Files et al. Critical Care (2015) 19:266
DOI 10.1186/s13054-015-0979-5

CRITICAL CARE

REVIEW Open Access

A conceptual framework: the early and late phases of skeletal muscle dysfunction in the acute respiratory distress syndrome

D. Clark Files[1,2*], Michael A. Sanchez[1] and Peter E. Morris[1,2]

Abstract

Patients with acute respiratory distress syndrome (ARDS) often develop severe diaphragmatic and limb skeletal muscle dysfunction. Impaired muscle function in ARDS is associated with increased mortality, increased duration of mechanical ventilation, and functional disability in survivors. In this review, we propose that muscle dysfunction in ARDS can be categorized into an early and a late phase. These early and late phases are based on the timing in relationship to lung injury and the underlying mechanisms. The early phase occurs temporally with the onset of lung injury, is driven by inflammation and disuse, and is marked predominantly by muscle atrophy from increased protein degradation. The ubiquitin-proteasome, autophagy, and calpain-caspase pathways have all been implicated in early-phase muscle dysfunction. Late-phase muscle weakness persists in many patients despite resolution of lung injury and cessation of ongoing acute inflammation-driven muscle atrophy. The clinical characteristics and mechanisms underlying late-phase muscle dysfunction do not involve the massive protein degradation and atrophy of the early phase and may reflect a failure of the musculoskeletal system to regain homeostatic balance. Owing to these underlying mechanistic differences, therapeutic interventions for treating muscle dysfunction in ARDS may differ during the early and late phases. Here, we review clinical and translational investigations of muscle dysfunction in ARDS, placing them in the conceptual framework of the early and late phases. We hypothesize that this conceptual model will aid in the design of future mechanistic and clinical investigations of the skeletal muscle system in ARDS and other critical illnesses.

Introduction

Improvements in general critical care and ventilator management of acute respiratory distress syndrome (ARDS) over the past four decades have led to a significant reduction in mortality, from 80 % in the initial reports to the current rate of 20 % to 30 % reported in clinical trials [1]. These trends have resulted in a growing number of ARDS patients who are ICU survivors: approximately 200,000 people per year in the United States alone [2]. Unfortunately, these patients commonly have lasting sequelae, including increased mortality [3–5], physical and cognitive impairment [6–8], and reduced quality of life [9]. With the introduction of such outcomes in clinical trials, the skeletal muscle system has been increasingly recognized as a major target organ in ARDS. Clinically apparent skeletal muscle weakness in the critically ill, termed ICU-acquired weakness (ICUAW) [10, 11], occurs in up to 60 % of patients and is independently associated with mortality [12, 13].

We propose, on the basis of observations of animal models and clinical studies, that muscle wasting in patients with ARDS can be divided into early and late phases. These phases differ in pathophysiology and potential underlying mechanisms and can be identified by their relationship to the time course of lung injury, recovery, and resolution. In this review, we will summarize major recent findings regarding clinical and mechanistic investigations into muscle wasting in ARDS and frame them in the context of the early and late phases. We propose that this conceptual framework will enhance the

* Correspondence: dfiles@wakehealth.edu
[1]Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA
[2]Critical Illness Injury and Recovery Research Center Chadwick Miller MD Department of Emergency Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA

design of future clinical and mechanistic investigations and aid in tailoring therapies designed to treat muscle wasting in ARDS.

ARDS is the more severe end of the spectrum of diseases requiring admission to an ICU. Although the muscle-wasting response of patients with ARDS has not been explicitly compared with that of critically ill patients without ARDS (that is, sepsis), patients with ARDS appear to have a very high incidence of ICUAW (up to 60 %) [12–15]. While the animal studies offer some clues to mechanistic differences between muscle wasting in ARDS and sepsis [16], further carefully controlled human studies are needed to determine whether clinical differences exist in the muscle injury and recovery trajectories of sepsis patients with and without concomitant ARDS. For these reasons, in this review, we will focus primarily on muscle wasting in ARDS, although we feel that this paradigm may prove useful in other critical illnesses, such as sepsis.

The diagnosis of intensive care unit-acquired weakness

Since the original report by MacFarlane and Rosenthal [17], muscle wasting associated with critical illness has been called acute quadriparetic myopathy, thick filament myopathy, critical illness myopathy, critical illness polyneuropathy, and ICU-acquired paresis, among other terms. These names reflect the varying associated pathologic and electrophysiologic characteristics. The nomenclature has recently been simplified, and the term ICUAW signifies clinically measureable weakness in a critically ill patient without other known precipitating factors causing nerve or muscle injury [10, 11].

The diagnosis of ICUAW is made by using either manual muscle testing (MMT) or grip strength meters and by using specified cutoff values to denote weakness. Unfortunately, MMT is effort-dependent and insensitive and likely under-represents the degree of muscle dysfunction present in these patients [18–20]. MMT, grip strength meters, and hand-held dynamometers also all lack the ability to clearly discern muscle fatigability, which may contribute to the long-term functional impairments in ICU survivors. Other functional tests - such as the short physical performance battery [21], six-minute walk distance [8], or walk speeds [22] - may provide more information about global function, although these composite functional tests can be affected by factors other than muscle dysfunction and require a cooperative, engaged patient.

Given the limitations of these volitional measurements of muscle function in critically ill patients and survivors, other methods for identifying ICUAW are needed. Nerve conduction and direct muscle stimulation may improve the sensitivity of diagnosing ICUAW in the non-cooperative patient [23] but are infrequently used at present. Skeletal muscle ultrasound is a promising modality that can non-invasively identify the loss of muscle mass in critically ill patients; muscle echointensity values may yield additional functional information [24, 25]. These modalities remain promising, although further research is needed in this area.

Systemic 'biomarkers' of ICUAW would also be helpful in identifying ICUAW. Creatine phosphokinase, the most common laboratory test used for identification of myositis in other contexts, is not helpful in identifying patients with ICUAW [11, 15]. In a pilot study, peak plasma neurofilament levels were higher in patients with ICUAW, but peak levels were not reached before patients could engage in MMT, limiting the utility of this as a biomarker [26]. Another study of post-cardiac surgery patients found that insulin-like growth factor 1 (IGF-1) levels were suppressed in patients who developed ICUAW but that growth and differentiation factor 15 levels were elevated [27]. Additional studies are needed to identify systemic biomarkers that can reliably identify patients at high risk for developing ICUAW. Identifying such patients may assist in targeted allocation of physical therapy or future pharmacologic interventions.

