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Monitoring of Changes in Muscle Mass and Function during Critical Illness Using Ultrasonography

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Abstract: Muscle comprises the largest protein pool in the body. Critical illness is characterized by substantial hormone- and cytokine-mediated protein metabolism changes in various organs, leading to increased breakdown and decreased synthesis rates. Medical therapeutic measures such as long-term sedation and mechanical ventilation during ICU stay can further enhance this muscle degradation (up to 2 % muscle mass per day. Each gram of nitrogen lost correlates to the loss of 30 g of lean tissue). The goal of the nutritional plan is to provide the necessary nutrient substrates to critically ill patients to prevent muscle atrophy and enhance patient's recovery. Muscle atrophy or ICU-acquired weakness (ICU-AW), which is considered a bilateral symmetrical muscle weakness in critically ill patients without prior neuromuscular disorders. These effects can be evident both directly from the harmful impact of drugs and from the disruption of microcirculation and also indirectly due to muscle atrophy from prolonged immobilization. Point-of-care ultrasound (POCUS) is rapid, accurate, repeatable, non-expensive, noninvasive, and without the risk of radiation. Diaphragm and skeletal muscle ultrasound provides a real-time image and a permanent record of function. This review aims to illustrate the role of ultrasound employment in detecting the changes of muscle mass and function during critical illness.

Keywords: *Malnutrition, Muscle atrophy, Critical Illness, Ultrasound.*

Introduction

Muscle comprises the largest protein pool in the body. Critical illness is marked by significant alterations in protein metabolism across multiple organs, driven by hormones and cytokines, resulting in increased degradation and reduced synthesis rates. Consequently, a considerable and life-threatening loss of muscle mass occurs [1].

Medical therapeutic measures such as long-term sedation and mechanical ventilation during ICU stay can further enhance this muscle degradation (up to 2 % muscle mass per day [3]) leading to clinically relevant symptoms known as ICU-acquired weakness (ICU-AW) [2, 4]. Which is considered a clinical symptom that is

classified as a secondary disorder [7]. If left unabated, these circumstances might strongly affect long-term patient outcomes [5].

Besides targeted medication and exercise, a quantitatively higher protein intake in critically ill patients might be reasonable to cover disease-specific increases in nitrogen/amino acid requirements and, thereby, contribute to overcome marked loss of functional proteins [8].

Energy and protein requirements may not change in a parallel way and should be considered separately. While a too large energy delivery could lead to overfeeding and refeeding, and may therefore be deleterious, increased protein delivery may be of benefit in critically ill patients.

It has been observed that in daily practice the amount of protein provided to most ICU patients is less than the loss [9], and is related to technical difficulties and commercial product composition not adequately enriched with proteins in comparison to the calorie content. In addition, 100 g of protein hydrolysate produces only 83 g of amino acids [10]. Recently products with a higher protein to energy ratio have become available.

Exercise has been suggested in several studies to be effective in preventing anabolic resistance [11, 12] reducing morbidity and improving the level of activity. However, some divergent results have also been published [13, 14]. Administration of increased protein intake together with increased physical activity should be further explored and seems to be promising [15].

Muscle atrophy during Critical Illness

Advancements in therapeutic methods and the management of critically ill patients have resulted in improved survival rates for this population. However, it has also been recognized that the effects of hospitalization in the Intensive Care Unit (ICU) due to acute illnesses extend beyond the immediate recovery phase and persist even after patients are discharged. A notable consequence of this is the development of muscle atrophy or weakness associated with ICU stays (ICU-AW), which is commonly observed as a clinical issue within the ICU setting [16].

Muscle weakness in critically ill patients is a prevalent issue observed in those admitted to the intensive care unit. This condition is marked by bilateral and symmetrical muscle weakness that occurs without any prior neuromuscular disorders. The underlying causes of this weakness can include axonal polyneuropathy, known as critical illness polyneuropathy, myopathy referred to as critical illness myopathy, or a combination of both conditions, termed critical illness polyneuromyopathy[6].

Prolonged bed rest is considered essential for all patients in the ICU, regardless of their specific conditions. However, extended stays in the ICU significantly impair patient mobility. Long-term care of critically ill patients leads to a reduction in hydrostatic pressure within the cardiovascular system, decreased workload on skeletal muscles, and a reduction in overall energy expenditure due to minimized power output. These effects can negatively impact various systems, particularly the musculoskeletal, cardiovascular, and circulatory systems, which experience the most significant deterioration [17].

