Detailed Echocardiographic Phenotyping in Breast Cancer Patients

Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up

BACKGROUND: Cardiovascular disease in patients with breast cancer is of growing concern. The longitudinal effects of commonly used therapies, including doxorubicin and trastuzumab, on cardiac remodeling and function remain unknown in this population. We aimed to define the changes in echocardiographic parameters of structure, function, and ventricular-arterial coupling, and their associations with left ventricular ejection fraction (LVEF) and heart failure symptoms.

METHODS: In a longitudinal prospective cohort study of 277 breast cancer participants receiving doxorubicin (Dox), trastuzumab (Tras), or both (Dox+Tras), we obtained 1249 echocardiograms over a median follow-up of 2.0 (interquartile range, 1.0–3.0) years. Left ventricular structure, diastolic and contractile function, and ventricular-arterial coupling measures were quantified in a core laboratory blinded to participant characteristics. We evaluated changes in echocardiographic parameters over time, and used repeated-measures regression models to define their association with LVEF decline and recovery. Linear regression models defined the association between early changes in these parameters and subsequent changes in LVEF and heart failure symptoms.

RESULTS: Overall, 177 (64%) received Dox, 51 (18%) received Tras, and 49 (18%) received Dox+Tras. With Dox, there was a sustained, modest decrease in LVEF over the follow-up duration (1-year change in LVEF –3.6%; 95% confidence interval [CI], –4.4% to –2.8%; 3-year change –3.8%; 95% CI, –5.1% to –2.5%). With Tras, a similar LVEF decline was observed at 1 year (–4.5%; 95% CI, –6.0% to –2.9%) and 3 years (–2.8%; 95% CI, –5.3 to –0.4%). Participants receiving Dox+Tras demonstrated the greatest declines at 1 year (–6.6%; 95% CI, –8.2 to –5.0%), with partial recovery at 3 years (–2.8%; 95% CI, –4.8 to –0.8%). LVEF declines and recovery were associated primarily with changes in systolic volumes, longitudinal and circumferential strain, and ventricular-arterial coupling indices, effective arterial elastance (Ea) and the coupling ratio Ea/Ees30, without evidence for effect modification across therapies. Early changes in volumes, strain, and Ea/Ees30 at 4 to 6 months were associated with 1- and 2-year LVEF changes. Similarly, early changes in strain and Ea were associated with worsening heart failure symptoms at 1 year.

CONCLUSIONS: Doxorubicin and trastuzumab resulted in modest, persistent declines in LVEF at 3 years. Changes in volumes, strain, and ventricular-arterial coupling were consistently associated with concurrent and subsequent LVEF declines and recovery across therapies.
Clinical Perspective

What Is New?

• This study is the first to comprehensively characterize the changes in left ventricular structure, function, and ventricular-arterial coupling in breast cancer patients receiving doxorubicin and trastuzumab over 3 years.
• Doxorubicin and trastuzumab resulted in early declines in left ventricular ejection fraction (LVEF) that were modest but persistent at 3 years.
• Across therapies, LVEF decline and recovery were consistently associated with systolic volumes, longitudinal and circumferential strain, arterial load, and ventricular-arterial coupling.
• Early changes in these measures at 4 to 6 months were associated with LVEF changes and heart failure symptoms 1 to 2 years after therapy initiation.

What Are the Clinical Implications?

• Persistent LVEF declines and changes in ventricular and arterial stiffness at 3 years suggest that patients with breast cancer exposed to doxorubicin and trastuzumab be monitored carefully for the potential development of subsequent heart failure of the reduced or preserved ejection fraction subtype.
• Volumes, longitudinal and circumferential strain, arterial load, and the ventricular-arterial coupling ratio are relevant to LVEF decline, recovery, and heart failure symptoms. This finding motivates investigation of these measures in patients as potential strategies to mitigate dysfunction.

Doxorubicin and trastuzumab (Herceptin) are highly effective and commonly used in the treatment of breast cancer. However, these agents can result in cardiomyopathy and heart failure (HF). Doxorubicin is an anthracycline chemotherapeutic that causes myocellular and vascular injury primarily via oxidative stress. Trastuzumab is a humanized monoclonal antibody that disrupts ErbB2 (HER2/neu) signaling, a pathway that plays a fundamental role in the maintenance of cardiac homeostasis, myocardial repair, and angiogenic signaling. These perturbations result in adverse cardiac and vascular remodeling. Left ventricular (LV) dysfunction develops in 9% to 26% of patients receiving doxorubicin, 13% of patients receiving trastuzumab, and up to 27% of participants receiving doxorubicin and trastuzumab (Herceptin) therapy remain unknown. A greater understanding of the natural history of cardiac function and remodeling during and after cancer therapy, including how changes in these component measures are related to the deterioration and recovery of LVEF, and the changes in HF symptoms, as well, is critical. This insight is fundamental to advance our understanding the pathophysiology and management of cardiac dysfunction in this population.

Thus, the objective of this study was to use detailed phenotyping by echocardiography to characterize the changes in LV structure, function, and VA coupling in a prospective cohort of breast cancer participants treated with doxorubicin and trastuzumab, and determine the association between these changes and LVEF decline, recovery, and HF symptoms.