Phases of muscle dysfunction in acute respiratory distress syndrome

Definition of the early phase

The early phase of muscle dysfunction, which occurs hours to days after the onset of illness, begins with the activation of acute lung and systemic inflammation characteristic of early lung injury. We define the early phase to begin with the onset of the acute illness and terminate when the acute inflammation-driven muscle atrophy program resolves (Fig. 1), usually within days.

Muscle atrophy is the predominant and characteristic feature of early-phase muscle dysfunction and is driven primarily by (a) acute systemic inflammation and (b) limb and diaphragmatic muscle disuse from enforced bed rest and mechanical ventilation, respectively. Nerve, neuromuscular junction (NMJ), or direct myofiber injury or a combination of these may variably initiate atrophy or contribute to muscle weakness during the early phase. Considering the ubiquity of inflammation- and immobility-induced atrophy in these patients, we hypothesize that all patients with ARDS experience early-phase muscle wasting. We propose that atrophy is the most universal feature of ICUAW, although other pathologies such as inflammatory myopathies, polyneuropathies, or combinations also occur. Factors such as age, illness severity, organ failures, medications, malnutrition, and hypoxia may drive the severity or type of muscle dysfunction in an ancillary fashion. The drivers and clinical significance of these differing phenotypes are poorly understood. However, it is clear that

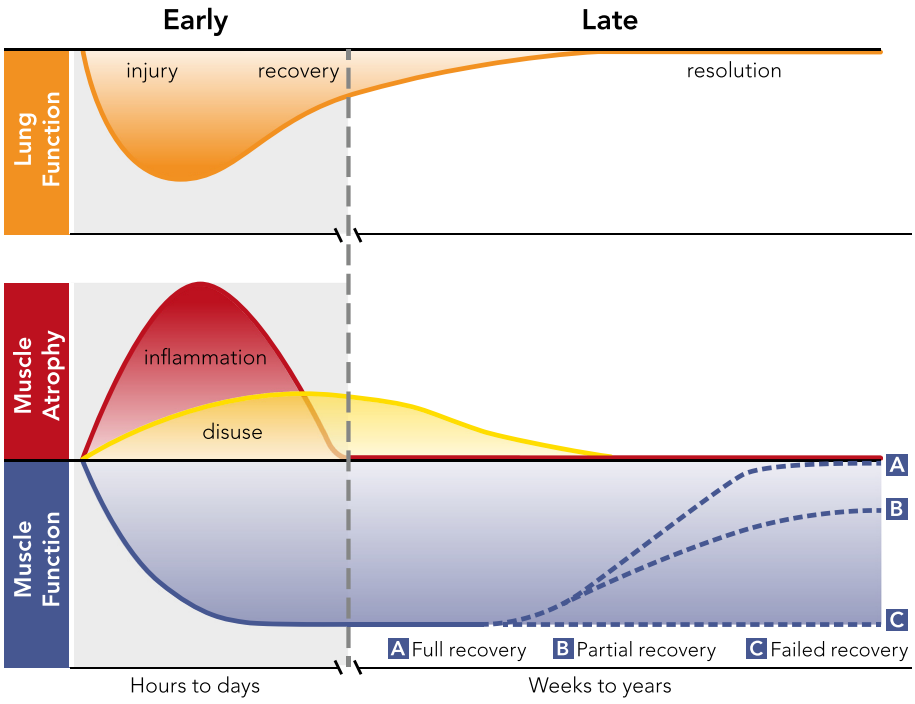

Fig. 1 The early and late phases of muscle wasting in acute respiratory distress syndrome. The early phase of muscle wasting begins with the onset of lung injury and is caused by lung and systemic inflammation and to a lesser degree disuse, both leading to muscle atrophy. The late phase of muscle wasting begins as lung function recovers and acute systemic inflammation resolves. Disuse continues in many patients during the late phase. Muscle function deteriorates in the early phase, and dysfunction persists in many patients during the late phase, which may last for years despite resolution of lung injury and cessation of ongoing muscle atrophy. Factors mediating recovery trajectories in the late phase are poorly understood

both limb [12] and diaphragmatic [28, 29] muscle weakness, regardless of the pathophysiology, independently contribute to early-phase mortality.

Definition of the late phase

The late phase of muscle dysfunction begins following resolution of the early acute lung and systemic inflammation characteristic of the early phase, usually following the first few days of illness and during the recovery phase of lung injury. Muscle atrophy may continue into the late phase, driven by disuse, but this factor usually resolves once patients are no longer bedridden. Similar to early-phase wasting, late-phase muscle weakness may occur from persistent or unresolved nerve or NMJ injury [30, 31].

The characteristic feature of late-phase muscle wasting is that muscle dysfunction persists despite recovery and resolution of lung injury in many patients [8, 20]. Factors such as age, baseline (pre-ARDS) muscle function, medications administered during or after the ICU stay, comorbidities, route of muscle injury (nerve versus NMJ versus myofiber), and nutrition may contribute to both the degree of injury and the rate of muscle functional recovery. However, the clinical characteristics associated with complete, partial, or failed recovery of muscle function in ARDS survivors (Fig. 1) are generally poorly understood.

One fundamental question is whether the recovery of muscle function in the late phase is associated with recovery of muscle mass or alternately whether weakness persists despite recovery of muscle mass. Answering this question would clarify potential mechanisms underlying persistent late-phase weakness. Unfortunately, since prehospital functional status of these patients is almost always unknown, it is difficult to know how baseline muscle function contributes to long-term functional outcomes. In many patients, the 'failure to recover' may reflect their baseline functional status pre-ARDS.

Prolonged metabolic disturbances and immune suppression have been described in survivors of burns [32] and sepsis [33]. The term post-intensive care syndrome has been used to refer to the constellation of psychiatric, cognitive, and physical function problems present in ICU survivors, including those with ARDS [34]. The relationship of systemic immunosuppression or hypermetabolism to late-phase skeletal muscle dysfunction in patients with ARDS deserves further attention.

