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TITLE: Exploring the potential effectiveness of combining optimal nutrition with electrical stimulation to maintain muscle health in critical illness: A narrative review

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ABSTRACT

Muscle wasting occurs rapidly within days of an admission to the intensive care unit. Concomitant muscle weakness and impaired physical functioning can ensue, with lasting effects well after hospital discharge. Early physical rehabilitation is a promising intervention to minimise muscle weakness and physical dysfunction. However there is an often a delay in commencing active functional exercises (such as sitting on the edge of bed, standing and mobilizing) due to sedation, patient alertness and impaired ability to cooperate in the initial days of ICU admission. Therefore, there is high interest in being able to intervene early through non-volitional exercise strategies such as electrical muscle stimulation.

Muscle health characterized as the composite of muscle quantity as well as functional and metabolic integrity, may be potentially maintained when optimal nutrition therapy is provided in complement with early physical rehabilitation in patients with critical illness; however, the type, dosage and timing of these interventions are unclear.

This paper explores the potential role of nutrition and electrical muscle stimulation in maintaining muscle health in critical illness. Within this paper we will evaluate fundamental concepts of muscle wasting and evaluate the effects of electrical muscle stimulation as well as the effects of nutrition therapy on muscle health, and clinical and functional outcomes in critically ill patients. We will also highlight current research gaps in order to advance the field forward in this important area.

ABSTRACT WORD COUNT: 228 words / 250 words

KEYWORDS: muscle wasting, critical illness, protein intake; intensive care unit; muscle stimulation, ICU nutrition

INTRODUCTION:

There is a growing population of survivors of critical illness with almost 90% of patients surviving the initial insult of critical illness [1]. However, approximately 50% of survivors [2] may develop intensive care unit acquired weakness (ICU-AW) and suffer ongoing significant morbidity in terms of physical, cognitive and psychological health [2-5]. Intensive care unit acquired weakness refers to clinically detectable global muscle weakness which develops as a result of no specific aetiology other than being critically unwell [6]. Individuals may have evidence of myopathy, polyneuropathy and/or significant muscle atrophy. Intensive care unit-acquired weakness contributes to significant impairments in physical functioning and decreased health-related quality of life (HRQoL), which persist years after hospital discharge [2-5]. Thus, it is essential to devote attention to the quality of survivorship in terms of both clinical and physical function outcomes [7].

The World Health Organisation defines rehabilitation as "a set of measures that assist individuals who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments"[8]. Traditionally, physical rehabilitation commences once the patient is awake and able to engage with therapy. There is promising data to suggest that commencing within the first few days of an ICU admission may be critical to minimizing the plethora of impairments that can ensue [9, 10]. However, in the early stages of the ICU admission there are numerous barriers, which can mean that it is challenging to provide 'active' rehabilitation [11, 12]. We now look to technology that can be used to enable patients to exercise without the need for volitional and direct patient engagement [13]. The evidence is emerging in terms of the potential utility of assistive technologies such as bedside cycle ergometry and electrical muscle stimulation [10, 14]. Muscle stimulation in particular is an attractive intervention as it enables targeted, artificial activation and loading of individual muscles, with parameters being adapted to provide strength or endurance load to the muscle.

Muscle health can be characterized as a composite of muscle quantity (measured as muscle mass, muscle cross-sectional area etc) as well as muscle quality (physical and metabolic function of skeletal muscle)[15]. In patients with critical illness, muscle health may be supported when optimal nutrition therapy is provided in addition to early physical rehabilitation; however, the type, dosage, and timing of these interventions are unclear [16-18]. Nutrition support delivered to ICU patients forms part of routine care for the majority of ventilated patients. Marked catabolism occurs during critical illness and hence protein in particular may assist in reducing at least some of the muscle wasting experienced in the ICU setting. However, delivery of nutrition does not equate directly to utilisation of energy in critical illness. In other words, although one may be providing nutrition support to ICU patients, patients' tissues may develop resistance to sufficiently taking up nutrients from enteral or parenteral feeds to meet their energy demands. Critically ill patients demonstrate a vast heterogeneity in energy needs as well as magnitude in mitochondrial dysfunction and dysregulated lipid oxidation that unfavourably influence energy generation in skeletal muscle [19]. As such, we

need to better understand the metabolic energy demands of exercise in critically ill patients to understand its bioenergetic implications and, ultimately, reduce muscle wasting and improve functional recovery[20].

Exercise is known to improve blood flow to skeletal muscle in non-critically ill populations, which would enhance nutrient and oxygen uptake by the muscle to maintain its integrity and function. Optimal protein intake and exercise could synergistically facilitate muscle protein deposition to maintain muscle health. However, can these same concepts be applied to a critically ill patient? Can muscle health be preserved with electrical muscle stimulation in an ICU patient? Can additional protein be delivered, and used by muscle in a critically ill patient in the same manner as a healthy individual? To address these questions, we will evaluate fundamental concepts of muscle wasting and evaluate the effects of electrical muscle stimulation as well as the effects of nutrition therapy on muscle health, and clinical and functional outcomes in critically ill patients. We will also highlight current research gaps in order to advance the field forward in this important area.

MUSCLE WASTING IN CRITICAL ILLNESS:

Skeletal muscle is a highly plastic and adaptive tissue, which responds to changes in mechanical loading and is one of the largest tissue groups in the human body [21-23]. Skeletal muscle is an integral tissue in predicting clinical, physical and metabolic outcomes [17, 24-26]. To evaluate muscle health, an aggregate of measures are essential including muscle mass and its integrity (i.e. metabolic and physical features; Figure 1) [15]. Low muscle mass is reported in 20-70% of ICU patients at the time of ICU admission [25, 26], and a further ~30% reduction in quadriceps muscle mass may occur within ten days of an ICU admission [27, 28]. Remarkably, low muscle mass is also reported up to 6 and 12 months following ICU discharge [24].

