**Impact:** This work investigates the myocardial fibro-fatty infiltration using a chemical-shift based water-fat separation MRI technique. This pilot study detected increased pericardial fat in Duchenne Muscular Dystrophy (DMD) patients compared to healthy controls, but intra-myocardial differences were found only at the apical level between the two groups. This data suggests that intra-myocardial fat is a late outcome in DMD.
Duchenne Muscular Dystrophy:

- A fatal X-linked genetic disorder characterized by progressive muscle weakness.
- 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 onset of microstructural remodeling in boys with DMD.
- Based on histology, some of the pathological changes in DMD are shared between skeletal and cardiac muscle, yet the onset of intra-myocardial fat and excessive pericardial fat remains understudied.

Chemical-shift based water-fat separation MRI techniques have been used to assess the level of fat infiltration in skeletal muscle of DMD subjects.

Study Objectives:
- Characterize and compare intra-myocardial signal fat fraction (sFF) between boys with DMD and healthy controls;
- Report and compare pericardial fat volume and sFF estimates in boys with DMD and healthy controls.

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1. Ryder S et al., OJRD 2017
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For more information regarding our work on cardiac MRI biomarkers for Duchenne Muscular Dystrophy see Program #2027.
DMD CARDIAC MRI EXAM AT 3T HAS POTENTIAL TO YIELD BIOMARKERS SENSITIVE TO MYOCARDIAL CHANGES

STUDY OBJECTIVES:
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IMAGING PROTOCOL:
The DMD cardiac MRI exam at 3T has potential to yield biomarkers sensitive to myocardial changes. This workflow includes both structural and functional imaging and features the following:

- High resolution, static black-blood imaging (A)
- Short- and long axis tagged images (B)
- Pre- and post-contrast T1 mapping and ECV (C and H)
- T2 mapping (D) and ADC mapping (not pictured)
- Dynamic (CINE) white blood bSSFP imaging (F)
- Post-contrast static late gadolinium enhancement (LGE) imaging (G).

Fat-Water Imaging (E)
The cMRI exam consisted of a multi-echo (Dixon) GRE sequence for fat-water separation imaging to assess fibro-fatty infiltration. These Images were acquired during free-breathing with ECG gating.

Imaging Parameters
Matrix size 192 x 108 mm²
Pixel size 2x2x8 mm³
Flip angle 12°
TE 1.27; 4.17; 6.7; 9.23 ms
TR 11.2 ms
IMAGING:

Boys with DMD (N=22, 13 ± 3.1 years) and healthy boys (N=11, 12.6 ± 2.5 years), were prospectively enrolled in an IRB-approved and HIPPA-compliant study for a cardiac MRI (cMRI) exam at 3T (Siemens Skyra) after providing informed consent.

STUDY OBJECTIVES:

- Characterize and compare intra-myocardial signal fat fraction (sFF) between boys with DMD and healthy controls;
- Report and compare pericardial fat volume and sFF estimates in boys with DMD and healthy controls.

STUDY POPULATION:

<table>
<thead>
<tr>
<th></th>
<th>DMD (N=22)</th>
<th>Control (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>13 (4.0)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Height* (cm)</td>
<td>134 (26.0)</td>
<td>163 (16.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50.0 (26.3)</td>
<td>50.8 (13.2)</td>
</tr>
<tr>
<td>BMI* (kg/m²)</td>
<td>26.1 (11.3)</td>
<td>17.9 (1.7)</td>
</tr>
<tr>
<td>Heart rate* (bpm)</td>
<td>87 (24)</td>
<td>65 (30)</td>
</tr>
<tr>
<td>LVEF* (%)</td>
<td>50.1 (11.5)</td>
<td>57.9 (7.28)</td>
</tr>
</tbody>
</table>

* p < 0.05

BMI - body mass index
LVEF - Left ventricular ejection fraction

INTRA-MYOCARDIAL AND PERICARDIAL FAT QUANTIFICATION

BOYS WITH DMD ARE SHORTER IN HEIGHT, HAVE INCREASED BMI AND HEART RATE, AND DECREASED LVEF COMPARED TO HEALTHY CONTROLS.