Pharmacologic and nutritional contributions to early- and late-phase muscle wasting

Some of the earliest reports of muscle weakness in critically ill patients associated the presence of what is now

called ICUAW with both glucocorticoids and neuromuscular blockade (NMB) [35, 36]. However, more current evidence suggests that glucocorticoids, but not NMB, is associated with ICUAW [20, 23, 37]. In the most compelling recent evidence, a randomized controlled trial of the neuromuscular blocker cisatracurium for severe ARDS, the incidence of ICUAW, measured by MMT, at hospital discharge was no different from control [38].

The association of ICUAW with glucocorticoids appears stronger than that of NMB. Increased duration of glucocorticoid use is independently associated with increased myosin degradation in the skeletal muscles of critically ill patients on mechanical ventilation [39]. In the ARDS Network Long Term Outcomes study, which followed ARDS survivors enrolled in ARDS network trials, both dose of corticosteroid and ICU length of stay were associated with reduced functional outcomes at 6 and 12 months [20]. These results suggest that drugs or interventions in the ICU, even administered for short durations, can impact long-term outcomes. Other data supporting the importance of glucocorticoids in muscle wasting in ARDS include the fact that the glucocorticoid receptor is an upstream modulator of muscle ring finger 1 (MuRF1) activation [40], an important contributor to early-phase muscle wasting (see 'The ubiquitin-proteasome system and muscle ring finger 1' section). Overall, the available data suggest that both endogenous and exogenous glucocorticoids contribute to muscle dysfunction in ARDS.

The role of nutrition in muscle weakness in critical illness and its contribution to muscle wasting is controversial, although recent evidence suggests that increased caloric intake during the early phase does not prevent late-phase muscle dysfunction. In the long-term follow-up of patients with ARDS in the EDEN (early versus delayed enteral nutrition) trial, muscle functional outcomes were unchanged between the two arms at 6 and 12 months [6]. Emerging evidence suggests that early parenteral nutrition (PN) is detrimental for muscle function in these patients [41]. The currently available data suggest that early and full caloric nutrition, either enteral [42] or parenteral [41], does not reduce the incidence of ICUAW in critically ill patients, although future investigation is warranted. Nutritional factors may be more important for improving muscle mass when administered during the late phase.

Early- and late-phase muscle dysfunction in acute respiratory distress syndrome: underlying mechanisms

Mechanisms of early-phase muscle wasting

As mentioned above, the cardinal feature of early-phase muscle dysfunction is atrophy, driven by inflammation and disuse. The net balance of protein synthesis and degradation determines myofiber size. Therefore, atrophy can occur through increased protein degradation, reduced protein synthesis, or both. In most experimental models of muscle atrophy, increased muscle protein degradation - not reduced protein synthesis - accounts for the loss of muscle mass [43], although some controversy remains [44]. With regard to ARDS-associated muscle dysfunction, both increased protein degradation and reduced protein synthesis contribute to early-phase atrophy, although the former mechanism predominates. In the largest recent study measuring protein synthesis and degradation in critically ill patients (which included, but was not limited to, patients with ARDS), rectus femoris cross-sectional area decreased by 18 % over 10 days. In this study, patients in the early phase (day 1) showed reduced protein synthetic rates compared with fasted controls. At this time point, muscle protein degradation predominated over protein synthesis. By day 7, protein synthetic rate had increased compared with day 1 and fasted controls, likely an attempt of the muscle to recover from the massive protein degradation and atrophy during the inflammation-driven early phase, although the balance remained favoring ongoing atrophy [45].

In recent years, three major pathways have emerged as the primary regulators of muscle atrophy: the calpain-caspase system, the ubiquitin-proteasome system (UPS), and the autophagy-lysosome system (autophagy) [43, 46]. All have been implicated in inflammation and disuse atrophy, but their relative contributions and interrelationships during the early phase of muscle wasting in ARDS remain incompletely understood.

Inflammation-driven atrophy

Both pro- and anti-inflammatory cytokines are present in the lungs and plasma of patients with ARDS [47]. Many of these pro-inflammatory cytokines are associated with muscle atrophy in humans and rodents, including tumor necrosis factor-alpha [48], interleukin (IL)-6 [49], IL-1β, and others [50, 51]. Muscle atrophy occurring via inflammatory cytokines classically requires activation of the transcription factor NF-κB (nuclear factor kappa light chain enhancer of activated B cells) [52–54], which in turn can increase muscle protein degradation, leading to rapid limb and respiratory muscle myofiber atrophy.

In lung-injured mice, marked early muscle atrophy occurs along with lung inflammation [16]. NF-κB activation in skeletal muscle is necessary for initiating the muscle atrophy during this early phase [55]. These data suggest that systemic mediators, such as inflammatory cytokines or other soluble factors that activate NF-κB, are important in the early phase of muscle atrophy in ARDS. These muscle proteolytic pathways may exist in order to provide nutritional substrates to an organism under major stress, such as massive infection or injury. In addition to promoting muscle protein degradation, pro-inflammatory cytokines may promote atrophy through

inhibition of the pro-hypertrophy IGF-1/AKT pathway [56], although this concept has received less attention.

Disuse-driven atrophy

There is little doubt that disuse contributes to the limb muscle atrophy associated with ARDS, given the profound limb and diaphragm disuse that characterizes these patients. In fact, recent work suggests that bed rest may 'prime' skeletal muscle for atrophy by increasing the expression of muscle surface TLR4 (Toll-like receptor 4) receptors, which, when activated, can promote atrophy [57, 58].

However, both animal models and human data support the concept that muscle wasting associated with lung injury is phenotypically different from that induced by immobility alone. A recent report of healthy persons confined to bed rest for one week documented a 4 % loss of lean body mass [57]. In a study of critically ill patients on mechanical ventilation, muscle mass loss was approximately 12 % [45] over that same time period. Likewise, in an animal model of hind-limb immobilization, an approximately 5 % muscle mass loss of the tibialis anterior muscle was seen at day 3.5 [59], and we find an approximately 22 % muscle mass loss in the tibialis anterior of lung-injured mice at this time point [16]. Collectively, these data support the concept that disuse atrophy contributes to the early phase of wasting, but less so than inflammation-driven atrophy.

