Global Longitudinal Strain as a Predictor of Chemotherapy-Induced Cardiotoxicity

Authors: Monica Samuel Avila, MD, PhD[b], Marco Stephan Lofrano Alves, MD, PhD[b], Silvia Moreira Ayub-Ferreira, MD, PhD[a], Mauro Rogerio de Barros Wanderley Junior, MD[a], Fatima das Dores Cruz, RN[a], Sara Michelly Gonçalves Brandão, RN[a], Ludhmila Abrahão Hajjar, MD, PhD[b,c], Roberto Kalil Filho, MD, PhD[b,c], Cecilia B.B. Vianna Cruz, MD[b,c], M. Cristina Abduch, VMD[b], Danilo Bora Moleta, MD, Edimar Alcides Bocchi, MD, PhD[a]

Affiliations:

a. Department of Heart Failure, Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

b. Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

c. Instituto do Câncer do Estado de São Paulo-USP, Brazil.

E mails: mo_avila@hotmail.com, mslalves@hotmail.com, silvia.ayub@incor.usp.br, maurowanderley@gmail.com, fatima.cruz@incor.usp.br, sara.brandao@incor.usp.br, ludhmila@terra.com.br, kalil@robertokalil.com.br, cbbvc@yahoo.com.br, abduchmc@gmail.com, dbmoleta@gmail.com, dcledimar@incor.usp.br.

Total Word Account: 3.379

DISCLOSURE STATEMENT

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the present manuscript.

FUNDING

No funding were used for this work.

Address for correspondence:
Monica Samuel Avila, MD, PhD
R. Dr. Eneas de Carvalho Aguiar 44
São Paulo Brazil, 05403900
E-mail: mo_avila@hotmail.com
Telephone and fax number: +551126615419
Twitter @monicaAGrinberg

Abstract

Background: Chemotherapy-induced cardiotoxicity (ChC) is an important complication among patients receiving anthracyclines. Biomarkers and imaging parameters have been studied for their ability to identify patients at risk of developing this complication. Left ventricle global longitudinal strain (LV-GLS) has been described as a sensitive parameter for detecting systolic dysfunction, even in the presence of preserved left ventricle ejection fraction (LVEF).

Objective: to evaluate the role of the LV-GLS as a predictor of ChC.

Methods**:** This study is a *post-hoc* analysis of CECCY trial (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity) that evaluated the primary prevention of cardiotoxicity with carvedilol during doxorubicin chemotherapy in a population with breast cancer. Cardiotoxicity was defined as a reduction ≥10% in LVEF. LV-GLS was obtained before chemotherapy in patients with no prior cardiovascular disease or echocardiogram abnormalities.

Results: Thirty-one patients who had a complete echocardiography study including measurement of LV-GLS before chemotherapy were included in this analysis. An absolute LV-GLS <16.9% before chemotherapy showed 100% sensitivity and 73% specificity for predicting cardiotoxicity (AUC=0.85; 95%CI 0.680 – 0.959, p<0.001). In this population, LVEF values before chemotherapy did not predict ChC (95%CI 0.478 to -0.842, p=0.17). The association of low LV-GLS (<17%) and BNP serum levels (>17 pg/mL) two months after chemotherapy increased the accuracy for detecting early onset ChC (100% sensitivity, 88% specificity, AUC=0.94; 95%CI 0.781 – 0.995, p<0.0001).

Conclusions: Our data suggest that LV-GLS is a potential predictor of chemotherapy-induced cardiotoxicity. Larger studies are needed to confirm the clinical relevance of this echocardiographic parameter in this clinical setting.

Keywords: Cardiotoxicity; Chemotherapy, Prevention, β-blockers, Echocardiogram, Strain

Acronyms and Abbreviations

ANT	anthracycline
BNP	brain natriuretic peptide
ARB	angiotensin receptor blocker
LV	left ventricular/ventricle
LVEF	left ventricular ejection fraction
LV-GLS	left ventricle global longitudinal strain
HF	heart failure
ACEi	angiotensin–converting-enzyme inhibitor
BP	systemic blood pressure
TnI	troponin I

Introduction

Cardiovascular effects of chemotherapeutic agents are responsible for a significant proportion of severe complications, particularly among female patients with breast cancer(1). One of the most widely used agents, (2, 3) anthracyclines (ANT), is responsible for early and late dose-related cardiotoxicity, particularly heart failure (HF). (4-6)

