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Myocardial Extracellular Volume by Cardiac Magnetic Resonance in Patients treated with Anthracycline-based Chemotherapy

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Abstract

We aimed to determine whether the myocardial extracellular volume (ECV), measured using T1 measurements obtained during cardiac magnetic resonance (CMR) imaging were increased in patients treated with anthracyclines. We performed CMR imaging, an echocardiogram, and measured the ECV in 42 patients with treated with anthracyclines. Data from the CMR study were compared to healthy volunteers. The anthracycline-treated cohort consisted of 21 males and 21 females with a mean age of 55±17 years, presenting a median of 84 months after chemotherapy with a cumulative anthracycline exposure of 282±65 mg/m², and a mean left ventricular ejection fraction of 52±12%. The ECV was elevated in anthracycline-treated patients in comparison to age and gender-matched controls (0.36±0.03 vs. 0.28±0.02, $p < 0.001$). There was a positive association between the ECV and left atrial volume (LAV) (ECV vs. indexed LAV, $r=0.65$, $p < 0.001$) and negative association between the ECV and diastolic function (E' lateral, $r=-.64$, $p < 0.001$). In conclusion, the myocardial extracellular volume is elevated in patients with prior anthracycline treatment and is associated with diastolic function and increased atrial volumes.

Keywords

Anthracyclines; Cardiac Magnetic Resonance; T1 Measurements; Extracellular Volume Fraction; Myocardial Fibrosis

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Detection of anthracycline-induced myocardial injury is limited by the long latency period between injury and clinical presentation,¹ and the methods of assessment employed.² Furthermore, measurements are usually within the normal range,³ missing the myocyte damage that occurs before a decline in ejection fraction (EF),^{3,4} and leading to the incorrect assumption that injury is absent.³ Anthracycline therapy results in myocardial fibrosis (MF).^{5,6} Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) is the gold standard for the non-invasive detection of MF.⁷ However, LGE is an infrequent finding in patients treated with anthracyclines despite a reduced EF.⁸ In comparison, MF as detected by pathology is ubiquitous in the hearts of patients treated with anthracyclines.^{6,9} Current CMR techniques require a normal reference myocardium, while anthracycline-cardiomyopathy is associated with diffuse myocardial involvement.^{6,9} To address this limitation, a CMR-based technique has been developed where measurement of myocardial T1 provides a quantitative measure of the myocardial extracellular volume (ECV) and reflects the pathological extent of MF,^{10–12} and is associated with cardiovascular mortality.¹³ Therefore, the goal of this study was to test whether the ECV is abnormal in patients treated with anthracyclines and to test the associations between the ECV and other indices.

Methods

The protocol was approved by the Institutional Human Subjects Review Committee. We performed an observational study in patients with prior anthracycline treatment referred for a clinically indicated CMR study between 2010 and 2012. Healthy controls for the cardiac magnetic resonance measures were recruited by open invitation. Requirements for inclusion were a history of anthracycline treatment, sinus rhythm, and the absence of an alternate pathological etiology of myocardial extracellular volume expansion. Significant coronary artery disease was excluded by either a negative coronary angiography or negative stress testing with imaging. Heart failure was determined by a combination of a detailed questionnaire at the time of the CMR study, measurement of cardiac function, and a review of the medical record for a history of heart failure. Results for the CMR indices were compared to age- and gender matched healthy volunteers (n=15). Volunteers were free of hypertension, diabetes, known coronary disease, malignancy, or sleep apnea.

