Longitudinal Assessment of Concurrent Changes in Left Ventricular Ejection Fraction and Left Ventricular Myocardial Tissue Characteristics After Administration of Cardiotoxic Chemotherapies Using T1-Weighted and T2-Weighted Cardiovascular Magnetic Resonance

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Background—In a murine anthracycline-related cardiotoxicity model, increases in cardiovascular magnetic resonance myocardial contrast-enhanced T1-weighted signal intensity are associated with myocellular injury and decreases with left ventricular ejection fraction. We sought to determine whether T1- and T2-weighted measures of signal intensity associate with decreases in left ventricular ejection fraction in human subjects receiving potentially cardiotoxic chemotherapy.

Methods and Results—In 65 individuals with breast cancer (n=51) or a hematologic malignancy (n=14), we measured left ventricular volumes, ejection fraction, and contrast-enhanced T1-weighted and T2-weighted signal intensity before and 3 months after initiating potentially cardiotoxic chemotherapy using blinded, unpaired analysis of cardiovascular magnetic resonance images. Participants were aged 51±12 years, of whom 55% received an anthracycline, 38% received a monoclonal antibody, and 6% received an antimicrotubule agent. Overall, left ventricular ejection fraction decreased from 57±6% to 54±7% (P<0.001) because of an increase in end-systolic volume (P<0.05). T1-weighted signal intensities also increased from 14.1±5.1 to 15.9±6.8 (P<0.05), with baseline values trending higher among individuals who received chemotherapy before study enrollment (P=0.06). Changes in T1-weighted signal intensity did not differ within the 17 LV myocardial segments (P=0.97). Myocardial edema quantified from T2-weighted images did not change significantly after 3 months (P=0.70).

Conclusions—Concordant with previous animal studies, cardiovascular magnetic resonance measures of contrast-enhanced T1-weighted signal intensity occur commensurate with small but significant left ventricular ejection fraction declines 3 months after the receipt of potentially cardiotoxic chemotherapy. These data indicate that changes in T1-weighted signal intensity may serve as an early marker of subclinical injury related to the administration of potentially cardiotoxic chemotherapy in human subjects. (Circ Cardiovasc Imaging. 2014;7:872-879.)

Key Words: anthracyclines ■ cardiotoxicity ■ chemotherapy ■ left ventricular function ■ magnetic resonance imaging

Commonly administered chemotherapeutic regimens are associated with acute and chronic cardiac injury and future cardiovascular events.1 Methods to detect early evidence of subclinical cardiac injury could be useful for selecting individuals who might benefit from therapeutic interventions to prevent deterioration in left ventricular (LV) performance or subsequent cardiovascular events.1,2 Cardiovascular magnetic resonance (CMR) assessed changes in myocardial T1 and T2 magnetic relaxation from ex vivo samples, small animal studies, and human case series have been observed after the administration of anthracycline-based chemotherapy (Anth-bC).1,4 Moreover, in one study, regional changes in LV lateral wall myocardial signal intensity occurred after the receipt of trastuzumab for breast cancer.6

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Previously in a murine model of Anth-bC cardiotoxicity, we demonstrated that increases in global T1-weighted late gadolinium contrast-enhanced signal intensity (LGE-SI) CMR (1) identified histopathologic evidence of myocardial injury consistent with anthracycline administration, and (2) predicted future decrements in LV ejection fraction (LVEF) during the longitudinal receipt of doxorubicin, an anthracycline.7 To
date, however, it is unknown whether similar changes in contrast-enhanced T1-weighted and T2-weighted CMR measures of signal intensity are associated with LVEF changes among patients receiving Anth-bC or other potentially cardiotoxic chemotherapy for breast cancer, leukemia, or lymphoma. In addition, it is uncertain whether regional (eg, lateral or septal wall) changes in these measures are associated with LVEF changes above and beyond global measures.

Accordingly, we performed a prospective longitudinal cohort study to determine whether either regional or global changes in T1-weighted and T2-weighted CMR signal intensity were associated with coincident changes in LV performance early after the receipt of potentially cardiotoxic chemotherapy.

