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Evaluation of Post-Contrast Myocardial T1 in Duchenne Muscular Dystrophy Using Cardiac Magnetic Resonance Imaging

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Abstract

Objectives—Perform a retrospective pilot study to evaluate the potential of myocardial T1 in assessment of Duchenne muscular dystrophy (DMD) cardiomyopathy.

Background—Early identification of DMD cardiac disease, particularly myocardial fibrosis, would allow earlier therapy, potentially improving outcomes. Shortened myocardial T1 measured by cardiac MRI (CMR) is a measure of cardiac fibrosis that may be detected before late gadolinium enhancement (LGE). We hypothesized that the post-contrast T1 obtained from the Look-Locker sequences (T1LL), an easily obtainable surrogate of myocardial T1, would be abnormally shortened in DMD compared with controls.

Methods—T1LL measurement was performed on 21 DMD subjects and 11 controls; to account for individual variations in gadolinium distribution, myocardial T1LL was divided by blood pool T1LL, deriving T1LL ratios.

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Ethical Standards:

This study was approved by the Vanderbilt Institutional Review Board. No patient consents were required for this retrospective study.

Conflict of Interest:

The authors have no conflicts of interest.

Results—DMD subjects had shorter mean T1LL ratio than controls (1.42 vs 1.72, $p<0.001$). Subset analyses in DMD subjects with normal LVEF and without LGE also demonstrated significantly shorter T1LL ratio (-0.28 , $p<0.001$ and -0.25 , $p=0.028$).

Conclusions—Post-contrast T1LL ratio is abnormally shortened in DMD compared with controls, even in DMD patients with otherwise normal CMRs. The application of more aggressive therapy for those with shorter T1LL may favorably alter morbidity and improve mortality associated with DMD cardiomyopathy. These data suggest that further, prospective evaluation of myocardial T1 will be of benefit to patients with DMD.

Keywords

Magnetic resonance imaging; Duchenne muscular dystrophy cardiomyopathy; Cardiomyopathy; T1 mapping; Myocardial fibrosis

Introduction

Duchenne muscular dystrophy (DMD) affects 1 in 3500 males, leading to severe skeletal and cardiac myopathy. The onset and progression of DMD cardiomyopathy (CM) are variable, but by 18 years of age, 70% of boys with DMD develop a depressed left ventricular ejection fraction (LVEF).[1,2] Cardiovascular disease is now the leading cause of death in DMD.[3] Prophylactic therapy with enalapril and other anti-failure medications delays onset of CM and mortality.[4,5] It is unclear, however, how early these prophylactic medications should begin; moreover, there are no non-invasive methods that can be used to evaluate medication efficacy.

Late gadolinium enhancement (LGE) by cardiac MRI (CMR) identifies myocardial scar in DMD, often before systolic dysfunction.[6,7] Although LGE is more prevalent in DMD subjects with decreased LVEF, it has not been demonstrated to predict DMD CM progression or mortality.[8] In addition, quantitative assessment of LGE in DMD is challenging[8] and the diffuse myocardial fibrosis expected in DMD may lead to ambiguous or even normal findings on LGE.[9,10] A noninvasive method of detecting diffuse, microfibrosis before standard imaging techniques would allow for earlier initiation of treatment, possibly delaying onset of systolic dysfunction and improving cardiovascular morbidity and mortality.[4] It would also provide a technique for serial evaluation of patients with normal function on prophylactic therapy, allowing for medication dose adjustment or alternate agents in those with increasing fibrosis.

Spatial mapping of the longitudinal relaxation time constant (T1) using CMR allows for myocardial tissue characterization by forming a parametric map having physical units. Because fibrosis shortens post-contrast T1, [11] these T1 maps may be able to identify diffuse areas of microfibrosis. Early animal studies support this hypothesis, demonstrating linear correlation between myocardial T1 and diffuse myocardial fibrosis.[12] In humans, post-contrast myocardial T1 mapping correlates with fibrosis from endomyocardial biopsies in both transplant and CM patients.[11,13]

