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An Exploratory Study Of Physiologic Responses To A Passive Exercise Intervention In Mechanically-ventilated Critically Ill Adults

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AN EXPLORATORY STUDY OF PHYSIOLOGIC RESPONSES TO A PASSIVE EXERCISE INTERVENTION IN MECHANICALLY VENTILATED CRITICALLY ILL ADULTS

By

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ABSTRACT

Muscle weakness is the most common and persistent problem after a critical illness. Early mobilization of the critically ill patient, beginning with passive exercise and progressing to ambulation, may mitigate muscle effects of the critical illness. However, mobilization may produce adverse effects, especially early in the illness when risk for physiologic deterioration is common. If safe, introducing a mobility intervention early in the illness may facilitate ventilator weaning, shorten intensive care unit and hospitals stays, and improve functional status and quality of life for mechanically ventilated critically ill patients.

The aim of this study was assess the cardiopulmonary and inflammatory responses to an early standardized passive exercise protocol (PEP) in mechanically ventilated critically ill patients. Using a quasi-experimental within-subjects repeated measures design, mechanically ventilated critically ill adults who were physiologically stable received a single standardized PEP within 72 hours of intubation. The PEP consisted of 20 minutes of bilateral passive leg movement delivered by continuous passive motion machines at a rate of 20 repetitions per minute, from 5-75 degrees, to simulate very slow walking. Physiologic parameters evaluated included heart rate (HR), mean blood pressure (MBP), oxygen saturation, and cytokine levels (IL-6 and IL-10), obtained before, during, and after the intervention. The Behavioral Pain Scale (BPS), administered before, during and after the intervention was used as a measure of participant comfort.

The study sample was comprised of 18 (60%) males and 12 (40%) females, with a mean age of 56.5 years (SD 16.9 years), who were primarily Caucasian (*N*=18, 64%). Mean APACHE II scores for the sample were 23.8 (SD 6.2) with a mean predicted death rate of 48.8 (SD 19.8), indicating moderate mortality risk related to illness severity. Number of comorbidities ranged

from 1-10 (X=4). All participants completed the intervention with no adverse events. Using repeated measures analysis of variance (rmANOVA), no significant differences were found in HR, MBP, or oxygen saturation at any of the four time points in comparison to baseline. BPS scores were significantly reduced (F(2.43, 70.42)=4.08, p=.02) at 5 and 10 minutes after the PEP was started, and were sustained at 20 minutes and for one hour after the PEP was completed. IL-6 was significantly reduced (F(1.60, 43.1)=4.351, p=.03) at the end of the intervention but not at the end of the final rest period. IL-10 values were not significantly different at any of the three time points, but IL-6 to IL-10 ratios did decrease significantly (F(1.61, 43.38)=3.42, p=.05) at the end of the PEP and again after a 60 minute rest period. Passive leg exercise was well tolerated by study participants. HR, MBP, and oxygen saturation were maintained within order set-specified ranges during and for one hour after activity, and patient comfort improved during and after the intervention. A downward trend in HR was noted in participants, which is contrary to usual HR response during exercise, and may represent clinical improvement in this population related to reduction in pain. Reduction of mean IL-6 values at the end of the PEP, but not after the rest period, suggests that the PEP was responsible for the initial IL-6 improvement. Improvement of IL-6 to IL-10 ratios from the end of the PEP to the end of the final rest period suggests that IL-10, although non-significant, may have had some effect, indicating that IL-10 increases may occur later than the time period of study.

Passive exercise can be used as an approach to facilitating mobilization in mechanically ventilated critically ill adults until they are ready to participate in more active exercise. It could be that more frequent and aggressive exercise, such as passive cycling at faster rates, four times daily, will be tolerated in this population. While the understanding of clinical significance of cytokine profiles in critically ill patients is still evolving, cytokine levels may be useful in

explaining benefits of mobilization in this population. Further study is required to replicate the impact of passive exercise on pain, and it may represent a novel approach to pain management in critically ill patients.

To my Husband, Tom,

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CHAPTER ONE: INTRODUCTION

Muscle weakness is the most common complication of critical illness, as well as the most persistent problem after a critical illness.[1] Fatigue, poor functional status and decreased health-related quality of life one year after a critical illness are all attributed to persistent muscle weakness.[4] The muscle weakness associated with critical illness is due to immobility as well as inflammation.[3] Inflammation diminishes both muscle mass and strength. Inflamed muscle is problematic in that it can prolong need for mechanical ventilation, extend hospital stay, and complicate recovery, as well as negatively impact quality of life for the individual with critical illness.[4] Mobilization is one approach to mitigating inflammation and muscle weakness after a critical illness.[5] It covers a wide range of progressive activities, from passive and active range of motion (ROM), to dangling, standing or lift transfer to a chair, and ambulation.[1,6,7] Mobilization is thought to preserve muscle strength and mass by improving blood flow, stimulating anti-inflammatory cytokine production and enhancing insulin activity and glucose uptake in muscle.[3]

Mobilization has been shown to improve outcomes for critically ill adults.[1,8] Improved outcomes include earlier ambulation, shorter lengths of intensive care unit (ICU) and hospital stays, and improved functional status as well as quality of life.[1,2,8] Whether a decrease in inflammation could be directly attributed to activity and improved outcomes is not yet known, but preliminary evidence suggests that 20 minutes of sustained activity daily can improve cytokine profiles in critically ill patients.[9]

Mobilization protocols, beginning with passive activity and advancing to ambulation, have been studied as a step-wise approach to activity progression but many study participants have been unable to move beyond passive activity.[1, 8] Primary reasons for failure to progress were decreased responsiveness and physiologic instability.[1, 6, 8] Physiologic instability in

mechanically ventilated critically ill patients may persist for days to weeks, delaying use of active mobility interventions. Passive exercise, a routine nursing procedure, may be the most appropriate activity for these patients in the early phase of illness.[10] However, limited empirical evidence exists to support the safety or efficacy of passive activity, particularly during periods of physiologic instability, and criteria to document readiness to institute active mobilization have not yet been developed. Tolerance of passive activity may be one signal that progression is appropriate.

Patient tolerance appears to be the limiting factor in application of mobilization activities.[10,11] Commonly used bedside physiologic measures, such as heart rate and blood pressure, have been suggested as approaches to identifying patient tolerance,[6, 11] and preliminary research has demonstrated physiologic stability in mechanically ventilated critically ill patients who were mobilized 5 days or longer after intubation.[12] However, waiting to start mobilization for 5 days or longer after intubation may miss an important window of opportunity to improve patient outcomes. Loss of muscle mass and strength is evident soon after critical illness onset; 2% of mass may be lost within the first 24 hours of critical illness.[3,10] With muscle changes appearing soon after onset of critical illness,[13] it is logical to consider implementation of mobilization soon after illness onset, as delay may add to disability.[14]

Concern has been expressed about early mobilization contributing to increased muscle inflammation, which may actually compound rather than prevent muscle weakness.[15] Inflammatory markers did not change significantly with passive activity (< 15 min), suggesting that passive activity does not increase inflammation.[16] However, further study would add to safety support for this measure.

To date, limited study has been done to evaluate safety of passive activity in early critical illness. Chapter 2 provides a review of the state of the science related to passive activity in critical illness. Passive activity, if demonstrated to be safe, may provide early benefit to those critically ill patients who are not yet able to tolerate progressive activity. Introducing a mobilization intervention early in the illness may facilitate weaning, shorten intensive care unit and hospitals stays, and improve quality of life for mechanically ventilated critically ill patients.

Study Purpose and Aims

The aim of this study was to assess the physiologic responses to a standardized passive exercise intervention instituted within 72 hours of intubation in mechanically ventilated critically ill patients. The specific research questions asked were:

1. What is the cardiopulmonary response to an early passive exercise protocol (PEP) in mechanically ventilated critically ill patients?
2. What is the intracranial pressure (ICP) response to an early passive exercise protocol (PEP) in mechanically ventilated critically ill patients?
3. What is the behavioral pain response to an early passive exercise protocol (PEP) in mechanically ventilated critically ill patients?
4. What is the inflammatory response to an early passive exercise protocol (PEP) in mechanically ventilated critically ill patients?

Theoretical Framework

The muscle weakness associated with critical illness is thought to be due to inflammation rather than immobility. A theoretical framework focused on inflammation is relevant to the study of critical illness myopathy, as it provides a more rational explanation for the muscle weakness

that occurs with critical illness than immobility alone. In muscle that has been immobilized, myosin filaments are typically retained while actin fibers are lost, leading to significant loss in mass and but not strength.[5] In contrast, inflamed muscle has been observed to lose both myosin and actin,[5] supporting the concept that inflammation plays a significant role in muscle weakness. Critical illness typically invokes a systemic inflammatory response.[17] Muscle weakness in critical illness represents a type of organ failure secondary to this systemic inflammatory response.[5] The systemic inflammatory response is thought to affect the muscle as follows.

Catecholamines released during the inflammatory response bind to muscle cell receptor sites to stimulate muscle proteolysis. The protective purpose of proteolysis is to provide readily available amino acids for gluconeogenesis. High catecholamine levels not only contribute to muscle protein loss, but also can also suppress protein synthesis through cytokine mechanisms.[18] Catecholamines upregulate the expression of the pro-inflammatory cytokines, IL-1 and tumor necrosis factor-alpha (TNF-*a),* which can have adverse effects on muscle. TNF-*a* affects muscle regeneration by inactivating a muscle proliferation transcription factor,[19] which ultimately decreases protein synthesis, resulting in decreased muscle mass. Concomitantly, IL-1*a* generates free radicals, which damage myosin filaments, resulting in decreased strength.[18,19] TNF-*a* also reacts with muscle receptors that block aerobic protein metabolism, thereby creating oxidative stress in the muscle, ultimately decreasing contractility.[19]

IL-1 activates IL-6, which has both pro- and anti-inflammatory effects. IL-6 stimulates neutrophil maturation and natural killer (NK) cell differentiation, but it also promotes release of anti-inflammatory cytokines and downregulates IL-1 and TNF-*a* over time.[19] Muscle cells have receptors for IL-6; those IL-6 receptors are thought to contribute to muscle proteolysis by recruiting infiltrative inflammatory products such as prostaglandins.[19] Muscle cells also express

IL-6, and this expression is thought to be linked to the glucose metabolism that is necessary for energy production and muscle repair.[19] In a homeostatic state, IL-6 activates IL-10, which mediates effects of IL-1, IL-6 and TNF-*a*, thus protecting muscle. Sustained production of pro-inflammatory cytokines can suppress anti-inflammatory cytokines.[19] Imbalance of pro- and anti-inflammatory cytokines is thought to contribute to muscle breakdown and impairment of repair mechanisms that characterizes the muscle weakness seen in critical illness.[20]

Systemic inflammation also produces cytokine-mediated microcirculatory changes. IL-1 increases endothelial adhesion of lymphocytes through activation of cell adhesion molecules, a process designed to prevent microbial invasion. As cells adhere, thrombosis of microcirculation and consequent muscle ischemia and micro-infarction can occur.[21] Tissue hypoxia upregulates IL-1 and TNF-*a* expression, compounding the process. Capillary permeability is also increased in the inflammatory response, due to expression of IL-1*b*, which stimulates release of prostaglandins. The resulting vascular permeability may allow greater exposure of muscle cells to cortisol. Cortisol is implicated in what has been termed an "acquired channelopathy," in which cortisol binding on muscle receptor sites dysregulates the sodium channels, resulting in decreased excitability of the muscle.[18]

Hyperglycemia is an additional factor in muscle damage. The relative insulin resistance produced in response to increased cortisol levels can exacerbate muscle catabolism.[5, 18, 19] Insulin has been found to play an important role in preventing muscle proteolysis as well as promoting muscle repair. Maintenance of normoglycemia may protect muscle.[22]

Prevention of muscle weakness in critical illness focuses on decreasing inflammation, promoting blood flow, and restoring normoglycemia.[22] Mobilization activities may produce all three benefits, and even passive activities may provide some muscle protection (Figure 1).

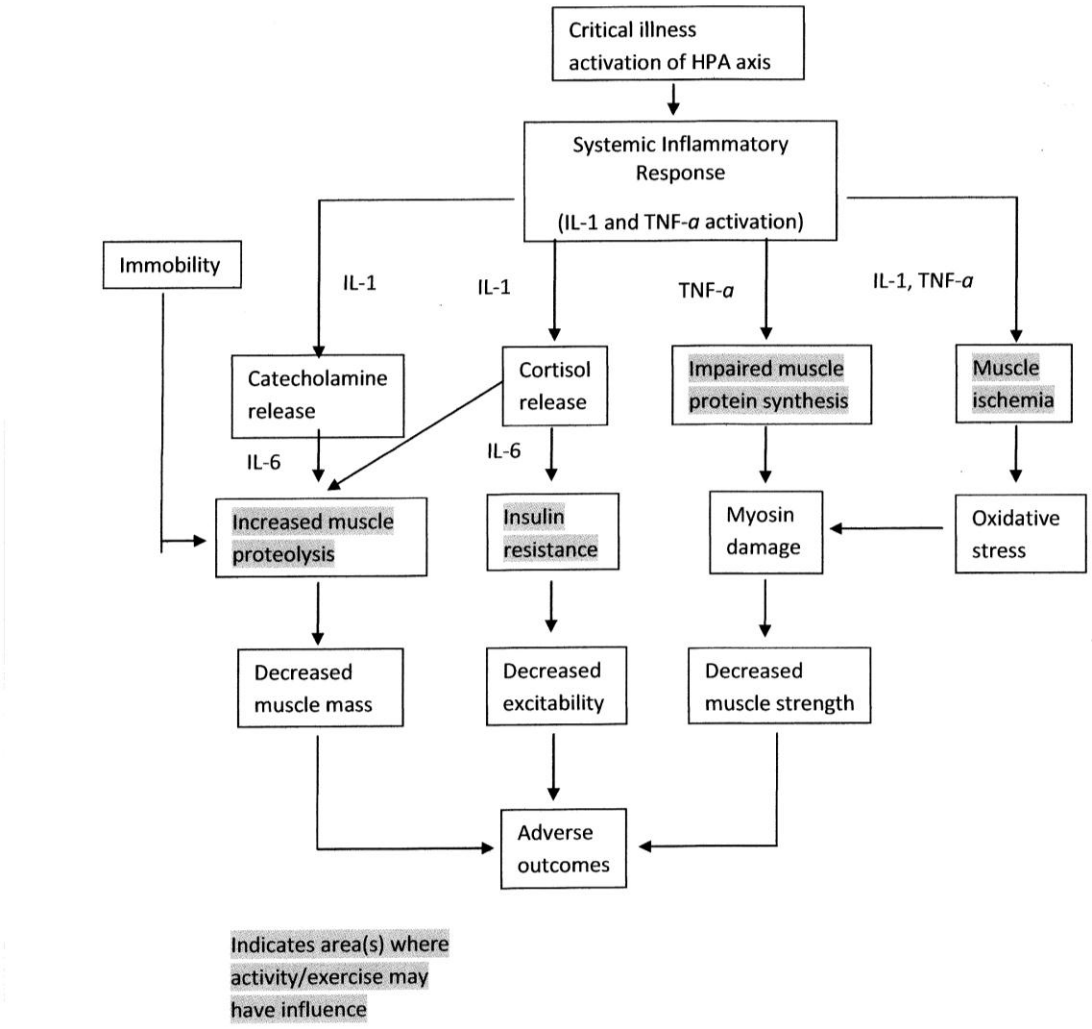

Figure 1. Interactions of inflammatory responses on muscle metabolism. Note that IL-1, IL-6, and TNF-α act as mediators for the inflammatory cascade. Not depicted here is the action of IL-10. As an anti-inflammatory cytokine, IL-10 is activated by IL-6 to mediate (downregulate) expression of IL-1 and TNF-α, in effect inactivating the inflammatory response.

Pedersen and Hoffman-Goetz suggest that activity and exercise stimulate release of inhibitory factors that decrease or turn off the inflammatory response.[23] The inhibitory factors are IL-1ra, which blocks IL-1 activity, and IL-10 which provides anti-inflammatory balance to the pro-inflammatory IL-6. Thus, activity mediates the magnitude and duration of the inflammatory

response.[23] Activity has been noted to increase pro-inflammatory cytokines, specifically IL-6.[23,24] However, the increase in IL-6 appears to be related to intense, prolonged exercise which typically would not be expected in the critical care setting. Similarly, decreased activity tolerance, which is anticipated in the critical care setting, has also been associated with an increase in IL-6.[23] Further evidence suggests that the IL-6 may be muscle-derived rather than circulating IL-6, which may actually contribute to muscle repair and protection.[20,24] Muscle activity has also been purported to reduce small vessel compression and improve blood flow which may reduce inflammatory factors present in the muscle.[24] Low resistance exercise, including passive or active range of motion, has been found to increase muscle blood flow and oxygen supply. Continuous passive exercise in one leg three times a day for seven days improved muscle blood flow and prevented myopathy in the treated leg in 5 critically ill patients.[25] Exercise also decreases insulin resistance,[24, 26] which may modulate the effects of hyperglycemia on muscle.

The inflammation framework provides multiple defined targets for intervention. The physiologic responses in the framework serve as measurement points that may be used to determine safety or efficacy of targeted interventions. The framework also crosses disciplines, so its utility is not limited to nursing alone. The major limitation in using this framework is that inflammation is a systemic response, not limited to muscle. It is feasible that other systemic effects may intervene, limiting therapeutic effects of any targeted interventions. In addition, the immune system focus limits additional factors, such as psychological stress, from contributing to outcomes.

Physiologic Responses to Passive Activity

Identifying safety and feasibility of a passive exercise intervention is a crucial first step in adopting prescribed mobilization into the multidisciplinary plan of care for a critically ill patient. This research study sought to provide safety and feasibility support in advance of a larger study that would evaluate efficacy of a progressive exercise intervention in critically ill patients. Following Institutional Review Board approval and after obtaining proxy consent, 30 mechanically ventilated critically ill adults from three intensive care units (neuroscience, multisystem, and trauma) in one tertiary care center were enrolled in the study. Following a rest period, participants underwent a 20 minute passive exercise protocol followed by an additional rest period. Physiologic variables, including heart rate, blood pressure, oxygen saturation, intracranial pressure, cytokine levels, and behavioral pain response, were monitored at specified time points throughout the study. Details of the study and its findings are found in Chapter 3.

Measurement of physiologic responses to mobilization presents several unique challenges in the critical care setting. The ability to replicate study findings and apply results to practice requires the selection of optimum variables to measure, appropriate timing of variable measurement, and adoption of approaches to assuring precision and accuracy in measurement. Issues related to measurement of physiologic variables appropriate for this study and setting are addressed in Chapter 4.