All images were acquired with ECG gating, breath-holding, and with the patient in a supine position. Subjects were imaged on a 3.0-T CMR system (Tim Trio, Siemens, Erlangen, Germany) and measurements for left ventricular (LV) size, LV function, LV mass, left atrial (LA) volume, T-2 weighted sequences, and LGE were performed as previously described.⁸ Gadopentetate dimeglumine at a dose of 0.15m/mol/L (MAGNEVIST®, Bayer HealthCare, Germany) was used as the contrast agent for all imaging in both healthy volunteers and patients.¹⁴ T1 measurements were performed with a Look-Locker sequence with a non-slice-selective adiabatic inversion pulse, followed by segmented gradient-echo cine acquisition for 17 cardiac phases/times after inversion, spread over 2 cardiac cycles (temporal resolution 80–100 ms pre-contrast, and 45–55 ms post-contrast, slice thickness 8 mm, TR > 3 RR intervals pre-contrast and 2 RR intervals post-contrast).^{11,15} The sequence was performed in a single mid-LV slice pre-contrast and was repeated in the same mid-LV short-axis slice 3–5 additional times after the injection of gadolinium (Figure 1). The second T1 measure was performed 3–4 minutes after the initial dose of contrast (0.05mmol/kg). Immediately after this second T1 measure, a second dose of contrast was given (0.10mmol/kg), as LGE imaging was also performed for completeness. The third T1 measure was performed 3–4 minutes after this second dose of contrast. The final T1 measure was performed just prior to the end of the study, an average of 30–35 minutes after the initial dose of contrast. Either 1 or 2 other T1 measures were performed after the third measure and prior to the final measure at no pre-set intervals. The signal intensity versus time curves for

each segment and the blood pool were used to determine segmental T1 through fitting to an analytical expression for the inversion recovery signal intensity. The reciprocal of T1 ($R1=1/T1$) was used to plot the myocardial R1 against the R1 in the blood pool, and calculate the slope by linear regression, using all measurement points with a blood pool R1 of less than 3 s^{-1} . From the slope of the relationship, the partition coefficient (λ_{Gd}), the ECV was obtained by multiplying each of the segmental λ_{Gd} by (1-hematocrit in percent/100) as reported previously.^{11,16} An ECV was then calculated by averaging the 6 myocardial segmental values from the mid-LV short axis slice. Segments containing LGE were excluded from the analysis.

The Vivid-7 ultrasound system (GE, Milwaukee, WI) was used for standard and tissue Doppler echocardiography. Left ventricular measurements were performed as recommended by the American Society of Echocardiography.¹⁷ Tissue Doppler myocardial velocities were acquired in early diastole (E') at the lateral and septal aspects of the mitral annulus in the apical 4-chamber view.¹⁸

Comparison of continuous data between the combined groups was made using either an unpaired Student t-test or a Wilcoxon Rank-Sum test. Nominal data were compared with a Fisher's exact test. We assessed the inter- and intra-observer variability in a randomly selected group of 16 subjects. Comparison of the inter-observer and intra-observer characteristics of the myocardial ECV were made using Bland-Altman plots and determination of the 95% limits of agreement between methods. A p value of < 0.05 was deemed significant and SAS was used for statistical analysis (SAS Institute, Cary).

Results

We studied 42 patients with prior anthracycline-based chemotherapy (Table 1). Nine patients had Hodgkin's Lymphoma, 17 had non-Hodgkin's, 7 had breast cancer, 5 had leukemia, and 4 had bone cancer. Two patients received liposomal doxorubicin and 2 patients received trastuzumab. We separated the anthracycline-treated group according to preserved or reduced EF. The group with preserved EF group were referred for a CMR study prior to ablation of atrial fibrillation ($n=14$) or for work-up of heart failure ($n=14$). The group with a reduced EF were referred for a CMR study for work-up of heart failure with reduced EF ($n=14$) (Table 1). Echocardiographic parameters are shown in Table 2. The tissue-Doppler derived E' was lower in patients with prior anthracycline use with a reduced EF as compared to those with a preserved EF.

