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Noninvasive Measures of Ventricular-Arterial Coupling and Circumferential Strain Predict Cancer Therapeutics–Related Cardiac Dysfunction

Hari K. Narayan, MD,[a] Benjamin French, PhD,[b] Abigail M. Khan, MD,[c] Theodore Plappert, RCVS,[c] David Hyman, BA,[c] Akinyemi Bajulaiye, BA,[c] Susan Domchek, MD,[d,e] Angela DeMichele, MD, MSCE,[b,d,e] Amy Clark, MD, MSCE,[d,e] Jennifer Matro, MD,[d,e] Angela Bradbury, MD,[d,e] Kevin Fox, MD,[d,e] Joseph R. Carver, MD,[c,e] Bonnie Ky, MD, MSCE[b,c,e]

ABSTRACT

OBJECTIVES This study sought to determine the relationships between echocardiography-derived measures of myocardial mechanics and cancer therapeutics–related cardiac dysfunction (CTRCD).

BACKGROUND Doxorubicin and trastuzumab are highly effective breast cancer therapies, but have a substantial risk of CTRCD. There is a critical need for the early detection of patients at increased risk of toxicity.

METHODS We performed a prospective, longitudinal cohort study of breast cancer participants undergoing doxorubicin and/or trastuzumab therapy. Echocardiography was performed prior to therapy initiation (baseline) and at standardized follow-up intervals during and after completion of therapy. Ejection fraction (EF), strain, strain rate, and ventricular-arterial coupling (effective arterial elastance [Ea]/end-systolic elastance [Ees_{sb}]) were quantitated. CTRCD was defined as a ≥10% reduction in EF from baseline to <50%. Multivariable logistic regression models were used to determine the associations between baseline levels and changes from baseline in echocardiographic measures and CTRCD. Receiver-operating characteristic curves were used to evaluate the predictive ability of these measures.

RESULTS In total, 135 participants contributed 517 echocardiograms to the analysis. Over a median follow-up time of 1.9 years (interquartile range: 0.9 to 2.4), 21 participants (15%) developed CTRCD. In adjusted models, baseline levels and changes in Ea/Ees_{sb}, circumferential strain, and circumferential strain rate were associated with 21% to 38% increased odds of CTRCD ($p < 0.001$). Changes in longitudinal strain ($p = 0.037$), radial strain ($p = 0.015$), and radial strain rate ($p = 0.006$) were also associated with CTRCD. Ea/Ees_{sb} (area under the curve: 0.703; 95% confidence interval: 0.583 to 0.807) and circumferential strain (area under the curve: 0.655; 95% confidence interval: 0.517 to 0.767) demonstrated the greatest predictive utility. Sensitivity analyses using an alternative CTRCD definition did not impact our results.

CONCLUSIONS Over an extended follow-up time, ventricular-arterial coupling and circumferential strain were strongly predictive of CTRCD. Our findings suggest a noninvasive strategy to identify high-risk patients prior to, during, and after cardiotoxic cancer therapy. (J Am Coll Cardiol Img 2016;■:■-■) © 2016 by the American College of Cardiology Foundation.

From the [a]Department of Pediatrics, Division of Cardiology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [b]Department of Biostatistics and Epidemiology, The University of Pennsylvania, Philadelphia, Pennsylvania; [c]Department of Medicine, Division of Cardiology, The University of Pennsylvania, Philadelphia, Pennsylvania; [d]Department of Medicine, Division of Oncology, The University of Pennsylvania, Philadelphia, Pennsylvania; and the [e]Abramson Cancer Center, The University of Pennsylvania, Philadelphia, Pennsylvania. This work was supported by National Heart, Lung, and Blood Institute grant R01-HL118018 to Dr. Ky; the McCabe Fellow Award to Dr. Ky; American Cancer Society Institutional Research Grant 78-002-30 to Dr. Ky; and NHLBI grant K23-HL095661 to Dr. Ky. Dr. Narayan was supported by NICHD T32-HD060550. Dr. Khan was supported by NHLBI T32-HL007891. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver-operating characteristic curve