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CHAPTER 2: LITERATURE REVIEW

Abstract

Muscle weakness is the most common and persistent problem after a critical illness. Early mobilization of the critically ill patient, beginning with passive exercise and progressing to ambulation, may mitigate muscle effects of critical illness. Although mobilization is quickly being incorporated into care for critically ill patients, standards for mobilization interventions are lacking. To identify evidence supporting timing and type of mobilization interventions for critically ill patients, a comprehensive literature search of electronic databases was conducted from 1990 to present, including CINAHL, MEDLINE the Cochrane Database of Systematic Reviews, and PubMed. Search terms used were mobilization, exercise, activity, and critical illness. Fifteen articles were identified for review. The analysis focused on what constitutes mobilization, which patients should receive it and when, and who should provide mobilization interventions.

The analysis revealed that a "toolbox" of mobilization activities is available to the bedside practitioner but specific guidelines for how and when to implement those activities are limited. Although early mobilization is advocated in literature, clear definition of "early" was lacking. Strict study inclusion criteria limited patient involvement in mobilization activities. Several different practitioners delivered mobilization interventions but most protocols were driven by physical therapists rather than nurses, although a team approach was advocated. Knowledge that supports decisions about how and when to mobilize critically ill patients is evolving. Comparing study outcomes is challenging with treatment routines varying so widely. Clinical trials that incorporate progressive mobilization across broad population of

critically ill patients are needed, along with studies that demonstrate that mobilization protocols can be implemented into practice at the bedside.

Introduction

Muscle weakness is the most common and persistent problem after a critical illness.[1] Fatigue, poor functional status and decreased health-related quality of life one year after a critical illness are all attributed to persistent muscle weakness.[2] Muscle weakness associated with critical illness cannot be explained by immobility alone. The inflammatory response resulting from the physiologic stressors of critical illness has been identified as a major contributor.[3,4] The inflammatory cascade of events that occurs consequent to critical illness has wide-reaching effects, well beyond the organ system affected by the illness, and muscle is only one organ of many that are affected.[4] Inflammation diminishes both muscle mass and strength. Inflamed muscle is problematic in that it can prolong need for mechanical ventilation, extend hospital stay, and complicate recovery, as well as negatively impact quality of life for the individual with critical illness.[5]

Mobilization is a progressive, interdisciplinary, goal-directed therapy that has been proposed as one approach to mitigate the muscle weakness after a critical illness.[6-8] Mobilization is thought to improve blood flow, stimulate anti-inflammatory cytokine production and enhance insulin activity and glucose uptake in muscle,[4,9] all of which may serve to preserve muscle strength and mass. Physical activity is also thought to reduce pain, decrease anxiety, improve delirium, promote sleep, and improve mood, all of which are beneficial in reducing effects of illness on muscle.[10,11] Recent studies have documented improvements in functional status and fewer ventilator and hospital days when mobilization was implemented into the plan of care.[12,13]

Although mobilization is quickly being incorporated into care for critically ill patients, standards for mobilization interventions are lacking. A critical analysis of current literature on mobilization in the critical care setting was conducted, with a focus on what constitutes mobilization, which patients should receive it and when, and who should provide these interventions. Results from this analysis may be used to develop evidence-based interventions in the future as well as direct research for mobilization interventions in critically ill patients.

Review of the Literature

A search of the literature was conducted using the search terms, mobilization, exercise, activity, and critical illness to identify studies that evaluated mobilization interventions in critically ill patients. Table 1 provides operational definitions for these terms.

Table 1. Operational Definitions.

Term	Operational Definition
Mobilization	A goal-directed interdisciplinary therapy that involves a variety of activities (on a continuum from passive to progressively active activities).
Activity	Movement in a patient initiated by the patient or an individual other than the patient, and without active resistance.
Exercise	Movement in a patient with a specified duration, intensity and frequency. Passive exercise without resistance, initiated by an individual other than the patient may include passive range of motion, passive cycle ergometry, and neuromuscular electrical stimulation. Active exercise, initiated by the patient or an individual other than the patient, may include active range of motion, sitting, standing, active cycling and walking.
Critical illness	Illness of sufficient severity that requires mechanical ventilation and/or care in an intensive care unit.

CINAHL, MEDLINE, the Cochrane Database of Systematic Reviews, and PubMed databases were examined from 1990 to 2012. Studies published from 1990 forward were considered in an effort to reflect current practices; 170 articles were identified that met search criteria. To be included in the final review, articles met the following criteria: 1) published in the English language, and 2) incorporated mobilization as an intervention in a critically ill (acute or chronic) sample, or 3) evaluated practitioner mobilization practices. Articles excluded from the review were those that were reviews only (109 excluded), addressed mobilization after resolution of the critical illness (29 excluded), were non-interventional studies (5 excluded) or written in a language other than English (12 excluded). Upon selection, articles were reviewed for descriptions of mobilization interventions, inclusion and exclusion criteria; when those interventions were implemented within the patient's illness trajectory; and which practitioners were involved in the implementation. Fifteen articles were found that met inclusion criteria for this review. Table 2 summarizes evidence found in the 15 articles.

Table 2. Summary of Mobilization in Critical Care Evidence.

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
Bailey, Thomsen, Spuhler, Blair, Jewkes, Bezdjian, et al., 2007	Determine whether physical activity was safe, feasible in resp. failure patients	103, M>F, 63 years mean age; 48% > 65 yrs of age Required MV for ≥4 days Responding to verbal stimuli FiO_2 < .6, PEEP < 10 cmH_20 (relative) Absence of orthostatic hypotension No catecholamine drips (relative)	Required MV for ≤4 days, Coma	Stabilization through ICU stay (mean time to dangle 6.6±5.5 days; sit 11.3±10.1 days; walk 12.4±10.7 days) Twice daily intervention	Pre and post 30 assist-control rest period Increased .2 FiO_2 before activity Progressive dangle, sit, ambulate	O_2 saturation (> 80%) BP (systolic 90-200 mmHg)	Adverse events Ventilator data Hospital disposition	17% died; 33% home Duration MV 18.7±15.4 days ICU LOS 22.7±15.9 days Hospital LOS 26.6±17 days No difference in >65 vs < 65 Adverse events occurred in .96% of activity events; did not prolong stay or increase costs	2.4% unable to tolerate activity at all 12% unable to complete some scheduled activities Did not require increased staffing Concluded to be safe and feasible No control group
Bourdin, Barbier, Burle, Durante, Passant, et al., 2010	To determine whether early activity in critical care setting is feasible and safe, and potential benefits	20 (13 before extubation, 7 after) MV > 2 days, ICU at least 7 days	Agitation, confusion, comatose; SBP < 90; vasopressors; $paO_2/FiO2$ ratio < 200; $paCO_2$ > 50; pH < 7.2; CRRT; IV sedation	Twice daily intervention beginning mean day 5	Chair sitting, tilt table, walking (mean durations were 150 min, 15 min, and 10 min respectively)	HR (<130 or within 20% or baseline); RR (<35 or within 20% of baseline); O_2 saturation (>88%); SBP (>90 or <180)	Adverse events	MV mean duration 7 days; ICU LOS 17 days Improved O_2 saturation with chair sitting Adverse events in 3%; no clinical consequences	43% were unable to receive interventions as scheduled Understaffing limited second episode during the day
Burtin, Clerckx, Robbeets,	To determine whether early	90, mean age 59 years	Cardiorespiratory instability	Day 5 or longer Randomized to	Passive activity to ambulation in	HR (>70% PM or > decrease),	SF 36 6MWD	Decreased O_2 saturation	Drop outs older Sedation and

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
Ferdinande, Langer, et al., 2009	passive exercise can improve function in critically ill compared to physical therapy	Eligibility determined by intensivist Anticipated MV > 7 days (only 15% of prolonged MV eligible)		control or treatment Mean enrollment day 10 in control group and day 14 in cycling group Daily intervention	both groups Additional cycling 20 minutes, 20 cycles/min; increased resistance if active (55% passive on initiation; 13% unable to progress to active)	SBP (>180 or > 20% decrease), DBP (> 20% decrease), O_2 saturation (<90%), RR Parameters normalized within 2 minutes	Quad Force Berg Scale Weaning Time LOS 1 year mortality	1.3+1.7% 16 sessions terminated early due to adverse events Treatment group had farther 6MWD (196 m vs 143 m: $p<.05$), higher SF- 36 (21 vs 15; $p<.01$), greater quad force 1.83 vs 2.37; $p=.002$) Hand grip force and Berg scale not different Weaning time, LOS ICU, LOS Hospital, and one-year mortality not different	NMB greater and LOS prior to inclusion longer in treatment group No clinical physiologic changes during cycling More patients discharged home
Garzon-Serrano, Ryan, Waak, Hirschberg , Tully, Bittner, Chipman, Schmidt, Kasotakis, Benjamin, Zafonte,	To evaluate whether mobilization practices differed between nurses and physical therapists	63; 232 mobilization events; all consecutive patients were included	None (in order to not limit mobilization attempts, a phase O category was used)	On admission	A progressive mobilization protocol	Continuous monitoring BP, HR, O_2 saturation; clinician discretion for phase 0	Phase (type) of mobilization; number of adverse events; barriers to mobilization	Nurses mobilized earlier than physical therapists; physical therapists mobilized to a greater extent (more active);	Avoid strict exclusion criteria for mobilization; capitalize on different team member contributions

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
Eikermann, 2011								identified barriers differed between groups; nursing severity score predicted mobilization	
Griffiths. Palmer, Helliwell, MacLennan, MacMillan, 1995	To examine whether PROM can prevent muscle wasting	5; MV with NMB for 7 days	MV and NMB	Time from intubation to beginning of therapy not specified; 3x daily while in ICU	Three 3-hour PROM treatments daily per CPM machine on one leg; SOC to other leg; leg randomized	NA	Muscle biopsy; limb weight	Fiber area slightly increased in treated leg (mean increase 11%); less protein loss in treated leg; treated leg weighed significantly more than untreated leg	PROM preserves muscle architecture but may not prevent wasting
Morris, Goad, Thompson, Taylor, Harry, et al., 2008	To identify frequency of patients receiving PT, site of therapy, and patient outcomes	330; 48 hours of intubation with MV, 72 hours of admission to ICU	Inability to walk or nonverbal prior to admission, immune compromise, NM disease, stroke, BMI >45, unstable fracture, DNR, cancer therapy within 6 months, ICU readmission within 30 days,	Daily intervention beginning within 48 hrs of intubation; actual timing of intervention start not reported	Block allocation design; 3 ICUs serving as control and treatment unit at different times PT as ordered daily (control) vs mobility protocol with progressive additive advance from PROM to active	O2 saturation >88%, MAP >65	Survivors to discharge who received PT; days until OOB; ventilator days; ICU LOS; hospital LOS	2.3% of events not initiated due to instability 47% of usual are group received PT while 80% received PT with mobility protocol (treatment group received more therapy, $p<.001$); treatment group OOB earlier (5.0 days vs 11.3	Standardized approach Only survivors included in data analysis No effect from steroids Average cost per patient less but not statistically significant

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
			new arrhythmia cardiac ischemia		transfer (treatment)			days; p<.001); 26.7% unable to progress beyond PROM; 7.1 mean days at PROM level No significant difference in ventilator days ICU LOS shorter for treatment group (5.5 vs 6.9; *p*=.025); hospital LOS shorter for treatment group (11.2 vs 14.5; p=.006)	
Pohlman, Schweickert, Pohlman, Nigos, Pawlik, et al., 2010	To determine feasibility of a protocol of early therapy and sedation interruption in mechanically ventilated critically ill patients; to identify adverse effects and barriers	49; age ≥18 years; MV < 72 hrs but expected at least an additional 24 hrs; Barthel Index ≥70 before admission	Rapidly evolving neuromuscular disease; cardiac arrest; irreversible condition; increased ICP; absent limbs; involvement in another trial	Within 72 hrs of intubation; time from intubation to intervention 1.5 days (1.0-2.1)	Daily interruption of sedation with therapy during that time; PT/OT screen; PROM of seven sets of joints (number of repetitions or duration not specified); progressed to sitting, standing, walking as	MAP<65; HR<40, >130; RR<5, >40; O_2 saturation <88%; increased ICP; active GI bleed; active myocardial ischemia; insecure airway; device dislocation	Number and duration of therapy sessions, types of activity Potential barriers to therapy Neurocognitive measures	Therapy occurred on 87% of days of study, 90% of days on MV; 81% of days post-ICU; duration 26±14 mins while on MV, 28±10 mins while in ICU, 28±10 post-ICU; 85% able to perform AROM; 69% dangled;	Enrolled 49 participants over 26 months Unsure as to use of CAM-ICU; no analysis reported

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
					tolerated			33% up to chair; 15% walked Potential barriers to therapy did not prevent therapy Adverse events occurred in 16% of all sessions (498) but all resolved after stopping therapy CAM-ICU was negative in 40% of patients and positive in 53% of patients	
Schweickert, Pohlman, Pohlman, Nigos, Pawlik, et al., 2009	To determine whether an early therapy protocol combined with sedation interruption improved functional and neuro-psychiatric outcomes	104; age ≥18 years; MV < 72 hrs but expected at least an additional 24 hrs; Barthel Index ≥70 before admission	Rapidly evolving neuromuscular disease; cardiac arrest; irreversible condition; increased ICP; absent limbs; involvement in another trial	Within 72 hrs of intubation; time from intubation to intervention 1.5 days (1.0-2.1)	Randomization to SOC or protocol; daily interruption of sedation with therapy during that time; PT/OT screen; PROM of seven sets of joints (number of repetitions or duration not specified); progressed to	MAP<65 or >110; systolic BP >200; HR<40 or >130; ; RR<5, >40; pulse ox <88%; increased ICP; active GI bleed; active myocardial ischemia; insecure airway; ventilator asynchrony; new	Functional status at discharge Number of hospital days with delirium (CAM-ICU) Number of ventilator-free days during hospital stay; length of ICU stay Adverse events	50% achieved functional independence at discharge (Barthel ≥70), 59% in protocol group and 35% in control (p=.02) In protocol group: less delirium (2.0 vs 4.0, p=.03); more ventilator-	Death assigned 0 ventilator-free days ICU stay approached significance in protocol group (p=.08); hospital LOS nonsignificant

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
					sitting, standing, walking as tolerated	arrhythmia		free days (23.5 vs 21.1; *p*=.05); therapy began at 1.5 days in protocol group and 7.4 days in SOC group; sedation and analgesia the same between groups One desaturation episode in 498 events	
Skinner, Berney, Warrillow, Denehy, 2008	To identify exercise prescription by PTs for MV patients and outcome measures commonly used	111; PTs working in ICUs in Australia; no returns from one region	NA	NA	NA- 24-item survey of PT practices in ICUs (response rate 75%)	PTs identified O2 saturation, HR, RR, and perception of fatigue as safety measures necessary	Only 34% used outcome measures; RR, O2 saturation, distance walked were used	94% of respondents prescribed PT regularly; 42% indicated that PT should be performed in all ICU patients except for those on inotropes, CRRT, ARDS; 5% thought PT should be restricted to those on MV; frequency varied widely; type of activity was	Even experienced practitioners have widely variable practices; evidence not applied to practice

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
								ROM, sit to stand, transfer, march, ambulate, tilt table; multiple factors were used to determine ability, frequency and duration;	
Stiller, Phillips , & Lambert, 2004	To determine hemodynamic and respiratory response to mobilization of the critically ill patient	31 participants receiving 69 treatments; HR <50% APN; O_2saturation >90%; paO_2/FiO_2> 300	PROM and mechanical transfers excluded; extensive exclusion criteria based on medical condition	3 different time periods to maximize variability; mean 29 days of intubation at onset of therapy	Progressive mobilization from dangle to ambulation;	HR; HR APN; systolic and diastolic BP; O_2 saturation; patient appearance	Number and type of therapies; change in HR, BP, and O_2 saturation from baseline	HR and BP significantly increased with mobility ($p<.001$) increased but not clinically significant; decreases in O_2 saturation evident but not significant ($p=.44$); 3 desaturation events required intervention	19% of patients in the ICU received this intervention; 83.8% received ROM
Stockley, Hughes, & Rooney, 2010	To determine PT passive ROM practices in ICUs in the UK	165, 152 of which reported using PROM in MV ICU patients; participants	Not working with ICU patients	NA	12-item questionnaire; open ended, closed and matrix questions	Monitoring parameters used were ICP, PAC, CVP, RR, HR/rhythm, BP O_2 saturation	Frequencies of therapies performed and safety parameters routinely	PROM performed by all study respondents daily; mean 5 repetitions per	Purposes for PROM may differ amongst diagnostic groups; monitoring is

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
		registered to National Health Service Return rate 67%					monitored by respondents	joint (1-20); on both UE and LE; single joint movements	essential component of therapy but monitoring guidelines not specified; longer duration and increased frequency needed to prevent changes in muscle architecture
Thelandersson, Cider, Volkmann, 2010	To determine if PROM had an impact on intracranial, cerebrovascular, and hemodynamic parameters	12 brain injured participants in neuro ICU; MV; IV or parenchymal catheter; arterial catheter in place; inability to move limbs actively	Fracture or other problem preventing PROM	Measures every minute for 10 min before, during PROM and at rest for 10 min	PROM by PT in defined position; 7 times in same order to UE/LE	ICP, BP, MAP, HR, O_2 saturation	TCD; ICP; BP; MAP; HR; pulsatility index	In treatment group: No significant difference at any time point between HR, BP, and CPP measures except for PI increased (p<.01); ICP was significantly lower after exercise (p<.01) In control group: MAP, and systolic BP showed significant decreases after	Used age and gender matched healthy control group Concluded PROM was safe

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
								PROM (p<.01); no between group hemodynamic or cerebrovascular differences; no within group differences in cerebrovascular parameters	
Wiles & Stiller, 2009	To investigate PROM practices among Australian PTs	51; PTs working in Level 3 ICUs in Australia	NA	NA	42-item questionnaire; closed end or semantic rating	NA	NA	86.3% had standing PT orders;13.7% required referral; only 13.7% performed daily passive ROM; most common technique used was manual, but other techniques were used and varied widely; aims of treatment influenced choice of method	PTs taught family to perform ROM or nurses performed it; PTs believed nurses did not perform PROM without direction; medical data dictated decision about treatment
Winkelman, Higgins, & Chen, 2005	To describe typical therapeutic activity in MV critically ill	20; physiologic stability; MV in critical care setting	Quadriplegia and stroke; recent surgery	5-15 days after intubation (mean day 10)	Observational study, 8 hours	NA	Motor Assessment and Activity Scale Actigraphy measured	Most common activities were turning an PROM; 73% of therapeutic	Placement of actigraphy device critical; actigraphy device records

Authors	Purpose	Inclusion, Sample Size	Exclusion	Timing	Intervention	Safety Measures	Outcome Measures	Statistically Significant Outcomes	Comments
	patients; to compare two activity measures						activity	activities initiated by nurse; 11 minutes of activity experienced during turning and 8 minutes for PROM per 8 activity was infrequent and of short duration	more than observed; precision a concern; no measure of activity intensity
Winkelman, 2010	Exploration of types and duration of activity; feasibility of analyzing serum (test the procedure in advance of a larger study)	17; Medical ICU or stepdown; COPD exacerbation; paO_2/FiO_2 100-400; FiO_2<.6	(see inclusion criteria)	First observation 48-60 hrs after unit admission; standardized time between 10a and 2p; 2 days of observation	60 minutes of rest prior to activity, 20 minutes planned activity, 10 minutes data collection; activity provided by nurse; serum collection immediately following rest and then activity	Vital signs, O_2 saturation	Activity duration (actigraph)	Mean duration of activity 18.8 minutes day 1, 20 minutes day 2; activity counts indicated low levels of activity; no difference between cytokine levels at rest or after activity; IL-6 decreased on day 2, IL-10 increased on day 2; O_2 saturation was within 2% of baseline, HR, BP, RR within 20% of baseline	Large sample size necessary to determine impact of low level activity on inflammation (data used to calculate sample size for future studies)

Legend: APN=age predicted norm; ARDS=acute respiratory distress syndrome; AROM=active range of motion; BMI=body mass index; CAM-ICU=Confusion Assessment Method-Intensive Care Unit; COPD=chronic obstructive pulmonary disease; CRRT=continuous renal replacement therapy; CVP=central venous pressure; DBP=diastolic blood pressure; DNR=do not resuscitate; F=female; FiO_2=fraction of inspired oxygen; GI=gastrointestinal; HR=heart rate; hrs=hours; ICP=intracranial pressure; ICU=intensive care unit; IV=intravenous; LE=lower extremity; LOS=length of stay; M=male; MAP=mean arterial pressure; MV=mechanical ventilation; NA=not applicable; NM=neuromuscular; NMB=neuromuscular blockade; OOB=out of bed; OT=occupational therapy; O_2=oxygen; PAC=pulmonary artery catheter; paO_2=partial arterial oxygen pressure; $paCO_2$=partial arterial carbon dioxide pressure; PEEP=positive end expiratory pressure; PI=pulsatility index; PM=predicted maximum; PROM=passive range of motion; PT=physical therapy; RR=respiratory rate; SBP=systolic blood pressure; SOC=standard of care; TCD=transcranial Doppler; UE=upper extremity; UK=United Kingdom; 6MWD=six minute walk distance

Findings

What Constitutes Mobilization?

