**Novel Approach to Early Detection of Doxorubicin Cardiotoxicity by Gadolinium-Enhanced Cardiovascular Magnetic Resonance Imaging in an Experimental Model**

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**Background**—We sought to determine whether cardiovascular magnetic resonance measures of gadolinium (Gd) signal intensity (SI) within the left ventricular myocardium are associated with future changes in left ventricular ejection fraction (LVEF) after receipt of doxorubicin (DOX).

**Methods and Results**—Forty Sprague-Dawley rats were divided into 3 groups scheduled to receive weekly intravenous doses of normal saline (n = 7), 1.5 mg/kg DOX (n = 19), or 2.5 mg/kg DOX (n = 14). Magnetic resonance determinations of LVEF and myocardial Gd-SI were performed before and at 2, 4, 7, and 10 weeks after DOX initiation. During treatment, animals were euthanized at different time points so that histopathologic assessments of the left ventricular myocardium could be obtained. Within-group analyses were performed to examine time-dependent relations between Gd-SI and primary events (deterioration in LVEF or an unanticipated death). Six of 19 animals receiving 1.5 mg/kg DOX and 10 of 14 animals receiving 2.5 mg/kg DOX experienced a primary event; no normal saline animals experienced a primary event. In animals with a primary event, histopathologic evidence of myocellular vacuolization occurred (P = 0.04), and the Gd-SI was elevated relative to baseline at the time of the event (P = 0.0001) and during the measurement period before the event (P = 0.0001). In all animals (including normal saline) without an event, measures of Gd-SI did not differ from baseline.

**Conclusions**—After DOX, low serial measures of Gd-SI predict an absence of an LVEF drop or unanticipated death. An increase in Gd-SI after DOX forecasts a subsequent drop in LVEF as well as histopathologic evidence of intracellular vacuolization consistent with DOX cardiotoxicity. (*Circ Cardiovasc Imaging. 2010;3:550-558.*)

**Key Words:** cardiotoxicity ■ chemotherapy ■ congestive heart failure ■ doxorubicin

Doxorubicin (DOX) is an important drug in modern therapy for breast cancer, soft-tissue sarcomas, acute leukemia, Hodgkin’s and non-Hodgkin’s lymphoma, and many childhood cancers.1 Unfortunately, the use of DOX, as well as other anthracyclines, is limited by cardiotoxicity that precipitates congestive heart failure (CHF).2

**Clinical Perspective on p 558**

DOX-induced cardiomyopathy is difficult to detect. Serial measures of left ventricular ejection fraction (LVEF) with radionuclide ventriculography or transthoracic echocardiography are often used to screen cancer patients for irreversible cardiotoxicity and congestive heart failure, but an observed drop in LVEF often occurs too late to avert irreversible cardiomyopathy.2,3 Also, current clinical surveillance imaging strategies do not identify early myocardial evidence of DOX cardiotoxicity.

Cardiovascular magnetic resonance (CMR) imaging can be used to characterize myocardial tissue and to identify myocardial necrosis and fibrosis without exposure to ionizing radiation or radioisotopes.5 This study was performed in animals receiving DOX to determine whether changes in gadolinium (Gd) signal intensity (SI) on T1-weighted CMR images would forecast a future drop (or preservation) of LVEF or histopathologic findings indicative of myocardial injury, necrosis, or fibrosis.

**Methods**

**Study Design**

This study was conducted at the Wake Forest University School of Medicine as part of a protocol approved by the animal care and use committee and funded by the National Institutes of Health (study identifier R21CA109224). A total of 40 male Sprague-Dawley rats...
were used for anesthesia during CMR acquisitions. After each CMR, inhalational isoflurane, 0.0004 mg/g IM ketamine, and 0.004 mg/g IM xylazine from ECG leads attached bilaterally to the paws. Scans were obtained with a 1.5-T scanner equipped with a small phased-array surface coil wrapped around the animals to enhance resolution.

### CMR Technique

Scans were obtained with a 1.5-T scanner equipped with a small phased-array surface coil wrapped around the animals to enhance signal to noise. Images were collected by cardiac gating obtained from ECG leads attached bilaterally to the paws. Inhalational isoflurane, 0.0004 mg/g IM ketamine, and 0.004 mg/g IM xylazine were used for anesthesia during CMR acquisitions. After each CMR procedure, the animals were allowed to recover under a warm light to preserve body heat.