Myocardial T1 has never been reported in DMD and the use of this quantitative tissue mapping method may afford researchers and clinicians the ability to characterize DMD myocardial fibrosis sooner and more objectively. Although T1 mapping requires prospective evaluation using modified Look-Locker (MOLLI) research sequences, analysis of myocardial T1 using the Look-Locker sequence correlates well with fibrosis on pathologic specimens and myocardial T1 derived from MOLLI.[13,14] Strategies that minimize or correct cardiac motion (e.g. adequate breath-holds or image registration) can help overcome potential limitations of the Look-Locker sequence. T1 measurements obtained from the Look-Locker sequence (T1LL) also have several advantages. Firstly, the Look-Locker is typically acquired with LGE studies and is available for retrospective evaluation. Secondly, MOLLI is currently not commercially available and its use is restricted to research applications, most often in MRI laboratories with independent pulse programming capability or research agreements with the MRI vendor. The purpose of this study was to evaluate the utility of T1LL, thus informing future, prospective analyses. We hypothesized that T1LL would be abnormally shortened in DMD patients compared with controls and that T1LL would demonstrate abnormalities even in patients without LGE.

Methods

Patient Selection

Following approval from the Vanderbilt Institutional Review Board, DMD subjects and controls that had undergone CMR between 2007–2013 were identified. A retrospective case-control study design was used for 23 DMD male subjects and 12 male controls; two DMD subjects and one control were removed due to poor image quality. The diagnosis of DMD was confirmed by skeletal muscle biopsy or presence of a dystrophin mutation in the setting of a clinical phenotype of skeletal muscle weakness. Control subjects were selected from patients with a normal CMR and normal cardiac evaluation. The reasons for their CMR referral were: rule out arrhythmogenic right ventricular dysplasia (N=4); rule out myocarditis, subsequently diagnosed with lobar bacterial pneumonia, myocarditis ruled out (N=1); chest pain (N=2); syncope (N=1); and poor image quality on prior echocardiogram (N=3). Control subjects exclusion criteria were: 1) congenital heart disease, 2) concern for hypertrophic cardiomyopathy with positive or unknown genotype, or 3) confirmed diagnosis of cardiac or extracardiac disease that could lead to myocardial edema, inflammation, or fibrosis, including arrhythmia other than premature ventricular contractions. All routine contraindications to CMR with gadolinium contrast applied.

Magnetic Resonance Imaging Methods

Imaging was performed on a 1.5T Siemens Avanto (Siemens Healthcare Sector, Erlangen, Germany) with an 8 channel cardiac coil. The CMR protocol consisted of 3 components: 1) ventricular function, 2) post-contrast T1 mapping, and 3) LGE. Ventricular function was assessed using breath-hold, retrospective electrocardiogram-gated, TrueFISP cine imaging sequences in 10–16 contiguous short axis images using conventional techniques.[15] Intravenous Gd-DTPA contrast (gadopentate dimeglumine, Magnevist®, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA) at a dose of 0.2mmol/kg was administered through a peripheral IV. The Look-Locker was obtained in the short axis plane at the level of the

papillary muscles 10 minutes after contrast administration with imaging parameters of: field of view 275–400mm × 340–400mm, matrix 66–96 × 192, slice thickness 8mm, flip angle 30 degrees, no parallel imaging. Standard Look-Locker imaging included 17–35 images acquired every other R-R interval with phase intervals of approximately 30ms. The images were ECG-gated and were acquired using segmented k-space during breath-holds. Late gadolinium enhancement was obtained in a stack of short axis slices using: 1) single shot inversion recovery TrueFISP with an optimized inversion time to null normal myocardium and 2) phase sensitive inversion recovery TrueFISP with an inversion time of 300ms.

Image Analysis

Left ventricular volume, mass, and ejection fraction were calculated from manually drawn contours of endocardial and epicardial borders in end-diastole and end-systole using the Leonardo Workstation (Siemens Healthcare Sector, Erlangen, Germany). Qualitative segmental assessment of LGE was performed by one reader (JS) and confirmed by a second reader (DP); both readers were blinded to T1LL results.[16] T1LL maps were created from the Look-Locker acquisition using MRMap (version 1.3, <http://mrmap.sourceforge.net>), an open source software program.[17,14] The DICOM image created with MRMap was then imported into MatLab (The MathWorks, Natick, MA, USA). LV mesocardial regions of interest (ROI) were manually drawn using MatLab, avoiding partial volume averaging with the blood pool or epicardial fat, for each LV segment using the standard segmentation model.[16] (Figure 1) The Look-Locker is acquired at multiple phases of the cardiac cycle, which can lead to motion artifact. This was partially corrected with image registration performed by MRMap and by limiting the region of interest (ROI) to the mesocardium.[17] The T1LL values for every voxel in each segment were exported for statistical analysis.

