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Chapter 9

Skeletal Muscle Dysfunction in Critical Illness

Yuki Iida and Kunihiro Sakuma

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Abstract

Despite improvements in critical illness survival rates with recent developments in medical care, many patients still have long-term physical disabilities following stays in the intensive care unit (ICU). Critical illness–induced muscle weakness, so-called ICU-acquired weakness (ICU-AW), is a common occurrence in approximately 50% of critically ill patients in the ICU requiring mechanical ventilation for >7 days. ICU-AW contributes to increases in duration of mechanical ventilation and lengths of ICU and hospital stays and may persist among survivors for several years after discharge. Risk factors for ICU-AW include systemic inflammatory responses, severe sepsis, muscle inactivity, hyperglycemia, and use of neuromuscular blockers. Thus, the development of muscle wasting is suggested to be associated with pathophysiological alterations leading to an imbalance between muscle proteolysis and proteosynthesis through several cellular signaling networks. This chapter presents a review of the literature regarding critical illness–induced muscle wasting and describes potential treatment of excessive muscle catabolism.

Keywords: critical illness, ICU-AW, muscle proteolysis, immobilization, neuromuscular electric stimulation therapy

1. Introduction

Skeletal muscle is one of the most dynamic and plastic tissues and is the largest organ in the body. Skeletal muscle is primarily involved in mechanical activity, which depends on muscle fiber contractions required for posture, physical activity, and respiratory movement. However, skeletal muscle is not only a component of the movement system, but it accounts for approximately 40% of the total body weight and contains 50–75% of all body proteins. In general, muscle mass depends on the balance between muscle protein synthesis and degradation. Both processes are sensitive to a number of factors, such as nutritional status, hormonal

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balance, physical activity, and inflammatory stimulation. The loss of lean mass is accompanied by a concomitant loss of muscular strength, which can lead to physical disability and loss of function. Muscle mass, strength, and function are also correlated with each other, and their decreases can lead to poor health outcomes and mortality [1].

Although the rates of survival from critical illness have improved due to recent developments in medical care, many patients have long-term physical disabilities following a stay in the intensive care unit (ICU) [2]. Many survivors of critical illness complain of generalized muscle weakness, so-called intensive care unit acquired weakness (ICUAW), for several months to years after discharge from hospital [3] and have persistent exercise limitations [4–6]. Severe neuromuscular weakness and muscle wasting often complicate recovery from critical illness.

This primary myopathy can take various morphological forms, and is assumed to be triggered by both sepsis and other factors, including the extensive use of neuromuscular blocking agents and corticosteroids [7]. However, diagnosis of ICUAW is difficult in the ICU, because either the preexisting disorder or complications arising during the ICU stay can cause muscle weakness. In addition, the patient's aggravated condition when first admitted to the ICU precludes careful clinical examination of ICUAW. Consequently, the attention of the physician is directed toward survival, and can delay diagnosis of ICUAW.

Electrophysiological investigations of peripheral nerves and muscles can help in the diagnosis of ICUAW at an early stage and to define prognosis, but they are time consuming and require the availability of skilled personnel.

Therefore, a guided approach to diagnosis is valuable. Management of ICUAW rests on supportive treatment, treatment of ongoing sepsis and multiorgan failure, and control of hyperglycemia. Recent evidence indicates that early rehabilitation can be carried out safely and effectively to maintain the physical function of ICU patients, requiring little patients sedation [3].

This chapter describes the incidence rates, major risk factors, epidemiology, and electrophysiological histological features of ICUAW. Major advances in early rehabilitation and protocols with little or no sedation in the ICU, which improve the functional independence of patients, are also discussed.

2. Epidemiology

Physicians have become aware of the existence of long-term functional impairment after ICU treatment. Herridge et al. [5] examined loss of muscle mass, muscle weakness, and easy fatigue 1 year after recovery from acute respiratory distress syndrome (ARDS). Even among relatively young patients, half were unable to work for 1 year after discharge, and some dysfunction persisted even after 5 years [6]. Such disorders have been noted as ICUAW, and awareness regarding these issues has increased in intensive care medicine [7, 8].

ICUAW is divided into three categories: critical illness myopathy (CIM), critical illness polyneuropathy (CIP), and critical illness neuromyopathy (CINM) that combines features of the former two conditions [9]. CIP is a pathological condition characterized by significant axonal

degeneration in sensory nerves, with no abnormalities in conduction velocity on electrophysiological analysis. In addition, the amplitudes of action potentials in muscle and sensory nerves are reduced [10]. Peripheral nerve microangiopathy due to inflammatory responses is involved in the pathophysiology of CIP [11, 12]. CIM is characterized by general muscle weakness and residual sensory function [13]. Catabolism accompanied by skeletal muscle disruption is often observed as the mechanism underlying its development. The muscle disorder caused by systemic inflammation and inactivity due to bed rest would be major factors [14, 15]. However, diagnosis of CIP and CIM is difficult because either existing disorders or complications occurring during the ICU stay causes muscle weakness. In addition, patient survival takes precedence in the ICU, and diagnosis of CIP and CIM is delayed or overlooked. Therefore, it is difficult to accurately determine the incidence rates of CIP and CIM [12, 16, 17]. Intriguingly, recent data suggest that CIP and CIM frequently coexist, a condition that has been termed CINM [18]. The pathophysiology of CINM/ICUAW is complex and includes the sequelae of bed rest, the effects of critical illness–induced cytokine production, and possibly the interplay of drugs, such as neuromuscular blocking agents and corticosteroids (**Figure 1**). Protein-energy malnutrition, electrolyte imbalances, and glutamine deficiency also play roles in the critically ill.

