Intramyocardial and Pericardial Fat Quantification in Boys with Duchenne Muscular Dystrophy and Healthy Controls at 3T.

Nyasha G. Maforo[1,2], Holden H. Wu[1,2,3], Patrick Magrath[1,3], Pierangelo Renella[1], Nancy Halnon[4], and Daniel B. Ennis[5]

[1]Department of Radiological Sciences, [2]Physics and Biology in Medicine Interdepartmental Program, [3]Department of Bioengineering, [4]Department of Pediatrics (Cardiology), University of California, Los Angeles, California. [5]Department of Radiology, Stanford University, Stanford, California.

Submission Category 1: CV: Myocardial Tissue Characterization
Submission Category 2: CV: Emerging Translational Methods

Synopsis
Duchenne muscular dystrophy (DMD) is a fatal X-linked genetic disorder characterized by progressive muscle weakness and pediatric onset cardiomyopathy and heart failure. Chemical-shift based water-fat separation MRI techniques are used to investigate myocardial fibro-fatty infiltration, to identify the onset of microstructural remodeling in boys with DMD. This study sought to: 1) characterize and compare intramyocardial signal fat fraction (sFF) between boys with DMD and healthy controls; and 2) report and compare pericardial fat volume and sFF estimates in boys with DMD and healthy controls. We detected no difference in myocardial [6.0(3.0)% vs. 5.0(2.5)%, p=0.8] and pericardial [61(25.5)% vs. 47(12)%, p>0.1] sFF values between DMD boys and healthy controls respectively. Boys with DMD presented with significantly more pericardial fat volume [7.56(3.31)cm^3 vs. 5.53(193)cm^3, p=0.03] compared to healthy boys.

Introduction:
Duchenne muscular dystrophy (DMD) is a fatal X-linked genetic disorder affecting 15.9 to 19.5 per 100,000 live births[1]. DMD is associated with pediatric onset cardiomyopathy and fatal heart failure. On-going research aims to investigate cardiac MRI biomarkers, including myocardial fibro-fatty infiltration, to identify the on-set of microstructural remodeling in boys with DMD[2]. Chemical-shift[3] based water-fat separation MRI techniques have been used to assess the level of fat infiltration in skeletal muscle of DMD subjects[4]. Based on histology, some of the pathological changes in DMD are shared between skeletal and cardiac muscle[5], yet the onset of intra-myocardial fat and excessive pericardial fat remains understudied. The 3T MRI study herein aims to: 1) characterize and compare intramyocardial signal fat fraction (sFF) between boys with DMD and healthy controls; and 2) report and compare pericardial fat volume and sFF estimates in boys with DMD and healthy controls.

Methods:
Imaging: Boys with DMD (N=18, 13±2.9 years, BMI=24.7±5.2 kg/m^2, HR=96±15.8 bpm) and healthy boys (N=11, 12.5±2.5 years, BMI=18.3±3.1 kg/m^2, HR=72±15 bpm) were prospectively enrolled in an IRB-approved study for a cardiac MRI (cMRI) exam at 3T (Siemens Skyra) after

providing informed consent. The cMRI exam consisted of a multi-echo (Dixon-like) GRE sequence for fat-water separation imaging[3]. Images were acquired during free-breathing with ECG gating. Imaging parameters were: matrix size = 192x144mm^2, pixel size=2x2x8mm^3, flip angle=12°,TE/TR=1.64,4.17,6.7,9.23/11.2ms.

Post-processing: For all subjects, water- and fat-separated images for a mid-ventricular short-axis slice were used to calculate maps of sFF = Fat/(Water+Fat) (MATLAB, MathWorks). To account for noise bias, the sFF in regions of low fat content were generated by: sFF = 1 – sWF (sWF = Water/(Water+Fat). As shown in FIG. 1, a region of interest (ROI) encompassing the left ventricular (LV) myocardium and ROIs containing pericardial fat were segmented, extracted, and analyzed for their corresponding sFF values. Summary statistics were extracted from all ROIs and pericardial fat volume (cm^3) was quantified from the corresponding regions for a single slice. Mann-Whitney U-tests were used to compare boys with DMD and healthy controls. Spearman's correlation test was performed to assess relationships between measured parameters (sFFs and pericardial fat volume) and demographic characteristics (age, height, weight, BMI, and HR) of DMD boys and healthy controls. Data is reported as median and IQR. $P<0.05$ was considered significant.

