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# Comparison of Rectus Femoris Cross-sectional Area and Rectus Femoris-Vastus Intermedius Muscle Layer Thickness as Markers of Muscle Wasting and Weakness During Early Critical Illness

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**Key Words**: Intensive Care; Critical Illness; Ultrasound; Muscle Wasting; Outcome Assessment

Muscle wasting during critical illness has been suggested to contribute to survivor functional disability(1). Two B-mode ultrasound measures measurements have been reported that quantify wasting(2, 3): (i) combined thickness of the Rectus Femoris (RF) and Vastus Intermedius muscles ('Muscle Layer Thickness', henceforth referred to as 'Thickness') (4, 5) and (ii) RF cross-sectional area ($RF_{CSA}$) which correlates with lower limb strength in other clinical circumstances (6). The degree to which either of these ultrasound measures reflect muscle weakness in the critically ill is unclear (7).

We hypothesised that like change in $RF_{CSA}$ ($\Delta RF_{CSA}$), change in Thickness (ΔThickness) would underestimate loss of muscle size as measured by the histological gold standard (myofibre thickness) and the biochemical gold standard of protein: DNA ratio measured in skeletal muscle biopsies. Secondly we hypothesised that $\Delta RF_{CSA}$ and ΔThickness would both be related to muscle weakness.

Subjects were patients of the Musculoskeletal Ultrasound in Critical Illness: Longitudinal Evaluation study (NCT01106300) (8), the original study having been approved by University College London Ethics Committee A. All patients were recruited within 24 hours of admission to a university hospital and a community hospital (August 2009-April 2011), and were expected to survive intensive care unit (ICU) admission after being invasively ventilated for > 48 hours and in the ICU >7 days. Excluded were those with pregnancy, lower limb amputation, primary neuromuscular pathology or disseminated cancer. Next-of-kin assent and retrospective patient consent were obtained.

Images were acquired on ICU days 1, 7 and 10. ICU $RF_{CSA}$ assessment and reliability have been previously described (8). Thickness was measured at the midpoint of Rectus Femoris between the two fascial lines. Images were excluded where the femur was not visible.

ΔThickness and $\Delta RF_{CSA}$ were compared with change In myofibre cross-sectional area ($\Delta fibre_{CSA}$) and protein:DNA in sequential Vastus Lateralis muscle biopsies acquired on days 1 and 7 as described previously (8).

Manual Muscle Testing was performed (9) on day 10 if patients could follow $\geq$3 of De Jonghe's 5-command criteria and the knee extension component score of $\leq$4/5 used to define lower limb weakness (10).

Bland-Altman comparisons were used to establish i) inter-rater reliability of Thickness measurements and ii) longitudinal bias between ΔThickness and $\Delta RF_{CSA}$ over the study period. Normality was assessed using D'Agostino and Pearson omnibus normality tests, and data were analysed using two-tailed Student's t-test or Mann Whitney U test as appropriate. Differential longitudinal change in muscle size (ΔThickness vs. $\Delta RF_{CSA}$) was compared using 2-way repeated measures of variance (ANOVA). A bivariable logistical regression was performed with knee extensor weakness as the dependent variable and ultrasound measurements as the independent variable.

Of the initial cohort of 62 patients with serial muscle ultrasounds, 8 had incomplete or missing electronic scan records. Of the remaining 54, 11 had $\geq$1 scan where the femur was not visualized. Two assessors analysed images at 21 time-points to establish inter-rater reliability. Thickness measurements were highly correlated between observers (AM and ZP: Pearson r=0.98) with an intra-class co-efficient of 0.986 (95%CI 0.965-0.994). A Bland Altman plot demonstrated minimal bias of -0.07±0.2 cm (95%CI -0.46-0.32 cm).

Nineteen patients had Thickness, $RF_{CSA}$, $fibre_{CSA}$ and protein/DNA ratio measured on Day 1 and Day 7. ΔThickness significantly underestimated $\Delta fibre_{CSA}$ (-4.6% (95%CI -14.19-4.95) vs. -16.4% (95%CI -32.0—0.74); p=0.025) and change in protein/DNA ratio ((-4.6% (95%CI -14.19-4.95) vs. -30.9% (95%CI -51.2—10.6); p=0.019). We have previously shown $\Delta RF_{CSA}$ to underestimate change in protein/DNA ratio (10.3% (95%CI 6.1-14.5) vs. 29.5% (95%CI 13.4-45.6%;p=0.03) but not $\Delta fibre_{CSA}$ (10.3% (95%CI 6.1-14.5) vs. 17.5% (95%CI 5.8-29.3);p=0.31) (8).

ΔThickness and $\Delta RF_{CSA}$ correlated ($r^2$=0.22, p=0.049) but a Bland Altman comparison between ΔThickness and $\Delta RF_{CSA}$ over 10 days revealed a bias of -8.3% ± 19.7% (95% CI-46.7-30.7) for Thickness resulting in significant underestimation of muscle wasting at days 7 and 10 (Figure 1A and table 1).

Of the 63 patients, 40 were able to obey commands and underwent volitional strength testing on Day 10, amongst whom Thickness was available in 27.

