Reducing the Minimum Detectable Change in Vastus Lateralis Fat Fraction Using MRI in Clinical Trials for Duchenne Muscular Dystrophy Therapy

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1 INTRODUCTION

- Muscle MR imaging provides important efficacy-response biomarkers for DMD trials[1]
- MRI proton density fat fraction (PDFF) is a sensitive and objective endpoint[2] for quantifying fat replacement in the vastus lateralis (VL) in DMD
- The largest source of variability in MRI-PDFF measurements is the initial analyst segmentation, likely due to variations in the cross-sectional boundaries[3]
- This presentation investigates ways to minimize variability in MRI-PDFF measurements using different regions of interest (ROIs)

2 AIMS

- Identify the variability introduced by segmentation errors at the VL cross-sectional boundary
- Determine the relative contribution of different regions of interest in the VL segmentation to overall variability

3 METHODS

- MRI scans of the lower limb (N=13) optimized for PDFF quantitation[4,5] were randomly extracted from an anonymous clinical trial data repository
- VL was segmented from T1-weighted images by 2 independent analysts in 3 axial slices at the user-defined widest cross-section of the VL and the full muscle volume
- Analyst segmentations were corrected or confirmed by a single, blinded radiologist
- Radiologist-reviewed segmentations were contracted by 2 mm to define additional ROIs

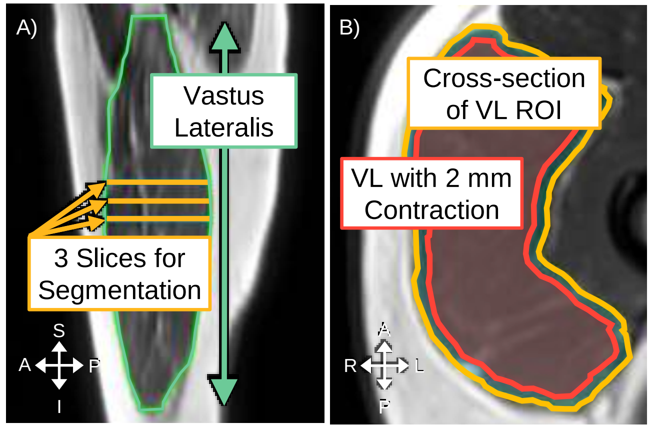

Fig. 1: Computation of Fat Fraction. A) T1-weighted MRI of thigh showing full volume and center 3 slices ROIs B) Cross section of VL ROI in T1-weighted images with and without a 2 mm contraction

- ROIs from T1-weighted images were co-registered to the PDFF map to calculate the average fat fraction within the ROI
- Fat fraction variability was assessed using single rating, absolute agreement, 2-way mixed-effects intraclass correlation coefficient (ICC), Bland-Altman plots, and minimum detectable change (MDC) estimates for the following ROIs:
  - Full muscle volume (Full Vol)
  - User-defined center three slices (User 3 Slices)
  - Automatically-selected center three slices from the full muscle volume (Auto 3 Slices)
  - All of the above, with a 2 mm contraction
- Muscle volume variability was assessed using a Bland-Altman plot
- Dice similarity coefficients were calculated between the contracted and non-contracted ROIs

4 RESULTS

- The contracted Auto 3 Slices ROI resulted in the least variability overall

Table. 1: Summary of fat fraction variability

	N	ICC (95% CI)	SEM (%)	MDC (%)
Full Vol	13	0.591 (0.105 - 0.853)	2.387	6.62
User 3 Slices	13	0.973 (0.918 - 0.992)	0.845	2.34
Auto 3 Slices	13	0.793 (0.466 - 0.931)	1.485	4.12
Contracted Auto 3 Slices	13	0.991 (0.972 - 0.997)	0.351	0.97

N = sample size, CI = confidence interval, SEM = standard error of measurement, MDC = minimum detectable change

- Contracting ROIs to limit non-muscle contributions at the segmentation boundary decreased the variability (Full Vol MDC = 2.35%; User 3 Slices MDC = 1.07%; Auto 3 Slices MDC = 0.97%)

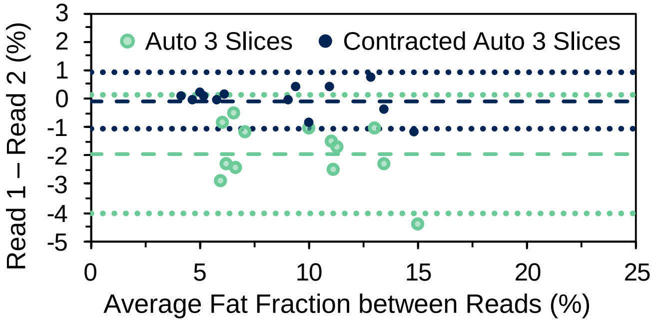

Fig. 2: Bland-Altman plot of automated center slice variability (green) and contracted automated center slice variability (blue) showing mean difference (dashed) and 95% limits of agreement (dotted)

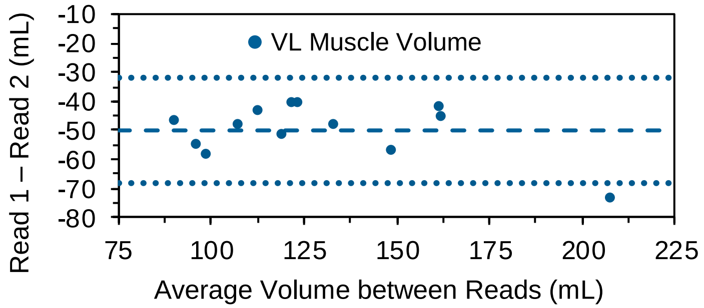

Fig. 3: Bland-Altman plot of VL volume showing mean difference (dashed) and 95% limits of agreement (dotted)

- Automatic selection of the muscle center increased variability due to differences in determining the muscle belly termini
- Contracting the ROIs maintains representation of the VL muscle cross section (Dice ≈ 0.83)

5 CONCLUSIONS

- A 2 mm contraction of the ROIs reduced a bias toward higher fat fraction by excluding non-muscle tissue, and the contracted automatically-selected slices of the VL resulted in the least variability overall for MRI-PDFF

6 REFERENCES

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