The detection of cardiotoxicity is routinely performed by left ventricular (LV) ejection fraction (EF). Although LVEF predicts the occurrence of heart failure, this parameter has limited sensitivity. (7) Failure in detect subtle changes in LV systolic function occurs for many reasons: need of geometrical assumptions for calculations, possible inadequate visualization of LV apex, impossibility in identifying marginal regional wall motion abnormalities and intrinsic variability of measurements. (8) Decreased LVEF after chemotherapy is often a sign of an already extensive myocardial damage and heart failure. (9)

Due to increased morbidity and mortality among patients with chemotherapy-related heart failure, markers with higher sensitivity for subclinical cardiac dysfunction and myocardial injury have been investigated to detect chemotherapy-induced cardiotoxicity. For this purpose, the evaluation of two-dimensional speckle-tracking imaging has emerged. This technique allows for a study of global and regional myocardial deformation. Several studies have already emphasized the role for left ventricle global longitudinal strain (LV-GLS) to detect subtle alterations in systolic function particularly related to anthracyclines chemotherapy. (10) The evaluation of GLS for detection of subclinical LV dysfunction induced by chemotherapy treatment is recommended by expert consensus. (11)

In the face of this new field accessing anthracycline induced cardiotoxicity using LV-GLS we conducted a *post-hoc* analysis of the randomized, double-blind placebo-controlled

CECCY CECCY (Carvedilol Effect in Preventing Chemotherapy Induced CardiotoxicitY) trial, which aim was to evaluate the LV-GLS before anthracycline chemotherapy as a predictor of cardiotoxicity.

Methods

Study design

This study is a *post-hoc* analysis of the randomized, double-blind placebo-controlled CECCY trial (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity) that evaluated the primary prevention of cardiotoxicity with carvedilol during doxorubicin chemotherapy in women with breast cancer. Cardiotoxicity was defined as a reduction ≥10% in LVEF. Patients were included and followed up in two different institutions, Heart Institute (InCor) and Cancer Institute (ICESP) from University of Sao Paulo, Sao Paulo, Brazil. The institutional review board of both institutions approved the trial protocol. All participants were informed about the research objectives, research protocol, treatment alternatives involved in the study, and all participants provided written informed consent to participate in the study. The trial was registered at the ClinicalTrials.gov (NCT01724450) before study initiation.

Study patients

CECCY Trial included patients with HER2-negative breast cancer tumor status and therapy that included anthracycline, cyclophosphamide, and taxane from April 2013 to January 2017. The standard chemotherapy protocol comprised four cycles of cyclophosphamide 600 mg/ m^2 and doxorubicin 60 mg/m^2 every 21 days (with a total cumulative dose of 240 mg/m^2), followed by paclitaxel 80 mg/m^2 weekly for 8 weeks. The design and results of the trial were described previously.(12)

Study procedures

The present *post hoc* analysis include only patients who underwent echocardiography studies and accomplished follow up at the Heart Institute from the University of Sao Paulo where the institutional protocol included speckle tracking echocardiography. Eligible patients underwent a comprehensive transthoracic echocardiography before starting chemotherapy including proper imaging acquired to perform strain analysis. Echocardiographic studies were performed with a commercially available system Vivid E9 (General Electric, GE-Vingmad Ultrasound AS), equipped with a 2-5 MHz transducer. All the measurements were performed and reported according to the recommendations of the American Society of Echocardiography (Lang 2015, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging). Left ventricular ejection fraction was measured by Simpson's rule.

For speckle tracking analysis, images were acquired with an adjusted device to record three cardiac cycles within a period of 100 msec before and after the cycle. The second harmonic image, in grayscale, with a frame rate of 40-80 frames/s were used. In order to measure LV-GLS, cardiac images were obtained through the apical windows (APLAX, A4C and A2C). After acquisition, studies were stored for offline analysis with the EchoPAC software (General Electric, GE-Vingmad Ultrasound AS). The analysis is performed for the sixteen LV segments, and the quantitative longitudinal strain is presented for each segment and for the whole LV during a cycle cardiac. All scans were read by experienced board certified echocardiographers who were blinded to all clinical information.