Mobilization was found to cover a wide range of practitioner-delivered *progressive activities*, from passive and active range of motion (ROM), to dangling, standing or lift transfer to a chair, and ambulation.[13-15] Range of motion was the most commonly applied mobilization intervention,[16-17] but actual ROM practices were found to vary widely in duration and intensity amongst studies. Schweickert, et al.[13] utilized 10 repetitions per joint in their study, while Thelandersson, Cider, and Volkmann[18] used 7 repetitions per joint, and Morris, et al.[19] used 5 repetitions per joint. No rationales were provided for these choices. Wiles and Stiller[20] identified 2-30 (mean=13) repetitions per joint in their survey of Australian physical therapist practices in intensive care units, while Stockley, Hughes, Morrison, and Rooney[21] reported 1-20 (mean 5) repetitions per joint in their study of physical therapist practices in the United Kingdom. Intensity, which constitutes partial to full stretch, was reported by therapists to also vary widely in both studies. All five studies reported provision of ROM to both upper and lower limbs.

In an attempt to provide ROM in a more standardized manner and meet prescriptive guidelines (frequency, duration and intensity of therapy), mechanical devices have been used to provide upper and lower extremity passive and active exercise. Devices used include continuous passive motion machines and cycle ergometers. Griffiths, et al.[22] found that three hours of passive movement daily in one leg of 5 critically ill patients increased muscle fiber and weight in the treated leg as compared to the untreated leg. Richard, Staley and Miller[23] used a continuous passive motion machine in the upper and lower extremities of critically ill burn patients, while Burtin, et al.[24] used a cycle ergometer for passive leg exercise in two 10 minute bouts, 20

cycles/minute in mechanically ventilated critically ill patients. This device also allowed participants to progress to active cycling as their condition improved. Additional devices found in the literature included use of a tilt table for weight bearing[25] and electrical stimulation of muscle contraction.[11, 26, 27]

More active and aggressive approaches to mobilization have been recently advocated, particularly in mechanically ventilated critically ill adults,[13, 28] and protocols have been used to specify step-wise succession of activity. Morris, et al.[19] described a mobilization protocol that consisted of a four-step approach which began with passive range of motion (PROM), then progressed to active range of motion, then sitting, and then transfer. Another began with sitting and progressed to ambulation.[10] Pohlman, et al.[12] presented an algorithm to guide progression from passive ROM to ambulation, while Schweickert, et al.[13] present a protocol that ranged from active ROM to ambulation. Protocols were noted to vary in their start and end points, but central activities (active range of motion, sitting, and transfer out of bed) were consistent. More recently, Hanekom, et al.[29] described development of a clinical mobilization algorithm developed by a 3-round Delphi process. However, the algorithm for unresponsive patients addressed only position changes while in bed, head of bed elevation, and daily passive range of motion as appropriate interventions, which may be insufficient for this population. While the consensus was significant (94%), less than 50% of statements were rated as essential, indicating provider disagreement about optimum approaches to mobilization. Further, Delphi participants were therapists and did not include other bedside practitioners such as nurses.

Many participants in each of these studies were unable to progress to the protocol end point. Morris, et al.[19] found that participants remained in the passive ROM stage of therapy for 7.1 days before progressing to more active exercise, and 44(26.7%) of participants in a

progressive mobility study were not able to progress further than passive ROM. Reasons were decreased responsiveness and physiologic instability. Pohlman, et al.[12] incorporated a mobilization protocol that began with active therapy, and found that even when participants (*N*=49) were able to perform active range of motion upon study entry, 13% were unable to participate in ongoing therapy sessions because of physiologic instability, and were reduced to passive activity only. Bailey, et al.[10] initiated activity only after sedatives and catecholamines were discontinued, and when patients were deemed to be physiologically stable. Ambulation still comprised only 42% of all activity events.

Who Should be Mobilized?

Study samples in this review varied widely (Table 2) but participants commonly had respiratory failure and were mechanically ventilated, in addition to other comorbidities. Recognizing the severity of critical illness as a significant factor in potential muscle weakness, inclusion criteria often addressed the anticipated need for mechanical ventilation for at least 48 hours.[10,12,13,19, 30] Stable respiratory status was also identified as an inclusion criteria, described as $FiO_2 < .6$ and PEEP $\leq$ 10 cm H_2O. Heart rate, blood pressure and oxygen saturation within unit-specified norms were common inclusion criteria. Although physical therapists usually consider cardiac reserve as an indicator for activity tolerance, little mention was made of those measures as being useful in guiding who to mobilize. Several studies included patients on vasoactive infusions or neuromuscular blockade,[15,22] while others excluded such participants.[12,13] The wide variation in mobilization study inclusion criteria suggests that clinician assessment is a critical component in deciding which patients should be mobilized. Lack of clearly defined evidence-

based protocols or algorithms leaves clinicians with broad leeway in who receives mobilization interventions.

The population of patients excluded from these studies warrants additional discussion. In the study by Stiller, Phillips and Lambert,[15] participants comprised only 19% of the total ICU population during the study. Exclusions were made on the basis of level of consciousness and cardiovascular or respiratory instability. Schweickert, et al.[13] excluded those with frequent desaturation, hypotension, new cardiac enzyme changes, new antidysrhythmic therapy, or recent ventilation mode change until those problems resolved. Additional exclusion criteria were: immunocompromise, cancer therapy, body mass index (BMI) > 45, greater than 72 hours of admission before intubation, non-ambulatory prior to admission, or do not resuscitate (DNR) status. The number of those excluded was not provided. Morris, et al.[19] excluded those with increased intracranial pressure, neuromuscular disease, cardiac arrest, absent limbs or an irreversible disorder, and Bailey, et al.[10] excluded any unresponsive patient. While the rationale for exclusion of some of these participants is logical, there is no empirical evidence to support many of the reasons for avoiding mobilization. Those excluded represent a substantial portion of the critically ill population, perhaps signaling important opportunities to improve outcomes.

When Should Mobilization be Started?

Optimum timing to initiate mobilization and duration of mobilization interventions is not clear in the literature, and patient condition alone does not appear to be the determining factor. A significant concern is that practitioners may perceive that mobilization is too difficult given the equipment or patient inability to participate, or it may be inappropriate due to concerns about

mobilization worsening physiologic instability.[11] Loss of muscle mass and strength is evident soon after critical illness onset; 2% of mass may be lost within the first 24 hours of critical illness and this loss can progress exponentially.[31] Since muscle changes appear soon after onset of critical illness,[32] it is logical to consider implementation of mobilization soon after illness onset. Yet, mobilization is often delayed until physical stability is evident, often after an acute phase of illness,[33] and delay may add to disability.[7]

Early mobilization is a term that has recently appeared in literature, denoting mobilization activities begun in the critical phase of illness. Several investigators have demonstrated that it is feasible to implement mobilization soon after critical illness onset. Pohlman, et al.[12] were able to institute mobilization in a mean 1.5 days after intubation, while Winkelman[14] enrolled patients within 48 hours of intubation, and Schweickert, et al.[13] enrolled participants within 72 hours of intubation. Although Burtin, et al.[24] identified their study as "early," participants were not considered for study entry before day 5 after intubation. However, even at 5 days, patients were mobilized sooner than the standard of care. Criteria to document readiness to institute mobilization have not yet been developed and require further exploration. Tolerance of passive exercise may be one signal that progression is appropriate.

As a *therapy*, mobilization requires evidence-based descriptions of duration, intensity, and frequency, but limited evidence was found regarding these parameters in the literature. Using direct observation and actigraphic measurement of activity, Winkelman, Higgins and Chen[17] documented 11 minutes of activity over an 8 hour period. In a subsequent study of 17 mechanically ventilated patients with COPD, Winkelman[14] was able to sustain progressive mobilization activities for 20 minutes, while Pohlman, et al.[12] found the mean duration of active therapy at 26 $\pm$ 14 minutes in their study of active exercise interventions. Burtin et al.[24] were able

to add an additional 20 minutes of passive activity to their current mobilization protocol. Intensity is implied through progression, and has consistently been left up to the discretion of the practitioner, with clinical recognition of tolerance used as the progression decision point (but not specified). Daily frequency of therapy was the norm in studies,[10,12,13,14,20] except for one study that reported passive ROM three times a day.[19] Although no rationale for the daily therapy was found, the daily routine was most likely reflective of physical therapy rather than nursing practices.

As a *goal-directed therapy*, the primary purpose of mobilization is to improve patient outcomes. This implies the need to continue mobilization interventions until measureable end points. Both short and long term outcomes have been reported in the literature. In a study of 330 intubated patients in seven intensive care units (ICUs) in one hospital in North Carolina, Morris et al.[19] demonstrated improved outcomes in participants who received a mobilization protocol (N=165) as compared to those who received standard of care (SOC; N=165). A mobility team, consisting of a critical care nurse, nursing assistant (NA) and physical therapist (PT), delivered the mobilization protocol to participants who met criteria. The mobility protocol was started as soon as possible after admission, and continued daily throughout the ICU stay. Those receiving SOC received physical therapy per physician order or passive range of motion per nursing unit protocol (specified as "prn"). The team was assigned to one of the seven units on a monthly rotating basis, and geographic location of the patient determined whether they received SOC or the intervention. Although ventilator days did not differ among the two groups, the mobilization protocol group was out of bed sooner (5 vs 11.3 days, p<.001), had a shorter length of ICU stay (5.5 days vs 6.9 days, p=.02), and shorter length of hospital stay (11.2 vs 14.5 days, p=.006).

Similarly, Schweickert, et al.[13] studied 104 critically ill mechanically ventilated patients from two academic medical centers that underwent daily interruption of sedation and mobilization. Using a computer-generated randomization scheme, participants were randomized to either SOC or a mobilization intervention; both groups received daily sedation interruption. The standard of care group (N=55) received physical therapy only as ordered by the physician. The intervention group (N=49) received daily passive range of motion, 10 times to each joint by a physical or occupational therapist. If the patient was able to interact, active-assisted and active range of motion (AROM) were added. If AROM was tolerated, then physical therapists began activities that progressed from sitting, to transfer, exercise in preparation for walking, and walking. The intervention group received significantly more therapy than the control group (p<.0001), and received therapy earlier (1.5 days vs 7.4 days, p<.0001). Only three patients in the SOC group progressed to ambulation while 12 patients in the intervention group progressed to ambulation. Although no significant differences were found in ICU or hospital lengths of stay between groups, the intervention group had higher functional status scores (p=.02), higher Barthel Index scores (p=.05), a higher number of independent ADLs (p=.06), and greater walking distance (p=.004) at hospital discharge than the SOC group. These findings are important in spite of the failure to impact length of stay data, as they may translate into lower costs for after hospital care and improved quality of life. After 5 days of intubation, Burtin, et al.[24] instituted a passive cycling protocol in addition to ROM and progressive mobility. In spite of the delay in mobilization, patients who received passive cycling had significantly better exercise tolerance (p < .05), increased muscle force (p< .01), and improved perception of functional capacity (p < .05) upon discharge as compared to those who did not receive cycling therapy. Exercise-induced decreases in inflammation were postulated as one reason for the

treatment group outcomes. Whether a decrease in inflammation could be directly attributed to activity and improved outcomes is not yet known, but preliminary evidence suggests that cytokine profiles in critically ill patients may be improved by 20 minutes of sustained daily activity.[14]

In spite of mounting evidence that mobilization improves outcomes, providers remain reluctant to order mobilization, citing safety concerns. Finding no empiric support for safety of mobilization in the critical care setting, Stiller, Phillips, and Lambert[15] attempted to demonstrate that progressive mobilization was safe in critically ill patients in Australia. Thirty-one patients that were prescribed mobilization therapy as part of their care were included; they were enrolled in the study over three separate two week time periods to maximize population diversity, and most (78%) were mechanically ventilated. The 31 participants underwent 69 mobilization events during the study. Mobilization consisted of progressive activities that moved from lying to sitting, transfer and walking; only one patient progressed to walking. Safety measures assessed were those readily available at the bedside, and included heart rate (HR), systolic and diastolic blood pressure (BP), and oxygen saturation (SpO_2). Oxygenation and respiratory reserve were calculated from available physiologic data. Safety measures were assessed immediately prior to mobilization, upon completion of the therapy, and after one minute of rest. Prior to mobilization, 91.3% of participants had evidence of limited (but not severely compromised) cardiac or respiratory reserve. Both HR ($p<.001$) and BP ($p<.001$) were significantly increased during mobilization as compared to the baseline, but these increases were not deemed to be clinically significant nor did the changes require the intervention to be stopped. Of the 69 mobilization events, three events were associated with desaturation and required intervention; baseline SpO_2 was considered the limiting factor but the sample size was too small to allow

prediction. The authors concluded that mobilization was safe, even in the face of limited cardiac and respiratory reserve. It is important to note that mobilization was started in this study at a mean of 29 $\pm$ 19.6 days after admission indicating that the mobilization therapies were implemented during a less critical phase of illness, perhaps at a time where participants had already developed substantial deconditioning and muscle weakness. Morris, et al.[19] enrolled study participants and began mobilization within 48 hours of intensive care admission; 44 (26.7%) of the intervention participants did not progress beyond the first mobility level (PROM) but tolerated the intervention without incident. Sessions were withheld in only 1.4% of participants due to blood pressure (BP) concerns and in 0.9% due to heart rate (HR) concerns. Fatigue rather than vital sign change was cited as the most frequent reason for ending a therapy session, and these findings led the authors to conclude that early mobilization was safe. Schweickert, et al.[13] began mobilization on study participants within 72 hours of intubation, and used standard unit blood pressure (<65 MAP or >110 MAP, or BP > 220 systolic), heart rate (<40 and >130), and oxygen saturation (<88%) parameters for provider notification as the guidelines for holding or stopping mobilization. Mobilization was stopped in 4% of participants in response to ventilator dyssynchrony, and only one episode of desaturation was noted, supporting the safety of mobilization within 72 hours of intubation. When mobilizing patients to the chair and ambulation after 5 days of intubation, Bailey, et al.[10] encountered only 14 adverse events in 1440 episodes of activity (1%). None of the adverse events added additional length of stay or cost. Commonly measured physiologic criteria served as safety measures and varied across studies, as did parameters for stopping or hold mobilization activities. All authors mention the need for ongoing safety assessments for any mobilization intervention. Limited information

was available on physiologic effects of passive activity alone, especially in patients with cardiopulmonary compromise.

Concern has been expressed about early mobilization contributing to increased muscle inflammation, which may actually compound rather than prevent muscle weakness.[6] An increase in inflammation in response to exercise may be measured via cytokine levels, specifically IL-6 and IL-10. Stability in cytokine levels would serve as a safety indicator for mobilization, while decline in pro-inflammatory cytokine levels or improvement in pro- to anti-inflammatory ratios would serve as an efficacy measure. Winkelman, Higgins and Chen[17] demonstrated no significant changes in cytokine levels with passive activity (< 15 min), suggesting that passive activity does not increase inflammation. However, further study would add to safety support for this intervention.

Physiologic instability in mechanically ventilated critically ill patients may persist for days to weeks, delaying use of mobilization interventions. The loss of muscle soon after critical illness onset suggests that muscle protective interventions should be started early in the course of critical illness, probably within the first twenty-four hours. Passive exercise may be the most appropriate activity for these patients in the early phase of illness.[8] However, empirical evidence supporting the safety or efficacy of passive activity was not found, particularly during periods of physiologic instability. Further, prescriptive parameters for passive activity have not been identified for this population.

Who Should Deliver Mobilization?

Several different practitioners, including nurses, nursing assistants, occupational therapists and physical therapists delivered mobilization interventions in the studies

reviewed.[10,12,15,19,34] While physical therapists and nurses were integral to all protocols, the protocols tended to be therapist-driven. Garzon-Serrano, et al.[35] reported that physical therapists mobilized patients at a higher level than nurses, and nurses more commonly used passive activity while therapists performed more active interventions. In addition, barriers perceived by nurses and therapists differed; nurses perceived hemodynamic instability and renal replacement therapy (RRT) as the two most significant barriers while therapists perceived neurologic impairment as the most significant barrier. Interestingly, no study has addressed whether hemodynamic instability or presence of RRT are true barriers to mobilization, as these factors have been used as exclusion criteria. Limited evidence exists that mobilization is appropriate for neurologically impaired patients.[18]

Although underemphasized, a team approach to mobilization was noted to be universal across studies. This could be due to the collaborative multidisciplinary approach that is more common in critical care, or the complexity of clinical decision-making required in this setting. Additionally, mobilizing a patient that may be unable to assist or that has a multitude of tubes, lines, and drains requires many hands. Garzon-Serrano, et al.[35] suggested that capitalizing on different team member contributions could enhance overall mobilization in the critical care setting. While mobilization is clearly within the scope of nursing practice, nursing involvement in study protocols and reports was limited. Only six of the15 studies included nurses as authors; three of those were primary authors. Nursing involvement was constrained to assessment, implementation of passive activity only, or assistance with mobilization under the direction of physical therapists.

