Early Physical Rehabilitation in the ICU and Ventilator Liberation

Pedro A Mendez-Tellez MD and Dale M Needham MD PhD

Critically ill patients requiring mechanical ventilation are frequently subjected to long periods of physical inactivity, leading to skeletal muscle atrophy and muscle weakness. Disuse muscle atrophy is the result of complex mechanisms, including altered protein turnover and disturbed redox signaling. These ICU-acquired complications are associated with longer duration of mechanical ventilation, prolonged ICU and hospital stays, and poorer functional status at hospital discharge. Similarly, there is growing evidence that continuous mandatory ventilation alters diaphragmatic structure and contractile function and promotes oxidative injury, resulting in a rapid-onset diaphragmatic atrophy and weakness, which most likely delays discontinuing mechanical ventilation. Physical rehabilitation, when started at the onset of mechanical ventilation, has been associated with shorter periods of mechanical ventilation, decreased ICU and hospital stay, and improved physical function at hospital discharge. This review summarizes the impact of both physical inactivity and mechanical ventilation on skeletal and diaphragmatic muscles structure and function. Also reviewed is the growing evidence demonstrating the feasibility and safety of early physical rehabilitation interventions for mechanically ventilated patients, as well as their benefit on patient outcomes. *Key words: physical therapy; mechanical ventilation; muscle atrophy; muscle weakness; intensive care; ICU; rehabilitation.* [Respir Care 2012;57(10):1663–1669.

Introduction

Physical inactivity and prolonged bed rest affect virtually all mechanically ventilated patients and contribute to neuromuscular abnormalities, resulting in skeletal muscle atrophy and muscle weakness.[1-3] Clinically important muscle weakness has been reported in 25–65% of subjects mechanically ventilated for at least 5 days, resulting in longer duration of mechanical ventilation (MV) and ICU

The authors are affiliated with the Outcomes After Critical Illness and Surgery Group, Johns Hopkins University, Baltimore, Maryland. Dr Mendez-Tellez is also affiliated with the Department of Anesthesiology and Critical Care Medicine; Dr Needham is also affiliated with the Division of Pulmonary and Critical Care Medicine, and the Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, Maryland.

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Correspondence: Pedro A Mendez-Tellez MD, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, Halsted 842, 600 North Wolfe Street, Baltimore MD 21287. E-mail: pmendez@jhmi.edu.

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and hospital stays.[1,4-8] Sedation and analgesia, which are commonly used to provide comfort, reduce perceived distress and facilitate MV, are commonly associated with prolonged periods of unconsciousness and physical inactivity, and prolonged mechanical ventilator support that ultimately delays patients' physical and cognitive recovery[9,12] Similarly, diaphragmatic function is a major determinant of the ability to successfully discontinue MV,[13] but there is growing evidence that continuous mandatory ventilation alters diaphragmatic structure and contractile function and promotes oxidative injury, resulting in a rapid-onset diaphragmatic atrophy and weakness,[14] which most likely delays discontinuing MV.[14] Physical rehabilitation, when started at the onset of MV, has been associated with shorter periods of MV, decreased ICU and hospital stay, and improved physical function at hospital discharge.[15-18]

The objective of this review is to summarize the effects and impact of both physical inactivity and MV on skeletal and diaphragmatic muscle structure and function. Also reviewed is the growing evidence demonstrating the feasibility and safety of early physical rehabilitation interventions for mechanically ventilated patients, as well as their benefit on patient outcomes.

Physical Inactivity and Skeletal Muscle Weakness

Physical inactivity is common in mechanically ventilated patients with acute respiratory failure.[19,20] Long periods of inactivity promote loss of muscle protein, fiber atrophy, and muscle weakness. In healthy young volunteers, 28 days of bed rest resulted in a 0.4 kg loss of lean leg mass and a 23% reduction in leg extension strength.[21] In healthy older adults, 10 days of bed rest resulted in a 1.5 kg whole body lean mass loss and a 15% reduction in muscle strength.