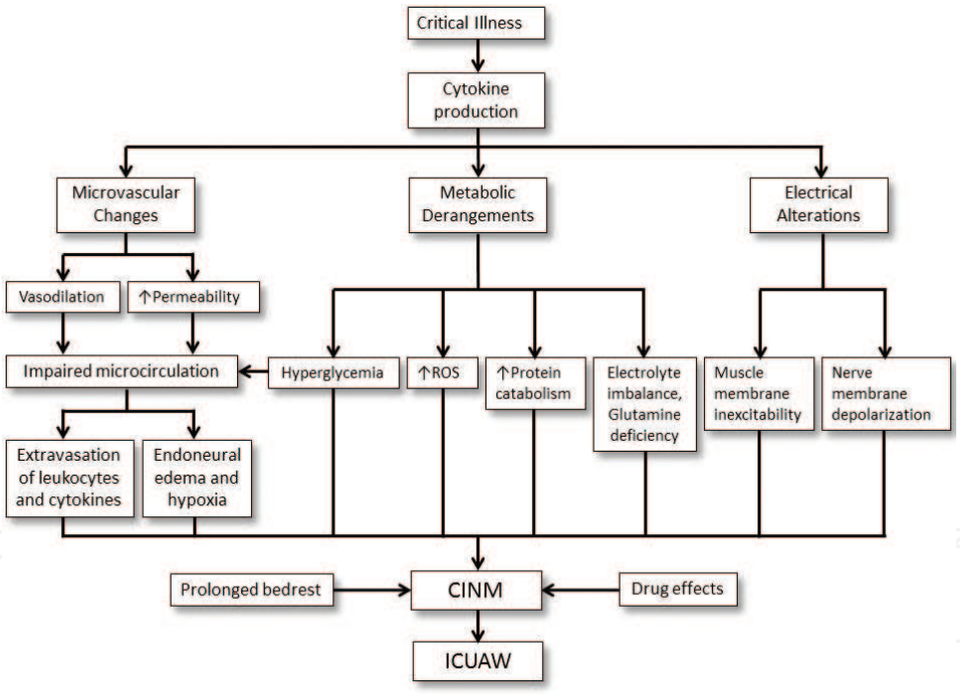


Figure 1. Pathophysiology of CINM/ICUAW. CINM, critical illness neuromyopathy; ICU, intensive care unit; ICUAW, ICU-acquired weakness; NMBA, neuromuscular blocking agent; ROS, reactive oxygen species.

Current estimates indicate that 70–80% of critically ill patients develop CIP, with a comparable percentage presumably developing CIM [16, 19, 20]. In subpopulations in which sepsis is complicated by multiple organ failure (MOF), the incidence rates of CIP and CIM could even reach 100% [20]. Approximately two-thirds of patients with ARDS exhibit these neuromuscular disorders [21], and in unselected patients that have required mechanical ventilation for at

least 4 days, the incidence rates of CIP and CIM range from 25 to 33% on clinical evaluation, and can reach 58% on electrophysiological evaluation [4, 17]. Furthermore, 49–77% of patients will have ICUAW when treated in an ICU for ≥7 days [22, 23].

ICUAW leads to prolonged physical disabilities that persist for months or years after ICU discharge [18, 24–26]. Nearly one-third of patients with ICUAW have difficulty in recovering independent walking or spontaneous breathing [27]. The effects of critical illness and ICU stay can result in serious weakness [3]. In the CRIMYNE study, the findings from the 1-year follow-up cohort study showed that patients with CIM recovered within 6 months, whereas those with CIP had a slower recovery or did not recover [17]. Mortality is increased in patients with CIP [4, 28].

The incidences of CIP and CIM are not clear, because of the wide variation in patient populations, risk factors, and diagnostic criteria, as well as in the timing of assessment [29]. In patients with mechanical ventilation beyond 7 days and with the presence of systemic inflammatory response syndrome (SIRS), the incidences of CIP and CIM were 33% on clinical assessment [22] and 30–58% on electrophysiological assessment [4, 10, 21]. The incidence rates were 34–60% in patients with ARDS [21], 24–77% in those with ICU stay beyond 1 week [10, 21, 22], 56–80% in those with multiorgan failure [15], and 100% in those with septic shock or severe sepsis [20]. A systematic review showed evidence of CIP and CIM in 46% of adult ICU patients that had lengthy periods of mechanical ventilation, sepsis, or multiorgan failure [10].

3. Risk factors for ICUAW

The ICUAW is regulated by several risk factors such as multiple organ failure, inactivity, hyperglycemia, corticosteroids, and neuromuscular blocking agents, although the pathogenic mechanism of ICUAW remains unclear (**Table 1**) [7, 30].

In particular, multiple organ dysfunction and immobility are important factors causing muscle dysfunction in patients in critical condition.

Multiple organ failure (MOF) is the major risk factor for ICUAW, but one needs to interpret it carefully. Neuromuscular organ failure of sepsis is the central element of the pathological condition in ICUAW. Indeed, sepsis, SIRS, and MOF develops the CIP [31]. Other diseases caused by SIRS, such as sepsis, induce mitochondrial injury [32], sodium channel inactivity [33], and have adverse effects on neuromuscular activity. Skeletal muscle proteolysis is the main pathogenic mechanism of CIM [28, 34]. The specific pathology of ICUAW reflects the structural deterioration of peripheral nerves and skeletal muscles, and not only disuse muscle atrophy [35].

Immobility also facilitates muscle wasting in critical illness. The conditions of low mechanical load, such as bed rest, immobilization, and disuse, induce marked losses of skeletal muscle mass, strength, and physiological function. Disuse muscle wasting involves a complicated cytokine and inflammatory response. Even a short period of bed rest for 5 days will results

SIRS/sepsis
Multiorgan failure
Hyperglycemia
Renal replacement therapy
Catecholamine administration
Female sex
Duration of mechanical ventilation
Corticosteroids
Neuromuscular blocking agents

SIRS, systemic inflammatory response syndrome.