The phrase "loss of muscle mass in ICU" refers to the alterations in both the structure and function of muscles. The clinical manifestation of muscular atrophy is marked by widespread muscle weakness, which, in extreme instances, may result in tetraplegia. Additionally, there may be a decrease or complete loss of tendon reflexes, along with challenges in the process of weaning patients off mechanical ventilation [18].

The primary contributors to muscle mass loss include disturbances in microcirculation that impact peripheral nerves and skeletal muscles, the existence of a systemic inflammatory response (known as systemic inflammatory syndrome or SIRS), sepsis, and the administration of medications that inhibit both the muscular and nervous systems, such as corticosteroids and neuromuscular blockers [19, 6].

Prolonged bed rest, the sedation and immobilization also contribute to the appearance of this problem. The immobilization therefore is a factor that helps the development of muscular atrophy [20]. Recent studies have indicated that electrical stimulation of the muscles, early patient mobilization, and the application of neuromuscular electrical stimulation can significantly reduce muscular atrophy [19, 21].

Etiology:

The ICU-acquired weakness is multifactorial. It can be apparent both directly due to the toxic action of drugs and due to the disruption of the microcirculation and also indirectly due to muscle atrophy from prolonged immobilization.

More specifically, during sepsis, the microcirculation is disrupted, leading to reduced blood flow and subsequent organ dysfunction. Endothelial cells benefit from a self-regulatory mechanism that triggers the release of nitric oxide, resulting in vasodilation. In contrast, peripheral nerve vessels lack this self-regulation, rendering them susceptible to hypoxia as a consequence of mitochondrial damage [16].

Additionally, the Cytokines released during sepsis enhance the permeability of the microcirculation. While the pathogenic role of these cytokines has been established, the precise mechanisms involved are still not fully understood. Currently, it is believed that cytokines and free radicals linked to systemic inflammatory response syndrome (SIRS) negatively impact the microcirculation and muscle tissue, leading to neuronal hypoxia, axonal degeneration, and muscle damage [16].

It is essential to recognize that catabolic processes play a significant role in the decrease of muscle mass, primarily through the breakdown of myosin. A notable example is calpain, which is regarded as a key proteolytic enzyme in skeletal muscles. The maintenance and development of muscle mass rely on the equilibrium between protein anabolism and catabolism. Catabolic activity tends to rise in various pathological conditions, including cachexia and sepsis. Additionally, prolonged bed rest and certain toxic medications can adversely affect muscle health. Calpain is instrumental in regulating the production cycle of muscle proteins, and there is evidence indicating heightened calpain activity in the skeletal muscles of patients experiencing ICU-acquired weakness [16].

Prolonged bed rest, even among individuals in good health, can result in considerable reductions in both muscle mass and strength. This occurs due to a decline in anabolic processes coupled with an increase in catabolic processes affecting muscle proteins. Research involving healthy individuals indicates that the rate of muscle loss can range from 4% to 5% per week during immobilization. Furthermore, when immobilization is combined with conditions such as sepsis or systemic inflammatory response syndrome, the degradation of muscle proteins is exacerbated, potentially leading to a loss of up to 2/3 within the initial five days [16].

Risk factors of muscle weakness:

A standard treatment for the ICU-AW has not been found. However, the effort to prevent the syndrome focuses on the control of those factors (pharmaceutical and non-pharmaceutical) which have been implicated in its appearance, such as the following**(figure 1)**:

Corticosteroids: The impact of corticosteroids on muscle mass loss in critically ill patients has been thoroughly investigated, primarily because of their catabolic properties. Numerous studies have highlighted the detrimental effects of corticosteroids on muscle mass in humans, especially among patients in intensive care units [6].

Neuromuscular blockers: Neuromuscular blocking agents have been directly linked to muscle mass loss in patients in the intensive care unit. A likely pathogenic mechanism may contribute to the functional denervation of skeletal muscle, leading to an accelerated degradation process [19].

Aminoglycosides: Aminoglycosides are frequently utilized in the intensive care unit (ICU) to treat severe infections. However, research indicates that their administration significantly increases the risk of muscular atrophy among ICU patients. According to the previous mentioned study highlights the detrimental impact of aminoglycosides on both the vestibular and cochlear nerves, which also plays a role in the reduction of muscle mass [22].