Inactivity-induced disuse muscle atrophy results from decreased protein synthesis, increased protein degradation, and disturbed redox signaling.[22] Recent evidence suggests that in humans the primary factor promoting disuse muscle atrophy is a decrease in protein synthesis.[22,23] Studies have demonstrated that the rate of muscle synthesis declines quickly (ie, within 6 h) after the onset of muscle inactivity, and reaches a new "lower" steady state of muscle protein synthesis within 18–48 hours.[22]

Severe trauma and injury amplifies the effect of inactivity on skeletal muscle mass loss. Critically injured blunt trauma patients may lose 16% of total body protein over a 21-day period, 67% of which comes from skeletal muscle.[24] Severely septic patients may lose 13% of total body protein over a 21-day period, with 67% of the protein loss from skeletal muscle[25] In addition, critically ill patients lose almost 1% per day of their lean body mass per day,[26] which is far greater than that produced by inactivity alone. The greatest loss in lean tissue occurs in skeletal muscle. Studies have shown that skeletal muscle fiber area decreases by 2−4% per day in the ICU, with atrophy occurring within days of onset of critical illness.[27,28]

In animal studies, disuse muscle atrophy is associated with increased protein degradation; however, in humans the role of proteolysis in disuse muscle atrophy is controversial.[22] Some studies have reported that prolonged inactivity is associated with limited increases in protein breakdown.[29,30] Conversely, others have reported elevated rates of protein breakdown.[31-33] Three main proteolytic systems contribute to muscle protein breakdown: lysosomal proteases (ie, autophagy), calcium-dependent proteases (ie, calpains), and the proteasome system. Lysosomal proteases are activated and contribute to protein degradation during prolonged inactivity, but their role appears limited.[34] Calcium-dependent proteases do not directly degrade contractile proteins such as actin or myosin. Calpains cleave myofibrillar proteins from the myofilaments generating protein fragments that can be degraded via adenosine triphosphate (ATP) dependent proteolysis.[35] In the proteasome-dependent proteolysis, ubiquitin covalently binds to misfolded or damage proteins. The ubiquitin-protein complexes are targeted by the S26 proteasome, a multi-catalytic complex of ATP-dependent enzymes. The binding of ubiquitin to protein substrates depends on coordinated activity of several enzymes including an ubiquitin-activating enzyme (E1), specific ubiquitin-conjugating enzymes (E2), and many specific ubiquitin protein ligases (E3).[34]

Disturbances in redox signaling and oxidative stress appear to also play an important role in disuse muscle atrophy. It is well known that radicals and other reactive oxygen species (ROS) are produced in both inactive and contractile skeletal muscle, but oxidative stress occurs when oxidant production exceeds the antioxidant capacity.[34] Animal and human studies have demonstrated that oxidative injury occurs during periods of skeletal muscle immobility and contributes to disuse muscle atrophy.[36]

Mechanical Ventilation and Diaphragmatic Weakness

Growing evidence demonstrates that MV promotes diaphragmatic fiber atrophy and weakness with ultra-structural and functional changes in diaphragm muscle fibers. MV leads to rapid-onset diaphragmatic atrophy, induces changes in protein turnover, and promotes oxidative stress injury and changes in gene expression and cell signaling.[37,38]

Continuous mandatory ventilation (CMV) induces a unique type of rapid-onset diaphragmatic atrophy. Animal studies have demonstrated that within 12–18 hours of CMV, the diaphragm shows substantial atrophy in both slow and fast twitch muscle fibers. In contrast, the skeletal muscles

show no signs of atrophy after 12–18 hours of inactivity.[39,40] Rapid-onset diaphragmatic atrophy has also been reported in humans subjected to diaphragmatic inactivity and CMV. In brain-dead organ donors, 18–69 hours of CMV was associated with marked diaphragmatic atrophy of both slow-twitch and fast-twitch fibers, with decreases in cross-sectional areas of 57% and 53%, respectively.[41]

Animal studies have also shown that CMV results in ultra-structural changes in diaphragmatic muscle fibers. CMV leads to areas of abnormal diaphragmatic myofibrils, as indicated by myofibrillar disarray, and alterations in z-line structure.[42] It promotes areas of diaphragmatic regeneration without signs of inflammation, and it results in an increase in cytoplasmic lipid vacuoles.[37] Similar ultrastructural changes have been reported in intercostal muscles of animals subjected to prolonged MV.[43]