Individual variation in timing and dose of gadolinium, clearance of gadolinium, and body composition can alter the volume of distribution of gadolinium. In this study, the dose of gadolinium was constant and the timing was relatively constant, so these parameters did not require correction. Although gadolinium clearance can be corrected using glomerular filtration rate (GFR), the GFR was incalculable due to the low muscle mass in DMD that invalidates creatinine. Therefore, we used the method described by Choi et al to correct for the volume of distribution of gadolinium. We drew a ROI in the center of the LV cavity to obtain the average T1LL of the blood pool, excluding papillary muscles. A T1LL ratio was then calculated using the following equation:[18]

$$T1LL\ Ratio = \frac{Myocardial\ T1LL}{Blood\ pool\ T1LL}$$

Statistical Analysis

Baseline functional characteristics were compared between groups using a Wilcoxon Rank Sum test for continuous variables and a Chi-square test or Fisher's exact test for categorical variables. A mean, standard deviation, and confidence interval of the myocardial T1LL and the T1LL ratio were calculated, and the distribution of individual medians were compared between DMD and control using a Wilcoxon Rank Sum test. The following subset analyses

of mean T1LL ratios were performed: 1) comparison of DMD subjects with normal LVEF to control subjects, 2) comparison of DMD subjects without LGE to control subjects, and 3) comparison of DMD segments without LGE to control segments. In order to perform the segmental analysis, only segments without LGE were included and each individual DMD segment was compared with the corresponding segment in controls (i.e. anterior segments in DMD subjects without LGE compared with anterior segments in controls).

Analyses were performed with the statistical programming language R, version 2.14.1 (R Development Core Team, Vienna, Austria) or IBM SPSS statistics, version 21.0 (Armonk, NY: IBM Corp). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt.[19]

Results

Demographic and LV Systolic Function Data

Demographic data of the study cohort are shown in Table 1. The mean LVEF was lower in DMD subjects compared with controls ($52.3 \pm 8.4\%$ vs $66.1 \pm 6.6\%$, $p=0.001$). Twelve (57%) of the 21 DMD subjects had an abnormal LVEF, defined as $LVEF < 55\%$. LV end diastolic and end systolic dimensions were not significantly different between DMD and controls, similar to previously described DMD cohorts with LV dysfunction and minimal LV dilation.[20] The lower LVEF in DMD likely results from a trend towards smaller LV end diastolic and larger LV end systolic volumes.

Fibrosis: LGE and T1LL Times

The Look-Locker sequence was performed a mean of 9.6 ± 0.8 min after contrast. LGE was present in 18 of 21 DMD subjects (analysis by segment noted in Table 1). No control subjects had LGE. DMD subjects with LGE had significantly decreased LVEF compared with DMD subjects without LGE (50.6% vs 62.7% , $p=0.02$). Six DMD subjects with LGE had normal LVEF; all subjects with abnormal LVEF had LGE. The mean T1LL values were significantly shorter in DMD myocardium compared with controls (-60.1 ms, 95% CI $(-109.1, -11.2)$, $p=0.016$) (Figure 2). DMD subjects demonstrated significant segmental variation, with shorter T1LL in the inferior, inferolateral, and anterolateral segments, whereas control subjects had more constant T1LL across all segments (Figure 3).

The mean T1LL ratio in DMD was 1.45 (range 1.14–1.76) while the mean T1LL ratio in controls was 1.78 (range 1.63–1.92). Table 2 demonstrates mean post-contrast myocardial T1LL, mean blood pool T1LL, and T1LL ratio. Significantly shorter mean T1LL ratios were present in DMD subjects as compared with controls (-0.32 , 95% CI $(-0.43, -0.21)$, $p<0.001$). DMD subjects with normal LVEF demonstrated shorter T1LL ratios compared with controls (-0.28 , 95% CI $(-0.40, -0.17)$, $p<0.001$). DMD subjects without LGE also demonstrated shorter T1LL ratios compared with controls (-0.25 , 95% CI $(-0.38, -0.11)$, $p=0.005$). The three DMD subjects without LGE had T1LL ratios of 1.47, 1.5, and 1.61, all of which fell below the shortest T1LL ratio found in controls (1.63). Analysis of DMD segments without LGE compared with control segments without LGE also demonstrated a statistically significant difference in all segments (Table 3).

