



## Review

# Respiratory and Peripheral Muscle Assessment in the Intensive Care Unit<sup>☆</sup>

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## ABSTRACT

Atrophy and weakness of the respiratory and peripheral muscles is a common problem in the intensive care unit (ICU). It is difficult to diagnose, particularly in the early stages of critical disease. Consequently, many cases are detected only in advanced stages, for example, when difficulties in mechanical ventilation weaning are encountered. The aim of this review is to describe the main tools that are currently available for evaluation of peripheral and respiratory muscles in the ICU. Techniques of varying complexity and specificity are discussed, and particular emphasis is placed on those with greater relevance in daily clinical practice, such as ultrasound.

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## Evaluación muscular respiratoria y periférica en la Unidad de Cuidados Intensivos

### RESUMEN

La atrofia y la debilidad de los músculos respiratorios y periféricos son un problema frecuente en las Unidades de Cuidados Intensivos (UCI). Su diagnóstico es dificultoso, especialmente en las primeras etapas de la enfermedad crítica. Esto determina que en muchos casos no sea detectada hasta etapas avanzadas, por ejemplo, frente a dificultad para la desvinculación de la asistencia ventilatoria mecánica. El objetivo de esta revisión es describir las principales herramientas con las que contamos actualmente para la evaluación muscular en la UCI, tanto periférica como respiratoria. Se mencionan técnicas con distinto grado de complejidad y especificidad, haciendo particular hincapié en aquellas con mayor aplicabilidad en la práctica clínica diaria, como la ecografía.

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## Introduction

Many patients admitted to the intensive care unit (ICU) develop wasting and weakness of the peripheral and respiratory muscles.<sup>1,2</sup> This impacts negatively on morbidity and mortality during hospitalization and after discharge, and is associated with difficulty in

weaning from mechanical ventilation (MV), longer stays in the ICU, and increased short and long-term mortality.<sup>3–14</sup>

Myopathy is the product of a combination of contractile dysfunction and muscle atrophy, and its pathophysiology in the critically ill patient is complex.<sup>15</sup> Contractile dysfunction (decreased intrinsic capacity of the muscle to produce force) may be caused by the combined action of a number of factors, such as mitochondrial dysfunction, oxidative stress, excitation–contraction disorders, and membrane potential.<sup>15</sup> Wasting (decreased muscle mass and myofiber size) is the result of an imbalance between the synthesis and degradation of proteins, in favor of the latter, due mainly to activation of the ubiquitin–proteasome system.<sup>16</sup> The clinical manifestations are, therefore, a result of decreased muscle mass and strength.

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Diagnosis and follow-up of muscle impairment can be difficult in critically ill patients. The aim of this narrative review is to summarize the main methods available for the functional and structural assessment of the peripheral and respiratory muscles in the ICU.

## Respiratory Muscles

Respiratory muscles are routinely not assessed in general, so diagnosis of diaphragmatic dysfunction is delayed until difficulties are encountered in weaning the patient from MV.<sup>17,18</sup> We will review below the main techniques for assessing respiratory muscles in critically ill patients.

### Maximum Inspiratory Pressure

Maximum inspiratory pressure (MIP) provides a useful overall assessment of inspiratory force.<sup>19</sup> MIP is the maximum negative pressure generated during an inspiratory effort against an occluded airway.<sup>20</sup> This technique requires patient collaboration, so higher values rule out significant weakness, but low values may reflect muscle weakness, an inefficient technique, or inadequate effort.<sup>17</sup> If the patient cannot cooperate, the maneuver can be carried out with a 1-way valve that allows expiration but not inspiration, obtaining MIP in a 20–25 s period.<sup>17</sup> Values of less than  $-30$  cmH<sub>2</sub>O show high sensitivity (but low specificity) for predicting failure to wean from MV.<sup>21</sup>

Another measurement, in addition to MIP, is sniff nasal inspiratory pressure (SNIP).<sup>19,22</sup> SNIP consists of a voluntary inspiratory maneuver, in the form of a short, rapid inhalation through a patent nostril. SNIP is a simple and reproducible measurement for evaluating inspiratory muscle strength. Moreover, the sniff nasal maneuver can be used to assess muscle function in association with other techniques, such as transdiaphragmatic pressure (Pdi) or ultrasonography. In critically ill patients, the feasibility of the SNIP is usually determined by the presence of an artificial airway.

### Esophageal And Transdiaphragmatic Pressures

Simultaneous recording of esophageal (Pes) and gastric (Pga) pressure can be used to calculate Pdi ( $Pdi = Pes - Pga$ ), a specific measurement of diaphragmatic force.<sup>17,19</sup> Pdi can be measured during quiet breathing or during voluntary maximum inspiratory (Pdi<sub>max</sub>) or nasal sniff (Pdi<sub>sn</sub>) maneuvers. The Gilbert index ( $\Delta Pga / \Delta Idps$ ) can be used to determine the contribution of the diaphragm to the total inspiratory effort (a higher score indicates greater contribution).<sup>19</sup> Other parameters, such as the pressure–time product (PTP) and tension–time index (TTI) can be used to estimate the energy expenditure of the diaphragm, although this analysis is complex.<sup>17</sup> PTP is the integration of respiratory pressure over time, normalized on the basis of maximum pressure in the case of TTI.<sup>23</sup> Its use is generally reserved for the field of research.<sup>17</sup>

Twitch, the electrical or magnetic stimulation of the phrenic nerve, is a technique used to measure Pdi<sub>max</sub> without the collaboration of the patient (Pdi<sub>tw</sub>).<sup>19,22,24</sup> In fact, Pdi<sub>tw</sub> determined by bilateral anterior phrenic nerve magnetic stimulation can be considered the gold standard for evaluating diaphragmatic strength in the ICU.<sup>19,24</sup> As an alternative to Pdi, pressure recorded at the end of the tracheal tube after phrenic nerve stimulation (Ptr<sub>tw</sub>) can be used as a parameter of diaphragmatic strength, without the need for catheters for recording Pes and PGA.<sup>25</sup> Values of PDI<sub>tw</sub> < 10 cmH<sub>2</sub>O or Ptr<sub>tw</sub> < 11 cmH<sub>2</sub>O are parameters of diaphragmatic weakness in critical patients.<sup>6,7,19</sup> Reduced PIM, Pdi<sub>tw</sub>, and PTR<sub>tw</sub> have been associated with difficulty in MV weaning and increased mortality.<sup>5–8,26</sup>