MV also leads to changes in diaphragmatic protein turnover, as it depresses protein synthesis and accelerates protein breakdown. In vitro studies have shown that 12–18 hours of CMV result in large increases in diaphragm protein degradation that is associated with increased calpain and 20S proteasome activity.[40] An animal study showed that 6 hours of CMV led to a 30% decrease in mixed protein synthesis and a 65% decline in the rate of myosin-heavy chain protein synthesis.[44] In humans, CMV has been associated with increased protein degradation. Within 18–69 hours of CMV, substantial increases were detected in caspase-3 activity and mRNA for 2 components of the ubiquitin-proteasome system: all markers of diaphragmatic proteolysis.[41]

Oxidative stress promotes diaphragmatic atrophy and contractile dysfunction during prolonged periods of CMV. Controlled MV lasting > 6 hours resulted in redox disturbances from increased reactive oxygen species production, as demonstrated by increased protein oxidation and lipid peroxidation,[37,40,45] and diminished antioxidant capacity, as demonstrated by decreased glutathione, glutathione peroxidase, and cooper zinc superoxide dismutase levels.[45]

Finally, MV results in substantial changes in diaphragmatic gene expression for numerous genes linked with the stress response, protein metabolism, and calcium regulation. In a rat model, microarray analysis revealed that MV resulted in > 350 changes in gene products after 6 and 18 hours of CMV.[46] These changes on diaphragmatic gene expression contribute to the atrophy and the extensive muscle fiber remodeling occurring during prolonged MV.[46]

Early Physical Rehabilitation of Mechanically Ventilated Patients

There is growing evidence that physical rehabilitation in the ICU, when started as early as 1 or 2 days after initiating MV, is feasible, safe, and beneficial. Benefits of early rehabilitation include improved exercise capacity and functional status at hospital discharge, decreased duration of MV, and shorter ICU and hospital stay.[16-18]

Critically ill patients are frequently perceived as "too sick" to participate in physical rehabilitation activities[47]; however, an earlier observational study[15] demonstrated that mobilization of patients with respiratory failure and prolonged MV (> 4 d) was feasible and safe. This resulted in impressive ambulation distances by ICU discharge. The study included 103 patients transferred to a respiratory ICU after a mean ICU stay of 10.5 day ± 9.9 days in other ICUs. Almost all patients (89%) were mechanically ventilated at respiratory ICU admission. Out of the 1,449 mobility activities in the respiratory ICU, 41% occurred in intubated patients, 42% of which were ambulation. In 8% of mechanically ventilated patients the pre-activity F_{IO_2} was ≥ 0.7. Adverse events, prospectively evaluated, occurred in < 1% of all activities, with no extubations and no consequential requirements for additional therapy, cost, or hospital stay. By respiratory ICU discharge, 69% of patients walked > 30 m. Among hospital survivors, 40% were discharged home.

Similarly, a non-randomized controlled clinical trial of 330 medical ICU patients requiring intubation and MV[16] demonstrated that implementation of an early mobility protocol with a dedicated multidisciplinary mobility team increased physical therapy (PT) activities. Patients in the protocol care group received more PT (80% vs 47%, $P < .001$) and were out of bed earlier (5 vs 11 d, $P = .01$) than the usual care group. Although there was no significant difference in the adjusted number of ventilator days between protocol and usual care groups (8.8 d vs 10.2 d, $P = .16$), there was a significant difference in adjusted duration of ICU stay (5.5 d vs 6.9 d, $P = .03$) and hospital stay (11.2 d vs 14.5 d, $P = .006$). Given the shorter stay, despite the additional rehabilitation resources, the average cost per patient was not significantly different between the protocol and the usual care group ($41,142 vs $ 44,302, $P = .26$), with the intervention group having improved outcomes.

Finally, a recent randomized, blinded clinical trial[17] showed that implementation of early PT and occupational therapy (OT) resulted in improved physical function and a reduced duration of delirium for 104 critically ill patients who were functionally independent at baseline. PT and OT were initiated from the beginning of MV versus "usual care" timing for PT and OT (1.5 d vs 7.4 d, respectively, $P < .001$). This intervention was combined with daily sedation interruptions and protocol-driven breathing trials (in both intervention and control groups), with early PT and OT resulting in improved days alive and breathing without assistance (23.5 vs 21.1 ventilator-free days, $P = .05$). The intervention group achieved several activity milestones while receiving MV, such as sitting at the side of the bed (78%), standing (51%), transferring to a chair

