardiotoxic insult has a lower myocardial reserve and is more susceptible to cardiovascular complications in the long term. In addition to the CTX diagnosis, it is important to remember that the identification of a GLS decrease showed prognostic value in retrospective studies.¹⁸

Although SUCCOUR was an eagerly awaited study expected to change the current cardio-oncologic monitoring paradigm, the superiority of GLS in the management of patients at risk for CTX has not been categorically confirmed. Therefore, its final message should be addressed using an alternative approach. The current clinical approach of monitoring and waiting for an LVEF decrease by more than ten points to a value of $< 50\%$ and only then intervening does not seem to be late in practical terms. However, the information brought by the GLS, whose detection of subclinical dysfunction is welcome and must be considered within a careful and vigilant clinical approach, should not be discarded. The cardiology monitoring of cancer patients at moderate to high risk of heart failure should include

all of the tools available to the cardiologist. However, in services and/or situations in which GLS monitoring is not possible (due to the unavailability of the technique or in patients whose echocardiographic images are inappropriate for analysis), LVEF screening is the correct approach for the time being. Although GLS is more sensitive and reproducible, there seems to currently be no advantage for treating asymptomatic and stable cancer patients based exclusively on its findings.

Conflict of interest

The authors have declared that they have no conflict of interest.

References

- Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al.; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016 Sep 21;37(36):2768-801. doi: <https://doi.org/10.1093/eurheartj/ehw211>
- Hajjar LA, Costa IB, Lopes MA, Hoff PM, Diz MD, Fonseca SM, et al. Brazilian Cardio-oncology Guideline - 2020. *Arq Bras Cardiol*. 2020;115(5):1006-43.
- Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22(11):1945-60. doi: <https://doi.org/10.1002/ehf.1920>
- Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2017;35(8):893-911. doi: <https://doi.org/10.1200/JCO.2016.70.5400>
- Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the american and european cardio-oncology guidelines. *J Am Heart Assoc*. 2020;9(18):e018403. doi: <https://doi.org/10.1161/JAHA.120.018403>
- Barberato SH, Romano MM, Beck AL, Rodrigues AC, Almeida AL, Assunção BM, et al. Position Statement on Indications of Echocardiography in Adults - 2019. *Arq Bras Cardiol*. 2019;113(1):135-81. doi: <https://doi.org/10.5935/abc.20190129>
- Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27(9):911-39. doi: <https://doi.org/10.1016/j.echo.2014.07.012>
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38(36):2739-91. doi: <https://doi.org/10.1093/eurheartj/ehx391>
- Liu J, Banchs J, Mousavi N, Plana JC, Scherrer-Crosbie M, Thavendiranathan P, et al. Contemporary role of echocardiography for clinical decision making in patients during and after cancer therapy. *JACC Cardiovasc Imaging*. 2018;11(8):1122-31. doi: <https://doi.org/10.1016/j.jcmg.2018.03.025>
- Lambert J, Lamacie M, Thampinathan B, Alaha MA, Esmailzadeh M, Nolan M, et al. Variability in echocardiography and MRI for detection of cancer therapy cardiotoxicity. *Heart*. 2020;106(11):817-23. doi: <https://doi.org/10.1136/heartjnl-2019-316297>
- Stankovic I, Dweck MR, Marsan NA, Bergler-Klein J, Holte E, Manka R, et al. The EACVI survey on cardiac imaging in cardio-oncology. *Eur Heart J Cardiovasc Imaging*. 2021;22(4):367-71. doi: <https://doi.org/10.1093/ehjci/jeaa111>
- Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018;19(6):591-600. doi: <https://doi.org/10.1093/ehjci/jeu042>
- Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2020;22(9):1504-24. doi: <https://doi.org/10.1002/ehf.1957>
- Santoro C, Esposito R, Lembo M, Sorrentino R, De Santo I, Luciano F, et al. Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction. *Eur Heart J Cardiovasc Imaging*. 2019;20(12):1345-52. doi: <https://doi.org/10.1093/ehjci/jez194>
- Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, et al.; SUCCOUR Investigators. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. *J Am Coll Cardiol*. 2021 Feb 2;77(4):392-401. doi: <https://doi.org/10.1016/j.jacc.2020.11.020>
- Moslehi JJ, Witteles RM. Global Longitudinal Strain in Cardio-Oncology. *J Am Coll Cardiol*. 2021;77(4):402-4. doi: <https://doi.org/10.1016/j.jacc.2020.12.014>
- Narayan HK, Finkelman B, French B, Plappert T, Hyman D, Smith AM, et al. Detailed echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. *Circulation*. 2017;135(15):1397-412. doi: <https://doi.org/10.1161/CIRCULATIONAHA.116.023463>
- Melo MDT, Paiva MG, Santos MVC, Rochitte CE, Moreira VM, Saleh MH, et al. Posicionamento Brasileiro sobre o Uso da Multimodalidade de Imagens na Cardio-Oncologia – 2021. *Arq Bras Cardiol*. 2021;1-64. doi: <https://doi.org/10.36660/abc.20200266>