HHS Public Access

Author manuscript

Muscle Nerve. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Muscle Nerve. 2015 November ; 52(5): 701–708. doi:10.1002/mus.24728.

QUANTITATIVE NEUROMUSCULAR ULTRASOUND IN INTENSIVE CARE UNIT ACQUIRED WEAKNESS: A SYSTEMATIC REVIEW

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Abstract

Intensive care unit acquired weakness (ICU-AW) causes significant morbidity and impairment in critically ill patients. Recent advances in neuromuscular ultrasound (NMUS) allow evaluation of neuromuscular pathology early in critical illness. We review application of ultrasound in ICU-AW. MEDLINE-indexed articles were searched for terms relevant to ultrasound and critical illness. Two reviewers evaluated the resulting abstracts (n=218) and completed full-text review (n=13). Twelve studies and 1 case report were included. Ten studies evaluated muscle thickness or cross sectional area (CSA); 8 reported decrease, and 2 reported no change. Two studies reported preservation of muscle thickness in response to neuromuscular electrical stimulation, and 1 found no preservation. One study found decreases in gray-scale standard deviation, but no change in echogenicity. One study described increases in echogenicity and fasciculations. Ultrasound reliability in ICU-AW is not fully established. Further investigation is needed to identify ultrasound measures which reliably predict clinical, electrodiagnostic, and pathologic findings of ICU-AW.

Keywords

quantitative neuromuscular ultrasound; intensive care unit acquired weakness; critical illness myopathy; critical illness polyneuropathy; critical illness

INTRODUCTION

Intensive care unit acquired weakness (ICU-AW) is increasingly recognized as a major contributor to morbidity, mortality, and impaired function at hospital discharge.[1,2] The causes of ICU-AW include critical illness myopathy, critical illness polyneuropathy, deconditioning, and disuse atrophy, in isolation or in combination. The reported prevalence of ICU-AW depends on the population studied, the criteria examined, and the presence of risk factors, but ranges from 25-100%.[3-6] Electrophysiologic testing frequently reveals

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evidence of polyneuropathy and myopathy in critically ill patients,[7,8] with abnormalities that can persist for months to years.[9] ICU-AW is associated with prolonged mechanical ventilation[10] and hospital length of stay,[11] and results in increased hospital and long-term care costs. Sedation, delirium, encephalopathy, and other factors which limit voluntary muscle strength testing may prevent early recognition.[12] Subsequent diagnosis is often made only following failure to wean from mechanical ventilation or recovery sufficient to allow participation in manual muscle testing.

Recent advances in NMUS have created novel ways to study muscle and nerve pathology early in the course of critical illness, which potentially may allow early diagnosis and intervention. While CT and MRI have been used in research settings to study nerve and muscle pathology in critical illness,[13,14] their high cost, lack of portability, ionizing radiation (CT), and cumbersome study logistics limit routine clinical use. Electrodiagnostic protocols are challenged by abundant ambient electrical noise in the ICU environment and require specialized equipment and expertise not available in every ICU. Nerve and muscle biopsies are invasive and expensive with potential for complications and require specialized expertise for obtaining and interpreting samples. Modern quantitative ultrasound provides a ready solution that maintains high resolution while remaining non-invasive, low cost, portable, and without ionizing radiation.

The goal of this review is to provide a thorough examination of the literature on ultrasound for evaluation of neuromuscular changes in critically ill populations and for investigation of ICU-AW. The methodology behind establishing the reliability of quantitative measures in the setting of critical illness is evaluated in depth. Meta-analysis of pooled data and outcomes was not conducted due to the amount, variability, and type of evidence available in this this nascent field. A brief description of technical aspects is additionally discussed.