According to previously published methods, cine white-blood, steady-state free-precession images were collected for measuring LV volumes and EF. These sequences were placed along the long axis of the left ventricle as a series of 3-mm-thick mid—short-axis slices separated by a 3-mm gap. Imaging parameters for these sequences included an 8.3-ms repetition time, a 3.0-ms echo time, a 6-cm field of view, a 256×256 matrix, and a 30° flip angle. Calculation of LV volumes and EF included an 8.3 ms repetition time, a 3.0 ms echo time, a 30° flip angle. Observation of Gd-SI included a Gd-enhanced inversion-recovery image with a 6 ms repetition time, a 10 ms echo time, a 30° flip angle. The CMR parameters for imaging strategy in this study was selected to detect myocardial fibrosis in the midwall of the left ventricle. The CMR parameters for observing Gd-SI included a Gd-enhanced inversion-recovery image with a 6 ms repetition time, a 2 ms echo time, a 6 cm field of view, a 256×256 matrix, and a 30° flip angle. Calculation of LV volume was performed according to previously published techniques by summing the endocardial area within each slice and multiplying by the slice thickness. To determine LVEF, the LV stroke volume was acquired by subtracting the LV end-diastolic volume from the end-systolic volume and then dividing by the end-diastolic volume.

### Determination of Gd Signal Characteristics

Animals were injected via the tail vein with 0.2 mm/kg gadoteridol (ProHance; Bracco Diagnosis, Princeton, NJ); the time of this injection was recorded. Twenty minutes from the time of contrast injection, a middle LV short-axis plane was acquired with a fast gradient-echo sequence incorporating a nonselective inversion pre-pulse. This slice was positioned perpendicularly across the middle left ventricle 6 mm from the LV apex at the midpapillary muscle level (Figure 1). This particular image-acquisition slice corresponded to the slice position used later for histopathologic sectioning. The imaging strategy in this study was selected to detect myocardial fibrosis in the midwall of the left ventricle. The CMR parameters for observing Gd-SI included a Gd-enhanced inversion-recovery image with a 6 ms repetition time, a 2 ms echo time, a 6 cm field of view, a 256×256 matrix, and a 3 mm slice thickness with an inversion delay designed to maximally reduce SI within the myocardium. These parameters provided an in-plane spatial resolution of 0.23×0.23 mm. The inversion time for the delayed enhancement images was adjusted on the first baseline image acquisition to provide a uniform dark myocardium. This inversion time and the time after contrast injection used to acquire the Gd-enhanced SI

### Table 1. Study Animals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Surviving Animals</th>
<th>Acceptable Gating During Image Acquisition</th>
<th>Histopathology</th>
<th>Unexpected Death</th>
<th>Appearance</th>
<th>LVEF (Mean ± SE), %</th>
<th>SI (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS (n=7)</td>
<td>0 wk 7</td>
<td>0 wk 7</td>
<td>7</td>
<td>0 wk 0</td>
<td>0</td>
<td>77±3</td>
<td>5.3±1.8</td>
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<tr>
<td></td>
<td>2 wk 7</td>
<td>0 wk 5</td>
<td>1</td>
<td>0 wk 0</td>
<td>0</td>
<td>67±2</td>
<td>2.4±1.3</td>
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<tr>
<td></td>
<td>4 wk 6</td>
<td>0 wk 0</td>
<td>0</td>
<td>0 wk 0</td>
<td>0</td>
<td>77±3</td>
<td>1.8±1.6</td>
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<tr>
<td></td>
<td>7 wk 6</td>
<td>0 wk 0</td>
<td>0</td>
<td>0 wk 0</td>
<td>0</td>
<td>78±2</td>
<td>3.1±3.1</td>
</tr>
<tr>
<td></td>
<td>10 wk 6</td>
<td>0 wk 0</td>
<td>6</td>
<td>0 wk 0</td>
<td>0</td>
<td>77±2</td>
<td>3.8±1.5</td>
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<tr>
<td>DOX 1.5 mg/kg (n=19)</td>
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<td>0</td>
<td>0 wk 0</td>
<td>0</td>
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<td>5</td>
<td>1/10/2/0/0</td>
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<td>73±2</td>
<td>3.1±1.0</td>
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<td>75±2</td>
<td>3.9±1.4</td>
<td>72±3</td>
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<tr>
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<td>7 wk 11</td>
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<td>72±3</td>
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<tr>
<td></td>
<td>10 wk 2</td>
<td>0 wk 2</td>
<td>2</td>
<td>0/0/1/1/0</td>
<td>67±9</td>
<td>21.7±17.3</td>
<td>77±2</td>
</tr>
<tr>
<td>DOX 2.5 mg/kg (n=14)</td>
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<td>0 wk 14</td>
<td>0</td>
<td>0/0/0/0/0</td>
<td>73±2</td>
<td>6.0±1.4</td>
<td>77±2</td>
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<tr>
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<td>2 wk 14</td>
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<td>12.8±5.1</td>
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<td>28.3±8.1*</td>
<td>55±6</td>
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<tr>
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<td>0/0/2/1/1</td>
<td>55±6</td>
<td>5.8±N/A</td>
<td>55±6</td>
</tr>
<tr>
<td></td>
<td>10 wk 1</td>
<td>0 wk 1</td>
<td>1</td>
<td>0/0/1/0/0</td>
<td>74±N/A</td>
<td>5.8±N/A</td>
<td>74±N/A</td>
</tr>
</tbody>
</table>

