Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

JACC Cardiovasc Imaging. Author manuscript; available in PMC 2021 February 18.

Published in final edited form as:

JACC Cardiovasc Imaging. 2017 June ; 10(6): 708–709. doi:10.1016/j.jcmg.2016.06.006.

Progressive three-month increase in left ventricular myocardial extracellular volume fraction after receipt of anthracycline based chemotherapy

Giselle C. Meléndez, MD[*,‡], **Jennifer H. Jordan, PhD**[*], **Ralph B. D'Agostino Jr, PhD**[†], **Sujethra Vasu, MD**[*], **Craig A. Hamilton, PhD**[§], **W. Gregory Hundley, MD**[*,††]

[*] Internal Medicine, Section on Cardiovascular Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[‡] Pathology, Section on Comparative Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[†] Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC

[§] Biomedical Engineering, Wake Forest School of Medicine, Winston-Salem, NC

[††] Radiological Sciences, Wake Forest School of Medicine, Winston-Salem, NC

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 cardiovascular magnetic resonance (CMR) assessments of extracellular volume (ECV) fraction (1;2). Seven years after receipt of anthracycline-based chemotherapy (Anth-bC), elevations of myocardial ECV are associated with a) LV diastolic and systolic dysfunction, b) future mortality, and c) 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 if 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 three 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 prior to enrollment.

CMR examinations were performed on a 1.5 Tesla scanner (Siemens Medical Solutions USA, Malvern, PA). T1 maps were acquired pre- and 15 minutes after administration of

Address for Correspondence: W. Gregory Hundley, MD, Department of Internal Medicine, Section on Cardiovascular Medicine, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, North Carolina 27157, ghundley@wakehealth.edu, (p) 336-716-6125 (f) 336-713-0163.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

gadolinium contrast (0.15 mmol/Kg) using a modified Look-Locker inversion recovery sequence (MOLLI) 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 (GCM) 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 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], aged 52 ± 13 years). Thirty-four percent (34 %), 13%, and 21%, of the participants respectively had hypertension or diabetes, or smoked. For those receiving Anth-bC (71%), the average received cumulative doxorubicin equivalent dose was 374.8 ± 0.56 mg/m^2. Body mass index did not change from baseline to three 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 three months post-treatment initiation compared to baseline. The elevation in ECV was prominent in those receiving Anth-bC (Anth-bC, p<0.001; non-Anth-bC, p=0.29). LVEF decreased from 62 ± 7 to 58 ± 7% (p<0.0001) and LV circumferential strain was −17.2 ± 3 at baseline and −16.4 ± 3 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, EDV or ESV (p= 0.2 to 0.9)

The results of our study are the first to indicate that ECV increases early (only three 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., where increased ECV values were found in adolescents with normal EF, 3–12 years after treatment with Anth-bC(4). 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 further studies are warranted to investigate the effects of cancer treatment, particularly with anthracycline based agents, on the LV myocardial extracellular matrix.

Acknowledgment:

Prohance contrast agent was provided for the study by Bracco Diagnostics (Princeton, NJ).

Financial Support: This research was supported in part by NIH grants R01CA167821, R01HL118740 and R01CA199167

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

(1). Kong P et al. The pathogenesis of cardiac fibrosis. Cell Mol Life Sci 2013.

(2). Kellman P, et al. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. J Cardiovasc Magn Reson 2012;14:63. [PubMed: 22963517]

(3). Neilan TG et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. Am J Cardiol 2013; 111(5):717–22. [PubMed: 23228924]

(4). Tham EB et al. Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. J Cardiovasc Magn Reson 2013;15:48. [PubMed: 23758789]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Cardiovascular magnetic resonance imaging measures for chemotherapy subgroups before and ~3 months after initiating treatment.

Characteristics mean ± SD, n (%)	Overall (n=56)		p-value	Anth-bC treated subjects (n = 40)		p-value	Non Anth-bC treated subjects (n=16)		p-value
	Baseline	3 Months		Baseline	3 Months		Baseline	3 Months	
Native T1 LV, ms	1051.8 ± 80.9	1062.8 ± 75.7	**0.03**	1058.0 ± 100.0	1071.4 ± 85.2	**0.02**	1036.3 ± 41.1	1041.2 ± 38.3	0.65
Native T1 LV Septum, ms	1042.1 ± 80.3	1053.4 ± 83.5	0.06	1047.7 ± 90.2	1062.4 ± 95.2	**0.03**	1028.1 ± 47.3	1031.1 ± 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