Methods

Study Population

This study was approved by the Institutional Review Board at the Wake Forest University School of Medicine, and all study participants provided written, witnessed informed consent. The study was funded by the National Cancer Institute of the National Institutes of Health, R33CA12196, and by the Susan G. Komen Foundation, BCTR07007769. Eligible participants, recruited through the Comprehensive Cancer Center of Wake Forest University School of Medicine, included those scheduled to receive Anth-bC and other known cardiotoxic agents used in the treatment of breast cancer, leukemia, or lymphoma. Participants were ineligible for enrollment if they exhibited a contraindication for CMR, history of myocardial infarction, or an estimated glomerular filtration rate <60 mL/min/1.73 m² calculated using serum creatinine obtained from blood draw before each CMR examination.8

T1 and T2 signal intensity based on heart rate. In accordance with prior publications, the T1 was selected for a uniform dark myocardium at the baseline CMR examination and held constant at the follow-up examination.7

Images were transferred off-line for postprocessing in MATLAB (The Mathworks, Inc., Natick, MA) software, where myocardial endocardial and epicardial boundaries were identified by carefully tracing the myocardial boundaries to avoid partial volume effects (Figure 1A and 1B). A spoke tool divided the LV myocardium into the 17-segment American Heart Association (AHA) model.9 Thereafter, the 3-dimensional coordinates of each voxel, corresponding segment number, and signal intensity values were exported for subsequent analyses. The mean and standard deviation of contrast-enhanced T1-weighted signal intensity (LGE-SI) was calculated for each AHA segment within the myocardium for each examination (Figure 1C).

Using this technique in our laboratory, we have performed repeated measures separated by 2 weeks in 7 asymptomatic, cancer-free individuals without a substantive change in their clinical condition. Images were analyzed in an unpaired, blinded fashion with excel lent correlation between repeated measures (y=0.87x+1.2, R²=0.98). We then performed a blinded reproducibility analysis with CMR examinations separated by 2 months and found excellent agreement between visits (6.38±0.67 versus 6.35±0.68) with high correlation (y=0.91x+0.1, R²=0.99).

Myocardial precontrast T1 was quantified in 10 participants at baseline and follow-up using a modified Look-Locker inversion recovery sequence.10 Breath-held T1 mapping images were acquired in the midcavity short-axis plane using a 380×342 mm field of view, 240×151 matrix, 1.5° flip angle, 110 Hz/pixel bandwidth, 8-mm slice thickness, 1.95-ms echo time, and 3.9-ms repetition time. Mean myocardial T1 was calculated after segmentation (Figure 1) and adjusted for heart rate.16

T2-Weighted Imaging

Breath-held dark-blood T2-weighted turbo spin echo images were acquired before contrast administration in the midcavity short-axis plane using a matrix, 0.0 mm field of view, 256×216 matrix, 1.5° flip angle, 780 Hz/pixel bandwidth, 66-ms echo time, and repetition time of twice the RR interval.11 Myocardial contours were drawn with the addition of region of interest in the serratus anterior muscle to measure T2-weighted signal intensity in the skeletal muscle. Myocardial relative enhancement was quantified as the ratio of myocardial to skeletal muscle signal intensity.12,13 Percentage myocardial edema was calculated from the amount of myocardial voxels with a relative enhancement ≥2.14

Statistical Analyses

All statistical analyses were completed using SAS statistical software (v9.2; Cary, NC). Statistical means and standard deviations were calculated for all continuous variables, and the frequencies and percentages for all categorical variables were tabulated. Serial measurements were compared using Student paired t tests. The study population was dichotomized for subgroup analyses into participants with or without prior chemotherapy exposure before current chemotherapy treatment. Two-sample Student t tests were used to test difference of means in subgroup analyses, and correlations of variables were analyzed by linear regression models and Pearson correlation coefficients. Categorical variables were compared between the subgroups using Fisher exact and χ² tests.

