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MR Imaging Biomarkers of Cardiac Function and Rotational Mechanics in Boys with Duchenne Muscular Dystrophy

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Synopsis

Duchenne Muscular Dystrophy (DMD) severely impacts heart health. Decreasing LV ejection fraction (EF) is a late and highly variable outcome in this cohort. Earlier indications of cardiac involvement would improve patient management and provide insight into the utility of emerging therapy. Boys with DMD (N=25) and healthy volunteers (N=8) underwent cardiac MRI exams including short-axis tagged images. EF, peak LV twist, and peak mid-wall circumferential strain (E_{cc}) were estimated. E_{cc} and twist were significantly reduced in patients (9.3°±4.3° vs. 14.8° ±3.6°, p< 0.004) and (-15.8±5.8% vs. -18.5±3.2%, p<0.02). Whereas, EF was not significantly different between groups. ~50% of DMD patients with normal EF had reduced twist and E_{cc}. Reduced peak LV twist and mid-wall E_{cc} measured by MR tagging may be earlier and more sensitive indicators of cardiac involvement in boys with DMD.

Background

Duchenne Muscular Dystrophy (DMD) is a fatal genetic disorder affecting 1 in 3000 boys. DMD severely impacts heart health, which has prompted recent clinical trials to include cardiac MRI biomarkers as end-points. Ejection fraction (EF) has been shown to decline ~2%/year, but is a late outcome and highly variable[1]. Identifying earlier indications of cardiac disease in this cohort may allow for more effective patient treatment and earlier insight to the utility of emerging therapies. Recent reports have indicated that peak mid-wall circumferential strain (E_{cc}) and LV twist are reduced in boys with DMD compared to healthy volunteers[2-3]. This work further characterizes both peak mid-wall E_{cc} and LV twist in a cohort of boys with DMD compared with healthy volunteers. The objective was to determine if reductions in peak mid-wall E_{cc} and LV twist can more sensitively distinguish cardiac dysfunction in this cohort compared to EF.

Methods

Study Population: In this IRB-approved and HIPAA-compliant prospective study, boys with DMD (N=25, age=14±5 years) and healthy volunteers (N=8, age=17±5 years) underwent a cardiac MRI examination after receiving informed consent.

MRI Protocol: Subjects were imaged at either 1.5T or 3T (Siemens Avanto/Skyra) using: 2D CINE images (1.4x1.4x6mm, TE/TRes=1.2/45.1 ms) and basal, mid, and apical LV short-axis tagged images (1.4x 1.4x8mm, TE/TRes=2.12/24-48 ms, 11-31 phases, tag spacing=8mm). Five DMD patients received a follow-up examination 12±5 months after the initial scan.

Data Processing and Statistical Analysis: LV Ejection Fraction (EF) was quantified from CINE images (Qmass, Medis; Argus, Siemens; and Circle CVI[42], Circle Cardiovascular Imaging). Peak mid-wall Ecc and peak LV twist were estimated from tagged MR images (Diagnosoft, Myocardial Solutions). Normally distributed data were compared with a two-tailed t-test. Non-parametric data were compared with a Kruskal-Wallice test. A Holm-Sidak post hoc correction accounted for multiple comparisons. Effect size (Cohen's d) was computed to determine the non-overlap of statistically significant results.