METHODS

Study Population

The CCT study (Cardiotoxicity of Cancer Therapy) is an ongoing, prospective, longitudinal cohort study of breast cancer participants at the Rena Rowan Breast Cancer Center at the University of Pennsylvania (Philadelphia, PA). This study was approved by the Institutional Review Board of the University of Pennsylvania, and all participants provided informed consent.

The study protocol has been previously described. In brief, participants were eligible to be included if they were at least 18 years of age, diagnosed with breast cancer, and treated with doxorubicin, trastuzumab, or the combination of these 2 therapies. The only exclusion criterion was pregnancy; participants with an abnormal baseline LVEF were not excluded. Treatment regimens were determined by the treating oncologist and classified into 3 primary categories: (1) doxorubicin (240 mg/m²) with concurrent cyclophosphamide, followed by paclitaxel (Dox); (2) trastuzumab with docetaxel and either cyclophosphamide or carboplatin (Tras); and (3) doxorubicin (240 mg/m²) with concurrent cyclophosphamide, followed by trastuzumab and paclitaxel (Dox+Tras).

Detailed clinical data, verified via physician medical records, and the MDASI-HF survey (MD Anderson Symptom Inventory—Heart Failure) assessing HF symptoms on a scale of 0 to 10, were obtained at baseline and follow-up. Echocardiograms were also performed at standardized time intervals according to the prescribed treatment regimen. In the Dox group, echocardiography was performed at baseline, at completion of paclitaxel (≈4 months after initiation of chemotherapy), and annually. In the Tras group, echocardiography was performed at baseline, every 3 months during trastuzumab, and annually. In the Dox+Tras group, echocardiography was performed at baseline, after doxorubicin, and trastuzumab, and the association between these changes and LVEF decline, recovery, and HF symptoms.
The current analyses were limited to those participants enrolled between August 2010 and August 2015 who had a baseline assessment of cardiac function and at least 1 follow-up echocardiogram, and include echocardiography data up to 3.2 years after initiation of therapy.

Echocardiography Acquisition

Transthoracic echocardiograms were performed by dedicated sonographers at an Intersocietal Accreditation Commission laboratory using GE Vivid 7 or E9 machines (GE Healthcare). Images from the apical, parasternal short axis at the midpapillary level, and parasternal long-axis views were acquired and digitally archived at 60 to 80 frames/s. Doppler interrogations of the LV outflow tract, mitral inflow, and mitral annulus were performed in the apical view.

Quantitative Echocardiographic Measures

Quantitation was performed at the University of Pennsylvania Center for Quantitative Echocardiography (Philadelphia). All measurements, including both 2-dimensional and strain analyses, were performed using TomTec Imaging Systems software. Measures of global function (LVEF); structure (LV end-diastolic and end-systolic volumes [LVEDV, LVESV], mass, and relative wall thickness); diastolic function (E/e'); contractile function (end-systolic elastance [Ees_b]); strain (longitudinal, circumferential, radial); and VA coupling (effective arterial elastance [Ea], wall stress [meridional, circumferential], coupling ratio [Ea/ Ees_b]) were quantified.

Measurements of LVEDV, LVESV, mass, and relative wall thickness provided insight into structure, size, and remodeling. The diastolic function index, E/e', provided insight into myocardial relaxation and preload. Contractile function was quantified by Ees_b, the slope of the end-systolic pressure volume relation, and longitudinal, circumferential, and radial strain. Ea provided an integrative measure of total arterial load. The impact of afterload on the LV was also measured through the quantification of meridional (longitudinal) and circumferential wall stress. Last, the net interaction between the arterial and ventricular system was indexed by the ratio Ea/Ees_ap, which provided insight into cardiovascular performance and efficiency.

The measurements and calculations used to derive each parameter have been previously described, and are detailed in the online-only Data Supplement Methods and online-only Data Supplement Table I. In a small subset of total studies (4%), primarily at baseline, echocardiograms or multigated acquisition scans were performed at an outside facility and images were not available for quantitative analyses. In this case, LVEF values based on visual estimation were used to describe the trajectory of change. Longitudinal, circumferential, and radial strain could not be reproducibly analyzed in 3%, 8%, and 8%, respectively, of the studies with a quantitated LVEF.

Reliability Assessment of Echocardiographic Measures

All 2-dimensional and strain measurements were performed by a single sonographer who is highly experienced in echocardiography quantitation (T.P.). All Doppler assessments were performed by 2 dedicated research sonographers. Intraobserver coefficients of variation for LVEDV, LVESV, stroke volume, and LVEF were 2.4%, 4.5%, 5.7%, and 4.4%, respectively. Intraobserver coefficients of variation for longitudinal, circumferential, and radial strain were 10.9%, 9.4%, and 26.2%, respectively. The intraobserver and interobserver coefficients of variation for mitral inflow E wave were 2.3% to 5.4% and 6.8%, respectively. The coefficient of variation range for Doppler timing intervals used to derive Ees_b, was 0.3% to 5.7%.