After overall cohort analyses, outcomes were investigated with a series of sensitivity analyses performed with analysis of covariance. Adjustments for multiple comparisons were made for sensitivity analyses after accounting for a maximum of 5 baseline covariates. Outcome variables were adjusted for only for covariates determined to be significant in sensitivity analyses. In addition, longitudinal mixed models were used to determine the association of serial measurements with segment, slice, and LV wall location. Logistic regression modeling was used to determine the prognostic value of the baseline LGE-SI in forecasting future LVEF changes. A preselect ed composite end point of a clinically significant LVEF decrease was defined as a decrease in the follow-up measurement ≥10% or an absolute value <50%. Prior chemotherapy and number of comorbidities
were included in the modeling to account for baseline risk factors that may affect LV fibrosis and LVEF for reasons other than chemotherapy. All values are reported as mean±standard deviation unless stated otherwise; a value of $P \leq 0.05$ was considered significant.

### Results

The demographic data of the study population including cardiovascular comorbidities and cancer diagnoses are displayed in Table 1. The total amount of anthracyclines in doxorubicin equivalent dosage ranged from 60 to 500 mg/m2, with a median dose of 240 mg/m2. Of the 23 participants previously treated with chemotherapy, 14 received an anthracycline (average dose of 240 mg/m2 11±21 months before enrollment). All baseline and change in CMR measurements are listed in Table 2 (see the Table in the Data Supplement for follow-up CMR measurements). No differences in baseline LVEF were identified for age ($P=0.76$), sex ($P=0.34$), cancer type ($P=0.43$), hypertension ($P=0.95$), diabetes mellitus ($P=0.58$), hyperlipidemia ($P=0.14$), or a history of tobacco use ($P=0.91$). Similarly, no differences in baseline contrast-enhanced T1-weighted measures (LGE-SI) were associated with age ($P=0.23$), cancer type ($P=0.29$), hypertension ($0.41$), diabetes mellitus ($0.71$), hyperlipidemia ($0.29$), or a history of tobacco use ($0.15$). The LV mass index did not statistically change at the follow-up examination (51±12 g/m2) compared with baseline values (54±11 g/m2, $P=0.35$).

A small increase in glomerular filtration rate was observed during the study from 96±18 mL/min/1.73 m2 at baseline to 100±20 mL/min/1.73 m2 at follow-up CMR examination ($P=0.02$). Overall, we observed no statistically significant change from baseline to follow-up in serum troponin-I levels (0.031±0.09 ng/mL to 0.045±0.05 ng/mL, $P=0.11$) or B-type natriuretic peptide levels (46.8±17.9 pg/mL to 44.1±16.8 pg/mL, $P=0.41$).

The LVEF declined among all participants from 57±6% to 54±7% 3 months postchemotherapy ($P=0.0002$, Figure 2). After accounting for prior chemotherapy administration, LVEF changed significantly ($P=0.01$) and was lower at baseline in those treated previously ($P=0.02$); however, the LVEF change was no different between the subgroups dichotomized by prior chemotherapy administration ($P=0.92$). In secondary analyses, the LVEF declined because of reduced contractility as measured by an increase in LVESV ($P<0.05$) rather than by volume depletion (LV end-diastolic volume did not change significantly [$P=0.32$]). The LVEF change was not affected by age ($P=0.75$), sex ($P=0.80$), cancer type ($P=0.60$), administration of anthracycline versus other chemotherapy drug classes ($P=0.29$), or cardiovascular risk factors including hypertension ($P=0.94$), hyperlipidemia ($P=0.78$), diabetes mellitus ($P=0.42$), or history of tobacco use ($P=0.61$).

No focal areas of increased LGE-SI consistent with an infarct or underlying fibrosis were visually appreciated in any study participant. At baseline, a reduced LVEF was not associated with increased T1-weighted signal ($R^2=0.02$, $P=0.25$). LGE-SI increased from 14.1±5.1 to 15.9±6.8 at follow-up ($P<0.05$). The standard deviation of LGE-SI did not significantly change during the 3 months ($\Delta \sigma = 0.17±2.1$, $P=0.52$). Changes in LGE-SI were not associated with

