Ultrasound for the Assessment of Peripheral Skeletal Muscle Architecture in Critical Illness: A Systematic Review

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SUPPLEMENTAL DIGITAL CONTENT

1. Electronic database search strategies

Search strategies for electronic databases used in this systematic review are presented below (Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, Excerpta Medica Database (EMBASE), Web of Science and Cochrane). Searching Scopus resulted in no results (search strategy not reported), and searches were not storable in the Physiotherapy Evidence Database (PEDro) however the search involved terms used in the summaries below.

CINAHL search strategy (EbscoHost)
S15 S7 and S10 and S14
S14 S11 OR S12 OR S13
S13 muscle*
S12 (MH "Muscle, Skeletal")
S11 muscle wasting OR muscle mass OR cross-sectional area OR fibre pennation angle OR pennation angle OR muscle thickness OR muscle layer thickness OR echo intensity OR echogenicity OR muscle architecture
S10 S8 OR S9
S9 ultrasound OR ultrasonography
S8 (MH "Ultrasonography")
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6 intensive care OR critical care OR critical illness OR ICU OR critically ill OR multi-organ failure OR sepsis
S5 (MH "Sepsis")
S4 (MH "Multiple Organ Dysfunction Syndrome")
S3 (MH "Intensive Care Units")
S2 (MH "Critical Illness") OR (MH "Critically Ill Patients")
S1 (MH "Intensive Care Units") OR (MH "Critical Care")

**MEDLINE search strategy (OvidSp)**
1. intensive care/
2. critical illness/
3. intensive care/ or intensive care unit/
4. sepsis/ or multiple organ failure/ or septic shock/
5. sepsis/
6. (intensive care or critical care or critical illness or ICU or critically ill or multi-organ failure or sepsis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. 1 or 2 or 3 or 4 or 5 or 6
8. (ultrasonography or ultrasound).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. muscle mass/ or muscle weakness/ or skeletal muscle/ or muscle/ or muscle atrophy/
10. muscle mass/
11. muscle/ or ultrasound/ or muscle atrophy/
12. muscle thickness/ or thickness/ or muscle/
13. skeletal muscle/ or muscle atrophy/
14. (muscle* or muscle wasting or muscle mass or cross-sectional area or fibre pennation angle or pennation angle or muscle thickness or muscle layer thickness or echo intensity or echogenicity or muscle architecture).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15. 9 or 10 or 11 or 12 or 13 or 14
16. ultrasound/
17. 8 or 16
18. 7 and 15 and 17

**EMBASE search strategy (OvidSp)**
1. intensive care/
2. critical illness/
3. intensive care unit/
4. critically ill patient/
5. multiple organ failure/
6. sepsis/
7. (intensive care or critical care or critical illness or ICU or critically ill or multi-organ failure or sepsis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. ultrasound/
10. (ultrasound or ultrasonography).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11. 9 or 10
12. muscle/
13. muscle atrophy/
14. muscle mass/
15. muscle thickness/
16. (muscle* or muscle wasting or muscle mass or cross-sectional area or fibre pennation angle or pennation angle or muscle thickness or muscle layer thickness or echo intensity or echogenicity or muscle architecture).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17. 12 or 13 or 14 or 15 or 16
18. 8 and 11 and 17

**Web of Science search strategy (Web of Knowledge)**

#4 #3 AND #2 AND #1
#3 Topic=(muscle* OR muscle wasting OR muscle mass OR cross-sectional area OR fibre pennation angle OR pennation angle OR muscle thickness OR muscle layer thickness OR echo intensity OR echogenicity OR muscle architecture)
#2 Topic=(ultrasound OR ultrasonography)
#1 Topic=(intensive care OR critical care OR critical illness OR ICU OR critically ill OR multi-organ failure OR sepsis)