Statistical Methods

Standard descriptive statistics were used to summarize participant characteristics at baseline. Repeated-measures linear regression models estimated the mean change in each echocardiographic measure at 1, 2, and 3 years since initiation of cancer therapy for each regimen. The model included interaction terms between regimen and time since initiation of cancer therapy (modeled nonparametrically as a cubic spline) and was adjusted for the baseline value of the noninvasive measure. A robust variance estimator was used to account for the correlation between repeated measures on participants over time.

Among all participants, repeated-measures linear regression models using generalized estimating equations were used to define the association between the change in each echocardiographic parameter (independent variable) and change in LVEF (dependent variable). Changes in each echocardiographic parameter were standardized by dividing the change in a particular parameter from its baseline value by the interquartile range (IQR) of that parameter across all participants at baseline. The use of standardized changes allowed for comparison of the magnitude of model coefficients across different echocardiographic parameters. The IQR was used instead of the standard deviation because several parameters had skewed distributions. Estimates were obtained for each treatment regimen by including interaction terms between regimen and the standardized change in the echocardiographic parameter. Statistical hypothesis tests (based on estimated interaction coefficients) evaluated equality in associations across regimens. All models were adjusted for baseline echocardiographic parameter, baseline LVEF, time since cancer therapy initiation (modeled nonparametrically for each regimen), baseline age, baseline body mass index (BMI), and time-varying heart rate. A robust variance estimator was used in all models. These analyses were limited to those participants who had quantitated echocardiograms at baseline and at least 1 follow-up visit to assess the change in quantitated parameters from baseline. The coefficients from these models estimate the average cross-sectional association between each echocardiographic parameter and LVEF across all time points, adjusted for time, and represent the change in LVEF that would be expected to occur per IQR increase in the echocardiographic parameter of interest.

Among participants who experienced cardiac dysfunction, defined by a quantitated LVEF decline ≥10% to a value <50%,13,30,31 repeated-measures linear regression models were used to estimate the association between the standardized change in each echocardiographic parameter and the change in LVEF. The purpose of these analyses was to gain insight into the associations between echocardiographic parameters and...
subsequent LVEF recovery once a clinically meaningful decline occurred. For these analyses, the first occurrence of cardiac dysfunction was defined as a new baseline, with subsequent changes calculated from this new baseline. These models used similar specifications, including a robust variance estimator, as the previously described models of change in LVEF regressed on standardized changes in echocardiographic parameters, except that regimen was included as an adjustment variable (and not as an interaction term) given limited sample size.

Next, ordinary least-squares linear regression models were used to determine the associations between standardized changes in echocardiographic parameters at 4 to 6 months and LVEF changes at 1 and 2 years. These models were similarly adjusted for baseline echocardiographic parameter, baseline LVEF, treatment regimen, timing of the 4- to 6-month echocardiogram (specified as a linear covariate), age, BMI, and heart rate. Last, with the use of the same model specifications, the associations between 4- to 6-month changes in echocardiographic parameters and changes in symptoms at 1 and 2 years, as assessed by components of the MDASH-HF, were explored. Here, instead of LVEF, the outcomes were either the change in the dyspnea severity or the change in the HF score (average response for 8 HF symptoms: severity of ankle edema, abdominal bloating, sudden weight gain, lack of energy, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, and palpitations). These models were adjusted for baseline dyspnea severity or HF score.

All analyses were completed by using R 3.2.2 (R Foundation for Statistical Computing).

RESULTS
Study Population
In total, 277 participants contributed 1249 echocardiograms to this study, with a median of 4 (IQR, 3–6) echocardiograms per participant. The maximum follow-up time was 3.2 years from cancer therapy initiation, and the median follow-up time was 2.0 (IQR, 1.0–3.0) years. Baseline characteristics and echocardiographic parameters are summarized in Table 1. Overall, 64% of participants received doxorubicin without trastuzumab (Dox), 18% received trastuzumab without doxorubicin (Tras), and 18% received both doxorubicin and trastuzumab (Dox+Tras). The median age was 48 (IQR, 41–57) years. Approximately 65% of the participants were white and 26% were black. Cardiovascular risk factors at baseline were prevalent, with diabetes mellitus, hypertension, hypercholesterolemia, and a tobacco history in 8%, 29%, 22%, and 39% of participants, respectively. Moreover, 27% were on an antihypertensive medication, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, or diuretics. The majority of participants were overweight, with a median BMI of 26.4 (IQR, 23.6–31.3) kg/m². A small subset of participants (4%) received per-
tuzumab in conjunction with trastuzumab therapy, and 57% underwent radiation therapy.

The median LVEF at baseline was 54.3% (IQR, 51.2–57.8%). The median LVEDV was 112 mL, LVESV was 51 mL, and LV mass was 129 g. The median E/e′ was 7.0, Ees,bo was 1.90 mmHg/mL, longitudinal strain was −15.7%, circumferential strain was −25.6%, and radial strain was 49.8%. Median Ea was 1.91 mmHg/mL and Ea/Ees,bo was 1.02. Longitudinal strain was borderline low, likely reflective of the broad inclusion criteria and high prevalence of cardiovascular risk factors within our cohort. At baseline, a worse longitudinal strain was significantly associated with increased age (P=0.01), black race (P=0.002), increased BMI (P=0.003), hypertension (P=0.012), increased systolic blood pressure (P=0.038), and a decreased LVEF (P<0.001). There were no significant differences between participants in the 3 treatment groups with regard to their baseline clinical characteristics, with the exception of expected differences in cancer stage and pertuzumab therapy.

