Muscle atrophy in critically ill patients: a review of its cause, evaluation, and prevention

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Abstract: Critically ill patients exhibit prominent muscle atrophy, which occurs rapidly after ICU admission and leads to poor clinical outcomes. The extent of atrophy differs among muscles as follows: upper limb: 0.7%–2.4% per day, lower limb: 1.2%–3.0% per day, and diaphragm 1.1%–10.9% per day. This atrophy is caused by numerous risk factors such as inflammation, immobilization, nutrition, hyperglycemia, medication, and mechanical ventilation. Muscle atrophy should be monitored noninvasively by ultrasound at the bedside. Ultrasound can assess muscle mass in most patients, although physical assessment is limited to almost half of all critically ill patients due to impaired consciousness. Important strategies to prevent muscle atrophy are physical therapy and electrical muscular stimulation. Electrical muscular stimulation is especially effective for patients with limited physical therapy. Regarding diaphragm atrophy, mechanical ventilation should be adjusted to maintain spontaneous breathing and titrate inspiratory pressure. However, the sufficient timing and amount of nutritional intervention remain unclear. Further investigation is necessary to prevent muscle atrophy and improve long-term outcomes.

Keywords: muscle atrophy, diaphragm, ultrasound, physical therapy, electrical muscular stimulation

INTRODUCTION

Mortality from critical illness has declined by 35% in the past few decades, accompanied by increased attention to functional impairments in survivors (1). One-third of patients have functional impairments following ICU discharge, which is now recognized as post-intensive care syndrome (PICS) (2). PICS encompasses impaired physical, mental, and cognitive functions (3). Even 5 years after intensive care, the patients’ physical function does not return to the standard level (4), and one-third of survivors never return to work (5). Muscle weakness and atrophy acquired in the ICU are major contributors to PICS (6).

Muscle weakness in the ICU has gained increased attention as ICU-acquired weakness (ICU-AW) (7). ICU-AW is bilateral muscle weakness newly acquired in the ICU and is observed in 40-50% of critically ill patients (8, 9). In the ICU, prolonged bed rest and inflammation increase catabolism and microcirculatory disturbances, which cause axonal degeneration and muscle protein breakdown (9). Therefore, ICU-AW is considered to be neuropathy (critical illness polynuropathy) or myopathy (critical illness myopathy), as well as the overlap of these two conditions (10). ICU-AW is associated with a prolonged ICU stay and high mortality (6).

Recently, many studies have investigated muscle atrophy because the diagnosis of ICU-AW is challenging (11, 12). Although the diagnosis of ICU-AW requires assessment of limb muscle strength, more than half of all critically ill patients cannot comply with the evaluation (13). In contrast, muscle atrophy can be evaluated for all critically ill patients. This muscle atrophy is associated with ICU-AW and encompasses the concept of ICU-AW (14). In addition to limbs, respiratory muscle can atrophy and impede weaning from mechanical ventilation (15). Recent studies found that early mobilization and neuromuscular electrical stimulation can prevent and treat muscle atrophy in critically ill patients (16). This review focuses on the causes, evaluation, and prevention of muscle atrophy in critically ill patients.

1. MUSCLE ATROPHY

Noticeable reduction of muscle mass starts within 3 days of ICU stay, and progressively worsens thereafter (17). Patients with acute respiratory distress syndrome (ARDS) had a weight loss of 18% at hospital discharge, mostly due to muscle atrophy (18). Even 6 to 12 months after ICU discharge, survivors of ARDS did not regain their original muscle mass proportion, and the decreased muscle mass was associated with impaired gait speed (r = 0.27–0.41, p < 0.05) and 6-minute walk distance (r = 0.36–0.42, p < 0.001) (19). The extent of muscle atrophy acquired in the ICU is different among skeletal muscles (20). Therefore, each muscle is explained separately.