Results:
We detected no difference in myocardial [6.0(3.0)% vs. 5.0(2.5)%, p=0.8] and pericardial [61(25.5)% vs. 47(12)%, p>0.1] sFF values between DMD boys and healthy controls respectively. Boys with DMD presented with significantly more pericardial fat volume [7.56(3.31)cm^3 vs. 5.53(1.93)cm^3, p=0.03] compared to healthy boys. This result is displayed by box plots in FIG. 2A-C. Summary statistics of possible covariates (Age, height, weight, BMI, and HR) and Spearman correlation tests are summarized in Tables 1 and 2 respectively.

Discussion:
The null result reported here for intramyocardial differences between DMD boys and healthy controls suggests that myocardial fatty infiltration is not readily apparent and is likely a late-stage outcome in DMD. A 13 year old early-stage and 17 year old late-stage DMD subject are shown in FIG.1 paired with late gadolinium enhancement (LGE) images where myocardial enhancement is only present in the late-stage subject. A healthy control is shown for comparison. Furthermore, a previous study reported fatty infiltration and edema in the upper arm and skeletal muscles, but not the myocardium of DMD boys with normal ejection fraction (EF)[4].

In FIG. 3A-F we observe a distinct separation between DMD boys and healthy controls for pericardial fat volume, and pericardial and myocardial sFF as a function of HR and BMI. While pericardial sFF is not significantly different between boys with DMD and healthy controls, FIG. 3C-D demonstrates a trend towards elevated pericardial sFFs in DMD as a function of HR and BMI. We also find other covariates (Age, weight, and HR) that significantly correlate to pericardial sFF .

We detect a significant difference in pericardial fat volume between DMD boys and healthy controls. Furthermore, a significant correlation between pericardial fat volume and age is observed (Table 2). It is unclear if the elevated pericardial fat volume and correlation with age is part of the cardiac disease process or due to increased BMI alone, thus warranting further investigation. A previous multi-ethnic study of atherosclerosis (MESA) reported that pericardial fat volume is associated with a higher risk of cardiovascular disease[6]. The three most affected DMD subjects are consistent outliers in FIG. 2 and 3.

To our knowledge this is the first report of intramyocardial and pericardial sFF and pericardial fat volume estimates in DMD subjects and healthy volunteers at 3T, hence, the reported values help to establish reference values for this cohort.

Conclusion

Herein, we detected no differences in myocardial and pericardial sFF between boys with DMD and age-matched controls. We find that DMD boys exhibit more pericardial fat compared to healthy controls. Additional work is needed to understand, for example, the correspondence of changes in sFF with age, BMI, and DMD severity.

References:

[1] Ryder S *et al*., OJRD 2017
[2] Mavrogeni S *et al*., BMC Neurology 2010
[3] Kellman *et al.*, MRM 2009
[4] Gaur L *et al.*, ACN 2016
[5] Moriuchi T *et al*., J Exp Med. 1993
[6] Ong KL *et al*., Atherosclerosis 2015

Acknowledgements:

Funding NIH R01 HL131975 to DBE.
Funding NSF DGE 1650604 to NGM.

	DMD (N=18) Median (IQR)	Control (N=11) Median (IQR)	Mann-Whitney *P* value
Age (years)	13(4.0)	13(4.25)	0.6
Height (cm)	139(21.3)	163(16.8)	0.003
Weight (kg)	50(19.3)	50.8(13.2)	0.7
Body mass index (kg/m^2)	24.8(8.25)	17.9(1.7)	0.002
Heart rate (bpm)	96(22)	65(29)	0.01
Myocardial sFF (%)	6.0(3.0)	5.0(2.5)	0.8
Pericardial sFF (%)	61(26)	47(12)	0.1
Pericardial volume (cm^3)	7.56(3.31)	5.53(1.93)	0.03

Table 1: Summary statistics for myocardial and pericardial sFF and pericardial fat volume, along with statistics of possible covariates (Age, height, weight, body mass index (BMI), and heart rate (HR)). Data is reported as median(IQR). Mann-Whitney U-test was performed for all comparisons between DMD boys and healthy controls. Test performed using a significance level of p=0.05.