Longitudinal Changes in LVEF According to Treatment Regimen
Changes in LVEF over the 3-year period are graphically depicted in Figure 1A. The mean adjusted changes in LVEF over time according to treatment regimen are noted in Table 2. With Dox, a modest but sustained decrease in LVEF was observed, with a 1-year change in LVEF of −3.6% (95% confidence interval [CI], −4.4% to −2.8%), and a 3-year change of −3.8% (95% CI, −5.1% to −2.5%). Participants receiving Tras showed similar early declines, with a 1-year change in LVEF of −4.5% (95% CI, −6.0% to −2.9%), and a 3-year change of −2.8% (95% CI, −5.3% to −0.4%). Participants receiving Dox+Tras demonstrated the greatest early declines, with a 1-year change in LVEF of −6.6% (95% CI, −8.2% to −5.0%), and partial recovery with a 3-year change of −2.8% (95% CI, −4.8% to −0.8%). Overall, doxorubicin was associated with a persistent decline in LVEF over time, whereas a small improvement was observed with trastuzumab. In all 3 treatment groups, LVEF remained lower at 3 years in comparison with baseline.

Longitudinal Changes in Structure, Function, and VA Coupling According to Treatment Regimen
We then sought to investigate the changes in cardiac remodeling, function, and VA coupling over time among the 3 groups. In the Dox group, there were nonsignificant changes in LVEDV; initial increases in LVESV; and an initial worsening of strain (Figure 2 and online-only Data Supplement Table II). It is interesting to note that we observed initial increases in LV mass and relative wall thickness and, in parallel, a decrease in wall stress. These changes were not sustained at 3 years. However,
Table 1. Characteristics of Study Participants at Baseline, by Treatment Regimen

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>All Participants (n=277)</th>
<th>Doxorubicin (n=177)</th>
<th>Trastuzumab (n=51)</th>
<th>Doxorubicin + Trastuzumab (n=49)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>48 (41–57)</td>
<td>49 (41–57)</td>
<td>53 (45–59)</td>
<td>46 (40–57)</td>
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<td>Race, n (%)</td>
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<td></td>
<td></td>
<td>0.14</td>
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<tr>
<td>White</td>
<td>179 (65)</td>
<td>108 (61)</td>
<td>41 (80)</td>
<td>30 (61)</td>
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<tr>
<td>Black</td>
<td>73 (26)</td>
<td>52 (29)</td>
<td>7 (14)</td>
<td>14 (29)</td>
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</tr>
<tr>
<td>Other or unknown</td>
<td>25 (9)</td>
<td>17 (10)</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Cancer and related therapies</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer side, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Left</td>
<td>125 (45)</td>
<td>79 (45)</td>
<td>24 (47)</td>
<td>22 (45)</td>
<td></td>
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<tr>
<td>Right</td>
<td>134 (48)</td>
<td>87 (49)</td>
<td>26 (51)</td>
<td>21 (43)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>18 (6)</td>
<td>11 (6)</td>
<td>1 (2)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1</td>
<td>56 (20)</td>
<td>23 (13)</td>
<td>24 (47)</td>
<td>9 (18)</td>
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<td>2</td>
<td>154 (56)</td>
<td>110 (62)</td>
<td>19 (37)</td>
<td>25 (51)</td>
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<tr>
<td>3</td>
<td>61 (22)</td>
<td>42 (24)</td>
<td>4 (8)</td>
<td>15 (31)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 (2)</td>
<td>2 (1)</td>
<td>4 (8)</td>
<td>0 (0)</td>
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<tr>
<td>Radiotherapy, n (%)</td>
<td>158 (57)</td>
<td>103 (59)</td>
<td>26 (51)</td>
<td>29 (60)</td>
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<td>Pertuzumab, n (%)</td>
<td>12 (4)</td>
<td>0 (0)</td>
<td>6 (12)</td>
<td>6 (12)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Medical history and risk factors</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>21 (8)</td>
<td>15 (8)</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>0.61</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>79 (29)</td>
<td>51 (29)</td>
<td>16 (31)</td>
<td>12 (24)</td>
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<tr>
<td>History of hyperlipidemia, n (%)</td>
<td>61 (22)</td>
<td>42 (24)</td>
<td>8 (16)</td>
<td>11 (22)</td>
<td>0.51</td>
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<tr>
<td>Tobacco use, n (%)</td>
<td></td>
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<td></td>
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<td>0.94</td>
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<tr>
<td>Current</td>
<td>18 (6)</td>
<td>13 (7)</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>91 (33)</td>
<td>58 (33)</td>
<td>16 (31)</td>
<td>17 (35)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>168 (61)</td>
<td>106 (60)</td>
<td>32 (63)</td>
<td>30 (61)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4 (23.6–31.3)</td>
<td>26.5 (23.8–31.5)</td>
<td>26.1 (23.5–30.2)</td>
<td>26.4 (23.2–31.2)</td>
<td>0.48</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125 (116–138)</td>
<td>125 (116–138)</td>
<td>121 (114–140)</td>
<td>127 (118–138)</td>
<td>0.94</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74 (69–81)</td>
<td>75 (69–81)</td>
<td>73 (69–79)</td>
<td>76 (70–84)</td>
<td>0.25</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>73 (68–82)</td>
<td>73 (66–82)</td>
<td>74 (70–83)</td>
<td>73 (70–79)</td>
<td>0.72</td>
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<tr>
<td>Cardiac medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antihypertensive, n (%)</td>
<td>74 (27)</td>
<td>48 (27)</td>
<td>16 (31)</td>
<td>10 (20)</td>
<td>0.45</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker, n (%)</td>
<td>37 (13)</td>
<td>27 (15)</td>
<td>7 (14)</td>
<td>3 (6)</td>
<td>0.25</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>19 (7)</td>
<td>14 (8)</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

