PERIPHERAL MUSCLE STRENGTH AND CORRELATES OF MUSCLE WEAKNESS IN PATIENTS RECEIVING MECHANICAL VENTILATION

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Background Intensive care unit–acquired weakness is a frequent complication of critical illness because of patients' immobility and prolonged use of mechanical ventilation.

Objectives To describe daily measurements of peripheral muscle strength in patients receiving mechanical ventilation and explore relationships among factors that influence intensive care unit–acquired weakness.

Methods Peripheral muscle strength of 120 critically ill patients receiving mechanical ventilation was measured daily by using a standardized handgrip dynamometry protocol. Three grip measurements for each hand were recorded in pounds-force; the mean of these 3 assessments was used in the analysis. Correlates of intensive care unit–acquired weakness (age, sex, illness severity, duration of mechanical ventilation, medications) were analyzed by using mixed models to explore the relationship to grip strength.

Results Median baseline grip strength was variable yet diminished (7.7 pounds-force), with either a pattern of diminishing grip strength or maintenance of the baseline low grip strength over time. With controls for days of measurement, female sex ($\beta = -10.4$; $P < .001$), age ($\beta = -0.24$; $P = .004$), and days receiving mechanical ventilation ($\beta = -0.34$; $P = .005$) explained a significant amount of variance in grip strength over time.

Conclusions Patients receiving prolonged mechanical ventilation had marked decrements in grip strength, measured by hand dynamometry, a marker for peripheral muscle strength. Hand dynamometry is a reliable method for measuring muscle strength in cooperative critically ill patients and can be used to develop interventions to prevent intensive care unit–acquired weakness. (*American Journal of Critical Care.* 2015;24:e91-e98)

Intensive care unit (ICU)–acquired weakness, defined as the development of severe paresis related to critical illness,[1] is a frequent complication of critical illness because of patients' prolonged immobility and bed rest,[2] particularly in patients receiving prolonged mechanical ventilation.[1] Respiratory and limb muscle strength are altered after 7 days of mechanical ventilation, leading to delayed extubation and prolonged mechanical ventilation.[3] Development of ICU-acquired weakness can also contribute to physical limitations in patients who recover from critical illness.[1,2]

Known risk factors for ICU-acquired weakness include older age, sepsis, electrolyte disturbances, receipt of corticosteroids and neuromuscular blocking agents, illness severity, and immobility; an indirect link has been proposed for sedation because of the reduced mobility of sedated patients.[4(p1880)] In addition, muscle mass and force of muscle contraction decrease with age, resulting in weakness that exceeds what would be expected in a patient with muscle atrophy.[5] In one study,[6] being female was significantly associated with ICU-acquired weakness. Of these known risk factors, ones that are not clinically modifiable include older age, sex, multisystem organ failure, sepsis, and the requirements of some patients for medications such as corticosteroids and neuromuscular blocking agents.[7] Modifiable risk factors include hyperglycemia and use of sedatives.[7]

Little is known about the pattern of muscle strength during mechanical ventilation, or if modifiable risk factors might directly influence muscle strength in patients experiencing prolonged mechanical ventilation. Measurement of muscle strength is also difficult in the critical care unit because noninvasive methods require alert and cooperative patients. One objective, directly quantifiable measure of peripheral muscle strength is handgrip dynamometry. Grip strength limited to 1 to 3 measurements has been used by other ICU researchers[1,4] as a marker of impaired functional status, with diminished grip strength linked to increased ICU mortality.[1] Few data are available on serial assessments of grip strength during mechanical ventilation. Thus, the purpose of this longitudinal study was to describe serial measurements of peripheral muscle strength and to identify factors associated with patterns of peripheral muscle strength during mechanical ventilation.

> Respiratory and limb muscle strength are altered after 5-7 days of mechanical ventilation.

