Review

Bench-to-bedside review: Mobilizing patients in the intensive care unit – from pathophysiology to clinical trials

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Abstract

As the mortality from critical illness has improved in recent years, there has been increasing focus on patient outcomes after hospital discharge. Neuromuscular weakness acquired in the intensive care unit (ICU) is common, persistent, and often severe. Immobility due to prolonged bed rest in the ICU may play an important role in the development of ICU-acquired weakness. Studies in other patient populations have demonstrated that moderate exercise is bene-ficial in altering the inflammatory milieu associated with immobility, and in improving muscle strength and physical function. Recent studies have demonstrated that early mobility in the ICU is safe and feasible, with a potential reduction in short-term physical impair-ment. However, early mobility requires a significant change in ICU practice, with reductions in heavy sedation and bed rest. Further research is required to determine whether early mobility in the ICU can improve patients' short-term and long-term outcomes.

Introduction

Bed rest has been prescribed for a wide range of conditions, from acute medical illnesses to postoperative convalescence. In intensive care units (ICUs) bed rest is especially common [1,2]. However, a meta-analysis of 39 randomized trials examining the effect of bed rest on 15 different medical conditions and procedures demonstrated that bed rest was not beneficial and may be associated with harm [3]. Immobility from prolonged bed rest is associated with many complications, including muscle atrophy, pressure ulcers, atelectasis, and bone demineralization [4].

With improving short-term survival among critically ill patients [5], there is a growing appreciation of the neuromuscular sequelae experienced by patients after hospital discharge. In some ICU survivors, weakness can persist for years after hospital discharge [6,7]. Although the etiology of this weakness is multifactorial, early mobilization of ICU patients may help to reduce the muscle atrophy, weakness, and deconditioning associated with bed rest. Exercise is effective

in decreasing inflammation and all-cause mortality in healthy individuals and patients with chronic disease [8,9]. This review outlines the etiology and potential mechanisms of ICU-acquired weakness. Furthermore, we highlight the potential risks, benefits, and challenges of early mobility in the critically ill to reduce ICU-acquired weakness and improve patient outcomes.

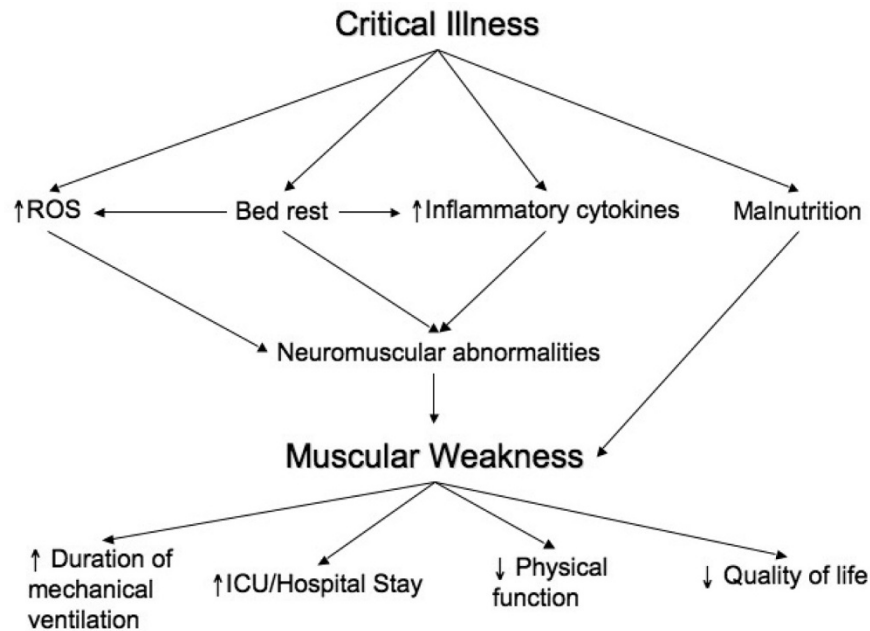## Risk factors for critical illness associated neuromuscular abnormalities

The etiology of ICU-acquired weakness is multifactorial, with a number of studies establishing independent risk factors for its development. Overall, disease severity (for instance, Acute Physiology and Chronic Health Evaluation II score), the presence of the systemic inflammatory response syndrome, and organ failure are associated with neuromuscular abnor-malities on electromyography/nerve conduction studies [10,11]. Moreover, the presence of clinically detectable muscle weak-ness was positively associated with the number of days with two or more organ dysfunctions in a multivariate analysis [12]. Other risk factors include the duration of mechanical ventilation [12] and ICU length of stay [13], as well as serum glucose levels [13], hyperosmolality [11], and use of paren-teral nutrition [11]. Use of potentially myotoxic or neurotoxic medications, such as corticosteroids [12] and nondepolarizing neuromuscular blocking agents [11], has been associated with neuromuscular abnormalities, although these findings have not consistently been reported in other studies [10].