Table 1. Risk factors implicated in the development of ICU-acquired weakness.

in significant decreases in the size of muscle fibers (3.5–10%) and muscle strength (9–13%) [36, 37]. However, as patients with ICUAW are usually under sedation, it is not clear how much sedation-induced inactivity affects the condition, apart from the severity of the disease. Therefore, to elucidate the pathology of ICUAW, factors of inactivity should be examined separately. Griffiths et al. [38] performed sustained passive exercise on one lower limb in a patient with severe respiratory failure in neuromuscular block, and examined the effects of intervention using the contralateral lower limb as a control limb. The results indicated that muscle strength and muscle protein level were significantly higher in the intervention limb. Thus, ICU patients suffer from long-term inactivity, and the methodology of physical activity in ICU should be reconsidered.

Diaphragmatic weakness, pulmonary injury, and atrophy develop rapidly during mechanical ventilation with sedation [39]. The duration of mechanical ventilation is independently associated with severe limb weakness or electrophysiological evidence of CIP [33, 40]. Respiratory muscle weakness also extends mechanical ventilation duration in the ICU. Respiratory muscle weakness elicits infection or sepsis, disease severity, and peripheral weakness [41, 42]. These data also suggest that ICUAW includes respiratory muscle weakness, because the diaphragmatic nerve and diaphragm also exhibit electrophysiological abnormalities similar to peripheral nerves and muscles [43].

Neuromuscular blocking agents and corticosteroids dose similar risks for ICUAW [44]. The risk of acute myopathy by the treatment with corticosteroid and neuromuscular blocking agent appears to increase after 24–48 hours of therapy. In addition, corticosteroids are the main determinants of impaired ability to exercise at 3 months in patients with critical illness myopathy [5]. After the first case report of profound frailty in asthma patients treated with corticosteroids and neuromuscular blocking agents [45], many similar findings were reported indicating that these two substances [28, 46] contribute to CIP/CIM or ICUAW. In animal studies, denervated and steroid-treated animals showed muscle changes similar to those observed in critical patients [47]. However, some studies have failed to confirm the adverse

effects of corticosteroids [22, 28, 48] or neuromuscular blocking agents [49]. The interaction between these drugs and ICUAW would ascribe to use as well as to complicated relationships with dose, timing, and other risk factors for ICUAW.

The other independent risk factors for ICUAW identified in previous studies are disease severity [22, 50], use of vasopressors and catecholamine [40], length of stay in the ICU [34, 40], renal failure and renal replacement therapy [50], hyperosmolality [28], parenteral nutrition [28], low serum albumin level [34], and neurological disorders [34]. Hyperglycemia was shown to be an independent risk factor for the electrophysiological and clinical signs of ICUAW, and increased insulin dose reduced the incidence of ICUAW [51]. Several studies indirectly demonstrated that the severity of disease is correlated with ICUAW, as reflected by acute inflammatory mediators and the use of vasopressors [40, 52]. Age is also an important risk factor for ICUAW [51]. As hospitalization in the ICU is often unpredictable, it is difficult to confirm the state of muscle function before onset. The motor function before hospitalization depends on many factors, but the muscle strength and muscle mass before onset reflect age to some extent.

4. Critical illness–induced muscle wasting

There are at least two phases, early and late phase, in the pathophysiological process of myopathy occurring in critically ill patients (**Figure 2**). The early phase progresses rapidly between the 3rd and 5th day after onset, whereas the late phase is slowly sustained from 5 days after onset. The following section describes how sepsis and inactivity, which are the main factors of ICUAW, influence myopathy in each phase.

4.1. Early phase

Pathophysiologically, the initial response to severe infection is in the activation of antigen-presenting immune cells. This occurs via pattern recognition receptors [53–55] with other immune mechanisms, such as cytokine release, endothelial and complement activation, and release of oxygen radicals. Inflammatory cytokines [tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1β] and complement factors (C3a and C5a) act as important mediators at this stage of inflammation [54]. Inflammatory stimulation causes muscle wasting mainly by degradation of muscle proteins [56]. Muscle proteins break down into amino acids and some are used in the liver for the synthesis of glutathione and acute proteins. Muscle proteins to be degraded are derived from myofibrillar proteins (actin, myosin), which account for 60–70% of muscle proteins [56]. Therefore, stressed patients lose 250 g/day of muscle protein corresponding to a muscle mass between 750 and 1000 g [57].

The muscle proteolysis in the early phase is caused by several cell signaling systems, but the major pathway of proteolysis activated in animal models of inflammatory muscle wasting are the calpain system and ubiquitin-proteasome system (UPS) (**Figure 3**). Calpain, a calcium-dependent protease, is activated first [58]. In septic rats, calpain activity seems to be increased by 70% as measured by the degradation products of azocasein in muscle extracts [59]. Although inhibition