Methods

Patients included in this descriptive, correlational study were a subset (n = 120) of patients receiving mechanical ventilation who were enrolled in a randomized clinical trial on self-management of anxiety with preferred, relaxing music.[8] Participants were recruited from 12 ICUs in 5 hospitals associated with the University of Minnesota, Minneapolis, Minnesota, and were receiving mechanical ventilation for a primary pulmonary problem.

Patients were enrolled from ICUs where care was delivered at the bedside by registered nurses in a 1 to 2 or 1 to 1 nurse to patient ratio. All of the participating ICUs had a written sedation administration protocol; however, protocols varied among sites. None of the participating ICUs had progressive mobility protocols in place at the time of enrollment. Patients remained enrolled in the parent study as long as they were receiving mechanical ventilation, up to 30 days; or until they were extubated, chose to withdraw from the study, were transferred from the ICU, or died. Patients were enrolled in the parent study for a mean of 5.7 days (SD, 6.4; median, 3.2; range 1-30).[8]

Patients met inclusion criteria if they were making their own daily care decisions, were interacting appropriately with staff, had stable hemodynamic status, and were not currently receiving paralytic medications. Patients provided their own consent because of the patient-directed nature of the intervention protocol. This study was approved by the human subjects' committees of the University of Minnesota and the participating sites. Details on the parent study have been reported elsewhere.[8]

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Table 1
Hand dynamometry grip-strength testing procedure

Ask patient, **"Are you right-handed or left-handed"**? Always test the dominant hand first!

Testing process
The ideal position for a patient undergoing testing is supine with the head of the bed (HOB) elevated at a 30° to 45° angle (per bed angle measurement device). If the patient is not in that position, ask the nurse if the patient can be repositioned. The patient must at least be supine. If the HOB angle cannot be changed, document the angle of the bed on the data form.
Demonstrate use of the device for the patient by stating the following: **"I want you to hold the handle like this and squeeze as hard as you can."** Demonstrate use and then give the dynamometer to the patient.
Remind the patient that it won't be a normal sensation of squeezing something moveable.
Reset the gauge to zero.
Assist patient in putting device in hand with gauge facing outward and arm extended and resting on the bed. The bottom of the device should rest on the bed.
Keep your hand close by the device, but not touching, to catch it or protect it if the patient loses control of it.
If the patient is unable to hold the device steady, you may use 2 fingers on top of the gauge to support the device.
Ask the patient if he or she is ready, then read the following script to the patient to obtain the first grip reading.

After the patient is positioned appropriately, say, "Are you ready? Squeeze as hard as you can." As the patient begins to squeeze, say, "Harder! . . . Harder! . . . Relax." Repeat with the same instructions for the second and third trial and on each hand.

After the first test, ask the patient, **"Was that okay?" "Was that painful?"** If not painful, continue with grip testing. If too painful, stop at this point and reassess or reattempt testing at the next visit. If a patient is unable to perform grip tests because of pain on 3 consecutive days, do not attempt further grip assessments on the patient.
Document the grip reading (**from the inner circle of numbers in pounds-force**).
Reset gauge to zero.
Place grip in opposite hand and repeat testing process.
Alternate testing between hands until you have obtained 3 readings from each hand.
Reset gauge to zero between each reading.
Document all readings and any pertinent comments such as HOB angle and patient's comments and concerns.

Measures

Grip-Strength Measurement via Hand Dynamometry. Peripheral muscle strength was determined by using handgrip dynamometry with the Jamar Hydraulic Hand Dynamometer (Patterson Medical), which measures the force or strength of a grip in pounds-force. The Jamar hand dynamometer is considered the standard for measurement of grip strength because of its high calibration accuracy at ±3% to 5%.[9,10] The standardized normal grip strength for adults is 101 to 121 pounds-force for men and 57 to 70 pounds-force for women,[9] providing a quantifiable measure for comparison.