Molecular targets for attenuating muscle atrophy in the early phase

The ubiquitin-proteasome system and muscle ring finger 1 Animal models and emerging human data suggest that the UPS plays a prominent role in the early phase of limb and diaphragmatic muscle wasting in ARDS. We and others have shown that the UPS-mediated atrophy is prominent in the early phase of muscle wasting in lung-injured mice [16, 55, 60]. The E3 ligase MuRF1, which coordinates the ubiquitination of myosin heavy chain (MyHC) and other contractile proteins for proteasomal degradation [61], is necessary for early-phase atrophy in this model. Support for the importance of this mechanism in ICUAW is the finding that selective MyHC degradation is a salient pathologic feature of critical illness myopathy [62]. Others have shown that 20S proteasome activity is upregulated in the vastus lateralis of patients on mechanical ventilation, which was also associated with upregulation of the forkhead box o (FoxO) transcription factors, MuRF1, and other atrophy-promoting genes [39]. In recent work evaluating serial biopsies in mechanically ventilated patients, the only consistent change in protein expression was in MuRF1 and atrogin 1 expression, both of which were downregulated over time [45], supporting the observation that this pathway is activated in the early phase. Another study reported reduced MuRF1 levels in the muscles of critically ill patients, although the varying time points for muscle biopsies limit the interpretation of this finding [63]. The currently available human and animal data suggest that the UPS plays a prominent role in the early phase of muscle atrophy in ARDS. As therapeutic agents targeting proteins involved in UPS-mediated atrophy are developed and tested [64], their use in the early phase of ARDS-associated muscle wasting should be considered.

Autophagy Briefly, macroautophagy (autophagy) is a ubiquitous process present in multiple cell types in which cellular proteins and cytoplasm are degraded and recycled via lysosomes. A focus on autophagy in skeletal muscle is relatively underexplored [65]. Increased autophagic flux can cause atrophy, although inhibition of autophagic flux can also induce atrophy, potentially through upregulation of the UPS [65, 66]. Interestingly, both the UPS and autophagy pathways can be regulated by the same FoxO transcription factors [67].

Evidence suggests that autophagy is involved in ARDS-associated muscle wasting. Diaphragmatic disuse due to mechanical ventilation in brain-dead humans is associated with the rapid appearance of autophagosomes and autophagy-related genes and proteins [68]. This finding could be due to either increased flux or a block in distal autophagy processing. In a pig model (combining mechanical ventilation, endotoxin, NMB, and corticosteroids), significant limb muscle atrophy was associated with reduction in critical autophagy genes and proteins [69].

In a prospective study of 600 patients in the EPaNIC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients) trial, 122 of whom underwent muscle biopsy, those randomly assigned to late PN had a reduced incidence of ICUAW compared with those with early PN; this result was associated with an increased LC3II-to-LC3I ratio, a marker of autophagosome formation [41]. These data suggest that autophagy induction is associated with improved muscle function.

The role of autophagy during the early phase of muscle wasting in ARDS is complex, given that either accelerated or impaired autophagy may be deleterious to muscle function. Details regarding the role of autophagy and its relationship with the UPS are still emerging, and more work is needed to determine the role of autophagy in the early phase of muscle wasting in ARDS. Other types of muscle autophagy, including microautophagy [70] and chaperone-mediated autophagy [71], also deserve future investigation in this context.

Caspases and calpains Caspases and calpains are early mediators in the breakdown of sarcomeric proteins that

can then undergo degradation by the UPS or autophagy pathway. Caspases and calpains have been investigated more extensively in both endotoxin- and mechanical ventilation-induced diaphragmatic dysfunction but not (to our knowledge) in animal models of lung injury. Supinski and colleagues [72] showed that calpain, caspase, and proteasome activity are upregulated in the diaphragm of endotoxin-treated mice. Likewise, diaphragm calpain activation peaks early (24 h) in the cecal ligation mouse model of sepsis. Co-administration of eicosapentoic acid prevented the loss of specific force-generating capacity in the diaphragm and prevented calpain activation [73, 74]. Others have shown that mechanical ventilation in humans causes atrophy and increased caspase 9 activity in diaphragm fibers [75]. As such, calpains and caspases remain attractive potential targets for intervention in the early phase of muscle wasting.

Neuropathy and other pathologies as potential therapeutic targets in the early phase

As mentioned above, polyneuropathy is found in a subset of patients with ICUAW. Critical illness polyneuropathy affects distal axonal sensory and motor nerves, which may lead to myofiber atrophy and contribute to weakness independent of atrophy. Histologically, peripheral nerves with [76, 77] or without [78] axonal degeneration have been described. The polyneuropathy in patients without nerve degeneration has been proposed to be due to a transient negative shift in voltage dependence of sodium channel fast inactivation leading to reduced excitability of the nerve, demonstrated in both rats and humans [79].

Autonomic dysregulation, which may be present in many patients with severe critical illness, may also contribute to polyneuropathy [80]. With this in mind, there has been recent interest in using β-blockade in patients with septic shock [81] as a way to attenuate sympathetic over-activation. Interestingly, stimulation of skeletal muscle β receptors leads to muscle hypertrophy through stimulating protein synthesis [82]. Therefore, muscle function should be incorporated into clinical trial design of future investigations of β-blockade in critical illness.

Epineurial and endneurial vascular leak [83] causing nerve edema is another proposed mechanism. Hyperglycemia, often characteristic of severe critical illness, could further impair nerve or muscle microcirculation [84]. This hypothesis may explain why intensive insulin therapy has been associated with a reduced incidence of ICUAW [85, 86]. Interestingly, the glucose transporter-4 (GLUT4) receptor, which modulates glucose uptake into muscle, appears mislocalized in patients with critical illness myopathy [87].

Additionally, reduced muscle membrane excitability is a common finding on electromyographic studies [23]. A series of studies has shown impaired sarcoplasmic reticulum calcium handling and impaired sodium channels in muscles of denervated and steroid-treated rodents [88–90], but to our knowledge this has not been studied in the context of lung injury. Owing to altered metabolism or increased muscle fatigue, muscle mitochondrial injury [91, 92] sustained during the early phase may contribute to muscle dysfunction.

Molecular targets for attenuating muscle atrophy in the late phase

Ongoing active muscle proteolysis through increased protein degradation does not appear to be a major contributing factor of weakness during the late phase. The massive inflammation-induced protein degradation has subsided at this time point [16, 45]. Therefore, therapies directed at attenuating muscle proteolysis are less likely to benefit as much as when administered during the early phase.