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**Figure 1.** A and B, Segmentation of endocardial (green) and epicardial (red) borders using splines for extraction of myocardial voxels in cardiovascular magnetic resonance (CMR) analysis. C, AHA 17-segment models for one participant at baseline and 3 months after chemotherapy demonstrating diffuse increases in contrast-enhanced T1-weighted signal intensity across the myocardium commensurate with a large left ventricular ejection fraction (LVEF) drop.
anthraclycine dose \((P=0.98)\) or anthracycline drug received \((P=0.91)\). Similarly, changes in LGE-SI were not associated with demographic variables, including age \((P=0.77)\), sex \((P=0.44)\), cancer type \((P=0.46)\), administration of Anth-bC versus other chemotherapy drug classes \((P=0.81)\), or cardiovascular risk factors including hyperlipidemia \((P=0.01)\), hypertension \((P=0.44)\), diabetes mellitus \((P=0.62)\), or history of tobacco use \((P=0.27; P<0.006\) considered statistically significant after correction for multiple comparisons). LGE-SI changes were not associated with a change in LV mass index \((P=0.55)\). In addition, LGE-SI changes were not associated with serum troponin-I and B-type natriuretic peptide levels \((P=0.68\) and \(P=0.18\), respectively).

### Table 1. Study Participant Descriptive Characteristics of Baseline Cardiovascular Risks and Cancer Treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Subjects ((n=65))</th>
<th>No Prior Chemo ((n=42))</th>
<th>Prior Chemo ((n=23))</th>
<th>No Prior vs Prior Chemo: (P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (15)</td>
<td>7 (17)</td>
<td>3 (13)</td>
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<td>Hypertension, n (%)</td>
<td>31 (48)</td>
<td>19 (45)</td>
<td>12 (52)</td>
<td>0.61</td>
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<tr>
<td>Hyperlipidemia, n (%)</td>
<td>15 (23)</td>
<td>10 (24)</td>
<td>5 (22)</td>
<td>1.00</td>
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<tr>
<td>Tobacco use, n (%)</td>
<td>29 (45)</td>
<td>18 (43)</td>
<td>11 (48)</td>
<td>0.80</td>
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<td><strong>Body mass index, kg/m²</strong></td>
<td>29 ±7</td>
<td>29 ±8</td>
<td>28 ±5</td>
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### Table 2. Cardiovascular Magnetic Resonance Measurements of Study Cohorts at Baseline Examination and Longitudinal Change From Baseline (3 Months–Baseline)

<table>
<thead>
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<th>Characteristics</th>
<th>All Subjects ((n=65))</th>
<th>No Prior Chemo ((n=42))</th>
<th>Prior Chemo ((n=23))</th>
<th>No Prior vs Prior Chemo: (P) Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline values</strong></td>
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<tr>
<td>LVEDV, mL</td>
<td>109 ±35</td>
<td>113 ±35</td>
<td>101 ±33</td>
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<tr>
<td>LVEDV indexed, mL/m²</td>
<td>57 ±13</td>
<td>58 ±12</td>
<td>55 ±15</td>
<td>0.47</td>
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<td>LVESV, mL</td>
<td>46 ±17</td>
<td>46 ±16</td>
<td>46 ±17</td>
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<td>LVESV indexed, mL/m²</td>
<td>24 ±7</td>
<td>24 ±6</td>
<td>25 ±8</td>
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<tr>
<td>Stroke volume, mL</td>
<td>63 ±21</td>
<td>67 ±21</td>
<td>55 ±18</td>
<td>0.02*</td>
</tr>
<tr>
<td>Stroke volume indexed, mL/m²</td>
<td>33 ±8</td>
<td>34 ±8</td>
<td>30 ±8</td>
<td>0.05</td>
</tr>
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</table>

### Change from baseline

<table>
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<tr>
<th>Characteristics</th>
<th>All Subjects ((n=65))</th>
<th>No Prior Chemo ((n=42))</th>
<th>Prior Chemo ((n=23))</th>
<th>No Prior vs Prior Chemo: (P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESV, mL</td>
<td>63 ±21</td>
<td>67 ±21</td>
<td>55 ±18</td>
<td>0.02*</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>0 ±17</td>
<td>–2 ±18</td>
<td>2 ±16</td>
<td>0.31</td>
</tr>
<tr>
<td>Stroke volume indexed, mL/m²</td>
<td>0 ±9</td>
<td>–1 ±10</td>
<td>2 ±8</td>
<td>0.22</td>
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The LGE-SI increased at follow-up across all AHA segments \((P<0.0001)\) and within each short-axis slice \((P=0.009)\) without a greater increase in any particular slice \((P=0.94)\) or AHA segment \((P=0.97)\). In addition, increase in LGE-SI was similar across wall regions of the left ventricle, specifically in the septal wall, anterior wall, and posterior-lateral walls \((P=0.92)\).