## Occlusion Pressure

The negative pressure generated during the first 100 ms of a quiet inspiration against an occluded airway (P<sub>0,1</sub>) can be used to assess central ventilatory stimulus.<sup>19,20</sup> High values of P<sub>0,1</sub> indicate an increased central stimulus, while low values of P<sub>0,1</sub> can be due not only to a reduced neuromuscular impulse, but also to nerve conduction problems, muscle weakness or fatigue.<sup>19</sup> It has been used in patients receiving MV as a parameter for predicting success in weaning. P<sub>0,1</sub> values  $\geq 6$  cmH<sub>2</sub>O predict weaning failure, while P<sub>0,1</sub>  $\leq 4$  cmH<sub>2</sub>O is considered favorable.<sup>19</sup> However, very low values (< 0.5 cmH<sub>2</sub>O) may represent a reduced central impulse that is insufficient to achieve weaning.<sup>20</sup>

### Electrophysiological Studies: Electromyography And Stimulation Test

Electromyography (EMG) is used to study muscular activity by recording action potentials.<sup>22</sup> Diaphragmatic EMG can be obtained from surface, esophageal or intramuscular electrodes.<sup>19</sup> Nasogastric feeding tubes with embedded esophageal electrodes (Maquet, Sweden) can be used to obtain a continuous processed signal called “diaphragmatic electrical activity” (EAdi).<sup>17</sup> Stimulation tests can be used to assess the efficiency of nerve and neuromuscular transmission with diaphragmatic electromyographic recording after phrenic nerve stimulation.<sup>19</sup>

### Diaphragm Ultrasonography

Diaphragm ultrasonography, available in most ICUs, is a non-invasive technique that can be used to monitor diaphragm dysfunction at the patient's bedside. Ultrasonography can assess the diaphragmatic mass using static measures such as diaphragm thickness (Tdi), and functional aspects can be evaluated with proactive measures such as thickness fraction (TFdi) or diaphragmatic excursion (Edi).<sup>27,28</sup>

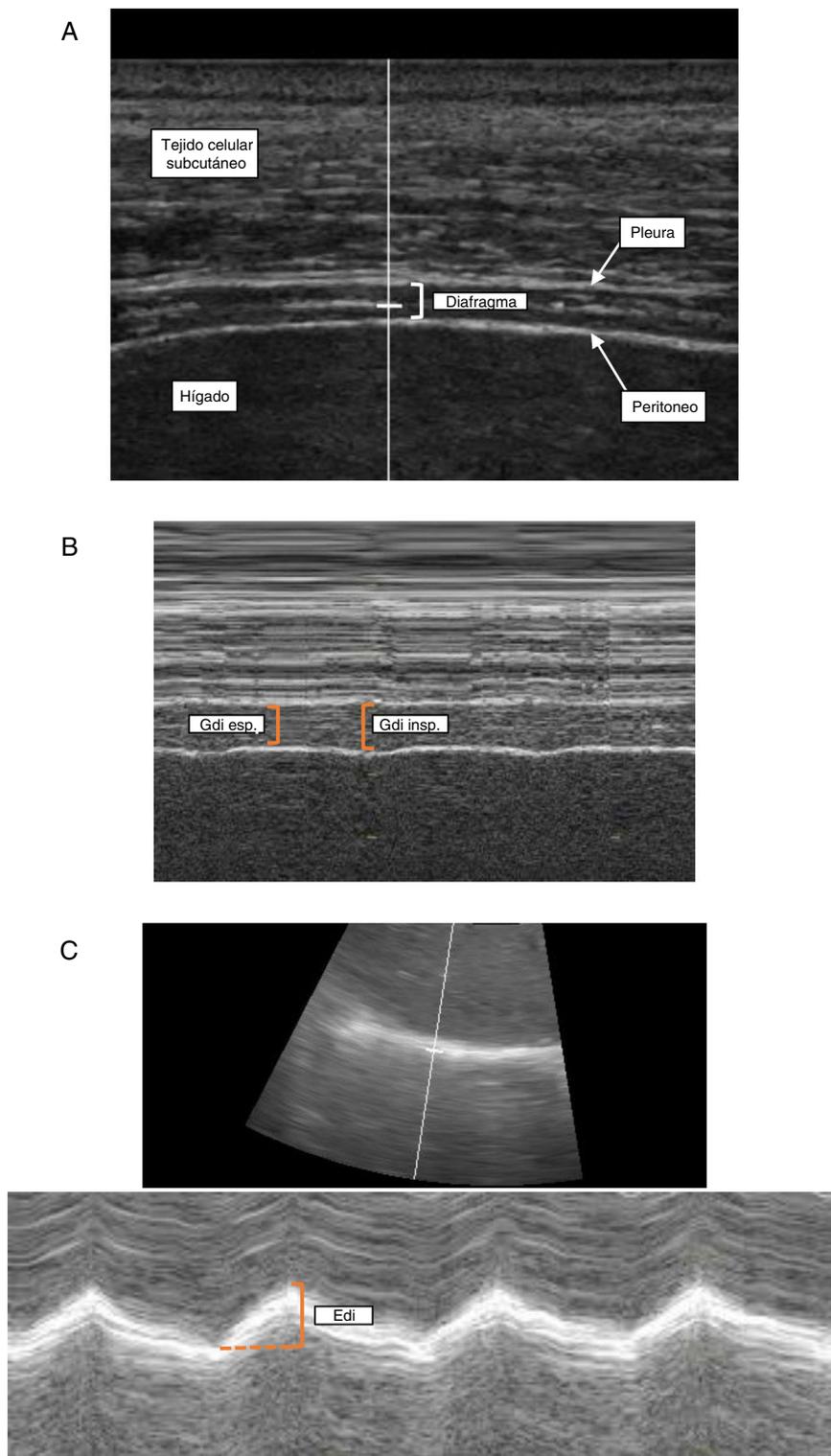
This technique can be used in most critical patients, and has excellent intra- and inter-observer reproducibility.<sup>27</sup> Although ultrasound evaluation can be performed both in the right and left hemidiaphragms, the left side presents greater technical complexity, making it more difficult to visualize in certain patients and reducing the reproducibility of the test.<sup>29</sup>