(Continued)
increases in E/e\textsuperscript{ʹ}, E\textsubscript{es}\textsubscript{sb}, and Ea at 1 year persisted at 3 years. In comparison, the Dox+Tras group demonstrated a significant decrease in LVEDV at 2 and 3 years. This group similarly experienced an initial worsening in strain at 1 year, and persistent increases in E/e\textsuperscript{ʹ}, E\textsubscript{es}b, and Ea from 1 to 3 years. At 1 year, the Dox+Tras group also developed an increase in mass and a concomitant increase in LVEDV. This resulted in a decreased relative wall thickness and an increase in wall stress. The changes in structure, function, and VA coupling in the Tras group were largely similar to those in the Dox+Tras group, although generally less pronounced. With the exception of measures of diastolic function and arterial and ventricular stiffness, the structural and functional changes were most evident at 1 year and diminished at 3 years across all groups.

### Associations Between Changes in Structure, Function, and VA Coupling and LVEF Decline

Next, we determined the associations between changes in echocardiographic parameters of structure, function, and VA coupling and LVEF decline over the entire study period in the 229 participants who had quantitated baseline and follow-up echocardiograms (Figure 3, online-only Data Supplement Table III). In these analyses, systolic volumes were associated with the largest effects on LVEF across treatment groups; an IQR increase in LVESV was associated with \approx 5% decrease in LVEF. Changes in LVEDV, longitudinal and circumferential strain, Ea, and Ea/E\textsubscript{es}b also had moderate associations across all treatment groups; an IQR increase in each of these measures was associated with \approx 2% to 3% decline in LVEF. Chang-
es in relative wall thickness, radial strain, and measures of end-systolic stress had smaller but significant associations with changes in LVEF; an IQR change in these measures was associated with a -1% to 2% change in LVEF. LV mass, diastolic function, and $E_{es_{wb}}$ were not consistently associated with changes in LVEF. Overall, there was no strong evidence for effect modification by treatment regimen. These findings indicate that, among the studied parameters, volumes, longitudinal and circumferential strain, and arterial load and VA coupling were most consistently associated with LVEF decline across therapies.

**Associations Between Changes in Structure, Function, and VA Coupling and LVEF Recovery**

After establishing the associations between structural and physiological measures and LVEF declines, we sought to define the associations between these parameters and LVEF recovery in those participants who developed cardiac dysfunction. Of the 229 participants who had quantitated echocardiograms at baseline and follow-up, 42 participants (18%) developed cardiac dysfunction, defined as a decline in LVEF ≥10% to a value <50% (Figure 1B). The median time to development of significant LVEF decline was 7 months (IQR, 4–12), occurring both during and after completion of therapy. At the time of significant LVEF decline, the median LVEF was 43% (IQR, 40%–44%). Of the participants who developed cardiac dysfunction, 20 (48%) had clinical symptoms of dyspnea or fatigue, 14 (33%) had a dose interruption or discontinuation, 12 (29%) were on an antihypertensive medication at baseline, and another 20 (48%) subsequently initiated a new antihypertensive medication.

**Table 2. Changes in Left Ventricular Ejection Fraction According to Treatment Regimen**

<table>
<thead>
<tr>
<th></th>
<th>1 y Estimate* (95% CI)</th>
<th>2 y Estimate* (95% CI)</th>
<th>3 y Estimate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (n=177)</td>
<td>-3.6% (-4.4% to -2.8%)</td>
<td>-3.0% (-4.0% to -2.0%)</td>
<td>-3.8% (-5.1% to -2.5%)</td>
</tr>
<tr>
<td>Trastuzumab (n=51)</td>
<td>-4.5% (-6.0% to -2.9%)</td>
<td>-3.6% (-5.2% to -2.0%)</td>
<td>-2.8% (-5.3% to -0.4%)</td>
</tr>
<tr>
<td>Doxorubicin and trastuzumab (n=49)</td>
<td>-6.6% (-8.2% to -5.0%)</td>
<td>-4.0% (-5.6% to -2.3%)</td>
<td>-2.8% (-4.8% to -0.8%)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Estimate corresponds to the marginal mean obtained from a linear regression model for the change in left ventricular ejection fraction, with full factorial interactions for cancer therapy regimen and time since cancer therapy initiation, and adjusted for baseline left ventricular ejection fraction.
In this subgroup of participants, we evaluated the associations between structural and physiological parameters and LVEF recovery (Figures 1B and 4, online-only Data Supplement Table IV). Here, the median follow-up after diagnosis of cardiac dysfunction was 14 (IQR, 7–25) months. These findings were similar...
to the above analyses of LVEF declines, with each IQR decrease in LVESV and Ea associated with an 8% and 5% increase in LVEF, respectively. IQR changes in longitudinal and circumferential strain and Ea/Ees\textsubscript{sb} were each associated with a \( \approx 2\% \) increase in LVEF. It is interesting to note that decreases in LV mass were also associated with a modest increase in LVEF. In summary, changes in systolic volumes, longitudinal and circumferential strain, total arterial load, and VA coupling (Ea/Ees\textsubscript{sb}) were most strongly associated with LVEF recovery.