Colistin: Colistin is an antibiotic belonging to the polymyxin class, gaining attention in recent years due to the emergence of resistant bacterial strains that are sensitive to its effects. However, the administration of colistin is associated with certain toxicities, primarily nephrotoxicity and neurotoxicity, which are generally mild and tend to resolve upon the prompt cessation of the treatment [23].

Direct toxic effects of drugs and toxins: Specific endotoxins can directly harm muscles and nerves, with their effects worsened by endothelial dysfunction that increases vascular permeability, allowing toxins to infiltrate

the interstitial space. Furthermore, medications like inotropes, vasoconstrictors, and catecholamines contribute to muscle loss in critically ill ICU patients [19, 6].

Malnutrition: Protein-energy malnutrition is a major factor in muscle mass reduction among critically ill ICU patients, who often receive less than 60% of their required caloric intake. This leads to significant protein loss, as amino acids are drawn from muscle tissue to meet increased metabolic demands [24].

Multi-organ failure: The literature shows a significant link between extended hospital stays and the simultaneous failure of multiple organ systems. This raises questions about whether muscle atrophy is a result of critical illness or a sign of an underlying issue in multi-organ failure [6].

Parenteral Nutrition: Certain case reports associate ICU-acquired weakness (ICU-AW) with the use of parenteral nutrition. The prevailing hypothesis in these instances suggests that intravenous lipids rich in polyunsaturated fatty acids may negatively impact peripheral nerves. Conversely, other reports propose that parenteral nutrition could be linked to a range of metabolic disturbances, including hyperglycemia, hyperosmolarity, and hypernatremia, which might exacerbate microcirculatory issues in patients suffering from systemic inflammatory response syndrome (SIRS) and sepsis [25].

Sepsis: There is a high correlation between sepsis and appearance of muscle loss in patients hospitalized in the ICU. The electromyographic disorders are found in all the patients with septic shock during the first week of ICU stay [26]. However, the pathophysiological link between sepsis and loss of muscle mass is unclear. The neuromuscular dysfunction appears of high correlation with sepsis and additionally it seems to be associated with hypotension and reduction of blood flow resulting in a change of the energy supply of the muscles, particularly in the region where there is a decreased irrigation [27].

Immobilization: The detrimental impact of immobility on the skeletal muscles of ICU patients is well-established, significantly increasing morbidity and leading to muscular atrophy in critically ill individuals. Muscle tissue is a highly adaptable organ, undergoing continuous cycles of breakdown and repair in response to mechanical demands and the body's requirements. When immobilized, muscles enter a state that triggers catabolic processes. Extended periods of bed rest result in diminished muscle protein synthesis, elevated urinary nitrogen levels (which indicate muscle breakdown), and a reduction in muscle mass, particularly in the lower limbs [28].

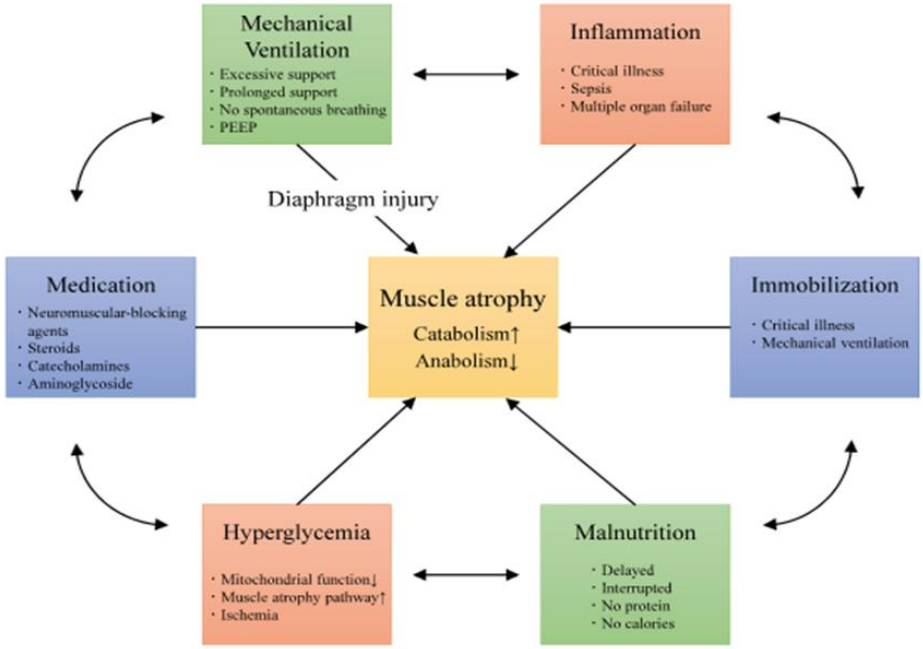

Figure 1. Risk factors associated with muscle atrophy [29].