METHODS

Search Strategy

MEDLINE-indexed articles published from 1966 to February 1, 2015 were searched for terms relevant to NMUS and critical illness. Key-word searches were performed for ultrasonography; Imaging, Ultrasonic; Quantitative Ultrasonography; Muscle, Skeletal/*ultrasonography; Peripheral Nerves/*ultrasonography; Diaphragm/physiopathology/*ultrasonography; Echogenicity; Echotexture; Gray-scale; Adiposity; Anisotropy; Cross-sectional area; Linear depth AND; Critical illness myopathy; Polyneuropathies, Critical Illness; Polyneuropathy, Critical Illness; Neuromyopathy, Critical Illness; ICU-acquired weakness; weakness; disuse atrophy; Muscular Atrophy; Muscle wasting; Muscle Mass; Musculoskeletal AND; Intensive Care; Intensive Care Unit; ICU; Critical Illness; Multiple organ failure; Acute Lung Injury; Coma; Unresponsive; Ventilator Dependent; Failure to wean; Sepsis; SIRS. (Note: semicolon denotes the use of the term “or.”) Inclusion criteria were use of ultrasound to quantify nerve or muscle characteristics in all human or non-human subjects with markers of critical illness. Exclusion criteria were use of therapeutic ultrasound, procedural ultrasound, or diagnostic ultrasound in populations not related to critical illness and ultrasound studies of solely optic nerve or diaphragm.

Eligible studies were assessed by 1 reviewer using criteria adapted from the Guidelines for reporting Reliability and Agreement Studies (GRRAS)[15], a consensus tool for rigorous reporting of Reliability and Agreement studies. Each study was evaluated according to whether it reported subject and rater characteristics and number, sampling methods, sample number rationale, observation methodology (intra- or interrater, time interval between measures, blinding, and independent conduction of measures), and statistical methods (analysis used, estimates of reliability, and estimates of uncertainty.) Each study was then given a methodological rating based on reliability of ultrasound as applied to critically ill populations. Studies that evaluated inter-rater reliability in critically ill populations with sample sizes greater than 15 and reported greater than 90% of key variables were given the rating of "Excellent." Studies that evaluated inter-rater reliability in critically ill populations with sample sizes greater than 15 and reported greater than 75% of key variables were given the rating of "Good." Studies that evaluated reliability in any population with sample sizes greater than 10 and reported greater than 50% of key variables were given the rating of "Fair." Studies that evaluated reliability in sample sizes less than 10 and reported fewer than 50% of key variables were given a rating of "Poor." Studies which did not provide sufficient information to assess reliability were given the designation "Unclear."

Additionally, data from each of the eligible studies were extracted by the same reviewer, including quantitative diagnostic accuracy of NMUS, correlation with biologic measures (muscle mass, muscle architecture, and nerve measures), and use as an outcome measure.

RESULTS

The search resulted in 218 articles dating from December 1974 to February 2015. Two reviewers independently evaluated the resulting abstracts (n=218) with subsequent full-text review (n=13) according to inclusion and exclusion criteria. Most studies were excluded due to focus on non-critically ill populations, use of ultrasound for evaluation of the diaphragm, or for a study target other than nerve or muscle.

Reliability and assessment of the methodological quality of individual studies

Establishing the reliability of quantitative NMUS measures in critically ill populations is an essential foundation to the development of diagnostic and outcome measures for conditions contributing to ICU-AW. Nine of the 13 studies reported assessments of quantitative ultrasound reliability: 7 for measures of muscle linear depth, 1 for CSA, and 1 for echogenicity. Validation of reliability was not reported in 2 studies,[16,17] and 2 studies reference another published paper.[18,19] (Table 1 with full data available in Supplementary Table S1, available online) No included studies reported the reliability of echotexture or nerve measures in critically ill patients. Methodological quality for establishment of reliability was poor overall; only 1 study received a rating of excellent, and 2 were given a rating of fair. The majority of studies did not assess reliability as a primary outcome, which may explain the lack of methodological rigor.

The only included study to receive a methodological rating of excellent was published by Puthucheary et al in 2013.[20] In a prospective study of muscle wasting in the critically ill using NMUS to measure rectus femoris CSA, validation was conducted using 2 blinded,

independent raters to measure rectus femoris CSA on 21 critically ill patients. [20] The resulting correlation coefficient (R^2) was 0.97. A Bland-Altman plot was generated with a resulting bias (SD) of 7 mm^2 (37mm^2) and 95% limits of agreement of −66.1 to 80.5mm^2 (Table 1)This study was limited in that only 1 measure at 1 muscle site was evaluated.