We measured midcavity myocardial T1 by mapping in 10 individuals, of whom 6 were newly diagnosed patients with cancer and 4 were previously treated with anthracyclines. Four newly diagnosed individuals received anthracyclines, and all others were treated with monoclonal antibodies. Overall, this subgroup had fewer cardiovascular risk factors than found in the rest of the study population \((0.50±0.53\) versus \(1.53±1.3\) total risk factors, \(P=0.0003)\). During 3 months, precontrast T1 did not change significantly \((973±36\) versus \(982±29\) ms, \(P=0.53)\). In these same individuals, the midcavity contrast-enhanced T1-weighted images remained stable between baseline and follow-up \((15.2±5.6–15.2±7.9, P=0.99)\)
as did the LVEF (56±6–56±7, P=0.93). T1 did not change significantly for participants whether newly diagnosed or previously treated (P=0.99 for both). The change in precontrast T1 values were significantly correlated with LGE-SI changes (R²=−0.64, P<0.05) and trended to correlate with LVEF changes (R²=−0.60, P=0.06).

In newly diagnosed patients with cancer (n=6), myocardial T1 trended toward a correlation with midwall T1 signal intensity (R²=0.27, P=0.08). These 2 measures were significantly correlated with one another in individuals previously treated with anthracyclines (R²=0.63, P=0.02). Myocardial T1 did not correlate with percentage edema in either subgroup (P>0.21 for both).

Analyzable T2-weighted images were acquired at baseline and follow-up in 52 individuals. Compared with baseline, we observed no appreciable differences 3 months after chemotherapy initiation in relative enhancement (1.3±0.3 at baseline versus 1.4±0.3 at 3 months, P=0.17) or percentage edema (4.2±12% versus 5.6±11%, P=0.70). No differences between those with or without prior chemotherapy were found for change in relative enhancement (P=0.23) or percentage edema (P=0.34). Similarly, no statistically significant changes in relative enhancement (P=0.27) and percentage edema (P=0.59) were observed among the 31 individuals treated with anthracyclines.

Stratified analyses were performed on individuals with and without chemotherapy treatment before enrollment. First, the LV stroke volume and consequently LVEF were reduced at baseline in participants with prior chemotherapy (P=0.02 and P=0.007, respectively). Three months after chemotherapy initiation, those receiving chemotherapy for the first time had decreases in LVEF from 59±6% to 55±6% (P=0.003) and increases in LGE-SI from 13.2±4.7 to 15.6±6.8 (P=0.04; Figure 3). In participants receiving their second or third course of chemotherapy, LVESV increased (P=0.006) and LVEF decreased from 55±6% to 52±7% (P=0.02) over the study. In these same participants, myocardial contrast-enhanced T1-weighted measures trended toward an elevation at baseline relative to newly diagnosed individuals (P=0.06), and a smaller increase in contrast-enhanced T1-weighted measures between baseline and follow-up was observed (15.7±5.3–16.5±7.0, P=0.60; Figure 3). LGE-SI was assessed in a 6-month follow-up examination in n=60 of the study participants and trended to remain elevated when compared with baseline values (15.4±6.6, P=0.10).

In participants with a low to moderate risk of developing coronary artery disease (≤2 cardiovascular comorbidities), we examined whether baseline LGE-SI, baseline LVEF, and prior chemotherapy exposure were predictive of a clinical LVEF decline at 3 months. Of the 52 participants, 19 experienced a primary event of clinical LVEF decline. After adjusting for prior chemotherapy administration, baseline LGE-SI signal and LVEF trended to be significant predictors of a LV decline (P=0.09 and P=0.16, respectively). For those with prior chemotherapy, a higher LGE-SI (β=0.28, P=0.07) or lower LVEF (β=−0.14, P=0.09) at baseline increased the probability of having the clinical LVEF decline 3 months after chemotherapy initiation.

