Introduction

Critical illness results in intensive care unit-acquired weakness (ICUAW), especially in patients with a protracted course of disease.(1, 2) ICUAW is associated with prolonged mechanical ventilation, longer ICU and hospital stay and increased mortality. In the longer-term, it also impairs rehabilitation and recovery to fully functional autonomy, leading to poor quality of life.(1, 3, 4)

ICUAW already starts within the first week of critical illness and is associated with this functional disability in the longer term. The ICUAW is the result of a combination of critical illness polyneuropathy and critical illness myopathy. Skeletal muscle wasting is the most typical clinical feature of ICUAW and stems from muscle atrophy. Therapeutic interventions are limited to early mobilization, blood glucose control and limiting the use of glucocorticoids and neuromuscular blocking agents.(5, 6)

Due to the lack of therapeutic options and the important long-term consequences of ICUAW and muscle wasting, their early detection may be essential to steer risk stratification and preventative measures. Assessment of limb muscle strength by functional, volitional measurements, such as the Medical Research Council (MRC)-sum score and handgrip strength, appears to be the gold standard. However, only fully awake and cooperative patients can undergo these measurements, potentially causing a delay in the diagnosis of ICUAW.(7) Therefore, non-volitional muscle strength measurements, such as an electromyogram to detect critical illness polyneuropathy and myopathy, have been used for the early screening for ICUAW. However, this technique is complex, requiring expert's interpretation.(2, 8)

Ultrasound measurements of muscle thickness are also considered to be a non-volitional surrogate for muscle strength.(9) The use of ultrasonography is well integrated in daily ICU-practice. In comparison with computer tomography (CT) and magnetic resonance imaging (MRI), ultrasound measurements of muscle thickness are inexpensive and logistically less cumbersome. When using a strict imaging protocol, the ultrasound measurements correlate well with the CT and MRI measurements.(7, 10, 11) In adult critically ill patients ultrasound measurements of m. quadriceps femoris muscle thickness were sensitive to detect a decrease in muscle mass in patients with a prolonged ICU-stay.(9) In a recent prospective, ultrasonographical evaluation of muscle wasting in critically ill patients, rectus femoris cross-sectional area was decreased by approximately 18% at day 10.(12) The recent paper of Tilluist et al. highlighted the reliability of bedside ultrasound in assessing muscle thickness in healthy volunteers.(13) However ICUAW is poorly characterized in children, with only case reports as evidence(14, 15). Neither the functional, volitional measurements of muscle strength nor the non-volitional measurements of muscle mass, such as ultrasonography have been validated in the pediatric critically ill patient population. Additionally, ultrasonographical measurements of muscle mass are harder to standardize due to the age-dependency of muscle mass.

In this study we therefore aimed to assess the reliability and accuracy of ultrasound measurements of muscle thickness during critical illness as a function of age, covering the spectrum from neonates to adults. The inter-observer and intra-observer variability were assessed in relation to a predefined decrease in muscle thickness (3).

Methods

Study Design and Population

This prospective observational study in a level III paediatric and adult ICU ran from October 2013 to June 2014 and was part of the PEPaNIC randomized controlled trial (clinicaltrials.gov number: NCT01536275). The study was approved by the ethics committee of the University Hospitals Leuven. Study patients were admitted to the ICU for various reasons such as cardiac surgery, respiratory failure and sepsis. Patients were only included when they were sedated, as a correct position is crucial for optimal scanning. Ultrasonography was performed during the first week of admission, to exclude patients with protracted critical illness. Patients with severe muscle disorders, severe edema, localized inflammation, fractures in the limb femoral lines or were on muscle relaxants were also excluded.

Ultrasonography Protocol

A linear array commercial real time ultrasound scanner (Vivid S6, GE Healthcare, Diegem, Belgium) was used with a 12-MHz transducer. Ultrasonographic images were collected from a transversal scan of the thigh with the patient in supine position, the knee extended and the muscle relaxed. The transducer was placed perpendicular to the long axis of the tight on three fifths of the distance from the anterior superior iliac spine to the superior patellar border. This position was defined beforehand with a surgical skin marker (Devon Surgical Skin Marker, Covidien, Mechelen, Belgium) after measuring the exact position with a tape measure.