Skeletal muscle atrophy is associated with morbidity, increased hospital length of stay (LOS) and mortality. Lower limb muscle mass is commonly associated with strength suggesting that reduction in muscle mass may also contribute to poorer physical performance [28-32] and these functional deficits may persist for years following ICU discharge [3] (Figure 1). Muscle atrophy has been linked to elevated tumor necrosis factor-alpha and interleukin-6 concentrations [33, 34] and these have been further associated with increased risk of infection in older adults [35, 36]. Given that skeletal muscle comprises > 75% of glucose disposal [37, 38], it is anticipated that glucose and lipid dysregulation may occur. For example, muscle atrophy as a result of acute immobility has been associated with impaired glucose tolerance [34], impaired glucose uptake [35] and reduced lipid oxidation [34]. Although most of the weight lost during critical illness is typically regained within one year following ICU discharge [39], there is evidence of sustained muscle atrophy with reduced muscle satellite cell content [40] and substantial fat gain [24] up to 6 months and 1 year, respectively, following ICU discharge. Thus, understanding the timeframe and mechanisms of muscle

atrophy will lead to developing methods that aim to preserve muscle mass and its physiological functions.

There are multifaceted factors that lead to skeletal muscle atrophy in critically ill patients including prolonged bed rest [21], catabolic signalling (including pro-inflammation and insulin resistance) [41], and undernourishment via low caloric and protein intakes [42, 43]. Insufficient caloric intake generally compromises protein intake, leading to reduced protein synthesis. Amino acids provide the substrate for protein synthesis [44], thus reduced untake may lead to reduced protein synthesis.

However, in the presence of reduced activity and insulin resistance, it is likely that critically ill patients also exhibit anabolic resistance, which is the reduced ability of the muscle to take up and use amino acids for protein synthesis [45]. To compensate for the body's high protein needs during critical illness, skeletal muscle degradation is enhanced to provide amino acids for synthesis of other proteins that may be needed for immune function, for example, resulting in muscle atrophy. On the other hand, bed rest, independent of illness, can result in muscle loss [21]. Reduced blood flow is related to reduced delivery of amino acids to skeletal muscle [46]; given the extent of bed rest combined with accelerated catabolic processes in a critically ill patient, reduced delivery of amino acids to skeletal muscle would likely contribute extensively to muscle wasting.

It is unequivocally important to assess the implications of morphological and metabolic deficits that evolve during ICU stay. Loss of muscle quality may be evidenced with infiltration of fat into skeletal muscle [47], which would likely impair muscle glucose and lipid metabolism. Muscle characteristics and architecture including pennation angle, echogenicity and fascicle length are fundamental to force production and consequently strength. During critical illness these features deteriorate [27, 28] resulting in functional and strength deficits at ICU discharge [28]. Skeletal muscle relies on proper regulation of the electrical excitability for adequate muscle contraction [48-50]. Lower activation of voltage-gated Na+ channels can reduce membrane excitability, which leads to attenuated muscle contraction and conseuqently muscle weakness [51]. This acute neuropathy is reported to be reversible – not degenerative – and may be related to electrolyte abnormalities during critical illness [48, 49]. While this neuropathic mechanism may be acute, the consequential muscle atrophy that results may be longer-term. Targeted rehabilitative approaches that require muscle contraction to preserve muscle mass or recovery from muscle atrophy would be essential to regaining proper neural processes in rehabilitation of muscle strength. However, given the unstable condition of many critically ill patients, we need to consider a continuum of exercise interventions that may begin with cost-effective and feasible strategies where participation is non-volitional in nature and then progresses to functional activities that require voluntary contraction as patient alertness and ability to engage improves.

PRINCIPLES OF ELECTRICAL MUSCLE STIMULATION:

The quadriceps muscle is the largest muscle group in the human body and integral to performance of activities such as standing from a chair, stair climbing and locomotion. Given its size and its importance in weight-bearing activities, it is the most widely examined muscle within the muscle stimulation literature.

An individual muscle consists of hundreds to thousands of fibres, which are arranged into functional groups called motor units. The motor unit is the final common pathway in motor processing, which would result in a physical action [52, 53]. Small motor units have small diameter axons and typically innervate 'slow twitch' (Type I) muscle fibres, which are largely fatigue resistant. Large motor units have large diameter axons and typically innervate 'fast twitch' (Type II) muscle fibres, which are less fatigue resistant but enable greater force production to be generated quickly [52, 54]. Physiologically, during volitional contraction muscle recruitment is asynchronous and is thought to follow the Hennemann's size principle with smaller units (i.e. slow twitch, fatigue resistant fibres) recruited first and as more force is needed, larger units are recruited [23]. The mechanism of recruitment with electrical muscle stimulation remains contentious.

Artificial muscle activation aims to preserve muscle mass and/or recover/improve muscle function [54, 55]. Skeletal muscle can be artificially stimulated to induce a visible and palpable muscle contraction in the absence of volitional control using two different methodologies:

1) Neuromuscular electrical stimulation (NMES), which often involves stimulation of isolated muscle groups in a non-functional manner (i.e. stimulated in supine) [55]

2) Functional electrical stimulation (FES), which generally involves stimulation of multiple muscle groups whilst undertaking a combined functional activity such as bedside cycling [55, 56] (Figure 2). The muscles are artificially stimulated to contract at the point in range at which volitional activation would occur during the functional activity. For example, during knee extension whilst cycling the quadriceps muscle would be stimulated to contract and on knee flexion the hamstrings would be activated. This alternating muscle recruitment potentially may enable longer time for contraction to be sustained prior to reaching a point of fatigue [57]

With both NMES and FES, there are a range of parameters, which can be adapted to achieve muscle contraction [14]. Table 1 provides an overview of these parameters. Sufficient quadriceps tension may be achieved with frequencies of 5-100 Hz and a pulse width of 100-400 usecs [55]. With lower pulse width there is preferential activation of sensory fibres, which can result in higher levels of

sensory discomfort for the patient. There is a direct inverse relationship between pulse width and amplitude. Higher amplitudes are required when using a lower pulse width in order to evoke muscle contraction. With higher tissue impedance, as can occur with presence of oedema and adipose tissue, longer pulse widths may be required. The size and location of surface electrodes can influence the efficacy of muscle stimulation. Ideally electrodes should be placed close to the motor point of a muscle – which is the point at which the motor units are most superficial to the skin surface.

ELECTRICAL MUSCLE STIMULATION IN THE ICU – WHAT DO WE KNOW?

There are a number of systematic and narrative reviews published in the last ten years on the topic of electrical muscle stimulation within the ICU setting [13, 14, 58, 59] in relation to muscle health.