Two studies were assessed to have fair methodological quality. In 2011, Baldwin et al published an observational methodological study evaluating the reliability of muscle linear depth of mid-upper arm, mid-forearm, and mid-thigh in 13 supine healthy subjects positioned as would be expected in the ICU.[21] They found intra-rater intra-class correlation coefficients (ICC) ranging from 0.998-1.0 (Table 1). The study was limited primarily by lack of evaluation of inter-rater reliability, absence of critically ill subjects, and measures separated in time. In 2014, Baldwin et al repeated the same protocol in patients who were critically ill and found intra-rater ICCs ≥ 0.976. This study was limited by lack of inter-rater reliability and limited reporting of key variables.

The remaining studies were assessed to have poor or unclear methodological quality for establishment of reliability. These studies were limited primarily by small or unclear sample size, validation in healthy norms rather than critically ill patients, unclear sampling methods, no assessment of inter-rater reliability, unclear observation methods, and no assessment of statistical certainty. Overall, these studies reported excellent reliability, though results should be interpreted with caution. Campbell et al reported intra-rater coefficients of variation (CV) for single linear depth measures between 2.3% and 2.9%, and for summary index of muscle depth a CV of 1.5%. Inter-rater CVs for single measures of linear depth were reported to be between 3.1% and 4.5%, and a CV for summary index of muscle depths was 1.9%.[22] (Table 1) Using Campbell's protocol, Reid et al reported coefficients of variation (CV) for single linear depth measures between 2.9% and 4.3%, and for summary index of muscle depth a CV of 2.5%.[19] These were not clearly designated as intra- or inter-rater measures. In 2 papers, Gruther et al reported intra-rater CVs for anterior thigh mean linear depth <1.3% and 0.35%.[23,24] They reported a coefficient of variation on repeat anterior thigh mean linear depth measures of 0.25%, but whether this represented intra- or inter-rater reliability was not reported.[24] In 2013, Grimm et al also evaluated muscle echogenicity using a Heckmatt qualitative scale.[25,26] Though overall validation of the ultrasound protocol is not reported, the authors address the use of the Heckmatt scale by intra-rater and inter-rater assessment of previously obtained images. This demonstrated an inter-image inter-rater ICC of 0.915 and an inter-image intra-rater ICC of 0.972 (Table 1).

Use as a diagnostic tool

We also intended to evaluate the selected studies using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies)[27], an evidence-based tool for the assessment of quality in systematic reviews of diagnostic accuracy studies, however no studies attempted to use quantitative measures to establish a diagnosis of critical illness myopathy, critical illness polyneuropathy, or other conditions associated with ICU-AW. The 13 studies included in this review report primarily observational changes occurring in muscle linear depth, muscle CSA, echo intensity, and echo texture. To date, no studies have reported the diagnostic accuracy of NMUS measures for diagnosis of critical illness myopathy, critical

illness polyneuropathy, or disuse atrophy using accepted reference standards of muscle biopsy, muscle strength testing, or electrodiagnostic testing.

Correlation with biologic measures

Assessment of muscle mass—Quantification of muscle mass may be 1 of the more facile applications of NMUS. Campbell et al utilized measures of muscle mass in the first systematic study of quantitative NMUS in the setting of critical illness.[22] They evaluated changes in muscle linear depth and whether serial muscle measurements were changed by the presence of limb edema. Nine ICU patients with multiple organ failure were included. Serial measures of muscle thickness of the mid-arm, anterior forearm and anterior thigh were performed every 1-4 days for 5 to 11 days. Mid-upper arm circumference was measured and used as a marker of limb edema. Muscle thickness, as measured by a sum index of the 3 measurements, decreased at a median of 6.0%/day. Changes in muscle mass were found to be independent of changes in mid-upper arm circumference. They also found in 70 healthy subjects that a summary index of muscle thickness of the mid-biceps, anterior forearm, and anterior thigh best predicted lean tissue mass determined by dual-energy X-ray absorptiometry (DXA) with an R^2 of 76.1% (Supplementary Table S2, available online).