Research by Mathiowetz and colleagues[9,11] has resulted in a standard protocol for assessing grip strength, which includes patient positioning and how to give verbal instructions for completing the assessment. Grip-strength measurements are more accurate when the mean of 3 grip trials is used rather than either a single grip trial or the highest reading of 3 trials.[9,11] Mathiowetz and colleagues[9,11] have reported high interrater reliability (right grip, $r = 0.99$; left grip, $r = 0.99$) and high test-retest reliability when the mean of 3 grip trials is used (right grip, $r = 0.88$; left grip, $r = 0.93$). No significant problems with variability in having multiple people performing assessments have been identified.[11]

Because the original measurement standards were developed with healthy persons in a seated position, an occupational therapist was consulted to modify the protocol for the patients in this study. Research nurses were trained by the occupational therapist in the Mathiowetz assessment procedure (Table 1). One Jamar device was stored at each hospital to ensure that patients used the same device throughout the study. Baseline handgrip strength was evaluated on the day of enrollment into the parent study and then assessed daily by using the protocol (Table 1). Hand dynamometry was discontinued for any day when a patient expressed any indications of pain or declined to complete the grip assessments.

Patients were approached for grip-strength measurement each day they were enrolled in the parent study. If a patient was not able to generate any grip strength on the Jamar dial, a value of zero was recorded for that day. If a patient was off the unit, unable to participate in measurement, or declined grip measurement, no value was recorded for that day.

Correlates of ICU-Acquired Weakness. Known correlates of ICU-acquired weakness explored were limited to correlates available from the parent study. Patient characteristics included risk and protective factors such as age, sepsis, receipt of corticosteroids, continuous insulin infusion, any receipt of neuromuscular blocking agents, and illness severity. The Acute Physiology and Chronic Health Evaluation III was used to measure illness severity. Scores on the evaluation were calculated on the basis of the ICU admission data. The higher the score (range, 0-299), the more ill a patient is and the higher the risk of ICU mortality.[12]

Use of sedatives throughout study enrollment allowed for summarizing dose frequency, termed

sedation frequency over 24 hours, and aggregate dose of medications, termed sedation intensity score (SIS), from disparate drug classes.[13] Eight commonly administered analgesics or sedatives (midazolam, lorazepam, fentanyl, morphine, dexmedetomidine, hydromorphone, propofol, haloperidol) were monitored, and a weight-adjusted dose for each medication administered during a 4-hour time block was calculated. A patient's mean SIS (quotient of sum of patient's SIS values and number of 4-hour intervals receiving mechanical ventilation) represents the mean sedative exposure per hour relative to all other patients. Details on calculating sedative exposure can be found elsewhere.[8,13]

Analysis

Descriptive statistics (frequencies for categorical data, measures of central tendency and dispersion), graphing, and mixed modeling were used to analyze the data. Mixed-effects models were used to analyze grip strength over time to accommodate data that were correlated and data that had variances that were not constant from one time point to another and to accommodate any missing values. When the data are used as they are, without imputation, within a mixed model, analysis has a lower type I error and higher power than with any type of imputation method used for missing data, which may result in biased estimates of effects and standard errors.

Possible patterns of change were explored by graphing each patient's grip strength vs time. Sedation patterns were also explored by graphing the SIS and sedation frequency by patient over time. The patients had a linear change over time, with a predominantly negative slope for grip strength, although variation did occur. An unconditional means model was used to assess 2 null hypotheses: no change across occasions and no variation between patients. Rejection of these null hypotheses warrants further analysis.

Determination of parameters and a final mixed-effects model proceeded as follows. First, an unconditional growth model was developed with Day added as a predictor that resulted in estimation of change coefficients. The best-fitting covariance structure was the autoregressive covariance structure with the assumption that correlations decrease as the lag time increases. Next, a conditional growth model introduced the effect of the covariates that were both associated with grip strength and clinically important, such as an effect from sedation

> Median number of days of ventilatory support prior to study enrollment was 6.7.

(SIS). An unstructured covariance structure was the best fit for this analysis.