During the writing of this paper we conducted a literature search and identified at least 23 papers, which have been published within the ICU literature specifically evaluating the safety, feasibility and/or efficacy of muscle stimulation (NMES or FES) since 1987 (Table 2). More than half of the literature (52%, n=12/23) has been published since 2015 highlighting the rapid and emerging interest in this area. While the majority of the research has been conducted in Europe (61%, n=13/23), publications from South America (n=3/23), Asia (n=3/23), North America (n=1/23) and Australia (n=1/23) are also evident.

Whilst the quadriceps muscle is the most widely evaluated muscle group, there was one study which reported on the preservation of muscle mass for pectoralis major and rectus abdominus muscles after NMES as well as reduced ICU LOS [60]. There is significant heterogeneity within the studies in terms of stimulation parameters, intervention duration and timing of delivery relative to time in the ICU (Table 2). The evidence is currently inconclusive in terms of providing definitive guidance on the efficacy of muscle stimulation within the ICU setting. In the studies, which reported the time to first intervention session, the majority commenced within the first five days of the admission period (65%, n=15/23) (Table 2). There is conflicting evidence for the preservation of muscle mass using NMES particularly in individuals with higher severity of illness [60-64]. Muscle biopsy data in one study demonstrated absence of atrophy of Type I and II muscle fibres [65]. Data suggesting a potential for accelerated gains in strength and physical function have been reported at the time of ICU and hospital discharge [66, 67]. However, there is limited evaluation of the potential longer-term benefits of muscle stimulation beyond hospital discharge, which is an important area for further evaluation.

Functional electrical stimulation literature first emerged in 2015 with a pilot case control FES cycling study in the ICU that primarily focused on determining the safety and feasibility of early intervention (i.e. within a couple of days of ICU admission) [56]. The study demonstrated safety, and feasibility with one transient adverse event (desaturation) and delivery of three-quarters of potential intervention sessions [56]. There was trend towards faster recovery of functional milestones and

reduced delirium and reduced need for rehabilitation post-hospital discharge [56]. Medrinal and colleagues [68] explored the impact of four different assistive rehabilitation strategies (passive range of motion exercises with therapist; NMES, cycle ergometry and FES) on cardiorespiratory response to exercise. The study demonstrated that FES cycling was the main intervention, which increased cardiac output and produced sufficient intensity of muscle work. However a recent study, which combined NMES and cycling, reported no difference in outcomes in terms of muscle strength and ventilator free days or HRQoL at six months [69].

Beyond the heterogeneity in muscle stimulation parameters, training duration and timing to intervene there are also potential confounding factors unique to the ICU population, which may contribute to the conflicting evidence regarding the efficacy of muscle stimulation. Tissue impedance will impact on the intensity and delivery of current flow towards the underlying motor units [54, 55, 70]. Increased oedema and high adipose tissue – two factors, which can be present in ICU patients, will negatively affect the ability to deliver the intended stimulation intensity. In these circumstances a higher pulse width and/or intensity will be required in order to induce a muscle contraction. However, this often results in poorer tolerance due to increased discomfort with sensory evoked pain. There is emerging interest in the role of thermally enhanced muscle stimulation, which may assist with some of the issues around oedema and sensory discomfort, while optimizing stimulation parameters [71]. Importantly, given that optimal muscle health may be achieved with combined muscle contraction and enhanced nutritional deliver, there is a need to investigate the potential synergism between NMES and optimized nutrition intervention in future research.

Although there are several merits to the use of EMS, various issues need to be addressed, which include:

- Developing optimal stimulation parameters (intensity, pulse width, frequency) without compromising muscle force production due to fatigability
- Identifying those who respond vs those who do not respond to muscle stimulation; does this modality work for all patients?
- Developing an objective means of quantifying the quality of muscle contraction
- Understanding the longer-term impact of muscle stimulation on patient-oriented outcomes
- Further evaluate the safety and feasibility of muscle stimulation

IS THERE A ROLE FOR PROTEIN TO IMPROVE MUSCLE HEALTH?

Protein delivery is considered vital for muscle maintenance in both health and disease. As critical care management shifts to focus on strategies to maintain muscle mass and function, attention has been placed on the role of protein in maintaining muscle health in this population [72]. Accordingly,

several narrative reviews advocate increased protein delivery to critically ill patients [73-76], most notably that by Hoffer and Bistrian that strongly suggested providing 2-2.5g/kg/d is safe, and could be optimal, during critical illness [77]. Delivery of greater protein doses are also recommended in a number of international guidelines: the 2016 update of the American Society for Parenteral and Enteral Nutrition critical care nutrition guidelines recommend delivery of protein doses of 1.2-2.0 g/kg/day or higher [78]; and the European Society of Parenteral and Enteral Nutrition Parenteral Nutrition Guidelines for Critical Care recommend providing 1.3-1.5g protein/kg/day [79]. These recommendations are however based on very low quality of evidence.

Early physiological studies show nitrogen balance is negative during states of inflammation [80]. More recently, stable isotope-labelled amino acid tracer techniques have been used to provide an estimate of protein metabolism (synthesis, breakdown, and oxidation) at the whole-body level. Rooyackers used this technique to demonstrate that critically ill patients with multi-organ failure have an increase in both protein synthesis and breakdown [81]. Further work from Sweden has shown that the addition of parenteral or enteral nutrition results in an overall small improvement in whole-body protein balance. While nutrient provision appears to stimulate protein breakdown, it also stimulates protein synthesis to a greater degree, resulting in an overall positive protein balance [82-84]. However, these studies only measure incorporation of labelled amino acids into the plasma, and hence it is unknown whether additional amino acids are delivered, taken up and utilised by the muscle during critical illness. An expert review published in 2017 thoroughly discusses the complexity of protein kinetics in critical illness, demonstrating that a greater understanding of the physiological response to protein supplementation during different clinical conditions is required [85].