In 2004, Reid et al published a study using Campbell's ultrasound protocol in a larger critically ill patient population.[19] Fifty critically ill patients with expected mechanical ventilation greater than 5 days, multiple organ failure, systemic inflammatory response syndrome, or sepsis were included. Serial measures of muscle thickness of the mid-upper arm, anterior forearm, and anterior thigh were performed at 1-3 day intervals for between 5 and 39 days. Mean arm circumference (MAC) was measured for comparison. In 48 patients muscle thickness decreased at a median rate of 1.6%/day. Muscle thickness increased at 1.1% and 0.6% per day in 2 subjects, and these subjects were notably excluded from analysis. The study found no statistically significant difference in muscle thickness changes between subjects with MAC decrease, or no change (P=0.48). The MAC increase group was not included in comparison with the other 2 groups due to small sample size. Additionally, in 24 of the patients, energy balance was calculated and found to have no effect on the rate of change in muscle thickness (Supplementary Table S2).

In 2008, Gruther et al used quantitative measures of mean combined vastus intermedius and rectus femoris thickness at 2 sites to correlate loss of muscle mass and length of ICU stay.[23] This study used a 2-armed design to overcome the challenges of ICU deaths and transfers to study longer term changes in muscle mass. In the first arm, muscle linear thickness in 17 patients was measured during the ICU stay (at non-specified times) and 28 days later. In a second arm, 101 patients had muscle linear thickness determined once at differing time points after admission. In the first arm, correlation analysis showed a significant negative correlation between muscle linear thickness difference and length of stay in the ICU (Right thigh P=0.006, left thigh P=0.003). This was again shown in the second arm (P< 0.0001 bilaterally). Curve estimation suggested the logarithmic transformation fit best with decreased muscle linear thickness of both thighs with respect to length of stay (R^2 =0.527) (Supplementary Table S2).

Baldwin et al published a prospective, cross-sectional design study of ultrasound measures in mechanically ventilated patients with sepsis.[28] Age- and gender-matched healthy volunteers were used as controls, though body mass index was not matched. The primary ultrasound measures were again mid-upper arm, mid-forearm, and mid-thigh muscle thickness bilaterally and diaphragm thickness at end-expiratory volume. Ultrasound assessment was conducted at a single point in time with a median of 16 days after ICU admission. Patients were included if they met sepsis criteria and were mechanically ventilated for greater than 5 days. Notably, patients were excluded if they were not sufficiently alert to give informed consent, potentially excluding more severely ill populations. A total of 16 critically ill patients and 16 healthy controls were enrolled. The study found that, when compared with health controls, mechanically ventilated patients with sepsis had no significant difference in diaphragm thickness but did have significantly thicker arm, forearm, and thigh muscle thickness (Supplementary Table S2). The study may not have been sufficiently powered to detect significant differences in diaphragm thickness.

In 2013, Puthucheary et al published a prospective study of muscle wasting in the critically ill by using neuromuscular ultrasound (NMUS) to measure rectus femoris CSA and to characterize muscle fiber CSA and protein synthesis and breakdown rates.[20] Ultrasound measures were conducted by measuring rectus femoris CSA on days 1, 3, 7, and 10. They enrolled 63 critically ill patients who were expected to be mechanically ventilated greater than 48 hours, have an ICU length of stay greater than 7 days, and to survive the ICU stay. One patient was not able to undergo ultrasound study due to morbid obesity. They found that in the overall patient group rectus femoris CSA decreased significantly from days 1 to 7 (−12.5%; $P = .002$) and continued to decrease to day 10 (−17.7%; $P < .001$). Additionally, increasing organ failure score correlated with change in rectus femoris CSA ($r^2 = 0.23$, $P < .001$). They also demonstrated a difference in the change of rectus femoris CSA in patients with multiorgan failure versus patients with single organ failure at hospital day 3 (−8.7% versus −1.8%, $P = 0.03$) and hospital day 7 (−15.7% versus −3.0%, $P < 0.001$). Change in rectus femoris CSA was greater in those with 4 or more failed organs than in those with 2 to 3 failed organs (−20.3% versus −13.9%; $P < 0.001$) (Supplementary Table S2).