SPSS, version 17 (IBM SPSS), and SAS, version 9.2 (SAS Institute Inc), software were used for analyses. Level of significance was determined a priori as $P \le .05$.

Results

Description of Patients

The patients in this study were mostly white women (51%) with a median age of 52 years. Most patients' indication for mechanical ventilation was respiratory failure (50%). Only 6.5% of patients had a diagnosis of sepsis, 38% received continuous insulin infusions, 56% received corticosteroids, and 10% received neuromuscular blocking agents. Patients were enrolled for a median of 4.2 (range, 1-30) days. Median number of days receiving mechanical ventilation before enrollment in the study was 6.7, with a median of 9 days in the ICU before enrollment. Disposition of patients at ICU discharge was 92% alive and 8% deceased (see Table 2 for details).

Grip-Strength Measurements

Median baseline grip strength was quite diminished, at 7.7 pounds-force, with a wide range, from 0 to 102 pounds-force (Table 2). A few patients (n = 6) could not generate any grip strength (zero on the Jamar dial) despite coaching and encouragement from research staff.

The median number of grip-strength measurements for patients was 4 (range, 0-30). As shown in Figure 1, the pattern of grip strength during mechanical ventilation indicates that patients either start at a higher grip strength and then their strength declines, or they start at a lower point and either stay at that diminished level or their strength continues to decline further over time. Only 3 patients had a pattern of increasing grip strength.

Figure 2 indicates median grip strength over time by sex. The data show a fluctuating pattern of grip strength over time in both men and women. By the end of the study, the data suggest a possible upward trend in grip strength as patients recover from a prolonged critical illness.

Sedative Exposure

Median overall SIS was 4 (range, 0-11), median dose frequency was 6.4 (range, 0-16) each study day, and 26% of patients received continuous infusions of sedatives or opiates.

Correlates Among Grip Strength, Patient Characteristics, and Sedative Exposure

Level 1 modeling showed significant unexplained variance in both grip strength over time ($z = 5.41$;

$P<.001$) and in initial grip strength ($z=5.37$; $P<.001$), indicating further analysis was appropriate. In level 2 modeling, with controls for days on protocol, being female ($\beta=-10.4$; SE, 2.5; $P<.001$), age ($\beta=-0.24$; SE, 0.08; $P=.004$), and days receiving mechanical ventilation ($\beta=-0.34$; SE, 0.12; $P=.005$) explained a significant amount of variance in grip strength over time (Table 3). Women started with a grip strength 10.4 pounds-force lower than the grip strength of men. For each year older a patient was, the grip strength diminished 0.24 pounds-force, and for each additional day of mechanical ventilation, grip strength decreased by 0.34 pounds-force. Scores on the Acute Physiology and Chronic Health Evaluation III ($\beta=-0.12$; SE, 0.07; $P=.09$), receipt of insulin, receipt of corticosteroids, sedative exposure, or neuromuscular blocking agents did not significantly contribute to an explanation of variance over time in grip strength.

Discussion

We provide data on serial measurement of grip strength in ICU patients whose clinical status was fairly stable and whose severity of illness was low. A majority of the sample did not have sepsis. To be eligible for the parent study, patients had to be awake and interacting appropriately with nursing staff. Thus, daily measurement of grip strength was a reasonable approach for tracking peripheral muscle strength in these cooperative patients. Patients had significant decrements in peripheral muscle strength at baseline (median day 6.7 of mechanical ventilation). Baseline measures were substantially lower than the norms for men and women, and patients did not show any substantial improvement in grip strength over time.