A number of observational studies show an association between greater protein delivery and improved clinical outcomes, including mortality and time to discharge from ICU alive [86-88]. However, few studies have shown a relationship between protein delivery and muscle health. Puthucheary et al conducted an observational study in 63 critically ill adults and reported an association between *greater* protein delivery and *increased* loss in ultrasound-derived quadriceps muscle [27]. Two RCTs of differing protein doses have been conducted thus far, which both were single-centered and evaluated the effect of protein dose on ultrasound-derived muscle size. The first by Ferrie et al, used parenteral nutrition to deliver augmented protein (1.1 g/kg/day) compared to standard care (0.9 g/kg/day) in 119 critically ill adults. Greater protein was associated with an increased forearm muscle thickness, with no difference in measures of strength [89]. Another Australian group showed that greater enterally-delivered protein to 60 critically ill patients was associated with attenuation of quadricep muscle loss at ICU discharge [90]. It is important to consider that there is much to be learned by the distinct study designs used in these studies that may have led to discrepant results. Future work exploring protein intervention on specific muscle

outcomes is necessary to better understand the role of protein delivery during critical illness (Figure 3).

There is also work being conducted on other nutrition strategies that may influence muscle health during critical illness. Bear et al are exploring the role of intermittent versus continuous enteral nutrition in critical illness on ultrasound-derived rectus femoris cross-sectional area for which results are expected this year (ClinicalTrials.gov NCT02358512). This same group is exploring the role of beta-hydroxy-beta-methylbutyrate (HMB), a derivative of leucine, on the same outcome (ClinicalTrials.gov NCT03464708). While physiological studies demonstrate improved protein balance with nutrition support during critical illness, and pilot studies show potential attenuation of muscle wasting with protein delivery, it is unknown whether nutrition therapy alone is able to reduce the significant muscle atrophy that occurs during critical illness, particularly early after injury where protein catabolism is at its greatest [91]. It also needs to be considered whether early physical rehabilitation during critical illness places a subsequent demand on increased nutrient availability to facilitate muscle synthesis. Therefore, it is thought that the combination of nutrition support and exercise therapy during critical illness may provide the greatest benefit on muscle attenuation and functional recovery.

HOW COULD WE COMBINE EXERCISE AND PROTEIN FOR BEST PATIENT OUTCOMES?

In health, the combination of exercise and amino acid delivery has been shown to enhance the capacity of the skeletal muscle to promote protein synthesis [92]. In non-ICU studies, combining protein and exercise demonstrate far greater benefits in terms of muscle mass, strength and physical functioning compared to either therapy on their own [92, 93]. Pennings et al showed low-intensity cycling and resistance-type tasks prior to amino acid consumption increased muscle protein synthesis rates when compared to rest [94]. Similarly, Biolo et al showed amino acid transport after exercise is 30-100% greater than following rest [95], and this may be related to exercise-induced nutrient-stimulated vasodilation [96]. Bed rest studies demonstrate the benefit of multimodal interventions. Trappe et al conducted a three-arm study in 24 healthy women in which during 60 days of bed rest participants underwent bed rest only, bed rest plus exercise regime, or bed rest plus a leucine-enhanced high protein diet to 1.6g/kg/day. Exercise therapy, which included a combination of aerobic and resistance exercises, was shown to have a positive impact on muscle attenuation, whilst it was reported that the greatest muscle loss occurred in those patients receiving the high protein diet [97].

In critical illness, despite the coupling of protein and exercise being identified as a key priority area during the International Summit of Critical Care experts [98], there are few studies, observational or

controlled interventions, that report data on both physical function and nutritional intake. In a poster abstract, Wappel and colleagues presented a sub-analysis of a pilot study that compared exercise alone, with an exercise-nutrition intervention that also included NMES on the outcome of cross-sectional area of the quadriceps [99]. While not powered to show an effect, the group receiving NMES and nutrition support had a two-fold reduction in loss of muscle CSA. In addition, there are two registered trials currently recruiting that combine exercise and nutrition interventions; (1) NEXIS (ClinicalTrials.org NCT03021902) combining cycle ergometry and amino acid supplementation versus standard care, and (2) ExPrEs (ClinicalTrials.org NCT02509520) combining NMES and leucine supplementation in elderly ICU patients.

In designing studies that provide both exercise and nutrition early in critical illness there are a number of factors that need to be carefully considered:

1. **The route of nutrition support is important.** We know that in critical illness, delayed gastric motility [100] and impaired nutrient absorption of both fat [101] and carbohydrate [102], affect nutrient uptake from enterally delivered nutrition. Whether enterally-delivered protein can be adequately absorbed and incorporated into muscle during critical illness is yet to be determined (ANZCTR Trials Registration; ACTRN12616001652460). While enteral nutrition may be the preferred, and commonly used, route when compared with parenteral nutrition, it is important to consider how much of the nutrition delivered is available for muscle uptake. In the elderly, post-prandial splanchnic extraction (uptake of amino acids for the splanchnic organs) is increased, reducing the availability of amino acids for muscle synthesis [103, 104]. Whether an exacerbation of splanchnic sequestration during critical illness occurs requires quantification.

2. **The duration of intervention should be contemplated.** The majority of large randomized controlled trials of nutrition interventions during critical illness are delivered for a short period of time, early in the ICU admission only. This is despite studies reporting reduced nutritional intake in survivors of critical illness [105, 106], which is likely to influence functional recovery.

3. **Timing of both nutrient and exercise therapy should be considered.** In critical illness, it is common practice to provide nutrition continuously, while exercise interventions are likely to be administered at set timepoints. As discussed by Bear and colleagues in their review on

the pros and cons of feeding modalities, there may be cause to believe that bolus or intermittent delivery of enteral nutrition will have a greater influence on muscle protein synthesis [107]. Based on this premise, the effect of intermittent versus continuous enteral nutrition on ultrasound-derived muscle wasting is being explored (ClinicalTrials.gov NCT02358512). Timing relative to the exercise (i.e. pre- vs post-exercise nutrition) may also have implications on the extent of protein synthesis and degradation [17, 94].

4. **Bioenergetics of critically ill patients need to be comprehensively investigated.** We need to understand the bioenergetics and physiological ability of the muscle to respond to muscle stimulation particularly in high severity of illness where there may be compromised muscle membrane function and mitochondrial dysfunction [20]. The metabolic demands of exercise are poorly understood within the ICU setting [20]. Pilot data demonstrates that energy requirements are likely to be higher in individuals with critical illness compared to the healthy population[108]. We postulate that energy demands will be lower with muscle stimulation compared to use of technology such as cycle ergometry or functional rehabilitation but this needs to be explored. We also need to better understand whether amino acid uptake and protein turnover maintain their capacity during critical illness to preserve muscle integrity.