### Diaphragm Thickness

Determining Tdi by ultrasound allows an assessment of the muscle mass that correlates very well with the direct measurement of muscle thickness on autopsy.<sup>30,31</sup> Tdi is measured at the end of a passive expiration, that is to say, at functional residual capacity (FRC). In healthy adults, the average values of Tdi range between  $1.7 \pm 0.4$  and  $3.3 \pm 1.0$  mm.<sup>30,32–36</sup> In critically ill patients receiving MV, values of between  $1.3 \pm 0.3$  and  $2.4 \pm 0.8$  mm have been reported.<sup>29,37</sup>

It is difficult to establish a cut-off point below which the diaphragm can be considered to be atrophied. However, performing serial ultrasounds after initiating MV can reveal an early, progressive decline in Tdi during the stay in the ICU.<sup>37–40</sup> However, the determination of Tdi as a static measurement has not proved useful as a parameter for predicting success in weaning from MV.<sup>14,41–43</sup>

**Technique.** The measurement of Tdi with ultrasound is performed in the right hemidiaphragm at the level of the zone of apposition. The zone of apposition is the area of the chest wall where the abdominal contents meet the lower rib cage, between the 8th and 10th intercostal space, at the level of the mid axillary line. With the patient supine ( $30$ – $45^\circ$ ), a high-frequency linear transducer ( $\geq 10$  MHz) is placed parallel to the intercostal space and perpendicular to the skin.<sup>27</sup> It is first used in 2-dimensional



**Fig. 1.** Diaphragmatic ultrasonography. Determination of diaphragm thickness in the zone of apposition with the chest wall in B-mode (A) and M-mode (B) and evaluation of diaphragmatic excursion (C). Edi: diaphragmatic excursion; Gdi esp: expiratory diaphragm thickness; Gdi insp: inspiratory diaphragm thickness; Tejido celular subcutáneo: subcutaneous cellular tissue; Hígado: liver; Diafragma: diaphragm; Pleura: pleura; Peritoneo: peritoneum.

mode (mode B) to obtain the best view and to select the scan line (Fig. 1A). In this area, the diaphragm is identified as a structure formed of 3 parallel layers (approximately 1.5–3.0 cm deep): a hypoechoic central layer (the diaphragm itself) demarcated by 2 hyperechoic layers (the peritoneum and parietal pleura).<sup>44</sup> The pulmonary artifact (corresponding to the costophrenic angle) can also be seen to erase the image of the diaphragm during inspiration.<sup>36</sup>

Keeping the transducer in position, M mode is used to determine Tdi, corresponding to the distance between both hyperechoic layers, measured approximately 2 cm from the costophrenic angle (Fig. 1B). As mentioned previously, Tdi is measured at the end of the passive expiration phase. However, determining Tdi during different stages of the respiratory cycle is useful for evaluating functional parameters such as TFdi.

### Diaphragmatic Thickness Fraction

During spontaneous ventilation, lung volume increases as the diaphragm contracts, shortens, and increases in thickness.<sup>30,45</sup> Diaphragmatic thickening during inspiration is a parameter of the contractile activity of the diaphragm and its ability to generate pressure.<sup>27,40,45</sup> This can be assessed on ultrasonography by measuring TFdi, which corresponds to the percentage of change in Tdi between the end of passive expiration and the end of inspiration (maximal inspiratory effort in spontaneous ventilation, or if that is not possible, inspiratory peak during MV).<sup>40</sup>

$$\text{TFdi} = \frac{\text{Inspiratory Tdi} - \text{Expiratory Tdi}}{\text{Expiratory Tdi}} \times 100$$

TFdi has shown good correlation with inspiratory muscle function parameters such as MIP, SNIP, Pdi, PTP and EAdi.<sup>29,34,42,45–47</sup>

In patients receiving MV, TFdi decreases progressively as the level of ventilatory support increases, becoming minimal in controlled ventilation with neuromuscular blockade.<sup>29,34,37</sup> In other words, the more work of breathing generated by the diaphragm, the greater the TFdi. The same technique could be used to monitor diaphragmatic activity during MV.<sup>37</sup> Goligher et al. showed that low levels of TFdi are associated with greater diaphragmatic wasting (decreased Tdi) in patients on MV.<sup>40</sup> The presence of reduced TFdi has been associated with failure to extubate, difficulty in weaning from MV, and prolonged ICU stay.<sup>9,14,41</sup> Although it is difficult to establish cut-off points, various studies have used TFdi values of between 20% and 36% to define the presence of diaphragmatic dysfunction.<sup>4,9,41,42</sup>

**Technique.** The determination of TFdi requires the measurement of Tdi at the end of the expiration phase and at the end of inspiration. In practical terms, this corresponds to minimum and maximum values, respectively, while measuring Tdi in M mode (Fig. 1B).<sup>27,29</sup>

### Diaphragm Excursion

Edi is another dynamic parameter that can provide information about the diaphragm. It is determined by visualizing and measuring the cephalocaudal shift of the dome of the diaphragm between expiration and inspiration. In individuals with spontaneous ventilation, Edi can be assessed in quiet breathing, deep inspiration and with a sniff nasal maneuver (in all cases at FRC). Edi during a deep inspiration correlates with MIP, SNIP, forced vital capacity and forced expiratory volume in 1 s.<sup>46,48</sup> According to the largest series reported in healthy volunteers, Edi is somewhat greater in men than in women: 1.8±0.3 cm vs 1.6±0.3 cm in quiet breathing, and 7.0±1.1 cm vs 5.7±1.0 cm in deep inspiration, respectively.<sup>48</sup> Similar values have been found in other studies.<sup>46,49,50</sup> In spontaneous ventilation, a decreased range of motion indicates diaphragmatic weakness, while the absence of movement or paradoxical movement is an indicator of diaphragmatic paralysis.<sup>50,51</sup> However, in patients receiving MV, Edi is a product not only of muscle contraction, but also of passive movement caused by ventilatory support.<sup>44</sup> As such, it has not been possible to correlate Edi with other parameters of diaphragmatic function in patients receiving MV.<sup>47</sup> However, Edi (less than 1.0–1.1 cm in quiet breathing) has been shown to be useful for predicting the failure of extubation when performed in patients during a spontaneous ventilation trial.<sup>3,52,53</sup>

**Technique.** With the patient sitting at a 30–45° angle, a convex transducer (3.5–5 MHz) is applied at the right subcostal level between the clavicular line and the anterior axillary line.<sup>27,48</sup> The transducer is moved in a medial, cephalic and dorsal direction, so that the ultrasonic beam reaches the posterior third of hemidiaphragm in a perpendicular position.<sup>44</sup> It is first used in mode B to obtain the best view and to select the scan line. In this mode, the diaphragm is identified as a hyperechoic line directly associated with the liver below and the pulmonary parenchyma above. Once the structures are identified in B-mode, the scan line is used

**Table 1**

MRC Scale for Manual Muscle Testing.