Results

Table 1 and Figure 1 summarize LV ejection fraction, peak mid-wall E_{cc}, and LV twist in boys with DMD and healthy volunteers. There was no significant difference in EF between groups (62.5±8.3% vs. 63.2±3.3%, p=N.S.). A significant reduction in LV twist (9.3°±4.3° vs. 14.8°±3.6°, p< 0.004) was observed in boys with DMD compared to volunteers. Peak mid-wall E_{cc} (-15.8±5.8% vs. -18.5±3.2%, p<0.02) was significantly lower in magnitude. The effect sizes for E_{cc} and LV twist were 0.29 and 0.56, which corresponds to a 21% and a 33% non-overlap of patient and volunteer data respectively. Figures 2 and 3 plot global LV peak mid-wall Ecc and LV twist as a function of EF. Patient and volunteer data were stratified into four categories: "normal EF, normal Twist/Ecc", "low EF, normal Twist/E_{cc}", "normal EF, low Twist/E_{cc}", and "low EF, low Twist/E_{cc}" using the smallest peak twist or E_{cc} values observed in our healthy volunteer cohort, and a clinical standard for cardiac dysfunction of EF<55%[4] as a cutoff. Minimum values for twist and E_{cc} observed in volunteers agree with prior reports[2,3]. For E_{cc} and LV twist respectively, 52% and 48% of DMD patients presented with "normal EF, low Twist/Ecc" compared to all healthy volunteers. 32% and 36% of patients were "normal EF, normal Twist/E_{cc}" respectively. 12% of patients had "low EF, low Twist/E_{cc}". 4% of patients were "low EF, normal E_{cc}" and "low EF, normal Twist" respectively. All volunteers had "normal EF and normal Twist/E_{cc}". Table 2 summarizes data for patients (N=5) who received a follow-up scan. LV EF, twist, and Ecc were all reduced compared to the first examination, but a larger cohort is needed to test for statistical significance.

Discussion & Conclusion

This data suggests that patients with DMD exhibit decreases in LV twist and peak mid-wall E_{cc} that likely precede decreases in EF as only a single patient with DMD was found to have "low EF, normal Twist/E_{cc}." Hence, LV twist and peak mid-wall E_{cc} measured by MR tagging may be earlier and more sensitive indicators of cardiac dysfunction in boys with DMD. Patients with reduced EF also displayed reductions in LV twist and E_{cc}, but importantly, ~50% of patients with normal EF had low twist and peak mid-wall E_{cc}. Further, early results with a limited sample size suggest that patients that have reduced EF on a follow-up exam also exhibit reductions in twist and E_{cc}. LV twist has a larger effect size than E_{cc} and consequently may be a more sensitive measure of early dysfunction. These results corroborate the strain reports of Hor et al. and twist results of Rehyan et al. While volunteers and DMD patients were not precisely age matched, peak mid-wall E_{cc} is known to decrease with age, and twist remains relatively constant until middle age[5]. Further investigation in a larger, longitudinal cohort is warranted.

Acknowledgements

This work was supported by NIH NHLBI R01 HL131975.

References

1. Hagenbuch, Sean C., et al. "Detection of progressive cardiac dysfunction by serial evaluation of circumferential strain in patients with Duchenne muscular dystrophy." The American journal of cardiology 105.10 (2010): 1451-1455.

2. Hor, Kan N., et al. "Regional circumferential strain is a biomarker for disease severity in duchenne muscular dystrophy heart disease: a cross-sectional study." Pediatric cardiology 36.1 (2015): 111-119.

3. Reyhan, Meral L., et al. "Effect of free-breathing on left ventricular rotational mechanics in healthy subjects and patients with duchenne muscular dystrophy." Magnetic resonance in medicine 77.2 (2017): 864-869.

4. Sweitzer, Nancy K., et al. "Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (≥ 55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (< 40%) fractions." The American journal of cardiology 101.8 (2008): 1151-1156.

5. Reyhan, Meral, et al. "Left ventricular twist, but not circumferential-longitudinal shear angle, increases with increasing age in normal subjects." Journal of Cardiovascular Magnetic Resonance 15.1 (2013): P7.

Figures

Table 1. Rotational Mechanics	DMD Patients	Normal Volunteers
Global Ecc (%)	-15.8 ± 5.8*	-18.5 ± 3.2*
Twist (degrees)	9.3 ± 4.3*	14.8 ± 3.6*
LV Ejection Fraction (%)	62.5 ± 8.3	63.2 ± 3.3

Table 1: Rotational Mechanics and circumferential strain in N=25 boys with DMD and N=8 Normal Volunteers shown as median ± standard deviation. * denotes a statistically significant difference at a confidence level of p<.05 with post hoc correction for multiple comparisons.