5. **The patient population needs to be clearly defined.** ICU studies are prone to including all-comers. However, it is important to recognise that the response to nutrition and exercise interventions are likely to be influenced by a number of patient characteristics, including sarcopenia, age, comorbidities, and obesity. Recent work has also proposed that genetic predisposition may predict the extent of muscle wasting [109]. Therefore consideration and categorization of the patient population is vital.

CONCLUSION: Muscle dysfunction is common for survivors of critical illness and remains a significant issue, and may influence strength and physical performance. Current research suggests early intervention within the first few days may be the critical window in which to improve strength and functional recovery outcomes. However, our understanding of the physiological changes that occur in muscle during critical illness needs to be further explored. This work would inform the potential effectiveness of combining optimal protein nutrition with electrical stimulation. To preserve muscle health and potentially improve clinical and patient-oriented outcomes, there is a continual and significant need to understand the mechanistic effects of combined therapies in conjunction with consideration of the dosage, timing and delivery methods.

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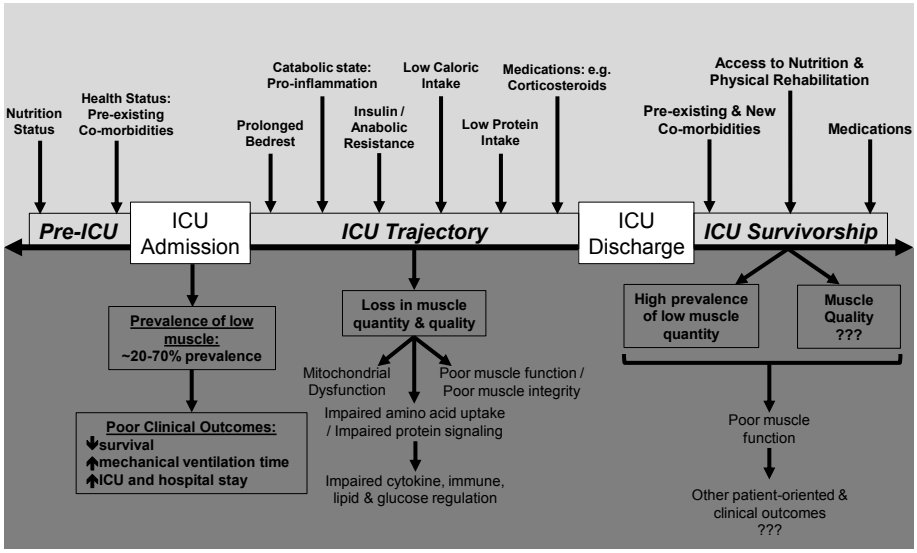
Figure 1. Factors affecting muscle health in pre-ICU, ICU trajectory and ICU survivorship. Abbreviations: EMS = Electrical Muscle Stimulation; ICU = Intensive Care Unit.

Figure 1. Factors affecting muscle health in pre-ICU, ICU trajectory and ICU survivorship.



Abbreviations: EMS = Electrical Muscle Stimulation; ICU = Intensive Care Unit.

Fig. 2 FES-cycling machine (RT-300 supine model and SAGE stimulator; Restorative Therapies, Ltd, Baltimore, MD). Reprinted from J Crit Care, 29(4), Parry SM et al, Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study, pp695.e1-7, 2014, with permission from Elsevier.

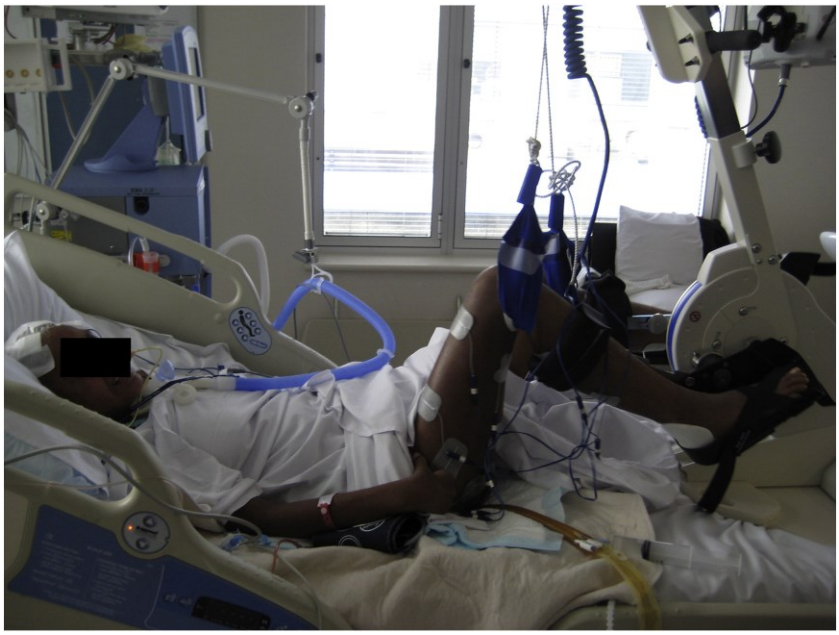
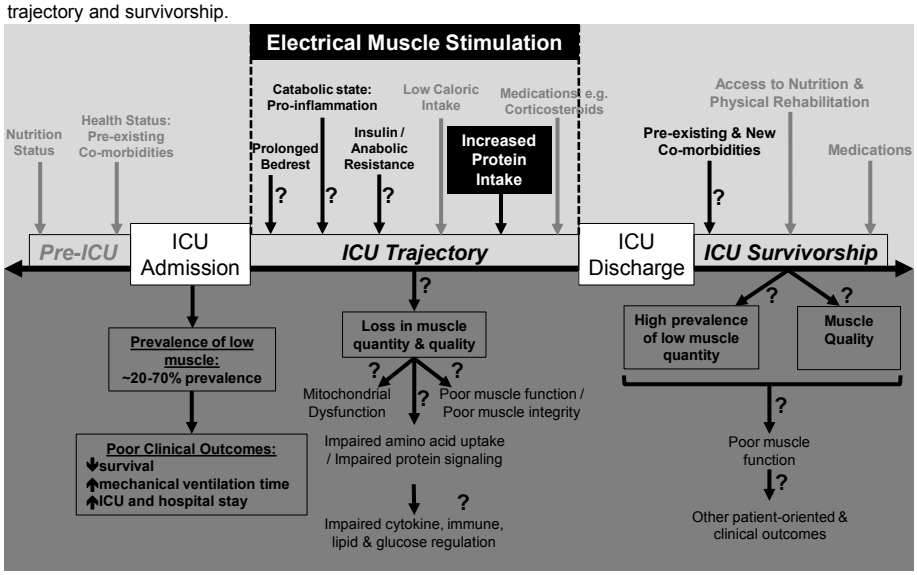


Figure 3. Potential effects of combined EMS and increased protein intake on muscle health during the ICU trajectory and survivorship. Abbreviations: EMS = Electrical Muscle Stimulation; ICU = Intensive Care Unit. Note: Text in light gray indicates factors that are likely to be unaffected by EMS.