Grade 0	No visible or palpable contraction
Grade 1	Flicker or trace of contraction, no limb movement
Grade 2	Movement with gravity eliminated
Grade 3	Movement against gravity over almost full range of motion
Grade 4	Movement against moderate resistance
Grade 5	Movement against complete resistance (normal power)

MRC: Medical Research Council.

in the most perpendicular position possible to the diaphragm and the M-mode is activated, in order to evaluate the movement of anatomical structures along the selected line (Fig. 1C). Edi will be measured as the diaphragmatic shift from the end of the expiration phase until the end of inspiration. This technique can also be used to determine other parameters, such as speed of contraction and relaxation (cm/s), inspiratory and expiratory times, and total duration of the cycle.<sup>27,49</sup>

### Peripheral Muscles

Peripheral muscle strength in the ICU can be studied with Medical Research Council (MRC) manual muscle testing or manual prehension dynamometry. Both methods require the collaboration of the patient, so their use during the early stages of critical disease is usually limited. It is at this stage that muscle impairment begins to develop, so other methods are needed for early detection.<sup>54</sup> In this respect, electrophysiology and ultrasonography may provide information on structural and functional alterations before the weakness becomes clinically evident.

#### Manual Muscle Testing

The overall assessment of strength using MRC manual muscle testing is currently the gold standard for the diagnosis of ICU-acquired weakness (ICUAW).<sup>55</sup> The MRC scale evaluates the strength of 3 muscle groups in each upper and lower limb, assigning a value to each muscle group of between 0 (paralysis) and 5 (normal strength), and a total value of 0 to 60 (Table 1).<sup>56</sup> The evaluation is carried out using certain standardized maneuvers (Table 2).<sup>57</sup>

An MRC score <48 (average of <4 in the muscle groups evaluated) is considered diagnostic of ICUAW.<sup>55,58</sup> The need for the patient to be awake and collaborative is the first limiting factor for its use. Moreover, reported interobserver variability has been variable.<sup>59–61</sup> However, an MRC score of <48 is associated with difficulty in weaning from MV, increased length of ICU and hospital, stay and higher costs and mortality.<sup>11,12</sup>

#### Manual Prehension Dynamometry

Manual prehension dynamometry has proved to be a useful tool for the study of muscle strength in the ICU. This technique has very good interobserver reproducibility.<sup>59,62–64</sup> To carry out the maneuver, the patient must have an MRC ≥3 in elbow flexion and wrist extension. While there are reference values for healthy individuals, values of grip strength (in the dominant hand) <11 kg for men and <7 kg for women have been used in critical patients to define ICUAW.<sup>11,65</sup> Muscle weakness diagnosed by this method has been associated with difficulty in MV weaning, extended ICU stay, and greater in-hospital mortality.<sup>11,13</sup>

#### Electrophysiological Studies

Electrophysiological assessment includes the study of nerve conduction, EMG, and the study of the neuromuscular junction.<sup>58,66</sup> It can help determine if weakness is caused by muscle or nervous

**Table 2**  
Manual Muscle Assessment Protocol (MRC) in the ICU.

Movement	Procedure
Shoulder abduction	Lift the outstretched arm out from side at shoulder level. Place a hand above the elbow and the other on the shoulder, apply resistance (grade 3, 4 or 5). If grade <3, place the patient in a supine position, support the arm above the elbow and at the wrist and ask them to move it out to the side. Grade 2 is assigned if the patient moves it with gravity eliminated. If they cannot move it, palpate the deltoid muscle to distinguish between grade 1 and 0.
Elbow flexion	Forearm supinated and flexed >90°. Place a hand above the wrist and the other on the shoulder, apply resistance (grade 3, 4 or 5). If grade <3, abduct the shoulder to 90° with the arm outstretched and thumb pointing up, holding it at the height of the elbow and wrist and ask the patient to flex it. Grade 2 is assigned if they can move it with gravity eliminated. If they cannot move it, position the arm at the side, with the forearm supinated, in 45° of elbow flexion, and palpate the biceps tendon to discriminate between grade 1 and 0.
Wrist extension	Arm at the side with the elbow flexed to 90°, forearm pronated and hand extended (support the elbow). Ask the patient to extend their hand as far as possible. Place one hand on the patient's hand, distal to the wrist, the other hand holding the forearm. Apply resistance (grade 3, 4 or 5). If grade <3, the elbow is flexed to 90° with the thumb pointing upwards. Support the elbow and wrist of the patient, and ask them to extend their hand. Grade 2 is assigned if they can extend it with gravity eliminated. If they cannot move it, in the same position palpate the extensor tendons in the wrist to discriminate between grade 1 and 0.
Hip flexion	Flex the hip with the knee bent. Place a hand above the knee and the other on the hip, apply resistance (grade 3, 4 or 5). If grade <3, the patient should lie down on the side not being tested. Support the leg with one hand below the knee, maintaining alignment with the hip with the other hand. Ask the patient to bend their hip toward their chest. Grade 2 is assigned if they can extend it with gravity eliminated. If they cannot move it, place the patient in a supine position and palpate the iliopsoas tendon and ask them to flex their hip to distinguish between grade 1 and 0.
Knee extension	Extend the knee (in a sitting position). Hold the ankle with one hand to apply resistance, while placing the other under the thigh, proximal to the knee (grade 3, 4 or 5). If grade <3, the patient should lie down on the side not being tested. Support the leg with one hand under the knee and the ankle with the other. Ask the patient to straighten their leg: if they can do this with gravity, grade 2 is assigned. If they cannot move it, place the patient in a supine position and palpate the quadriceps tendon and ask them to push their knee down to distinguish between grade 1 and 0.
Ankle dorsiflexion	Patient sits with their heel on the floor (or lying, if they cannot sit up), foot in full dorsiflexion. Apply resistance with one hand on the top of the foot, holding the leg proximal to the ankle with the other (grade 3, 4 or 5). If less than grade 3 but there is partial movement against gravity, assign grade 2. If it is less than grade 2, palpate the tibialis anterior tendon to determine grade 1 or 0.