In contrast, enhancing protein synthesis may be useful during the late phase. Two studies suggest that there is actually already increased protein synthesis in the late phase. One study showed muscle activation of the pro-synthesis AKT-mTOR-S6k (AKT-mammalian target of rapamycin-ribosomal protein S6 kinase) pathway of critically ill patients from muscle biopsies that were obtained predominantly in the late phase [63]; a second study showed increased protein synthesis in the muscles of critically ill patients at day 7 [45]. This may be a compensatory mechanism to recover from the early phase, and studies are needed to determine whether augmenting protein synthesis pathways can improve muscle mass during the late phase. Therefore, we propose that late-phase therapies to improve muscle mass focus on enhancing protein synthesis or other factors to enhance myofiber size, such as through the myostatin pathway [93].

Neuropathy and other pathologies as potential therapeutic targets in the late phase

Evidence suggests that denervation injury may persist into the late phase. In a cohort of mechanically ventilated critically ill patients, muscle biopsies at about day 12 revealed upregulation of the muscle acetylcholine receptor γ mRNA, a marker of muscle denervation [39]. Late-phase wasting may also exist due to persistence of some factors initiated during the early phase, such as disuse, nerve or NMJ injury, excitation contraction uncoupling, inflammatory myopathy, or mitochondrial dysfunction.

Additional targets during the late phase include enhancing muscle regeneration by targeting muscle stem (satellite) cell activation/repair [94]. Additionally, enhancing autophagy, as a way to 'clean up' the misfolded

proteins and other debris that accumulated during the early phase, may theoretically benefit.

Many questions remain about the relationship of the early phase to the late phase. For instance, is late-phase wasting due to persistent injuries sustained in the early phase or are the two phases mechanistically independent? Is late-phase wasting purely a reflection of a return to a pre-hospital level of reduced muscle function in patients with underlying neuromyopathies or sarcopenia? Answering these questions will clarify potential therapies to improve muscle function in ARDS survivors. Figure 2 illustrates potential clinical factors and mechanisms associated with early- and late-phase muscle wasting in ARDS.

Currently available therapeutic approaches

Insulin administration and tight glycemic control appear to reduce ICUAW [85], although this approach has been tempered with the results of the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation) trial, which suggested an increased risk of death in the tight glycemic control arm, possibly due to hypoglycemia [95]. Perhaps strategies that reduce hyperglycemia without the risk of hypoglycemia will reduce the incidence of ICUAW.

Currently, early mobilization/rehabilitation is the most readily available therapy for the attenuation of ICUAW. Evidence has demonstrated that early rehabilitation of critically ill patients is safe and has the benefit of improving other outcomes in addition to muscle strength [96–99]. Emerging evidence suggests that passive loading of the leg in a rat model of mechanical ventilation and paralysis prevented atrophy and degradation of myosin [100]. In a small study of mechanically ventilated critically ill patients, passive movement of the leg attenuated loss of specific force (but not atrophy) measured by single-fiber contraction [101]. We have recently shown that a model of early mobilization in lung-injured mice attenuates the MuRF1-mediated loss of muscle mass and force during the early phase, through an NF-κB-mediated mechanism [102]. This suggests that early mobility may attenuate the inflammation-induced atrophy in the early phase. As such, early mobilization (even passive movement) remains the best available therapy for critically ill patients to attenuate early- and late-phase muscle wasting in ARDS.

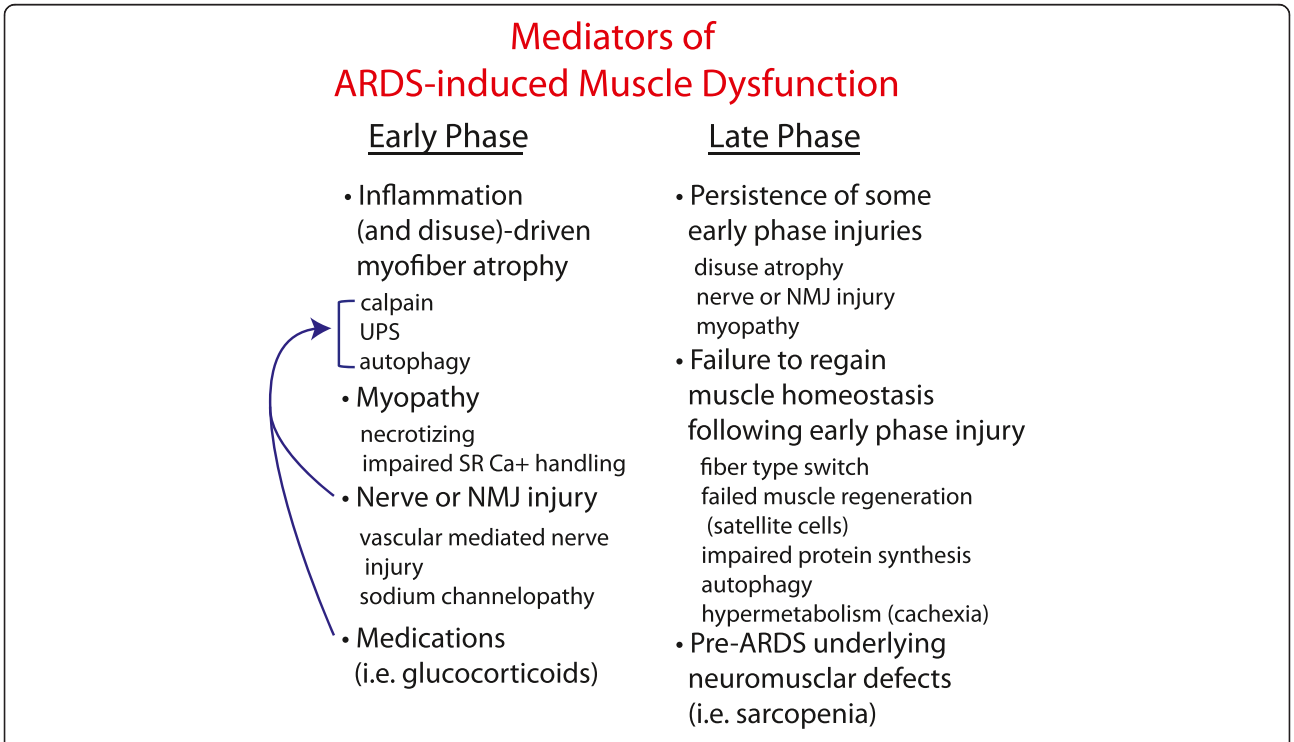

Fig. 2 Mediators of acute respiratory distress syndrome (ARDS)-induced muscle dysfunction. Skeletal muscle atrophy is the most universal feature of the early phase, which is driven fundamentally by inflammation and disuse. Other factors such as neuropathic injury and medications can exacerbate atrophy (blue arrow) 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 may 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 pre-ARDS neuromuscular defects. NMJ, neuromuscular junction; SR Ca^{+}, sarcoplasmic reticulum calcium; UPS, ubiquitin-proteasome system

Unfortunately, despite evidence that early mobility is safe and effective, there are limitations to its adoption, and implementation worldwide remains low [103, 104].