### Association Between Early Changes in Cardiac Structure, Function, and VA Coupling and Subsequent Changes in LVEF

We next examined the associations between early changes in echocardiographic parameters at 4 to 6 months and subsequent changes in LVEF at 1 and 2 years postcancer therapy initiation (Figure 5, online-only Data Supplemental Table V). In these analyses, we found consistent and significant associations between early changes in LVEDV, LVESV, longitudinal strain, and Ea/Ees\textsubscript{sb} with changes in LVEF at both 1 and 2 years, with each IQR increase in each of these measures being associated with a \( \approx 1\% \) to \( 3\% \) decline in LVEF at 2 years. An early worsening in circumferential strain was significantly associated with a LVEF decline of \( \approx 2\% \) at 1 year (\( P<0.001 \)) and approached statistical significance at 2 years (\( P=0.09 \)). Changes in radial strain at 4 to 6 months tended toward an association with changes in LVEF at 1 year (\( P=0.07 \)) and were significantly associated with LVEF at 2 years (\( P=0.02 \)). A decrease in relative wall thickness and early increases in Ea and measures of end-systolic stress were significantly associated with LVEF declines at 1 year (\( P<0.05 \) for all) but not at 2 years, whereas early changes in LV mass, E/e\textprime, and Ees\textsubscript{sb} were not associated with subsequent LVEF changes. In summary, early changes in LV volumes, strain, and VA coupling were associated with subsequent changes in LVEF with doxorubicin and trastuzumab therapy.

<table>
<thead>
<tr>
<th>Echo Parameter</th>
<th>Median (IQR)</th>
<th>Doxorubicin</th>
<th>Trastuzumab</th>
<th>Doxorubicin + Trastuzumab</th>
<th>P\textsubscript{Interaction}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular structure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>112 (98, 125)</td>
<td>0.044</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>51 (44, 60)</td>
<td>0.94</td>
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<tr>
<td>LV mass, g</td>
<td>129 (113, 151)</td>
<td>0.097</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.36 (0.32, 0.42)</td>
<td>0.049</td>
<td></td>
<td></td>
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<tr>
<td><strong>Left ventricular diastolic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/e\textprime</td>
<td>7.0 (5.6, 8.7)</td>
<td>0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left ventricular contractility</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ees\textsubscript{sb}, mmHg/ml</td>
<td>1.90 (1.51, 2.33)</td>
<td>0.60</td>
<td></td>
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<tr>
<td>Longitudinal strain, %</td>
<td>–15.7 (–17.7, –13.8)</td>
<td>0.36</td>
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<tr>
<td>Circumferential strain, %</td>
<td>–25.6 (–28.8, –22.2)</td>
<td>0.58</td>
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<tr>
<td>Radial strain, %</td>
<td>49.8 (36.8, 63.2)</td>
<td>0.021</td>
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<tr>
<td><strong>Ventricular−arterial coupling</strong></td>
<td></td>
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<tr>
<td>Ea, mmHg/ml</td>
<td>1.91 (1.65, 2.23)</td>
<td>0.39</td>
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<tr>
<td>Meridional ESS, 10\textsuperscript{3} dynes/cm\textsuperscript{2}</td>
<td>82.9 (70.8, 99.0)</td>
<td>0.83</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Circumferential ESS, 10\textsuperscript{3} dynes/cm\textsuperscript{2}</td>
<td>136 (122, 155)</td>
<td>0.78</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ea/Ees\textsubscript{sb}</td>
<td>1.02 (0.88, 1.20)</td>
<td>0.25</td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 3. Associations between echocardiographic parameters and changes in left ventricular ejection fraction according to treatment regimen.**

Point estimates and confidence intervals for the associations between changes in echocardiographic parameters and changes in left ventricular ejection fraction (LVEF) are graphically represented for participants receiving doxorubicin (orange), trastuzumab (green), and doxorubicin+trastuzumab (purple). Data also displayed in tabular format in the online-only Data Supplement. Each point estimate corresponds to the absolute change in LVEF for each interquartile range increase (27 mL) in end-diastolic volume over the entire duration of follow-up. For longitudinal and circumferential strain, which are negative values, an IQR decrease in LVESV and Ea associated with an 8% and 5% increase in LVEF, respectively. IQR increases in LV mass, E/e\textprime, diastolic function index; Ees\textsubscript{sb}, end-systolic elastance; ESS, end-systolic stress; IQR, interquartile range; LV, left ventricle; and LVEF, left ventricular ejection fraction.
Association Between Early Changes in Cardiac Structure, Function, and VA Coupling and Subsequent Changes in HF Symptoms