MRC: Medical Research Council; ICU: intensive care unit.

involvement or both. However, the need for equipment and specialized staff, as well as the technical difficulties inherent in critical patients (tissue edema, etc.), means that it is not readily applicable in most ICUs. Recently, the use of simplified electrophysiological studies, such as the peroneal nerve test, showed high sensitivity and specificity in the diagnosis of neuromyopathy in critical patients.<sup>67</sup>

#### Peripheral Muscle Ultrasonography

Ultrasonography has become a valuable tool for the structural assessment of peripheral muscles in the ICU, with an excellent interobserver reproducibility.<sup>68–70</sup> Numerous studies have used the thickness or cross-sectional area (CSA) of different muscle groups as a parameter of muscle mass in critically ill patients, demonstrating the progressive development of wasting during the stay in the ICU.<sup>54,71–77</sup>

Various muscles in both upper and lower limbs have been evaluated. Campbell et al. reported that the combined analysis of muscle thickness in the anterior aspect of the arm, forearm and thigh correlates most closely with lean body mass (in healthy individuals); this method has been subsequently used by several authors in critical patients.<sup>73,74,77,78</sup> A correlation between thickness or CSA and muscle strength has been described in healthy individuals and critical patients.<sup>75,77,79</sup> The association between muscle wasting and weakness has been demonstrated in septic patients, in whom a further reduction of the CSA of the quadriceps correlated with less strength at the time of ICU discharge.<sup>75</sup> However, in a recent study, a single isolated measure of muscle thickness at the time of awakening did not discriminate between patients with and without ICUAW.<sup>80</sup> Recently, Puthuchery et al. specifically compared changes in quadriceps thickness with the CSA of the rectus femoris, showing that the latter is a more sensitive and reliable measurement for assessing muscle wasting and weakness in the ICU.<sup>81</sup> Moreover, muscle echogenicity increases in critical patients, possibly due to edema, inflammation, fibrosis, fatty infiltration, or necrosis.<sup>71,78,82,83</sup> Specifically, an increase in muscle echogenicity predicts the development of myonecrosis (on histology) in the ICU.<sup>83</sup> Although an inverse correlation between echogenicity and

muscle strength has been established in non-critical patients, this association is not so evident in the ICU setting.<sup>71,78</sup>

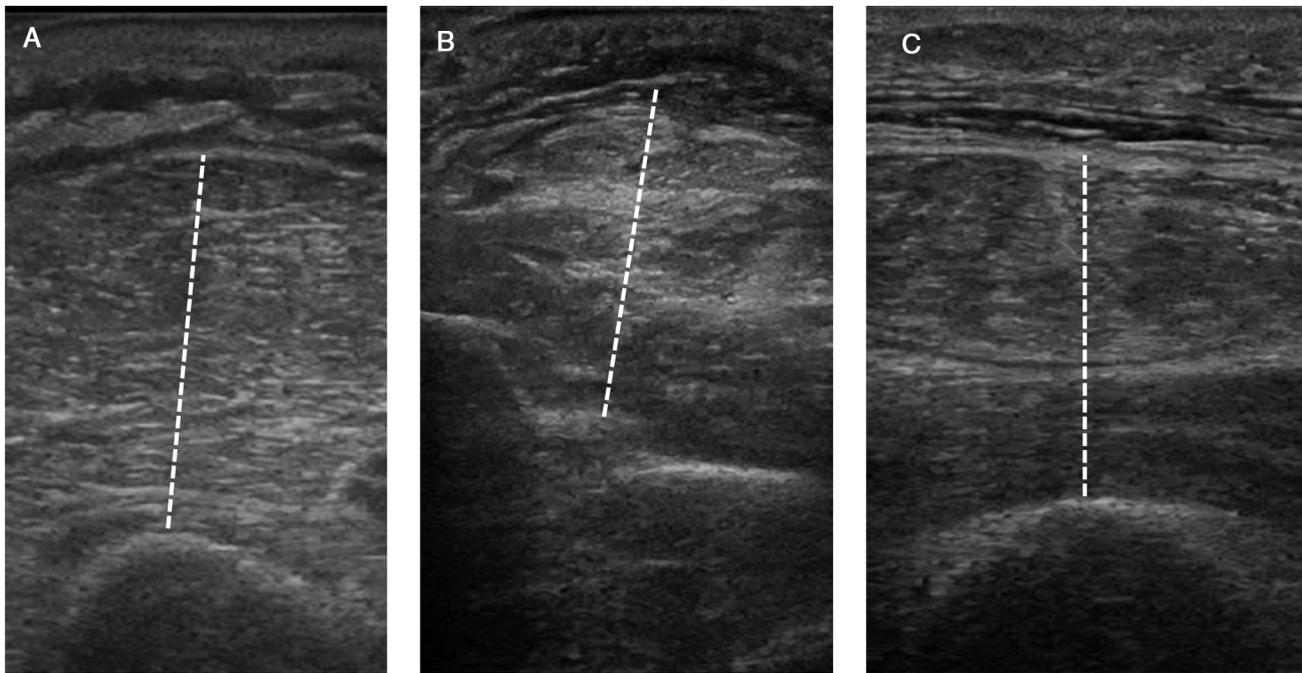
**Technique.** Several anatomical sites and technical variations have been used in the assessment of peripheral muscle, making it difficult to compare results between studies. Although reference values for muscle thickness and echogenicity have been established in healthy individuals, changes in these values over time seem to be a more valuable parameter in critical patients.<sup>84</sup> It is essential that the measurement site and position is precisely identified and standardized. It is important to avoid compression of the muscle during the procedure, so excess conductive gel must be used, and minimal pressure must be applied to the transducer when obtaining the image.

Recordings are obtained with a linear transducer ( $\geq 10$  MHz) positioned in a transverse direction, perpendicular to the underlying bone. The angle of insonation can affect the measurements, so it must be kept constant. Thickness is measured as the maximum distance between the fat–muscle interface and the bone or interosseous membrane (Fig. 2). Table 3 describes the technique for arm, forearm, and thigh.<sup>33,73,85,86</sup>

Muscle echogenicity can be evaluated semi-quantitatively (Heckmatt scale) or quantitatively using grayscale analysis.<sup>70,71,78,82,87</sup>

#### Computed Tomography

Computed tomography (CT) is a validated method to determine muscle mass.<sup>69</sup> The CSA of muscle tissue in a single slice (usually at the level of the third lumbar vertebra) has been shown to reliably represent body muscle mass.<sup>88–90</sup> Moreover, structural muscle changes, such as fat infiltration, can be detected by analyzing muscle density on CT. In critical patients evaluated by CT, muscle wasting, decreased density, and an increase in intermuscular fat are associated with an increase in mortality.<sup>90,91</sup> The major limitations of this technique are the need to move the patient and exposure to radiation.