An excess of contact gel was applied to minimize image distortion. By obtaining maximal reflection of the bone, optimal transducer orientation was achieved and oblique scanning was

minimized. A staff member of the department of radiology extensively trained the two independent researchers (TF, AH) to perform these measurements correctly and individually. All images were analyzed directly on the ultrasound scanner (Figure 1). Muscle thickness was defined as the distance between the superior border of the muscle and the cortex of the femur. Each limb of the patient was measured two times by the two investigators, independently of each other.

Statistical Analysis

The coefficient of variation was calculated for duplicate measurements. In the linear regression analysis (Pearson correlation coefficient), results are represented with R^2. In the Bland-Altman test the 95% limit of agreement, defined as ± 1.96 Standard Deviation (SD) of the means of the non-absolute differences between the paired measurements by the two observers were represented. Further the absolute differences, i.e. independent of the sign of the difference (both positive and negative values), was computed. Reliability was assessed by the intraclass correlation coefficient (ICC), using a model for 2-way random single measures (consistency). Reliability is higher when the ICC is closer to 1.0. A p-value of less than 0.05 was deemed statistically significant. For the statistical analyses Matlab (R2012a The MathWorks Inc, Natick, MA, USA) was used.

Results

Pediatric group

A group of 30 patients were included in the study. The patients' demographics are shown in table 1. In one child the measurement could not be done because of a central venous line in the femoral vein. The coefficient of variation of duplicate measurements (n=105) was 4.51% for operator 1 and 5.1% for operator 2. The coefficient of determination (R^2) was 0.94 ($p<0.0001$). The average muscle thickness was 1.67 cm (SD: 0.55 cm) as shown in table 2. The absolute intra-observer variability, as expressed by the limits of agreement (± 1.96 SD, containing 95% of the samples for normally distributed samples), was 0.42 cm for operator 1 and 0.45 cm for operator 2. Both distributions of the non-absolute differences are visualized in a Bland-Altman plot in Figure 2. The median absolute inter-observer variability was 0.07 cm [IQR 0.032 – 0.19 cm]. The intraclass correlation coefficient between the two observers covering measurements was 0.98 for single measures.

Adult Group

A group of 14 patients were included in the study. The patients demographics are shown in table 1. The coefficient of variation of duplicate measurements (n=86) was 1.91% for operator 1 and 1.32% operator 2. The coefficient of determination (R^2) was 0.99 ($p<0.0001$). The average muscle thickness was 2.10 cm (SD: 0.85 cm) as shown in table 3. The absolute intra-observer variability, as expressed by the limits of agreement (± 1.96 SD, containing 95% of the samples for normally distributed samples), was 0.33cm for operator 1 and 0.12 cm for operator 2. Both

distributions of the non-absolute differences are visualized in a Bland-Altman plot in Figure 3. The median absolute inter-observer variability was 0.05 cm [IQR 0.03 – 0.09 cm]. The intraclass correlation coefficient between the two observers covering 86 measurements was 0.99 for single measures.

The intra-observer 95% CI of ultrasound measurement of muscle thickness is greater than the predefined 20 % decrease in the average muscle thickness in our pediatric ICU population.(3) In adult critically ill patients the intra-observer 95% CI of the ultrasound measurements (0.22 cm) is well below the predefined decrease in muscle thickness. The accuracy in relation to the predefined decrease in muscle thickness is shown in table 5. The 95 % CI Bland- Altman is the average of both absolute intra observer variability as the sign of the differences is not clinical relevant.

Discussion

Ultrasonographical measurement of muscle thickness in critically ill children can easily be done in sedated critically ill children and adults with low inter-observer variability. However, the moderate accuracy and high intra-observer variability do not allow reliably detecting a decrease in muscle thickness in the pediatric ICU population.

