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

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ABSTRACT

Background. Use of ultrasound to assess peripheral skeletal muscle architecture during critical illness is rapidly gaining research popularity but systematic review evidence is lacking.

Objectives. To critically evaluate and summarize identified evidence for the use of ultrasound to measure peripheral skeletal muscle architecture during critical illness.

Data Sources. Seven electronic databases (Medline, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Physiotherapy Evidence Database, Scopus, Excerpta Medica Database and Web of Science (including Science Citations and Conference Proceedings)), and personal libraries were searched for relevant articles. Cross-referencing further identified references.

Study selection. Quantitative study designs excluding abstracts, published in English, including adult critically ill patients in the intensive care unit, evaluating peripheral skeletal muscle architecture during critical illness with ultrasound. Studies utilizing ultrasonographic muscle data as outcome measures in interventional trials were excluded.

Data Extraction. Performed by one reviewer using a standardized data extraction form and cross-checked by a second reviewer. Quality appraisal was undertaken by two independent reviewers - studies were classified, graded and appraised according to standardized algorithms and checklists. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were adhered to.

Data Synthesis. Seven studies with independent patient cohorts totaling 300 participants were included. One study adopted a case-control design, the remainder were case series. Ultrasound data demonstrated deficits in a variety of peripheral skeletal muscle architecture parameters across a range of muscle groups associated with critical illness. Ultrasound

offered more accurate data compared to limb circumference measurement and has excellent reported reliability, but underestimated data acquired via more invasive muscle biopsy.

Conclusion. Ultrasound provides clinical utility for assessing the trajectory of change in peripheral skeletal muscle architecture during critical illness, supplementing more detailed characterization, albeit rarely used, from muscle biopsy analysis. Adoption of standardized operating protocols for measurement will facilitate future meta-analysis of data.

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299

INTRODUCTION

Peripheral skeletal muscle wasting is a major complication of critical illness. Described clinically as intensive care unit acquired weakness (ICU-AW), it is associated with prolonged weaning, delayed rehabilitation, increased hospital length of stay and mortality (1-6) with residual deficits in physical functional ability persisting up to five years following the index ICU admission (7). Risk stratification of patients with peripheral muscle wasting is therefore vital for optimizing clinical management (8), including delivery of exercise therapy, rehabilitation and other therapeutic interventions.

Volitional methods of measuring muscle strength such as manual muscle testing (9), whilst clinically appealing, are restricted to alert, awake and cognitively intact patients able to produce maximal efforts. Distinguishing true muscle weakness from poor motivation or inability to complete the task is challenging and use of manual muscle testing in the early stages of critical illness is limited (10, 11). Non-volitional techniques involving electrical (12, 13), or magnetic (14-17) motor nerve stimulation to elicit twitch force responses require no patient cooperation but can be technically complex to perform, particularly in the ICU environment, requiring expensive dedicated equipment and skilled personnel for assessment and interpretation (18). Consequently, recent attention has focused on the utility of ultrasound to monitor the trajectory of muscle wasting in critically ill patients (19).

Principles of the neuromuscular ultrasound technique have been described previously (20-22), with ultrasonographic differences evident between healthy and diseased skeletal muscle (23, 24) and a number of characteristics of peripheral skeletal muscle architecture including cross-sectional area, fiber pennation angle, muscle layer thickness and

echogenicity measurable (25). In addition, ultrasound has both pragmatic and clinical advantages. It is widely available across ICUs, and is portable, simple and quick to perform. It is also effort-independent, free of ionizing radiation, can be performed at the bedside, and with training can be implemented by non-specialist clinicians.

The objective of this systematic review was to critically evaluate and summarize identified evidence for the use of ultrasound to measure peripheral skeletal muscle architecture during critical illness, and was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26).

METHODS

Registration

This systematic review was registered on the National Institute for Health Research (NIHR) International Prospective Register of Systematic Reviews (PROSPERO) (Registration reference CRD42013004892, available at http://www.crd.york.ac.uk/prospero/).

Eligibility criteria

Study characteristics for eligibility are detailed in Table 1, including participants, interventions, control groups and outcome measures.

Information sources

Confirmation that a review of this nature had not been published or was in progress was obtained prior to commencement, from a search of the Cochrane Library, Physiotherapy Evidence Database (PEDro) and the NIHR PROSPERO databases.

