Whole-heart T2-mapping at 7T quantifies dystrophic myocardial pathology in mdx/utrn+/- mice

Ronald John Beyers[1], Christopher Ballmann[2], Joshua Selsby[3], Nouha Salibi[1,4], John Quindry[2], and Thomas S Denney[1]

[1]MRI Research Center, Auburn University, Auburn University, AL, United States, [2]Kinesiology, Auburn University, Auburn University, AL, United States, [3]Department of Animal Science, Iowa State University, Ames, IA, United States, [4]MR R&D, Siemens Healthcare, Malvern, PA, United States

Purpose: Duchenne muscular dystrophy (DMD) causes age-related cardiac dysfunction with up to 40% of DMD deaths attributable to cardiac pathologies. Novel interventions are needed to quantify and counter these cardiac complications[1]. Recent findings indicate that increased PGC-1α activity increases utrophin expression (utrn), among other benefits, and attenuates disease pathology in dystrophic skeletal muscle[2]. While previous studies have relied solely on histology there has been little application of cardiac MR (CMR) to quantify DMD cardiac pathology that includes myocardial inflammation and edema. We tested two hypotheses in a mouse model of DMD: 1) apply T2-mapping CMR to quantify whole-heart myocardial T2 changes, 2) apply dietary quercetin, a SIRT-1/PGC-1α activator, to protect the myocardium and alleviate inflammatory complications.

Methods: DMD mice with haploinsufficiency of the utrophin gene (mdx/utrn$^{+/-}$) were assigned to two groups (n=8/group) and fed standard chow (MDXU), or a 0.2% quercetin enriched diet to age 10 months (MDXUQ). Age-matched C57 normal mice were fed a control diet (Control, n=8). All mice received CMR at age 10 months to quantify whole-heart myocardial T2-maps. Our T2-mapping sequence was developed from a T2prep-T2w contrast sequence previously described[3]. Our T2prep mapping sequence acquired cardio-synchronized, multislice T2w images at TE=10, 20, 40 and 60 ms for subsequent per-pixel, 4-point, monoexponential curve-fit and resulting T2 map images. Six contiguous short-axis slices were acquired per heart by 2 interleaved sets of 3 slices, all triggered by ECG R-wave. CMR parameters include: 7T human scanner (Siemens) with custom mouse quadrature birdcage coil, FOV=32x20 mm, slice thick=1.0 mm, TR=2000 ms, BW=488 Hz/pix, flip angle=65 deg, matrix= 128x80 (interpolated to 256x160), averages=1. T2 curve-fit maps were calculated with a custom Matlab program (Mathworks, Natick, MA). T2 map statistics included each slice's mean T2 level within the hand-segmented left ventricular (LV) myocardial region (see Fig 1). Per group totals are the mean and standard error measured (SEM) from all the slices per group. Two-tailed t-tests were run between each group where $p<0.05$ was condidered statistically significant.

Results: Myocardial T2 maps were consistent with minimal artifacts. Fig 1 shows representative T2 maps from each group with LV segmentation lines (white) and red arrows indicating example regions of elevated T2 found in only the MDXU group. All three mice groups had low variation in T2 data which resulted in low SEM (error bars) and strong t-test significance. Fig 2 presents each group's entire LV myocardial T2 in milliseconds (mean±SEM) as: 30.02±2.03 for MDXU, 23.00±0.23 for MDXUQ, and 22.72 ± 0.34 for Control. The MDXU T2 was significantly higher than both MDXUQ and Control groups with $p<0.000001$ for each. The MDXUQ and Control groups had no significant T2 difference (p=0.173), therefore the MDXUQ T2 was unaffected by DMD.

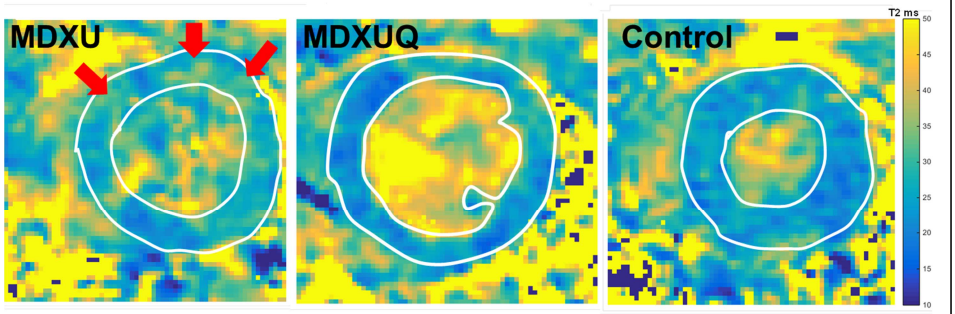

Fig 1-Representative T2-maps with LV segmentation lines (white) and arrows (red) indicating elevated T2 regions in MDXU mice. T2 milliseconds color scale is on the right.

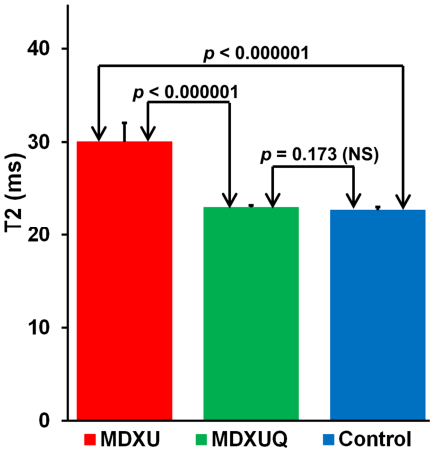

Fig 2-Whole-heart T2 results (mean±SEM). MDXU group T2 is significantly higher than both MDXUQ and Control groups.

Discussion: T2-mapping CMR was applied and accurately quantified a significantly elevated T2 in untreated mdx/utrn$^{+/-}$ (MDXU) mice hearts compared to both quercetin treated (MDXUQ) and control hearts. Our control T2=22.72 ± 0.34 result agrees with the 22.5±1.7 reported by Coolen, *et al*[4]. The elevated T2 in MDXU was spread throughout the LV and was not confined or localized. Importantly, quercetin treatment prevented T2 change at 10 months age in mdx/utrn$^{+/-}$ mice. Additional Cine Functional CMR results also showed degraded MDXU LV function, but preserved LV function in quercetin treated hearts (data not shown).

Conclutions: Whole-heart T2-mapping CMR applied in mice at 7T can non-invasively quantify T2 changes. Quercetin demonstrates cardio-protection in mdx/utrn$^{+/-}$ mice at age 10 months. Continued research is warrented to further develop and apply CMR T2-mapping in humans. Additional research is needed to ellucidate the specific mechanisms with quercetin in DMD-related and other pathologies.

References:

1. Miles SL, "Molecular and physiological…disease", Nutr Rev 72(11):720-34
2. Ballmann C, "Histological and biochemical…enrichment", Exper Physio, doi:10.1113/expphysiol.2014.083360
3. Beyers RJ, "T2-weighted MRI of post-infarct…in mice", MRM 67(1):201-9
4. Coolen BF, "Quantitative T2 mapping…T2 preparation", MRM 72(2):409-17