Discussion and Implications

Knowledge that supports decisions about how and when to mobilize critically ill patients is evolving. Nurses and other bedside practitioners have a "toolbox" of mobilization activities that can be used to progressively mobilize their patients, but the evidence supporting specific mobilization approaches is limited. Treatment routine and starting and ending points varied across studies, and even standard of care differed when randomization was used. With treatment routines varying so widely, comparing study outcomes is challenging at best. Clinical trials that incorporate progressive mobilization across broad populations of critically ill patients are needed, along with studies that demonstrate benefit of creative approaches to mobilization at the bedside.

Differing perceptions of what constituted adequate mobilization may have accounted for protocol variations. Little attention was given to passive activity in the studies reviewed. This may be due to the fact that passive therapies are not billable services for physical therapists, and passive activity is often relegated to the realm of nursing care. However, it may be that passive activity is the most appropriate initial mobilization activity for most critically ill patients. Passive exercise can be delivered early in critical illness, but further study is needed to clarify the optimum method, duration, and frequency. Criteria for patients who should be mobilized must be broadened beyond the strict inclusion criteria for studies in this review, as many critically ill patients may be unnecessarily denied this important intervention. Empirical evidence for those who should not be mobilized requires further development as well.

Nurses and physical therapists differ in their approaches to mobilization. It is evident that a team approach is required to implement mobilization protocols, and nurses are key members. Nurse-driven protocols for early mobilization require further development, and team roles

require further delineation. While nurses have many competing agendas that may limit ability to implement mobilization activities, mobilization should not be solely within the realm of physical therapy. Nurses must view mobilization from the perspective of a prescriptive therapy, and address greater intensity, longer duration, and greater frequency concerns, especially with passive activity.

Addressing practitioner perceived barriers to mobilization is necessary, particularly if the perceived barriers are not supported by evidence. Perceived barriers represent opportunities for education as well as research. Approaching mobilization as an interdisciplinary process may also limit perceived barriers.[36] Sedation is one important barrier to mobilization that has received little attention in the studies reviewed. Limiting amount and duration of sedation, or providing a "sedation vacation" may significantly impact the mobilization provided as well as improve outcomes.[35]

Development of evidence-based clinical decision tools that can be implemented across settings may facilitate implementation of mobilization protocols for critically ill patients. It is beyond time to question whether mobilization is of benefit, but rather time to move toward evidence that supports optimum approaches.

The rationale for why mobilization may be effective in improving outcomes from critical illness deserves further attention. The current logic is that mobilization may diminish inflammatory effects on muscle, but limited evidence exists supporting this logic. Inflammatory markers may provide explanation for benefit of mobilization as well as indicators for those who should not be mobilized.[37] Additional benefits of mobilization also requires further exploration. It could be that mobilization may decrease pain, anxiety, delirium, need for sedation, and even insulin requirements. Reduction of these factors may provide some degree of muscle protection.

Limitations to this review included the exclusion of non-English articles. Further, substantial practice changes have occurred from the time of the earliest article reviewed (1994). However, thirteen of the articles reviewed for this analysis appeared in literature from 2004 forward.

Summary

Immobility and inflammation weaken muscle in critically ill patients. Mobilization is thought to produce physiologic effects that preserve muscle function. Several different and progressive approaches to mobilization, beginning with passive range of motion, may be used, with progression of activity based on patient tolerance. With muscle damage occurring early after critical illness onset, early mobilization is advocated, but safety concerns abound. Passive activity, if demonstrated to be safe, may provide early benefit to those critically ill patients who are not yet able to tolerate progressive activity. Gaps in the literature are related to inconsistent use of a mobilization techniques, lack of identification of optimum timing for initiation of mobilization, and lack of inclusion of a population in great need of muscle protection. Further, findings related to the inflammatory response to activity are contradictory, requiring further exploration.

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CHAPTER 3: FINDINGS

Abstract

Muscle weakness is the most common and persistent problem after a critical illness. Early mobilization of the critically ill patient, beginning with passive exercise and progressing to ambulation, may mitigate muscle effects of the critical illness. However, mobilization may produce adverse effects, especially early in the illness when risk for physiologic deterioration is common. If safe, introducing a mobility intervention early in the illness may facilitate weaning, shorten intensive care unit and hospitals stays, and improve quality of life for mechanically ventilated critically ill patients.

The aim of this study was to assess the cardiopulmonary, neurodynamic, pain and inflammatory responses to an early standardized passive exercise protocol (PEP) in mechanically ventilated critically ill patients. Using a quasi-experimental within-subjects repeated measures design, mechanically ventilated critically ill adults who were physiologically stable underwent a single standardized passive exercise intervention within 72 hours of intubation. The intervention consisted of 20 minutes of bilateral passive leg movement delivered by continuous passive motion machines at a rate of 20 repetitions per minute, from 5-75 degrees, to simulate very slow walking. Physiologic parameters evaluated included heart rate (HR), mean blood pressure (MBP), oxygen saturation, intracranial pressure (ICP) and cytokine levels, obtained before, during, and after the intervention. The Behavioral Pain Scale, administered before, during and after the intervention was used as a measure of participant comfort.

The study sample was comprised of 18 (60%) males and 12 (40%) females, with a mean age of 56.5 years (SD 16.9 years), who were primarily Caucasian (*N*=18, 64%). Mean APACHE II scores for the sample were 23.8 (SD 6.2) with a mean predicted death rate of 48.8 (SD 19.8),

indicating moderate mortality risk related to illness severity. Number of comorbidities ranged from 1-10 (X=4). All participants completed the intervention with no adverse events. Using repeated measures analysis of variance (rmANOVA), no significant differences were found in heart rate, blood pressure, or oxygen saturation at any of the four time points in comparison to baseline. Behavioral Pain Scale scores were significantly reduced (p=.02) at 10 and 20 minutes after the PEP was started, and were sustained. IL-6 was significantly reduced (p=.03) at the end of the intervention but not at the final time period. IL-10 values were not significantly different at any of the three time points, but IL-6 to IL-10 ratios decreased significantly (p=.05) from Time 0 to Time 3, and Time 3 to Time 4.

Passive leg exercise was well tolerated. HR, MBP, and oxygen saturation were maintained within unit specified range during and for one hour after activity, and patient comfort improved during and after exercise. A downward trend in heart rate was noted in participants, which is contrary to usual heart rate response during exercise, but may actually represent clinical improvement in this population. Reduction of mean IL-6 values at Time 3 but not Time 4 suggests that the PEP was responsible for the improvement. Improvement of IL-6 to IL-10 ratios over both time periods suggests that IL-10 improvements may occur later than the time period of study.

Passive exercise should be studied as an approach to facilitating mobilization in mechanically ventilated critically ill adults until they are ready to participate in more active exercise. It could be that more aggressive exercise, such as passive cycling at faster rates, will be tolerated in this population. Cytokines may be used to explain benefits of mobilization in this population.

Introduction and Background

Muscle weakness commonly occurs after a critical illness, contributing to fatigue, poor functional status and decreased health-related quality of life long after the critical illness has resolved.[1,2] Immobility and the inflammatory process diminish both muscle mass and strength, which can prolong need for mechanical ventilation, extend hospital stay, and complicate recovery, as well as negatively impact quality of life for the individual with critical illness.[3,4] Progressive mobilization interventions, from passive and active range of motion (ROM), to dangling, standing or lift transfer to a chair, and ambulation,[5-7] have been recommended as one approach to minimizing muscle weakness after a critical illness.[8] Mobilization is hypothesized to preserve muscle strength and mass by improving blood flow, stimulating anti-inflammatory cytokine production and enhancing insulin activity and glucose uptake in muscle.[4]

Mobilization has been shown to improve outcomes for critically ill adults. Positive outcomes related to mobilization include significantly shorter lengths of intensive care unit (ICU) and hospital stays and improved functional outcomes.[5,7] In one study where ventilator time and length of stay were not significantly decreased after employing an exercise protocol, significantly lower costs for after-hospital care and improved quality of life were noted.[9]

Several issues complicate the delivery of mobilization interventions, including timing of the interventions, widely variable practices, and the possibility that mobilization and related factors such as pain can aggravate the inflammatory process. Optimal timing for initiating mobilization is not known. Several studies have begun mobilization 5 days or longer after illness onset,[6,10] but with muscle loss beginning within the first twenty-four hours of critical illness, this time frame misses an important window of opportunity to improve outcomes. Early mobilization (within the first 24-48 hours of critical illness) has been advocated,[11,12] and the feasibility of

early mobilization, within 24 hours of intubation, has recently been demonstrated.[5,13] However, physiologic instability commonly occurs early in critical illness, and providers may be reluctant to mobilize a patient who is physiologically unstable. Activity intolerance, manifested as unstable vital signs, is often a limiting factor in application of mobilization activities,[5,8] and many patients have been unable to participate in progressive therapy sessions because of physiologic instability.[13] Physiologic instability in mechanically ventilated critically ill patients may persist for days to weeks, delaying active mobility interventions, which may add to disability.[9,14] It may be that passive exercise is the most appropriate activity for critically ill patients in the early phase of illness,[8] and it can be employed until a patient is ready to progress to more active interventions. However, limited empirical evidence exists to support the safety or efficacy of passive activity, particularly during periods of physiologic instability. Further, criteria to document readiness to institute or progress mobilization have not yet been developed. Tolerance of passive activity may be one signal that institution and progression are appropriate.

Another concern is that mobilization practices vary widely. Practices for active mobilization include active or resistive range of motion, chair sitting, dangling, standing, ambulating, and use of a tilt table.[5-7] Passive activities also vary. Passive activity can be delivered manually by therapists or nurses, or via machines such as cycle ergometers or continuous passive motion machines. Studies have reported manual passive exercise repetitions of 5, 7, and 10 per joint, but no rationales were provided for these choices.[5,15,16] In two separate surveys of physical therapist practices, 2-30 (mean=13) repetitions per joint and 1-20 (mean 5) repetitions per joint per day in were reported. [17,18] Several studies used a specified time rather than repetitions per joint for ROM. Time periods ranged from 20 minutes[19] to 26 $\pm$ 14 minutes.[13] Burtin et al. added 20 minutes of passive activity via a passive cycling machine to a mobilization

protocol.[10] With treatment routines varying widely, it is difficult to compare patient outcomes. Standardized mobilization routines that consider therapeutic parameters of duration, intensity and frequency, and that may be readily replicated and applied in critically ill patients are critical to demonstrating improved outcomes from mobilization. Mechanical devices, such as continuous passive motion machines and passive cycling devices, have been suggested as an approach to standardize therapy at a duration and intensity that can meet prescriptive guidelines.[10,15]

Further concern has been expressed that early mobilization contributes to increased muscle inflammation, which may compound rather than prevent muscle weakness.[20] Inflammatory markers did not significantly change with passive activity less than 15 minutes duration, suggesting that passive activity does not increase inflammation.[21] Whether a decrease in inflammation could be attributed to activity and improved outcomes is not yet known, but preliminary evidence suggests that 20 minutes of sustained activity daily could improve cytokine profiles in critically ill patients.[19] Further study would add to safety support for this measure as well as possibly provide a physiologic explanation for benefit of mobilization.

The effect of mobilization on pain in critically ill patients has not been studied, and it is not known whether mobilization causes or reduces pain.[22,23] Pain increases cortisol secretion and production of pro-inflammatory cytokines, which may be deleterious to muscle.[24] Administration of morphine for pain management decreases inflammatory cytokines, suggesting that managing pain may be muscle protective.[25] Studying the pain response to mobilization may add additional support to benefits of mobilization or dictate precautions during implementation.

Passive activity, if demonstrated to be safe, may provide early benefit to those critically ill patients who are not yet able to tolerate progressive activity. This study sought to identify physiologic, pain and inflammatory responses to a standardized passive exercise intervention

instituted early in critical illness. Introducing a passive exercise intervention early in critical illness may be muscle protective, which could facilitate weaning, shorten intensive care unit and hospitals stays, and improve quality of life for mechanically ventilated critically ill patients.

Methods

Design and Consent

This study used a quasi-experimental within-subjects repeated measures design, with subjects serving as their own controls. Study participants were enrolled within 48 hours of intubation, and received a single 20 minute standardized passive exercise intervention within 72 hours of intubation. This time frame was designed to test the intervention on participants early after intubation, and allowed the intervention to be delivered within a consistent time frame.

Institutional review boards at the clinical agency and university approved the study. Informed consent was obtained from the proxy for the critically ill patients who met eligibility criteria. If the patient was responsive at the time of consent, they would have been approached for consent, but all eligible patients were either sedated or unresponsive.

Setting and Sample

The study was conducted in a tertiary care setting in southeastern United States. Subjects were recruited from three critical care units: burn-trauma, neuroscience and multisystem. Care in these settings was directed by either medical or surgical intensivists. The intensivists provided assent for participant involvement in the study. The electronic medical record was screened daily in each unit for potential participants.

A convenience sample of 32 critically ill adults was enrolled in the study between October 2011 and February 2012. Figure 2 demonstrates the screening to enrollment flow chart.

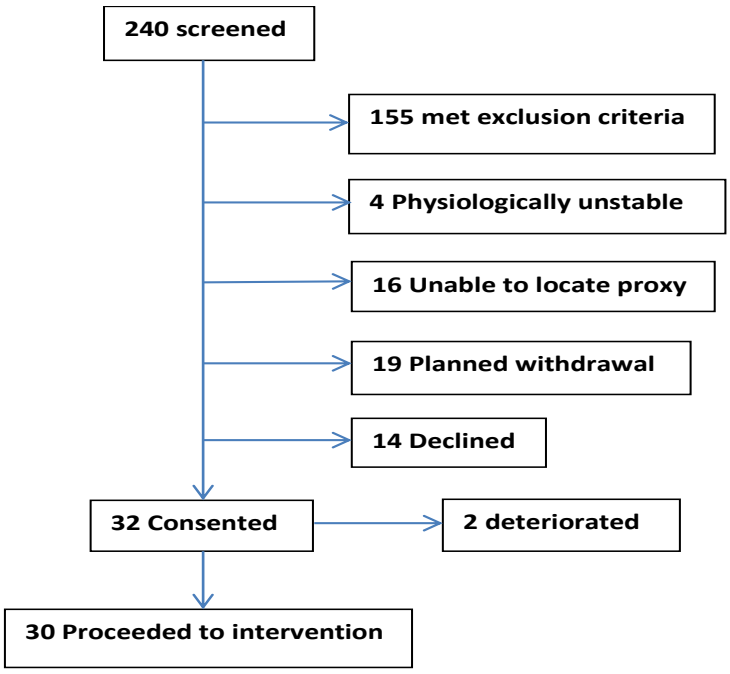

Figure 2. Screening to enrollment flow chart.

Inclusion criteria were: age 18 years or older; intubation and mechanical ventilation initiated within 48 hours of enrollment and anticipated for at least 72 hours; ambulatory prior to admission, presence of a vascular access device for blood sampling; and vital signs within unit-specified norms (Table 3).

Table 3. Order Set Specified Normal Ranges of Vital Signs.

Variable	Normal Range
Heart rate	Heart rate > 50/min but < 130/min
Blood pressure	Mean arterial blood pressure > 60 mmHg but < 130 mmHg
Oxygen saturation	>88% (to accommodate for potentially low hemoglobin levels, oxygen saturation >90% was used for this study)
Intracranial pressure	Intracranial pressure ≤ 20 mmHg

Persons who were hospitalized or non-ambulatory prior to critical illness onset, or with evidence of active cardiac ischemia, absent or injured limbs, inadequate lower extremity range of motion, or spinal, pelvic or lower extremity instability were excluded. Two hundred forty patients were screened and 155 initially met exclusion criteria. Spinal, pelvic or lower extremity instability was the most common exclusion criteria, followed by evidence of cardiac ischemia. Patients that were physiologically unstable or had no known proxy were screened daily until stability was attained, a proxy was located, or the time frame was extended beyond the intervention window. This resulted in exclusion of an additional 20 patients. Planned withdrawal of life support provided an additional 19 exclusions, and 14 families declined study involvement. The intervention was not tested on two participants that were consented: one due to surgery and the other due to unplanned extubation.

Using G-Power a-priori to calculate sample size, for a medium effect size of .25, a significance level of .05, power of .80, and the four time point comparisons to baseline, sample size was calculated at 24. With only three time points for the cytokine values, the calculated sample size rose to 28. Because the study variables were collected over a short period of time (about 2 hours), attrition rate was expected to be low once the intervention was begun. However, because attrition could occur from the time of consent to implementation of the intervention, allowing for a10% attrition rate, a total sample of 31 was anticipated.

Measures

Demographic and Cardiopulmonary Measures

Demographic data were obtained from the electronic medical record. Existing bedside monitoring systems (Phillips Intellivue M70) were used to continuously measure heart rate,

arterial blood pressure, oxygen saturation and ICP. Measures of ICP were obtained when available but were not required for study enrollment. Standardized placement of monitoring devices was assured prior to starting the study and measures were taken to assure precision and accuracy of heart rate, blood pressure, oxygen saturation and ICP measures (Table 4).

Table 4. Measures for Standardized Data Collection of Dependent Variables.

Measure	**Measurement Technique**	**Standardized Approach**
Heart rate	5-lead electrocardiogram	Lead placement as follow: right arm- under right clavicle at right bursal junction; right leg- anterior midline between 7^{th} and 8^{th} right ribs; left arm- under left clavicle at left bursal junction; left leg- anterior midline between 7^{th} and 8^{th} left ribs; V- between fourth and fifth intercostal spaces, and between left sternal border and midclavicular line; waveform visible on monitor
Blood pressure	Arterial catheter	Transducer placed at phlebostatic axis; waveform visible with three-notch waveform on monitor corresponding to arterial pulsations; zeroed against atmospheric pressure.
Oxygen saturation	Pulse oximetry	May be placed on finger, toe, earlobe; waveform visible with pulsatility on monitor corresponding to heart rate
Intracranial pressure	Ventricular catheter	Transducer placed level with external auditory meatus; waveform visible with three-notch waveform on monitor corresponding to arterial pulsations; stopcock set to monitor only.

All physiologic values were obtained using the Phillips Intellivue M70 monitoring systems which are standard at the bedside in the units of study. Sensitivity and specificity data for this monitoring system is within industry standards and may be found in the operational manual (both are >.9). Monitor alarms were set at the parameters indicated by critical care order

sets (Table 3). To assure that measures were synchronous with the intervention, the investigator used the time displayed on the bedside monitor which was timed to be congruent with data that downloaded into the electronic medical record.