NA indicates not applicable. Appearance score includes numbers of animals with respective appearance scores of 1/2/3/4/5, where 1 = excellent: active, eating/drinking; 2 = good: active, slight hair loss; 3 = fair: less active, slight bloating; 4 = poor: reluctant to move, poor appetite and pallor, diarrhea; 5 = critical: marked pallor, not eating/drinking.

*p<0.05 vs 0 weeks.

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images (20 minutes) were kept constant at baseline and during subsequent CMR examinations for all of the animals in the study.

**CMR Data Analysis**

During acquisition, images were identified without reference to animal identifiers with a code generated before beginning the study. Each calculation of Gd-SI and LVEF was analyzed by an individual blinded to animal identifiers, other components of the corresponding CMR examination, and prior CMR exams of the same measure (a blinded, unpaired read). Random sorting of the data was performed so that the analyst was unaware of the animal’s treatment (NS or DOX).

On the Gd-SI acquisitions, regions of interest encompassing the LV myocardium on the multislice, short-axis acquisition were drawn by hand (Figure 1). Great care was taken to avoid including high SIs associated with the blood pool in the LV cavity or myocardial fat outside the heart. The SI and location (x, y, z coordinates) of each voxel within the region of interest were recorded on the Gd-SI images. In addition, a region of interest was drawn separately in air on the images. Values for mean Gd-SI for analysis were derived by subtracting the intensities from the mean background noise noted from the region of interest within air.

**Animal Euthanasia and Pathology Data**

After animal euthanasia (ketamine/xylazine 80/12 mg/kg IM followed by CO₂ asphyxiation), gross examination of the rats included an assessment of heart failure based on the presence of ascites, pleural effusion, and cardiac dilation. The hearts were fixed with chilled paraformaldehyde for 24 hours and then transferred to 70% ethanol. Appropriate sections were trimmed as determined by the same landmarks used to obtain the middle short-axis view on the CMR images (6 mm from the LV apex at the midpapillary muscle level). The sections were embedded in paraffin, processed routinely for histology, cut at 4 to 6 μm, and then stained with hematoxylin and eosin and Masson’s trichrome. All slide preparations were then examined by light microscopy. The sections were also stained by immunohistochemistry for cleaved caspase-3 according to standard methods (Cell Signaling Corporation, Danvers, Mass). All sections were examined by an American College of Veterinary Pathology board–certified veterinary pathologist in a blinded fashion. The hematoxylin and eosin sections were examined for signs of injury, including myocellular degeneration, necrosis, edema, variation in fiber size, shape, staining, and inflammation.

