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## LETTERS TO THE EDITOR

### Progressive 3-Month Increase in LV Myocardial ECV After Anthracycline-Based Chemotherapy

Following myocardial injury, the left ventricular (LV) myocardial extracellular matrix (ECM) can undergo abnormal expansion (due to inflammation and interstitial fibrosis) that can be identified with cardiac magnetic resonance (CMR) assessments of extracellular volume fraction (ECV) (1,2). Seven years after receipt of anthracycline-based chemotherapy (Anth-bC), elevations of myocardial ECV are associated with: 1) LV diastolic and systolic dysfunction; 2) future mortality; and 3) exercise intolerance (3). Identifying the onset of CMR-derived measures of LV myocardial ECV in those treated with Anth-bC could facilitate therapeutic interventions to prevent the accumulation of LV myocardial interstitial fibrosis that is associated with these adverse outcomes.

Accordingly, the goal of this study was to determine whether LV myocardial ECV increased during the initial receipt of potentially cardiotoxic chemotherapy. To accomplish this, we obtained serial CMR-derived measures of ECV before and 3 months after chemotherapy initiation. Additionally, T2 maps, LV volumes, and circumferential myocardial strain were assessed. Individuals evaluated for treatment of breast cancer, soft tissue sarcomas, or lymphoma from rural northwest North Carolina treated within the Comprehensive Cancer Center at Wake Forest School of Medicine served as our study population. Participants were ineligible for enrollment if they had a history of myocardial infarction 28 days before enrollment.

CMR examinations were performed on a 1.5-T scanner (Siemens Medical Solutions USA, Malvern, Pennsylvania). T1 maps were acquired pre- and 15 min after administration of gadolinium contrast (0.15 mmol/kg) using a modified Look-Locker inversion recovery sequence in a mid-cavity short-axis slice. ECV (corrected for hematocrit and heart rate) was calculated for each of 6 mid-cavity myocardial segments. Offline image-paired analysis was performed by an experienced observer (G.C.M.) blinded to whether maps were baseline or 3-month examinations. Next, the change from baseline to 3 months was calculated for each CMR measure, and descriptive statistics were obtained. Paired Student *t* tests were calculated to assess whether longitudinal changes occurred in these measures. Subgroup analyses were also performed in those that did and did not receive Anth-bC.

The study population included 56 participants (66% women [71% white and 29% black], age 52 ± 13 years). Thirty-four percent of the participants had hypertension or diabetes (13%), or smoked (21%). For those receiving Anth-bC (71%), the average cumulative doxorubicin equivalent dose received was 374.8 ± 0.56 mg/m$^2$. Body mass index did not change from baseline to 3 months ($p = 0.98$). There were no differences in baseline ECV values among subjects with or without hypertension or diabetes (ECV LV $p = 0.92$, ECV septum $p = 0.66$). Overall, ECV was found elevated 3 months post-treatment initiation compared with baseline (Table 1). The elevation in ECV was prominent in those receiving Anth-bC (Anth-bC $p < 0.001$; non-Anth-bC $p = 0.29$). LV ejection fraction (EF) decreased from 62 ± 7% to

**TABLE 1 CMR Imaging Measures Before and ~3 Months After Initiating Treatment**

| | Overall (n = 56) | | | Anth-bC-Treated Subjects (n = 40) | | | Non-Anth-bC-Treated Subjects (n = 16) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 3 Months | p Value | Baseline | 3 Months | p Value | Baseline | 3 Months | p Value |
| Native T1 LV, ms | 1,051.8 ± 80.9 | 1,062.8 ± 75.7 | **0.03** | 1,058.0 ± 100.0 | 1,071.4 ± 85.2 | **0.02** | 1,036.3 ± 41.1 | 1,041.2 ± 38.3 | 0.65 |
| Native T1 LV septum, ms | 1,042.1 ± 80.3 | 1,053.4 ± 83.5 | 0.06 | 1,047.7 ± 90.2 | 1,062.4 ± 95.2 | **0.03** | 1,028.1 ± 47.3 | 1,031.1 ± 35.7 | 0.80 |
| T2 LV, ms | 51.0 ± 2.7 | 51.8 ± 3.3 | 0.06 | 50.8 ± 2.9 | 51.6 ± 3.5 | 0.18 | 51.5 ± 2.2 | 52.4 ± 2.9 | 0.22 |
| T2 LV septum, ms | 51.0 ± 2.8 | 52.0 ± 3.7 | **0.03** | 50.7 ± 2.7 | 51.9 ± 3.8 | **0.04** | 51.6 ± 3.1 | 52.3 ± 3.2 | 0.43 |
| Post-contrast T1 LV, ms | 436.8 ± 44.3 | 431.3 ± 46.2 | 0.42 | 445.1 ± 40.9 | 435.3 ± 42.7 | 0.21 | 416.0 ± 46.9 | 421.3 ± 54.1 | 0.71 |
| Post-contrast T1 LV septum, ms | 432.4 ± 45.0 | 426.6 ± 46.5 | 0.40 | 439.3 ± 41.6 | 428.8 ± 42.3 | 0.17 | 414.9 ± 49.6 | 420.9 ± 56.8 | 0.68 |
| ECV LV, % | 26.8 ± 3.1 | 28.3 ± 3.3 | **0.001** | 26.9 ± 3.1 | 28.6 ± 3.0 | **<0.001** | 26.7 ± 3.3 | 27.7 ± 3.8 | 0.29 |
| ECV LV septum, % | 27.1 ± 3.3 | 28.6 ± 3.4 | **0.003** | 27.3 ± 3.1 | 29.1 ± 3.1 | **<0.001** | 26.6 ± 3.8 | 27.5 ± 3.3 | 0.41 |