Electronic databases (n=7) were searched by one reviewer (BC) using a systematic detailed and reproducible search strategy to identify published evidence (Table 2). Databases were accessed via King's College London, UK, and included Medline (1946-present), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981-present), Cochrane Library (2013), PEDro (1993-present), Scopus (1960-present), Excerpta Medica Database (EMBASE) (1980-present) and Web of Science (including Science Citations and Conference Proceedings) (1900-present), with the last search run 16th October 2013. Full search strategies are included in the Supplemental Digital Content (SDC). Additional references were identified by cross-checking reference lists of included articles and searching personal libraries of the authors.

Search

Trial registries, conference proceedings and electronic databases were searched using the following terms: intensive care, critical care, critical illness, critically ill, multi-organ failure, sepsis, ultrasound, ultrasonography, muscle, muscle wasting, muscle mass, cross-sectional area, fiber pennation angle, muscle layer thickness, echo intensity, echogenicity, muscle architecture (Table 2).

Study selection

Figure 1 summarizes the study selection process. From the initial search, two independent reviewers (BC, VM) adopted a standardized approach to assess studies for eligibility against predefined eligibility criteria using article titles and abstracts (Table 1). In the absence of sufficient detail to inform decision-making, full texts were sourced and the process repeated. In the event of disagreement, a consensus approach was taken to reach a

decision. A third reviewer (NH) was employed to make the final decision if this could not be achieved. At each stage, level of agreement was determined using percentage agreement and Kappa statistic (SPSS for Windows, Statistical Version 20, IBM, New York, NY). All references were stored in Endnote software, Version 6 (Thomson Reuters, Philadelphia, PA).

Data extraction

Using a bespoke data collection form, data extraction from included studies was performed by one reviewer (BC) and cross-checked by a second (AL). Data were stored in either Microsoft Excel or Word for PC 2007 (Windows 7, Microsoft Corporation, Redmond, WA).

Data items

Data extraction was conducted on all eligible studies including: 1) study design – type, author first name and country, publication journal and year, aim/objective; 2) participant characteristics; 3) ultrasound detail – timing of measurement, muscle groups and muscle architecture characteristics assessed, detail of technique, and results.

Risk of bias in individual studies

Two independent reviewers (BC, VM) assessed included studies. Study design was determined using a published classification algorithm from the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Care Excellence with associated relevant checklists employed to assess study quality (27, 28). Studies were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence (29). In addition methodological quality and risk of bias in randomized controlled trials (RCTs)

were determined using the PEDro scale (30), and the Newcastle-Ottowa Scale (NOS) (31) for nonrandomized observational studies.

RESULTS

Study Selection

Searching of the seven databases resulted in 672 potentially eligible studies, with a further 11 articles identified through cross-referencing and personal libraries (Figure 1). Studies not published in English were excluded (n=1). Two conference proceedings were checked but no relevant studies identified. For the remaining conference abstracts (n=10), two studies within the author's own library contained data pertaining to four of these. Authors of a further two abstracts were contacted to determine if data were available in peer-reviewed publication format, following which neither study was included. No contact was made with the remaining four abstract authors as data had been collected in non-ICU settings (n=2), in healthy subjects (n=1) or no email address or other contact details were available (n=1).

High levels of agreement between the two independent reviewers were evident for potentially relevant titles and abstracts (percentage agreement=90.2%, Kappa=0.72) and full-text articles (percentage agreement=100.0%, Kappa 1.0). The reviewers disagreed on four potentially eligible studies based on title and abstract. Following consensus, agreement was reached on all four studies and no study was included. Input from a third reviewer was not required. Review of title, abstract and full text resulted in the inclusion of seven original articles each evaluating unique patient cohorts.

Study Characteristics

Study design characteristics are summarized in Table 3. None of the seven included studies (32-38) were randomized controlled trials. Six were primarily single group studies, classified as case series (33-38). One of these studies involved comparison with an unmatched control group (35). The final study adopted a case-control design (32). All studies were Level 4 evidence grade (29). Significantly, the majority of included studies were published between 2012 and 2013 (32, 34, 35, 37) indicating the emerging research interest in ultrasound as a technique for evaluating peripheral skeletal muscle architecture during critical illness. Five studies were European (33, 35-37, 39), with one conducted in Australia (32) and one in North America (34). Patient characteristics of included studies are reported in Table 4.