Statistical analysis

The data are expressed as median and 95%CI. We tested the normality of a variable distribution using the D'Agostino-Pearson test. For comparisons between two independent samples, an unpaired *t* test was used for variables with Gaussian distribution, and the Mann-Whitney rank sum test was applied for variables with non-Gaussian distribution. For comparison between paired samples with Gaussion distribution the paired t-test was used, while in non-Gaussian distribution the Wilcoxon matched pairs rank test was used. We used receiver operating characteristic (ROC) curve analysis to determine the accuracy and optimal cutpoints. The best cutpoint for each variable was chosen through the shortest distance from the upper left angle to the curve obtained in the graph of the ROC curve by the method of DeLong et al.(13) A p value <0.05 was considered significant.

Results

In this *post-hoc* analysis of the randomized, double-blind placebo-controlled CECCY trial we evaluated 31 patients who underwent speckle tracking echocardiography. The baseline characteristics of the patients are described in Table 1. In this group, 3 (9.7%) developed cardiotoxicity (LVEF decrease ≥10% from baseline). LV-GLS predicted the development of cardiotoxicity (cutoff value ≤16.9%), with 100% sensitivity and 73.1% specificity (AUC 0.859, p <0.001). Serum BNP >16 pg/mL measured 2 weeks after starting chemotherapy was also associated with cardiotoxicity, with sensitivity of 100% and specificity of 69.2% (AUC 0.878, p <0.001) (Figure 1, Central Illustration). On the other hand, baseline LVEF (AUC 0.680, p = 0.17) and serum troponin (AUC 0.577, p = 0.69) were not associated with the incidence of cardiotoxicity.

Table 2 shows the median and 95%CI values for serum LVEF, BNP and troponin before and after 2, 4 and 24 weeks after starting chemotherapy, stratified according to baseline LVGLS. Baseline LVEF was not significantly different in patients with LV-GLS ≤16.9% or >16.9%. Similarly, there was no difference on baseline BNP or troponin values in the two groups. However, LVEF was significantly lower after 4 weeks of chemotherapy in the group with baseline LV-GLS ≤16.9% ($p = 0.003$). Furthermore, serum BNP measured after 4 weeks of chemotherapy treatment was higher in the group with LV-GLS ≤16.9% ($p = 0.004$). There was no significant difference for troponin values at any of the time points between the two groups.

Figure 2 shows median and 95%CI for LVEF and LV-GLS before and after 12 months after chemotherapy. We observed that LV-GLS showed significant decrease from baseline values ($p=0.005$), which did not occur with LVEF. In the follow up period after chemotherapy, LV-GLS decreased more than 5% and 10% from baseline in 77% and 66% of patients, respectively. While LVEF decreased more than 10% in only 9.7% of patients.

Discussion

In this *post-hoc* analysis of the randomized, double-blind placebo-controlled CECCY trial that evaluated the role of the speckle tracking echocardiogram in the anthracycline-induced cardiotoxicity, the measurement of the LV-GLS is a potential predictor of chemotherapy-induced cardiotoxicity in patients with low prevalence of cardiovascular comorbidities and risk factor for cardiovascular disease. In this scenario, LV-GLS showed to be a better predictor of cardiotoxicity than the LVEF. Also, the combination of LV-GLS and BNP during the follow-up could be a predictor of cardiotoxicity.

There has been great interest in the early detection of cardiotoxicity to reverse and prevent cardiomyopathy related to chemotherapy.(14) Left ventricular ejection fraction is known to be a strong predictor of cardiac events, but it lacks sensitivity for the detection of subclinical changes in cardiac function. (15) Strain is defined as change in the length of the myocardium divided by the original length of the myocardium and peak systolic deformation between systole and diastole.(16) Global longitudinal strain has emerged as the main measurement of subclinical myocardial disfunction and demonstrated utility in predicting subsequent reductions in LVEF in patients after cancer treatment. (7, 17, 18) Ali MT et al.(7) demonstrated that LV-GLS absolute value less than – 17.5% was associated with an increase of heart failure in patients with hematologic cancer undergoing anthracyclines chemotherapy. Charbonnel et al (10) showed that a LV-GLS greater than -17.45% obtained after 150 mg/m2 of anthracycline therapy is an independent predictor of future cardiotoxicity.