Point-of-Care Ultrasound: A Powerful Tool for Critical Care

Point-of-care ultrasound (POCUS) is rapid, accurate, repeatable, non-expensive, noninvasive, and without the risk of radiation. It can visualize a large muscle area and deeper located muscles. It can be used in both stable and unstable patients. Performing repeated ultrasound examinations in critical patients is essential and improves the overall sensitivity of the examination, which has become a standard of care in critical care [30].

It was believed that perhaps the respiratory muscles in humans were spared any loss of muscle protein during starvation because of their constant activity. Respiratory muscle function decreases dramatically, due to alterations in contractile properties and atrophy [43]. Although it is likely that the diaphragm is much more sensitive than any other muscle to disuse, intercostal muscles too, along with other major respiratory muscles, are thought to be involved [44]. In a necropsy study designed to assess the diaphragm in health and disease, it was found that alterations in body weight and muscularity profoundly affect the diaphragm muscle mass [33].

- Diaphragm Ultrasound:

1-Diaphragm thickness

Diaphragm thickness was measured by using a 6-12MHZ linear Transducer by M-mode or with a 2D image during non-forced expiration. The patients will be in a semi-recumbent position. The transducer was placed vertical to the chest wall, at the eighth or ninth intercostal space, between the anterior axillary and the mid-axillary lines **(figure 2)**, to observe the zone of apposition of the muscle 0.5 to 2 cm below the costo-phrenic sinus. The inferior border of the costo-phrenic sinus has been demonstrated by the level of lung artifact caused by the ultrasound reflected by the air in the lung. The diaphragm structure has three layers: two parallel echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypoechoic structure between them (the muscle) [36].

2-Diaphragm thickening fraction

Diaphragm thickness is measured using a 6-12MHZ linear transducer at end expiration and at peak inspiration, and thickening fraction is calculated offline as follows: diaphragm thickening fraction (TFdi) equals peak inspiration thickness minus end-expiratory thickness divided by end expiratory thickness. Diaphragm thickness variation can be used as an indicator of diaphragm capacity to generate pressure [37, 46]. A variation of <20% may be considered as a predictor for failure to wean [38].

Figure 2: Probe position for B and M mode diaphragmatic thickness measurements in the zone of apposition with 10–12 MHz probe.

In this area, the diaphragm is observed as a structure made of three distinct layers **(Figure 3)**: a non-echogenic central layer bordered by two echogenic layers, the peritoneum and the diaphragmatic pleurae [39]

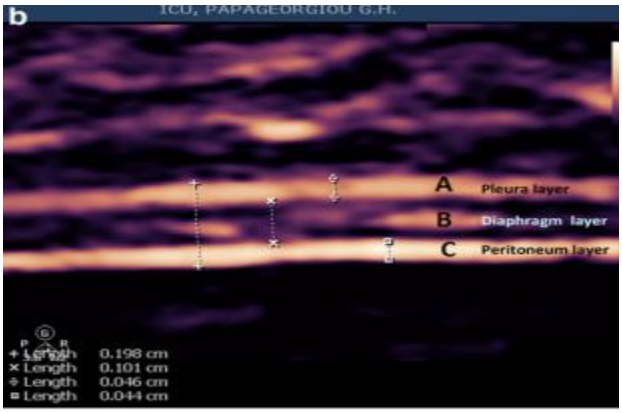

Figure 3: B-mode sonography of the diaphragm in the zone of apposition [39]**.**

A- Echogenic diaphragmatic pleura
B- non-echogenic central layer
C- Echogenic peritoneal layer.

3-Diaphragm excursion

To evaluate diaphragm motion (excursion) the convex 3-5MHZ probe has been positioned below the rib cage at the level of the mid-clavicular line, directing the ultrasound beam perpendicularly toward the posterior third of the hemi-diaphragm using M-mode. The diaphragm can be seen as a hyper-echogenic line. The excursion was measured as the difference between the end of the inspiration and the end of expiration (cm) **(figure 4)**.Normal values in healthy non-ventilated patients differ between men and women (18±3 and 16±3mm, respectively) [40], similarly to baseline values in mechanically ventilated patients [41]. Diaphragm dysfunction is defined as an excursion of less than 10mm these values are also good predictors of failure to wean [42].