Immobility and muscle loss

The mechanisms by which critical illness leads to muscle weakness are complex and involve several inter-related processes (Figure 1). Pathophysiologically important mecha-nisms for weakness include immobility, as well as local and systemic inflammation, which act synergistically to promote significant muscle loss in the critically ill patient. Importantly,

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ICU = intensive care unit; IL = interleukin; ROS = reactive oxygen species; TNF = tumor necrosis factor.

Figure 1

Mechanisms and outcomes of neuromuscular weakness in critical illness. ICU, intensive care unit; ROS, reactive oxygen species.

prolonged bed rest associated with critical illness leads to decreased muscle protein synthesis, increased urinary nitrogen excretion (indicating muscle catabolism), and decreased muscle mass, especially in the lower extremities [14]. These changes lead to deleterious effects on muscle weakness, with 1% to 1.5% of quadriceps muscle strength lost for each day of bed rest in healthy individuals [15,16]. Both preclinical and clinical studies suggest a more profound effect of immobilization in the elderly, with a greater loss of lean body mass [14,17]. Additionally, the interaction of bed rest and critical illness appears to result in more significant muscle loss than bed rest alone [18-21].

Disuse atrophy is associated with specific structural and metabolic changes in muscle. Specifically, animal studies have demonstrated that proteolysis occurs during immobility through three major pathways: calcium-dependent calpains [22], lysosomal cathepsins [23], and the ubiquitin-proteasome system [24]. Further muscle loss is mediated through decreased protein synthesis by inhibition of initiation factors by inhibitory 4E-BP-1 mRNA [25,26]. Modulation of these pathways during immobility leads to a net loss in muscle mass and cross-sectional muscle area, reduced contractile strength, and a general shift from slow twitch (type I) to fast twitch (type II) muscle fibers [26-29].

In addition to its direct effects on muscle, immobility can lead to a pro-inflammatory state caused by increased systemic inflammation via increases in pro-inflammatory cytokines

[30,31]. Long-term immobility may result in increased levels of IL-1β, which plays an important role in muscle loss in other conditions, such as the cachexia associated with chronic obstructive pulmonary disease [32,33]. Levels of IL-2 and interferon-γ pro-inflammatory cytokines are also elevated after prolonged bed rest [33]. This cytokine shift may potentiate the systemic inflammatory milieu that is commonly observed during critical illness, leading to further muscle damage and loss [34]. However, the exact role that that cytokines play in muscle loss during immobilization must still be more fully elucidated.

The pro-inflammatory state associated with bed rest also may cause increased production of reactive oxygen species (ROS), with a concomitant decrease in anti-oxidative defenses [35,36]. ROS may play a role in tumor necrosis factor (TNF)-α induced oxidization of myofilaments, resulting in contractile dysfunction and atrophy [37-39]. Additionally, ROS may trigger activation of both nuclear factor-κB and FOXO signaling pathways, resulting in protein loss, possibly through the ubiquitin-proteasome pathway [40]. This increase in ROS and imbalance in the cytokine profile can further disrupt the balance between muscle synthesis and proteolysis, with a net loss of muscle protein and subsequent muscle weakness [38,39].

In addition to immobility, critically ill patients commonly experience protein-energy malnutrition, both before hospitalization and during their ICU stay. Up to 40% of all hospitalized

patients may be undernourished at the time of admission [41]. Moreover critically ill patients commonly receive less than 60% of their goal nutritional intake during their ICU stay, thus further compounding this malnutrition [42,43]. Protein-energy malnutrition, combined with the hypermetabolic stresses of critical illness, results in significant protein loss in the form of amino acids derived primarily from muscle [44].

Impact of immobility

Long-term immobility is associated multiple clinical complications (Table 1), having detrimental effects on patients during and after their ICU stay. After 7 days of mechanical ventilation, 25% to 33% of patients experience clinically evident neuromuscular weakness, with severity of illness and duration of ICU stay being important risk factors [12,10]. Patients with ICU-acquired weakness have an increased duration of mechanical ventilation and length of stay [45].