Discussion

We found that DMD subjects had shortened myocardial T1LL when compared with controls; this is clinically significant because T1LL may identify early fibrosis, potentially allowing for earlier and more effective treatment. The shortened T1LL also occurs in DMD subjects with normal LVEF and those without LGE. Because there were only three DMD subjects without LGE, segmental analysis was also performed. This analysis demonstrated shortened T1LL in all segments without LGE, or segments that would be interpreted as normal using standard imaging techniques. This study is the first, to our knowledge, to evaluate CMR derived myocardial T1LL in DMD subjects.

The segmental pattern of T1LL shortening corresponds to the fibrosis seen in previous DMD pathological specimens.[21–23] In DMD skeletal muscle, fatty replacement is a common finding in addition to fibrosis.[23] Although fatty replacement of the myocardium has been described in DMD and could lead to decreased T1LL, pathologic studies describe fibrosis as the principal histologic feature, [21–24] suggesting that the shortened T1LL most likely represents early fibrosis. Fatty replacement of the myocardium also represents a pathologic condition that would be expected to decrease myocardial function and increase morbidity and mortality. Therefore, both fibrosis and fatty replacement are of clinical significance in this population and further prospective evaluation of fatty replacement would be beneficial.

Sibley, et al evaluated T1 measurements in patients with cardiomyopathy using the Look-Locker sequence. They compared T1LL to fibrosis as assessed by endomyocardial biopsy and demonstrated a good correlation between T1LL and fibrosis. Similar to our study, they found shortened T1LL in patients without LGE but with significant fibrosis on biopsy specimens.[13]

Our data suggest that T1LL can detect diffuse fibrosis in DMD myocardium, even in the absence of LGE. When paired with a concurrent hematocrit, prospective evaluation of native and post-contrast T1 allows calculation of an extracellular volume (ECV) fraction, a marker of adverse myocardial remodeling.[25–27] T1 mapping and ECV hold clinical promise both for earlier identification of myocardial disease and for modification of anti-failure therapy in patients with worsening fibrosis. In addition, these techniques may serve as surrogate endpoints for the evaluation of the cardiovascular effects of novel medical therapies. This study suggests that future, prospective evaluation of T1 and ECV mapping is warranted.

Limitations

The calculation of myocardial T1 can be minimally affected by heart rate, time in cardiac cycle, and hematocrit. As any T1 mapping method is applied to pediatric patients with faster heart rates, future work to define a maximum heart rate threshold as well as possible techniques to correct for heart rate should be undertaken. In addition, the importance of image registration and adequate breath-holds in DMD patients with higher heart rates must be recognized. Unlike pre-contrast T1, however, which is very sensitive to elevated heart rates, multiple studies have demonstrated trivial to no heart rate effect on post-contrast T1. [28,29] In this study, the mean DMD heart rate of 96 bpm provided adequate time for magnetization recovery (1250ms) given a mean T1LL of 355 ms. While a cyclical

difference in post-contrast myocardial T1 has been shown, previous studies demonstrate a trivial difference of only 2% (12ms), which is far outweighed by the large difference in T1LL between DMD subjects and controls.[30] Although variations in hematocrit can lead to small variations in T1, studies suggest that hematocrit levels do not lead to significant variation in the time points of interest (greater than 5 minutes after contrast injection).[28]

A control population of children is ethically difficult to obtain. Following completion of a comprehensive cardiovascular clinical and imaging evaluation, no cardiac pathology was identified in the control population. The control subjects may have had subclinical disease leading to a shortening of their T1LL, which would have made statistical significance in this study more difficult to obtain.

Summary

CMR derived post-contrast myocardial T1LL is abnormal in DMD when compared with controls. The shorter T1LL ratio in DMD subjects without LGE suggests early fibrous replacement of the myocardium. We recommend further evaluation of T1 mapping and ECV in patients with DMD as these methods may aid in the initiation and modification of anti-failure therapy.

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Abbreviations

T1	longitudinal relaxation time constant
T1LL	T1 time obtained from analysis of the Look-Locker sequence
T1LL ratio	(myocardial T1LL)/(blood pool T1LL)
DMD	Duchenne muscular dystrophy
CM	cardiomyopathy
LVEF	left ventricular ejection fraction
LGE	late gadolinium enhancement
CMR	cardiac magnetic resonance imaging
ECV	extracellular volume

LV

left ventricle

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Figure 1. Myocardial segmentation

Myocardial segmentation in short axis (A). Representative T1LL map (B).