Figure 3. Potential effects of combined EMS and increased protein intake on muscle health during the ICU trajectory and survivorship.



Abbreviations: EMS = Electrical Muscle Stimulation; ICU = Intensive Care Unit.
Note: Text in light gray indicates factors that are likely to be unaffected by EMS.

Table 1: Parameters of relevance in muscle stimulation [14]

Parameter	Description
Amplitude (intensity)	Quantity of energy flowing per second measured in milliamplitude (mA)
Pulse width (duration)	Duration of electrical impulse measured in microseconds (usecs)
Frequency	Number of electrical impulses per second (Hertz); affected by twitch summation phenomenon, commonly frequency is set between 35-50 Hz. With higher frequencies > 100 Hz tetany of the muscle will occur and there is risk of faster fatigability.
Ramp up	Current intensity will increase (ramp up) to a preset maximum over a defined period of time
Ramp down	Current intensity will decrease (ramp down) to a preset minimum over a defined period of time
On:Off duration	Length of time over which each individual electrical impulse is delivered versus no stimulation can be preset with some muscle stimulators. For example an On:Off duration of 5:1 means that the electrical impulse is delivered for 5 seconds and off for one second.

Table 2: Summary of studies examining electrical muscle stimulation in intensive care

Author Year, Location	N	Population	Time to first session	Muscles stimulated	EMS parameters	Main Findings
Neuromuscular Electrical Stimulation						
Bouletreau 1987, France [110]	10	Hospitalized for at least 8 days in the ICU	8 or 12 days (depending on allocation)	Gastroc Quads	*Patient Position* Not specified *Stimulation Parameters* 0-120 V, 1.75 Hz, 3000 usecs On: Off Time 5:5 secs *Training Parameters* 30 mins 2x day for 4 days	Significant reduction in excretion of 3MH in NMES
Gerovasili 2009 [111], Routsi 2010 [61], Karatzanos 2012 [112]Greece	52	ICU patients with APACHE II > 13 stratified based on age and gender	2 days	Quads peroneus longus	*Patient Position* Not specified *Stimulation Parameters* Mean mA for quads 38 (10) and 37 (11) mA for peroneus longus	Preservation of RF and VI muscle thickness observed in NMES group (RF: -8%; VI: -13%) vs control (RF: -14%; VI:-22%) [111] No significant absolute or

					45 Hz, 400 usecs On/Off Time: 12 secs/6 secs Ramp time: 0.8 secs *Training Parameters* 55 mins per day until ICU DC	relative differences in handgrip strength [112] Higher MRC scores and less ICU-AW with NMES group [61, 112]
Meesen 2010, Belgium [113]	19	Hospitalised in ICU with MV > 1 day	Unclear	Quads	*Patient Position* Supine with half roll under knee (to enable knee flexion) *Stimulation Parameters* 0-5 mins: 35-85 mA, 5Hz, 250 usecs; Stimulation intensity (mA) gradually increased in 2-10 mA steps proportional to	Reduced thigh circumference loss in NMES vs control limb

					stimulation intensity in warm up trial 5-11 mins: 60 Hz, 330 usecs 11-19 mins: 100 Hz, 250 usecs 19-25 mins: 80 Hz, 300 usecs 25-30 mins: 2 Hz, 250 usecs On/Off Time: 90: 30 secs (5 mins); 10: 20 secs (6 mins); 10: 20 secs (8 mins); 7:14 secs (6 mins); 90: 30 secs (5mins) *Training Parameters* Daily 30 mins session as long as intubated/sedated (NMES – right leg; sham – left leg)	
Gruther 2010, Austria	16	Short (< 7 days) and long term ICU patients (>	ST Group 3(2) days;	Quads	*Patient Position*	Significant increase in quadriceps muscle

[62]		14 days)	LT group 33 (15) days		Not specified *Stimulation Parameters* Max tolerated – mA not specified 50 Hz, 350 usecs On/Off Time: 8 secs/24 secs *Training Parameters* 30 mins / day in Week 1 60 mins/day in Week 2-Week 4 5 sessions per week for 4 weeks	thickness (+4.9%) vs sham (-3.2%) for long term group. Significant loss of quadriceps muscle thickness in both the short term NMES and sham groups (~37-39%).
Rodriguez 2012, Argentina [63]	14	ICU patients with sepsis	2 [1-2] days	Biceps Quads	*Patient Position* Not specified *Stimulation Parameters* 100 Hz, 300 usecs On/Off Time: 2 secs: 4 secs	No change in biceps thickness or circumference with NMES Higher MRC scores for biceps and quadriceps with NMES

					Training Parameters 30 mins 2x day continued until successful extubation	
Poulsen 2011, Denmark [64]	8	ICU patients with septic shock	NR; baseline measures assessed 26 [16-52 hrs]	Quads	*Patient Position* Not specified *Stimulation Parameters* 31 (23-48) mA for VM and 42 (37-54) mA for VL 35 Hz, 300 usecs On/Off Time: 4 secs:6 secs Ramp time: 0.5 secs *Training Parameters* 60 mins daily for one week	No preservation of quadriceps muscle volume observed with NMES. Both group had significant reduction within one week (NMES 20%; Control 16%).