Our study is also in concordance with other studies that showed the strain measure before chemotherapy predicts the development of cardiotoxicity. (17)

Recently, the SOCCOUR trial compared cardioprotection guided by changes in LV-GLS *versus* LVEF in patients undergoing anthracycline chemotherapy. In the trial, 331 patients were randomized to receive angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers and beta-blockers guided by ≥ 12% relative reduction in LV-GLS (GLS-guided arm) or 10% absolute reduction in LVEF (EF guided arm). Patients were followed for LVEF and cancer therapy-related cardiac dysfunction (symptomatic drop of >5% or asymptomatic drop of >10% to <55%). At one year of follow-up, the LVEF did not change significantly in both groups. However, in the GLS-guided arm there was a greater use of cardioprotection and fewer patients met the cardiotoxicity criteria (5.8% vs. 13.7%; p = 0.02). Patients who received cardioprotection

in the EF-guided arm had a larger reduction in LVEF at follow-up than in the GLS-guided arm (9.1 ± 10.9% *vs*. 2.9 ± 7.4%; p = 0.03) supporting the use of GLS in surveillance for cardiotoxicity. (19)

Other biomarkers have been studied as a strategy for early detection and monitorizing cardiotoxicity. The most studies biomarkers in cardiotoxicity are the troponin and the B-type natriuretic peptide. Regarding troponin there is a strong evidence that favors this biomarker in predicting cardiotoxicity and cardiac events. (20, 21) However, the utility of BNP for chemotherapy-related cardiotoxicity remains controversial with many studies reporting no prognostic value for BNP in this scenario. (22) Our study showed that the combination of the LV-GLS pre-chemotherapy with BNP during follow-up (until 24 weeks) could be a greater predictor of a decrease in the LVEF greater than 10%. However, the combination of LV-GLS with troponin showed no prognostic value to cardiotoxicity.

Limitations

This study is a post hoc analysis of CECCY trial, so the findings were not pre specified. We also included a small sample size due to difficulties in obtain the images of the strain. In addition, we had low incidence of cardiotoxicity that could impair the results.

Conclusion

Measurement of the LV-GLS is a potential predictor of chemotherapy-induced cardiotoxicity in patients with low prevalence of cardiovascular comorbidities and risk factor for cardiovascular disease. Left ventricular global longitudinal strain showed to be a better predictor of cardiotoxicity than the LVEF and a combination of LVGLS and BNP during the follow-up could be a predictor of cardiotoxicity. Overall, our findings confirm the ability of LV-GLS in detecting subclinical cardiotoxicity and emphasize the need of early evaluation of LV-GLS to detect cardiotoxicity.

Clinical Competencies in Patient Care and Procedural Skills, and System Based Practice. In patients undergoing ANT chemotherapy, left ventricle global longitudinal strain a potential predictor of chemotherapy-induced cardiotoxicity. Moreover, the association of low LV-GLS and BNP serum levels two months after chemotherapy increased the accuracy for detecting early onset cardiotoxicity

Translational Outlook. Our study could stimulate the development of new methodology to diagnose myocardial injury during chemotherapy.

References

1. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13(3):R64.

2. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol. 2015;12(9):547-58.

3. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89.

4. Suter TM, Ewer MS. Cancer drugs and the heart: importance and management. Eur Heart J. 2013;34(15):1102-11.

5. Valachis A, Nilsson C. Cardiac risk in the treatment of breast cancer: assessment and management. Breast Cancer (Dove Med Press). 2015;7:21-35.

6. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart. 2018;104(12):971-7.

7. Ali MT, Yucel E, Bouras S, Wang L, Fei HW, Halpern EF, et al. Myocardial Strain Is Associated with Adverse Clinical Cardiac Events in Patients Treated with Anthracyclines. J Am Soc Echocardiogr. 2016;29(6):522-7.e3.

8. Santoro C, Arpino G, Esposito R, Lembo M, Paciolla I, Cardalesi C, et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. Eur Heart J Cardiovasc Imaging. 2017;18(8):930-6.

9. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55(3):213-20.

10. Charbonnel C, Convers-Domart R, Rigaudeau S, Taksin AL, Baron N, Lambert J, et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity. Eur Heart J Cardiovasc Imaging. 2017;18(4):392-401.

11. 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. Eur Heart J Cardiovasc Imaging. 2014;15(10):1063-93.

12. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR, das Dores Cruz F, Gonçalves Brandão SM, Rigaud VOC, et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. J Am Coll Cardiol. 2018;71(20):2281-90.

13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.

14. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981-8.

15. 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.