**Statistical Analyses**

By design, there were 3 treatment groups of animals (NS, DOX 1.5 mg/kg, and DOX 2.5 mg/kg), and animals within each group were measured at different numbers of time points based on the prespecified study design (ie, for planned animal sacrifice at specific time points). All analyses that examined changes within groups accounted for the within-animal correlation by using paired t tests, and analyses that compared groups at a fixed point in time were performed with ANOVA or 2-sample t tests for comparisons (depending on whether the comparisons were between all 3 groups or between 2 groups). One variable, the appearance score, was a nominal variable with 5 levels (Table 1) and was compared among groups by the Kruskal-Wallis test. Only when there were overall significant differences in appearance among the 3 groups at 1 time point would pairwise comparisons be tested between the NS and other 2 DOX groups. Fisher’s exact tests were used for comparing other categorical outcomes.

The first set of comparisons within groups was compared over time by paired t tests to determine whether there were any changes in measures (heart rate, LVEF, and SI) over time within 1 of the 3 treatment groups (NS, DOX 1.5, and DOX 2.5). In addition, our NS animals served as a control population that was not exposed to DOX. Next, comparisons between groups were made to determine whether the change in SI within the LV myocardium could predict the primary outcome (referred to henceforth as event-yes) or those that did not (referred to henceforth as event-no), that is, a primary event.

Several different potential outcomes were then derived to see whether any were related to the event-yes/event-no groupings (Figure 2). Mean values for each of these measures were compared between groups (event-yes/event-no) by 2-sample t tests. Next, receiver operating characteristics analyses were performed to determine whether a cutpoint could be identified for each of the 7 defined analyses that could accurately discriminate animals that would be event-yes or event-no. Sensitivity and specificity estimates were then calculated for the optimal cutpoints.

Comparisons were also made between groups for the histopathologic findings, including necrosis, inflammation, and myofiber vacuolization by Fisher’s exact tests to see whether groups that exhibited larger LVEF changes had corresponding differences in pathologic outcomes. All values are reported as mean±SE unless stated otherwise; a value of P<0.05 was considered significant. For all analyses, SAS version 9.1 was used.
Results

Appearance and demographic data for the animals in the study are presented in Table 1. At baseline, the appearance was identical in the 3 groups, whereas heart rate, LVEF, and mean SI were similar among the groups. Also shown are the numbers of animals scanned, euthanized, and experiencing an unexpected death at each time point in the study. Animals with inadequate cardiac gating (and consequent imaging artifacts) at the time of CMR were not included in the analysis. By week 2, animals receiving low or high doses of DOX showed a significantly worse appearance relative to the animals in the NS group ($P<0.0034$ from the Kruskal-Wallis test for 3-group comparison; $P=0.0023$ for the 1.5-mg/kg group; and $P=0.028$ for the 2.5-mg/kg group). The worsening appearance scores persisted at 4 weeks and beyond ($P<0.001$ at week 4 [for overall and both 2-way comparisons], $P<0.002$ at week 7 [for overall and both 2-way comparisons], and $P<0.021$ at week 10 [for overall and both 2-way comparisons]).

Two weeks after receipt of DOX, LVEF remained relatively unchanged (Table 1). At 7 weeks, however, LVEF averaged 78%±2%, 72%±3%, and 55%±6% in the animals receiving NS, 1.5 mg/kg DOX, and 2.5 mg/kg DOX, respectively (Table 1). As shown in Figure 3, of the animals receiving 1.5 mg/kg DOX, 6 of 19 experienced a primary event (3 developed an LVEF drop <65% and 3 died unexpectedly overnight). Of the 14 animals receiving 2.5

![Diagram of study design](image)

**Figure 2.** Gd-CMR sample points and intervals. Longitudinal study design showing the multiple sample points and intervals for assessing the relation between SI and LVEF measures. For animals not experiencing events, the last point in time sampled for the animal served as their final sample point (D on the figure).

**Figure 3.** Study design. As shown, 7, 19, and 14 animals were initiated into this study in groups receiving NS, 1.5 mg/kg per week of DOX, and 2.5 mg/kg per week of DOX, respectively. At the end of the experiment, 24 animals had not experienced a primary event and 16 animals experienced a primary event (13 with a drop in LVEF; 3 with sudden death).

Abbreviations: LVEF = left ventricular ejection fraction.
mg/kg DOX, 10 experienced a primary event, all with a substantial drop in LVEF.

