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Abnormalities in 3-Dimensional Left Ventricular Mechanics With Anthracycline Chemotherapy Are Associated With Systolic and Diastolic Dysfunction

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ABSTRACT

OBJECTIVES The objective of this study was to evaluate the changes in three-dimensional (3D) speckle-tracking echocardiography–derived measures of mechanics and their associations with systolic and diastolic dysfunction after anthracyclines.

BACKGROUND An improved understanding of the changes in 3D cardiac mechanics with anthracyclines may provide important mechanistic insight and identify new metrics to detect cardiac dysfunction.

METHODS A total of 142 women with breast cancer receiving doxorubicin (240 mg/m^2) with or without trastuzumab underwent 3D speckle-tracking echocardiography at standardized intervals prior to, during, and annually after chemotherapy. Left ventricular ejection fraction (LVEF), global circumferential strain (GCS), global longitudinal strain (GLS), principal strain, twist, and torsion were quantified. Linear regression analyses defined the associations between clinical factors and 3D parameters. Linear regression models with cluster robust variance estimators determined the associations between 3D measures and 2-dimensional (2D) LVEF and Doppler-derived E/e′ over time.

RESULTS There were significant abnormalities in 3D LVEF, GCS, GLS, and principal strain post-doxorubicin compared with control subjects ($p < 0.001$). The 3D parameters worsened post-anthracyclines, and only partially recovered to baseline over a median of 2.1 years (interquartile range: 1 to 4 years). Higher blood pressure and body mass index were associated with worse post-anthracycline 3D GCS and GLS, respectively. All 3D measures were associated with 2D LVEF at the same visit; only 3D LVEF, GCS, GLS, and principal strain were associated with 2D LVEF at subsequent visits ($p < 0.05$). In exploratory analyses, 3D LVEF and GCS were associated with subsequent systolic function independent of their corresponding 2D measures. The 3D LVEF, GCS, principal strain, and twist were significantly associated with concurrent, but not subsequent, E/e′.

CONCLUSIONS Anthracyclines result in early and persistent abnormalities in 3D mechanics. The 3D LVEF and strain measures are associated with concurrent and subsequent systolic dysfunction, and concurrent diastolic dysfunction. Future research is needed to define the mechanisms and clinical relevance of abnormal 3D mechanics. (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

GCS = global circumferential strain

GLS = global longitudinal strain

IQR = interquartile range

LVEF = left ventricular ejection fraction

STE = speckle-tracking echocardiography

Anthracycline-induced cardiotoxicity is a leading cause of cardiovascular morbidity among cancer survivors (1). Although heart failure may take months or years to manifest clinically, cardiomyocyte apoptosis can occur within days of doxorubicin exposure (2). In fact, circulating measures of troponin are detectable in some patients immediately after anthracycline therapy, indicative of early myocardial injury (3,4). However, the temporal changes in cardiac mechanics early after anthracycline exposure are not comprehensively understood.

Left ventricular ejection fraction (LVEF) derived from 2-dimensional (2D) echocardiography is the primary parameter used to assess cardiac function after cancer therapy. Although a valid measure, LVEF is limited by temporal and observer variability (5) and declines may occur late, after substantial cardiac injury. As such, there is an active body of research evaluating the use of more sensitive echocardiographic measures to detect early subclinical changes in cardiac function. Multiple prior studies, including one from our own research group, have demonstrated potential utility for 2D longitudinal and circumferential strain in the diagnosis and prediction of cardiac dysfunction after cancer therapy (6,7). 2D speckle-tracking echocardiography (STE), however, may be limited by suboptimal tracking of the endocardial border, sensitivity to acoustic shadowing, and the inability to detect out-of-plane motion of speckles (8).

Three-dimensional (3D) STE has the potential to overcome some of the technical limitations of 2D STE by tracking the movement of speckles within the entire scan volume (8). Compared with 2D STE, 3D STE may have greater accuracy for the quantitation of strain and left ventricular (LV) volumes. Furthermore, 3D STE measurements have been noted to be more reproducible than corresponding 2D STE measurements (9,10), although temporal resolution and image quality may limit the feasibility of 3D STE (11,12). 3D STE also allows for the quantitation of principal strain, the change in myocardial length along the axis of maximal shortening, as well as twist and torsion, which reflect rotational displacement along the LV long axis. Twist is defined as the absolute apex-to-base difference in LV rotation, and torsion is the base-to-apex gradient in rotation angle along the long axis of the left ventricle, expressed in degrees per centimeter (8). Despite these potential advantages of 3D STE technology for the assessment of cardiac function and mechanics, the clinical role for 3D STE remains to be proven. Whereas 2D STE has been studied in the setting of anthracycline chemotherapy, there are only a few small studies reporting changes in 3D STE parameters with chemotherapy (11,13–15). Importantly, a comprehensive understanding of the changes in 3D LV mechanics with anthracyclines and their ability to predict subsequent cardiac dysfunction may inform and improve the management of cancer patients.

The overall objectives of this study were to characterize the changes in 3D LV mechanics over time with a specific focus on the post-anthracycline chemotherapy timepoint, to identify the clinical characteristics that predispose to abnormalities in these parameters, to determine the associations between 3D LV mechanics and concurrent and subsequent systolic and diastolic dysfunction during and after anthracycline therapy, and to explore the potential incremental benefit of 3D over 2D STE. These analyses were performed in a subcohort of participants from an ongoing prospective, longitudinal breast cancer cohort of women who were receiving doxorubicin with or without trastuzumab.

METHODS

STUDY PARTICIPANTS. The Cardiotoxicity of Cancer Therapy study is a prospective, longitudinal cohort study of women with breast cancer receiving treatment at the Rena Rowan Breast Center at the University of Pennsylvania (Philadelphia, Pennsylvania) (7). Eligible participants were women age ≥18 years receiving anthracyclines with or without trastuzumab for the treatment of breast cancer. Pregnancy and inability to provide informed consent were the only exclusion criteria.

Chemotherapy regimens were prescribed at the discretion of the oncology providers and consisted of doxorubicin (240 mg/m^2) and cyclophosphamide followed by paclitaxel with or without trastuzumab. Trastuzumab was dosed according to standard guidelines. Echocardiograms were obtained after completion of anthracyclines and annually thereafter in participants receiving anthracyclines alone. Participants treated with trastuzumab underwent echocardiograms every 3 months during therapy and annually thereafter (7). Detailed clinical data were obtained at baseline and at each subsequent visit. The current analysis is restricted to participants with analyzable 3D echocardiograms at the post-anthracycline visit and at least 1 additional follow-up 2D echocardiogram.

In addition to the participants with breast cancer, a control group of healthy female volunteers (n = 21) who were determined to be free of any medical illness by history and physical examination underwent a