Figure 2. Boxplot of post-contrast myocardial T1LL

DMD subjects have shorter myocardial T1LL when compared with controls, especially in the inferior, inferolateral, and anterolateral segments of DMD; control subjects have relatively constant myocardial T1LL across segments.

Figure 3. Representative T1LL maps

Representative maps of post-contrast myocardial T1LL in control (A) and DMD (B). Note significant difference in T1LL of blood pool and of myocardium, despite identical color maps. Map of T1LL ratio (myocardial T1LL/blood pool T1LL) in control (C) and DMD (D) demonstrates more comparable T1LL ratio of “normal” myocardium and blood pool, allowing for better comparison between patients. Post-contrast myocardial T1LL in DMD is visibly shorter in the inferior, inferolateral, and anterolateral segments as compared with control myocardium.

Table 1

Characteristics of Control and Duchenne muscular dystrophy (DMD) subjects

	Control N=11	DMD N=21	95% CI	Wilcoxon p-value
Age (years)	16.9 ± 1.3 (range 11–19)	16.2 ± 2.0 (range 8–22)	(–2.7, 2.1)	p=0.630
BSA ^a (m ²)	2.00 ± 0.30	1.55 ± 0.33	(–0.7, –0.2)	p=0.002
Resting Heart Rate (bpm)	73.2 ± 16.1	95.7 ± 14.9	(10.9, 34.2)	p=0.001
LVEF ^b	64.4% ± 7.5	52.3% ± 8.4	(–18.2, –5.8)	p=0.001
Indexed LVEDV ^c (ml/m ²)	72.2 ± 15.0	71.4 ± 16.3	(–13.5, 11.9)	p=0.542
Indexed LVESV ^d (ml/m ²)	26.6 ± 8.6	33.5 ± 10.5	(–1, 14.8)	p= 0.115
Indexed LV mass (g/m ²)	64.8 ± 12.6	61.3 ± 11.0	(–12.6, 5.6)	p=0.642
LGE ^e abnormal	0%	86% (N=18)		p<0.001
Anteroseptal	0%	14% (N=3)		
Inferoseptal	0%	24% (N=5)		
Inferior	0%	52% (N=11)		
Inferolateral	0%	76% (N=16)		
Anterolateral	0%	81% (N=17)		
Anterior	0%	29% (N=6)		

Data expressed as mean ± SD or as percentage

^aBody surface area (BSA)^bLeft ventricular ejection fraction (LVEF)^cLeft ventricular end diastolic volume (LVEDV)^dLeft ventricular end systolic volume (LVESV)^eLate gadolinium enhancement (LGE)

Table 2

Mean post-contrast T1 measurements (T1LL), blood pool T1LL, and T1LL ratio with standard deviation

	Myocardial T1LL (ms)	Mean number voxels	Blood pool T1LL (ms)	T1LL Ratio $\pm$ SD
DMD ^a	362	335	253	1.45 $\pm$ 0.16
DMD no LGE ^b	375	200	257	1.53 $\pm$ 0.077
DMD normal LVEF ^c	374	281	254	1.49 $\pm$ 0.15
Control	422	276	239	1.78 $\pm$ 0.098

^aDuchenne muscular dystrophy (DMD)

^bLate gadolinium enhancement (LGE)

^cLeft ventricular ejection fraction (LVEF)

Table 3

Comparison of post-contrast T1 measurements (T1LL) in Duchenne muscular dystrophy (DMD) segments without late gadolinium enhancement (LGE) to T1LL values in control segments.

Segment	DMD	Controls	Mean T1LL difference (95% CI)	Wilcoxon p-value
Anteroseptal	N=18	N=11	-0.31 (-0.43, -0.2)	p<0.001
Inferoseptal	N=16	N=11	-0.30 (-0.41, -0.2)	p<0.001
Inferior	N=10	N=11	-0.30 (-0.42, -0.18)	p<0.001
Inferolateral	N=5	N=11	-0.27 (-0.38, -0.17)	p<0.001
Anterolateral	N=4	N=11	-0.23 (-0.35, -0.11)	p=0.001
Anterior	N=15	N=11	-0.32 (-0.44, -0.19)	p<0.001