**Fig. 2.** Peripheral muscle ultrasonography. Muscle thickness assessed in the flexor compartment of the arm (A), the flexor compartment of the forearm (B) and quadriceps (C).

**Table 3**  
Peripheral Muscle Ultrasonography Protocol.

Arm	With the elbow flexed to 90°, search for the halfway point between the acromion and the olecranon. Then, with the elbow extended and forearm supinated, place the linear transducer on the anterior surface, at the level of the previously identified mid-point. Position the transducer in a transverse direction, perpendicular to the skin. At the site of maximum thickness, measure the flexor muscle compartment between the fat–muscle interface and the humerus.
Forearm	With the elbow extended and forearm pronated, identify the point equidistant between the crease of the elbow and the ulnar styloid process. Place the linear transducer on the anterior surface at this point, in a transverse direction, perpendicular to the skin, measuring the thickness of the flexor compartment between the fat–muscle interface and the interosseus membrane.
Thigh	With the knee extended, mark the halfway point between the greater trochanter and the joint line of the knee. Place the linear transducer in the anterior surface above this point, in a transverse direction, perpendicular to the skin. Measure the thickness of the quadriceps muscle group at this level as the distance between the fat–muscle interface and the femur. CSA of the rectus femoris is obtained using the planimetric technique, after delimiting its internal margin (echogenic line) with the cursor.

CSA: cross-sectional area.

### Electrical Bioimpedance

Electrical bioimpedance (EBI) analysis can be used at the bedside to determine the patient's lean body mass, although it does not directly quantify muscle mass.<sup>92</sup> This can be estimated from regression equations designed for healthy individuals.<sup>93</sup> A recent study showed that the capacity of EBI to detect reduced muscle mass in ICU patients is acceptable, although new studies are needed to validate this technique in critical patients.<sup>94</sup>

### Biomarkers

The use of biomarkers could facilitate early diagnosis and follow-up of muscle impairment in the ICU. Various substances have been evaluated for this purpose (myoglobin, creatine kinase, troponin I, etc.). Although high levels have been detected in the context of injury or muscle overload, their usefulness for detecting muscle wasting or weakness in critically ill patients has not yet been demonstrated. Micro-RNAs may represent a new class of biomarkers with enormous potential. It has been suggested that different micro-RNAs participate in the pathogenesis of ICUAW.<sup>95–98</sup> Determination of these molecules in plasma might lead to early diagnosis or even predict the development

of muscle impairment in critical patients.<sup>96</sup> Furthermore, the expression profile of micro-RNAs could vary according to whether the impairment is respiratory, peripheral or both.

### Conclusions

Muscle wasting and weakness is a common problem in the ICU, and diagnosis and follow-up can be a real challenge. The use of various clinical parameters and additional methods can facilitate early detection. New non-invasive, accessible, reproducible tools, such as ultrasound, have emerged as valid options for the evaluation of both peripheral and respiratory muscles. The discovery of specific biomarkers will be an area of great interest for future research. The serial evaluation of critically ill patients using ultrasound techniques and the determination of plasma biomarkers could become a new model for the assessment of ICU-acquired muscle wasting and weakness.

### Conflict of Interests

The authors state that they have no conflict of interests.