Neuromuscular electrical stimulation (NMES) may develop as an alternative therapy [105, 106], particularly for those who cannot participate in active physical therapy. In a small study, NMES attenuated type 2 myofiber atrophy, which was associated with relocalization of the GLUT4 receptor and improved glucose metabolism [87]. Further research is certainly warranted for this potential therapy.

Conclusions

As new therapies for inhibiting muscle protein degradation become available [64], it will be critical to administer them early in critically ill patients. As we propose that muscle atrophy is the most universal feature of ICUAW and that neuropathy will also lead to downstream myofiber atrophy, therapies that attenuate muscle protein degradation during the early phase have the highest theoretical benefit to improve in-hospital and long-term outcomes. Investigators interested in the early treatment of ARDS, such as the Prevention and Early Treatment of Lung Injury (PETAL) Network, could consider approaches that aim to attenuate the early phase of muscle wasting in patients with ARDS. This approach may open a new paradigm of therapies in ARDS, a syndrome that imparts a profound and lasting effect on the musculoskeletal system.

Abbreviations

AKT: Protein kinase B; ARDS: Acute respiratory distress syndrome; FoxO: Forkhead box o; GLUT4: Glucose transporter-4; ICUAW: Intensive care unit-acquired weakness; IGF-1: Insulin like growth factor 1; IL: Interleukin; MMT: Manual muscle testing; MuRF1: Muscle ring finger 1; MyHC: Myosin heavy chain; NF-κB: Nuclear factor kappa light chain enhancer of activated B cells; NMB: Neuromuscular blockade; NMES: Neuromuscular electrical stimulation; NMJ: Neuromuscular junction; PN: Parenteral nutrition; UPS: Ubiquitin-proteasome system.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

DCF would like to thank his mentors, Michael T Crow and Landon S King, without whom none of this work would be possible. The authors thank Karen Klein for editorial assistance and Nick Weir at Creative Communications for the illustrations. This work was supported by institutional funds from the Wake Forest School of Medicine, the Department of Medicine (DCF), the Claude D. Pepper Older Americans Independence Center (grant P30-AG21332), the Parker B. Francis Foundation (DCF), the American Thoracic Society Foundation (DCF), the National Institutes of Health (grant 1R01NR011186-01 to PEM), and the Department of the Army (ERMS #12340010 to PEM).

Published online: 02 July 2015

References

1. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122:2731–40.
2. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685–93.
3. Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, de Keizer NF. Determinants of mortality after hospital discharge in ICU patients: literature review and Dutch cohort study. Crit Care Med. 2013;41:1237–51.
4. Lone NI, Walsh TS. Impact of intensive care unit organ failures on mortality during the five years after a critical illness. Am J Respir Crit Care Med. 2012;186:640–7.
5. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. JAMA Intern Med. 2015;175:523–9.
6. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am J Respir Crit Care Med. 2013;188:567–76.
7. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185:1307–15.
8. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364:1293–304.
9. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme Jr JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171:340–7.
10. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med. 2014;190:1437–46.
11. Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med. 2009;37:S299–308.
12. Ali NA, O'Brien Jr JM, Hoffmann SP, Phillips G, Garland A, Finley JC, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med. 2008;178:261–8.
13. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190:410–20.
14. Sharshar T, Bastuji-Garin S, Stevens RD, Durand MC, Malissin I, Rodriguez P, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. Crit Care Med. 2009;37:3047–53.
15. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288:2859–67.
16. Files DC, D'Alessio FR, Johnston LF, Kesari P, Aggarwal NR, Garibaldi BT, et al. A critical role for muscle ring finger-1 in acute lung injury-associated skeletal muscle wasting. Am J Respir Crit Care Med. 2012;185:825–34.
17. MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. Lancet. 1977;2:615.
18. Bohannon RW. Manual muscle testing: does it meet the standards of an adequate screening test? Clin Rehabil. 2005;19:662–7.
19. Connolly BA, Jones GD, Curtis AA, Murphy PB, Douiri A, Hopkinson NS, et al. Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. Crit Care. 2013;17:R229.
20. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, et al. Risk factors for physical impairment after acute lung injury in a national, multicenter study. Am J Respir Crit Care Med. 2014;189:1214–24.
21. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49:M85–94.
22. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA. 2011;305:50–8.
23. Weber-Carstens S, Deja M, Koch S, Spranger J, Bubser F, Wernecke KD, et al. Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. Crit Care. 2010;14:R119.
24. Connolly B, MacBean V, Crowley C, Lunt A, Moxham J, Rafferty GF, et al. Ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review. Crit Care Med. 2015;43:897–905.
25. Grimm A, Teschner U, Porzelius C, Ludewig K, Zielske J, Witte OW, et al. Muscle ultrasound for early assessment of critical illness neuromyopathy in severe sepsis. Crit Care. 2013;17:R227.