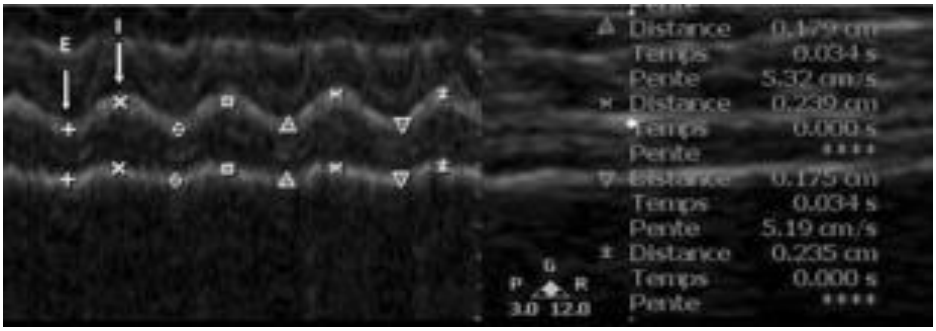

Figure 4: Sonography of the diaphragm in the zone of apposition, in B-mode (right) and M-mode (left) during quiet breathing. E and I arrows indicates expiration and inspiration, respectively.

- Parasternal Intercostal Muscle Ultrasound

linear transducer (frequency: 7– 13MHz) is positioned perpendicular to the anterior thorax surface in the longitudinal scan, at the level of the second right intercostal space, approximately 6 to 8 cm lateral to the sternal edge with a window visualizing the second and third ribs. The second right parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes respectively running from the anterior and posterior aspects of the adjoining ribs, and a medial portion with muscle echo texture. Using M-mode, the ultrasound beam is perpendicularly directed at the midsection of the muscle, where it is the thinnest at end-expiration. The thickness of the parasternal intercostal muscle was measured on frozen images at end expiration and at end inspiration **(figure 5)**. Change in thickness determined the thickening fraction of the parasternal intercostal muscle as follows: parasternal intercostal muscle thickening fraction (TFic) equals peak inspiration thickness minus end-expiratory thickness divided by end-expiratory thickness [thickness at

inspiration - thickness at expiration]/ [thickness at expiration] × 100. All measurements are repeated on at least three separate breaths and their average will be reported [45]

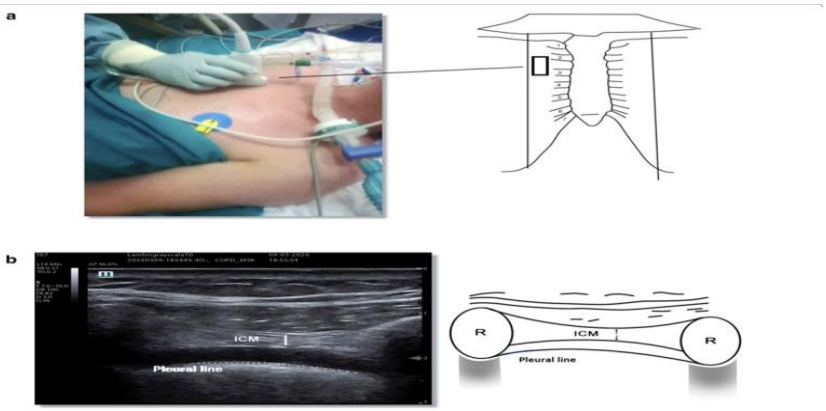

Figure 5: Intercostal muscle ultrasound. The figure depicts an ultrasound image of parasternal intercostal muscle ultrasound. **A**) The ultrasound probe position at the parasternal space. **B**) The ultrasound image depicted by ultrasound using a B-mode setting in which the intercostal muscle lies between two ribs (R), cranial to the pleural line, behind the pectoral muscle. The left side is a schematic view of the ultrasound image. ICM intercostal muscle [45].

Skeletal muscles assessment:

Muscles of the lower limb are more prone to early atrophy as they are weight bearing compared to the muscles of the upper limb as shown in previous studies [31, 32]. They showed that the size of the flexor compartment of the elbow did not show any change in the first 10 days of admission, whereas the size of the anterior compartment muscles of the lower limb showed a greater decrease of thickness within the first 5 days.