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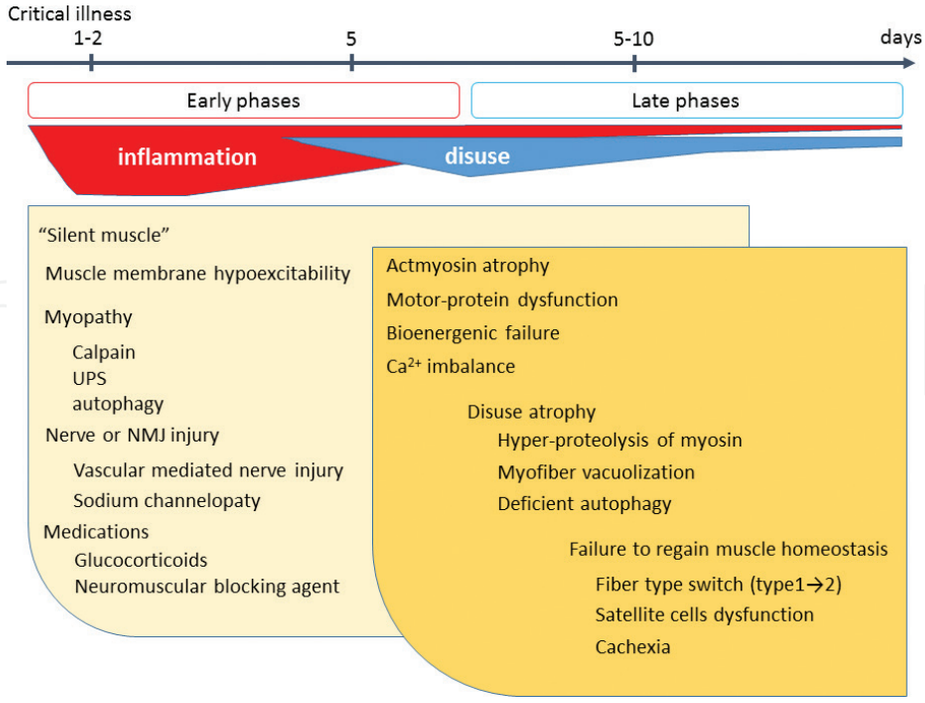


Figure 2. Mediators of critical illness-induced muscle dysfunction. Skeletal muscle atrophy is the most universal feature of the early phase, which is driven fundamentally by inflammation and disuse. Other factors, such as neuropathic injury and medications, can exacerbate atrophy and independently cause muscle dysfunction. Therefore, inhibiting muscle protein degradation is the most promising potential early-phase therapy. The late phase is marked by cessation of inflammation-induced muscle proteolysis, and therefore potential treatments at this time point will differ. Mediators of the late phase would involve persistence of some early-phase injuries or a failure to regain muscle homeostasis following the early phase. Late-phase dysfunction may be compounded by underlying premorbid neuromuscular defects. NMJ, neuromuscular junction; UPS, ubiquitin-proteasome system.

of calpain function cannot suppress muscle weight reduction, the sarcomere structure and contractile tension per unit area of muscle fibers are maintained at normal levels [60]. These findings suggest that the calpain system targets cytoskeletal proteins that maintain the sarcomere structure. Activated calpain does not directly degrade contractile proteins, such as actin and myosin, but degrades cytoskeletal proteins, such as titin and nebulin [61]. The activity of calpastatin, a calpain system inhibitor, is also decreased by 40–60% in the muscles of septic rats [62]. As a result, myofibrils, such as actin and myosin, are released into the cytoplasm in the monomeric state.

At the next stage, activation of the UPS rapidly degrades the myofibrils. UPS is the major decomposition system in various myopathies causing muscle atrophy, such as inactivity, inflammation, cell energy stress, and malnutrition. The forkhead box O (FOXO) family of transcription factors stimulates the expression of two important regulators of UPS-mediated proteolysis of ubiquitin ligase atrogin-1 and muscle-specific RING finger protein-1 (MuRF1) [63–65]. In animal models, both MuRF1 and atrogin-1 recruitment, and UPS activation, mainly contribute to the loss of muscle mass, such as inactivation-induced atrophy, acute illness, chronic disease, and CIM [63, 66, 67]. In human studies, mRNA expression levels of components of the UPS are increased in septic muscle. Muscle-specific E3 protein, MuRF1, and atrogin-1 in the vastus lateralis of critical patients are elevated at both mRNA and protein

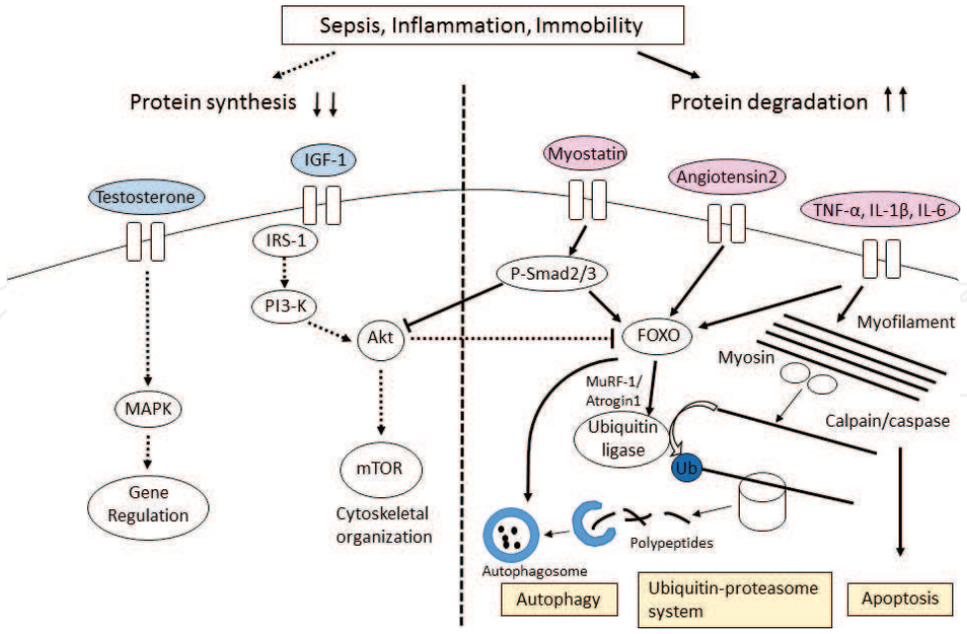


Figure 3. Muscle protein homeostasis in critical illness. The diagram depicts changes in protein metabolism caused by pathophysiological processes in critical illness, including sepsis, inflammation, and immobility. Upper circles denote altered regulation of major steps in protein synthesis (left) and degradation (right). PI3-K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, also known as protein kinase B; mTOR, mechanistic target of rapamycin; MAPK, mitogen-activated protein kinase; FOXO, forkhead box-O; Ub, ubiquitin; IRS, insulin receptor substrate.

levels [68]. The chymotrypsin-like peptidase activity of the membrane-associated proteasome is increased by 30% in limb muscle of critical patients [69].