Of the seven studies included, each involved independent general ICU patient populations, overall totaling 300 patients, where the primary purpose involved assessment of peripheral skeletal muscle function during critical illness with ultrasound as the evaluation tool. Sample sizes ranged between 9 (33) and 118 (36) patients. Eligible patient populations in studies were characterized according to either clinical diagnostic descriptors (e.g. multi-organ failure and sepsis) (33-35), ICU admission-related descriptors (e.g. duration of mechanical ventilation and length of stay) (36, 37), or a combination of both (32, 38). Only four studies reported actual illness severity of their patient cohorts using standard critical care scoring systems (APACHE) scores) (32, 35, 37, 38), of which three further reported actual duration of mechanical ventilation for their patient cohorts (32, 35, 37).

Muscle thickness was the most common characteristic of muscle architecture evaluated (five studies) (32-34, 36, 38) (SDC, Table 1). In one study this was termed muscle layer thickness and used to reflect muscle mass (36). Muscle composition using echogenicity was

investigated in two studies (34, 35), and cross-sectional area in one (37). A combination of mid-upper arm, forearm and thigh muscle groups were all measured in four studies (32, 33, 35, 38). In addition, tibialis anterior and abductor digiti minimi muscle were also reported (34, 35). Quadriceps muscle alone was measured in two studies (36, 37). Details of measurement procedure were provided in all studies. Timings of measurements varied between single measurements performed at specific time-points during ICU admission (32, 34-37), or sequentially throughout the duration of ICU admission (33, 38).

Results of Individual Studies

Change in muscle architecture of critically ill patients was evident in six studies and associated with duration of time in the ICU (33-38) (SDC, Table 2). In the remaining case-control study, muscle thickness was found to be significantly reduced compared to case-controlled healthy subjects at the single time-point assessed (32). Rates of reported muscle wasting varied between 6.0% per day (33) and 1.6% per day, with more notable wasting in patients with greater muscle layer thickness at baseline (38). A third study reported a 12.5% reduction between days 1 and 7, which further differed significantly between those with single and multiple organ failure (37). A quantifiable measurement of degree of muscle wasting was not given in one study (36). Muscle quality (echogenicity) was shown to be affected during critical illness with increases in image grey-scale values (34, 35), which were significantly different to healthy controls, albeit an unmatched population (35). Three studies reported high levels of ultrasound image reproducibility in critically ill patients (intraclass correlation coefficients (ICC) >0.9), for inter-image (muscle thickness and muscle echogenicity) (32, 35), intra-rater (muscle echogenicity) (35) and inter-observer (muscle cross-sectional area) (37) agreement. Reid *et al* (38) also presented reproducibility data,

reporting a coefficient of variation (CV) for total muscle thickness of 2.5% although this was in a separate cohort of healthy volunteers rather than their ICU patient cohort. Similarly, Campbell *et al* (33) reported an intra-observer CV of 1.5% and an inter-observer CV of 1.9% for total muscle thickness in a cohort of healthy subjects assessed within their study.

Risk of bias within studies

Two independent reviewers (BC and VM) agreed on the study design of included studies (percentage agreement=100%). Due to the nature of study design assigned to the majority of studies (n=6, case series) involving single groups of patients receiving ultrasound measurements of peripheral skeletal muscle architecture during critical illness, no tool was available to assess risk of bias in these studies (27). The reviewers considered that the design of one of the studies (35) involving comparison with an unmatched control group did not meet the criteria for categorization as a case-controlled study with associated quality review. The single identified case-controlled study (Baldwin *et al* (32)) demonstrated positive scoring on seven out of eleven binary outcome criteria, according to the SIGN checklist (63.6%), and percentage agreement of 84.6%, however no grading system exists to equate this to an overall descriptor of quality level (27). This article scored 6 on the NOS indicating 'good' overall quality (31).

Synthesis of results

Meta-analysis or pooling of results was not appropriate due to the observational nature and design of studies included, heterogeneity of patient cohorts, and varying results related to different aspects of peripheral skeletal muscle architecture measured.

DISCUSSION

This systematic review identified and included seven studies evaluating the effect of critical illness on peripheral skeletal muscle architecture assessed using ultrasound. Each study reported a general ICU population in patients presenting with sepsis and multi-organ failure with ICU lengths of stay of at least seven days. Changes in a range of muscle architecture parameters were reported across a range of muscle groups, with ultrasound assessment demonstrating clinical reliability and utility.