Pain Measure

The Behavioral Pain Scale, used clinically at the bedside at the time of study, was used as a pain measure during the study period. It has demonstrated adequate internal reliability with Cronbach alphas ranging from .64-.72 and intra-class correlations of .95.[26, 27] Significant changes in Behavioral Pain Scale scores have been noted during painful procedures in minimally responsive adults, supporting validity in this setting.[27] Inter-rater reliability for the Behavioral Pain Scale between the investigator and nurse educator was .95. All Behavioral Pain Scale measures were obtained by the investigator.

Inflammatory Markers

Interleukin (IL)-6 and IL-10 were used as markers for inflammation during the study period. The study intervention was completed between 0800 and 1400 to minimize diurnal effects on cytokine values. Plasma cytokine levels were obtained from either an intra-arterial catheter or venous access device. There is no known difference between cytokine values obtained by arterial or venous sampling; however, a direct stick may induce an inflammatory response and artificially elevate the cytokine levels.[28] An established arterial or venous access device suitable for blood sampling was part of inclusion criteria. Blood samples were obtained, prepared and analyzed by the investigator according to a predetermined protocol to assure precision and accuracy (Appendix A). Following generation of a standard curve using known concentrations of each interleukin, IL-6 and IL-10 values were obtained using a commercially

prepared human enzyme-linked immunosorbent assay (ELISA). Assays for IL-6 and IL-10 samples were conducted in duplicate and all values were expressed as mean concentrations for each of the three time periods. The IL-6 to IL-10 ratio was also calculated for each of the three time points. The ratio between the two values may be clinically important as IL-6 is a pro-inflammatory cytokine while IL-10 is an anti-inflammatory cytokine that are usually maintained in approximately 2or 3:1 balance.[29]

Procedures

Once informed consent was obtained, inclusion and exclusion criteria were re-reviewed and a decision about the participant's ability to proceed to the intervention was affirmed. The study period began with a 30-minute rest period. Prior to start of the rest period, care activities, such as repositioning, suctioning, examination or hygiene measures, were performed by the direct care nurse in order to limit the influence of other activity on study outcomes. At the end of this rest period (T0), baseline measures were obtained: 1) cardiopulmonary measures of heart rate, mean blood pressure, and oxygen saturation; 2) ICP and the calculated cerebral perfusion pressure (CPP), if available, 3) a Behavioral Pain Scale score; and 4) a blood sample to assess cytokine levels. Legs were placed in the continuous passive motion (CPM) machines by the investigator, and the intervention was started.

Heart rate, systolic, diastolic and mean arterial blood pressures, oxygen saturation, ICP (if available) and Behavioral Pain Scale score were assessed at 5 minutes (T1) and 10 minutes (T2) during the intervention, and upon completion of the intervention (at 20 minutes, T3). Legs were removed from the CPM machines, and 60-minute rest period began. At the end of the rest period (T4), heart rate, mean blood pressure, oxygen saturation, ICP (if available) and Behavioral Pain

Scale score were again assessed (T4). A blood sample for assessment of cytokine levels was obtained upon completion of the PEP (T3) and at the end of the rest period (T4).

Any patient-initiated or provider-initiated activity during the study period was recorded by the investigator. Family members were allowed to be at the bedside during the intervention if requested and their presence was also recorded. The investigator was present in the room during the entire study period and all physiologic measures were directly downloaded into the medical record and recorded by the investigator.

Intervention

The passive exercise protocol (PEP) consisted of 20 minutes of 20 flexion-extension (from 70^{o} flexion to 5^{o} flexion) episodes per minute in each leg simultaneously. Leg movements were alternated so that one leg was flexed while the other was extended, simulating slow walking.

The CPM machines, manufactured by Furniss Corporation are movement therapy devices that are approved for use in hospital, rehabilitation and home settings. Two CPM machines were used for each intervention to standardize the degree of knee and hip flexion. To assure precision in delivery, the same device was used on each right leg and each left leg for each participant. The device was placed on the flat surface of the bed below the leg; the leg was positioned in thigh, calf and foot supports. Supports were padded to prevent skin breakdown, and a stabilizing device at the knees prevented lateral rotation at the knee or hip. A handheld device was used to set the number of flexion-extension repetitions per minute (range 1-20) as well as degree of flexion (range 0^{o}-95^{o}). The CPM machine had a resistance alarm which halted movement as an additional safety measure. Precision and accuracy have been determined by the manufacturer;

electrical safety of the equipment was determined by the biomedical engineering department at the institution. The investigator completed a training program offered by the supplier and delivered the intervention.

Study End Points

The primary study endpoints were safety endpoints, and included maintenance of heart rate, mean blood pressure, oxygen saturation, and ICP within the range specified by critical care order sets (Table 3), during and for 60 minutes after the passive exercise protocol. The secondary endpoints were maintenance of observed pain level during and 60 minutes after the passive exercise protocol within one point of baseline, and cytokine levels upon completion and 60 minutes after maintained within 5% of baseline values.

Data Analysis

Repeated measures analysis of variance (rmANOVA) was used to determine whether a significant change occurred in the heart rate, mean arterial blood pressure, oxygen saturation, ICP and Behavioral Pain Scale score from baseline (T0) at any of the four subsequent time points (T1-T4). Repeated measures analysis of variance was also used to determine whether a significant change occurred in IL-6 and IL-10 levels as well as the ratio between the two from baseline (T0) at any of the two subsequent time points (T3 and T4). The *a-priori* level of significance was set at 0.05 for these tests. As this was primarily a safety study, lack of significant change in variables was the anticipated outcome. Because changes in the variables may be statistically significant without being clinically significant, any statistically significant change in the dependent variables was compared to the clinical parameters previously defined.

Only statistical significance of change in cytokine levels was considered because clinical significance is currently unknown.

Results

Sample

Demographic data and baseline characteristics for all participants are summarized in Table 5.

Table 5. Baseline Sample Characteristics.

Variable	**Descriptor** Mean (SD) or Frequency (%)
Age in years	56.5 (16.9); Range 21-90 years
Race	
Caucasian	19 (63.3%)
African-American	7 (23.3%)
Asian	4 (13.3%)
Ethnicity	
Hispanic	8 (26.7%)
Non-Hispanic	22 (73.3%)
Gender	
Male	18 (60%)
Female	12 (40%)
APACHE II Predicted Death Rate Mean	23.77 (6.2); Range 13-39 48.8 (19.8); Range 16.5-89.8
BMI	28.7 (SD 9.3) 12 overweight 4 Grade I obesity 4 grade III obesity (morbidly obese)
Primary Reason for Admission	
Neurologic	15 (50)
Respiratory	7 (23)
Abdominal	4 (13)
Cardiac	1 (3)
Hematologic	1 (3)
Sepsis/Infection	1 (3)
Other	1 (3)
Co-morbidities*	3.93 (1.9); Range 1-8

Variable	Descriptor Mean (SD) or Frequency (%)
Respiratory Cardiac Endocrine Hematologic Other Urinary Sepsis/Infection Abdominal Neurological Musculoskeletal	33 22 21 12 10 8 6 4 1 1 All participants had at least one co-morbid condition; 4 had multiple co-morbidities within the same system
Sedation* Yes No	 25 (83.3%) 5 (17.7%)
Neuromuscular Blockade* Yes No	 1 (3.3%) 29 (96.7%)
Beta-Blockers within 48 hours of study participation Yes No	 5 (16.7%) 25 (83.3%)
Narcotics* Yes No	 23 (76.6%) 7 (23.3%)
Glasgow Coma Scale Score*	7.8 (2.8); Range 3-13
Hemoglobin, mg%*	10.2 (1.8); Range 7.0-14.5
Glucose, mg/dl*	Mean 149.8 (48.7); Range 84-322
Ventilator Mode* SIMV Assist control	 16 (53.3%) 14 (46.7%)
Pressure Support cmH_20* Yes No	11.2 (2.3); Range 10-18 17 (56.7%) 13 (43.3%)
Minute Volume, L/min*	8.5 (2.5); Range 5.5-16.4
Fraction of inspired oxygen (FiO_2)*	35.33% (7.5); Range 30%-60%
Positive end-expiratory pressure, cmH_2O*	5.5 (1.5); Range 5-10 All participants received PEEP
Ventilator change during study period Yes No	 1 (3.3%) 29 (96.7%)
Activity during the rest period 1	

Variable	Descriptor Mean (SD) or Frequency (%)
Yes	8 (26.7%)
No	22 (73.3%)
Activity during the rest period 2	
Yes	17 (56.7%)
No	13 (43.3%)
Hours after intubation	38.0 (17.6); Range 4.8-67.5
Hours after admission	38.9 (18.3); Range 4.0-67

*at start of intervention

The mean age for participants was 56.5 years (range 21-90 years, SD 17 years); they were predominantly white (63.3%), non-Hispanic (73.3%), and male (60%); and admitted for neurologic (50%), respiratory (23%), or gastrointestinal problems (13%). All participants had at least one co-morbid condition (X=3.93, SD 1.9). The majority of participants were sedated at the time of the intervention (83.3%) and the mean Glasgow Coma Scale score was 7.8 (SD 2.8). Drugs used for sedation included fentanyl (70%; mean dose 96.7mcg/hr), midazolam (30%; mean dose 3.67 mg/hr), and propofol (26.7%; mean dose 35 mcg/kg/min). Seven (23.3%) participants received a combination of fentanyl and midazolam; 7 (23.3%) received fentanyl and propofol; 5 (16.7%) received fentanyl alone; 4 (13.3%) received propofol alone; and 2 (7%) were on benzodiazepines for sedation. Participants were treated with synchronized intermittent mandatory ventilation (53.3%), pressure support (56.7%) at a mean of 11.2 cmH_20 (SD 1.5), mean minute volume of 8.5 L/min (SD 2.5) , mean FiO_2 of 35% (SD 7.5), and all received positive end expiratory pressure (mean 5.5 cmH_2O, SD 1.53). Mean APACHE II score was 23.8 (SD 6.2), with a mean predicted death rate of 48.8 (SD 19.8). The intervention was implemented a mean 38 hours (SD 17.56) after intubation (mean 38.9 hours after admission, SD 18.34). All participants were able to complete the intervention, and no adverse events were encountered.

Physiologic Responses to the PEP

Mean systolic blood pressures ranged from 130.77-135.03 mmHg, diastolic blood pressures ranged from 65.13-66.10 mmHg, and mean arterial pressure ranged from 86.97-88.20 mmHg across time points. Heart rate means ranged from 91.03-96.20 beats/minute and oxygen saturation means ranged from 98.07%-98.40% across time points. Sample means were well within the normal ranges for physiologic variables at all study points (Table 6).

Table 6. Means and Standard Deviations for Physiologic Variables and Behavioral Pain Scale.

Time	**Systolic BP**		**Diastolic BP**		**Mean BP**	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
0	134.07	19.47	65.67	12.60	88.20	11.60
1	131.37	17.36	66.10	13.27	87.43	10.99
2	135.03	28.73	65.13	12.27	86.97	10.66
3	133.70	19.84	65.23	12.51	87.70	11.93
4	130.77	19.41	65.87	14.78	87.10	14.40

Time	**Heart Rate**		**Oxygen Saturation**		**Behavioral Pain Scale Score**	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
0	96.20	18.78	98.07	2.49	3.77	1.04
1	94.77	19.43	98.10	2.40	3.27	.58
2	93.70	17.70	98.40	1.92	3.23	.63
3	93.00	18.57	98.33	2.06	3.27	.83
4	91.03	17.52	98.40	2.09	3.27	.64

Systolic, diastolic and mean blood pressures and oxygen saturation did not change significantly from baseline at any of the time points (Table 7).

Table 7. One-way rmANOVA Analyses for Physiologic Variables.

Variable	*df*[a]	*F*[a]	*p*[a]
Systolic BP	2.04, 59.20	.81	.45
Diastolic BP	1.98, 57.54	.14	.87
Mean BP	2.10, 60.82	.28	.77
Heart rate	2.32, 67.28	2.84	.06
Oxygen saturation	1.85, 53.65	.65	.52
Behavioral Pain Scale score	2.43, 70.42	4.08	**.02**[b]

[a]Mauchly's sphericity was significant; the Greenhouse-Geisser epsilon correction is reported;
[b]Partial eta-squared was .12, suggesting a moderate effect size

Although a downward trend in heart rate was noted, the change was not statistically significant (p=.06). No clinically significant changes warranting discontinuation of the intervention were noted in any of the physiologic variables.

Only 5 participants had ICP monitoring devices in place at the time of study, which prevented statistical analysis of the values. Mean ICP values ranged from 5.8-8.8 mmHg, indicating normal ICP values. The lowest mean ICP was noted at T3. Cerebral perfusion pressure (CPP), calculated by the monitor interface, ranged from 77-81.2 mmHg, indicating normal CPP values. The highest mean CPP was noted at T3.

Pain Responses to the PEP

Mean values for the Behavioral Pain Scale scores ranged from 3.23-3.77 and were low (Table 6), indicating minimal presence of pain behaviors. A significant difference (Table 7) in the Behavioral Pain Scale scores over time were noted (F(2.43, 70.42)=4.08, p=.02). Pairwise comparisons showed a significant decrease in pain scores from Time 0 to Time 1 and from Time 0 to Time 2; the decrease was sustained at Times 3 and 4. No clinically significant change warranting discontinuation of the intervention was noted in the Behavioral Pain Scale score.

Inflammatory Responses to the PEP

Sample means, standard deviations and ranges are presented in Table 8.

Table 8. Cytokine Variables

Variable	**Time 0 Mean (SD)**	**Time 3 Mean (SD)**	**Time 4 Mean (SD)**	***df*[b]**	***F*[b]**	***p*[b]**
IL-6[a]	872.33 (1432.65)	828.53 (1398.69)	763.28 (1151.03)	1.60, 43.10	4.35[a]	.03[c]
IL-10[a]	30.37 (38.23)	29.94 (38.18)	27.78 (35.34)	1.60, 43.22	3.03	.07
IL-6:IL-10 Ratio[a]	28.82 (47.10)	28.38 (48.81)	28.31 (42.33)	1.61, 43.38	3.42	.05[d]

[a]Log transformation; [b]Mauchly's sphericity was significant, the Greenhouse-Geisser epsilon correction is reported; [c]Partial eta squared = .14, suggesting moderate effect size; [d]Partial eta squared = .11, suggesting moderate effect size

Baseline IL-6 levels in the sample ranged from 6.77-11048.9 pg/ml; only three participants had normal IL-6 levels (<29 pg/ml). Baseline IL-10 levels ranged from 6.46-1014.57 pg/ml; only four participants had IL-10 levels within normal range (<10 pg/ml). No correlations were found between baseline IL-6 values and APACHE II scores or APACHE II predicted death rates. Additionally, no correlation was found between baseline IL-6 and glucose values. Extreme outlier values were noted in two of the participants; those participants were excluded from the final analysis.

A significant difference (Table 8) in the IL-6 values over the three time periods was noted ($F(1.60, 43.1)=4.351$, $p=.03$). Pairwise comparisons showed a significant decrease in IL-6 values from time 1 to time 3 but not from time 3 to time 4. No significant difference was noted in IL-10 values over the three time periods (Table 8). A significant effect was noted on IL-6 to IL-

10 ratios over the three time periods ($F(1.61, 43.38)=3.42$, $p=.05$). Pairwise comparisons showed a significant decrease from Time 0 to Time 3 and from Time 3 to Time 4.

Discussion

Early delivery (X=38 hours after intubation) of the PEP was feasible, and limited only by the protocol-specified time frame (between 0800 and 1400) required to minimize diurnal variation in cytokine levels. It is possible that the intervention could have been delivered earlier after mechanical ventilation if the specific time frame for cytokine specimens was not needed. The physiologic variables used as safety measures were readily available at the bedside and had direct clinical application to the participant's care. Baseline hemoglobin values in this sample were low, supporting the need for a higher minimum (90% vs 88%) oxygen saturation level as a safety indicator.

The intervention did not adversely change heart rate, blood pressure or oxygen saturation over the study period, indicating that 20 minutes of passive exercise is safe for critically ill patients early in the course of their illness. Only 5 (16.7%) participants had received beta-blockers within 48 hours of the intervention, indicating that a potential increase in heart rate in response to activity was likely not blunted. The participant tolerance for this level of activity suggests that multiple episodes of passive activity in a twenty-four hour period may be tolerated but warrants further research. In addition, more aggressive activity, for example, greater flexion, more repetitions per minute or longer episodes, may also be tolerated. The CPM machines were deployed at the maximum rate but greater flexion degrees or longer episodes could have been utilized, or other options such as passive cycling could have been employed.

Although only 5 participants had ICP measurements, the trend of the values over time was interesting. ICP values stayed within normal range during and after the intervention, and the intervention was able to be completed without any adverse change in ICP. Values trended downward by the end of the intervention. Similarly, Thelanderson, Cider, and Volkmann studied ICP response to passive range of motion in 12 participants with parenchymal or intraventricular catheters and reported a decreased in ICP values from 15 mmHg to 14 mmHg after exercise.[16] Their findings combined with data from this indicate the need for further investigation of passive activity as an approach to lowering ICP in patients with critical neurological illness. This is especially important as previous studies have found activity to be associated with an increase in ICP.

The statistical significance of the change in the Behavioral Pain Scale scores during and after the intervention was an unexpected finding. It may be that mobilization improves patient comfort level. The *clinical* significance of a decreased in pain score from 3.77 to 3.23 is unknown. However, it is important to note that pain score improvement was accompanied by a decrease in heart rate which supports the clinical significance of the improved pain score in this sample. Further, because the participants were sedated, minimal change in observed pain behaviors could be clinically significant.

The high mean and wide range of baseline IL-6 levels is not an unusual finding in critically ill patients. This study found IL-6 levels to be much higher and IL-10 levels to be much lower than those reported in another study of chronically critically ill patients.[29] However, the higher IL-6 and lower IL-10 values are consistent with levels in the earlier phase of illness. It is unusual that baseline IL-6 levels did not correlate with the APACHE II scores and predicted death rates, as IL-6 is considered to be a reliable indicator of illness severity.[30, 31] It may be that

an injury severity measure would be a more reliable measure than APACHE II given that trauma patients were included in this study. Timing of the APACHE II measure in relation to study participation may provide additional explanation. APACHE II scores reflect the first 24 hours of admission, while the intervention was implemented at a mean of 38 hours after admission. IL-6 levels have also been found to correlate with admission glucose levels, [30, 32] but no correlation was noted between baseline IL-6 and glucose levels in this study. This may be because glucose levels recorded for this study were obtained in proximity to the intervention, rather than at admission. It is likely that glycemic control would have been implemented by the time of the study start, at a mean of 38 hours after admission.