As shown in Table 2, LVEF was similar at baseline and at 2 weeks in animals receiving NS, DOX without a primary event, and DOX with a primary event. Relative to baseline values, LVEF remained relatively constant throughout the study in NS animals and in those receiving DOX without an event. In the animals receiving DOX with an event, an initial small change (not meeting the criteria for a cardiac event) in LVEF occurred relative to baseline at 2 weeks (74±2% at baseline and 70±1% at 2 weeks, P=0.05 vs 0 weeks).

The mean SI averaged 5.3±1.8, 3.0±1.0, and 6.0±1.4 at baseline in animals receiving NS, 1.5 mg/kg DOX, and 2.5 mg/kg DOX, respectively. Throughout the experiment, the average SI did not exceed 1 SD of the baseline value at the 2-, 4-, 7-, or 10-week interval in the animals receiving NS (Table 2). The average SI in the animals receiving 1.5 mg/kg DOX also did not increase by >1 SD in value from the baseline measure until the seventh week of the experiment. In the animals receiving 2.5 mg/kg DOX, the SI increased to 12.8±5.1 at the 2-week sample point and increased further to 28.3±8.1. In animals receiving 2.5 mg/kg DOX, the SI was significantly higher than the SI observed in the other 2 groups, as well as the SI relative to baseline (P<0.05 for all comparisons).

For those animals that experienced a primary event (Table 2), the mean SI at 7 weeks was higher compared with either the animals receiving DOX that did not experience a primary event (P=0.02) or the animals receiving NS (P=0.03). At the time of the drop in LVEF, the mean Gd-SI was 33.5±5.2, versus 6.6±3.2 in animals that did not experience a primary event (P=0.0001). The difference in SI in those experiencing a primary event versus the combined NS and animals receiving DOX without an event was high (P=0.004). Relative to the NS controls and the animals receiving DOX that did not experience a primary event, the average SI at 2 weeks significantly increased in the animals that subsequently experienced a primary event later in the study (P=0.03). Examples of histograms from animals demonstrating receipt of NS versus those animals receiving DOX with and without a cardiac event are shown in Figure 4.

To determine whether measures of Gd-enhanced SI could be used to predict future primary events (a measure of potential clinical utility), measures of Gd-SI from exams before events were assessed relative to baseline measures, as well as measures obtained from the preceding intermediate period (Figure 2). In the animals with an event, the mean SIs at the measurement point before the event averaged 22.3±3.5, versus 3.0±2.9 in animals without an event (P<0.0001). In these same animals with and without events,
when the difference between the measurement point Gd-SI before the event was compared with the measurement at a point in time 2 intervals before the event, the mean difference in SI was 14.8 /H11006 5.4 in the animals that experienced an event versus 2.3 /H11006 4.3 in animals without an event (P/H11005 0.098).

The change from baseline in Gd-SI to the measurement point before a primary event was 17.0 /H11006 3.8, versus 0 /H11006 3.2 in animals without a primary event (P/H11005 0.0009). Similarly, the change in SI over time was equally different between the sample point in measurements before the primary event versus baseline relative to animals without a primary event (P=0.0007). Results were similar after accounting for the time intervals associated with these changes occurring relative to baseline (P=0.001 for both intervals 6 and 7 in Figure 2).

We did not perform a formal test/retest assessment of the SI measurements; however, we examined the change from baseline for all NS animals and found that the average difference was 2.58 with an SD of 4.5, indicating that there was some variability in this measure with “healthy” animals over time. When we examined the magnitude of the changes seen in the DOX-treated animals, the observed change in SI was several-fold larger than the SD of SIs found in NS animals. In fact, the effect was nearly 5 times as large as the SD for the change in SI across all NS measures.

A receiver operating characteristics curve was generated to determine the optimal times to assess characteristics in SI at time points before an event that would forecast a future event. As shown in Figure 5, there was no significant increase in fibrosis, myocellular death, or apoptosis among the hearts of animals experiencing a drop in LVEF compared with those animals that did not. Importantly, however, clear intracytoplasmic myocellular vacuoles and variation in myofiber size and tinctorial quality were regularly present in animals with a drop in LVEF and an increase in CMR SI (Figures 4 and 6). These findings are consistent with vacuolar degeneration resulting from intracellular edema.12 None of the animals without a change in Gd-SI developed myocellular degeneration.