Assessment of Muscle Architecture—Cartwright et al evaluated echotexture and echogenicity via gray-scale measures and assessed muscle thickness in a pilot study of critically ill subjects.[16] In 16 patients admitted to the ICU with acute respiratory failure, gray-scale mean and standard deviation and muscle thickness measurements were conducted over 14 days. Death or discharge prohibited completion of the full 14 day analysis in 12 of the 16 initial patients. A significant increase was found in the gray-scale mean of the tibialis anterior (138.29 to 166.39, $P=0.027$) indicating increased muscle echogenicity. A significant decrease in gray-scale standard deviation in the tibialis anterior (33.87 to 28.01, $P=0.001$) and rectus femoris (31.40 to 28.73, $P=0.041$) indicating increased muscle homogeneity and muscle breakdown (Supplementary Table S2). These changes were not found in other muscle groups. The authors postulated that these changes may have indicated muscle breakdown and loss of muscle architecture, inflammation, or fluid retention. No significant change in muscle thickness was found in any of the study muscles. They postulated that this may have been due to the limited study period.

In 2013, Grimm et al also evaluated muscle echogenicity and fasciculations in a prospective study comparing patients with sepsis to controls.[25] In 28 patients with severe sepsis or septic shock, muscle ultrasound and nerve conduction studies were conducted on days 4 and 14 after the onset of sepsis. Ultrasound evaluation included assessment of echogenicity graded semiquantitatively on a 4- point scale as previously described by Heckmatt et al[26] and observation for fasciculations. The authors at times use echotexture and echogenicity interchangeably, but they seem to be evaluating echogenicity alone. Study sites included biceps brachii, wrist extensors, rectus femoris, and tibialis anterior with the average of all 4 sites calculated. The same protocol was also performed on 26 healthy controls. Of 28 patients enrolled 6 died before the second assessment could be performed. The study found that 92% of controls had normal mean echogenicity (grade 1 to 1.25) and that 75% of patients had mean echogenicity greater than 1.5, which was the maximal value found in the control group. (Time point not specified.) Significant differences were found between mean muscle echogenicity of controls and patients at days 4 and 14 ($P<0.001$, mean not specified). Mean echogenicity in patients increased between days 4 and 14 but did not reach statistical significance ($P=0.085$, mean not specified). Fasciculations were observed in both healthy patients and controls, however using the Cochran-Armitage test for an trend comparing patients versus controls they found no significant difference at day 4 ($P=0.08$) but a significant difference at day 14 ($P=0.002$) (Supplementary Table S2). The advantages of using a semiquantitative scale are its ready application in a clinical setting, though potentially adding an additional source of error.

Assessment of Nerve—We could find no studies that assessed quantitative measures of nerve in critical illness. Grimm et al noted all patients who underwent nerve conduction studies showed abnormalities consistent with CIP, though correlation with ultrasound findings is not reported.[25]

Use of Quantitative Ultrasound Metrics as Study Outcome Measures

In 2002, Moukas et al investigated changes in muscle mass in hemiplegic ICU patients treated with dexamethasone and atracurium.[29] In this non-randomized study, 37 patients were grouped into 4 categories: 1) patients who had received no drug, 2) recipients of dexamethasone alone, 3) recipients of dexamethasone and atracurium, or 4) non-hemiplegic controls. The mean of 3 ultrasound measurements of linear muscle thickness of the elbow flexor compartment was used. Measurements were at days 1 and 10 in the affected arm in hemiplegic patients or right arm in controls. They found linear depth decreased from days 1 to 10 in all groups by a mean of −20.1% ($p<0.001$). Patients who received both drugs showed a significant mean decrease in muscle thickness (−24.38%, $P<0.01$), as did those who received dexamethasone alone (−22.1 %, $P<0.05$) when compared with controls who decreased by a mean of −15.15%. Patients who received no drugs did not differ significantly from controls [mean decrease of −19.77% (Supplementary Table S2)]. Patients with systemic inflammatory response syndrome, sepsis, or multi-organ failure were excluded from the trial.