The change in IL-6 levels over time was an unexpected finding. The significant change in IL-6 from baseline to the end of the intervention combined with the lack of significant change at the end of the second rest period supports not only that the PEP did not worsen inflammation, but it may have been responsible for a decrease in IL-6. Although IL-10 values did not change significantly over the three time periods, IL-6 to IL-10 ratios significantly improved from baseline to Time 3 and from Time 3 to Time 4. This suggests that although IL-10 values did not change significantly, there may have been some contribution from IL-10 increases to the ratio as IL-6 values did not change significantly from Time 3 to Time 4. It may be that IL-10 changes occur over a longer period of time than was measured in this study.

While respiratory failure requiring intubation and mechanical ventilation was common to all participants, this study included participants that were commonly excluded from other mobilization studies. Participants included those on vasopressors, with neurologic impairment, intracranial pressure monitoring, open abdomen and intra-abdominal pressure monitoring, and

neuromuscular blockade. Inclusion of those participants supports passive exercise use in a broader population of patients than previously considered.

A few limitations were identified. The intervention was delivered between 0800 and 1400 to minimize the influence of diurnal variations on cytokine levels. Participants may be more fatigued and have less activity tolerance later in the day, and responses may be different if the intervention is delivered later. Only one episode of passive exercise was studied; it is unknown how repeated episodes over time will be tolerated. Attempts were made to limit patient and provider-initiated activity before and after the intervention, but 26.7% of participants had activity in the rest period before the intervention, and 56.7% had activity in the post-intervention rest period. While this pattern of activity reflects the care necessary in the critical care setting, it may have influenced results. Participant mobility level other than not being bedbound prior to admission was not identified and could also have influenced results.

Implications for Practice and Research

Findings from this study support the safety of early passive exercise in critically ill patients. Nurses should consider incorporating at least 20 minutes of passive exercise early into the plan of care for mechanically ventilated critically ill patients so as not to miss opportunities to improve patient outcomes. Assessment of physiologic values that are commonly monitored in the critical care setting were used as safety indicators in this study and those same values can be readily translated into clinical practice. While this study incorporated commonly monitored values of heart rate, blood pressure and oxygen saturation, it may be that parameters monitored need to be individualized to the patient. Several study participants had additional physiologic monitoring to assess cardiac output, intracranial pressure (ICP), and intra-abdominal pressure,

and while anecdotally no changes were noted, further study is required. This is particularly important since these types of monitoring are commonly in use, and many mobilization protocols have excluded patients with these types of monitoring.[5, 13]

While this study lends further support to safety and feasibility of passive exercise in the critical care setting, future research should focus on efficacy of early passive exercise within the context of a mobilization protocol. This study did not include patients with non-invasive positive pressure ventilation nor with oscillator ventilations, which are commonly used in critical care settings. Safety, feasibility and efficacy of passive activity should be further investigated in persons receiving those types of ventilatory support.

Adaptations of passive exercise incorporated into this study should be further explored. Frequency may be increased from daily up to two, three or four times daily, and duration may be increased from 20 to 30 minutes per episode. Passive cycling devices have the capacity to increase duration and frequency beyond the abilities of CPM machines.[33] Machines that provide axial loading and passive walking are available in rehabilitation settings, but have yet to be studied in the critical care setting.[34] Comparative efficacy studies should be conducted to determine optimum protocols for passive activity.

The finding that passive exercise decreased pain behaviors indicates that mobilization may serve as a novel approach to pain management in the critically ill patient. Future studies should incorporate pain responses to mobilization to attempt to replicate these findings. In addition, future studies should investigate whether mobilization decreases need for narcotics in the critical care setting.

Although the clinical significance of changes in cytokine values obtained from these study participants is not known, other studies have demonstrated decreased IL-6 and increased

IL-10 levels over time in response to regular prescribed exercise.[35] Further study of ongoing passive exercise, rather than the single episode used in this study, may provide clinical significance for changes in cytokines profiles in response to activity in the critically ill patient.

Despite broader inclusion of critically ill patients in this study, many patients are still unable to be mobilized. Creative alternatives for those patients should be developed and investigated. Active arm cycling devices are available but have not yet been adapted for passive use.[33] Electrical muscle stimulation may be used to produce muscle contraction without stretch and might be a suitable alternative to support muscle integrity in persons with spinal, pelvic or lower extremity fractures.[33] Presence of an arterial or venous access device in the groin was an exclusion criteria for this study which may have been unnecessary. Perme found no catheter-related complications in a study of 30 patients who sat, stood or walked with a femoral artery catheter in place.[36]

Sedation was administered to 83% of participants in this study. Practice guidelines for the study units dictate sedation to be adjusted to a Ramsey sedation score of 3 or better, but the mean GCS score for the study group was 7.8, indicating that patients may have been more deeply sedated. Passive exercise was not timed with daily sedation withdrawal in this study but could be considered in future studies. It would also be interesting to see whether early passive exercise decreases delirium, agitation and the amount of sedation required in mechanically ventilated critically ill adults. Delirium measures were not incorporated into this study, and previous studies have used delirium measures only as an explanation for lack of mobilization.[5,13] Future studies should incorporate delirium scales as outcome measures.

The mean baseline blood glucose level for this sample was elevated (149.8 mg/dl; SD 48.7), but glucose level in response to passive exercise was not evaluated. Hyperglycemia is a

common consequence of critical illness, and it has a direct correlation with IL-6 levels.[32] Activity is known to decrease insulin resistance and increase muscle utilization of glucose.[4,32] It is possible that repeated episodes of passive exercise may not only decrease blood glucose levels and insulin requirements in critically ill patients, but may decrease IL-6 levels as well. The relationship between mobilization, IL- 6, blood glucose levels and insulin requirements in critically ill patients should be explored further.

Conclusion

A passive exercise protocol was well tolerated in a sample of mechanically ventilated critically ill participants; heart rate, mean blood pressure, and oxygen saturation remained within unit specified ranges throughout the study period. Behavioral Pain Scale score reductions over the study period indicated that passive exercise decreased pain during and after the intervention. Passive exercise reduced IL-6 values but further study will contribute to understanding the clinical significance of such reductions. Cytokine values may be useful in explaining physiologic reasons for benefits of mobilization in critically ill adults.

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CHAPTER 4: METHODOLOGY

Abstract

The objective of this study is to identify physiologic variables that could be measured in response to mobilization interventions in critically ill adults.

Physical activity may mitigate muscle damage from critical illness, but critically ill patients may have limited activity tolerance. Physiologic measures may be most useful in identifying safety and efficacy of mobilization in this population.

A comprehensive literature search of electronic databases was conducted from 1990 to present, including CINAHL, MEDLINE the Cochrane Database of Systematic Reviews, and PubMed. Search terms used were mobilization, exercise, activity, and critical illness. Seventeen articles were identified for review. Physiologic measurement approaches were reviewed for precision and accuracy.

Cardiopulmonary measures comprised the majority of physiologic variables identified, and multiple measures were used. Physiologic measures were primarily used as indicators of safety, although several efficacy measures were identified. Only one standardized tool was found that could be suitable as a safety measure, the Borg Rating of Perceived Exertion. The Medical Research Council Muscle Strength Grading Scale could be used as a physiologic outcome measure. Inflammatory biomarkers may be used as a novel measure of physiologic response. Descriptions of approaches to assure precision and accuracy of physiologic response measures were extremely limited.

Multiple physiologic variables should be measured when considering response to mobilization in critically ill patients. Attention should be paid to procedures to assure accuracy

and precision in measurement. Future studies including physiologic measures should include inflammatory biomarkers, and other measures of physiologic function, such as pain assessment.

Introduction

Muscle weakness is a common complication of critical illness, and prevention of muscle weakness is a key factor in recovery from critical illness. Mobilization has been suggested as one intervention to mitigate muscle weakness (Lee and Higgins 2010). Mobilization activities are a progressive "class of interventions" (p. 22; Choi, Tasota and Hoffman 2008); interventions begin with passive range of motion and progress to walking, representing a wide continuum of activities. Many patients are unable to progress through a continuum of activities in the critical care, but even minimal activity may be beneficial in preventing muscle weakness. Griffiths et al. (1995) found that continuous passive exercise in one leg three times a day for seven days prevented muscle weakness in the treated leg of 5 critically ill patients. Progressive activity in the critical care setting has been attributed to decreased weaning time in mechanically ventilated patients, shorter length of stay, and improved function (Bailey et al. 2007; Bourdin et al. 2010; Burtin et al. 2009; Chiang et al. 2006; Morris et al. 2008; Pohlman et al. 2010; Schweickert et al. 2009). Physical activity is also thought to reduce pain, decrease anxiety, improve delirium, promote sleep, and improve mood, all of which are beneficial in reducing effects of illness on muscle (Bailey, Miller and Clemmer 2009; Choi, Tasota and Hoffman 2008).

Although research is beginning to substantiate the benefits of early mobilization, concerns exist that potential risks mitigate benefits. In healthy individuals, physiologic stress is an anticipated response to exercise. However, many critically ill individuals have activity intolerance due to their illness. Primary safety concerns are focused around activity creating

physiologic instability in a population that is often unstable at baseline. Stiller (2000) proposed monitoring physiologic responses in critically ill patients during mobilization as the guide for determining safety, with physiologic responses determining not only when a patient is ready to begin activity, but also when activity should be halted. Physiologic responses are changes in measures of physiologic function. Many physiologic functions, such as heart rate, oxygen saturation, temperature, and blood pressure, are commonly measured by biomedical instrumentation in use at the bedside in the critical care setting. Physiologic function may also be measured directly through analysis of metabolic or cellular products in the lab setting, or indirectly by using tools, such as perception of exertion. Measuring physiologic responses to activity in critically ill patients serves as the primary measure of safety, and researchers interested in studying benefits of exercise in critically ill patients cannot study those benefits without concern for patient safety. This paper critically analyzes specific measures used to evaluate physiologic responses to mobilization in critically ill patients.

Review of the Literature

A search of the literature was conducted using the search terms, mobilization, exercise, activity, and critical illness to identify studies that incorporated measures of physiologic responses to exercise interventions; Table 1 provides operational definitions for these terms.

CINAHL, MEDLINE, the Cochrane Database of Systematic Reviews, and PubMed databases were examined from 1990 to present. Studies published from 1990 forward were considered in an effort to reflect current practices; 165 articles were identified that met search criteria. To be included in the final review, articles met the following criteria: 1) published in the English language, 2) incorporated mobilization as an intervention in a critically ill (acute or

chronic) sample, and 3) utilized at least one type of physiologic measure in data collection. Articles excluded from the review were those that were reviews only (76 excluded), addressed functional or other outcomes alone, without discussion of physiologic measures (35 excluded), addressed mobilization after resolution of the critical illness (19 excluded), or written in a language other than English (19 excluded). Upon selection, articles were reviewed for types of physiologic measures used as well as approaches taken to assure precision and accuracy.

Results

Seventeen articles were found that met inclusion criteria; a summary of articles reviewed may be found in Table 9.

Table 9. Summary of Physiologic Measures Used to Evaluate Response to Mobilization.

Author	Sample and Setting	Intervention	Measurements*	Precision and Accuracy Approaches	Additional Measures
Astorino, Tyerman, Wong, & Harness, 2008	9 spinal-cord injured participants, ages 26-54 years (mean 40.6 years); community setting	30 minutes of mechanical lower extremity passive exercise, with incremental increases; repeated one week later	• VO_2 and VCO_2 by mass flow sensor • Systolic and diastolic blood pressures recorded before, after 15 minutes, and immediately after intervention • Peripheral oxygen saturation • Heart rate • Borg Rating of Perceived Exertion (RPE) every 5 minutes during intervention	• Gas analyzers calibrated against standard available precision gases; test-retest reliability reported at .92 • Manual recordings of blood pressure with recording of first and fourth sounds; inter-rater reliability reported at .98 and .93 • Oxygen saturation and heart rate measured by available standard biomedical instrumentation • Patient diary of exercise and diet habits the day before each intervention (to assure situations were as similar as possible)	
Chiang, Wang, Wu, Wu, & Wu, 2006	24 males and 8 females; post-ICU, alert, mechanically ventilated; post-ICU setting	Participants were randomized to either physical training (progressive upper/lower extremity range of motion ROM exercises) or standard of care; both groups	• Peripheral oxygen saturation • Borg Rating of Perceived Exertion (RPE) at end of intervention • Maximum morning ET pressures (PImax and PEmax)	• Oxygen saturation measured by available standard biomedical instrumentation • Use of standardized device to measure ET pressures • Standard rest period before ET pressure	• Barthel Index (BI) and Functional independence Measure (FIM) at admission, and at 3 and 6 weeks after admission (BI and FIM assessed by a therapist trained in its use)

Author	Sample and Setting	Intervention	Measurements*	Precision and Accuracy Approaches	Additional Measures
		subjected to same weaning protocol	• Upper/lower extremity physical strength measures on admission, at 3 and 6 weeks after admission	measure; repetition of 3-5 ET pressure measures with averaging of 3 highest values • Strength measures obtained by dynamometer following written directions to standardize assessments; two raters pre-tested with 5 subjects to establish intra-rater (ICC .91) and inter-rater (ICC .83) reliability	
Higuchi, Kitamura, Kawashima, Nakazawa, Iwaya, & Yamasaki, 2006	7 males with complete quadriplegia, ages 20-34 years and six nondisabled males, ages 25-35 years; community setting	Machine guided passive leg movement while in upright position at preset incremental rates, from 20-50 movements/minute	• VO_2, VE by mass flow sensor • Respiratory rate • Heart rate- recorded only the last 10 secs of each incremental stage • VO_2/Heart Rate ratio calculated • Blood lactate via earlobe sample before and after intervention	• Gas analyzers calibrated against standard available precision gases • Heart rate and respiratory measured by available standard biomedical instrumentation • Blood lactate measured using calibrated point of care lactate meter • Refrained from food, caffeine, and nicotine for 3 hours prior to intervention • Controlled ambient temperature and humidity	
Morris, Goad, Thompson, Taylor, Harry,	93 males and 72 females, mean age 54 years received mobility	Passive range of motion delivered three times a day by a trained nursing	• Limb strength using Medical Research Council (MRC)	• Limb strength graded by physical therapists who have demonstrated inter-	• Days to first out of bed • Ventilator days

Author	Sample and Setting	Intervention	Measurements*	Precision and Accuracy Approaches	Additional Measures
Passmore, et al., 2008	protocol; 88 males 77 females, mean age 55.4 years received usual care; ICU setting	assistant; five repetitions per joint	examination at discharge • Heart rate • Blood pressure • Oxygen saturation	rater reliability on MRC • Heart rate, blood pressure and oxygen saturation measured by available standard biomedical instrumentation	• ICU length of stay • Hospital length of stay
Muraki & Tsunawake, 2008	10 males, 10 females; healthy; ages 18-22 years; community setting	Passive leg cycling while seated; progressive increase from 0-70 rpm over 30 minutes	• VO_2 and VCO_2 by mass flow sensor • Muscle oxygen saturation using near-infrared spectroscopy at precisely measured location • Continuous heart rate (measurement technique not specified)	• Gas analyzers calibrated against standard available precision gases • Gas measurements taken each breath and calculated to average minute intervals • Muscle oxygen saturation collected each second and averaged over 30 minutes • Controlled ambient temperature and humidity	• Threshold identification
Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010	49 sedated, mechanically ventilated participants (27 females, 22 males); mean age 57.7 years (range 36-69 years); ICU setting	ROM exercises starting on day 1.5 (range 1-2) after mechanical ventilation commenced; activity progressed as tolerated to transfer	• Heart rate • Systolic blood pressure • Diastolic blood pressure • Mean blood pressure • Respiratory rate • Peripheral oxygen saturation • All above recorded at rest, monitored during activity and recorded at completion of intervention	• All values measured by available standard biomedical instrumentation • Standardized rest period prior to intervention	• Ventilator dysynchrony • Ambulation distance, balance • Ability to perform ADLs • Barthel Index (BI) and Functional independence Measure (FIM) on study entry and at hospital discharge
Richard, Staley, &	10 critically ill burn patients; 4	Passive or active ROM delivered by a	• Heart rate • Systolic blood pressure	• All values measured by available standard	

Author	Sample and Setting	Intervention	Measurements*	Precision and Accuracy Approaches	Additional Measures
Miller, 1994	males, 6 females; ages 21-80 years (mean 48 years); eight were mechanically ventilated; ICU setting	physical therapist on mean day 13.6 (range 2-47 days) after injury for mean duration 22.6 of minutes (range 15-30 minutes) in supine (in bed) position	• Diastolic blood pressure • Mean blood pressure • All values measured continuously but recorded before and after intervention	biomedical instrumentation	
Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009	104 sedated, mechanically ventilated participants; 29 females, 20 males in intervention group (mean age 57.7 years); 23 females, 32 males (mean age 54.4 years) in control group; ICU setting	Participants randomized to exercise and mobilization on day of enrollment or standard of care; exercise started with 10 repetitions of passive range of motion to each extremity/joint and progressed to transfer	• Systolic blood pressure • Diastolic blood pressure • Mean blood pressure • Heart rate • Respiratory rate • Peripheral oxygen saturation • Upper/lower extremity physical strength measures using Medical Research Council (MRC) examination at discharge • Hand grip strength at discharge	• Blood pressure, heart rate, respiratory rate, peripheral oxygen saturation measured by available standard biomedical instrumentation • Strength measures assessed by two therapists; assessment therapists (ATs) different from interventional therapists (ITs); ATs blinded from treatment	• Distance walked independently at discharge • Hospital and ICU length of stay • Functional independence Measure (FIM) and Barthel Index (BI) at hospital discharge (Assessments conducted by two therapists; assessment therapists (ATs) different from interventional therapists (ITs); ATs blinded from treatment)
Stiller, Phillips, & Lambert,	31 (18 male, 13 female) participants, ages	Mobilization protocol started after screening for safety	• Heart rate recording from a bedside monitor • Calculated age-predicted	• ECG tracing satisfactory • Arterial lines calibrated daily per hospital	

Author	Sample and Setting	Intervention	Measurements*	Precision and Accuracy Approaches	Additional Measures
2004	20-81 years (mean 57 years); ICU setting	parameters; began with movement from lying to sitting position and progressed	maximum heart rate • Systolic and diastolic blood pressures recorded from oscillometric sphygmomanometer or from bedside monitor if arterial line pressures displayed • Peripheral oxygen saturation • PaO_2/FIO_2 calculated if data available	protocol	
Winkelman, 2010	14 females, 3 males with acute COPD exacerbations and mechanical ventilation; ages 35-74 (mean age 60 years); ICU setting	Observation of routine therapeutic mobility as it occurred; activity occurred for a minimum of 20 minutes; activity consisted of passive range of motion with turning and progression to ambulation	• Peripheral oxygen saturation • Partial pressure of arterial oxygen when available (calculated P/F ratio) • Interleukin-6 and Interleukin-10 at rest and after activity • Vital signs (type not specified)	• Standardized period of observation to mitigate diurnal effects • Standardized timing for collection of resting and activity blood samples • Vital signs measured by available standard biomedical instrumentation • Intra-rater reliability established for all data collection points • Samples obtained and prepared for analysis by limited number of people • Samples stored at same temperature and analyzed in duplicate by same method throughout study	• Duration of activity observed • Activity counts using an objective monitor

Author	Sample and Setting	Intervention	Measurements*	Precision and Accuracy Approaches	Additional Measures
				• Sensitivity of analysis technique 0.5 pg/ml	
Winslow, White, & Tyler, 1990	183 critically ill adults from 3 hospital settings (part of a larger study, age range and gender NA)	Turning to lateral position; side determined randomly in a standardized position	• SVO_2 • Heart rate • Recorded every minute for 4 minutes	• Standardized rest period prior to turning • Peripheral oxygen saturation and heart rate measured by available standard biomedical instrumentation	
Zannotti, Felicetti, Maini, & Fracchia, 2003	24 ventilator-dependent, bed-bound patients with severe end-stage COPD; mean age 65.2 years; post-ICU setting	Two groups both received range of motion twice a day for 30 minutes; one group randomized to range of motion plus standardized electrical stimulation of quadriceps and vastus muscles for 30 minutes twice a day (5 min at 8Hz pulses with 25 min of 35 Hz pulses)	• Peripheral oxygen saturation • Heart rate • Respiratory rate • Muscle strength using Medical Research Council (MRC) examination at study onset and weekly for study duration	• Inter-rater reliability of muscle strength • Peripheral oxygen saturation , heart rate and respiratory rate measured by available standard biomedical instrumentation	• Number of days before chair transfer • Ability to be weaned

*measurements are continuous unless otherwise specified

Legend: COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; ET=endotracheal; FiO_2=fraction of inspired oxygen; ICU=intensive care unit; paO_2=partial arterial oxygen pressure; ROM=range of motion; SvO_2=venous oxygen saturation

Physiologic responses were typically measured before, during and after mobilization, and physiologic variables were used as indicators of safety or efficacy, or both. Physiologic measures characteristically evaluated cardiopulmonary function but other measures were used as well (Table 10). Multiple rather than single measures of physiologic responses were used, and efficacy-focused studies incorporated both physiologic variables as well as measures of functional outcome.