**Cochrane search strategy (Cochrane)**

#1 intensive care or critical care or critical illness or ICU or critically ill or multi-organ failure or sepsis:ti, ab, kw
#2 ultrasound or ultrasonography:ti, ab, kw
#3 muscle* or muscle wasting or muscle mass or cross-sectional are or fibre pennation angle or pennation angle or muscle thickness or muscle layer thickness or echo intensity or echogenicity or muscle architecture:ti, ab, kw
#4 MeSH descriptor: (Intensive Care) explode all trees
#5 MeSH descriptor: (Critical Care) explode all trees
#6 MeSH descriptor: (Critical Illness) explode all trees
#7 MeSH descriptor: (Critical Illness) explode all trees
#8 MeSH descriptor: (Sepsis) explode all trees
#9 MeSH descriptor: (Ultrasonography) explode all trees
#10 MeSH descriptor: (Muscles) explode all trees
#11 #4 and #5 and #6 and #7 and #8
#12 #1 or #11
#13 #3 or #10
#14 #2 and #9
#15 #14 and #13 and #12
2. **Detail of peripheral skeletal muscle architecture measured using ultrasound in included studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Technical detail</th>
<th>Muscle architecture parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al (35)*</td>
<td>ALOKA SSD 500 portable US machine, equipped with 3.5MHz linear array transducer. Measurements made using built-in electronic calipers on frozen, real-time cross-sectional images. Mean of three measurements at each site used for statistical analysis.</td>
<td>Muscle thickness</td>
</tr>
<tr>
<td></td>
<td>Biceps (biceps brachia and coracobrachialis), forearm, thigh (quadriceps muscle group)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Midupper arm anteriorly</strong></td>
<td>Patient supine, elbow flexed to 90°, point marked on the skin midway between the tip of acromion and tip of the olecranon. With the subject supine, elbow extended, and forearm supinated, thickness of the flexor compartment was measured over the biceps between the superficial fat-muscle interface and the humerus.</td>
</tr>
<tr>
<td></td>
<td><strong>Forearm</strong></td>
<td>Patient supine, with the elbow extended and the forearm supinated, point marked midway between the antecubital skin crease and the ulnar styloid. Thickness of the flexor compartment was measured anteriorly between the superficial fat-muscle interface and the interosseus membrane.</td>
</tr>
<tr>
<td></td>
<td><strong>Thigh</strong></td>
<td>Patient supine, with the knee extended, midway point between the tip of the greater trochanter and the lateral joint line of knee was identified. Thickness of the quadriceps muscle group between the superficial fat-muscle interface and the femur was measured.</td>
</tr>
<tr>
<td>Author</td>
<td>Device Description</td>
<td>Measurement Details</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gruther et al (38)</td>
<td>HDI-100 ATL portable US machine, using an L7-4 transducer with a 5cm linear array footprint</td>
<td>Mean MLT calculated as the mean of both measurements (measuring points i) and ii) on each leg. Vastus intermedius and rectus femoris assessed bilaterally at i) the border between the lower and upper two-thirds, and ii) the mid-point between the anterior superior iliac spine and the upper pole of patella, with the patient in supine and legs relaxed lying flat in extension.</td>
</tr>
<tr>
<td>Reid et al (40)</td>
<td>ALOKA Echo Camera SSD-210DXII portable ultrasound machine with a 5MHz linear array transducer</td>
<td>Measurements made using built-in electronic calipers on frozen, real-time cross-sectional images. Mean of three measurements used for statistical analysis. Mean values from three sites combined to indicate total lean body mass.</td>
</tr>
</tbody>
</table>

**Muscle mass (muscle layer thickness)**

**Mid-upper arm (biceps and brachialis), forearm, thigh**

**Midupper arm**
Patient positioned in supine. Measured over the biceps down to the humerus, at a point midway between the tip of the acromion and the tip of the olecranon, with the elbow extended and forearm supinated.

**Forearm**
Patient positioned in supine. Measured down to the interosseus membrane at a point midway between the antecubital skin crease and the ulnar styloid, with the elbow extended and forearm supinated.