1-1. Lower limbs

In our previous study, we found that the rectus femoris thickness and cross-sectional area decreased by 18.8% and 20.7%, respectively, during the first 7 days (17). In other studies, the muscle mass of the rectus femoris decreased by 10.6% or 17.7–29.9% over 7 or 10 days (14, 21, 22). The muscle mass decreased by 29.7% in the vastus intermedius, by 14.1%–22.9% in the vastus lateralis, and by 11.6% in the gastrocnemius (22, 23) over 10 days. The mass of the tibialis anterior muscle decreased by 21% over 9 days (24). Thus, the atrophy rate in lower limbs is 1.2%–3.0% per day (17, 21-23). Similarly, in pediatric patients, the thickness of the quadriceps femoris muscle decreased by 1.5% per day (25). The decreased quadriceps cross-sectional area during the ICU stay further decreased 7 days after ICU discharge, and the muscle atrophy remained in 73% of patients with...
impaired physical function 6 months after ICU discharge (26).

1.2. Upper limbs

Muscle atrophy in upper limbs is controversial. In our previous study, the thickness and cross-sectional area of the biceps brachii muscle decreased by 13.2% and 16.9%, respectively, over the 7 days of ICU admission (17). Similarly, in septic patients, the muscle thickness decreased by 7.6% over the 7 days (14). On the other hand, Turton et al. found that the muscle thickness of the upper limbs in ICU patients did not decrease significantly from ICU admission to the 10th day (3.20 ± 0.58 cm to 2.98 ± 0.83 cm, p = 0.62), although the lower limb muscle mass significantly decreased (23). In another study, the muscle thickness of the upper limbs did not change in bed-ridden healthy volunteers (27). The differences may be explained by the severity of illness or patient's consciousness because less critical patients can use their arms during bed rest, and such activation of biceps brachii muscles may have counteracted the atrophy. Similarly, in critically ill pediatric patients, biceps muscle atrophy did not significantly change (-1.71% vs. 95% CI, -8.15% to 4.73%; p = 0.59) over the 6 days (25). In conclusion, the atrophy rate of the upper limbs is lower than that of the lower limbs, at 0.7%–2.4% per day in critically ill patients (14, 17, 23).

1.3. Pectoralis major muscle

The pectoralis major muscle is important in critically ill patients because a larger pectoralis major muscle was related to a higher 6-month survival rate (odds ratio [OR], 1.03; 95% CI, 1.01-1.04; P < .001) (28). Over the 5 days of ICU admission, the atrophy of the pectoralis major muscle was limited to only 29% of patients, and the change in thickness was not significant (5.6 mm [4.8–6.9] to 5.9 mm [4.9–7.0], p = 0.308) (29). Similarly, Levine et al. found that the muscle fibers of the pectoralis major muscle did not differ between mechanically ventilated patients and control subjects, although the study only compared 22 patients with different pathologies (30). Further investigation is needed to conclude the rate of atrophy of the pectoralis major muscle.

1.4. Diaphragm

Patients undergoing prolonged mechanical ventilation have sustained diaphragm muscle loss, which leads to poorer clinical outcomes (15). Diaphragm muscle atrophy occurs in 41–44% of patients according to previous studies (15, 31). Diaphragm muscle atrophy is separated from limb muscle atrophy because it is constantly activated by mechanical ventilation, whereas the limb muscles are not constantly active. Thus, in a previous study, it is constantly activated by mechanical ventilation, whereas the muscle atrophy is separated from limb muscle atrophy because of patients according to previous studies (15, 31). Diaphragm muscle atrophy occurs in 41–44% of mechanically ventilated patients (15, 31). In patients with diaphragm hyperfunction, the diaphragm thickness increased by approximately 17% over the 8 days of mechanical ventilation. The diaphragm muscle can be thickened by insufficient ventilatory support and excessive inspiratory load because this condition functions as resistance training of the diaphragm muscle (34). As such, diaphragm hypertrophy is associated with prolonged mechanical ventilation (OR, 1.38; 95% CI, 1.00–1.90) (15). However, the clinical implications of diaphragm hypertrophy require further investigation because few studies have been reported (15, 34).

1.5 Other respiratory muscles

In addition to the diaphragm, other respiratory muscles play an important role in moving the rib cage in patients with acute respiratory failure who have difficulty breathing (37). Among other respiratory muscles, the intercostal muscles exhibited atrophy in rabbits (38). In the study, the intercostal muscle mass decreased by 29% over the 48 hours of mechanical ventilation. In chronic obstructive pulmonary disease (COPD), the intercostal muscle can atrophy due to progression of the disease (39). However, the atrophy of intercostal muscles and other accessory respiratory muscles, including the sternocleidomastoid and rectus abdominis muscles, is unclear in critically ill patients.