Discussion
This study has 4 important conclusions: first, the mean voxel intensity within the LV myocardium obtained on Gd-enhanced inversion-recovery imaging 20 minutes after administration of Gd increases in animals that experience a deterioration in LVEF after receipt of DOX. Second, the increase in mean SI within the LV myocardium after Gd that occurs during receipt of DOX in animals that do not experience a drop in LVEF or an unexpected death after receipt of DOX do not experience an increase in SI within the LV myocardium after Gd. Fourth, animals that have a drop in LVEF and experience an early increase in Gd-SI after receipt of DOX exhibit myocellular vacuolization, a phenomenon previously described histopathologically after DOX.

The imaging strategy used in this study enabled us to assess the utility of serial MR measures and their relation to important adverse cardiac outcomes in animals receiving DOX. As shown in Table 2, animals experiencing a primary
event also exhibited an increase in Gd-CMR SI as the LVEF dropped. This underlying marker of change in tissue characteristics has the potential for future clinical use to identify the presence or absence of DOX cardiotoxicity in cancer patients who may experience a change in LVEF for reasons other than DOX toxicity (volume depletion, infection, etc). As shown in Figures 2 and 5, we were able to use our data to generate receiver operating characteristics curves demonstrating several metrics that may be useful in future studies for identifying characteristics of CMR SI change that forecast future adverse events related to DOX administration. In addition, when serial measures of T1-weighted signal characteristics did not change, the animal’s LVEF remained preserved, and no adverse events occurred (Table 2).

The method of analysis of the Gd-enhanced images used in this study differs from those used previously to identify myocellular injury after a myocardial infarction, in which myocellular injury is defined in voxels with an SI $>2$ SDs above background intensity within nonenhanced LV myocardium.6 Methods that visualize well-circumscribed myocardial infarcts are not well suited for a process that causes diffuse cardiac injury throughout the heart. To overcome this limitation, we developed a method to determine the mean voxel intensity of all voxels within the short-axis slice of the left ventricle (Figure 1). This method evaluates a process that may involve the LV myocardium in a global, more randomly distributed pattern.

Our study incorporated histopathologic correlation with the CMR findings, thereby allowing investigation of the possible reasons for the increases in SI. Previously, heightened SI with delayed enhancement Gd-CMR has been considered the result of myocardial necrosis and fibrosis. In fact, we hypothesized that fibrosis would be the etiology of events in this study. Importantly, however, Masson’s trichrome staining confirmed an absence of fibrosis in the hearts of our animals.

Histopathologically, there was no or little fibrosis, substantial necrosis, or apoptosis in our specimens; thus, vacuolar degeneration, an indication of intracellular edema, seems the most likely cause for the increased CMR SI observed in this study. As cells become dysfunctional with membrane damage, there are osmotic imbalances that cause water to accumulate within them. With early cellular injury, Gd could also accumulate extracellularly, due to cellular disarray without cellular destruction. Because Gd, an intra- and extracellular contrast agent, changes the relativity of the water in spaces where it has accumulated, the SI on our T1-weighted images would therefore increase.13 Interestingly, recent data have demonstrated the utility of T2-weighted imaging (highly sensitive to water accumulation without the need for contrast administration) in various forms of cardiomyopathy due to inflammation.5 Our particular study design did not allow us to acquire T2-weighted images; however, given our histopathologic findings suggestive of myocardial intra- and extracellular water accumulation, further investigation of T2-weighted imaging methods in DOX cardiotoxicity is warranted.

The imaging technique used in this study was based on the selection of a consistent TI throughout the study. This allowed us to appreciate differences in SI relative to the baseline condition. In practice, however, this technique requires precise timing of image acquisition relative to contrast administration. Also, the magnet surface coil arrangement, shim, and prescan parameters must be relatively constant on successive examinations. In longitudinal human studies, these conditions could be difficult to achieve. Recently, T1-mapping strategies have been reported for identification of processes that affect the myocardium in a diffuse pattern14,15; these T1-weighted mapping strategies may be of use and also warrant further study.