Values are mean ± SD. The **bold** p values are statistically significant.

Anth-bC = anthracycline-based chemotherapy; CMR = cardiac magnetic resonance; ECV = extracellular volume; LV = left ventricle/ventricular.

58 ± 7% ($p < 0.0001$), and LV circumferential strain was −17.2 ± 3.0 at baseline and −16.4 ± 3.0 at 3 months ($p = 0.19$) with a weak, but positive, association between the 3-month change in ECV and LV circumferential strain ($r^2 = 0.0983$; $p = 0.05$). There were no significant relationships between ECV with LV EF, end-diastolic volume, or end-systolic volume ($p = 0.2$ to 0.9).

The results of our study are the first to our knowledge to indicate that ECV increases early (only 3 months after initiation of chemotherapy), and these ECV increases are prominent in participants receiving Anth-bC. These results are similar to observations by Tham et al. (4), where increased ECV values were found in adolescents with normal EF, 3 to 12 years after treatment with Anth-bC. Our data do not address the mechanism by which LV myocardial ECV increases after receipt of potentially cardiotoxic chemotherapy. Expansion of the myocardial interstitial space could occur in the presence of inflammation and edema induced by cardiomyocyte apoptosis, or as interstitial fibrosis initiates within the ECM. In order to ultimately define the underlying cause of ECV increases or ECM expansion, future studies involving myocardial biopsies would be helpful.

In summary, these results raise the possibility that interstitial fibrosis may initiate early during or immediately after receipt of Anth-bC and suggest that further studies are warranted to investigate the effects of cancer treatment, particularly with anthracycline-based agents, on the LV myocardial ECM.

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## Observations With Simultaneous 18F-FDG PET and MR Imaging in Peripheral Artery Disease

Imaging modalities such as simultaneous magnetic resonance imaging (MRI) and positron emission tomography (PET) may offer new opportunities for noninvasive characterization of atherosclerosis. The aim of this study was to assess: 1) the feasibility of atherosclerotic plaque imaging in the superficial femoral artery (SFA) using simultaneous PET/MRI; 2) the relationship of 18F-fluorodeoxyglucose (18F-FDG) PET tracer and MR contrast uptake in peripheral artery disease (PAD); and 3) the potential of noninvasive plaque characterization by PET/MR imaging compared with histology of excised plaques.

Eight patients with Rutherford claudication (category 2 to 3) and circumscribed SFA de novo stenosis ≥50% as assessed by duplex sonography were examined. Patients received an intravenous injection of 18F-FDG (mean activity 358 ± 33 MBq, circulation time 2 h 16 min ± 37 min) and underwent simultaneous PET/MR imaging (Biograph mMR, Siemens, Erlangen, Germany). MRI T2-weighted (T2-w) Turbo Spin Echo (TSE), and T1-w TSE pre- and 5 to 7 min post-contrast (0.1 mmol/kg Magnevist, Bayer Schering Pharma AG, Berlin, Germany) sequences were performed. MRI plaque size (plaque diameter determined on T2-w TSE) and contrast enhancement (signal intensity ratio T1-w TSE pre- and post-contrast) were analyzed using MATLAB R2012a analysis software (The Mathworks, Natick, Massachusetts). PET and MR images were fused and FDG uptake was measured on the axial MR image representing the largest plaque burden. The arterial PET standard uptake value (SUV) in the arterial stenosis was normalized to the adjacent vein SUV yielding the target-to-blood ratio (TBR). Similarly, a corresponding control location was analyzed in the asymptomatic contralateral SFA (1). Plaques were excised by directional atherectomy (SilverHawk, Medtronic, Plymouth, Minnesota) and stained by hematoxylin/eosin and for CD68-positive macrophages.