**Thigh**
Patient positioned in supine. Measured down to the femur, on the anterior surface of the thigh, midway between the tip of the greater trochanter and the lateral joint line of the knee identified.
<table>
<thead>
<tr>
<th>Study</th>
<th>Equipment Details</th>
<th>Muscle Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldwin et al (34)*</td>
<td>DP-6600 Shenzhen Mindray Biomedical Electronics portable US machine with a 10MHz 38mm linear transducer array</td>
<td>Muscle thickness&lt;br&gt;Mid-upper arm, mid-forearm, mid-thigh&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;Three measurements taken per muscle group&lt;br&gt;Transducer placed at the most anterior facing aspect of each segment, in the transverse plane from the mid-segment point&lt;br&gt;Technique in keeping with that previously reported by Baldwin et al (45)&lt;br&gt;Image analysis software not specified</td>
</tr>
<tr>
<td>Cartwright et al (36)*</td>
<td>Esaote Biosound MyLab 25 portable ultrasound machine with an 18-MHz linear-array transducer</td>
<td>Muscle thickness, subcutaneous tissue thickness, mean (standard deviation) of grey-scale values&lt;br&gt;Tibialis anterior, rectus femoris, abductor digiti minimi, biceps brachii and brachialis complex&lt;br&gt;Measurements taken at 5cm distal to fibular head (tibialis anterior), 15cm proximal to the superior portion of the patella (rectus femoris), middle of the fifth metacarpal (abductor digiti minimi), 10cm proximal to the antecubital fossa (biceps brachii and brachialis complex)</td>
</tr>
</tbody>
</table>
where large volume of subcutaneous edema require alternative settings to view muscle.

For grey-scale data, 2cmx2cm region of interest was placed over the representative muscle (1cmx1cm for abductor digiti minimi).

Image J (NIH, US) off-line software used for analysis.

<table>
<thead>
<tr>
<th><strong>Grimm et al. (37)</strong></th>
<th>Siemens Acuson portable US machine with a 9-13MHz linear transducer array scanner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Settings – kept constant during all examinations excluding depth, which was altered individually to visualize complete muscle</td>
<td></td>
</tr>
<tr>
<td>Echogenicity graded using the Heckmatt scale – 4-point scale where higher grades of echotexture correlates to severity of muscle impairment; echotexture scores for four muscle regions averaged to generate a mean echotexture</td>
<td></td>
</tr>
<tr>
<td>Muscle echogenicity</td>
<td></td>
</tr>
<tr>
<td>Biceps brachii, quadriceps femoris, forearm extensors, tibialis anterior</td>
<td></td>
</tr>
<tr>
<td>Patients supine with arms and legs in relaxed extension; muscles scanned in both axial and longitudinal planes; measurements taken at the midline between origin and insertion (biceps brachii and quadriceps femoris), the first third distance between elbow and processus styloideus radii (forearm extensors) and first third between knee and malleolus lateralis (tibialis anterior)</td>
<td></td>
</tr>
</tbody>
</table>
Analysis of images performed both online and offline; precise detail not reported

<table>
<thead>
<tr>
<th>Score</th>
<th>Cross-sectional area</th>
<th>Quadriceps rectus femoris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puthucheary et al (39)</td>
<td>PLM805 Toshiba Medical Systems portable US machine, B-mode with an 8MHz 5.6cm linear transducer array; Philips Envisor HD 1.3 portable US machine, B-mode, using a 6-15MHz 4cm linear transducer array</td>
<td>Cross-sectional area using in-built planimetric software, and off-line Image J software (NIH, US) for each machine respectively</td>
</tr>
<tr>
<td></td>
<td>Transducer placed perpendicularly along the superior aspect of the thigh, two-thirds distance between anterior superior iliac crest and the superior patellar border; patients in supine with 30° head elevation unless clinically unfeasible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall cross-sectional area taken as the average of three consecutive measurements within 10%</td>
<td></td>
</tr>
</tbody>
</table>

*only detail provided regarding peripheral skeletal muscle data in critically ill patients. Campbell et al (35) additionally measured calf, trunk and triceps muscle groups in healthy subjects, Baldwin et al (34) additionally measured the diaphragm in the critically ill cohort, and all muscle groups in healthy controls, Cartwright et al (36) additionally measured the diaphragm.

