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Sources of Variability in Vastus Lateralis Fat Fraction Measurements Using MRI in Clinical Trials for Duchenne's Muscular Dystrophy (DMD) 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 key endpoint[2] for quantifying fat replacement in the vastus lateralis (VL) in DMD
- Central review of images in multi-center trials is recommended to reduce observer variability
- Initial technologist measurement is overread/adjusted by a central physician reviewer in many trials
- This presentation reviews sources and degrees of variability in MRI-PDFF measurements from each stage in the central review process

2 AIMS

- Identify source and degree of variability associated with MRI-PDFF central review of VL fat fraction measurement
- Determine relative contribution of the selection of axial slices to be measured versus the muscle segmentation to the overall variability

3 METHODS

- MRI scans of the lower limb (N=13) optimized for PDFF quantitation[3,4] were randomly extracted from an anonymous clinical trial data repository.
- VL was segmented from T1-weighted images in 3 axial slices, centered at the midpoint of the VL by 2 independent technologists
- Segmentation contours were corrected or confirmed by 2 independent physicians
- Segmentation from T1-weighted images applied to the PDFF map to calculate the average fat fraction in the VL from those 3 slices

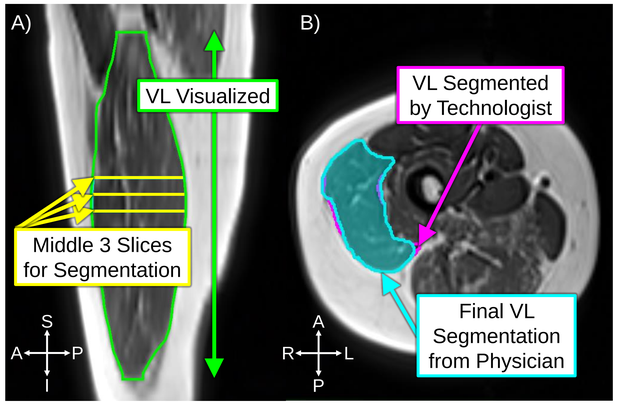

Fig. 1: Computation of Fat Fraction. A) T1-weighted MRI of lower limb B) VL segmented by physician overread in T1-weighted images C) Fat fraction measured from PDFF map

- Read variability was assessed using an intraclass correlation coefficient (ICC) based on a single rating, absolute agreement, 2-way random-effects model (ICC [2,1]), Bland-Altman plots, and minimum detectable change (MDC) estimates for the following:
  - Inter-technologist variability
  - Inter-technologist variability in a subset (Overlap Subset; N=8) where fat fraction was calculated using only the overlapping slices between technologists
  - Inter-physician variability with the same technologist
  - Intra-physician variability with different technologists

4 RESULTS

- Overall reproducibility of VL fat fraction measurement was excellent

Table. 1: *Summary of statistical measurements of variability*

	N	ICC (2,1) (95% CI)	SEM (%)	MDC (%)
Inter-technologist	13	0.972 (0.914 - 0.991)	0.853	2.37
Inter-technologist (overlap subset)	8	0.973 (0.883 - 0.994)	0.903	2.50
Inter-physician (1 technologist)	13	0.996 (0.983 - 0.999)	0.321	0.89
Intra-physician (2 technologists)	13	0.972 (0.917 - 0.992)	0.844	2.34

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

- The use of a single technologist results in a minimum detectable difference for fat fraction of <1%

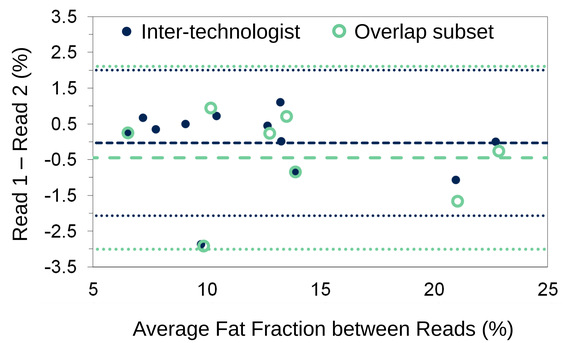

Fig. 2: Bland-Altman plot of inter-technologist variability (blue) and overlap sub-set of inter-technologist variability (green) showing mean difference (dashed) and 95% limits of agreement (dotted)

- Restricting the analysis to only overlapping slices between the technologists did not improve variability

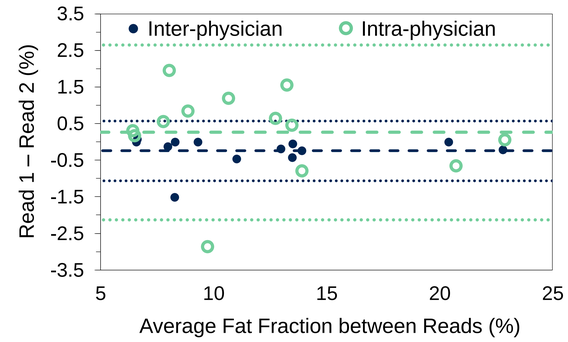

Fig. 3: Bland-Altman plot of inter-physician variability with the same technologist (blue) and intra-physician variability with different technologists (green) showing mean difference (dashed) and 95% limits of agreement (dotted)

- The physician overread of the segmentation does not correct for the inter-technologist variability

5 CONCLUSIONS

- The greatest source of variability in VL fat fraction measurement is the initial technologist contour, which is dominated by the effect of differences in segmentation rather than in slice selection

6 REFERENCES

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