**Discussion**

Three conclusions can be drawn from the results of this study. First, global measures of contrast-enhanced T1-weighted images obtained 10 minutes after the administration of 0.2 mmol/kg of gadoteridol contrast are associated with a decline in LVEF in patients receiving chemotherapy for the treatment of breast cancer or a hematologic malignancy. These findings persist regardless of age, sex, cancer treatment, or the presence of underlying cardiovascular comorbidities. The observed LVEF declines were driven by increases in LVESV (P=0.05), a measure of reduced myocardial contractility, rather than declines in LV end-diastolic volume (P=0.32) that may occur in patients with cancer who are in poor health and can exhibit intravascular volume depletion. Second, patients previously receiving chemotherapy trended toward higher resting measures of contrast-enhanced T1-weighted signal intensity within the LV myocardium relative to newly diagnosed patients without prior chemotherapy (P=0.06; Table 2).
Finally, increases in contrast-enhanced T1-weighted signal intensity occur globally and diffusely throughout the LV myocardium without regional differences among LV myocardial segments ($P=0.92$) or slice locations ($P=0.94$). This increase in T1 signal intensity occurred without evidence of increased myocardial edema measured on T2-weighted images after chemotherapy administration ($P=0.70$).

Previously, we have shown that LV dysfunction occurs early after cardiotoxic chemotherapy because of an increase in LVESV and diminished contractility measured by myocardial strain with CMR.9 Furthermore, increased LGE-SI forecasted clinical cardiotoxicity with histopathologic evidence of vacuolization and acute myocardial injury.7 In this study, we sought to determine whether similar changes in T1-weighted imaging occur commensurate with LVEF in human subjects treated for cancer. No participants with prior infarction were enrolled into the study and no participants had evidence of focal hyperenhancement because of acute infarction throughout the study. Glomerular filtration rate remained >60 mL/min/1.73 m² throughout both examination study points and is therefore presumed to minimally impact repeated T1-weighted measurements. Furthermore, the small increase in glomerular filtration rate observed in this study would, if anything, increase gadolinium clearance and bias the results toward the null.

Baseline mean contrast-enhanced T1-weighted signal intensity was increased in participants previously treated with chemotherapy versus chemotherapy-naive participants. There are several possibilities for this finding. First, recent studies using T1 mapping strategies have shown an increase in T1 values in the setting of chronic cardiomyopathy and fibrosis.16,20–23 Because our baseline T1-weighted measures were obtained several years after initial receipt of cardiotoxic chemotherapy, chronic replacement fibrosis may have been present in our participants. Second, as we have previously shown in animals, acute, subacute, and chronic myocellular injury can be appreciated with CMR.19 Furthermore, increased LGE-SI and cardiomyopathies.26 In this study, we observed similar findings in individuals treated with anthracycline-based or trastuzumab-based chemotherapy for breast cancer or a hematologic malignancy.

Blood biomarkers and T2-weighted measures of edema did not significantly change at the 3-month follow-up visit. The timing of our blood collection and image acquisition relative to the dosing of chemotherapy may have contributed to this finding. In prior CMR studies of acute ischemia or inflammation associated with T2-related changes associated with myocardial edema occur commensurate with the disease process and resolve by 2 weeks.24 Our study design scheduled the 3-month follow-up CMR examination to precede chemotherapy administration on the day of the study visit, thereby reflecting a predose rather than postdose effect which has been evaluated in other studies.5,25 Future serial CMR studies during the subacute phase immediately after a cycle of chemotherapy are needed to determine whether T2-weighted imaging or T2 mapping may detect active myocardial water accumulation associated with acute or immediate injury in addition to T1 mapping, which can appreciate both acute and chronic injury.20,25

The major therapeutic agents received by enrolled participants (Table 1; anthracyclines, antimicrotubules, and monoclonal antibodies) are each associated with heart failure.26 Anthracyclines and antimicrotubules, however, are also associated with EKG changes and myocardial ischemia/infarction; monoclonal antibodies are associated with LV dysfunction and cardiomyopathies.26 In this study, we observed similar findings in individuals treated with anthracycline-based or trastuzumab-based chemotherapy for breast cancer or a hematologic malignancy.