2. RISK FACTORS

2.1. Inflammation

Inflammation is the main cause of muscle atrophy in the early course of critical illness (Fig. 1) (40). In patients who develop ICU-AW, the level of inflammatory cytokines, including interleukin 6, 8, and 10, was significantly higher (OR, 1.35; 95% CI, 1.18–1.55) in the first 4 days after ICU admission (41). Intramuscular inflammation causes catabolism and impairs anabolic signaling with consequent muscle mass reduction (42, 43). Sepsis accompanies systemic inflammation, and leads to upper and lower limb muscle atrophy (14). Moreover, multiple organ failure, which is often the consequence of inflammation, leads to prominent muscle atrophy (21).

2.2. Immobilization

Critically ill patients are often immobilized due to the severity of illness and equipment such as mechanical ventilation (44). This immobilization leads to muscle atrophy (45). Even in healthy volunteers, the bed-ridden state causes the lower limb muscles to atrophy by 0.2%–0.6% per day (27, 46). However, patients in the ICU exhibit more prominent muscle atrophy at 1.2%–3.0% per day due to multiple causes (45).

2.3. Nutrition

Although catabolism plays a greater role in muscle atrophy than impaired synthesis (47), malnutrition is also an important cause of muscle atrophy (45). The nutrition of critically ill patients is often delayed or interrupted (48). Moreover, patients in the ICU frequently have problems absorbing the nutrition due to the enteral intolerance (49).

2.4. Hyperglycemia

Hyperglycemia is often a consequence of inflammation, but it is identified as an independent risk factor for muscle atrophy because it impairs mitochondrial function (50) and promotes the muscle atrophy pathway (51). Moreover, hyperglycemia secondarily causes ischemia of muscles and nerves (10), and is associated with ICU-AW (OR, 2.86; 95% CI, 1.30–6.30; p = 0.009) (52).

2.5. Medication

Neuromuscular-blocking agents are often used for ARDS as a lung-protective strategy. However, their effects on muscle and physical function are unclear. In a recent study of ARDS, neuromuscular-blocking agents lead to a higher incidence of ICU-AW, although not significantly (47.3% in intervention vs. 39.0% in the control) (13). In a meta-analysis of a general ICU population, neuromuscular-blocking agent usage was associated with the
risk of ICU-AW (OR, 2.03; 95% CI, 1.22–3.40) (53). For the diaphragm, neuromuscular-blocking agents caused significant muscle atrophy (-16.4% [IQR, -28.4% to -7.0%] for neuromuscular-blocking agents vs. -7.3% [IQR, -10.9% to 0%] for control, p = 0.036) (35).

Steroids are frequently used in the ICU, but they should be used carefully because they inhibit protein synthesis and activate protein degradation (54). Indeed, steroid use is associated with pectoral muscle atrophy (Atrophy ratio: 58% in patients treated by steroids vs. 14% in the control, p = 0.006) (28) and ICU-AW (OR, 1.84; 95% CI, 1.26–2.67) (55). The combined use of steroids and neuromuscular-blocking agents is more deleterious to muscle than steroids alone (56).

Catecholamines can maintain organ perfusion in shock. Although arrhythmias and ischemia are well-known side effects, a recent study found that catecholamines are associated with ICU-AW (OR, 3.20; 95% CI, 1.29–7.95) (55). During the use of catecholamines, the stimulation of β-adrenergic receptors has toxic effects on skeletal muscle, as reported in animal studies (57, 58).

Aminoglycoside is a widely used wide-spectrum antibiotic. Among its side effects, it is toxic to peripheral neurons and has well-known ototoxicity (59). The use of aminoglycoside increased the incidence of ICU-AW (OR, 2.27; 95% CI, 1.07–4.81; p < 0.05) (53).