Abbreviations: MOF = multi-organ failure. US = ultrasound. ICU = intensive care unit. LOS = length of stay. MLT = muscle layer thickness.
3. Data regarding changes in muscle architecture measured using ultrasound during critical illness from included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Timing of measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al (35)*</td>
<td>Commenced within 5d of MOF onset and ICU admission Serial measurements performed every 1-4 days for between 5 and 11 days, with a minimum of 5 measurements per patient</td>
<td>Median (max-min) rate of muscle wasting (expressed as percentage of first measurement), 6.0 (2.0-9.2)%/day Significant negative correlation between muscle thickness and time (max-min $r=\text{-}0.919$ to $\text{-}0.978$, $p=0.027$ to $&lt;0.001$)</td>
</tr>
</tbody>
</table>
| Gruther et al (38) | Group A: measurements performed twice, once at baseline (random LOS, at least 1 day after ICU admission) and after 28d of ICU admission Group B: one measurement performed after a random ICU LOS | **Group A**  
MLT measurements in both legs showed a reduction ($n=27$ thighs) and an increase ($n=7$ thighs) between time-points  
High significant negative correlation between MLT of the right ($p=0.005$) and left ($p=0.004$) thigh, and MLTD (MLT difference at 28days) for the right ($p=0.006$) and left ($p=0.003$) thigh, and LOS at ICU baseline measurement time  
LOS at ICU baseline measurement time the only variable influencing MLTD on the right ($p=0.006$) and left ($p=0.003$) thigh  

**Group B**  
High significant negative correlation between MLT of the right ($p<0.0001$) and left ($p<0.0001$) thigh and LOS at ICU baseline measurement  
LOS at ICU baseline measurement ($p<0.0001$) and thigh circumference ($p=0.006$) were the only variables that influenced right thigh MLT  
LOS at ICU baseline measurement ($p<0.0001$), thigh circumference ($p<0.0001$) and...
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid et al (40)</td>
<td>Measurements performed every 1-3 days, in keeping with method described by Campbell et al (35), for between 7 (5-39 days)</td>
<td>Total muscle thickness decreased with time in 96% of patients (n=48/50) ( r^2 = -0.953, p&lt;0.001 ); median (range) rate of decrease as percentage of baseline 1.6 (0.2-5.7)%/day; 2 patients demonstrated increases of 1.1 and 0.6%/day Non-significant difference in percentage change in muscle thickness between those patients whose mid-upper arm circumference decreased (% change -1.3(-0.2 to -4.0)) or remained the same (% change -1.6 (-0.3 to -4.2)) Loss of muscle thickness over the first 7 days significantly higher in patients with greater muscle thickness at baseline (at baseline ‘thicker’ muscle 5.25 (4.3 to 6.8)cm vs. ‘thinner’ muscle 3.75 (2.6 to 4.2)cm, p&lt;0.001; total change in 7 days -0.8 (-0.2 to -2.3)cm vs. -0.35 (0.0 to -1.1)cm, p=0.001); when loss expressed as percentage of first measurement p=0.051</td>
</tr>
<tr>
<td>Baldwin et al (34)*</td>
<td>Measurements performed at median (IQR) 16 (11-29) days of ICU admission</td>
<td>Excellent reproducibility of triplicate measurements of peripheral skeletal muscle thickness (intraclass correlation class coefficient ≥0.976) Muscle thickness significantly lower in critically ill patients compared to healthy controls - upper arm (25.1±4.3 vs. 20.6±4.4mm, mean difference 4.5mm, 95% CI 1.3-7.6mm, p&lt;0.01), forearm (29.8±4.6 vs. 22.6±4.9mm, mean difference 7.2mm, 95%CI 3.8-10.6mm, p&lt;0.001), thigh (29.0±5.8 vs. 16.8±6.1mm, mean difference 12.2mm, 95%CI 7.9-16.5, p&lt;0.001) – when corrected for fat-free mass, only thigh muscle thickness was significantly reduced Significant difference in all peripheral skeletal muscle thicknesses compared to the diaphragm (p&lt;0.001)</td>
</tr>
<tr>
<td>Cartwright et al (36)*</td>
<td>Measurements performed at baseline (within 80 hours of ICU</td>
<td>Significant increase in TA mean grey-scale value over 14 days of ICU admission (138.39 to 166.39, p=0.027), with significant reduction in grey-scale standard deviation (33.87 to</td>
</tr>
</tbody>
</table>
admission), and days 3, 7, 14 after baseline (if still in hospital); 2, 4 and 6 months after hospital discharge