$\Delta RF_{CSA}$ was greater in those with knee extensor weakness than those without (20.7% (95CI% 13.7-27.7) vs. 8.4% (95%CI 2.5-14.3) respectively p=0.012). ΔThickness did not differ between these groups (12.6% (95%CI 0.94-24.2) vs. 12.1 (95%CI2.7-21.5)

respectively, p=0.95) (Figure 1B). In a bivariable logistical regression, $\Delta RF_{CSA}$ was associated with knee extensor weakness (OR 1.101 (95%CI 1.011-1.199); p=0.027), but ΔThickness was not (OR 1.001 (95%CI 0.960-1.044); p=0.947).

All other things being equal, muscle strength and size are proportional - the latter acting as a proxy for the former in ICU, where non-volitional objective measures of strength are logistically challenging. Our results suggest that $\Delta RF_{CSA}$ reflects knee extensor weakness and muscle loss better than ΔThickness. ΔThickness also underestimated $\Delta RF_{CSA}$ (a -8% bias on Bland Altman plot being relevant, given that a 10% change in $RF_{CSA}$ is considered sufficient to affect function(11))- in part, perhaps, because it is a unidimensional measure when compared to (2D) muscle area or (3D) volume. The specific relationship of tissue edema to ultrasound measures remains unclear (3, 8), though edema may also affect $Fibre_{CSA}$ (12).

Although these data are derived from the largest cohort available for longitudinal radiopathological correlation, our study is limited by its size. The cohort size was further limited by a third of patients not being able to perform volitional strength testing, albeit this being in keeping with published rates (13). Finally, measurement of Thickness was not an original primary goal of image analysis, a fact which might account for the lack of femoral image availability in one third. Although considered unlikely to have impacted on the observations made, non-random bias cannot be excluded.

We have previously shown $RF_{CSA}$ studies to indicate muscle quality (3) and not to underestimate muscle $fibre_{CSA}$. We now show that Thickness measurements significantly underestimate ICU muscle wasting compared to $RF_{CSA.}$ In addition $RF_{CSA}$ is a more reliable proxy for muscle strength in a setting where volitional and non-volitional muscle strength measurements are challenging. We suggest measurement of $\Delta RF_{CSA}$ as a biomarker for proximal lower limb muscle loss and knee extensor weakness during early critical illness.

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**Figures and Tables**

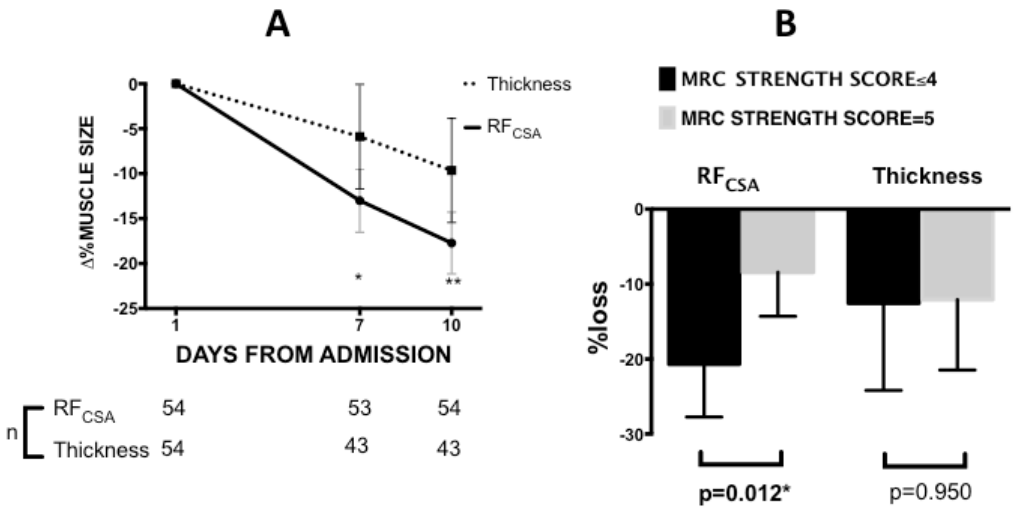


**Figure 1AB: (A) Change in Rectus Femoris Cross Section Area ($RF_{CSA}$) and Muscle Layer Thickness (Thickness) over 10 days of critical illness. * Represents p<0.05 and ** p<0.01 using Two-way repeated measures Analysis of Variance (ANOVA). (B) Knee Extensor Medical Research Council (MRC) Strength Score and loss of muscle size as measured by Rectus Femoris Cross Sectional Area ($RF_{CSA}$) and Muscle Layer Thickness (Thickness) (n=27). *Represents p<0.05 using 2-tailed unpaired Student's T-test.**

| | **ΔTHICKNESS** | **Δ$RF_{CSA}$** | |
|---|---|---|---|
| **Day 7** | -5.88% (-11.69—0.06%) | -13.0%(-16.52—9.48%) | **0.031*** |
| **Day 10** | -9.36% (-15.43—3.84%) | -17.72 (-21.15—14.29) | **0.004*** |

**Table 1: Comparison of change in Muscle Limb Thickness (ΔTHICKNESS) and Rectus Femoris Cross Sectional Area (Δ$RF_{CSA}$) at days 7 and 10 of critical illness. *Represents p<0.05 using 2-way repeated measures Analysis of Variance (ANOVA).**