Significance of findings

Ultrasound data characterized the negative effects on peripheral skeletal muscle architecture associated with acute critical illness. Nonetheless, meta-analyses of data were not possible due to variability in muscle group and architecture parameter assessed, study protocols, and the extent and clarity of data reporting. Hence consideration of confounding factors such as age, illness acuity or nutritional management on muscle architecture during critical illness was limited.

Five studies measuring muscle thickness (32-34, 36, 38) produced varying results, possibly contributed to by inconsistency in baseline measurement point resulting in an underestimation of muscle wasting during ICU admission. Three of these analyzed total muscle thickness, calculated as the average across a variety of muscle groups (33, 36, 38). The remaining two studies reported, but did not compare, muscle thicknesses for individual muscles, (32, 34). As a result, the relative degree and significance in distribution of peripheral skeletal muscle wasting was unknown. Muscle echogenicity increased in two studies, albeit measured using different methods, suggesting presence of myopathic

changes in the muscle during critical illness possibly due to edema from capillary leak during acute sepsis with loss of the typically organized muscle architecture occurring during breakdown (34, 35). Biopsy data from our own group, from days 1 and 7 of ICU admission, confirmed this, demonstrating muscle necrosis and macrophage cellular infiltrate (37). Finally, no study reported measurement of fiber pennation angle, which in combination with anatomical cross-sectional area values allows calculation of physiological cross-sectional area, in turn associated with the force-generating capacity of a muscle (25). The clinical advantages of this potentially more complex parameter require further investigation.

The relationship between muscle wasting in critically ill patients and functional outcome was not investigated in any studies. Clinically significant muscle loss has yet to be defined, even when changes are at a statistical level. Strength correlates with peripheral muscle cross-sectional area in healthy subjects and patients with chronic co-morbidity (13, 40-42), albeit there are few data for critically ill patients. Ideally, contemporaneous measures of muscle force would validate ultrasound measures of peripheral skeletal muscle architecture, and which could then be mapped to levels of physical functional ability.

Technical considerations of ultrasound

Ultrasound measurements were feasible across all patients in all studies with the exception of two circumstances. Puthucheary *et al* (37) reported one patient unable to complete assessment of quadriceps rectus femoris cross-sectional area due to morbid obesity, and diaphragm echotexture was not assessed by Cartwright *et al* (34) as the muscle was too thin for accurate measurement. High reliability of the ultrasound technique was evident in three included studies (32, 35, 37).

All studies reported technical detail of ultrasound measurement including make and model of machine and transducer specification. However, there was a lack of reported detail regarding image acquisition settings e.g. scanning depth or gain. Furthermore, despite commonality in a number of muscle groups assessed, variation was evident in patient position and probe location on the muscle group. Whilst protocol standardization within studies provides internal validity for the use of ultrasound as a tool for monitoring change in muscle architecture, variation across studies limited pooling of data to determine overall effect and influences external validity.

Ultrasound findings all indicated superiority over results of limb circumference, where performed, due to the confounding problem of subcutaneous edema influencing measurement accuracy. Typically whilst muscle cross-sectional area or thickness decreased, limb circumference remained unchanged (33, 36, 38). Ultrasound measures of muscle architecture have also been shown to correlate closely with data obtained via magnetic resonance imaging (43) and computed tomography (41) scanning modalities, supporting clinical benefit over techniques that are more costly, time-consuming and involve radiation. Although these data originate from healthy subjects or stable patients with chronic co-morbidity, they are nonetheless valuable as conducting similar studies in critically ill patients has limited feasibility.

However, additional investigation by Puthucheary *et al* (37) highlighted a limitation in ultrasound data interpretation. A subset of their cohort underwent additional measures of muscle wasting, including quadriceps vastus lateralis muscle biopsy and quantification of protein to deoxyribonucleic acid (DNA) ratio. Ultrasound of muscle cross-sectional area not

only underestimated fiber cross-sectional area, but also actual loss in muscle mass with the greatest reduction observed in the protein/DNA ratio over the 10 day study period. Indeed, as the protein/DNA ratio is unaffected by water content of the muscle and these data strongly support the observation that quadriceps rectus femoris ultrasound underestimated muscle loss as a consequence of muscle oedema. Evaluation of muscle composition using grey-scale analysis may assist in determining level of intramuscular fluid to provide a clinically applicable assessment of muscle quality, albeit further validation of echogenicity findings is required. The additional analyses undertaken by Puthucheary *et al* (37) were invasive, costly, required expertise to conduct, analyze and interpret and these invasive measurements were only feasible in a very select patient group. As previously described, ultrasound demonstrates advantages in all these areas and these data should not detract from the clinical utility of the tool.