Myocardial Fibrosis by LGE imaging was an infrequent finding and was observed in 3 patients (Table 3). It was found in a basal distribution. There was no quantitative or qualitative evidence of edema in anthracycline-treated patients by T-2 weighted imaging (relative T2 signal intensity, 1.6 ± 0.2). The mean differences within and between observers for the ECV measurement were acceptable (Figure 2). The average ECV in healthy controls was 0.28 ± 0.02 . The myocardial ECV was elevated in patients treated with anthracycline-based chemotherapy compared to healthy controls (Table 3). There was no segmental variation in the ECV in patients (0.35 ± 0.03 , 0.36 ± 0.03 , 0.35 ± 0.03 , 0.37 ± 0.03 , 0.37 ± 0.03 , 0.36 ± 0.03 , clockwise from anterior to the antero-septal segment, $p = 0.57$). There was no association between the ECV and the heart rate ($r=-0.06$) or blood pool T1 values ($r=-0.08$). There was a direct association between the ECV and indexed LA volume (Figure 3A), there was an inverse association between the ECV and both the medial E' (Figure 3B) and the lateral E' (Figure 3C), and a direct association between the ECV and the ratio of the transmitral E wave to the tissue-Doppler derived E' (Figure 3D). The ECV was higher in patients with a reduced EF as compared to those with a preserved EF (Figure 4).

Discussion

We measured the myocardial ECV in patients with prior anthracycline use. The ECV was increased in patients as compared to healthy controls. The ECV was elevated in patients treated with anthracyclines and presenting with heart failure with both reduced and preserved EF. There was a direct association between the ECV and left atrial volume and non-invasively estimated left atrial pressure, and an inverse association with diastolic function.

Myocardial fibrosis as assessed using LGE was an infrequent finding in patients with prior anthracycline treatment.⁸ However, pathologically, MF is generally ubiquitous in patients with prior anthracycline therapy and present diffusely throughout the entire LV.^{6,9} LGE likely lacks sensitivity in a diffuse cardiomyopathy; LGE imaging is an imaging of the contrast comparison between normal and pathologic areas. Data are limited, but in anthracycline-cardiotoxicity, the myocardial involvement is likely diffuse, and a normal background myocardium is likely absent. To address these limitations, we used an evolving technique to quantify the myocardial ECV. The ECV is elevated in pathological conditions such as aortic stenosis, heart failure, infiltrative cardiomyopathy, and hypertrophic cardiomyopathy.^{10,12,19} There is a strong association between the elevated ECV and the histological extent of MF,¹² and an association between an elevated ECV and cardiac mortality.¹³ The ECV is based on the principle that when the contrast distribution is at equilibrium between blood and tissue, the ratio of the R1 changes reflects the distribution volume of the extracellular contrast agent.^{11,12,20}

While MF is a likely cause of the extracellular matrix expansion, other conditions such as edema and infiltration need to be considered.^{19,21} In anthracycline-cardiotoxicity, there are limited prior clinical CMR data.²² Some of our cohort had a preserved EF and no clinical evidence of heart failure, leading one to postulate that expansion of the ECV is a transition step from normal to irreversible replacement fibrosis and may be potentially reversible.²³ In general in patients with a reduced EF, modulation of the renin-angiotensin-aldosterone (RAA) system reverses pathological MF, attenuates adverse cardiac remodeling, and decreases mortality.²⁴ However, detection of diffuse MF is currently limited to invasive techniques and treatment of all patients treated with anthracyclines with inhibitors of the RAA system has met with limited success.²⁵ Therefore, identifying and validating a novel non-invasive technique for prediction and detection of cardiac injury, as well as identifying a cohort likely to benefit from aggressive cardiovascular therapy, is relevant.

We specifically studied patients referred for a clinically indicated CMR study and not all patients who received anthracyclines. Referral is based on provider preference and not based on protocol or screening of all patients. Also, we did not perform myocardial biopsies. Therefore this study only proves that symptomatic anthracycline-treated patients show ECV expansion. We also only measured the ECV in the middle slice of the left ventricle. We did this to try and limit the time extension of a clinical study. Therefore, we cannot comment on whether the enlargement of the ECV involves the entire ventricle or is homogenous throughout the ventricle. Finally, we did not measure serum biomarkers,⁴ or more sensitive echocardiographic techniques such as strain or strain rate.²⁶ We did not perform an ECG or an echocardiogram in our healthy volunteers.

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Myocardial Fibrosis Protocol

Figure 1.

We used the following protocol for myocardial fibrosis imaging. For the myocardial ECV measurement, images were acquired pre-contrast and up to 3–5 time points post-contrast after a total of 0.15 mmol/kg of gadolinium. LGE imaging was performed starting 10–15 minutes after administration of gadolinium. This figure is a reproduction of a similar protocol image that is part of another manuscript in press.