When evaluating ICU patients' muscle function using electromyography and nerve conduction studies, critical illness-associated neuromuscular abnormalities are even more common. A systematic review [46] demonstrated that 46% of the 1,421 ICU patients evaluated in 24 studies had critical illness-associated neuromuscular abnormalities. These abnormalities were associated with an increase in duration of mechanical ventilation and length of stay. During follow up after hospital discharge, more than 50% of patients developing critical illness-associated neuromuscular abnormalities had persistent neuromuscular abnormalities [47], with 28% suffering from severe disability such as tetraparesis, tetraplegia, or paraplegia [48].

During 1 year of follow up, one study of acute respiratory distress syndrome [49] reported poor physical function and decreased exercise tolerance in all survivors. These impairments were attributed to the loss of muscle bulk, proximal muscle weakness, and fatigue [49]. For years after hospital discharge, physical aspects of quality of life are frequently impaired (compared with age-matched and sex-matched norms) in survivors of critical illness [50,51].

Prevention and treatment

At present, there are few options for the prevention and/or treatment of ICU-acquired weakness [46,52,53]. In the ICU, hyperglycemia [54,55] and certain medications (for example, corticosteroids [12] and neuromuscular blocking agents [56]) may be associated with the development of clinical weakness and/or critical illness-associated neuromuscular abnormalities. Strict glycemic control using intensive insulin therapy may decrease neuromuscular abnormalities in patients mechanically ventilated for 7 or more days [52,54,55]. Currently, controversies exist over the risks and benefits of tight glycemic control in critically ill patients. In addition, a causal relationship between the use of certain medications and increased rates of neuromuscular abnormalities has not been clearly established. Specifically, no studies have

Table 1

Selected adverse effects of prolonged bed rest

Musculoskeletal
- Decreased muscle protein synthesis [14]
- Muscle atrophy and decrease in lean muscle mass [80]
- Decreased muscle strength [14]
- Decreased exercise capacity [81]
- Connective tissue shortening and joint contractures [82]
- Decreased bone density [80]
- Pressure ulcers [83]

Pulmonary
- Atelectasis [84]
- Pneumonia [85]
- Decreased maximal inspiratory pressure and forced vital capacity [81]

Cardiovascular
- Decreased total cardiac and left ventricular size [86]
- Decreased lower extremity venous compliance [87]
- Orthostatic intolerance [88]
- Decreased cardiac output, stroke volume, and peripheral vascular resistance [86,89,90]
- Impaired microvascular function [91]
- Decreased cardiac response to carotid sinus stimulation [89]

Endocrine and Metabolism
- Decreased insulin sensitivity [91]
- Decreased aldosterone and plasma renin activity [92]
- Increased atrial natriuretic peptide [93]

demonstrated that avoidance of either corticosteroids or nondepolarizing neuromuscular blocking agent results in reduced incidence of neuromuscular abnormalities.

Beneficial effects of exercise

A potential therapeutic option to reduce ICU-acquired weakness is avoidance of bed rest via early mobilization in the ICU setting. In addition to improved strength, exercise may decrease oxidative stress and inflammation [57,58]. During moderate to strenuous exercise (60% to 75% of maximal oxygen intake) in unfatigued skeletal muscle, small increases in ROS activated cell-signaling pathways (for example, the nuclear factor-κB pathway) are responsible for increased protection against oxidative stress, by increased production of antioxidants such as mitochondrial superoxide dismutase, glutathione peroxidase, and γ-glutamylcysteine [57,59,60]. In addition, moderate exercise leads to a shift toward increased production of anti-inflammatory cytokines [9]. Typically, IL-6 (which has anti-inflammatory properties) is the first cytokine to rise during exercise, increasing up to 100-fold greater than pre-exercise levels, and then declines shortly after discontinuation of exercise (<30 minutes) [61,62]. Furthermore, both the IL-1 receptor antagonist and soluble TNF-α receptor, inhibitors of pro-inflammatory cytokines, are also elevated during exercise, without concomitant increases in the pro-

inflammatory cytokines TNF-α and IL-1β [9,62]. Taken together, antioxidant formation and a shift toward anti-inflammatory cytokines during moderate exercise may play an important role in muscle preservation and protection.

Physical therapy in the intensive care unit

Physical therapy practices vary greatly across ICUs, ranging from passive range of motion to transferring patients from the bed to a chair. In general, more intensive physical therapy (for example, ambulation) seldom occurs in mechanically ventilated patients [2,63]. A recent multisite study [43] demonstrated that only 27% of patients with acute lung injury received any physical therapy in the ICU, with treatments occurring during only 6% of ICU days. Another observational study of 20 physiologically stable patients with an ICU stay of 5 to 15 days [64] demonstrated that therapeutic activity beyond simple turning and range of motion exercises was rare, with only 1.5% of observed activities involving more intensive therapy such as sitting in a chair or standing. One study of patients mechanically ventilated via tracheostomy [65] demonstrated that only 63% of patients sat out of bed, with a median of two occasions per patient during the entire ICU stay.