Similar mechanisms contribute to respiratory muscle weakness in the acute phase. MuRF1 activity in the diaphragm is increased in critical patients under artificial respiratory management [70]. Postoperative respiratory muscle weakness would be caused by increased postoperative inflammatory cytokine production [71]. Mechanical ventilation as a substitute for diaphragm immobility is an important trigger, especially when combined with sedation, leading to weakness of the diaphragm [70].

The major etiology in the acute phase of CIP may be axonal dysfunction due to membrane depolarization disorders [72]. A disorder of the blood-nerve barrier is a pathogenic event induced in the absence of ultrastructural injury in the peripheral nerves [73]. Especially in peripheral nerves, the lack of autoregulation in capillary vessels leads to impairment of microcirculation. When the vascular permeability is increased, edema occurs in the endoneurium and ischemia develops in the tissue, resulting in microcirculatory insufficiency of peripheral nerve vessels [72]. In particular, damage to structural proteins of axons with high energy demand causes CIP with axonal degeneration of peripheral nerves.

4.2. Late phase

Risk factors of muscle wasting in severe patients directly or indirectly induce muscle inactivity. In the late phase, inactivity is the main cause of skeletal muscle contraction. Inactivity directly affects muscle wasting, even if there are no systemic inflammatory changes [74].

Some studies demonstrated the adverse effects of one-leg suspension and casting in bed rest on skeletal muscle mass in humans—the muscle mass and the cross-sectional muscle area were significantly decreased in the inactive leg. Muscle atrophy begins within hours of commencement of sleep and deep sedation. Muscle mass and muscular strength decline greatly within 10 days of rest, especially in the lower limbs, even in healthy people [75].

Anomalies in action potentials due to inactivity occur within several hours. As the general state of health recovers, potential anomalies readily improve [33]. However, this improvement reaches a plateau within 3–6 months, and some patients do not recover normal function even in 1–2 years. Little is known about the pathophysiology of CIP in this latter type of sustained ICUAW.

Electrical nonirritability of muscle has been reported in rat denervation and steroid administration models [76]. The primary cause of hypoexcitability of steroid-denervated fibers is the combination of resting potential depolarization and hyperpolarized shift in the voltage dependence of NaV1.4 sodium channel inactivation [77]. Depolarization of stationary membranes causes muscle inactivity and could be an important mechanism accounting for significant muscle weakness during immobility [78]. Upregulation of NaV1.5 sodium channels has been demonstrated in the muscle of rats with chronic sepsis, suggesting that several risk factors lead to muscle electrical nonexcitability [79]. A negative shift in sodium channel gating in peripheral nerves of muscle is distinguished from CIM as a characteristic disorder in CIP [80].

Recently, autophagy, a bulk degradation system of the cytoplasmic matrix, was shown to potently induce muscle atrophy [81]. Animal models of muscle atrophy (demyelination, sepsis, starvation) show increased autophagy, and FOXO transcriptional regulators modulate expression of several autophagy supporting genes [82–84]. However, autophagy dysfunction in mice caused enhanced oxidative stress inducing myofiber protein aggregates, abnormal muscle mitochondrial accumulation, and myofiber degeneration [85]. Thus, titration of the degree of autophagy appears to be essential for maintaining healthy muscle mass. That is, excessive autophagic activity leads to muscle atrophy, whereas toxic products accumulate and lead to muscle degeneration under conditions of autophagy failure.

Some studies showed UPS activation in acute CIM and septic human atrophic skeletal muscle [68, 86, 87], but others showed muscle protein degradation with low levels of MuRF1/atrogin-1 [88]. These discrepancies seem to be due to the dynamics of expression of UPS component mediators in muscle wasting. For example, in animal models, MuRF1/atrogin-1 mRNA levels increase only in short-term denervated or unweighted muscles, but do not increase over a long period of time [66]. Likewise, MuRF1 mRNA expression was also increased in the lateral vastus muscle of healthy volunteers with short-term rather than long-term periods of inactivity [89]. In chronic complete spinal cord injury patients, there were significant reductions in atrogin-1, MuRF1, and myostatin mRNA levels, and in FOXO1, FOXO3a, and atrogin-1 protein levels [90]. Therefore, another pathway seems to be promoted in the late phase instead of UPS.

Hussain et al. [91] reported that autophagy contributes to the induction of diaphragm muscle proteolysis in ICU patients. Induction of autophagy increased protein oxidation and enhanced expression of the FOXO1 gene, but not the FOXO3A gene. Controlled mechanical ventilation

also triggered the inhibition of both Akt expression and FOXO1 phosphorylation. In addition, the decrease in mature autophagic vesicles and accumulation of p62 (a protein degraded by autophagy) indicated deficiency of autophagy in the muscle of critically ill patients [92]. In severe conditions, autophagy would be the cause of muscle atrophy, and participate in the mediation of acute or persistent CIM.

Nuclear import of FOXO activates both UPS and autophagy pathways, and promotes muscle protein degradation of myotube cells, 70% of which is due to autophagy [61]. The expression of autophagy-related genes in skeletal muscle is markedly increased by fasting and denervation, and autophagy appears to be an important degradation system for chronic muscle atrophy in sarcopenia and cachexia [93]. In addition, FOXO and p38 mitogen-activated protein kinase (MAPK) induce expression of the muscle-specific E3 gene as well as expression of the autophagy-related gene Atg7 [94]. Furthermore, autophagy-related molecules, such as Beclin-1 and LC3-II proteins, are elevated in skeletal muscle under denervation for 7 days [95]. The elevated levels of LC3 and Beclin-1 mRNA expression were also reported in skeletal muscle after 3 or 7 days of denervation [64]. Under such conditions of inactivity, such as the late phase, autophagy seems to modulate muscle atrophy accompanying inactivity [96].