DMD	Spearman correlation coefficient	*P v*alue
Pericardial volume, Age	0.65	0.002
Pericardial sFF, Age	0.63	0.004
Pericardial sFF, Weight	0.50	0.03
Pericardial sFF, HR	-0.61	0.006
Control	**Spearman correlation coefficient**	***P* value**
Pericardial volume, Height	0.68	0.02
Pericardial sFF, Weight	0.70	0.02

Table 2: Significant correlations resulting from a Spearman test between measured parameters (pericardial fat volume and sFF, and myocardial sFF) and possible covariates (age, height, weight, BMI, and HR). Tests were performed using a significance level of p=0.05.

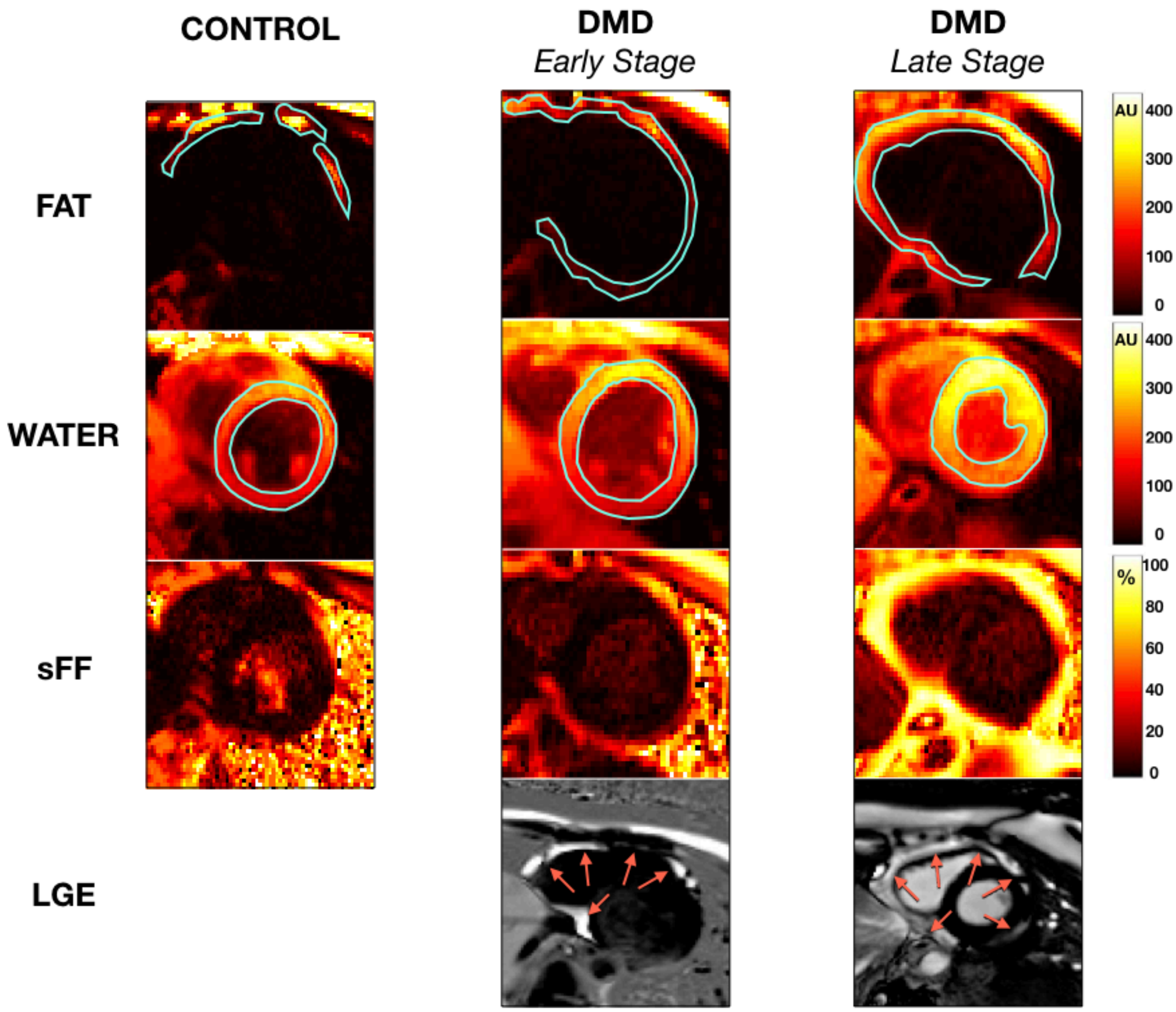
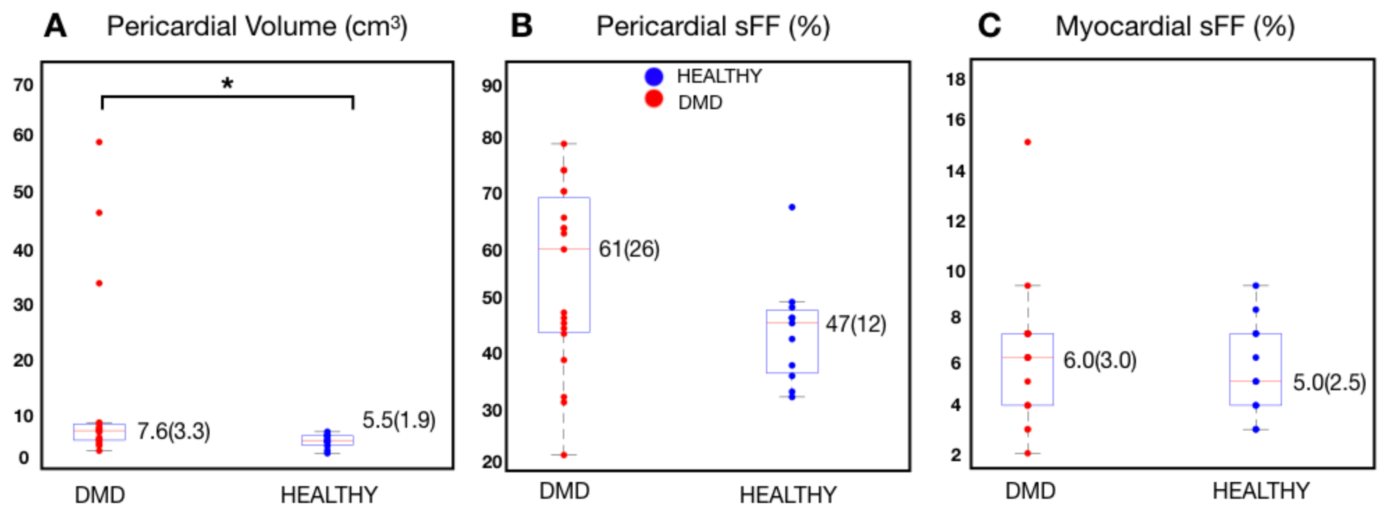