Figure 2. Bland-Altman plots displaying the bias in the intra-observer (A) and inter-observer (B) agreement in the ECV in 16 randomly selected subjects. The mean difference within an observer for the ECV measurement was 0.01 ± 0.005 and the mean difference for the ECV between observers was 0.01 ± 0.005 .

Figure 3.

There was a positive association between the ECV and indexed maximal LA volume (LAV_i , A, $r = 0.65$, $p < 0.001$), a negative association between the ECV and medial E' (B, $r = -0.63$, $p < 0.001$) and lateral E' (C, $r = -0.64$, $p < 0.001$) and a positive association between the ECV and ratio of the E/E' (D, $r = 0.61$, $p < 0.001$).

Figure 4.

Box and whisker plot displaying the mean and range of values for the myocardial extracellular volume derived from T1 measurements in healthy controls (CTRL), all patients with prior anthracycline treatment (AC-ALL), patients with prior anthracycline treatment with preserved EF (AC-PEF), and patients with prior anthracycline treatment presenting with a reduced EF (AC-REF). Patients treated with anthracyclines had a markedly elevated extracellular volume fraction (ECV) as compared to normal healthy controls. The ECV was also increased in patients with a reduced EF as compared to patients with a preserved EF. (# $p < 0.001$ for the comparison between all patients treated with anthracyclines as compared to healthy controls; ¶ $p = 0.03$ for the comparison between patients with a preserved as compared to a reduced EF).

Table 1

Baseline Characteristics of Healthy Controls (CTRL), all Patients treated with anthracyclines (AC-ALL), and Patients treated with Anthracyclines Separated according to the a Preserved or Reduced Ejection Fraction

Variable	CTRL (15)	AC-ALL (42)	AC-PEF (28)	AC-REF (14)	p Value (AC-ALL vs. CTRL)	p Value (AC-PEF vs. AC-REF)
Age of chemotherapy (yrs)	-	47±17	48±19	47±16		0.78
Chemo to clinical presentation (mean, mths)	-	89±40	83±30	105±49		0.99
Age at CMR study (yrs)	56±13	55±17	56±17	56±15	0.78	0.99
Male,	7 (47%)	21 (50%)	13 (46%)	8 (57%)	0.81	0.74
Anthracycline Dose (mg/m ²)	-	282±65	272±59	301±72		0.17
Chest radiation,	-	12 (29%)	7 (25%)	5 (36%)		0.49
Risk Factors,						
Hypertension	-	14 (33%)	10 (36%)	4 (29%)		0.74
Atrial Fibrillation (history of)	-	19 (41%)	15 (54%)	4 (29%)		0.19
Family History Cardiomyopathy	-	5 (12%)	3 (11%)	2 (14%)		1.00
Body Mass Index (kg/m ²)	-	28±4	27±4	28±5		0.98
Systolic BP (mmHg)	124±10	114±16	114±18	116±16	0.03	0.73
Diastolic BP (mmHg)	75±9	71±12	71±8	71±13	0.18	0.95
Heart Rate (beats/min)	72±11	78±13	78±12	77±14	0.001	0.90
Medication,						
ACE/ARB	-	33 (76%)	20 (71%)	13 (93%)		0.23
Beta-blocker	-	37 (88%)	24 (86%)	13 (93%)		0.65
Spironolactone	-	3 (7%)	0 (0%)	3 (21%)		0.03
Diuretics	-	29 (69%)	17 (61%)	12 (86%)		0.16
Antiarrhythmic	-	13 (31%)	10 (36%)	3 (21%)		0.49
Coumadin	-	14 (33%)	12 (43%)	2 (14%)		0.09
Aspirin	-	12 (29%)	11 (39%)	1 (7%)		0.04
Statin	-	16 (38%)	11 (39%)	5 (36%)		1.00
Glomerular Filtration Rate (ml/min/1.73m ²)	-	95±31	99±24	87±28		0.21
Hematocrit	42±4	41±3	41±3	40±3	0.56	0.94

All data are mean ± SD unless otherwise indicated; Chemo to clinical presentation = time from chemotherapy to presentation with either HF or AF; ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; glomerular filtration rate using the Modification of Diet in Renal Disease formula; p value AC-ALL vs. healthy control (CTRL) = p value control group vs. all patients treated with anthracyclines; p Value (AC-PEF vs. AC-REF) = comparison between prior anthracycline use with preserved EF vs. prior anthracycline use with a reduced EF.