Angelopoulos 2013, Greece [114]	31	Acute Group: presence of SIRS criteria or diagnosis of sepsis for 3-5 days at time of session ICUAW Group: individuals who had confirmed ICUAW using MRC-SS	Unclear	Quads Peroneus Longus	*Patient Position* Not reported *Stimulation Parameters* <u>High Frequency Protocol</u> 57-87 mA; 75 Hz, 400 usecs On/Off Time: 5 secs / 21 secs Ramp time: 1.5 secs up / 0.8 down <u>Medium Frequency Protocol</u> 45 Hz, 400 usecs On/Off Time: 5 secs / 12 secs Ramp time: 1.5 secs up / 0.8 down *Training Parameters* 30 mins (with additional 5 min warm up and 5 min recovery phase using 10 Hz current of 400	Both medium and high frequency stimulation induced microcirculatory changes to skeletal muscle

					usecs), single session (pre/post evaluation)	
Hirose 2013, Japan [115]	25	Coma within first 24 hrs of hospitalization; first time stroke or TBI injury; 16-75 years of age with paralysis of both or one limb	> 7 days after admission	Quads Tib ant Hamstrings Gastroc	*Patient position* Not specified *Stimulation Parameters* 40 mA, Hz and usecs not specified On:Off Time – 10:10 secs *Training Parameters* 30 mins daily starting 7 days after admission (3 mins warm up; 25 mins training; 2 mins cool down) Ceased after 14 days	Preservation of leg muscle mass observed with CT in EMS group (compared to control)
Flavigna 2014, Brazil[116]	11	Adult ICU patients MV for up to 48 hours		Quads Tib Anterior	*Patient Position* Not specified1 *Stimulation Parameters* 18-60 mA, 50 Hz,	Goniometry measurement of ankle dorsiflexion range was higher in the EMS limb compared to control

					400 usecs On: Off time – 9: 9 secs On time consisted of: 2 secs rise time, 5 secs of contraction, 2 secs fall time *Training Parameters* 20 mins / daily until patient attained Grade 4 strength for muscle stimulated	No significant difference in MRC scores for muscle strength No significant difference in circumference measures except at 10cm distance for the thigh - lower scores in control group
Segers 2014, Belgium [117]	50	SICU/MICU patients enrolled on Day 3-5 of admission whom had an expected prolonged LOS for at least 3 more days	Day 3	Quads	*Patient Position* Supine, head up 30° Legs in neutral – solid knee support roll placed under knees to achieve approx. 15° hip flex & 30° knee flex *Stimulation Parameters* 0-80 mA, 50 Hz, 300-500 usecs	Non responders (unable to elicit muscle contraction) were more likely to have sepsis, oedema and receipt of vasopressors Inverse r/ship between oedema quantity and type of muscle contraction Could not predict

					Series time 8 secs, Series pause 20 secs Ramp time 2 secs *Training Parameters* 5 times per week (Mon-Fri) 25 mins/day until ICU DC (5-min warm up)	adequate contraction using NCS or EMG With 50% of sessions erythema evident under the electrodes – but disappeared immediately post. No significant cardiovascular or respiratory response changes with NMES
Dirks 2015, Netherlands [65]	9	Expected sedation time of > 3 days and admitted to the ICU	<4.5 days	Quads	*Patient Position* Not specified *Stimulation Parameters* Intensity set to level at which full contractions were visible & palpable, intensity □ every 3 mins Averaged 29.9 mA in first session and progressively increased to 32.3 mA in final	NMES leg showed no atrophy in Type I or II muscle fibres compared to control leg which had a significant decline of 16(9)% and 24(7%) in type I and II muscle fibre CSA.

					session Warm up 5 mins (5 Hz, 250 usecs) Stimulation period (30 mins 100 Hz, 400 usecs, 5 s on (0.75 s rise, 3.5 s contraction, 0.75 s fall) and 10 s off Cool down 5 mins (5 Hz, 250 usecs) *Training Parameters* 2 sessions per day over period of 3-10 days (NMES leg and control leg)	
Akar 2015, Turkey [118]	30	Diagnosis of COPD and respiratory failure Rx with IMV without comorbidities	Unspecified	Deltoid quads	*Patient Position* Not specified *Stimulation Parameters* 20 mA-25 mA, 50 Hz, pulse width not reported, 6 s duration, 1.5 s increase and 0.75 s	NMES and NMES+exercise groups had significant improvements in lower extremity strength whilst upper limb strength increased across all groups No difference for weaning time or

					decrease *Training Parameters* 5 times per week for a total of 20 sessions duration not specified	functional milestones
Kho 2015, USA [66]	34	Adult ICU patients MV>24 hrs and expected to require >2 days more in the ICU	4.6 (1.8) days	Quads Tib Ant Gastroc	*Patient Position* Not specified *Stimulation Parameters* Ramp up/down: 2 s: <1s, 50 Hz Quads: 400 usecs, On:Off Time – 5s:10s Tib Ant/Gastroc: 250 usecs; On:Off Time – 5 s: 5 s (alternating recruitment of Tib Ant and Gastroc) *Training Parameters* 60 mins per day (either single or 2x 30 mins sessions)	63% (n=146/230) sessions completed No significant difference in leg muscle strength at hospital discharge (however studies discontinued before reaching a priori sample size) Patients receiving NMES had larger increase in leg strength between ICU awakening and ICU discharge, and between ICU awakening and hospital discharge. NMES group walked more than 2 times further at

					9.1 (8.7) days of NMES delivered	hospital discharge compared to control group
Fischer 2016, Austria [67]	54	Adult ICU patients undergoing cardiothoracic surgery and expected to remain in ICU>48 hrs	Day 1	Quads	*Patient position* Not specified *Stimulation Parameters* Median NMES intensities was 40-40.5 mA range [2-120] mA 0.4 ms, 66 Hz On:Off Time – 3.5s: 4.5s Ramp up down: 0.5 s *Training Parameters* 2x30 mins, 7 days a week during entire ICU stay (but not more than 14 days)	94% sessions delivered (n=136/145) NMES no significant effect on MLT quadriceps ; NMES group regained strength 4.5 times faster than patients in control group
Dall'Acqua 2017, Brazil [60]	25	Adults hospitalized for no longer than 15 days and > 24 hrs of	<48hrs of IMV	Pec Major Rectus abdominas	*Patient Position* Supine *Stimulation*	No complications or significant changes in vital signs

		invasive MV			*Parameters* Pec Major: 53 (15) mA Rec Abdominas: 68 (18) mA 50 Hz, 300 usecs ramp up down - 1 s On:Off Time – 3 s: 10 s *Training Parameters* NMES 30 mins daily, ceased on Day 7 or when patient extubated or if deceased (whichever occurred first)	Significant difference with NMES in terms of muscle thickness and shorter ICU LOS Preservation of muscle mass in NMES group (compared to control group where significant decrease in muscle mass across time)
Patsaki 2017, Greece [119]	128	ICU patients MV > 72 hrs and level of consciousness adequate to respond to at least 3 of 5 commands	ICU discharge	Quads Peroneus Longus	*Patient Position* Not specified *Stimulation Parameters*	No difference in MRC scores, handgrip strength, functional status and hospital LOS between NMES and control groups