Safety concerns

There are unique challenges and safety concerns when considering early mobilization of critically ill patients in the ICU. However, existing data demonstrate that mobilization, including ambulation, of mechanically ventilated patients can be safe. In a study of 31 ICU patients who received a total of 69 mobilization treatments [66], a change in clinical status occurred in only three (4%) of sessions. All three events involved a transient decrease in oxygen saturation that responded to an increase in supplemental oxygen. Moreover, in a study of 103 ICU patients involving 1,449 activity events, ranging from sitting in bed to ambulation, there were only 14 (<1%) minor adverse events in nine patients, with none involving extubation or other unanticipated events requiring additional therapy, cost, or duration of stay in hospital [67]. In a controlled trial of a dedicated ICU mobility team [63] there were no adverse events, despite patients in the mobility protocol group receiving significantly more physical therapy sessions. Guidelines currently exist regarding physical therapy in the critically ill [68-70] that are based on expert opinion, experience, and existing studies. These studies illustrate that critically ill patients can be safely mobilized.

Culture change and feasibility of early mobility in the intensive care unit

Barriers to early mobilization of ICU patients are multifactorial and include lack of prioritization, long-established assumptions regarding the need for bed rest during critical illness, and standing orders for activity restriction in the ICU [2,71]. These barriers illustrate the importance of ICU culture to successful early mobilization of patients [72]. In one study of mechanically ventilated patients undergoing an intra-hospital

transfer from a traditional ICU to an ICU in which early mobilization was a priority [73], patients were 2.5 times more likely to be ambulated after transfer. This increase in ambulation could not be accounted for by differences in severity of disease or underlying pathology, suggesting that many ICU patients have an unmet potential for physical therapy and are subjected to 'unnecessary immobilization' [68,73]. This discrepancy between actual activity and patients' potential for activity poses an important target for improving rehabilitation in the ICU. Indeed, the need for early activity in critically ill patients was recently reinforced by European guidelines for physiotherapy in the ICU [68].

A multidisciplinary focus on early mobilization is necessary as part of daily clinical routines in the ICU. Early mobilization begins immediately after physiologic stabilization. The definition of 'physiologic stabilization' varies among published studies, but it usually takes into account neurologic, respiratory, and cardiovascular stability [63,66,67,69].

In addition to physiologic stability, clinicians may believe mobilization is not feasible because of the presence of an endotracheal tube, vascular access device, or other medical equipment. However, in one prospective cohort study [67] patients with an endotracheal tube participated in 593 activity events ranging from sitting on the edge of the bed to ambulation. Despite 42% of these events involving ambulation, there were no accidental extubations [67]. Moreover, during a total of 1,449 activity events, there was only one incident of equipment dislodgment, which involved the accidental removal of a feeding tube [67]. These results are further reinforced by a controlled trial of a mobility protocol on 145 intubated ICU patients [63], in which no incidents of accidental removal of devices were reported. These studies indicate that early mobility in the ICU is feasible in ICUs with a supportive culture.

Clinical outcomes after early mobility

Recent studies have demonstrated improved clinical outcomes with early mobility in the ICU. A prospective cohort study of 103 mechanically ventilated patients [67] demonstrated that an early mobility program led to 69% of patients ambulating more than 100 feet before ICU discharge. Additionally, in another study of 104 ICU patients [73] an early activity protocol resulted in 91 (88%) of patients ambulating a median of 200 feet at ICU discharge. Although there was no control group in these studies, this activity level is far greater than existing reports of usual care in traditional ICUs [63], in which ambulation therapy is frequently delayed until after ICU discharge [74].

Recently, a controlled trial of mechanically ventilated medical ICU patients [63] evaluated the benefits of an early mobility protocol that provided rehabilitation therapy 7 days per week via a dedicated mobility team. Through use of a mobility team (consisting of a nurse, nurse assistant, and physical therapist)

and automated orders for physical therapy, more patients received physical therapy during their ICU stay (73% in the protocol versus 6% in the usual care group), with a trend toward decreased hospital mortality (12.1% versus 18.2%; $P = 0.125$). After adjusting for differences in body mass index, Acute Physiology and Chronic Health Evaluation II score, and vasopressor use between the protocol and usual care groups, early mobilization was associated with decreased lengths of stay in the ICU (5.5 days versus 6.9 days; $P = 0.025$) and hospital (11.2 days versus 14.5 days; $P = 0.006$) among survivors, and a trend toward decreased duration of mechanical ventilation (8.8 days versus 10.2 days; $P = 0.163$). Despite addition of the dedicated mobility team, there was no difference in average hospital costs per patient ($41,142 versus $44,302 for protocol versus usual care group; $P = 0.262$) [63].