Age, being female, and lengthy periods of mechanical ventilation contributed to diminished grip strength in our patients, regardless of illness severity. Our sample of patients had lower severity of illness scores than did patients in other studies[1,4] in which grip strength was measured or in a study[5] that revealed significant and sustained weakness in ICU survivors with acute respiratory distress syndrome. However, our results indicate decreases in peripheral muscle strength regardless of diagnosis or how ill a patient was upon ICU admission. Schweikert and Hall[7] have suggested several areas for risk-factor modification in patients at risk for ICU-acquired weakness. Although glycemic control is one area with evidence of benefit, receipt of continuous insulin infusions did not affect grip strength in our study; however, we did not assess overall blood glucose control. Likewise, medications linked to evidence for harm, corticosteroids and neuromuscular blocking agents, were also not significant correlates in our study. One area of indirect evidence

for the modification of ICU-acquired weakness is sedation-sparing protocols. Although sedative exposure did not significantly contribute to decrements in peripheral muscle strength in our study, it could have indirectly contributed to lengthy periods of mechanical ventilation, which was a significant correlate in our study.

Limitations

Our study had several limitations. Generalizability of the findings is relevant only to those ICU patients with characteristics similar to the characteristics of our sample. We did not obtain any data on disability before ICU admission that could have affected assessments of grip strength. We did not know if patients were already weak and had decrements in muscle strength before ICU admission.

Table 2
Demographic and clinical characteristics of 120 study participants[a]