Critically ill patients lose muscle as a result of an inability to maintain rates of protein synthesis above those of protein breakdown [97]. Decline in muscle protein synthesis is observed very early in the period of inactivity. Studies using inactivity models, such as rat tail suspension and casting fixation, suggest that muscle protein synthesis declines rapidly within 6–24 hours after commencement of inactivity and that level is maintained during inactivity [98]. Therefore, the decrease in muscle protein synthesis contributes to muscle atrophy in the very early stages of inactivity. Insulin-like growth factor-1 (IGF-1) secreted from skeletal muscle along with physical activity binds to the IGF-1 receptor and promotes the activation of PI3K-Akt-mammalian target-mediated signaling of the rapamycin (mTOR) pathway. Subsequently, protein synthesis is promoted through phosphorylation of p70S6K involved in the initiation of downstream translation and inactivation of the translational repressor factor 4E-BP1. The PI3K/Akt pathway is an important network known to induce muscle protein synthesis and muscle growth [60]. Interestingly, Akt activation has been shown to block the progression of FOXO nuclear translocation and atrophy, demonstrating mutual signaling between muscle atrophy and hypertrophy induction [99].

The levels of Akt1, mTOR, p70S6K, and 4E-BP1 phosphorylation in the soleus muscle of rats are decreased by tail suspension for 7 days [100]. Signaling pathways regulating muscle protein synthesis are repressed in critically ill patients. For the mTOR pathway, a sepsis model showed interference with protein translation and inhibition of protein synthesis [101]. Protein phosphorylation was decreased for all signaling proteins of Akt1, PKB, GSK3, mTOR, p70S6K, and 4E-BP1 in a study of vastus lateralis muscle biopsies in 10 critical patients [86]. Therefore, in inactive skeletal muscles in which mechanical stress is relieved, decreases in IGF-1/PI3K/Akt signals cause reductions in muscle protein synthesis. These findings indicate that the signal transduction activity promoting protein translation is reduced in inactive patients.

5. Interventions for ICUAW

Effective interventions for ICUAW have not yet been established. As a strategy, avoiding or diminishing iatrogenic risk is of primary importance [44]. Risk factors for the occurrence of ICUAW include sepsis, hyperglycemia, inactivity, malnutrition, corticosteroids, and the use of neuromuscular blockers. All of these are risk factors causing hypercatabolic states, and avoiding these factors is a useful intervention strategy for muscle dysfunction.

5.1. Intensive insulin treatment

Several Randomized controlled trials (RCTs) have been reported for glycemic control in the ICU [102–104]. Many large clinical trials indicated that hyperglycemia should be avoided [105]. Increases in insulin resistance causing hyperglycemia occur frequently in critically ill patients, and are more apparent in CIM patients [106]. As a mechanism, GLUT-4 translocation impairment to myocytes would decrease glucose supply in patients. In a study based on muscle biopsy specimens, intensive insulin therapy (IIT) improved insulin resistance and GLUT-4 translocation in skeletal muscle [107]. RCT was performed to evaluate the effects of IIT (glycemic target 80–110 mg/dl) on neuromuscular function in ICU patients. IIT reduced the incidence of severe CIP from 49 to 25% in electrophysiological screening studies of long-term hospitalized surgery patients [40]. In another study, ITT decreased the duration of mechanical ventilation [108]. The relative risk for developing CIP by IIT was 0.65 (95% confidence interval 0.55–0.77) [44]. Its effect was ascribed to glycemic control rather than insulin dose [40], and it was observed only in patients in whom blood glucose was controlled within the normal range [103]. Similar findings were obtained in a retrospective study on the incidence of electrophysiological abnormalities before and after IIT [109].

On the other hand, Derde et al. [110], using muscle biopsy samples, demonstrated that IIT does not affect myofiber size, myofibrillar protein synthesis ability, or muscle proteolytic markers. ITT is considered to primarily have a neuroprotective role [107], but no neurological data are available. In the NICE SUGAR trial, it was questionable whether the blood glucose level should be strictly controlled within the normal range as a general treatment in critical care patients. In addition, intervention of IIT in critically ill patients increases the incidence of hypoglycemia and mortality rate [102]. These results would be due to methodological differences among the trials [111]. A strategy to reduce hyperglycemia without the risk of hypoglycemia is appropriate to reduce the incidence of ICUAW.

5.2. Early mobilization

In both the early and late phase, bed rest and mechanical unloading induce catabolism, muscle atrophy, and weakness. Therefore, minimizing the duration of inactivity would reduce the incidence of ICUAW [112, 75].

The first step to shorten the duration of inactivity is to reduce sedation. Reducing sedation seems to have a number of beneficial effects, including shortened period of mechanical ventilation and ICU stay, and lessened delirium [113]. However, there have been no studies

of its role in prevention of muscle function decline. Reduction of sedation could contribute to early mobilization in critically ill patients. The combination of approach to minimize sedation and early mobilization was investigated in critically ill patients with long-term mechanical ventilation [114]. Early mobilization and standard treatment were compared in 104 patients that received daily sedation interruption. Early mobilization improves exercise function at discharge, and shortens the duration of delirium and the duration of mechanical ventilation [114]. As there was no significant decrease in the incidence of ICUAW, reducing sedation would not improve the muscle strength itself but would help the patient to exercise efficiently.