Several studies have evaluated the effect of neuromuscular electrical stimulation (NMES) on muscle mass using quantitative ultrasound. Gerovasili et al published the first study

employing this approach in 2009.[18] Forty-nine critically ill patients were randomized to receive daily NMES of bilateral quadriceps and fibularis longus muscles or no intervention. Cross sectional diameters (CSD) of the vastus intermedius and rectus femoris were measured on enrollment and at day 7 or 8. Of the initial 49 patients, 10 died or were discharged before the study was completed. Notably, 12 of the initial 49 patients were excluded for edema that interfered with ultrasound measures, which limits applicability to the critically ill patient populations. Rectus femoris and vastus intermedius CSD decreased in all groups and anatomical sites. However CSD showed significantly less absolute decrease in the NMES group than controls in the right rectus femoris (*P*=0.009) and bilateral vastus intermedius (Right p=0.034, Left *P*= 0.018). This comparison did not reach significance in the left rectus femoris (*P*=0.07) (Supplementary Table S2).

Gruther et al published a pilot study evaluating NMES in 2010.[24] Forty-six patients admitted to the ICU were randomized to NMES or sham treatment, receiving 1 session daily, 5 sessions weekly for 4 weeks. Ultrasound measurements of the bilateral vastus intermedius and rectus femoris were conducted at 2 points on the anterior thigh at baseline and after 4 weeks. For analysis, patients were stratified into acute (<7 days after admission to ICU) and long-term patients (>14days). Thirty-three patients completed the study with 9 deaths, 2 acute transfers, and 7 discontinuing the intervention. In the acute patient group both stimulation and sham groups demonstrated decreases in muscle thickness by 36.7% and 38.9%, respectively from baseline (*P*=0.457). In long-term patients, muscle thickness increased by 4.9% in the stimulation group and decreased by 3.2% in the sham group, a statistically significant difference (*P*=0.013) (Supplementary Table S2).

In 2012, Rodriguez et al conducted a study that included ultrasound measures of total brachialis and biceps thickness as a secondary outcome.[17] Sixteen septic patients requiring mechanical ventilation were treated with NMES of the biceps brachii and vastus intermedius on 1 side, using the contralateral limb as a control. Biceps thickness decreased in both limbs over the limited ultrasound study period of 8 days but were not significant (*P*-value not reported). The difference in decrease between stimulated and non-stimulated limbs also did not reach statistical significance (*P*=0.29) (Supplementary Table S2). The use of the contralateral limb may not be a reliable control as growth factors, blood supply, metabolic rate, and other unknown variables are likely not limited to the stimulated muscle alone.

DISCUSSION

Recent advances in quantitative NMUS have opened new possibilities to evaluate nerve and muscle dysfunction in critical illness, better understand the pathophysiology of ICU-AW, offer better prognostication, obtain earlier diagnosis, improve clinical guidance, and monitor the effectiveness of interventions. The body of literature to date indicates limited research has begun in this regard with emphasis on the effects of critical illness on changes in muscle mass, the effects of NMES, and initial efforts to evaluate muscle echogenicity, echotexture, and fasciculations. No studies, to our knowledge, have evaluated pathoanatomic changes in nerves using ultrasound in this population.

Importantly, the methodological underpinning of quantitative NMUS in the ICU setting does not appear to be fully established. Ensuring reproducibility of data and outcomes will require further research to ensure the accuracy and reliability of ultrasound measures in critically ill populations. The ICU setting poses challenges to making reliable ultrasound measures, and it is important that these measures be evaluated not only in healthy norms, but in the critically ill. Although Puthucheary et al adequately validated 1 measure at 1 muscle site, the validation of ultrasound measures reviewed here otherwise was largely limited by small numbers of subjects or observers, repeat measures not separated significantly in time, flawed methodology, or validation in only healthy subjects. Most studies evaluated intra-rater or inter-rater validity with repeat measures conducted during the same session. No studies evaluated inter-rater reliability of muscle linear depth, echotexture, or echogenicity in the critically ill. Ideally inter-machine validity would also be established to maximize accessibility in the ICU setting.