Table 10. Description of Physiologic Measures.

Type of Measure	Description
Heart rate	Electrodes placed on the chest wall to continuously measure changes in electrical voltage emanating from the heart during depolarization and repolarization. Voltage changes are amplified and displayed on an oscilloscope, and converted into a numerical representation of the systematic depolarization and repolarization. Heart rate is calculated per minute as the distance between each atrial repolarization/ventricular depolarization event (the R-R interval).
Blood pressure	Directly measured using an indwelling arterial catheter connected to a transducer with a fluid interface; the arterial pressure waveform is displayed on an oscilloscope, and converted into a numerical representation. Indirectly measured by sensing arterial oscillations via an automated cuff; a representation of the phenomenon is converted into a numerical representation and displayed on the monitor. Systolic blood pressure (SBP) is the pressure measured in the arterial system during left ventricular systole, while diastolic blood pressure (DBP) is the pressure measured in the arterial system during left ventricular diastole. Mean pressure represents the average arterial pressure during one cardiac cycle of systole and diastole. Direct and indirect approaches measure systolic and diastolic pressure and often provide a calculation of mean pressure.
Respiratory rate	Measured by direct observation, sensor detection of movement, or flow-direction sensing via a breathing circuit attached to a ventilator.
Oxygen saturation	Measured by exposing hemoglobin to red and infrared light using a light emitting diode (LED). Oxygenated hemoglobin absorbs more infrared light, while non-oxygenated hemoglobin absorbs red light. As light passes through the hemoglobin, a light receiving diode (LRD) sensor calculates the percentage of each type of light and displays the value as a percentage; complete saturation is 100%. Pulse oximetry is

Type of Measure	Description
	the most commonly used measure of oxygen saturation and is a standard monitoring technique in the critical care setting. The LED and LRD are placed over an accessible peripheral arterial bed, and an external monitor converts two wavelengths of light signal into a numeric display with a waveform corresponding to arterial pulsation. Many sites on the body may be used for sensor placement, including the fingertip, toe, ear lobe, tip of the nose, heel, hand, or forehead. Central venous oxygen saturation may be measured by an indwelling catheter that emits light and senses received light as blood flows past. The device may be placed in the jugular vein or pulmonary artery, and is used to calculate oxygen extraction by comparing values to arterial samples (thus, it is a direct measure of oxygen consumption). It is invasive, used only in the critical care and surgical settings (and not widely used even in those settings), and requires skilled personnel for insertion and use. Intra-arterial devices that continuously detect oxygen saturation are also available.
Metabolic activity: oxygen consumption and carbon dioxide production	Metabolic activity is estimated by VO_2 (the difference between inhaled and expired oxygen concentration), as well as VCO_2, (the difference between inhaled and expired CO_2 concentration); the values are inversely related. The two values may be measured by a volume-displacing or flow sensing spirometer. VO_2 may also be used in additional calculated measures.
Neurodynamic measures	Intracranial pressure may be directly measured via a catheter placed in the intracranial compartment. The catheter may be placed in the ventricles (most common), brain parenchyma, subarachnoid or epidural spaces. It is invasive, used only in the critical care settings and requires skilled personnel for insertion and use. Fiberoptic and fluid-filled systems are available. Fiberoptic systems require calibration prior to insertion. Fluid-filled systems require zeroing, and the transducer must be placed at the level of the external auditory meatus. Fiberoptic systems allow measurement of brain temperature and oxygen when intraparenchymal catheters are used. Cerebral blood flow is measured noninvasively using Doppler technology; flow is sensed by placing the probe over windows in the skull.

Efficacy studies rarely incorporated physiologic outcome measures. Only two standardized tools were located that addressed physiologic responses. One, the Borg Rating of Perceived Exertion (RPE), represents a safety measure in this population. The other, the Medical Research Council (MRC) Muscle Strength Grading Scale, represents an efficacy measure.

Overall, descriptions of approaches to assure precision and accuracy of physiologic response measures were extremely limited. Discussion of specific measures used to evaluate physiologic responses to activity or exercise in the critical care setting and related measurement concerns follows.

Specific Physiologic Measures and Measurement Concerns

Heart Rate

Heart rate (HR) was utilized as a determinant of safety in 12 studies (Table 11).

Table 11. Parameters Used in Studies of Physiologic Responses to Mobilization.

Parameter	Studies Utilized
Heart rate	Astorino, Tyerman, Wong, & Harness, 2008; Bourdin, Barbier, Burle, Durante, Passante, et al., 2010; Burtin, Clerckx, Robbeets, Ferdinande, Langer, et al., 2009; Clini, Crisafulli, Antoni, Beneventi, Trianni, Costi, et al., 2011; Higuchi, Kitamura, Kawashima, Nakazawa, Iwaya, & Yamasaki, 2006; Morris, Goad, Thompson, Taylor, Harry, Passmore, et al., 2008; Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010; Richard, Staley, & Miller, 1994; Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009; Stiller, Phillips, & Lambert, 2004; Thelandersson, Cider, & Volkmann, 2010; Winslow, White, & Tyler, 1990; Zannotti, Felicetti, Maini, & Fracchia, 2003
Blood pressure	*Systolic and Diastolic:* Astorino, Tyerman, Wong, & Harness, 2008; Burtin, Clerckx, Robbeets, Ferdinande, Langer, et al., 2009; Stiller, Phillips, & Lambert, 2004 *Systolic, Diastolic and Mean:* Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010; Richard, Staley, & Miller, 1994; Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009 *Mean only:* Bourdin, Barbier, Burle, Durante, Passante, et al., 2010 *Not specified:* Bailey, Thompsen, Spuhler, Blair, Jewkes, Bezdjian, et al., 2007; Clini, Crisafulli, Antoni, Beneventi, Trianni, Costi, et al., 2011; Morris, Goad, Thompson, Taylor, Harry, Passmore, et al., 2008; Thelandersson, Cider, & Volkmann, 2010
Respiratory rate	Bourdin, Barbier, Burle, Durante, Passante, et al., 2010; Burtin, Clerckx,

Parameter	Studies Utilized
	Robbeets, Ferdinande, Langer, et al., 2009; Higuchi, Kitamura, Kawashima, Nakazawa, Iwaya, & Yamasaki, 2006; Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010; Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009; Zannotti, Felicetti, Maini, & Fracchia, 2003
Oxygen saturation	*Peripheral oxygen saturation:* Astorino, Tyerman, Wong, & Harness, 2008; Bailey, Thompsen, Spuhler, Blair, Jewkes, Bezdjian, et al., 2007; Bourdin, Barbier, Burle, Durante, Passante, et al., 2010; Burtin, Clerckx, Robbeets, Ferdinande, Langer, et al., 2009; Chiang, Wang, Wu, Wu, & Wu, 2006; Clini, Crisafulli, Antoni, Beneventi, Trianni, Costi, et al., 2011; Morris, Goad, Thompson, Taylor, Harry, Passmore, et al., 2008; Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010; Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009; Stiller, Phillips, & Lambert, 2004; Winkelman, 2010; Zannotti, Felicetti, Maini, & Fracchia, 2003 *Central venous oxygen saturation:* Winslow, White, & Tyler, 1990
Metabolic activity	*VO_2/VCO_2:* Astorino, Tyerman, Wong, & Harness, 2008; Higuchi, Kitamura, Kawashima, Nakazawa, Iwaya, & Yamasaki, 2006
Neurodynamic parameters	Thelandersson, Cider, & Volkmann, 2010
Cytokines	Winkelman, Higgins, Chen, & Levine, 2007; Winkelman, 2010
Others	*Borg RPE*: Astorino, Tyerman, Wong, & Harness, 2008; Chiang, Wang, Wu, Wu, & Wu, 2006 *Airway pressures:* Chiang, Wang, Wu, Wu, & Wu, 2006; Clini, Crisafulli, Antoni, Beneventi, Trianni, Costi, et al., 2011 *Muscle strength measures:* Chiang, Wang, Wu, Wu, & Wu, 2006; Clini, Crisafulli, Antoni, Beneventi, Trianni, Costi, et al., 2011; Morris, Goad, Thompson, Taylor, Harry, Passmore, et al., 2008; Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009; Zannotti, Felicetti, Maini, & Fracchia, 2003 *CAM-ICU:* Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010; Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009

Heart rate was measured by a five-lead electrocardiogram (ECG). This measure was commonly available at the bedside, or included as part of a measurement cart. Although increase

in heart rate (achievement of a target heart rate) is a desired outcome with exercise, an increase in heart rate carried a different significance in critical care, and was considered an adverse or detrimental response. No studies mentioned acceptable heart rate ranges, and only one study mentioned a specific percent increase in HR (Richard, Staley and Miller 1994). In order to address clinical significance of heart rate change in this setting, the definitions of an acceptable or unacceptable heart rate should be addressed. An unstable heart rate may be defined as outside of accepted parameters (i.e., above or below 60-100/minute), or a percentage increase above baseline.

Heart rate measures should be timed to capture responses as they occur. Timing was routinely specified as before (at baseline) and after (upon completion but no longer term) an intervention. Several studies included measures during the intervention as well, but time points varied. For example, Higuchi et al. (2006) measured heart rate for 10 seconds before each change in passive exercise level. Consideration must be given to timing intervals so as to capture optimum data reflective of the phenomenon of study.

Heart rate alone may be an insufficient measure of cardiac response to mobilization. Cardiac arrhythmias may be detected on continuous 5-lead ECG monitoring during activity, but 5-lead ECGs may be otherwise limited in the information they supply. If concerns exist about the passive exercise creating cardiac ischemia, 12-lead or ST-segment monitoring may be more appropriate measures. Although these monitoring options are available at the bedside, none of the studies reviewed utilized these advanced forms of monitoring.

Precision and accuracy of HR data depends on standard lead placement. No study identified that standard lead placement was considered. Further, monitoring devices vary in accuracy and precision, and these data were rarely reported. Manufacturer reports of accuracy

and precision should be considered when using bedside monitoring data for variable measurement. One last concern is that many extraneous factors, particularly medications, may influence heart rate. For example, for patients receiving beta-adrenergic antagonists, tachydysrhythmias may absent as an indicator of activity intolerance.

Blood Pressure

Blood pressure (BP) was measured in eleven of the seventeen studies as a safety measure (Table 11). The method of measurement (direct vs indirect) was specified in five of the nine studies. Both measures are available in the critical care setting. One study used an auscultated method, listening to the first and fourth Korotkoff's sounds as the BP measure (Astorino et al. 2008). This measure is subject to the individual's hearing acuity and speed of recognition and is infrequently used in the critical care setting.

Three different blood pressure values are possible: systolic, diastolic and mean. All three values are readily available in the critical care setting. Of the 10 studies reporting blood pressure values, 3 reported systolic and diastolic values only, 3 reported systolic, diastolic and mean values, one reported mean pressure only, and 3 did not specify blood pressure value measured. Consideration should be given to which of the three values is most appropriate for the purpose of measurement. It may be that diastolic pressure is of greatest importance since it represents the baseline pressure against which the heart needs to pump. Astorino et al. (2008) indicated that diastolic pressure was the most significant BP measure of safety during mobilization.

Timing of measurement is a concern. The direct method allows for continuous measure and display of BP values, while the indirect method can provide values as frequently as every minute. Timing in studies reviewed was routinely specified as before (baseline), during (at

specified intervals), and after (upon completion but not longer term) an intervention. For example, Pohlman et al. (2010) used continuous direct BP measures to cross all three time frames, while Stiller et al. (2004) measured BP indirectly in between activity tasks. Further considerations in choice of BP method relate to availability and invasiveness. Several researchers mentioned use of whichever BP method was available at the bedside (Schweickert et al. 2009; Winkelman 2010). The invasive nature of the direct approach to BP measurement may not be warranted when precision and accuracy of the indirect method can be assured. However, repeated cuff measurement can produce pain-induced physiologic changes which may also affect accuracy of the BP measure.

Precision and accuracy of BP data depend on standard arm and cuff placements and appropriate sizing for the indirect method or proper transducer placement (at the phlebostatic axis) for direct measurement. Further, the direct method requires zeroing against atmospheric pressure. No study in this review identified that standard placements or zeroing were considered. Monitoring devices vary in accuracy and precision, and similar to heart rate, researchers referred readers to manufacturer sources for precision and accuracy data. Patient condition or medication may alter vascular tone and resistance to flow, and should be considered when interpreting the clinical significance of BP values. Schweickert et al. (2009) identified vasoactive medications used but did not relate these to BP measures.

Respiratory Rate

Respiratory rate (breaths per minute) was measured in six of the 17 studies (Table 11); methods for measuring respiratory rate were not specified in those studies. The myriad influences on respiratory rate render this parameter the least precise measure of response to

activity, and likely account for the less frequent use of this measure in studies. Bourdin et al. (2010) used respiratory rate as a safety measure, finding that rate increased with walking and arm exercise but not with other activities; increase in respiratory rate did not result in stopping the exercise activity nor did it contribute to adverse events.

A respiratory lead attached to the chest wall senses movement with inspiration and expiration. Lead placement, depth of respirations, and body habitus determine accuracy of this approach. The flow-sensing technology in a ventilator has been calibrated by the manufacturer against a standard and provides the greatest precision and accuracy for this measure. However, even with flow-sensing technology, critically ill patients that are paralyzed or sedated and on a controlled mode of ventilation are unlikely to demonstrate change in respiratory rate.

Oxygen Saturation

Twelve of the 17 studies reviewed included peripheral oxygen saturation via pulse oximetry as a physiologic measure (Table 11). Pulse oximetry is the most commonly used measure of oxygen saturation and is a standard monitoring technique in the critical care setting. Central venous oxygen saturation was reported in only one of the studies (Winslow, White & Tyler, 1990); this approach is invasive and infrequently used in the critical care setting. Muscle oxygen saturation has been used as a physiologic measure in exercise studies Muraki and Tsunawake 2008), but this measure provides only a focal measure of oxygen saturation, is invasive, and not readily available in critical care settings.

Precise and accurate peripheral oxygen saturation values require standard placement of the LED/LRD sensor, but given the placement options, can vary widely. An adequate waveform suggests an adequate sample for testing; oxygen saturation values are inaccurate when arterial

pulsations are not detected. Interpretation of values also requires knowledge of hemoglobin level; low hemoglobin levels may artificially inflate saturation. Additionally, any factor that affects peripheral blood flow in the region of measurement can provide inaccurate values. Examples include systemic vasoconstriction due to disease, drugs, or body temperature. None of the studies addressed sensor placement, hemoglobin values, confounding factors or waveform adequacy. The threshold for desaturation was described in 4 reports (Bailey et al. 2007; Burtin et al. 2009; Pohlman et al. 2010; Schweickert at al. 2009), and varied from <80% to <90%, with no mention of consideration of hemoglobin values. Monitoring devices also vary in accuracy and precision, and researchers consistently referred readers to manufacturer sources for precision and accuracy data.

Oxygen Consumption and Carbon Dioxide Production

VO_2 (the difference between inhaled and expired oxygen concentration), as well as VCO_2, (the difference between inhaled and expired CO_2 concentration) were reported measures in 2 studies (Astorino et al. 2008; Higuchi et al. 2006). Flow-sensing spirometry was used, and precision was determined by calibration against precision gases. Specific protocols were implemented to standardize timing of measurement in relation to intervention, and ambient temperature and humidity were controlled to improve precision (Astorino et al. 2008; Higuchi et al. 2006). Ventilators used in this setting often have built in flow sensors that have the capability to provide continuous feedback of ventilatory measures, and if available, could be used. However, these measures do not reflect daily practice. To assure precision and accuracy, ventilators are calibrated by the manufacturer against standard precision gases and periodically during use in the same manner per manufacturer guidelines. In the critical care setting, pressure

support and volume controls may alter these values and must be considered when interpreting the values. Ventilator parameters should not be changed during measurement periods where possible. Bailey et al. (2007) described increasing FiO_2 by 0.2 prior to mobilization as a pre-emptive approach.

Neurodynamic Parameters

Intracranial pressure (ICP) and cerebral blood flow (CBF) are two neurodynamic parameters routinely used in patients with critical neurologic illness. Only one study was found that measured neurodynamic parameters. Thelandersson, Cider and Volkmann (2010) directly measured ICP via a ventricular catheter, and indirectly measured CBF using transcranial Doppler. ICP monitoring is invasive, and CBF measured by transcranial Doppler is noninvasive. Invasive measures of CBF are available but infrequently used in clinical settings.

Accuracy and precision of ICP are dependent on transducer placement and stopcock direction if a drainage system is used. The monitoring system was not specified, but may require calibration prior to insertion, or zeroing if a fluid interface is used. Accuracy and precision of transcranial Doppler measurement of CBF is dependent on practitioner training as well as device standards determined by the manufacturer.

