# THE ADDED VALUE OF LEFT ATRIAL STRAIN IN CANCER-THERAPY-RELATED CARDIAC DYSFUNCTION

Laura Romero[1] and Michele Nanna[1]

[1]Cardiac Care & Vascular Medicine

April 02, 2024

THE ADDED VALUE OF LEFT ATRIAL STRAIN IN CANCER-THERAPY-RELATED CARDIAC DYSFUNCTION

By

Laura Romero, MD and Michele Nanna, MD

Albert Einstein Coll of Med/ Cardiac Care and Vascular Medicine, Bronx, NY

Correspondence:

Michele Nanna, MD,

Associate Professor of Medicine, Albert Einstein College of Medicine/ Cardiac Care and Vascular Medicine

1461 Astor Ave, Bronx, NY 10469, USA

Email: mnannamd@cardiovascularcare.org

Cancer-therapy-related cardiac dysfunction (CTRCD) is an undesirable side effect of chemotherapy that occurs in approximately 10% of the patients [1]. Targeting early detection and advances in treatment increases cancer survivors [2]. The American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines recommend the use of Speckle-Tracking-derived LV Global Longitudinal Strain (LV-GLS) as a more objective and accurate method to identify subclinical LV deterioration in patient undergoing chemotherapy [3].

In cancer patients, assessment of Left Atrium (LA) function by Speckle Tracking has emerged as a potential tool for predicting CTRCD and its associated morbid arrhythmias such as atrial fibrillation (AF), a frequent complication in this patient population [4-6].

Early research work used volumetric approaches to derive LA function parameters. Volumetric parameters are widely used in standard clinical practice and current guidelines assigns prognostic value to end-systolic LA volume in patients with suspected LV diastolic dysfunction [3]. The relationship between LV filling and volumetric parameters is not linear and reduction in LV filling pressures reduces but rarely normalizes LA volumes. LA functional parameters, as measured by novel methods of deformation analysis, more reliably detect reductions in LV filling independent of LA volumes changes [7]. Speckle tracking echocardiography–derived analysis of LA strain provides quantitative parameters for all phases of LA function (reservoir, conduit, and booster pump) and carries similar prognostic significance to that provided by volumetric approaches, in different pathological conditions including cancer patients[5,8].

Knowing the impact that LA functions has in detecting CTRCD the study by Lassen and colleagues has tested LA strain in the evaluation of CTRCD as a tool for early detection of myocardial damage induced by chemotherapy [9].

In this retrospective cohort study a total of 170 women with HER2+ breast cancer (stage I-IV) undergoing treatment with trastuzumab were studied at baseline, 3 months into treatment and 1 year since treatment initiation. Of note, 77 (45.3%) of participants had prior exposure to anthracycline. Also of note, during the 1- year follow-up, 23 (13.5%) patients had trastuzumab held or stopped for either a decline in Left Ventricular Ejection Fraction (LVEF) in 82.6% of cases or other non-cardiac reasons in the remaining cases.

A total of 36 patients developed CTRCD during follow-up. At 3-month follow-up, CTRCD patients had lower LVEF, LV-GLS, LA reservoir strain (LA εres), and LA conduit strain rate (LAεcon-sr) compared to patients that did not develop CTRCD. In the 36 patients developing CTRCD, there was a decline in LVEF from baseline to 3-months follow-up with partial recovery at 1-year follow- up. LV-GLS also declined at 3 months, however, contrary to LVEF a recovery did not occur at 1 year follow up. In the 134 patients who did not develop CTRCD during follow-up, LA Volume Index increased from baseline to 3-month follow-up and then modestly recovered at 1-year. LA strain parameters also declined during follow-up but to a lesser degree than in the CTRCD group suggesting its value as a more sensitive parameters of subtle functional changes. This study is one of the largest studies in patients with breast cancer that has assessed changes in LA strain parameters following treatment with transtuzumab.

The new information provided by Lassen et al. is in demonstrating that cancer and its treatment with Transtuzumab may negatively affect atrial function and that measurements of LA strain can detect functional changes related to cardiotoxic effects of chemotherapy. Other studies also support the fact that cancer and chemotherapy can modified LA function earlier than LV function. For example, Laufer-Perl et al. identified that cancer itself caused LA εres to be 17% lower with a further 10% relative reduction in LA εres or a decrease in LA εres below 35% in half of a population of patients undergoing chemotherapy with anthracycline. [10]. Park et al. demonstrated that while both LA εres and LV-GLS were early markers in the detection of CTRCD, LA εres reduction was more sensitive and specific than LV-GLS in predicting CTRCD [6]. Similar abnormalities in LA function were demonstrated by Tadic et al. who showed that LA reservoir and conduit function were reduced, while booster pump function was increased in cancer patients [11]. Combined with the observation by Laufer- Perl and colleagues, this raises the question as to whether LV dysfunction is only the consequence of anti- cancer therapy or if cancer itself leads to abnormalities in function. Thus, both the pathology and the therapy for that pathology can lead to LA functional impairment, which is associated with a higher risk of AF, a frequent arrhythmia in cancer patients with an impact on prognosis [4, 12].