Methodological error may be contributing to heterogeneity in muscle wasting data; some studies report increases in muscle mass and others report decreases. Technical challenges related to NMUS may be broadly considered to fall into 2 categories: machine considerations and operator considerations. Ultrasound is frequently described as an operator-dependent imaging modality, so a close examination of these factors is important.

A wide variety of ultrasound machines and transducers are available for clinical and research purposes. Most frequently, ultrasound machines available for use in the ICU setting are small portable units, and the transducers included with the machine may vary widely in frequencies, field of view, probe shape and intended use across settings. The most important factors in transducer selection are frequency and field of view. The frequencies for the clinical evaluation of neuromuscular measures ranges from approximately 2-20 MHz. Higher frequencies offer better resolution but have less tissue penetration and therefore cannot evaluate deeper structures. Lower frequencies, conversely, can visualize deeper structures but have lower resolution. Low frequency probes typically operate from 1-5 MHz, while high frequency probes typically operate from 10-15 MHz. Both may be required, depending on the depth of the structure of interest and the body habitus and volume status of the patient. The field of view varies depending roughly on the length of the transducer and the number of piezoelectric crystals in the array: a short transducer, such as may be used for establishing vascular access, may not produce a large enough field of view to accurately measure neuromuscular structures.

Operator competence and experience are also important in generating reliable and accurate ultrasound images of neuromuscular structures. If care is not taken by the operator, muscle and nerve can be compressed by transducer pressure on the skin during the study, which can alter muscle thickness and CSA measures. The angle of the probe alters apparent muscle thickness by providing an oblique view through muscle. Anisotropy, the variable reflectivity of tissues depending on the angle of approaching sound waves, is also influenced by the angle of the probe and may change the apparent echogenicity of tissue. The physics of ultrasound and the algorithms designed to interpret ultrasound waves additionally create several types of artifact which can affect ultrasound measures of nerve and muscle tissue. Due to assumptions made about the speed of sound in tissue, muscle linear thickness is

underestimated by 3%, though consistently so. Errors in image display caused by variations in beam width or common ultrasound artifacts such as reverberation, refraction, attenuation, shadowing, and mirror imaging may lead to measurement error if they are unrecognized. The protocol used to obtain images by the operator is also important for accuracy and reproducibility. If consistent landmarks are not used, large differences in muscle and nerve measurements may result. In general, the use of easily recognizable bony landmarks and a clear, standardized scanning protocol enables a high level of inter-rater reliability, even in novice sonographers.[30]

Obtaining reliable quantitative ultrasound measures in the ICU setting poses additional challenges. The positioning needs of the patient, inability of many patients to participate in the study, and presence of ventilators, monitors, and central and peripheral lines all limit the potential study sites and introduce variables which make reliable repeat measures challenging. Ideally, study sites should be selected which maximize ease of study, reliability of measures, and the comfort and medical needs of the patient. Volume status could potentially interfere with obtaining reliable repeated measures, as critically ill patients frequently have tissue edema that influences the depth of subcutaneous tissue. This may require lowering ultrasound frequency to achieve required depth, potentially altering the characterization of nerve and muscle measures. Additionally, there is sometimes so much edema that it alters surface anatomy and makes it difficult to ensure repeat measures are conducted at the same study site. In order to ensure measures are representative of the actual nerve and muscle changes occurring in the critically ill populations, more efforts should be made to establish protocols which can be repeated with confidence by different operators, machines, and points in time. These protocols could use detailed limb positioning, clear landmarks, and techniques to reduce tissue compressibility (such as stand-off pads) to decrease the chance of operator-dependent measurement error.