2-6. Mechanical ventilation

Mechanical ventilation is associated with diaphragm atrophy (30). Diaphragm atrophy progresses rapidly after mechanical ventilation and prolonged mechanical ventilation is a risk factor for prominent atrophy (31). The extent of atrophy differs among ventilator settings. Excessive ventilatory support causes diaphragm atrophy (60). Based on diaphragm biopsy, the patient group without spontaneous breathing presented significant diaphragm atrophy (61). Positive end-expiratory pressure (PEEP) also resulted in diaphragm atrophy by excessive stretching of muscle fibers (62). These structural changes of the diaphragm are termed myotrauma, and recognized as a serious complication of mechanical ventilation (63).

3. EVALUATION AND DIAGNOSIS

3-1. Physical assessment

Physical assessment is useful to evaluate muscle weakness. For ICU-AW, the medical research council (MRC) score is used for diagnosis (64). The MRC score is based on the manual testing of 6 muscle groups on both sides (0–60 score) (12). ICU-AW is defined as an MRC score of less than 48 without preexisting neuromuscular problems (64). As physical assessments require the patient’s cooperation, the assessment of ICU-AW was incomplete for 53.9% of mechanically ventilated patients and 51.2%–67.5% of acute respiratory distress syndrome (ARDS) patients (13, 65). Moreover, some patients have impaired muscle strength at admission (66).

3-2. Ultrasound

Ultrasound is the most commonly used method for monitoring of muscle mass because it is noninvasively available at the bedside (67). In contrast to assessment by MRC score, ultrasound can assess muscle atrophy for all critically ill patients regardless of their consciousness level and preadmission status. The measurement is conducted using a linear transducer and generous amounts of gel to avoid compression of the muscles (67). However, the measurement site is not consistent among studies. The most common site of muscle mass measurement is the rectus femoris muscle. Its measurement is reproducible (R² = 0.74–0.99) (17, 21, 68) and needs only minimal training (69). The measurement site is midway or one-third from the proximal patella to the anterior superior iliac spine or 10 cm above the proximal patella (17, 21, 67, 70). Measurement by ultrasound should be conducted using the cross-sectional area (Fig. 2ab) rather than thickness because muscle thickness is inaccurate (71). Moreover, the

Figure 1. Risk factors associated with muscle atrophy

Critically ill patients are exposed to numerous risk factors for muscle atrophy. PEEP, positive end-expiratory pressure
cross-sectional area reflects the muscle strength (72). Although edema was reported to influence ultrasonographic assessment, it is not significant because most fluid is not retained in muscle and is instead in subcutaneous tissues (73, 74). The diaphragm thickness is evaluated by a perpendicularly placed transducer at 0.5–2 cm below the right costophrenic sinus, which is termed the zone of apposition (Fig. 2c) (75). The muscle echo intensity is useful for assessing muscle atrophy because it increases in atrophied muscle (22). This high intensity reflects the increased percentage of interstitial fibrous tissue (76).

3-3. BIA (Bioelectrical impedance analysis)

BIA can be used at the bedside (Fig. 3). BIA indirectly measures whole-body muscle mass from the impedance using a weak electric current. The muscle mass, measured by BIA, correlates well with the CT assessment in critically ill patients (77). However, edema complicates the impedance and muscle mass measurement, and muscle mass was thus overestimated in edematous patients (77). Muscle mass monitoring during ICU stay may be unreliable because critical ill patients exhibit an abnormal fluid status (78).

3-4. CT, MRI, and DEXA

Computed tomography (CT), magnetic resonance imaging (MRI), and dual energy x-ray absorptiometry (DEXA) are reliable methods of muscle mass assessment but are unavailable at the bedside (79). Furthermore, CT and X-ray expose patients to extra radiation, and transferring patients to the examination room involves some risks. Therefore, these methods are not suitable for muscle mass monitoring in critically ill patients.

3-5. Biomarkers

Creatine kinase is normal or mildly high in ICU-AW, but it is not a specific biomarker (64, 65). Growth and differentiation factor-15 (GDF-15) is considered to be a mediator of muscle atrophy, and the level of GDF-15 increased in the muscle atrophy group (80). Furthermore, the GDF-15 level in plasma was higher in ICU-AW (7239 pg/mL vs. 2454 pg/mL, p = 0.001) (81). Therefore, the measurement of GDF-15 is promising for the diagnosis of muscle atrophy. In a recent study, the serum creatinine to serum cystatin C ratio was reported to correlate with muscle mass (r = 0.62, p < 0.001) (82), but it is limited to patients without acute kidney injury. Under normal renal function, urinary creatinine and 3-methylhistidine are also useful for monitoring proteolysis and evaluating muscle atrophy (83, 84).