Last, we performed exploratory analyses examining the associations between early changes in echocardiographic measures at 4 to 6 months and the severity of HF symptoms at 1 year, as assessed by components of the MDASI-HF questionnaire (Figure 6, online-only Data Supplement Table VI, online-only Data Supplement Figure I). In these analyses, we found that early adverse changes in LVEF ($P=0.04$), longitudinal strain ($P=0.04$), circumferential strain ($P=0.04$), circumferential end-systolic stress ($P=0.03$), and Ea ($P<0.001$) were associated with worse dyspnea at 1 year. Increases in Ea at 4 to 6 months were also associated with an increase in HF score ($P<0.001$). Of note, the associations between Ea and both dyspnea and HF score were stronger than the associations of LVEF with subsequent symptoms. It is interesting to note that a decrease in LVEDV was also associated with an increased HF score ($P=0.02$). There were no significant associations between echocardiographic parameters and HF symptoms at 2 years. In summary, these exploratory analyses suggest that early changes in LVEF, strain, and arterial load were associated with a worsening of subsequent HF symptoms.

DISCUSSION

Our detailed, quantitative analyses of 1249 echocardiograms in 277 breast cancer participants undergoing therapy with doxorubicin and trastuzumab is the first study in cardio-oncology to comprehensively characterize changes in cardiac structure, function, and VA coupling from cancer therapy initiation over an extended follow-up period. In a prior study from this cohort, we determined that measures of strain and VA coupling were diagnostic and predictive of cardiac dysfunction. Our current analyses provide important and additive insight by delineating the changes in LV structure, function, and VA coupling with Dox and Tras cancer therapy; determining their associa-
tions with LVEF decline and recovery; and characterizing the associations between early changes in these parameters and subsequent changes in LVEF and HF symptom severity. We present a number of key findings. First, doxorubicin and trastuzumab, individually and additively, result in early LVEF declines and incomplete recovery at 3 years. Participants treated with doxorubicin and trastuzumab experienced modest but persistent declines, and those receiving both therapies demonstrated the greatest initial declines and partial recovery. Second, the echocardiographic parameters most consistently associated with LVEF decline are volumes, longitudinal and circumferential strain, arterial load, and the VA coupling ratio, and these relationships are largely consistent across all 3 treatment regimens. Third, LVEF recovery in participants who experienced cardiac dysfunction is similarly associated with LV systolic volumes, longitudinal and circumferential strain, arterial load, and VA coupling. Fourth, early changes (4–6 months) in volumes, longitudinal strain, and VA coupling were also associated with subsequent changes in LVEF at 1 and 2 years postcancer therapy initiation. Last, exploratory analyses suggest there are associations between early changes in measures of strain and arterial load and HF symptom severity at 1 year. In summary, our study highlights important relationships between LV volumes, strain, and VA coupling and cardiac dysfunction and recovery with doxorubicin and trastuzumab, and provides motivation for future research into the potential relevance of diagnostic and therapeutic strategies focused on these measures.
In our cohort, LVEF deteriorated in the first year and incompletely recovered, to varying degrees, at 3 years in all treatment groups. Prior studies have found that the majority of LV dysfunction with anthracyclines typically occurs in the first year after completion of anthracycline exposure.\textsuperscript{3,12,33} Our data in participants exposed to doxorubicin without trastuzumab also suggest that LVEF declines occur early, and mild LVEF decreases persist even at 3 years. Prior studies of participants receiving trastuzumab have suggested that acute declines in LVEF are followed by high rates of recovery, leading to the notion that trastuzumab-associated cardiotoxicity is largely a transient, reversible process in contrast to the potentially irreversible injury caused by anthracyclines.\textsuperscript{34} Conversely, there are also data to suggest that depressed function may persist or recur in a number of patients.\textsuperscript{35,36} Our findings suggest that although trastuzumab-associated cardiac dysfunction may potentially be more reversible than doxorubicin-associated cardiotoxicity, it may not be completely reversible at 3 years. Longer-term follow-up is necessary to determine whether these changes persist over time. Last, participants in our cohort receiving both doxorubicin and trastuzumab demonstrated the greatest declines at 1 year, a finding that is consistent with prior studies that have suggested a synergistic cardiotoxic effect of both agents.\textsuperscript{2,37,38}

We also observed early increases in LV mass and relative wall thickness without increases in LV volumes in participants receiving doxorubicin without trastuzumab.
Concurrently, wall stress initially decreased then increased. Our results are consistent with a recent study demonstrating increases in LV mass in breast cancer participants receiving anthracyclines, but do contrast with prior studies that have reported decreases in LV mass and relative wall thickness according to time or anthracycline dose. The differences with these studies may be a result of the timing (within the first year after therapy initiation in comparison with late in survivorship) or modality (cardiac MRI) of assessment. In exploratory analyses, we did find that changes in LV mass were associated with time-varying changes in systolic blood pressure (P=0.01) and BMI (P<0.001), and this may offer some explanation to these findings. It is possible that early increases in mass may play a partial, compensatory role to initially reduce wall stress. This mechanism, however, may be inadequate, and the subsequent increase in wall stress contributes to the persistent declines in LVEF. These changes in LV mass could also reflect myocardial edema or early changes in cardiac architecture, including the development of fibrosis, and our finding of an association between decreases in LV mass and recovery of LVEF potentially supports this hypothesis. Further delineating the changes in LV mass over time in this cohort also provide motivation for continued, long-term follow-up.