Inflammatory Markers

Critical illness has been associated with inflammation (Winkelman, Higgins, Chen, & Levine 2007), and exercise has been reported to both increase and decrease inflammation (Sari-Sarraf, Reilly, & Doran, 2006). This suggests that inflammatory markers may be useful in identifying both beneficial and adverse responses to activity in critically ill patients. Cytokine levels have been used as an in vitro indicator of inflammation, marking illness severity as well as

a response to therapeutic interventions. Cytokine sample must be obtained in a precise manner if it is to be an accurate marker. Specific approaches that enhance precision and accuracy of cytokine values obtained are (Zhou et al. 2010):

- Obtaining the sample from the appropriate source. Cytokines may be found in many bodily fluids and tissues, such as blood, breast milk, urine, and saliva (Sari-Sarraf, Reilly and Doran 2006). Natural cytokine levels may differ in each of these areas, so consideration must be given to using the correct source. Blood provides the optimum systemic measures of cytokine activity, but salivary samples may be considered because they are more easily obtained.
- Obtaining the sample at the appropriate time. Diurnal influences may cause cytokine levels to differ by time to day. Obtaining samples at a consistent time of day is important in sample reliability.
- Limiting extraneous influences on cytokine levels. Activity, especially seizures, agitation and shivering can alter cytokine levels. Care should be taken to control activity to the extent possible or provide a period of rest before sampling to assure reliability. Feedings and lipids can also increase cytokine levels. Sampling should be timed during a fast for accuracy; if fasting samples are not possible, then the influence of feeding on cytokine level should be taken into consideration.
- Obtaining the sample in the appropriate manner. No evidence was found of any difference between arterial and venous cytokine levels, but a needle stick or venous catheter may invoke a local inflammatory response. Use of existing arterial or venous access devices may eliminate this influence. It is also important to obtain the appropriate amount of sample, usually a minimum of 3 ml.

- Preparing and storing the sample appropriately. Cytokines degrade soon after a sample is obtained, and should be prepared immediately after a draw. The blood sample is centrifuged, and serum is removed and frozen at -80^{o}C until analyzed.
- Analyzing the samples in the most beneficial manner. Multiplex arrays allow analysis of cytokine interactions rather than providing simple levels as ELISA measures do.

Winkelman (2010) collected blood samples for IL-6 and IL-10 immediately before and after a 20 minute activity period. Samples were obtained from existing venous or arterial access, aliquoted and frozen according to a specific protocol, and analyzed in duplicate for accuracy using established detection limits and sensitivity of 0.5pg/ml. In a related study, Winkelman, Higgins, Chen, and Levine (2007) used an ELISA analysis with predetermined sensitivity and precision.

Other Measures

Borg Rating of Perceived Exertion

Perceived exertion is often used as a compare measure to physiologic responses in exercise studies. Two of the 17 studies used the Borg Rating of Perceived Exertion (RPE) scale in studies of physiologic responses to mobilization (Astorino et al. 2008; Chiang et al. 2006). The Borg RPE (Table 12) was initially developed in 1970, with the intention of using it as a proxy measure of intensity in research studies evaluating exertion during exercise (Borg 1970).

Table 12. Borg Rating of Perceived Exertion (Chen, Fan, and Moe 2002).

Score	Verbal Anchor
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Therapeutic exercise has three domains: duration, intensity and frequency. Intensity is the most subjective domain, and the Borg RPE was developed as an attempt to quantify this domain in relation to physiologic variables. It was normed in healthy adult males exercising to exhaustion on a cycle ergometer. The unidimensional scale has numeric ratings from 6 to 20 with verbal anchors along the scale that are purported to indicate sequentially increasing exercise intensity. The scale range corresponds to one-tenth of the heart rate. Numeric values were added to render the tool less subject to psychological variables impacting perceived exertion. Initial work revealed strong correlations between heart rate and the Borg RPE. One concern with the scale is that the verbal anchors of numerical values imply interval level data when the data is actually categorical. Yet, Dawes (2010) found good agreement between verbal anchors and numerical values with intra-class correlations of .96-.98, and box plots showed a sigmoid shaped curve which corresponded with differences in ratings. Criterion-related validity has been

reported at .8-.9, but a recent meta-analysis of 164 studies using the RPE showed validity coefficients in the .5-.6 range (Chen, Fan and Moe 2002). Concurrent validity, test-retest reliability, and sensitivity have been demonstrated in numerous additional studies. Since the introduction of the RPE, two important adaptations have occurred. One is the CR-10, which is uses the same verbal anchors as the RPE but rates exertion on a 0-10 scale. The other uses the 6-20 scale but substitutes breathing-related exertion anchors. Contemporary use is more common in fitness rather than research settings, although it has been used in studies of COPD patients (Scott 2004).

There are several limitations to use of the tool that deserve mention. Since the tool was normed in a healthy population on cycle ergometry, it should be re-evaluated in other populations using other exercise approaches. Dawes, et al. (2010) found that brain-injured persons were unable to clearly distinguish anchor differences, which is not surprising since tool completion requires cognitive appraisal which may be dampened in individuals with brain injury. Age extremes present similar challenges, with decreased reliability noted in younger children and older adults. As with many tools, reliability decreases when scores lie at either end of a tool. Lower correlations have been found when the RPE is compared to physiologic changes other than heart rate, such as lactate levels or muscle oximetry. One last concern relates to sensitivity and reliability. Grant et al. (1999) found that Borg RPE demonstrated lower sensitivity to change than the visual analogue equivalent, but greater sensitivity when used as a measure of fatigue.

The RPE would be challenging to use in the study of physiologic responses to passive exercise in critically ill population for several reasons. First, minimal exercise is the goal of mobilization in this population, and scale reliability is lower at this end of the scale. Second, the population of critically ill adults tends to be older in age, and reliability has been found to be

lower in older adults (Groslambert and Mahon 2006). Further, with cardiac and other hemodynamic monitoring being the norm in this setting, it is not necessary to use a proxy measure of exertion. Last, the cognitive appraisal required for scale completion may be lacking in study participants because of factors such as illness severity, and concomitant use of pain medication and sedation.

Muscle Strength

Comparative muscle strength has been used as a measure in mobilization studies. Five studies of passive exercise incorporated muscle strength as an outcome measure (Zannotti et al. 2003; Chiang et al. 2006; Morris et al. 2008; Schweickert et al. 2009; Clini et al 2011). Several different approaches to measurement were used. Use of a dynamometer to measure strength is considered the gold standard of strength measurement (Paternostro-Sluga et al. 2008) but only two of the studies used this device as a strength measure, and grip strength of hand muscles was the sole measure. A dynamometer measures muscle strength against a strain-gauge applied resistance, and devices such as this are not portable and consequently, not readily available in the critical care setting. Accuracy of dynamometer measures is dependent on manufacturer standards, but also depends on a consistent position of the extremity measured (Chiang et al. 2006). Repeated measures should be obtained and averaged; adequate time between measures should be allowed to minimize the effect of fatigue on the muscle.

Manual muscle testing (MMT) was used most commonly to measure strength as an outcome in the studies; it involves strength assessments by an experienced observer who evaluates muscle strength against the examiner's resistance. The examiner then scores the

strength assessed on the 0-5 Medical Research Council (MRC) Muscle Strength Grading Scale (Table 13).

Table 13. Medical Research Council Muscle Strength Grading Scale (Paternostro-Sluga, et al. 2008).

Rating	Observation
0	No muscle contraction is detected.
1	A trace contraction is noted in the muscle upon palpation
2	Active movement when gravity is eliminated
3	Active movement against gravity but not resistance
4	Active movement against some resistance
5	Active movement to overcome resistance

The MRC scale was developed in 1976 as a way to standardize muscle assessments for studies that used muscle strength as an outcome measure. A modified MRC (Paternostro-Sluga et al. 2008) has been developed which considers range of motion in addition to strength in the assessments. Inter-rater and intra-rater reliability have been established in a number of studies (Paternostro-Sluga et al. 2008). Reliability is greatest at the scale ends (0 and 5) while reliability between scores of 3 and 4 is weakest. MRC scale ratings are dependent on examiner expertise as well as patient cooperation. To assure reliability of strength measures obtained, the examiner must be appropriately trained, have inter-rater and intra-rater reliability established, and take action to assure patient cooperation. Morris et al (2008) established inter-rater reliability among therapists using the MRC scale for their study, and used therapists performing muscle strength assessments were blinded to the protocol arm as measures of precision and accuracy.

One unique muscle strength measure found relates to airway pressures. Chiang et al. (2006) and Clini et al. (2011) used maximum inspiratory and expiratory pressures as a strength

outcome measure. To assure reliability of measures obtained, the patients were suctioned before measurement, seated at 45^{o} head of bed elevation, and instructed to maximally inhale then exhale. Tracheostomy cuff pressures were checked to eliminate the influence of a possible leak, and a single standardized manometer was used by a single examiner to measure 3-5 pressures each, which were averaged (Chiang et al. 2006). While this standardized approach can provide a reliable measure of respiratory muscle strength, it does require patient cooperation which can be a limitation in the critical care setting.

Discussion and Recommendations

While purpose of measurement guides the specific approach chosen, the setting of the population of interest determines to a large degree what is possible to measure and how measures can best be obtained. Responses to passive exercise in the critical care setting are best measured by cardiopulmonary physiologic variables for several reasons. These variables are reflective of the type of metabolic activity that exercise produces and translatable across studies. In addition, physiologic variables are not only readily available in the critical care setting, but those variables also represent an important safety parameter which can be crucial in the conduct of research in this setting. Safety of any intervention must be established before efficacy can be demonstrated. Additional physiologic measures, such as muscle biopsy and electromyography could be considered when the primary focus is on outcomes of mobilization. However, other less invasive outcome measures, such as walking distance and grip strength, are available.

Measurement of multiple physiologic variables should be considered where possible. In this review, no study used just a single measure of physiologic response to passive exercise. Multiple measures of the same construct improve reliability as well as validity (Waltz, Strickland

and Lenz 2010). In the critical are setting, use of multiple measures may decrease the influence of extraneous factors on the measures obtained. Although one tool (the Borg RPE) is available as a substitute measure for physiologic variables, its substantial limitations in the setting render the measure less useful than more direct measures of physiologic response.

Noticeably lacking were measures related to comfort, anxiety, mood, and sleep outcomes related to mobilization. Pain is routinely assessed in critically care settings using valid and reliable tools for patients unable to verbally indicate pain, such as the Behavioral Pain Scale (Payen et al. 2001). Two studies in this review included the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) as a delirium measure (Schweickert, Pohlman, Pohlman, Nigos, Pawlik, Esbrook, et al., 2009; Pohlman, Schweickert, Pohlman, Nigos, Pawlik, Esbrook, et al., 2010). Pohlman, et al. (2010) used the CAM-ICU to explain lack of activity progression, while Schweickert, et al. (2009) identified fewer CAM-ICU positive days with exercise. This tool has established reliability and validity in mechanically ventilated and critically ill patients, and could be considered as an important measure of cognitive response in mobilization studies. Additional measures of sleep and mood could be considered as significant physiologic outcome measures in future mobilization studies.

Measurement of some physiologic variables can be invasive, and an invasive device does not always guarantee greater precision or accuracy. The need for precision and accuracy must be balanced against the invasiveness of the measurement device. Access is another concern. Most studies of physiologic variables in the critical care setting capitalize on available monitoring, and give secondary consideration to invasiveness, precision and accuracy.

Little mention was made in the studies of procedures taken to assure accuracy and precision when measuring physiologic variables using available monitoring equipment.

Researchers must become very familiar with the proper use of biomedical instrumentation at the bedside in the critical care setting to enhance accuracy and precision. Consulting manufacturer data about methods using to determine sensitivity, specificity, error rates, and other precision data is essential if the instrumentation is to provide reliable and valid measures of physiologic data. Further, devices must be utilized in the same manner for each measure, and according to manufacturer guidelines. These are perhaps the greatest obstacles to accurate and precise measurement in the clinical setting.

Timing of physiologic measures was consistently identified as before, during, and after the exercise intervention in this review, but specific time frames beyond that were variable. Variable timing of measures renders comparisons between studies difficult. Timing of measurements can be challenging, as it may be difficult to identify the best time to capture a specific phenomenon. Many of the physiologic variables utilized were continuously displayed or multiple measures taken and averaged over time. Clearly, if physiologic variables are to be used in research studies, extensive consideration should be given to timing of those observations.

No mention was made in the studies reviewed of other physiologic variables that can be measured in the clinical setting that may be affected by passive exercise. For example, temperature can increase in response to exercise, but it was not mentioned as a variable in any of the studies. Interestingly, one of the studies reviewed mentioned control of ambient temperature as an important procedure for assuring reliability of other physiologic measures (Higuchi et al. 2006). Temperature is another physiologic measure that is readily available at the bedside in critical care setting, but is subject to the same concerns as other physiologic measures using existing biomedical instrumentation. Consideration should be given to technique (tympanic, oral,

or core measures) timing of the measurement, and precision and accuracy of the measurement device.

Mobilization study criteria often excluded participants with neurological problems, and only one study (Thelandersson, Cider & Volkmann 2010) was found that measured neurodynamic responses to passive exercise. Further study of intracranial pressure and cerebral blood flow responses to passive exercise is necessary before excluding study participants with neurologic problems. Of note is that Thelandersson, Cider and Volkmann (2010) found no change in ICP during passive exercise, and ICP significantly decreased after passive exercise, suggesting that activity may improve neurodynamic values. Muscle blood flow is known to increase during activity, yet no study to date has directly measured muscle blood flow, although one study was found that measured an analogue, that of muscle oxygen saturation, but in healthy adults (Muraki and Tsunawake 2008). Future studies may consider measurement of additional variables to better understand outcomes.

Physiologic measures were used infrequently as outcome measures in studies reviewed, unless the study outcome focused on safety. Further, in studies evaluating efficacy of passive exercise, no connection was made between physiologic variables and outcomes. It would interesting to evaluate whether patients receiving passive or progressive exercise in the critical care setting actually have improved physiologic parameters (lower resting heart rate or greater heart rate and blood pressure variability, indicating better vascular tone) in addition to looking at just functional outcome measures.

Cytokines are the only physiologic variables found in this review that can be identified as both an outcome measure and a safety measure, and only two studies identified use of cytokine levels as a physiologic variable to be evaluated in response to mobilization in critically ill adults.

Understanding of the contribution of inflammation to muscle damage is rapidly evolving. Future studies should include inflammatory biomarker measurements as they may be more accurate measures of the true physiologic response to exercise in the critically ill than the cardiopulmonary measures consistently found in this literature review.

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APPENDIX A: BLOOD SAMPLING PROTOCOL

1. Assess patency of existing arterial or venous access device prior to study start.
2. For venous access, swab port for 15 seconds with alcohol swab. Place a 10 ml syringe on the port and withdraw 2 ml for discard. Swab port again for 15 seconds with alcohol swab. Place a new 10ml syringe onto the port and withdraw 3ml blood. Swab port for 15 seconds again with alcohol swab. Flush per protocol (2-5 ml in a 10 ml syringe, depending on device). Transfer sample into a 5 ml green top tube and place on ice. Label the specimen with the de-identified participant identification code.
3. For arterial access, remove yellow cap (while turned off to the cap) and place a 3 ml syringe to stopcock. Turn the stopcock and withdraw 2 ml for discard. Return stopcock to off position. Place a new 3ml syringe over the stopcock. Turn the stopcock and withdraw 3ml blood. . Return stopcock to off position. Replace the yellow cap and flush per protocol. Transfer sample into a 5 ml green top tube and place on ice. Label the specimen with the de-identified participant identification code.
4. Once blood specimen is obtained, allow it to clot for 20 minutes, then centrifuge for 20 minutes at 4^{o}C, at 1000g. Aliquot the serum and freeze in a -80^{o}C freezer. (Specimens will be stored in a research freezer at Orlando Regional Medical Center.)
5. Serum cytokine levels will be analyzed collectively after completion of enrollment and intervention. Analysis will be conducted using ELISA in the Research Laboratory at Orlando Health Corporate Medical Education, Research and Training Center, under the direction of Dr. Ewa Jaruga-Killeen.

APPENDIX B: IRB APPROVAL

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Christina M. Amidei**

Date: **October 05, 2011**

Dear Researcher:

On October 5, 2011, the IRB approved the following human participant research until 9/27/2012 inclusive:

Type of Review:	UCF Initial Review Submission Form Full Board Review
Project Title:	An Exploratory Study of Physiologic Responses to a Passive Exercise Intervention in Mechanically-ventilated Critically Ill Adults
Investigator:	Christina M. Amidei
IRB Number:	SBE-11-07750
Funding Agency:	None

The Continuing Review Application must be submitted 30days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at https://iris.research.ucf.edu .

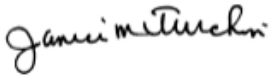
If continuing review approval is not granted before the expiration date of 9/27/2012, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

Use of the approved, stamped consent document(s) is required. The new form supersedes all previous versions, which are now invalid for further use. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Participants or their representatives must receive a signed and dated copy of the consent form(s).

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Sophia Dziegielewski, Ph.D., L.C.S.W., CF IRB Chair, this letter is signed by:

Signature applied by Janice Turchin on 10/05/2011 12:46:05 PM EDT



IRB Coordinator

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ORIGINAL

September 6, 2011

Christina Amidei MSN, RN, CNRN
12201 Research Parkway
Orlando, FL 32816

Dear Ms. Amidei:

Concerning the following Study:
Our Study # 1106407
Protocol Title: An Exploratory Study of Physiologic Responses to a Passive Exercise Intervention in Mechanically-ventilated Critically Ill Adults

In response to the contingent approval letter dated 9/1/2011, the conditions for approval have been satisfied and the following items have received Institutional Review Board (IRB) approval: the Human Research Review Application, Protocol dated 6/17/2011 and the informed consent form dated 7/1/2011 for your project stated above. Upon review of the protocol, it was determined by the Board that a Data Safety Monitoring Board will not be required by the IRB for this study; however, your responsibilities as a principal investigator still pertain as outlined on page 2 of this letter. The committee has approved this study at all Orlando Health, Inc. facilities and your office. The Institutional Review Board review process is in compliance with GCP's and included review of potential risks to subjects, risk benefit ratio, subject selection criteria and safety, content of the informed consent, confidentiality and appropriate safeguards. The project was reviewed in detail at the 9/1/2011 Institutional Review Board meeting and was approved by a majority of membership with quorum present as greater than minimal risk.

Subjects may be enrolled in your project from the date of this letter through 8/31/2012. For approval to be extended after that date, a continuing review report must be submitted to the Institutional Review Board meeting prior to the deadline date. A form for continuing review is available on the IRB website (click "For Medical Professionals") at www.orlandohealth.com. If you wish to terminate your project before the expiration date, please notify the IRB office at 321-841-5895.