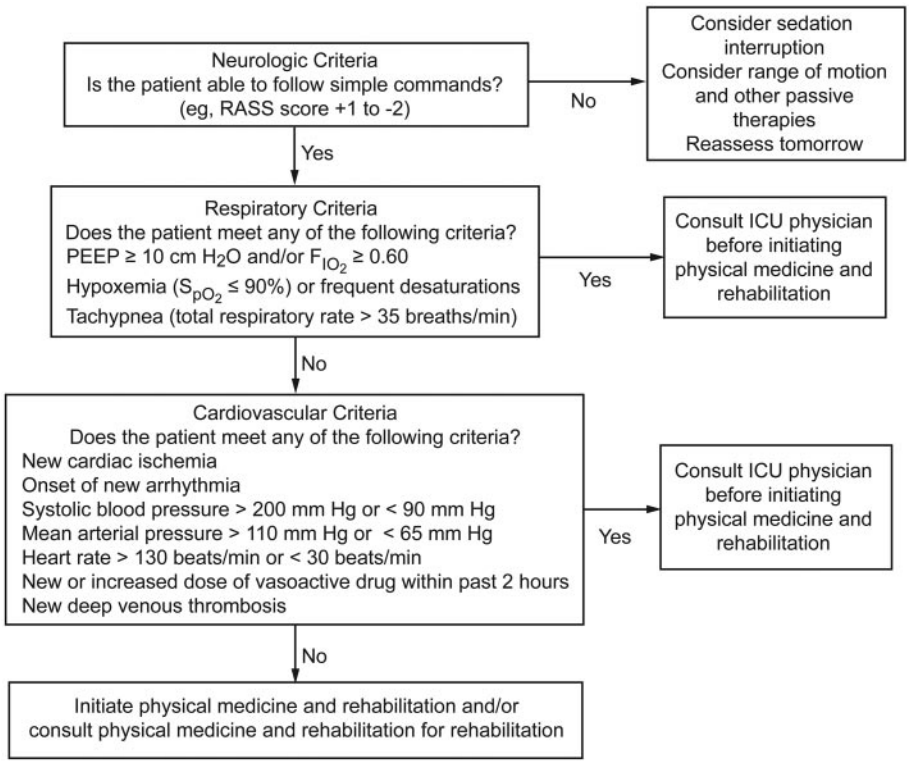

Fig. 1. Daily screening algorithm to evaluate for appropriateness for physical medicine and rehabilitation activity. RASS = Richmond Agitation Sedation Scale. (From Reference 51, with permission.)

(43%), walking 2 or more steps (24%), and walking > 30 m (6%). There was no difference in ICU stay (5.9 d vs 7.9 d, $P = .08$), hospital stay (13.5 d vs 12.9 d, $P = .93$), or hospital mortality (18% vs 25%, $P = .53$); however, there was a trend toward a better discharge-to-home rate (intervention 43% vs control 24%, $P = .06$). The study demonstrated that when a strategy of very early physical rehabilitation is combined with daily sedation interruptions and spontaneous breathing trials, it could result in shorter duration of MV and better physical recovery after critical illness.

Initiating an Early Physical Rehabilitation Program for Mechanically Ventilated Patients

Implementation of an early physical rehabilitation program is feasible in most ICUs, through use of a structured quality improvement process.[48] Successful implementation requires a multifaceted approach that includes engaging key hospital administrators, and ICU and rehabilitation leaders who will support the program and help promote change in ICU culture; assembling a multidisciplinary team of frontline clinicians, including champions from all relevant disciplines (eg, critical care medicine, nursing, respiratory therapy, and physical medicine and rehabilitation); creating a common goal and shared expectation of early rehabilitation for all patients with focused efforts to identify and resolve barriers to achieving this goal; and obtaining basic equipment to facilitate early rehabilitation.[49,50]

The multidisciplinary team will be in charge of planning, executing and evaluating the program. Engaging and educating other ICU stakeholders is assisted by conducting interactive educational sessions to provide information about the safety and benefits of early PT; arranging return visits by ICU patients to share their experiences with sedation, delirium, and inactivity or early ambulation; and arranging visits by "experts in the field" and/or site visits to centers of excellence in ICU early rehabilitation to reinforce the feasibility and benefits of increased activity levels.[49]

The multidisciplinary team will also identify local barriers to early mobilization and rehabilitation, such as over-sedation and delirium, and develop strategies to overcome them, such as encouraging changes in sedation practices and promoting routine screening for delirium.[49] The team will also establish safety-related guidelines and/or screening protocols to assist implementing early rehabilitation for critically ill patients.[51] Figure 1 provides an example of a daily screening algorithm to evaluate for appropriateness for active rehabilitation therapy.