Although most parameters had returned to baseline by 3 years postcancer therapy initiation, there were persistent, significant increases in E/e', Ees', and Ea. Although there were initial increases in LVEDV, diastolic volumes returned to baseline or were mildly decreased by the end of the study period. We postulate that these changes may be related to increased ventricular and arterial stiffness with these cancer therapies. It is interesting to note that increases in Ea and decreases in LVEDV were associated with worse HF symptoms at 1 year. A comprehensive characterization of measures of diastolic function and investigation into the potential development of a HF with preserved ejection fraction phenotype in the long term are warranted to gain further insight into these findings.

Changes in LVESV were strongly and consistently associated with changes in LVEF in all our analyses, and LVEDV demonstrated more modest associations with LVEF in comparison. As noted above, we observed late decreases in LVEDV, and, in exploratory analyses, we evaluated the impact of time on the associations of changes in LVEDV and LVESV with LVEF [online-only Data Supplement Table VII]. Increases in LVEDV were associated with LVEF declines before 2 years (P<0.001), but not after 2 years, with the exception of the Tras group (P<0.001). Thus, although late decreases in LVEDV are observed, these do not appear to be associated with changes in LVEF.

Longitudinal and circumferential strain, total arterial load, and the VA coupling ratio were also associated with declines in and recovery of LVEF. There was little evidence for effect modification by treatment regimen on these associations, suggesting that these relationships did not differ according to type of therapy. A number of studies have demonstrated abnormalities in longitudinal strain after cardiotoxic cancer therapies and the diagnostic and predictive utility of longitudinal strain. Our results add to these findings by further highlighting the associations between longitudinal strain and both the decline and recovery of cardiac function with doxorubicin without trastuzumab. Moreover, early changes in longitudinal strain were associated with subsequent changes in LVEF, further supporting its potential role as an early indicator of cardiac dysfunction in cardio-oncology. Circumferential strain was also noted to be strongly associated with LVEF change. This measure has been hypothesized to reflect a compensatory dimension of contractility, with deterioration reflecting late injury, and has also been previously shown to be associated with and predictive of dysfunction and recovery of LVEF. Our results parallel these findings, and suggest a need for further study of circumferential strain and associated mechanics in recovery. Ea, a measure of total arterial load, and Ea/Ees', a measure of VA coupling, were also associated with changes in LVEF at the same and subsequent visits. In prior studies, changes in arterial load have been noted in patients exposed to these therapies, although the relationship between changes in arterial load and VA interaction and recovery of LV function has not been previously described. Our findings reinforce the hemodynamic importance of afterload in HF and add to the body of work emphasizing the significance of afterload and VA coupling in cardio-oncology.

In exploratory analyses, early changes in arterial load, in addition to worsening of longitudinal and circumferential strain, demonstrated associations with a subsequent worsening of HF symptoms as assessed by the MDASI-HF. These analyses suggest clinically relevant associations between these echocardiographic parameters and patient-reported symptom severity. However, we did not find significant associations between echocardiographic parameters and HF symptoms at 2 years. The reasons for this are unclear, but suggest that additional studies with larger sample sizes and more novel, sensitive, and specific HF symptoms are warranted to examine this important question. It may also be that echocardiographic phenotyping alone is insufficient to capture the systemic effects of cancer therapy that may be contributing to these symptoms in the long-term.

We acknowledge the potential limitations to our study. First, although our overall sample size is the largest to date that comprehensively examines changes in LV remodeling in cardio-oncology, we cannot exclude the possibility of type II error. In particular, sample size limited our ability to examine differences between treatment groups and effects of antihypertensive and HF medica-
tions as they relate to recovery. We also maintained a limited set of confounders to avoid model instability. Measurement error is possible, although our laboratory has demonstrated excellent reliability with low observer variability. Our strain vendor analysis package and participant characteristics may have contributed to the borderline abnormal longitudinal strain values at baseline. In addition, because this is an observational study of echocardiographic measurements, we are only able to assess correlative rather than causal relationships among parameters. Future studies of diagnostic and therapeutic interventions targeting specific parameters could help determine whether the relationships we have described are, in fact, causal in nature. Last, the study period of 3 years may be insufficient to capture late effects and to discern how cardiac structure and function may further change (ie, with continued recovery or subsequent declines). Longer follow-up is warranted and ongoing.

In conclusion, doxorubicin and trastuzumab result in significant and sustained changes in LVEF. Although the patterns of LVEF change differed across treatment groups, the structural and physiological associations with LVEF change were largely similar. Measures of LV volumes, strain, and VA coupling are strongly associated with LVEF decline and recovery, and early changes in these measures are associated with subsequent changes in LVEF 2 years posttherapy. Our findings provide evidence to support the importance of volumes, strain, and VA coupling in LVEF changes with cancer therapy, and motivate potential future studies of diagnostic and therapeutic strategies focused on these measures.

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DISCLOSURES

None.

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FOOTNOTES

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