| Grimm et al (37) | Measurements performed between days 2-5, and day 14, after onset of severe sepsis or septic shock | Inter-image measurements of echogenicity demonstrated ICC of 0.915 between raters, and intrarater ICC of 0.972.  
75% of patients demonstrated a mean echotexture >1.5 (the maximum reported in a comparative non-matched healthy control group); a significant difference in mean muscle echotexture between patients and controls was found at both measurement time-points (both p<0.001); non-significant increase in mean echotexture grades in patients between measurement time-points (p=0.085); non-significant difference in comparison of echogenicity between proximal and distal muscles in patients at either measurement time-point; significant (p<0.001) tests for trend per visit and anatomical muscle region for echotexture score |
|-----------------|-------------------------------------------------|-------------------------------------------------|
| Puthucheary et al (39) | Measurements performed on days 1, 3, 7 and 10 of ICU admission | Significant reduction in rectus femoris cross-sectional area from days 1 to 7 (-12.5% (95%CI -35.4 to 24.1%), p=0.002), with a continued decrease to day 10 (-17.7% (95%CI -25.9 to 8.1%), p<0.001)  
Significant association seen between change in RF_{CSA} and ICU length of stay (p<0.001); increased organ failure correlated with change in RF_{CSA} (r²=0.23, p<0.001); change in |
RF<sub>CSA</sub> differed between patients with multi- and single-organ failure (day 3, -8.7% (95%CI -59.3% to 50.6% vs. -1.8% (95%CI -12.3% to 10.5%) respectively, p=0.03), day 7, -15.7% (95%CI -27.7 to 11.4% vs. -3.0% (95%CI -5.3 to 2.1%) p<0.001); change in RF<sub>CSA</sub> greater in those with ≥4 failed organs (-20.3% (95%CI -34.7 to 17.5%)) vs. 2-3 failed organs (-13.9% (95%CI -25.7 to -9.8%)) (p<0.001)

Change in RF<sub>CSA</sub> at day 10 was negatively associated with serum bicarbonate, PaO<sub>2</sub>:FiO<sub>2</sub> and Hb concentration at ICU admission (r<sup>2</sup>=0.51, p<0.001) and positively associated with degree of organ failure, mean C-reactive protein level and total protein delivered during study period

Age (odds ratio (OR) 1.05/yr, 95%CI (1.01-1.07/yr)), bicarbonate level at admission (OR 0.72mmol (95%CI 0.65-1.00mmol)), and PaO<sub>2</sub>:FiO<sub>2</sub> (OR 0.88, 95%CI (0.87-0.97)) found to be associated with >10% loss in RF<sub>CSA</sub> at day 10

Inter-observer agreement ICC 0.97 (n=21 patients), Bland Altman analysis demonstrated bias (SD) and 95% limits of agreement of 7 (37)mm<sup>2</sup> and -66.1 to +80.5mm<sup>2</sup>

*only detail provided regarding peripheral skeletal muscle data in critically ill patients.

Abbreviations: MOF = multi-organ failure. MLT = muscle layer thickness. MLTD = muscle layer thickness difference. LOS = length of stay. ICU = intensive care unit. ICC = intraclass correlation coefficient. RF = rectus femoris. RF<sub>CSA</sub> = rectus femoris cross-sectional area.