- Ultrasound measurement of quadriceps muscle layer thickness:

While the patient in supine position, bi-dimentional mode is used, and a linear transducer (frequency: 7–13MHz). The linear probe will be placed perpendicular to the long axis of the thigh on its anterior surface at the two thirds of the length between the anterior inferior iliac spine and the upper border of the patella **(figure 6)**. Once the image has been obtained, the following structures must be identified: Skin; Subcutaneous tissue (fat); Muscular fascia; Rectus femoris; Second interface; Vastus intermedius; Bony surface. After identifying the muscle tissue, the thickness of the quadriceps muscle will be obtained by measuring the distance between the cortex of femur and the most superficial muscular fascia **(figure 7).** Measurements will be performed by applying maximal compression on the probe without inflicting pain to prevent underestimation of muscle wasting linked to subcutaneous edema. Measurement will be made on the dominant side. Every time, three ultrasound measurements will be taken and the average of three measurements will be used and combined to provide total muscle depth [34]**.**

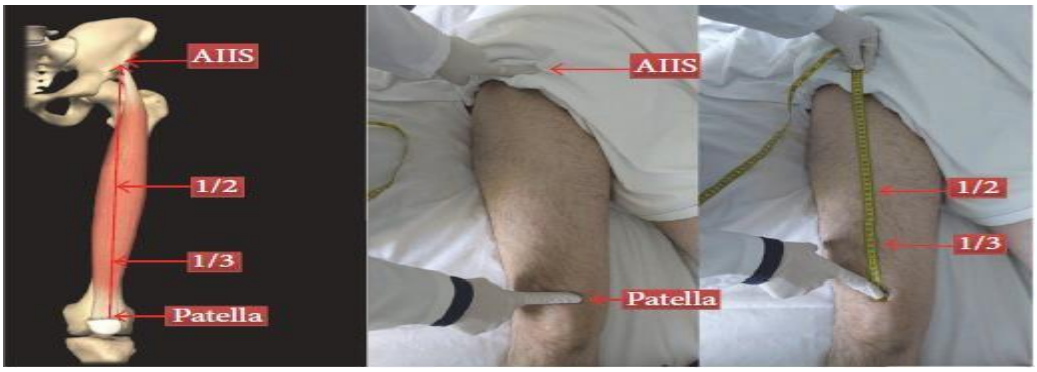

Figure 6: Finding the right place to measure. AIIS: anterior inferior iliac spine. [35]

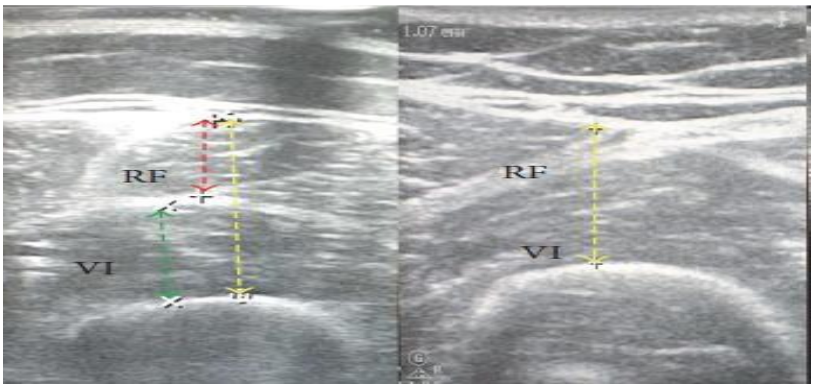

Figure 7: Measurements RF: rectus femoris; VI: vastus intermedius. From left to right: thicknesses using minimal pressure, thickness using maximal pressure (landmark: 1/3 using minimal pressure). [35]

Conclusion:

Muscle quantification at ICU admission and changes over time is potential surrogate outcome measures for muscle function as well as overall muscle health. In combination with other measures, future work in muscle quantification may help to identify those who would benefit most from targeted nutrition and rehabilitative therapy. Intervention evaluation aimed at preventing or reducing muscle loss requires an accurate and precise set of tools. Respiratory muscle function decreases dramatically due to alterations in contractile properties and atrophy. Although it is likely that the diaphragm is much more sensitive than any other muscle to disuse, intercostal muscles too, along with other major respiratory muscles, are thought to be involved**.** Ultrasound has several advantages in providing a noninvasive, nonvolitional, and accessible approach to measure quantity and quality of muscle. Although it represents a potential option for measurement of muscle mass in real time in clinical facilities, first a universal protocol needs to be identified and validated that can be easily implemented in the critical care setting to enhance and advance studies whose aim is to improve muscle rehabilitation in survivors of critical illness

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