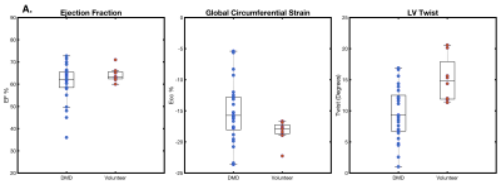

Figure 1: (A) Ejection Fraction, **(B)** Peak mid-wall E_{cc}, and **(C)** LV Twist for boys with DMD and Healthy Volunteers. There is no significant difference between patients and volunteers for EF. There is a significant difference in peak mid-wall E_{cc} and LV twist. Peak mid-wall E_{cc} and LV twist may be effective indicators of early cardiac dysfunction in DMD prior to changes in EF.

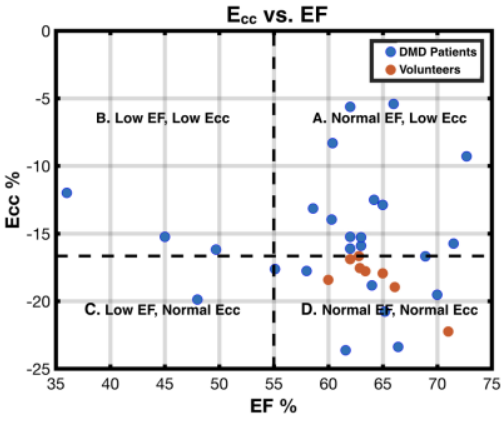

Figure 2: Peak mid-wall (E_{cc}) plotted as a function of EF for healthy volunteers (orange) and boys with Duchenne's muscular dystrophy (blue). **A.** The "Normal EF, Low E_{cc}" quadrant contains boys with DMD who have early signs of cardiac dysfunction and accounts for 52% of the patient cohort. **B.** "Low EF, Low E_{cc}" identifies 12% of boys with DMD. **C.** "Low EF, Normal E_{cc}" identifies 4% of boys with DMD. **D.** "Normal EF, Normal E_{cc}" contains all the healthy volunteers and 32% of boys with DMD and limited cardiac involvement.

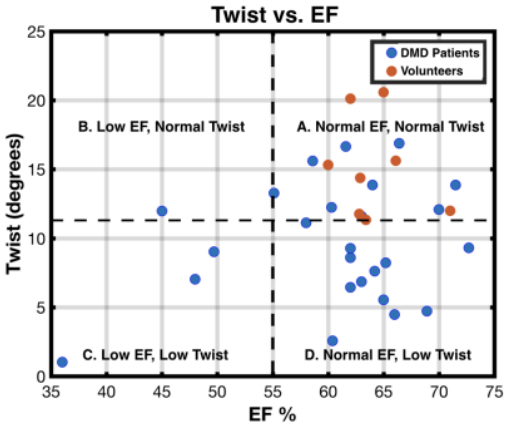

Figure 3: Peak Twist plotted as a function of EF for healthy volunteers (orange) and boys with Duchenne's muscular dystrophy (blue). **A.** The "Normal EF, Normal Twist" quadrant contains all the healthy volunteers and 36% of boys with DMD and limited cardiac involvement. **B.** "Low EF, Normal Ecc" identifies 4% of boys with DMD. **C.** "Low EF, Low Twist" identifies 12% of boys with DMD. **D.** The "Normal EF, Low Twist" quadrant contains boys with DMD who have early signs of cardiac dysfunction and accounts for 48% of the patient cohort.

Table 2. Follow Up Examination	First Exam	Second Exam
Global Ecc (%)	-17.7 ± 4.2	-15.7 ± 4.3
Twist (degrees)	11.7 ± 7.0	11.1 ± 5.2
LV Ejection Fraction (%)	67 ± 5.0	56 ± 8.0

Table 2: Follow up exams for boys with DMD (N=5), 12±5 months after the initial examination. The data suggests that patients exhibit a reduction in peak mid-wall E_{cc}, twist, and EF between the two examinations.