During the past 25 years, 3 other studies (2 in animals and 1 in humans) have demonstrated an association between increased T1 relaxation and DOX cardiotoxicity. In the 2 animal studies, excised myocardial tissue exposed to DOX was found to have increased T1 relaxation measured with
inversion-recovery pulse sequences or nuclear magnetic resonance spectroscopy. In human subjects, increased early relative enhancement (as measured with T1-weighted images in the first 2 minutes after Gd contrast administration) was associated with future congestive heart failure after DOX. The current study contributes to these studies in that it confirms that changes in SI on T1-weighted images are associated with DOX cardiotoxicity, demonstrates that an absence of change in SI on T1-weighted images is associated with a preservation of LVEF after receipt of DOX, and finally identifies a histopathologic correlate of DOX toxicity in animals that have a drop in LVEF and experience an increase in T1-weighted SI within the LV myocardium.

A small decrement in LVEF was observed at the 2-week time interval in animals that developed a primary event (Table 2). Detection of a small change in LVEF was possible in this study due to the high reproducibility and accuracy of 3-dimensional CMR techniques. The 3-dimensional CMR assessment of LV volumes and LVEF has been shown previously to be able to discern 3% changes in LVEF after an intervention.

Our study has limitations. First, we did not include animals with existing LV dysfunction. Animals with existing cardiomyopathies may have abnormal resting SIs for which our imaging strategy could have lower utility. Second, our CMR methodology required precise selection of inversion times and coordination of image acquisition after Gd contrast administration. This level of precision could be difficult to replicate in a busy clinical private outpatient or hospital-based CMR center. Further studies that involve strategies that would not necessarily require specific inversion times but could account for differences in imaging conditions over time, such as T1 mapping, may have greater utility. Third, our study design correlated CMR T1-weighted image SI changes with histopathology; animals were therefore euthanized relatively early in the course of DOX administration. CMR correlations with more advanced cardiac injury were not obtained, nor did we assess whether the early lesions would reverse after discontinuation of DOX. Fourth, anthracyclines such as DOX have been shown to cause nephrotoxicity due to oxidative stress. In this study, we have no histopathologic data from the kidneys of the animals, and therefore, we are uncertain whether potential renal damage influenced animal outcomes in the study. Finally, we used a Sprague-Dawley animal model of cardiotoxicity that exhibits genetic variability and thus, less susceptibility to cardiotoxicity after DOX exposure. Other animals including dogs, nonhuman primates, or mice have been shown to be highly susceptible to DOX and may be useful in future studies.

In conclusion, we demonstrate that changes in SI within the LV myocardium on T1-weighted, Gd-enhanced images identify animals that develop future adverse cardiac events (primarily a fall in LVEF) after DOX. In animals without a change in T1-weighted SI after Gd, adverse cardiac events do not occur. Early changes in Gd-SI are associated with intracellular vacuolization, an indication of myocardial degeneration consistent with DOX cardiotoxicity. The results of this study and others suggest that future human studies should be performed to determine the role of CMR for detecting DOX cardiotoxicity and preventing congestive heart failure in patients treated for cancer.

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Disclosures

None.

References

This article explores the utility of a new magnetic resonance imaging method for identifying subclinical cardiotoxicity due to doxorubicin chemotherapy. At present, surveillance strategies for doxorubicin cardiotoxicity involve serial assessments of left ventricular ejection fraction by radionuclide or echocardiographic techniques. However, these strategies identify the end result of doxorubicin injury late in its course, after such injury may be irreversible. In this article, we describe a new magnetic resonance imaging method that identified abnormal myocardial tissue characteristics early after doxorubicin exposure and before marked changes in left ventricular ejection fraction. Moreover, an absence of change in magnetic resonance imaging tissue characteristics predicted preserved left ventricular ejection fraction longitudinally over time. These results suggest that new imaging strategies in human subjects may be used to identify early evidence of doxorubicin cardiac injury before irreversible changes in left ventricular ejection fraction have occurred.
Novel Approach to Early Detection of Doxorubicin Cardiotoxicity by Gadolinium-Enhanced Cardiovascular Magnetic Resonance Imaging in an Experimental Model


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