The mean contrast-enhanced T1-weighted signal intensity increased globally and diffusely across all LV myocardial segments of the 17-segment AHA model ($P<0.0001$). Regional changes in LV lateral wall myocardial signal intensity after the receipt of trastuzumab for breast cancer have been observed previously; however, we did not find any regional T1 changes with respect to LV wall region ($P=0.92$) or short-axis slice ($P=0.94$). Perhaps the inclusion of only participants with confirmed trastuzumab-induced cardiomyopathy in the retrospective report by Fallah-Rad is responsible for the prior finding. At that time, more pronounced fibrosis may have been present, or participants may have experienced a secondary viral type infection after their cancer treatment.27 Our prospective study sought to identify early noninvasive markers of myocardial tissue changes using serial imaging across a somewhat diverse population that included several cancer types and treatment regimens that have been previously associated with the development of chemotherapy-induced cardiotoxicity.

Importantly, the histopathologically validated quantitative methodology tested previously in animal models identified elevations in T1 signal commensurate with small but significant declines in LVEF related to increases in LV end-systolic volume after the receipt of cardiotoxic chemotherapy. Previous studies have measured T1 and extracellular volume (ECV) in adult and pediatric survivors of cancer, showing disparate results. Both pediatric studies found T1 and ECV of survivors within normal ranges, yet showed associations with reduced functional capacity and anthracycline dose.24,29 In adult survivors, ECV was elevated compared with controls.30 We found no longitudinal change in precontrast T1; however,
this healthier subgroup had fewer cardiovascular risk factors than the rest of the study population, which may also explain the stable longitudinal LGE and LVEF measurements in this subgroup. Further studies are needed to investigate changes in T1 in the subacute and acute phases of cardiotoxicity.

Our study does have potential limitations. First, we did not obtain myocardial biopsy samples for correlation with CMR image results, but our methodology has been validated histopathologically in a previous animal model of chemotherapy-induced cardiotoxicity. Second, we were ethically unable to include subjects with cancer who had chemotherapy withheld as a control group in our study. To address this, we have previously quantified the variability of the method in case-control animal model study and the reproducibility in human subjects free of acute or chronic disease with no change in their medical condition ($R^2=0.99$). Third, our study population included an admixture of chemotherapy treatments and patient demographics. Larger studies could clarify the utility of this methodology and newer techniques to determine whether those receiving specific chemotherapeutic regimens were more or less susceptible to cardiac injury based on their demographics, including preexisting cardiovascular disease and LV dysfunction. Finally, the T1-weighted and T2-weighted imaging methodology requires constant imaging parameters at successive visits (such as the inversion time and time passed between contrast administration and image acquisition). We were unable to obtain direct T1, T2, or ECV quantification in most of our study participants because of the limited availability of mapping sequences at the time this study was conducted and as such, are underpowered to draw conclusions regarding these results. These findings, however, demonstrate that changes in magnetic relaxation, upon which T1 and T2 mapping sequences are based, are associated with myocardial injury early after chemotherapy exposure in an admixture of patients with cancer. Moreover, qualitative T1-weighted and T2-weighted imaging sequences are commercially available unlike mapping sequences that are limited to academic centers for development currently. It will be advantageous in future studies to include emerging quantitative T1 (native and postcontrast), T2, and ECV mapping to discriminate acutely injured myocardium from chronically injured myocardium.

In conclusion, similar to our findings observed in animals, potentially cardiotoxic chemotherapy is associated with an increase in signal intensity on T1-weighted images and a decline in LVEF in humans receiving chemotherapy. In individuals without prior exposure to chemotherapy, a further increase in signal intensity within the LV myocardium on contrast-enhanced T1-weighted images is associated with a decline in LVEF on the receipt of potentially cardiotoxic chemotherapy. The results of this study suggest that future studies should be conducted to determine whether newer quantitative methods of myocardial T1 and T2 mapping identify subclinical myocardial injury in patients receiving potentially cardiotoxic chemotherapy.