		Stratified based on age and diagnosis of ICU-AW (MRC sum score ≤ 48 or > 48)			45 Hz, 400 usecs On:Off time – 12 s: 6s Rise / Fall time – 0.8s: 0.8s *Training Parameters* 55 mins daily 7 days/week until hospital discharge	In patients with ICU-AW the NMES group had significantly higher MRC scores at two weeks compared to control
Shen 2017, Taiwan	25	ICU patients MV > 72 hrs	Enrolled on ICU Day 3	Biceps Quadriceps	*Patient position* Not specified *Stimulation Parameters* 0-75 mA, 15000 Hz, pulse width NR *Training Parameters* 32 mins daily 5 days per week	68% of patients unable to complete handgrip strength No significant difference in handgrip strength and MV time between groups
Silva 2017, Brazil [120]	11	Adult APACHE II score > 13, MV 24-48hrs with prediction	ICU Day 1	Glut Max Gastroc	56 (15) mA for Glut Max 55 (13) mA Quads	<u>Feasibility and Safety:</u> N=83 (85%) of

	to remain MV for at least 3 days by senior ICU physician on admission	Tib Ant Hamstrings Quads	52 (13) mA hamstrings 57 (13) mA tib ant 57 (11) mA Gastroc During the three days pulse width 550 (170) usecs Glut Max 450 (150) hamstrings 500 (200) usecs quads 550 (150) usecs tib ant 450 (150) usecs gastroc Daily for 3 days Once a day for 15 mins (90 contractions) pulse width equal to chronaxie, 100 Hz ON:OFF time – 5s:5s No rise time or decay No warm up or	sessions completed N=99 (100%) of sessions a visible contraction present No skin burns Set up time: 107 (24) mins <u>Other:</u> NS change in CPK levels

					cool down period 3 times total of 45 minuntes	
Woo 2017, Korea [121]	10	Patients aged 20 years or older admitted to ICU and required MV for at least 24 hrs	Unclear	Quads	*Patient Position* Supine knee extended *Stimulation Parameters* Lowest intensity with visible muscle contraction 35 Hz, 250 secs ON:Off time – 10s: 12 s *Training Parameters* Cycling provided prior and separately to isolated muscle stimulation. 10 mins rest prior to NMES which was applied for 20 mins on left thigh. Single session	No difference in circumference and quads CSA between legs (no additive benefit of NMES with cycling)

Functional Electrical Stimulation						
Parry 2015, Australia [56]	16	Adults admitted with a diagnosis of sepsis or severe sepsis & predicted to be MV>48 hrs and remain in ICU>4 days	Median of 15.3 [12-31.5] hrs between recruit to first Rx	Quads Hamstrings Gluteals Gastroc	*Patient Position* Supine head up 30° *Stimulation Parameters* 0-140 mA, 300-400 usecs, 30-50Hz *Training Parameters* 20-60 mins/day, 5x week until ICU discharge	73% of sessions delivered. One transient episode of desaturation – nil other safety events. Trend towards earlier and faster recovery of functional milestones in intervention group compared to control Fewer individuals required inpatient rehabilitation in the intervention group (43%) vs control (86%). Lower frequency of delirium vs control (25:87%) although not significant. Duration of delirium was significantly shorter in intervention group (0 [0-3] days) vs control (6 [3.3-

						13.3])
Medrinal 2018, France [68]	19	Patients > 18 years MV at least 24 hrs and ventilated with pressure support	Unclear	Quadriceps	*Patient Position* During FES cycling NMES synchronized with knee extension, otherwise supine *Stimulation Parameters* Stimulation intensity aimed to obtain a palpable contraction 300 usecs, 35 Hz no ramp time *Training Parameters* 4 Consecutive 10 min sessions of bed exercise (10 mins PROM, 10 mins NMES, 10 mins cycle ergometry, 10 mins FES-cycling), order of intervention/s randomised. 30 mins rest between each intervention.	<u>Safety:</u> Only FES cycling increased CO and produced sufficient intensity of muscle work Increase in CO by 1L/min after 9 mins of FES cycling No change in CO over time with NMES Significant increase in HR, TAPSE and MAP during FES cycling. FES cycling increased CO and physiological cardiorespiratory response and reduced muscle HbO2

				Single session.	
Fossat 2018, France [69]	Patients > 18 years, admitted to ICU < 72 hrs prior to randomisation and expected to need another 48 hrs in the ICU, independent mobility	31 [19-46] hrs	Quads	*Patient Position* Supine *Stimulation Parameters* Based on Routsi [61] *Training Parameters* 15 mins cycling + 50 mins NMES 5 days/week until ICU discharge	Safety – 1 skin allergy to electrode pads for NMES No difference in combined cycling+NMES in addition to usual care in terms of global muscle strength t ICU discharge No significant difference in ventilator free days or self reported HRQoL at 6 months

***Abbreviations**: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CSA, cross sectional area; FES, functional electrical stimulation; Gastroc, Gastrocnemius; HR, heart rate; hrs, hours; HRQoL, health related quality of life; Hz, hertz; ICU, intensive care unit; ICU-AW, intensive care unit-acquired weakness; ICU DC, ICU discharge; IMV, invasive mechanical ventilation; LOS, length of stay; LT, long term; mA, milliamplitude; MAP, mean arterial pressure; mins, minutes; MRC, Medical Research Council; MV, mechanical ventilation; NMES, neuromuscular electrical stimulation; n, number; NR, not reported; NS, not significant; Pec Major, pectoralis major; RF, rectus femoris; Rx, treatment; ST, short term; Tib Ant, tibialis anterior; TBI, traumatic brain injury; Quads, Quadriceps; V, voltage;*

VI, vastus intermedius; usecs, microseconds; 3-MH, 3-methylhistidine; %, percentage; >, greater than; <, less than.