Critique of the method

This systematic review was conducted and reported in line with PRISMA guidelines (26), specifically identifying studies primarily evaluating peripheral skeletal muscle architecture during critical illness using ultrasound. Data regarding respiratory musculature changes were excluded, including from two eligible studies (34, 44). However, this topic has recently been reported in two comprehensive reviews (45, 46), with growing evidence documenting diaphragm atrophy during critical illness and weaning from mechanical ventilation (32, 34, 47-49). Furthermore, interventional trials using change in peripheral skeletal muscle architecture as an outcome measure were also excluded. The majority of these related to electrical stimulation for preservation of muscle mass during critical illness (50-54), itself also the topic of a recent, more focused systematic review (55). That the current review

failed to identify all studies reported by Parry *et al* (55), highlights the pragmatic limitations of robustly identifying all potential interventional trials where peripheral skeletal muscle architecture measured using ultrasound could be an outcome measure. Prior knowledge of the intervention would be required to facilitate database searching using relevant indexing terms.

We included studies based only within the ICU, focusing on early critical illness. Two sources of excluded evidence and one included study reported ultrasound data of peripheral skeletal muscle architecture following ICU discharge on the ward (56), up to 6 (34) and 12months post discharge (39) suggesting utility of the technique for longitudinal monitoring of the trajectory of recovery of peripheral skeletal muscle architecture following critical illness. This could further assist in identifying the optimum time for delivery of exercise-based rehabilitation interventions following hospital discharge.

We acknowledge potential publication bias through database searching that may have excluded non-peer-reviewed publications. Despite this, our chosen databases were wide-ranging and identified conference proceedings and other citations. We did not search clinical trial registries due to the observational nature of the review topic. As per usual, data available in abstract form only were excluded due to lack of technical detail provided in these summaries, and this accounted for only one item. Mampilly *et al* (57) reported reduced rectus femoris cross-sectional area values for critically ill patients compared to healthy subjects (n=5 each group; 4.5 ± 0.6cm^2 vs. 10.1 ± 0.8cm^2, p<0.002), but similar to those found in ambulatory patients with chronic obstructive pulmonary disease (n=5; 5.8 ± 0.7cm^2, p=0.22).

We adhered to recognized classification algorithms for determining study design (27) and we acknowledge the majority of included studies were non-comparative case series. Whilst this is perhaps not unsurprising given the observational nature and purpose of the review, there was no tool available to assess the quality of these studies, which is a limiting factor to their methodological robustness.

Future considerations

Currently, there is no gold standard for the measurement of peripheral skeletal muscle architecture using ultrasound, and this review demonstrates a variety of parameters employed in the critical illness population. Further work is necessary to determine uniformity of technical application. Minimum reporting detail would include make and model of machine, probe specification, image acquisition settings, and precise description of patient position and location on the muscle for measurement. Inclusion of standard operating protocols as supplementary materials to data publication would strongly facilitate future consensus on this. Future studies are required to determine the relationship between ultrasound measurements, both single and sequential measurements, and clinically relevant functional outcomes of the patient and the temporal change in the muscle itself.

CONCLUSION

Ultrasound is gaining in profile as a tool for evaluating changes in peripheral skeletal muscle architecture during critical illness. Whilst the technique has been shown to underestimate the extent of muscle wasting obtained from invasive muscle biopsy techniques, its practical and clinical advantages, when supplemented with data demonstrating high levels of

reliability, strongly confirm the clinical utility of ultrasound. Further investigation with regards to muscle composition using grey-scale analysis of images will assist in corroborating detailed muscle biopsy data. Standardization of protocol detail will improve external validity for performance of future studies, and permit future meta-analysis of data and investigation of confounding factors associated with alteration of peripheral skeletal muscle architecture during critical illness.

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FIGURE LEGEND

Figure 1. Flow diagram summarizing article selection

Abbreviations: CINAHL = Cumulative Index to Nursing and Allied Health Literature. EMBASE = Excerpta Medica Database. PEDro = Physiotherapy Evidence Database. ICU = intensive care unit. US = ultrasound.