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Disclosures

None.

References


CLINICAL PERSPECTIVE
This study is an important translation of previously published animal work exploring the utility of cardiovascular MRI for identifying subclinical cardiotoxicity because of chemotherapy. Current surveillance strategies seek to serially assess the left ventricular ejection fraction by radionuclide or echocardiographic techniques. These strategies, however, identify the late cardiotoxic effects of chemotherapy after which the injury may be irreversible. In this article, we quantify myocardial tissue characteristics using longitudinal assessments of T1-weighted and T2-weighted cardiovascular MRI before and after the receipt of chemotherapy in a cohort of 65 adult patients with cancer receiving potentially cardiotoxic chemotherapies. Newer mapping techniques were assessed in a subset of study participants. Three months after chemotherapy initiation, measures of contrast-enhanced T1-weighted signal intensities increased globally and diffusely throughout the left ventricle commensurate with a decline in the left ventricular ejection fraction, without evidence of myocardial edema measured via T2-weighted images. Elevated baseline contrast-enhanced T1-weighted signal intensities were observed among patients with cancer who were treated previously with chemotherapy suggesting persistent myocardial injury from prior chemotherapy exposure. These findings corroborate previous results in animal studies, indicating that myocardial tissue characterization techniques with cardiovascular MRI may be used to identify early subclinical evidence of myocardial injury after the receipt of potentially cardiotoxic chemotherapy. Our findings of T1-weighted and T2-weighted tissue changes lay an important foundation for future studies with T1, T2, and extracellular volume mapping techniques to identify and elucidate the development of myocardial injury, edema, and fibrosis associated with potentially cardiotoxic chemotherapy treatments.
Longitudinal Assessment of Concurrent Changes in Left Ventricular Ejection Fraction and Left Ventricular Myocardial Tissue Characteristics After Administration of Cardiotoxic Chemotherapies Using T1-Weighted and T2-Weighted Cardiovascular Magnetic Resonance


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Supplemental Table 1. CMR measurements of study cohorts at 3 month follow-up examination.

<table>
<thead>
<tr>
<th>CMR Measurements at 3 Month Follow-up</th>
<th>All Subjects (n=65)</th>
<th>No Prior Chemo (n=42)</th>
<th>Prior Chemo (n=23)</th>
<th>No Prior vs Prior Chemo: p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate, bpm</td>
<td>77±15</td>
<td>77±14</td>
<td>75±17</td>
<td>0.59</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>113±32</td>
<td>115±31</td>
<td>112±33</td>
<td>0.72</td>
</tr>
<tr>
<td>LVEDV indexed, ml/m²</td>
<td>59±16</td>
<td>58±17</td>
<td>61±13</td>
<td>0.47</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>51±18</td>
<td>50±16</td>
<td>54±21</td>
<td>0.38</td>
</tr>
<tr>
<td>LVESV indexed, ml/m²</td>
<td>27±9</td>
<td>25±9</td>
<td>29±9</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke Volume, ml</td>
<td>62±18</td>
<td>65±19</td>
<td>57±15</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke Volume indexed, ml/m²</td>
<td>33±8</td>
<td>34±8</td>
<td>32±7</td>
<td>0.39</td>
</tr>
<tr>
<td>T2w Relative Enhancement</td>
<td>1.4±0.3</td>
<td>1.4±0.3</td>
<td>1.3±0.3</td>
<td>0.53</td>
</tr>
<tr>
<td>Myocardial Edema, %</td>
<td>5.6±11</td>
<td>7.0±13</td>
<td>3.2±6.9</td>
<td>0.15</td>
</tr>
<tr>
<td>LGE-SI</td>
<td>15.9±6.8</td>
<td>15.6±6.8</td>
<td>16.5±7.0</td>
<td>0.62</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54±7</td>
<td>56±6</td>
<td>52±7</td>
<td>*0.02</td>
</tr>
</tbody>
</table>

Values reported as mean ± standard deviation. \( p < 0.05 \) considered statistically significant (*). 

\( p \)-values reported in last column from t-test of differences in means for continuous variables and Fisher’s exact / chi-square tests for categorical differences between subgroups of prior chemotherapy.