CI = confidence interval

CTRCD = cancer therapeutics-related cardiac dysfunction

Ea = effective arterial elastance

Ees_{sb} = end-systolic elastance

EF = ejection fraction

HF = heart failure

IQR = interquartile range

LV = left ventricular

Doxorubicin and trastuzumab (Herceptin) are highly effective cancer therapies used widely in the treatment of cancer that have led to important survival gains. However, these agents carry a substantial risk of cardiotoxicity when used in combination. Doxorubicin results in a dose-dependent risk of cardiomyopathy, which may occur in ~10% of patients at dosages of 250 mg/m^2 (1). Furthermore, doxorubicin-induced cardiomyopathy carries a poor prognosis, with a 3.5-fold increased risk of death or cardiac transplantation compared to idiopathic cardiomyopathy (2). When used in combination, doxorubicin and trastuzumab may result in left ventricular (LV) dysfunction in up to 27% of individuals, and heart failure (HF) in up to 4% (3). Despite the magnitude of this problem, a fundamental question remains: How can we identify the patient who is at high risk for cancer therapeutics-related cardiac dysfunction (CTRCD) (4)? Early detection of cardiac dysfunction could enable the implementation of cardioprotective strategies prior to late, potentially irreversible changes in cardiac function.

Currently, cardiac function prior to, during, and after cancer therapy is determined by assessment of ejection fraction (EF), typically by echocardiography or multi-gated acquisition scanning. Although a valid measure, EF lacks the sensitivity to detect early changes and can underestimate the degree of subclinical myocardial damage (5). Recent studies in cardio-oncology have suggested that newer echocardiography-derived measures of myocardial mechanics, such as strain and strain rate, provide important insight into cardiac function (6,7). Strain and strain rate quantify the fractional change and rate of change in myocardial length during each cardiac cycle, and can be assessed in the longitudinal, circumferential, or radial dimensions. However, insight into the relevance of early changes in these measures and subsequent CTRCD, particularly after cancer therapy completion, remains limited.

Moreover, other measures of myocardial mechanics such as ventricular-arterial coupling (the ratio of effective arterial elastance [Ea], which integrates arterial load, and LV end-systolic elastance [Ees_{sb}], which quantifies chamber stiffness and contractility) have not previously been studied in cardio-oncology. As an index of the interaction between the ventricular and arterial system, it provides an assessment of cardiovascular performance and efficiency. Higher ratios of Ea/Ees_{sb} reflect compromised ventricular-vascular matching and are prognostic in HF (8). As data suggest that arterial stiffening may be caused by doxorubicin and trastuzumab, we hypothesized that these agents might also result in ventricular-vascular uncoupling and that this ratio may help diagnose and predict CTRCD (9,10).

The overall objective of this study was to define the cross-sectional and longitudinal relationships between measures of myocardial mechanics and doxorubicin- and trastuzumab-induced CTRCD, to characterize their diagnostic and predictive utility. We comprehensively evaluated the associations of strain indices and ventricular-arterial coupling (Ea/Ees_{sb}) with CTRCD at the same visit and subsequent visit in a prospective longitudinal cohort of women with breast cancer.

METHODS

STUDY POPULATION. The CCT (Cardiotoxicity of Cancer Therapy) study is an ongoing, prospective longitudinal cohort study of women with breast cancer recruited from the Rena Rowan Breast Cancer Center of the Abramson Cancer Center at the University of Pennsylvania (Philadelphia, Pennsylvania). The primary inclusion criteria were women at least 18 years of age diagnosed with breast cancer, prescribed doxorubicin and/or trastuzumab therapy. The only exclusion criterion was pregnancy. Treatment regimens were at the discretion of the oncology provider, and consisted of 1 of the following 3 main combinations: 1) doxorubicin (240 mg/m^2) and cyclophosphamide, followed by paclitaxel; 2) doxorubicin (240 mg/m^2) and cyclophosphamide, followed by paclitaxel and trastuzumab; or 3) cyclophosphamide or carboplatin with docetaxel and trastuzumab (**Figure 1**). Trastuzumab dosing was prescribed as per standard guidelines (11).

Prior to initiation of chemotherapy and at each follow-up visit, participants provided detailed clinical data via standardized questionnaires. Clinical data were verified via review of medical records. Transthoracic echocardiograms were performed at standardized intervals according to the treatment regimen (**Figure 1**). Briefly, those patients treated with doxorubicin without trastuzumab underwent echocardiograms at baseline, at completion of chemotherapy, and annually. Those patients treated with doxorubicin and trastuzumab underwent an echocardiogram at baseline, after doxorubicin completion, every 3 months during trastuzumab therapy, and annually. Those patients treated with trastuzumab without doxorubicin underwent echocardiograms at baseline, every 3 months during trastuzumab