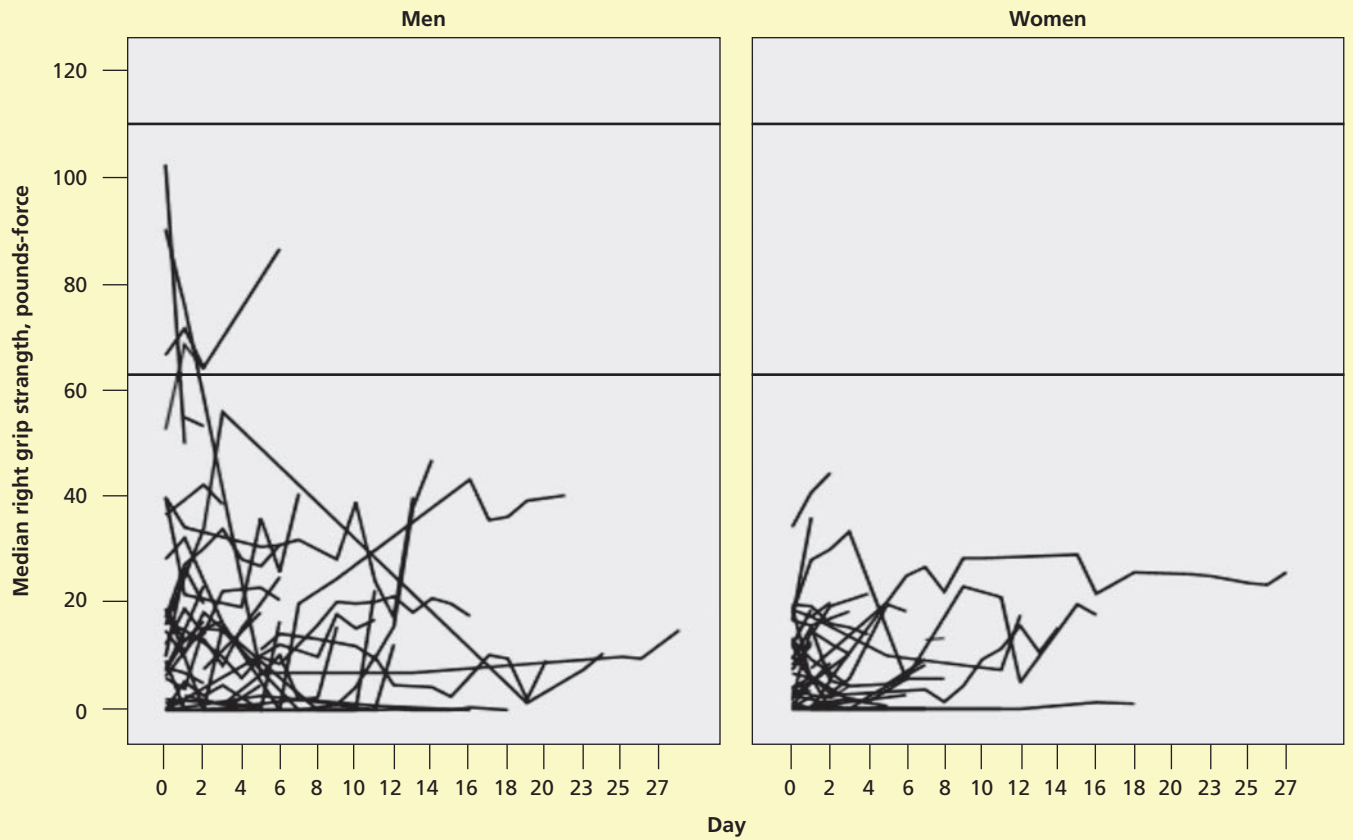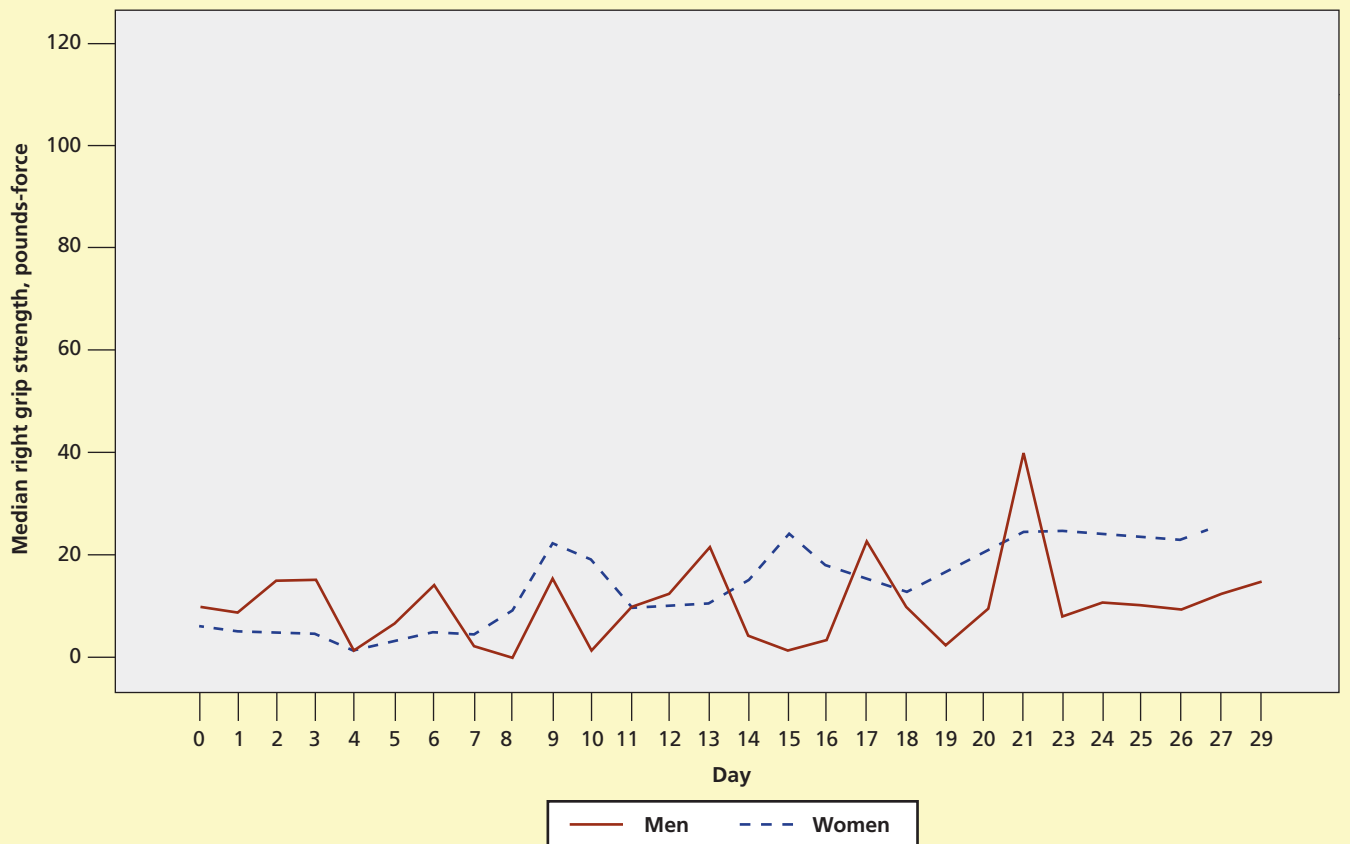| Variable	Frequency, %	Mean (SD)	Median (range)
Age, y			52 (23-93)
Sex			
Male	49		
Female	51		
Race			
White	84		
Black	14		
Asian	2		
APACHE III score at time of study enrollment		61.3 (20.7)	
Baseline grip strength, pounds-force			7.7 (0-102)
Baseline grip strength first day, pounds-force			
Men			13.2 (0-90)
Women			13.0 (0-34)
Days of ventilatory support before enrollment			6.7 (0.2-38.0)
Days in ICU before enrollment			9 (1-41)
Length of study enrollment, days			4.2 (1-30)
Indication for mechanical ventilation			
Respiratory failure	50		
Respiratory distress	32		
Hypoxemia	14		
Acute respiratory distress syndrome	4		
Medical diagnosis at ICU admission			
Respiratory	39		
Cardiovascular	26		
Infectious process	5		
Gastrointestinal	7		
Neurological	15		
Other; surgical admission	8		