To shorten the length of inactivity, early rehabilitation is carried out even with the use of a life-support device, such as mechanical ventilator or left ventricular assist device. There have been several reports that early rehabilitation is safe and feasible even in the early phase in the ICU, and is beneficial for reducing ICU and hospital stay [115, 116]. RCT comparing "cycling exercise 20 minutes at the bedside every day" and "standard physical therapy" during ICU stay did not report the occurrence of muscle weakness, but the isometric knee extensor strength and 6-minute walking distance were significantly higher in the intervention group [117].

However, there are several barriers to early rehabilitation, which may prevent the penetration of this approach [116, 118]. Although many ICUs have successfully implemented early rehabilitation into routine clinical care, widespread implementation remains low, with only 8–12% of mechanically ventilated patients mobilized out of bed as reported in two large multisite point prevalence studies [119, 120]. Although it is impossible to change illness severity and consciousness level of the patient, sedation levels [121] and intentions for treatment of therapists [122] can be corrected appropriately. For implementation of rehabilitation, appropriate protocols in the ICU are necessary to confirm the balance between beneficial effects and risk of mobilization, and to select the correct treatment intensity for the patients.

A study of 49 people that were not weaned from the ventilator for at least 14 days showed that whole-body rehabilitation and respiratory muscle training could improve muscular strength, ventilator weaning, and functional status [123]. Intriguingly, Connolly et al. [124] reported that rehabilitation after discharge is beneficial. Physical therapy during the recovery phase in ICUAW plays an important role, as the disuse syndrome during the late phase and anabolic resistance are added to the muscle dysfunction following early phase. As this problem has not been resolved, it is unclear how much such a strategy will promote recovery from ICUAW.

5.3. Neuromuscular electrical stimulation

Critically ill patients in the ICU have unstable cardiopulmonary dynamics and mental state, and in some cases are controlled by ventricular assist devices or hemodialysis. Therefore, not all patients undergo active physical activity. Under these restrictions, neuromuscular electrical stimulation (NMES), which involves muscle contraction by outside electrical stimulation, is used.

Some studies indicated the effects of NMES on patients in the ICU. In septic patients with mechanical ventilator management, NMES was applied to one lower limb and the other was used as a control limb. Muscle strength and muscle protein synthesis were improved more on

the stimulated side limb, although the muscle cross-sectional area and muscle mass decreased in both limbs [125, 126]. A previous RCT using NMES indicated increased muscle strength and decreased mechanical ventilator duration and the incidence of ICUAW decreased from 39.3 to 12.5% in the NMES intervention group [127].

NMES intervention for Chronic obstructive pulmonary disease (COPD) patients under mechanical ventilation improved the muscle strength and reduced the number of days needed to transfer from bed to chair [128]. Another RCT in COPD patients within the ICU did not show the occurrence of ICUAW in patients treated with NMES [129]. In addition, in the NMES group, the quadriceps muscle strength measured with a dynamometer and the walking distance were increased [130]. Although not performed in patients in the ICU, NMES intervention was shown to increase muscle strength and exercise tolerance [131]. NMES for critically ill patients in the ICU would ameliorate muscle weakness and improve mobility [132, 133].

Several basic studies examined the direct effects of NMES on muscle function in the ICU. Factors of muscle dysfunction, such as ICUAW, include neuropathy and muscle protein degradation caused by inflammation, peripheral microcirculation disorder, increased insulin resistance, and abnormal energy metabolism due to mitochondrial dysfunction [134]. NMES improves these factors that promote muscle catabolism [135–139]. In addition, NMES for patients undergoing cardiac surgery reduced the postoperative excretion of 3-methylhistidine as an indicator of muscle proteolysis [140]. A preliminary study using muscle biopsy specimens from patients at risk for ICUAW indicated that NMES could improve AMPK activation, glucose utilization, and GLUT-4 translocation [106].

Taken together, these findings indicated that NMES can inhibit catabolism and promote the anabolic pathway (**Figure 4**). As NMES can stimulate muscle contraction quantitatively and independent of intention in the patient, performance of NMES from the early phase is the most effective intervention for ICUAW. However, NMES research data should be interpreted carefully because of significant differences in baseline characteristics among patients, including APACHE II score and certain comorbidities [141]. There are several methodological problems, such as small sample size and incomplete results, and therefore these findings should be confirmed in large-scale trials. Although the amount of stimulation is unclear, it is important to maintain muscle contraction even at the early phase of critical illness.

5.4. Nutritional strategies

Malnutrition develops rapidly in critically ill patients due to dysfunction of the gastrointestinal tract. Hence, rich nutrition management in the acute phase may be considered, but the scientific evidence is not yet clear.

Although patients undergoing esophagectomy or pancreaticoduodenectomy did not receive enteral nutrition during the 6 days postoperatively, there were no significant differences in grip strength, respiratory muscle strength, or recovery of walking ability, compared with nutritionally fed patients after jejunostomy [142]. In the EPaNIC study, 4640 patients were randomized to early parenteral replacement therapy (early PN group) or tolerating caloric deficiency for first week in ICU (late PN group) [143]. The late PN group