4. PREVENTION AND TREATMENTS

As inflammation is the main cause of muscle atrophy in the early course of critical illness, treating the causative disease should be prioritized. As additional interventions, rehabilitation and nutritional support are indispensable for preventing muscle atrophy (Table 1).

4-1. Physical therapy

Early mobilization has been demonstrated to be an effective method to prevent physical disabilities (85) and improve long-term outcomes (86). Early physical therapy prevented muscle atrophy by preserving the muscle fiber cross-sectional area at day 7 of ICU admission (2.4% ± 22.5% in the intervention group vs. -25.8% ± 21.6% in the control, p = 0.005) (11). Moreover, early mobilization was confirmed to be effective in preventing ICU-AW (87). Physical therapy for respiratory muscles can improve both inspiratory and expiratory muscle strength (88).

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**Figure 2.** Typical ultrasonographic images of upper limbs, lower limbs, and diaphragm.

- a. Cross-sectional area of the biceps brachii muscle in the transverse plane.
- b. Cross-sectional area of the rectus femoris muscle in the transverse plane.
- c. Diaphragm thickness from the right intercostal view.

**Figure 3.** Bioelectrical impedance analysis.

The whole-body muscle mass was measured by bioelectrical impedance analysis (InBody S10®, InBody Co., Seoul, South Korea). Patient consent was obtained for the use of this image.
4-2. EMS (Electrical muscular stimulation)

EMS uses electrical currents to induce muscle construction, and can be used safely as additional rehabilitation for ICU patients (Fig. 4) (89). EMS aided in preserving muscle mass in critically ill patients over the 7 or 8 days of ICU stay (cross-sectional area of the rectus femoris muscle; -8% ± 3.9% in the EMS group vs. -13.9% ± 6.4% in the control, p < 0.05) (90). In contrast, a recent study reported adding EMS to the lower legs did not preserve muscle mass at the day of ICU discharge (thickness of the rectus femoris; -1.9 mm [-8.0 to 0.2 mm] in the intervention group vs. -2.4 mm [-7.1 to -0.3 mm] in the control, p = 0.17) (91). In this randomized controlled trial, early physical therapy was conducted for both groups (the control group had early standardized rehabilitation). Patients who have sufficient physical therapy may benefit little from EMS, but it may be useful for patients with limited mobility because active patient cooperation is not required. Which patients will benefit the most from these additional rehabilitation methods needs to be clarified. In previous studies, EMS was effective for patients requiring a prolonged ICU stay (92) or prolonged mechanical ventilation (12). EMS preserved muscle thickness of the rectus femoris only in patients requiring long-term ICU stay (4.9% in the intervention group vs. -3.2% in the control, p = 0.013). Similarly, in patients under prolonged mechanical ventilation, the leg circumference was preserved (47.5 ± 8.3 cm in the intervention group vs. 44.6 ± 5.7 cm in the control, p = 0.004) (12). One previous study evaluated the effects of EMS on one side of the upper limbs, and the non-stimulated arm circumference decreased significantly over 13 days (-1.00 cm [IQR, -2.50 to 0.00 cm], p = 0.015) (93). However, the recommendation of EMS for critically ill patients is not consistent in the guidelines due to the limited number of studies (94, 95).

EMS to the diaphragm through the phrenic nerve has been investigated in an animal study, and it was effective in preventing diaphragm muscle atrophy (diaphragm thickness/ initial value; 1.10 [IQR, 1.02–1.24] in the intervention group vs. 0.84 [IQR, 0.78–0.89] in the control, p = 0.001) (96). Its application in humans is currently under investigation (97).