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.
[a] Blank cells indicate not applicable or not determined.

Figure 1 Spaghetti plot of individual patients' median grip strength over time for men and women.

Figure 2 Median grip strength during study period by sex of patients.

Table 3
Final models of correlates of peripheral muscle weakness (grip-strength assessment; N = 120)

Variable	Screening model with sedation frequency[a]		Screening model with sedation intensity[b]		Final model	
	β (SE)	P	β (SE)	P	β (SE)	P
APACHE III score	-0.12 (0.07)	.09	-0.12 (.07)	.09		
Age	-0.23 (0.09)	.01	-0.23 (0.09)	.02	-0.24 (0.08)	.004
Female sex	-10.7 (2.7)	<.001	-10.6 (2.7)	<.001	-10.4 (2.5)	<.001
Sepsis	-1.1 (4.6)	.80	-1.1 (4.6)	.81		
Continuous insulin infusion	-3.6 (2.8)	.18	-3.6 (2.7)	.19		
Neuromuscular blockade	-0.33 (4.5)	.94	-0.38 (4.6)	.93		
Steroids	2.3 (2.8)	.42	2.2 (2.8)	.43		
Total ICU days	0.20 (0.16)	.20	0.21 (0.16)	.20		
Days on protocol	-0.19 (0.20)	.33	-0.18 (0.19)	.35	-0.04 (0.18)	.82
Days of mechanical ventilation	-0.54 (0.19)	.007	-0.53 (0.19)	.007	-0.34 (0.12)	.005
Sedation frequency	-0.005 (0.20)	.98				
Sedation intensity			0.09 (0.29)	.77		

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.
[a] Any sedative or analgesic administered in a 4-hour time block summed over 24 hours.
[b] Aggregate score summed over 24 hours.

We also did not know when and if patients regained their muscle strength or if they experienced any decreases in functional domains and quality of life. Likewise, we did not obtain any measurement of respiratory muscle strength, strength that may have influenced total duration of mechanical ventilation. Finally, assessment of grip strength during early stages of mechanical ventilation was challenging. We were able to enroll patients only around day 6 or 7 of mechanical ventilation, because of the inclusion criteria of the parent study. However, as clinical practice guidelines that call for minimizing sedation are more widely implemented, handgrip dynamometry may be a feasible option for tracking peripheral muscle strength over the entire course of mechanical ventilation.