Figure 2 illustrates the feasibility of early mobilization of mechanically ventilated patients. The availability of ap-

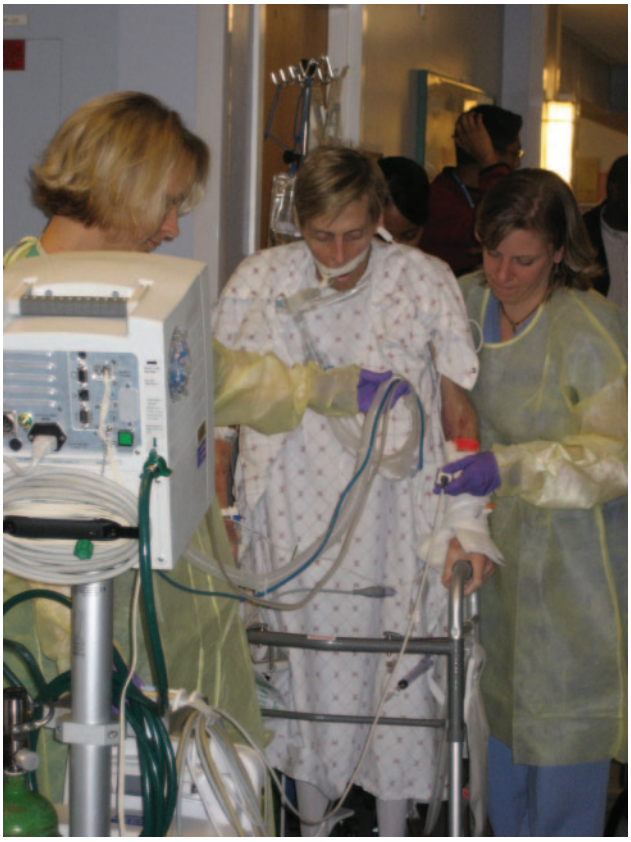

Fig. 2. A 56-year-old man in the Johns Hopkins medical ICU with acute respiratory and renal failure, ambulating while mechanically ventilated, with the assistance of a respiratory therapist, nurse, physical therapist, and a physical therapy technician. (From Reference 49, with permission.)

propriate equipment and personnel is essential to ensure the safety of ICU rehabilitation activities. For instance, mechanically ventilated patients require close monitoring during ambulation. A portable cardiac monitor and pulse oximeter allow continuous monitoring of vital signs. Ventilatory support can be provided with the patient's own battery-powered ventilator, a portable transportation ventilator, or a simple bag-valve-mask, as appropriate. A walker is generally required to provide balance and support during ambulation, and a wheelchair is usually pushed behind the patient for rest breaks. A combination of appropriately trained staff, which may include a nurse, physical therapist, technician/assistant, and respiratory therapist, is desirable to assist with ambulation of mechanically ventilated patients.[51]

Conclusions

Critically ill patients who required prolonged MV are frequently subjected to long periods of inactivity and deep sedation that result in disuse atrophy of skeletal and diaphragmatic muscles. Disuse atrophy is the result of complex mechanisms, including altered protein turnover and disturbed redox signaling. The result of these ICU-acquired complications is longer duration of MV, prolonged ICU and hospital stay, and poorer functional status at hospital discharge. Thus, preventing disuse atrophy and muscle weakness by early initiation of physical rehabilitation and minimizing deep sedation is of great importance.

Studies have demonstrated that early rehabilitation interventions for mechanically ventilated patients are safe and feasible. Furthermore, the benefits of early physical rehabilitation include improved functional status at hospital discharge and shorter ventilation duration and ICU and hospital stay. Finally, growing evidence demonstrates that when PT and OT interventions started at the onset of critical illness are combined with daily sedation interruptions and spontaneous breathing trials, they result in improved physical recovery and a reduced duration of delirium in critically ill patients requiring MV.

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