16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14.

17. Clasen SC, Scherrer-Crosbie M. Applications of left ventricular strain measurements to patients undergoing chemotherapy. Curr Opin Cardiol. 2018;33(5):493-7.

18. Thavendiranathan P, Amir E. Left Ventricular Dysfunction With Trastuzumab Therapy: Is Primary Prevention the Best Option? J Clin Oncol. 2017;35(8):820-5.

19. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021;77(4):392-401.

20. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol. 2010;28(25):3910-6.

21. Zamorano JL, Lancellotti P, Muñoz DR, Aboyans V, Asteggiano R, Galderisi M, et al. [2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines]. Kardiol Pol. 2016;74(11):1193-233.

22. Chaudry M, Banchs J, Chavez-MacGregor M. Anthracycline or trastuzumab-related cardiotoxicity: do we have a predictive biomarker? Biomark Med. 2016;10(3):315-28.

Legends of Figures

Figure 1. ROC curves analysis for LVGLS measured before the onset of chemotherapy (A) and BNP after 2 weeks of chemotherapy (B) and their association with cardiotoxicity. BNP - brain natriuretic peptide, LV-GLS - left ventricle global longitudinal strain (Central Illustration)

Figure 2. Median and 95% CI for LVGLS and LVEF before and after 12 months of chemotherapy. LV-GLS - Left ventricle global longitudinal strain, LVEF- Left Ventricular Ejection Fraction

Table 1. Baseline characteristics of the study population

Characteristic	Population (n=31)
Age – year +	51 ± 9.69
Menopause – no. of patients (%)	
Pre menopause	14 (45)
Post menopause	17 (55)
Therapy – no. of patients (%)	
Neoadjuvant	17 (55)
Adjuvant	14 (45)
Drug carvedilol - no. of patients (%)	18(48)
Body-mass index (Kg/m2) +	27.1 ± 7.45
Cardiovascular risk factors – no of patients (%)	
Hypertension	1 (3.2)
Diabetes mellitus	1 (3.2)
Hypercholesterolemia	1 (3.2)
Current/Past smokers	11 (35.4)
Systolic blood pressure (mmHg) +	121 ± 12.46
Diastolic blood pressure (mmHg) +	79 ± 8.1
Heart rate (b.p.m.) +	79 ± 11.5
Serum troponin I baseline ng/ml + +	0.005 (0.005-0.005)
Serum BNP pg/mL++	14 (7.0-20.0)

+ Data are expressed as mean + SD or numbers.

++ Data expressed in median (p25-75)

Table 2. Evolution of LVEF, serum troponin and BNP after 2, 4 and 24 weeks of chemotherapy divided by LVGLS value before chemotherapy

	LVGLS ≤16.9% (N=10)	**LVGLS >16.9% (N=21)**	***p* value**
LVEF before ChT, %	61.5 (59.9-64.0)	63.5 (60.9-64.4)	NS
LVEF 2-weeks, %	61.0 (58.2-66.0)	65.0 (62.8-67.0)	NS
LVEF 4-weeks, %	58.0 (56.1-62.9)	61.2 (62.5-65.5)	0.003
LVEF 24-weeks, %	63.0 (53.0-68.9)	63.0 (61.0-64.9)	NS
BNP before ChT, pg/mL	18.0 (7.42-46.9)	12.0 (9.2-19.2)	NS
BNP 2-weeks, pg/mL	19.0 (1.24-46.9)	9.0 (6.2-16.5)	NS
BNP 4 weeks, pg/mL	16.0 (-11.2-88.3)	13.0 (8.8-21.8)	NS
BNP 24 weeks, pg/mL	18.5 (-39.9-167.7)	8.0 (5.7-10.7)	0.004
Troponin before ChT, mg/mL	0.005 (0.003-0.011)	0.005 (0.004-0.006)	NS
Troponin 2-weeks, mg/mL	0.008 (0.005-0.016)	0.005 (0.006-0.011)	NS
Troponin 4-weeks, mg/mL	0.029 (0.014-0.077)	0.028 (0.025-0.054)	NS
Troponin 24-weeks, mg/mL	0.024 (0.015-0.048)	0.016 (0.009-0.037)	NS

LV-GLS - Left ventricle global longitudinal strain. LVEF - Left ventricle ejection fraction; ChT-chemotherapy; BNP – brain type natriuretic peptide.