Several limitations should be noted. CTRCD is a serious complication of anticancer therapy that can be

classified into Type I exemplified by anthracyline- induced cardiac dysfunction characterized by irreversible myocardial damage due to cumulative administered dose and type II exemplified by

trastuzumab- induced cardiac dysfunction that is dose independent and reversible. The mechanism of cardiac toxicity in both types is not well defined. Current ACC/AHA guidelines recommend that patients who develop Heart Failure (HF) while receiving potentially cardiotoxic therapies should have these therapies discontinued while a diagnostic workup is undertaken to ascertain the cause of HF [12, 13]. These guidelines acknowledge that, particularly in patients receiving trastuzumab, asymptomatic decreases in LVEF can occur in approximately 10% of patients, yet, a high recovery rate is observed and discontinuation of therapy is not always necessary. [13, 14].

Accordingly, trastuzumab is often continued in patients deemed low risk while neurohormonal blockade

Is initiated usually with guideline directed medical therapy to improve LV function such as beta blockers

and ACEi. While the authors report discontinuing or holding trastuzumab in 23 (13.5%) patients, they do not mention adjuvant treatment with neurohormonal blockade that might have influenced the results. Partial improvement of some parameters (LA εres and LVEF) at 12 months follow-up in patients who developed CTRCD raises the possibility that treatment with adjuvant therapy might be responsible for the beneficial changes. Another important limitation is the lack of additional echocardiographic parameters potentially related to LA function. A significant association exists between impaired LA strain and LV filling pressure

(E/E' ratio), pulmonary pressure (tricuspid regurgitation velocity), and RV systolic function (RVFAC) [15]. None of these parameters have been described in the manuscript.

From a research perspective, future investigations should be mindful of the association between reduction in LV filling pressure and improvement in LA function as indicated by the improvement in LA strain and a more holistic approach should be used reporting echocardiographic parameters related to

LV filling (i.e. E/E' ratio, LA stiffness index or E/E'/LA reservoir strain). Although Strain and Strain Rate are increasingly used, deformation analysis of the LA offers unique challenges. Anatomic challenges as well as specific expertise and training required for accurate data acquisition and processing remain a significant impediment to a widespread clinical use. Advances in cardiac imaging in the field of speckle tracking echocardiography, including machine learning algorithms, may help overcome these obstacles and provide a more reliable and fast functional assessment of the LA.

Despite the limitations the manuscript convincingly confirms previous reports that have demonstrated the added value of LA strain in the assessment of various pathologic conditions affecting LV function and reinforces the need for further work to establish its role in clinical applications such as risk stratification and decision-making strategies.

BIBLIOGRAPHY

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

2. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev. 2013; 22(4):561-70.

3. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29(4):277-314.

4. Galderisi M, Esposito R, Sorrentino R, et al. Atrial Fibrillation, Cancer and Echocardiography. J Cardiovasc Echogr. 2020; 30(Suppl 1):S33-S7.

5. Sarvari SI, Haugaa KH, Stokke TM, et al. Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2016; 17(6):660-7.

6. Park H, Kim KH, Kim HY, et al. Left atrial longitudinal strain as a predictor of Cancer therapeutics-related cardiac dysfunction in patients with breast Cancer. Cardiovasc Ultrasound. 2020; 18(1):28.

7. Huynh QL, Kalam K, Iannaccone A,et al. Functional and Anatomic Responses of the Left Atrium to Change in Estimated Left Ventricular Filling Pressure. J Am Soc Echocardiogr. 2015; 28(12):1428-33.e1.

8. Donal E, Behagel A, Feneon D. Value of left atrial strain: a highly promising field of investigation. Eur Heart J Cardiovasc Imaging. 2015; 16(4):356-7.

9. M C Lassen, F Arya, T Biering-Sørensen, et al. Left Atrial Strain is Reduced Following Trastuzumab in Breast Cancer Patients. Echocardiography (InPress).

10. Laufer-Perl M, Arias O, Dorfman SS, et al. Left Atrial Strain changes in patients with breast cancer during anthracycline therapy. Int J Cardiol.2021; 330:238-44.

11. Tadic M, Genger M, Cuspidi C, et al. Phasic Left Atrial Function in Cancer Patients Before Initiation of Anti-Cancer Therapy. J Clin Med.2019; 8(4).

12. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022; 79(17):e263-e421.

13. Guarneri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol. 2006; 24(25):4107-15.

14. Wang SY, Long JB, Hurria A, et al. Cardiovascular events, early discontinuation of trastuzumab, and their impact on survival. Breast Cancer ResTreat. 2014; 146(2):411-9.

15. Santos AB, Roca GQ, Claggett B, et al. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016; 9(4):e002763.