Thus, early mobilization of critically ill patients may improve physical function and shorten length of stay. However, the results of these studies require further confirmation with randomized controlled trials.

Other important changes to facilitate early mobilization

Despite safety, feasibility, and potential short-term benefits, barriers to early mobility remain because of established approaches to sedation, incomplete knowledge, and lack of resources in some ICUs [69]. Critically ill patients frequently receive heavy sedation, especially when they are mechanically ventilated [75]. Continuous sedative infusions are widely used [76] and associated with increased duration of mechanical ventilation [77]. Heavy sedation prevents patients from participating in mobility activities. Daily interruption of sedation infusions can result in decreased duration of mechanical ventilation (4.9 days versus 7.9 days; $P = 0.004$) and ICU length of stay (6.4 days versus 9.9 days; $P = 0.02$) [78]. Use of lighter sedation also is potentially associated with decreased long-term psychologic disturbances such as post-traumatic stress [79]. Combined early mobility and decreased sedation may have synergistic benefits.

Given many competing illnesses and treatments accompanying critical illness, early mobility often fails to be a high priority in daily ICU patient care. Transforming ICU culture requires prioritizing physical therapy. Culture change may be assisted by clinician education regarding the significant and persistent morbidity that occurs after critical illness, as well as the safety, feasibility, and potential benefits of early mobility. Targets for ICU culture change include institutional leadership to support early mobility, as well as bedside clinicians (for example, physicians, nurses, and physical therapists), who play a crucial role in changing routine care [72].

The ICU environment may be unfamiliar to some physical medicine and rehabilitation staff, just as rehabilitation therapy may be unfamiliar to ICU staff. Familiarity with ICU equipment, including cardiac monitors and ventilators, can help rehabilitation staff to feel more comfortable in mobilizing critically ill patients. Moreover, interdisciplinary education, involving specialists from critical care, physical therapy, occupational therapy, and nursing, will help to address these knowledge gaps.

Specific resources can assist with a successful early mobility program in the ICU. Adequate staffing from physical medicine and rehabilitation clinicians is key. Such clinicians may include physical and occupational therapists and a rehabilitation physician. A general neurologist or neuromuscular subspecialist may also provide insights into investigation of neuromuscular weakness. An overall leader for an early mobility program can help to establish the necessary coordination and cooperation among the multidisciplinary team. However, with teamwork, training, and restructuring, it may be possible to provide a higher level of physical activity in the ICU without requiring additional resources [72].

Future directions

Our current understanding of the pathophysiology of ICU-acquired weakness and the potential role of early mobility in the ICU, including its safety, feasibility, and clinical benefit, is at a relatively early stage. Future studies are needed to elucidate the multiple mechanisms by which immobility and other aspects of critical illness lead to muscle dysfunction and loss. Although emerging data have demonstrated the safety, feasibility, and potential benefit of early mobility in critically ill patients, multicenter randomized, controlled trials are needed to evaluate the potential short-term and long-term benefits for patients' muscle strength, physical function, and quality of life. Future studies in critically ill patients with primary trauma, surgical, and neurologic issues will complement the existing research that has focused predominantly on ICU patients with medical conditions. In addition, important differences in clinical practice between North America and Europe, especially in the use of physiotherapists in the ICU, may introduce variations in care that limit generalizability. A study focused on studying such geographic differences in practice would permit better comparison. Finally, other interventions, such as neuromuscular electrical stimulation, cycle ergometry, and optimization of nutrition, warrant additional future investigation [69].

Conclusions

As the survival of critically ill patients continues to improve, there is growing awareness of the significant long-term neuromuscular complications that may occur after intensive care. Bed rest in the ICU should not be viewed as benign and may affect patients' short-term and long-term recovery. Immobility in the ICU contributes to neuromuscular sequelae through several mechanisms, including a shift in cytokines, increased inflammation, and disuse atrophy of skeletal muscle. Interventions to prevent or treat ICU-acquired weakness are few. Early mobility can be a safe and feasible

option, with potential to improve clinical outcomes. Through ongoing preclinical and clinical research into the mechanisms, prevention, and treatment of ICU-acquired weakness, we can improve physical function and quality of life for ICU survivors.

Competing interest

The authors declare that they have no competing interests.

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