26. Wieske L, Witteveen E, Petzold A, Verhamme C, Schultz MJ, van Schaik IN, et al. Neurofilaments as a plasma biomarker for ICU-acquired weakness: an observational pilot study. Crit Care. 2014;18:R18.
27. Bloch SA, Lee JY, Wort SJ, Polkey MI, Kemp PR, Griffiths MJ. Sustained elevation of circulating growth and differentiation factor-15 and a dynamic imbalance in mediators of muscle homeostasis are associated with the development of acute muscle wasting following cardiac surgery. Crit Care Med. 2013;41:982–9.
28. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. Crit Care. 2013;17:R120.
29. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med. 2013;188:213–9.
30. Semmler A, Okulla T, Kaiser M, Seifert B, Heneka MT. Long-term neuromuscular sequelae of critical illness. J Neurol. 2013;260:151–7.
31. Fletcher SN, Kennedy DD, Ghosh IR, Misra VP, Kiff K, Coakley JH, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. Crit Care Med. 2003;31:1012–6.
32. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, et al. Persistence of muscle catabolism after severe burn. Surgery. 2000;128:312–9.
33. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis. 2013;13:260–8.
34. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:502–9.
35. Gutmann L, Blumenthal D, Gutmann L, Schochet SS. Acute type II myofiber atrophy in critical illness. Neurology. 1996;46:819–21.
36. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med. 1992;327:524–8.
37. Puthucheary Z, Rawal J, Ratnayake G, Harridge S, Montgomery H, Hart N. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? Am J Respir Crit Care Med. 2012;185:911–7.
38. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363:1107–16.
39. Derde S, Hermans G, Derese I, Guiza F, Hedstrom Y, Wouters PJ, et al. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med. 2012;40:79–89.
40. Baehr LM, Furlow JD, Bodine SC. Muscle sparing in muscle RING finger 1 null mice: response to synthetic glucocorticoids. J Physiol. 2011;589:4759–76.
41. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1:621–9.
42. Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ. 2013;346:f1532.
43. Bonaldo P, Sandri M. Cellular and molecular mechanisms of muscle atrophy. Dis Model Mech. 2013;6:25–39.
44. Phillips SM, McGlory C. CrossTalk proposal: the dominant mechanism causing disuse muscle atrophy is decreased protein synthesis. J Physiol. 2014;592:5341–3.
45. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310:1591–600.
46. Wing SS, Lecker SH, Jagoe RT. Proteolysis in illness-associated skeletal muscle atrophy: from pathways to networks. Crit Rev Clin Lab Sci. 2011;48:49–70.
47. Janz DR, Ware LB. Biomarkers of ALI/ARDS: pathogenesis, discovery, and relevance to clinical trials. Semin Respir Crit Care Med. 2013;34:537–48.
48. Adams V, Mangner N, Gasch A, Krohne C, Gielen S, Hirner S, et al. Induction of MuRF1 is essential for TNF-alpha-induced loss of muscle function in mice. J Mol Biol. 2008;384:48–59.
49. Munoz-Canoves P, Scheele C, Pedersen BK, Serrano AL. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J. 2013;280:4131–48.
50. Bhatnagar S, Mittal A, Gupta SK, Kumar A. TWEAK causes myotube atrophy through coordinated activation of ubiquitin-proteasome system, autophagy, and caspases. J Cell Physiol. 2012;227:1042–51.
51. Spate U, Schulze PC. Proinflammatory cytokines and skeletal muscle. Curr Opin Clin Nutr Metab Care. 2004;7:265–9.
52. Li YP, Chen Y, John J, Moylan J, Jin B, Mann DL, et al. TNF-alpha acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1/MAFbx in skeletal muscle. FASEB J. 2005;19:362–70.
53. Li YP, Lecker SH, Chen Y, Waddell ID, Goldberg AL, Reid MB. TNF-alpha increases ubiquitin-conjugating activity in skeletal muscle by up-regulating UbcH2/E220k. FASEB J. 2003;17:1048–57.
54. Cai D, Frantz JD, Tawa Jr NE, Melendez PA, Oh BC, Lidov HG, et al. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell. 2004;119:285–98.
55. Langen RC, Haegens A, Vernooy JH, Wouters EF, de Winther MP, Carlsen H, et al. NF-kappaB activation is required for the transition of pulmonary inflammation to muscle atrophy. Am J Respir Cell Mol Biol. 2012;47:288–97.
56. Schulze PC, Gielen S, Adams V, Linke A, Mobius-Winkler S, Erbs S, et al. Muscular levels of proinflammatory cytokines correlate with a reduced expression of insulin-like growth factor-I in chronic heart failure. Basic Res Cardiol. 2003;98:267–74.
57. Drummond MJ, Timmerman KL, Markofski MM, Walker DK, Dickinson JM, Jamaluddin M, et al. Short-term bed rest increases TLR4 and IL-6 expression in skeletal muscle of older adults. Am J Physiol Regul Integr Comp Physiol. 2013;305:R216–23.
58. Doyle A, Zhang G, Abdel Fattah EA, Eissa NT, Li YP. Toll-like receptor 4 mediates lipopolysaccharide-induced muscle catabolism via coordinate activation of ubiquitin-proteasome and autophagy-lysosome pathways. FASEB J. 2011;25:99–110.
59. Caron AZ, Drouin G, Desrosiers J, Trensz F, Grenier G. A novel hindlimb immobilization procedure for studying skeletal muscle atrophy and recovery in mouse. J Appl Physiol (1985). 2009;106:2049–59.
60. Haegens A, Schols AM, Gorissen SH, van Essen AL, Snepvangers F, Gray DA, et al. NF-kappaB activation and polyubiquitin conjugation are required for pulmonary inflammation-induced diaphragm atrophy. Am J Physiol Lung Cell Mol Physiol. 2012;302:L103–10.
61. Bodine SC, Baehr LM. Skeletal muscle atrophy and the E3 ubiquitin ligases MuRF1 and MAFbx/atrogin-1. Am J Physiol Endocrinol Metab. 2014;307:E469–84.
62. Larsson L, Li X, Edstrom L, Eriksson LI, Zackrisson H, Argentini C, et al. Acute quadriplegia and loss of muscle myosin in patients treated with nondepolarizing neuromuscular blocking agents and corticosteroids: mechanisms at the cellular and molecular levels. Crit Care Med. 2000;28:34–45.
63. Jespersen JG, Nedergaard A, Reitelseder S, Mikkelsen UR, Dideriksen KJ, Agergaard J, et al. Activated protein synthesis and suppressed protein breakdown signaling in skeletal muscle of critically ill patients. PLoS One. 2011;6:e18090.
64. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov. 2015;14:58–74.
65. Sandri M. Autophagy in skeletal muscle. FEBS Lett. 2010;584:1411–6.
66. Masiero E, Agatea L, Mammucari C, Blaauw B, Loro E, Komatsu M, et al. Autophagy is required to maintain muscle mass. Cell Metab. 2009;10:507–15.
67. Mammucari C, Milan G, Romanello V, Masiero E, Rudolf R, Del Piccolo P, et al. FoxO3 controls autophagy in skeletal muscle in vivo. Cell Metab. 2007;6:458–71.
68. Hussain SN, Mofarrahi M, Sigala I, Kim HC, Vassilakopoulos T, Maltais F, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. Am J Respir Crit Care Med. 2010;182:1377–86.
69. Banduseela VC, Chen YW, Kultima HG, Norman HS, Aare S, Radell P, et al. Impaired autophagy, chaperone expression, and protein synthesis in response to critical illness interventions in porcine skeletal muscle. Physiol Genomics. 2013;45:477–86.
70. Li WW, Li J, Bao JK. Microautophagy: lesser-known self-eating. Cell Mol Life Sci. 2012;69:1125–36.
71. Cuervo AM, Wong E. Chaperone-mediated autophagy: roles in disease and aging. Cell Res. 2014;24:92–104.
72. Supinski GS, Wang L, Song XH, Moylan JS, Callahan LA. Muscle-specific calpastatin overexpression prevents diaphragm weakness in cecal ligation puncture-induced sepsis. J Appl Physiol (1985). 2014;117:921–9.
73. Supinski GS, Callahan LA. Calpain activation contributes to endotoxin-induced diaphragmatic dysfunction. Am J Respir Cell Mol Biol. 2010;42:80–7.
74. Supinski GS, Vanags J, Callahan LA. Eicosapentaenoic acid preserves diaphragm force generation following endotoxin administration. Crit Care. 2010;14:R35.
75. Tang H, Lee M, Budak MT, Pietras N, Hittinger S, Vu M, et al. Intrinsic apoptosis in mechanically ventilated human diaphragm: linkage to a novel Fos/FoxO1/Stat3-Bim axis. FASEB J. 2011;25:2921–36.

76. Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry. 1984;47:1223–31.
77. Bolton CF, Laverty DA, Brown JD, Witt NJ, Hahn AF, Sibbald WJ. Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry. 1986;49:563–73.
78. Latronico N, Fenzi F, Recupero D, Guarneri B, Tomelleri G, Tonin P, et al. Critical illness myopathy and neuropathy. Lancet. 1996;347:1579–82.
79. Novak KR, Nardelli P, Cope TC, Filatov G, Glass JD, Khan J, et al. Inactivation of sodium channels underlies reversible neuropathy during critical illness in rats. J Clin Invest. 2009;119:1150–8.
80. Axer H, Grimm A, Porzelius C, Teschner U, Schumacher U, Witte OW, et al. Impairment of small somatic and autonomic nerve fibres in intensive care unit patients with severe sepsis and critical illness polyneuropathy - a single center controlled observational study. BMC Neurol. 2013;13:159.
81. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA. 2013;310:1683–91.
82. Sato S, Shirato K, Tachiyashiki K, Imaizumi K. Muscle plasticity and beta-adrenergic receptors: adaptive responses of beta-adrenergic receptor expression to muscle hypertrophy and atrophy. J Biomed Biotechnol. 2011;2011:729598.
83. Fenzi F, Latronico N, Refatti N, Rizzuto N. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. Acta Neuropathol. 2003;106:75–82.
84. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10:931–41.
85. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 2007;175:480–9.
86. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64:1348–53.
87. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, et al. Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. Am J Respir Crit Care Med. 2013;187:387–96.
88. Rich MM, Pinter MJ. Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. J Physiol. 2003;547:555–66.
89. Kraner SD, Wang Q, Novak KR, Cheng D, Cool DR, Peng J, et al. Upregulation of the CaV 1.1-ryanodine receptor complex in a rat model of critical illness myopathy. Am J Physiol Regul Integr Comp Physiol. 2011;300:R1384–91.
90. Kraner SD, Novak KR, Wang Q, Peng J, Rich MM. Altered sodium channel-protein associations in critical illness myopathy. Skelet Muscle. 2012;2:17.
91. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360:219–23.
92. Weiss SL, Selak MA, Tuluc F, Perales Villarroel J, Nadkarni VM, et al. Mitochondrial dysfunction in peripheral blood mononuclear cells in pediatric septic shock. Pediatr Crit Care Med. 2015;16:e4–12.
93. Lee SJ, Reed LA, Davies MV, Girgenrath S, Goad ME, Tomkinson KN, et al. Regulation of muscle growth by multiple ligands signaling through activin type II receptors. Proc Natl Acad Sci U S A. 2005;102:18117–22.
94. Wang YX, Rudnicki MA. Satellite cells, the engines of muscle repair. Nat Rev Mol Cell Biol. 2012;13:127–33.
95. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367:1108–18.
96. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373:1874–82.
97. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36:2238–43.
98. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med. 2009;37:2499–505.
99. Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. Arch Phys Med Rehabil. 2010;91:536–42.
100. Renaud G, Llano-Diez M, Ravara B, Gorza L, Feng HZ, Jin JP, et al. Sparing of muscle mass and function by passive loading in an experimental intensive care unit model. J Physiol. 2013;591:1385–402.
101. Llano-Diez M, Renaud G, Andersson M, Marrero HG, Cacciani N, Engquist H, et al. Mechanisms underlying ICU muscle wasting and effects of passive mechanical loading. Crit Care. 2012;16:R209.
102. Files DC, Liu C, Pereyra A, Wang ZM, Aggarwal NR, D'Alessio FR, et al. Therapeutic exercise attenuates neutrophilic lung injury and skeletal muscle wasting. Sci Transl Med. 2015;7:278ra232.
103. Nydahl P, Ruhl AP, Bartoszek G, Dubb R, Filipovic S, Flohr HJ, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. Crit Care Med. 2014;42:1178–86.
104. Berney SC, Harrold M, Webb SA, Seppelt I, Patman S, Thomas PJ, et al. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. Crit Care Resusc. 2013;15:260–5.
105. Maffiuletti NA, Roig M, Karatzanos E, Nanas S. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. BMC Med. 2013;11:137.
106. Parry SM, Berney S, Granger CL, Koopman R, El-Ansary D, Denehy L. Electrical muscle stimulation in the intensive care setting: a systematic review. Crit Care Med. 2013;41:2406–18.