REFERENCES:
1. Ryder S et al., OJRD 2017
2. Mavrogeni S et al., BMC Neurology
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**DMD boys with who are LGE+ have an increased heart rate and a decreased LVEF compared to DMD boys who are LGE-.**

<table>
<thead>
<tr>
<th>Study Population</th>
<th>LGE+ (N=6)</th>
<th>LGE- (N=13)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>12 (7.0)</td>
<td>13 (4.5)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>130 (17.0)</td>
<td>133 (16.8)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>49.9 (14.6)</td>
<td>50.5 (31.5)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>25.2 (5.1)</td>
<td>27.3 (12.5)</td>
</tr>
<tr>
<td><em><em>Heart rate</em> (bpm)</em>*</td>
<td>73.5 (13)</td>
<td>98 (24.3)</td>
</tr>
<tr>
<td><em><em>LVEF</em> (%)</em>*</td>
<td>43.3 (11.6)</td>
<td>54.4 (10.1)</td>
</tr>
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*D p < 0.05

**BMI** - body mass index

**LVEF** - Left ventricular ejection fraction

**STUDY OBJECTIVES:**
- Characterize and compare intra-myocardial signal fat fraction (sFF) between boys with DMD and healthy controls;
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POST-PROCESSING:
- Water- and fat-separated images for basal, mid-ventricular, and apical short-axis slices were used to calculate maps of signal fat fraction.
  \[ sFF = \frac{\text{Fat}}{\text{Water} + \text{Fat}} \]
- To account for noise bias, the sFF in regions of low fat content were generated by:
  \[ sFF = 1 - sWF \]
  \( (sWF = \text{Water}(\text{Water} + \text{Fat}). \)
- 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 each slice location.
- 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.

STUDY OBJECTIVES:
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<td>Apex*</td>
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**PERICARDIAL SFF (%):**

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WE OBSERVE SIGNIFICANTLY MORE PERICARDIAL FAT IN DMD COMPARED TO HEALTHY CONTROLS ACROSS ALL SLICE LOCATIONS.

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WE OBSERVE INCREASED PERICARDIAL SIGNAL FAT FRACTION IN DMD COMPARED TO HEALTHY CONTROLS ACROSS ALL SLICE LOCATIONS.

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Myocardial sFF increases with age and height in DMD and healthy controls, but decreases with LVEF in DMD patients.

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<tbody>
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<td>LGE+ (N=6) Median (IQR)</td>
<td>LGE- (N=13) Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>8.38 (4.89)</td>
<td>8.47 (3.81)</td>
<td></td>
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<tr>
<td>Mid</td>
<td>6.78 (2.94)</td>
<td>7.12 (2.98)</td>
<td></td>
<td></td>
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<tr>
<td>Apex</td>
<td>5.91 (4.93)</td>
<td>5.54 (2.62)</td>
<td></td>
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</table>

| PERICARDIAL SFF (%) | | | | |
|---------------------|-----------------|--|-----------------|
| LGE+ (N=6) Median (IQR) | LGE- (N=13) Median (IQR) | | |
| Base | 68 (25) | 65 (19) | | |
| Mid | 50 (25) | 66 (14) | | |
| Apex | 52 (25) | 67 (23) | | |

| MYOCARDIAL SFF (%) | | | | |
|---------------------|-----------------|--|-----------------|
| LGE+ (N=6) Median (IQR) | LGE- (N=13) Median (IQR) | | |
| Base | 6.1 (6.4) | 7.5 (2.7) | | |
| Mid | 4.9 (8.7) | 5.2 (2.1) | | |
| Apex | 5.8 (4.1) | 5.9 (4.8) | | |

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**DISCUSSION:**

- Herein we have shown the potential for water-fat separation MRI to detect fibro-fatty infiltration in the heart of boys with DMD and healthy controls.
- We report pericardial fat volume, pericardial sFF, and myocardial sFF from the basal, mid-ventricular, and apical slice locations.
- We observed increased amounts of pericardial fat and, subsequently, an increased signal fat fraction in DMD patients compared to healthy controls.
- 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.
- A previous multi-ethnic study of atherosclerosis (MESA) reported that pericardial fat volume is associated with a higher risk of cardiovascular disease.
- We observed no detectable intra-myocardial sFF differences at the basal and mid-ventricular level, but we found increased myocardial sFF in DMD near the apex. It is unclear if that is the initial site of fibro-fatty accumulation in the DMD heart.

**COMPARED TO HEALTHY CONTROLS, DMD PATIENTS HAVE:**

1. **INCREASED PERICARDIAL FAT VOLUME**
2. **INCREASED PERICARDIAL sFF**
3. **INCREASED MYOCARDIAL sFF ONLY AT APICAL LEVEL**

**CONCLUSION:**

- We found that DMD patients have increased pericardial fat, pericardial sFF, and increased myocardial sFF only near the apex.
- Additional work is needed to understand the correspondence of changes in sFF with age, BMI, and DMD severity.

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Tyler
Matt
Jessica
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Amanda

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