Implications for Practice

Our findings provide additional evidence of the detrimental effects of prolonged mechanical ventilation and immobility in ICU patients. Older, female patients may require additional efforts to minimize ICU-acquired weakness during lengthy courses of ventilatory support. Mobility programs may be useful in addressing at least some of the decreases in peripheral muscle strength during mechanical ventilation; however, for mobility programs to be successful, patients must be awake and interactive. Nurses will need additional training in mobility programs and alternatives to sedative medications for symptom management to promote alert and interactive patients who can be involved in maintaining or even improving peripheral muscle strength while receiving mechanical ventilation.

The significant decreases in grip strength at the time of enrollment and the sustained decreases without improvement in peripheral muscle strength during the study period in our patients suggest urgency in instituting activity and mobility interventions. One place to start may be to omit the "early" label and institute a culture where more awake and engaged patients are the expectation, not the exception, thereby increasing opportunities for mobility interventions. Implementation of interventions that sustain or preserve muscle strength and muscle mass is needed. Because of the projected increase in the number of patients who will require prolonged mechanical ventilation by 2020[14] and the financial burden of providing care for these patients, these trends have important implications. Clinicians need to carefully examine ICU care processes and the marked burden of critical illness on survivors' recovery. Innovative interventions and care processes beyond progressive mobility are needed.

Nurses need to take the lead in managing the care in several different ways for patients treated with mechanical ventilation. Nurses can facilitate development of mobility protocols, implementing and coordinating activity and out-of-bed interventions as soon as possible in a safe manner.

> The results indicate decrements in peripheral muscle strength regardless of diagnosis.

Symptom management requires ongoing intervention with both pharmacological and nonpharmacological interventions[15] to manage patients distressful signs and symptoms and promote increasing patient movement. All members of the multidisciplinary care team must take accountability and collaborate to develop and implement innovative strategies based on the best available evidence to promote muscle preservation in critically ill patients. This group of care providers includes physical and occupational therapists, who can optimize rehabilitation resources related to mobility, as well as physicians and respiratory therapists, who can optimize ventilatory management.

Implications for Future Research

In our study, older women who had prolonged periods of mechanical ventilation had the greatest decreases in grip strength, a marker of peripheral muscle strength. Future longitudinal studies are needed to evaluate the feasibility of performing handgrip assessments throughout the entire course of mechanical ventilation, the predictive value of handheld dynamometry on patients' functional outcomes,[16] and the usefulness of grip strength assessment in guiding intervention strategies.

Novel interventions to preserve muscle mass and strength in ICU patients need to be developed and tested. These strategies could include interventions that can be performed in the bed or in a chair to maintain or improve strength even when active mobility may not always be an option.

Innovative mobility protocols that are safe and do not place an unnecessary burden on the ICU staff are needed. Because of the demands of high-acuity care, staffing patterns, the increasing need for interdisciplinary support, and the aging of the nursing workforce, these factors need to be considered and supported when developing and testing new ICU care protocols.

Summary and Conclusions

ICU-acquired weakness is a common problem in patients receiving prolonged mechanical ventilation. Our findings add to the evidence on the detrimental influence of prolonged mechanical ventilation and immobility, particularly in older female patients. Understanding the causes, pathophysiology, and risks factors of ICU-acquired weakness is important for prevention.[2] A recent review[5] presents information on clinical phenotypes and possible molecular mechanisms of ICU-acquired weakness that may inform innovative treatments for patients. Multidisciplinary team efforts are needed to quantify ICU-acquired weakness throughout the course of mechanical ventilation and to develop interventions to prevent or at least minimize ICU-acquired weakness.

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