## References

- Barreiro E. Models of disuse muscle atrophy: therapeutic implications in critically ill patients. *Ann Transl Med.* 2018;6:29.
- Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. *Intensive Care Med.* 2017;43:1441–52.
- Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med.* 2011;39:2627–30.
- Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Med.* 2016;42:853–61.
- Demoule A, Molinari N, Jung B, Prodanovic H, Chanques G, Matecki S, et al. Patterns of diaphragm function in critically ill patients receiving prolonged mechanical ventilation: a prospective longitudinal study. *Ann Intensive Care.* 2016;6:75.
- Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. *Crit Care.* 2013;17:R120.
- Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med.* 2013;188:213–9.
- Medrinal C, Prieur G, Frenoy E, Robledo Quesada A, Poncet A, Bonnevie T, et al. Respiratory weakness after mechanical ventilation is associated with one-year mortality—a prospective study. *Crit Care.* 2016;20:231.
- Lu Z, Xu Q, Yuan Y, Zhang G, Guo F, Ge H. Diaphragmatic dysfunction is characterized by increased duration of mechanical ventilation in subjects with prolonged weaning. *Respir Care.* 2016;61:1316–22.
- De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA.* 2002;288:2859–67.
- Ali NA, O'Brien JM Jr, Hoffmann SP, Phillips G, Garland A, Finley JC, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med.* 2008;178:261–8.
- Hermans G, van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med.* 2014;190:410–20.
- Cottareau G, Dres M, Avenel A, Fichet J, Jacobs FM, Prat D, et al. Handgrip strength predicts difficult weaning but not extubation failure in mechanically ventilated subjects. *Respir Care.* 2015;60:1097–104.
- Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical Intensive Care Unit patients. *Am J Respir Crit Care Med.* 2017;195:57–66.
- Batt J, dos Santos CC, Cameron JI, Herridge MS, et al. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med.* 2013;187:238–46.
- Files DC, d'Alessio FR, Johnston LF, Kesari P, Aggarwal NR, Garibaldi BT, et al. A critical role for muscle ring finger-1 in acute lung injury-associated skeletal muscle wasting. *Am J Respir Crit Care Med.* 2012;185:825–34.
- Doorduyn J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. *Am J Respir Crit Care Med.* 2013;187:20–7.
- Heunks LM, Doorduyn J, van der Hoeven JG. Monitoring and preventing diaphragm injury. *Curr Opin Crit Care.* 2015;21:34–41.
- American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002;166:518–624.
- Magalhaes PAF, Camillo CA, Langer D, Andrade LB, Duarte M, Gosselink R. Weaning failure and respiratory muscle function: what has been done and what can be improved? *Respir Med.* 2018;134:54–61.
- El-Khatib MF, Bou-Khalil P. Clinical review: liberation from mechanical ventilation. *Crit Care.* 2008;12:221.
- Caruso P, Albuquerque AL, Santana PV, Cardenas LZ, Ferreira JG, Prina E, et al. Diagnostic methods to assess inspiratory and expiratory muscle strength. *J Bras Pneumol.* 2015;41:110–23.
- Grinnan DC, Truitt JD. Clinical review: respiratory mechanics in spontaneous and assisted ventilation. *Crit Care.* 2005;9:472–84.
- Dres M, Demoule A. Diaphragm dysfunction during weaning from mechanical ventilation: an underestimated phenomenon with clinical implications. *Crit Care.* 2018;22:73.
- Watson AC, Hughes PD, Louise Harris M, Hart N, Ware RJ, Wendon J, et al. Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. *Crit Care Med.* 2001;29:1325–31.
- De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med.* 2007;35:2007–15.
- Matamis D, Soilemezi E, Tsaourias M, Akoumianaki E, Dimassi S, Boroli F, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. *Intensive Care Med.* 2013;39:801–10.
- Dube BP, Dres M. Diaphragm dysfunction: diagnostic approaches and management strategies. *J Clin Med.* 2016;5:113.
- Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. *Intensive Care Med.* 2015;41:734.
- Wait JL, Nahormek PA, Yost WT, Rochester DP. Diaphragmatic thickness–lung volume relationship in vivo. *J Appl Physiol.* (1985). 1989;67:1560–8.
- Cohn D, Benditt JO, Eveloff S, McCool FD. Diaphragm thickening during inspiration. *J Appl Physiol.* (1985). 1997;83:291–6.
- Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. *Muscle Nerve.* 2013;47:884–9.
- Baldwin CE, Paratz JD, Bersten AD. Diaphragm and peripheral muscle thickness on ultrasound: intra-rater reliability and variability of a methodology using non-standard recumbent positions. *Respirology.* 2011;16:1136–43.
- Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. *Intensive Care Med.* 2012;38:796–803.
- Santana PV, Prina E, Albuquerque AL, Carvalho CR, Caruso P. Identifying decreased diaphragmatic mobility and diaphragm thickening in interstitial lung disease: the utility of ultrasound imaging. *J Bras Pneumol.* 2016;42:88–94.
- Orozco-Levi M, Gayete A, Rodriguez C, Ramirez-Sarmiento A, Mendez R, Tous F, et al. Evaluación funcional no-invasiva de la reserva ante la fatiga y la estructura del diafragma mediante ecografía transtorácica en modos B y M. *Arch Bronconeumol.* 2010;46:571–9.
- Zambon M, Beccaria P, Matsuno J, Gemma M, Frati E, Colombo S, et al. Mechanical ventilation and diaphragmatic atrophy in critically ill patients: an ultrasound study. *Crit Care Med.* 2016;44:1347–52.
- Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm muscle thinning in patients who are mechanically ventilated. *Chest.* 2012;142:1455–60.
- Schepens T, Verbrugghe W, Dams K, Corthouts B, Parizel PM, Jorens PG. The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study. *Crit Care.* 2015;19:422.
- Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of diaphragm thickness during mechanical ventilation. Impact of inspiratory effort. *Am J Respir Crit Care Med.* 2015;192:1080–8.
- DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Thorax.* 2014;69:423–7.
- Ferrari G, de Filippi G, Elia F, Panero F, Volpicelli G, Apra F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Crit Ultrasound J.* 2014;6:8.
- Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. *Am J Respir Crit Care Med.* 2017;195:57–66.
- Umbrello M, Formenti P. Ultrasonographic assessment of diaphragm function in critically ill subjects. *Respir Care.* 2016;61:542–55.
- Ueki J, de Bruin PF, Pride NB. In vivo assessment of diaphragm contraction by ultrasound in normal subjects. *Thorax.* 1995;50:1157–61.
- Cardenas LZ, Santana PV, Caruso P, Ribeiro de Carvalho CR, Pereira de Albuquerque AL. Diaphragmatic ultrasound correlates with inspiratory muscle strength and pulmonary function in healthy subjects. *Ultrasound Med Biol.* 2018;44:786–93.
- Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. *Crit Care.* 2015;19:161.
- Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. *Chest.* 2009;135:391–400.
- Ayoub J, Cohendy R, Dauzat M, Targhetta R, De la Coussaye JE, Bourgeois JM, et al. Non-invasive quantification of diaphragm kinetics using m-mode sonography. *Can J Anaesth.* 1997;44:739–44.
- Gerscovich EO, Cronan M, McGahan JP, Jain K, Jones CD, McDonald C. Ultrasonographic evaluation of diaphragmatic motion. *J Ultrasound Med.* 2001;20:597–604.
- Supinski GS, Morris PE, Dhar S, Callahan LA. Diaphragm dysfunction in critical illness. *Chest.* 2018;153:1040–51.
- Jiang JR, Tsai TH, Jerng JS, Yu CJ, Wu HD, Yang PC. Ultrasonographic evaluation of liver/spleen movements and extubation outcome. *Chest.* 2004;126:179–85.
- Spadaro S, Grasso S, Mauri T, Dalla Corte F, Alvisi V, Ragazzi R, et al. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role of diaphragmatic rapid shallow breathing index. *Crit Care.* 2016;20:305.
- Puthuchery ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. *JAMA.* 2013;310:1591–600.
- Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med.* 2014;190:1437–46.
- Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve.* 1991;14:1103–9.
- Ciesla N, Dinglas V, Fan E, Kho M, Kuramoto J, Needham D. Manual muscle testing: a method of measuring extremity muscle strength applied to critically ill patients. *J Vis Exp.* 2011;50, pii: 2632.
- Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med.* 2009;37:S299–308.

59. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. *Muscle Nerve*. 2012;45:18–25.
60. Hough CL, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. *Crit Care*. 2011;15:R43.
61. Connolly BA, Jones GD, Curtis AA, Murphy PB, Douiri A, Hopkinson NS, et al. Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. *Crit Care*. 2013;17:R229.
62. Baldwin CE, Paratz JD, Bersten AD. Muscle strength assessment in critically ill patients with handheld dynamometry: an investigation of reliability, minimal detectable change, and time to peak force generation. *J Crit Care*. 2013;28:77–86.
63. Vanpee G, Segers J, van Mechelen H, Wouters P, Van den Berghe G, et al. The interobserver agreement of handheld dynamometry for muscle strength assessment in critically ill patients. *Crit Care Med*. 2011;39:1929–34.
64. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*. 2011;40:423–9.
65. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S, et al. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil*. 1985;66:69–74.
66. Latronico N, Shehu I, Guarneri B. Use of electrophysiologic testing. *Crit Care Med*. 2009;37:S316–20.
67. Latronico N, Nattino G, Guarneri B, Fagoni N, Amantini A, Bertolini G, et al. Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. *F1000Res*. 2014;3:127.
68. Mayans D, Cartwright MS, Walker FO. Neuromuscular ultrasonography: quantifying muscle and nerve measurements. *Phys Med Rehabil Clin N Am*. 2012;23:133–48, xii.
69. Paris M, Mourtzakis M. Assessment of skeletal muscle mass in critically ill patients: considerations for the utility of computed tomography imaging and ultrasonography. *Curr Opin Clin Nutr Metab Care*. 2016;19:125–30.
70. Sarwal A, Parry SM, Berry MJ, Hsu FC, Lewis MT, Justus NW, et al. Interobserver reliability of quantitative muscle sonographic analysis in the critically ill population. *J Ultrasound Med*. 2015;34:1191–200.
71. Parry SM, el-Ansary D, Cartwright MS, Sarwal A, Berney S, Koopman R, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care*. 2015;30:1151, e9–14.
72. Gruther W, Benesch T, Zorn C, Paternostro-Sluga T, Quittan M, Fialka-Moser V, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. *J Rehabil Med*. 2008;40:185–9.
73. Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. *Am J Clin Nutr*. 1995;62:533–9.
74. Reid CL, Campbell IT, Little RA. Muscle wasting and energy balance in critical illness. *Clin Nutr*. 2004;23:273–80.
75. Borges RC, Soriano FG. Association between muscle wasting and muscle strength in patients who developed severe sepsis and septic shock. *Shock*. 2018. May 11, doi: 10.1097/SHK.0000000000001183. [Epub ahead of print].
76. Connolly B, Maddocks M, MacBean V, Bernal W, Hart N, Hopkins P, et al. Non-volitional assessment of tibialis anterior force and architecture during critical illness. *Muscle Nerve*. 2018;57:964–72.
77. Baldwin CE, Bersten AD. Alterations in respiratory and limb muscle strength and size in patients with sepsis who are mechanically ventilated. *Phys Ther*. 2014;94:68–82.
78. Grimm A, Teschner U, Porzelius C, Ludewig K, Zielske J, Witte OW, et al. Muscle ultrasound for early assessment of critical illness neuromyopathy in severe sepsis. *Crit Care*. 2013;17:R227.
79. Freilich RJ, Kirsner RL, Byrne E. Isometric strength and thickness relationships in human quadriceps muscle. *Neuromuscul Disord*. 1995;5:415–22.
80. Witteveen E, Sommers J, Wieske L, Doorduyn J, van Alfen N, Schultz MJ, et al. Diagnostic accuracy of quantitative neuromuscular ultrasound for the diagnosis of intensive care unit-acquired weakness: a cross-sectional observational study. *Ann Intensive Care*. 2017;7:40.
81. Puthuchery ZA, McNelly AS, Rawal J, Connolly B, Sidhu PS, Rowleron A, et al. Rectus femoris cross-sectional area and muscle layer thickness: comparative markers of muscle wasting and weakness. *Am J Respir Crit Care Med*. 2017;195:136–8.
82. Cartwright MS, Kwayisi G, Griffin LP, Sarwal A, Walker FO, Harris JM, et al. Quantitative neuromuscular ultrasound in the intensive care unit. *Muscle Nerve*. 2013;47:255–9.
83. Puthuchery ZA, Phadke R, Rawal J, McPhail MJ, Sidhu PS, Rowleron A, et al. Qualitative ultrasound in acute critical illness muscle wasting. *Crit Care Med*. 2015;43:1603–11.
84. Arts IM, Pillen S, Schelhaas HJ, Overeem S, Zwarts MJ. Normal values for quantitative muscle ultrasonography in adults. *Muscle Nerve*. 2010;41:32–41.
85. De Bruin PF, Ueki J, Watson A, Pride NB. Size and strength of the respiratory and quadriceps muscles in patients with chronic asthma. *Eur Respir J*. 1997;10:59–64.
86. Seymour JM, Ward K, Sidhu PS, Puthuchery Z, Steier J, Jolley CJ, et al. Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. *Thorax*. 2009;64:418–23.
87. Heckmatt JZ, Leeman S, Dubowitz V. Ultrasound imaging in the diagnosis of muscle disease. *J Pediatr*. 1982;101:656–60.
88. Shen W, Punyanyitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* (1985). 2004;97:2333–8.
89. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33:997–1006.
90. Weijs PJ, Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. *Crit Care*. 2014;18:R12.
91. Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Twisk JW, Oudemans-van Straaten HM, et al. Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. *Crit Care*. 2016;20:386.
92. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. *J Parenter Enteral Nutr*. 2015;39:787–822.
93. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physiol* (1985). 2000;89:465–71.
94. Kuchnia A, Earthman C, Teigen L, Cole A, Mourtzakis M, Paris M, et al. Evaluation of bioelectrical impedance analysis in critically ill patients: results of a multicenter prospective study. *JPEN J Parenter Enteral Nutr*. 2017;41:1131–8.
95. Bloch SA, Lee JY, Syburra T, Rosendahl U, Griffiths MJ, Kemp PR, et al. Increased expression of GDF-15 may mediate ICU-acquired weakness by down-regulating muscle microRNAs. *Thorax*. 2015;70:219–28.
96. Bloch SA, Donaldson AV, Lewis A, Banya WA, Polkey MI, Griffiths MJ, et al. miR-181a: a potential biomarker of acute muscle wasting following elective high-risk cardiothoracic surgery. *Crit Care*. 2015;19:147.
97. Garros RF, Paul R, Connolly M, Lewis A, Garfield BE, Natanek SA, et al. MicroRNA-542 promotes mitochondrial dysfunction and SMAD activity and is elevated in Intensive Care Unit-acquired weakness. *Am J Respir Crit Care Med*. 2017;196:1422–33.
98. Connolly M, Paul R, Farre-Garros R, Natanek SA, Bloch S, Lee J, et al. miR-424-5p reduces ribosomal RNA and protein synthesis in muscle wasting. *J Cachexia Sarcopenia Muscle*. 2018;9:400–16.