4-3 Ventilator settings

Ventilator settings preventing diaphragm muscle atrophy are termed “muscle-protective ventilation” (98). This strategy aims at maintaining spontaneous breathing and titrating ventilatory support to obtain sufficient respiratory effort, but some patients with ARDS need ventilator settings without spontaneous breathing to avoid ventilator-induced lung injury (99). However, the setting without spontaneous breathing should be carefully used because this mode leads to prominent diaphragm atrophy of -7.5% ± 12.3% per day (60). Similarly, excessive inspiratory support should be avoided because higher inspiratory pressure leads to further diaphragm atrophy (daily atrophy ratio; -5.6% ± 12.9% in ≥ 12 cmH₂O vs. -1.5% ± 10.9% in 5–12 cmH₂O) (60). The optimal ventilator settings can be adjusted by ultrasonographic measurement of the diaphragm thickening fraction [thickness at inspiration – thickness at expiration]/ [thickness at expiration] × 100 (%) (34). The diaphragm thickening fraction represents the respiratory effort by the patient (100). For better clinical outcomes, the thickening fraction should be maintained from 15% to 30%, which is the same range during spontaneous breathing in healthy adults (15).

4-4 Nutrition

4-4-1 Early enteral and parenteral nutrition

Early enteral or parenteral nutrition is not promising for phys-
ical function. In a previous study, early and full enteral nutrition during the first 6 days did not change physical function 6 and 12 months after ICU discharge (101). Similarly, early parenteral nutrition, compared with late parenteral nutrition beyond the first week, did not prevent muscle atrophy and only increased adipose tissue (102). Moreover, early parental nutrition was associated with ICU-AW (p = 0.021) (103), mainly due to unutilized nutrition in the acute phase of critical illness (104). Indeed, 63% of early intake is excreted (105). Hyperglycemia and dyslipidemia, which are common complications of early nutrition, are harmful to muscles and nerves (106).

4-4-2 Protein
Protein intake from 1.2–1.5 or 1.2–2.0 g/kg/day is recommended for lower mortality (107, 108). However, the necessary amount of protein to prevent muscle atrophy is unclear. In a randomized controlled trial of non-septic critically ill patients, protein intake was decided by nitrogen balance (difference between given amount and urinary excretion), and the actual protein intake was 1.47 g/kg/day in the intervention group vs. 0.56 g/kg/day in the control. However, the higher protein intake did not change the physical quality of life at 6 months (109). In another study on septic patients, a higher protein intake was associated with prominent muscle atrophy (OR, 1.29; 95% CI, 1.00-1.67; P < 0.049), possibly due to the deteriorated autophagy activity in septic patients (21, 110). In contrast, a higher protein intake was reported to increase the forearm muscle thickness on ultrasound (3.2 ± 0.4 cm vs. 2.8 ± 0.4 cm, p < 0.0001), although the actual difference in protein intake was small (0.9 g/kg vs. 1.1 g/kg) (111). Results regarding the necessary amount of protein to prevent muscle atrophy are conflicting. The existence of negative data suggests that nutritional intervention alone is insufficient to prevent muscle atrophy, and that it should be combined with physical therapy.

4-4-3 Calories
In recent years, permissive underfeeding is recommended in the first week of critical illness (107, 109). In an observational study, low caloric intake on day 3 (< 10 kcal/kg/day) was associated with good physical status at ICU discharge (112). In another study, calorimetry-based full calorie intervention did not change the physical quality of life at 6 months (1877 kcal/day in the control) (109). The benefits of permissive underfeeding are being investigated in many trials.

4-5 Glucose control
Intensive insulin therapy (blood glucose levels of 80 to 110 mg/dl) reduced the incidence of ICU-AW (50.5% in the intervention group vs. 38.9% in the control, p = 0.02) (113). In addition to the benefits of preventing abnormal glucose levels, insulin can promote muscle anabolism (114).

5. CONCLUSIONS
Progressive muscle atrophy occurs in critically ill patients because they are exposed to numerous risk factors. As muscle atrophy leads to poor clinical outcomes, muscle mass should be monitored by ultrasound because of its noninvasiveness and demonstrated utility. For prevention, rehabilitation and EMS will help preserve muscle mass, and their combination with nutritional management is promising. Further investigation is necessary to prevent muscle atrophy and improve long-term outcomes.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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