Table 2

Echocardiographic Characteristics

Variable	AC-All (42)	AC-PEF (28)	AC-REF (14)	p Value (AC-PEF vs. AC-REF)
Left Ventricular Internal Dimensions in Diastole (mm)	50±6	47±4	55±4	<0.001
Left Ventricular Ejection Fraction (%)	51±12	58±5	37±7	<0.001
Pulmonary Artery Systolic Pressure (mmHg)	36±8	34±7	39±10	0.05
Transmitral E (cm/sec)	75±20	74±16	75±22	0.97
Transmitral A (cm/sec)	73±16	72±14	76±18	0.45
E/A	1±0.4	1.1±0.4	1±0.3	0.51
E' medial (cm/sec)	6.2±1.1	6.5±0.8	5.4±0.7	<0.001
E' Lateral (cm/sec)	6.6±1.5	7.1±0.9	5.9±1	0.01
E/E'	12±4	12±3	13±4	0.15

All values are mean ± SD; p Value (AC-PEF vs. AC-REF) = comparison between prior anthracycline use with preserved EF vs. prior anthracycline use with a reduced EF.

Table 3

Cardiac Magnetic Resonance Imaging Characteristics

Variable	CTRL (15)	AC-ALL (42)	AC-PEF (28)	AC-REF (14)	p Value (AC-ALL vs. CTRL)	p Value (AC-PEF vs. AC-REF)
Left Ventricular Diastolic Volume (mls)	133±25	175±43	161±34	201±45	0.001	0.003
Left Ventricular Diastolic Volume index (mls/m ²)	71±12	90±21	84±17	101±22	0.002	0.01
Left Ventricular Systolic Volume (mls)	51±12	86±38	67±16	125±45	0.001	<0.001
Left Ventricular Systolic Volume index (mls/m ²)	27±7	44±19	35±8	63±21	0.002	<0.001
Left Ventricular Ejection Fraction (%)	62±5	52±12	58±8	38±8	0.004	<0.001
Left Ventricular Mass (grams)	117±13	106±28	111±17	96±10	<0.001	<0.001
Left Ventricular Mass index (g/m ²)	65±6	55±16	58±16	48±7	0.002	<0.001
Maximal Left Atrial volume (mls)	66±14	113±29	102±18	136±2	<0.001	<0.001
Indexed Maximal Left Atrial volume (mls/m ²)	37±9	58±14	47±10	68±12	<0.001	<0.001
Right Ventricular Diastolic Volume (mls)	128±26	142±37	132±33	160±42	0.21	0.02
Right Ventricular Diastolic Volume index (mls/m ²)	68±11	73±17	69±15	80±17	0.35	0.03
Right Ventricular Systolic Volume (mls)	59±12	70±26	61±14	89±36	0.11	<0.001
Right Ventricular Systolic Volume index (mls/m ²)	32±7	36±12	31±7	42±8	0.20	<0.001
Right Ventricular Ejection Fraction (%)	54±5	51±11	52±6	39±15	0.18	0.04
Late Gadolinium Enhancement, number	0 (0%)	3 (7%)	1 (3.5%)	2 (14%)	0.55	0.25
Extracellular volume fraction	0.28 ±0.02	0.36 ±0.03	0.36 ±0.02	0.38 ±0.03	<0.001	0.03

All values are mean ±SD; p value AC-ALL vs. CTRL = p value control group vs. all patients treated with anthracyclines; p Value (AC-PEF vs. AC-REF) = comparison between prior anthracycline use with preserved EF vs. prior anthracycline use with a reduced EF.