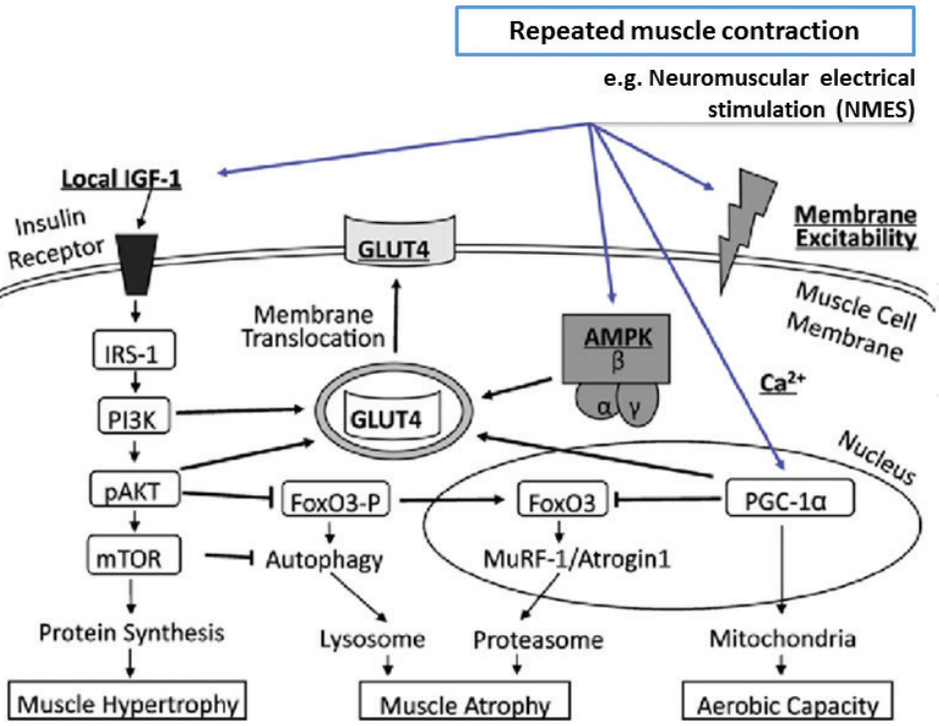


Figure 4. Suggested beneficial effects of neuromuscular electrical stimulation (NMES) with regard to muscle hypertrophy, atrophy, aerobic capacity, membrane excitability, and membrane translocation of GLUT4. NMES may preserve membrane excitability. Membrane translocation of GLUT4 is regulated by IGF-1, AMPK, PGC-1α, and its downstream targets, which may all be affected by NMES. Atrophy gene expression (MuRF-1, atrogin-1) increases upon dephosphorylating of FOXO3 transcription factors, which is inhibited by downstream insulin signaling.

showed promotion of recovery, decreased mechanical ventilator duration, and reduced complications compared to the early PN group. In addition, whole-body muscle strength assessment using the Medical research council scores was performed in patients predicted to be at high risk of developing ICUAW [144]. Evaluation of muscle strength was conducted three times a week from day 8 until ICU discharge or death. The incidence of ICUAW was significantly lower in the late PN group compared with the early PN group. In the muscle biopsy specimens of 122 patients with EPaNIC, LC3II and LC3I ratios associated with autophagosome formation were higher in patients in the late PN group than the early PN group [144]. This study indicated that the muscle fiber autophagy pathway was more efficient in the late PN group.

Another large RCT was performed in 1372 ICU patients to compare conventional management with early parenteral nutrition. This study indicated a greater degree of muscle wasting in patients under conventional management [145]. The Eden trial examined enteral nutritional management versus nutritional feeding in 1000 ICU patients with acute lung injury [146]. At 6- and 12-month follow-up, the physical abilities of 174 survivors were significantly lower than the predicted values. However, no significant differences were found in MRC total score, grip strength, maximum inspiratory pressure, 6-minute walking distance, or quality of life between the two groups [147]. Therefore, high energy intake from the early phase showed no evidence of improved physical function, but rather may worsen muscle wasting.

Treatment with various supplemental nutritional components has been studied. Glutamine concentrations in plasma and skeletal muscle are low in critical patients and are independent predictors of mortality [57]. Glutamine is an essential amino acid and its supplementation improves muscle function [57, 148]. A meta-analysis of glutamine supplementation in critically ill patients reported beneficial effects on prognosis [149]. In contrast, two RCTs indicated no such effect of glutamine supplementation [150, 151]. Although the effects on muscle function have not been studied, an increase was observed in mortality in critical patients with multiple organ failure [151]. The use of other micronutrients against oxidative stress is sensible from the pathophysiological point of view. Two meta-analyses concluded that antioxidant micronutrients may be beneficial for critically ill patients [152, 153]. Preliminary data from animal studies indicated that mitochondrial reactive oxygen species (ROS) is an important factor in the progression of diaphragm atrophy and contractile dysfunction occurring during mechanical ventilation [154]. However, the effects on muscle weakness were not examined, and a recent large RCT showed no beneficial effect of antioxidants in critical patients with multiple organ failure [151]. Therefore, early nutritional therapies enriched with immunomodulatory nutrients would not reduce the incidence of ICUAW compared with standard nutritional therapy for critically ill patients [155].

6. Summary and future directions

ICUAW is a common complication and an important contributor to the physical disabilities persisting in ICU survivors. Although various interventions have been used to prevent the adverse effects of ICUAW, no established therapy is available. Early rehabilitation can be an important preventative therapy for ICUAW. "Silent muscle" in the early phase of ICUAW leads to muscle catabolism through the protein degradation signaling pathway. Strategies aimed at minimizing the duration of immobilization would contribute to the suppression of muscle wasting during critical illness. Promotion of intermittent muscle contraction, such as NMES, would mitigate the severity and incidence of muscle wasting. Sakuma et al. [156] reported that resistance training combined with amino acid-containing dietary supplements would be the best way to prevent the muscle wasting and weakness, including sarcopenia. This proposal can also be applied to preventive strategies for ICUAW, especially in the late phase. Further research is required to design novel rehabilitation strategies for initiating anabolic reaction and improving muscle function in patients that cannot actively participate in physical therapy in the acute phase of critical illness.

Author details

Yuki Iida[1]* and Kunihiro Sakuma[2]

*Address all correspondence to: y2iida@na.commufa.jp

1 Department of Rehabilitation Medicine, Kainan Hospital, Yatomi, Japan

2 Tokyo Institute of Technology, Tokyo, Japan

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