In adult critically ill patients, the measurement of the thickness of the M. quadriceps femoris with ultrasound may be a good indicator of muscle wasting (16). Dubowitz and Heckmatt showed that ultrasonography may be useful in children in the diagnosis of neuromuscular diseases (17, 18). Little data is available about ICUAW and muscle wasting in pediatric critical illness. The incidence may be lower as their risk factors, multiple organ failure and protracted critical illness, are less common (3). Parenteral nutrition, supplementing insufficient enteral nutrition, as often administered to prevent muscle wasting in critically ill children. However in adult critical ill patients it has been recognized that aggressive nutritional therapy does not prevent loss of lean body mass and leads to increase of adipose tissue (19, 20). In critically ill children no large clinical trials have looked at the impact of PN on patient centre outcome (21). One study suggest that even 6 months after a burn injury muscle protein deposition cannot be improved by amino acid infusions (22).

Alongside the PEPaNIC randomized controlled trial, in which early versus late initiation of parenteral nutrition is compared in critically ill children, this study assessed the accuracy and reliability of ultrasound measurements of muscle thickness to detect muscle wasting. Similar measurements were done in critically ill adults, as more data are available in this population.

In our pediatric population the inter-observer variability is acceptable and comparable to the measurements in the adult population. However, the intra-observer variability was much larger in the pediatric than in the adult population. When taking into account the predefined decreases of muscle thickness, ultrasound measurements of muscle thickness may only be just accurate and reliable enough in the adult population.

This may explain why rectus femoris muscle thickness, assessed by ultrasound, did not decrease over time (1, 23). There are ample reasons to explain this high intra operator variability: slight changes in angle, alteration in application of pressure and the presence of edema in critically ill patient. These pitfalls for inappropriate accuracy can only be compensated by rigorous training of the examiners and strict standardization of the ultrasound settings and protocol.

Our measurements correlate with the results in the recent paper of Tillquist et al and highlight the accuracy of and reliability of ultrasonography in muscle thickness assessment by different observers.(13) The differences in reliability between the operators in this paper and the latter might be correlated with the study population. The majority of the study patients in this study were in ICU for a longer time upon muscle thickness assessment. Certainly, more studies, that cover a wide range of critically ill patients regarding their severity of disease but also their baseline muscle mass, need to be done to confirm the potential of ultrasound measurement of muscle thickness in critically ill adults.

Instead of muscle thickness as a marker, ultrasound assessment of muscle echogenicity and the measurement of the cross-sectional area of the muscle may be promising alternatives (3,8). However all these surrogate markers of ICUAW need to be validated against patient centered functional outcomes. Quantification of muscle mass by CT-scan, with an inter-observer CV of 0%

and an ICC of 0.998, appears to be much more reliable than ultrasound measurements (20). However, the risks associated with CT-scanning currently do not outweigh the benefit of an early detection of a rather limited (10-30%) loss in muscle mass without the prospect of treatments for muscle wasting. These risks of CT scanning encompass patient instability during transportation but also secondary malignancies in the long run(24).

This study has several limitations though. First, no serial assessments of muscle thickness were done to evaluate the decrease in muscle thickness over time. Instead we tested the ultrasound measurements against predefined values, based on the literature, as it is impossible to predict the length of stay in the ICU. Second, the ultrasound measurements of muscle thickness were neither compared with muscle cross-sectional area or echogenicity, nor with functional markers, such as handgrip strength or MRC-SUM. Third, we mainly included newborns and young children, since this represents the vast majority of critically ill children in tertiary referral pediatric ICUs. As muscle mass increases with the bodyweight (25), it can be hypothesized that from a certain body weight onwards the intra-observer variability may become acceptable.

In conclusion, ultrasonographical assessment of muscle thickness is hampered by high intra-observer variability. It may be used in critically ill adults to evaluate muscle wasting. However, its low accuracy and reliability, in light of the small drop in muscle thickness to be detected, make it unsuitable for the pediatric ICU population. Further standardization of the ultrasound protocols may improve its performance.

Conflicts of interest

The authors declare no conflict of interest.

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