Once consistent and reproducible protocols and measures in the critically ill population are established, quantitative ultrasound can be utilized as a biomarker for evaluation of diagnostic or therapeutic neuromuscular interventions. For example, conducting parallel electrophysiologic measures and muscle biopsies could determine if changes seen on ultrasound were predictive of critical illness myopathy or critical illness polyneuropathy. Additionally, ultrasound findings may show correlation with meaningful clinical and health care utilization metrics such as length of hospital stay, duration of mechanical ventilation, mortality, and discharge disposition. Given the high rate of functional impairments seen in survivors of critical illness, correlation with functional, patient-centered outcomes such as the Short Form-36 or 6-minute walk test may hold the most utility of all. With appropriate substantiation, ultrasound measures of muscle and nerve could be routinely monitored in the ICU to guide interventions such as NMES and therapies to maximize functional outcomes. Eventually, studies using ultrasound measures as disease correlates could be designed to evaluate the effects of interventions in the setting of critical illness.

CONCLUSIONS

Neuromuscular dysfunction is increasingly recognized as a contributor to morbidity and loss of function in critically ill populations. Detection of nerve and muscle changes early in the

course of illness will aid in our understanding of the biology and pathophysiology of ICU-AW ,speed diagnosis, improve prognostication, and guide and monitor early interventions. Quantitative NMUS offers a potential solution with advantages suited to critically ill populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support:

Catherine Hough and Aaron Bunnell, MD

R01 HL096504 (Hough, PI) 04/01/10 – 03/31/15

NIH/NHLBI

Project title: “ICU-Acquired Neuromuscular Dysfunction and Outcomes in Acute Lung Injury”

Abbreviations

CSA	Cross Sectional Area
CSD	Cross Sectional Diameter
CV	Coefficient of Variation
DXA	Dual-energy X-ray Absorptiometry
ICC	Intra-class Correlation Coefficient
ICU	Intensive Care Unit
ICU-AW	Intensive Care Unit Acquired Weakness
MAC	Mid-upper Arm Circumference
NMES	Neuromuscular Electrical Stimulation
NMUS	Neuromuscular Ultrasound

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TABLE I

VALIDATION OF ULTRASOUND PROTOCOLS

		Methods							Results		
		Rater	Subjects		Observations						
Article	**Measure**	**n**	**n**	**Type**	**Type**	**n**	**Independ. / Blinded**	**Interval between measu res**	**Statistical Analysis**	**Est. of Reliability**	**Methodologic Assessment**
Campbell 1995	LD	1 5	8 1	Healthy NR	Intra Inter	NR NR	N/A NR	Daily × 5 day NR	CV CV	1.5 - 2.9 % 1.9 - 4.5°%	Poor Poor
Moukas 2002	LD	NR	NR	Critically Ill	Intra	3	N/A	NR	CV	<2.0%	Unclear
Reid 2004	LD	1	30	Healthy	NR	3	NR	Daily × 3 days	CV	2.5 - 4.3 %	Poor
Gruther 2008	MLD	1	NR	Critically Ill	Intra	2	N/A	NR	CV	< 1.3%	Unclear
Gruther 2010	MLD	1	33	Critically Ill	Intra	NR	N/A	NR	CV	0.25%	Poor
Baldwin 2011	LD	NR	13	Healthy	Intra	2	N/A	NR	ICC	0.985 - 1.0	Fair
Puthucheary 2013	CSA	2	21	Critically Ill	Intra	3	Both	Consecutive	CC Bias	R^2 = 0.97 Bias = 7mm^2	Excellent
Grimm 2013	IE	NR	NR	Critically Ill	Intra Inter	NR NR	N/A NR	NR NR	ICC ICC	0.915 0.972	Unclear Unclear
Baldwin 2014	LD LD	NR NR	16 16	Critically Ill Healthy	Intra Intra	3 3	N/A N/A	Consecutive Consecutive	ICC ICC	0.976 NR	Fair Unclear

Full table results given in Supplementary Table S1

Reid 2008, Gerovasili 2009, Cartwright 2012, Rodriquez 2012 do not report independent validation of reliability.

LD = Linear Depth, MLD = Mean Linear Depth, CSA = Cross Sectional Area, IE = Interimage echogenicity, N/A=Not Applicable NR = Not reported Intra = Intra-rater, Inter = Inter-rater