FIG. 1: A mid-ventricular short-axis example of a healthy control aged 17 (Column 1), DMD (early stage) aged 13 (Column 2) , and DMD (late stage) aged 17 (Column 3) subject. First Row: Fat-separated maps with pericardial fat ROI(s). Second Row: Water-separated maps with myocardial and blood pool contours. Third Row: sFF maps. Fourth Row: Late gadolinium enhancement (LGE) imaging was acquired in DMD subjects only. Arrows point to enhancement found in pericardium and myocardium (late stage). ROIs were processed for sFF values in all subjects.



**** p-value <0.05***

FIG. 2A-C: Box plots of pericardial fat volume, pericardial sFF, and myocardial sFF measured in DMD subjects and healthy controls at 3T. Median(IQR) is reported next to each box plot. (A) DMD boys present with significantly more pericardial fat compared to healthy controls. (B-C) A trend towards elevated pericardial and myocardial sFF is observed in DMD boys.

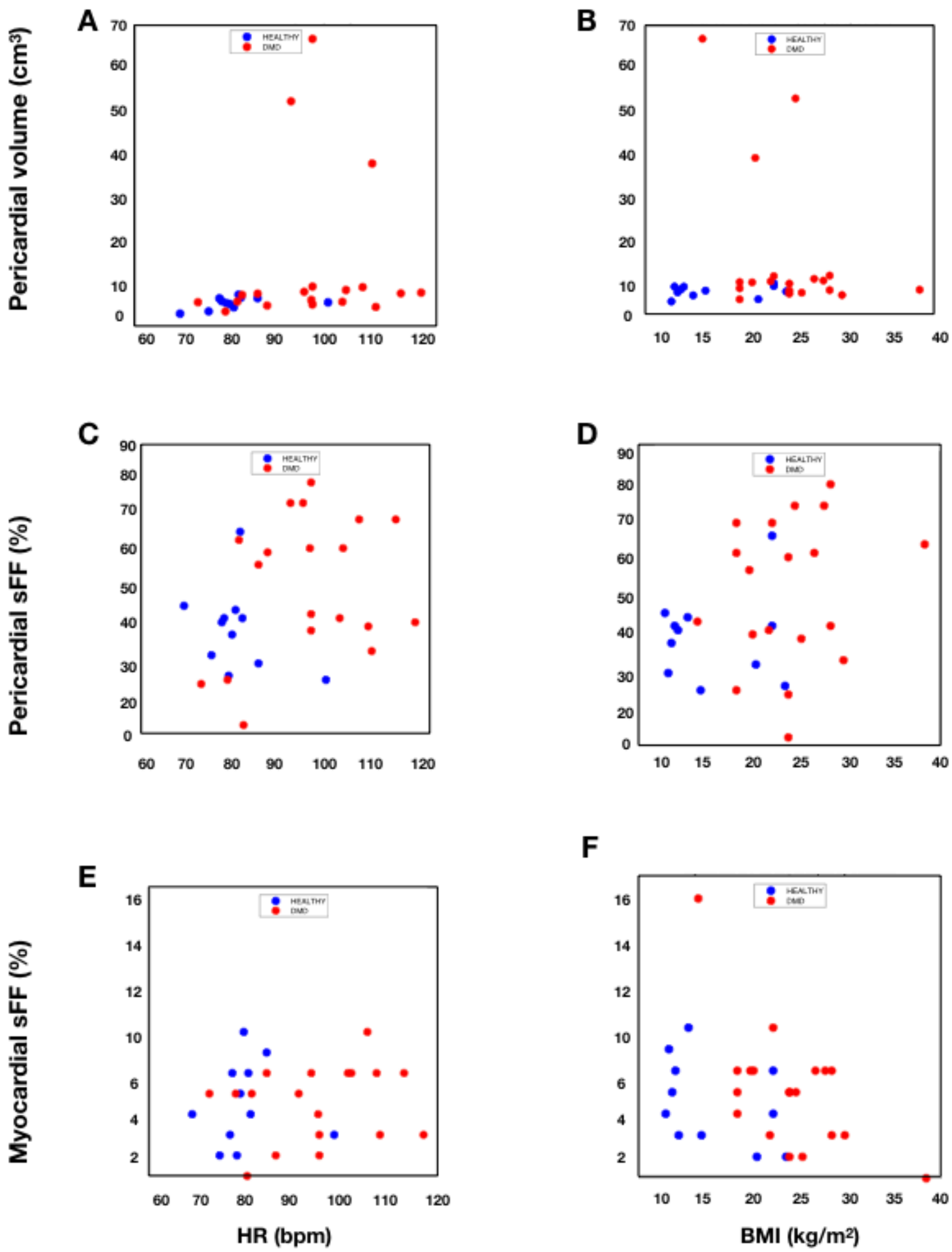


FIG. 3A-F: Pericardial fat volume, pericardial sFF, and myocardial sFF as a function of possible covariates (HR and BMI). Distinct differences between DMD boys and healthy controls are observed in all parameters (A-F). (C) A significant correlation is found between pericardial sFF and HR[r=-0.61,p=0.006].