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TOPICAL REVIEWS

Structure to function: muscle failure in critically ill patients

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Impaired physical function and reduced physical activity are common findings in intensive care unit (ICU) survivors. More importantly, reduced muscle strength during critical illness is an independent predictor of survival. Skeletal muscle wasting as a direct consequence of critical illness has been suggested as the cause. However, data on the physiological processes regulating muscle mass, and function, in these critically ill patients are limited as this is not only a technically challenging research area, but also the heterogeneity of the patient group adds complexity to the interpretation of results. Despite this, clinical and research interest in this area is growing. This article highlights the issues involved in measurement of muscle function and mass in critically ill patients and the physiological complexities involved in studying these patients. Although the data are limited, this article reviews the animal and healthy human data providing a rational approach to the potential pathophysiological mechanisms involved in muscle mass regulation in critically ill patients, including the established muscle wasting 'risk factors' such as ageing, immobility and systemic inflammation, all of which are common findings in the general critical care population.

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Introduction

Impaired physical function is a common finding in intensive care unit (ICU) survivors (Herridge *et al.* 2003), who may be unable to perform their usual activities of daily living for up to 2 years following hospital discharge (Cheung *et al.* 2006). ICU-acquired muscle weakness has been suggested as a causal factor of such impairment (Griffiths & Hall, 2009; NICE, 2009). It is both common, with a reported prevalence of between 25% and 100% depending on the method of assessment (Coakley *et al.* 1993; Bolton, 2000; De Jonghe *et al.* 2002; Latronico *et al.* 2005), and harmful. Specifically, ICU-acquired muscle weakness has been shown to be an independent predictor of delayed weaning from mechanical ventilation, as a consequence of associated respiratory muscle weakness (De Jonghe *et al.* 2007), and mortality (Niskanen *et al.* 1996; Ali *et al.* 2008). Not surprisingly, research in this field is technically challenging, and this is reflected in the relative paucity

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of physiological studies and interventional clinical trials. Furthermore, due to limited availability of electromyogram (EMG) and nerve conduction study (NCS) testing in the ICU and the limited data ascertained from EMG and NCS in patients unable to co-operate, currently the diagnosis of ICU-acquired muscle weakness is a clinical one only achieved in patients with a satisfactory conscious level, which limits diagnostic certainty. Nevertheless, interest in this area, including extending our understanding of the pathophysiology of the disease processes, is increasing (Griffiths & Hall, 2009; NICE, 2009). Finally, objective physiological measurements that both quantify and stratify patients at risk and the magnitude of muscle wasting need to be developed.

Patient heterogeneity

Patient heterogeneity is a serious challenge to researchers working in ICU. In developed countries, the most common indication for admission to critical care includes acute respiratory failure, trauma, sepsis and acute coronary syndromes, although there is significant overlap observed. In particular, the generalisability of evidence from a specific patient population (e.g. trauma or coronary artery bypass surgery) to the general intensive care population is difficult given the disparity in disease processes (Trouillet *et al.* 1996). Furthermore, critical illness is the rapid progression of end organ damage and subsequent multiorgan failure and this often overshadows the chronic respiratory and cardiac disease, despite these factors contributing to skeletal muscle wasting (Mancini *et al.* 1992; Gosker *et al.* 2003). Immobilisation promotes muscle wasting (Tomanek & Lund, 1974; Duchateau & Hainaut, 1987; Caron *et al.* 2009), which in humans has been observed to be the consequence of reduced muscle protein synthesis (MPS) (Gibson *et al.* 1987). Whilst the lack of tracer studies prevents definite conclusions being drawn on the role of muscle protein breakdown (MPB), upregulation of muscle atrophy signalling suggests a simultaneous increase in MPB (Jones *et al.* 2004). In clinical observational studies, sepsis and systemic inflammation are reported to act as powerful catalysts of muscle weakness (De Jonghe *et al.* 2002; Sharshar *et al.* 2009). Although animal models demonstrate that inflammation suppresses MPS and increases MPB, such data in critically ill patients are lacking (Voisin *et al.* 1996; Murton *et al.* 2009). However, diverse aetiological factors drive similar physiological derangement which can be quantified in physiological scoring systems and used, with variable success, to predict ICU outcome (Vincent, 2010). Perhaps for this reason, muscle biopsies from critically ill patients demonstrate histopathological similarities across different disease groups (Gamrin *et al.* 1996; Helliwell *et al.* 1998), suggesting at least some commonality in an underlying process.

Identification of ICU-acquired muscle weakness

Electromyogram and nerve conduction studies. Muscle weakness can result from motor neurone dysfunction, or from the direct impact of critical illness on muscle itself. Pure, severe neuropathy is unusual (Bednarik *et al.* 2003). Neuropathy in critically ill patients was first described in 1984 (Bolton *et al.* 1984) with electrophysiological abnormalities of muscle and nerve inexcitability observed in ICU patients within the first 2–5 days. Although EMG and NCS observations in critically ill patients have been previously described, these vary from reduction in compound muscle action potential and sensory nerve action potential to normal or near normal nerve conduction velocities. Furthermore, an absence of a decremental response to repetitive nerve stimulation is not uncommon (Coakley *et al.* 1993; Bolton, 2000; Tennila *et al.* 2000). However, routine EMG and NCS cannot distinguish between neuropathy and myopathy in unconscious patients and significant technical skills are required for collecting and interpreting the data (Latronico *et al.* 1996; De Jonghe *et al.* 2002). In addition, studies have reported a universal rate of EMG and NCS abnormalities in ICU patients, not necessarily related to the severity of muscle function loss, indicating that these electrophysiological studies have limited sensitivity to stratify patients who could benefit from treatment (Coakley *et al.* 1993; Berek *et al.* 1996). These issues, combined with the difficulty in nomenclature in this field, highlight the need for clarity in reporting of neuromuscular changes observed in ICU patients. Specifically, ICU-acquired weakness is based on a functional measure of strength, whereas the diagnosis of critical illness neuromyopathy is determined by electrophysiological measurement.

Assessing muscle function and cross-sectional area in the ICU. There are intrinsic difficulties in assessing muscle function in the ICU setting in patients with cognitive impairment. However, it is possible to make objective measurements of function through determination of the force generated by an isolated muscle group using electrically or magnetically evoked contractions (Edwards *et al.* 1977; Polkey *et al.* 1996; Harris *et al.* 2000). From these studies, weakness has been characterised in the diaphragm, quadriceps and adductor pollicis (Harris & Moxham, 1998; Harris *et al.* 2000; Watson *et al.* 2001). Repetitive magnetic stimulation allows quadriceps endurance to be assessed in a non-volitional manner in chronic disease states, although this technique has yet to be applied to patients during and after critical illness (Swallow *et al.* 2007). Such approaches have shown that

Table 1. The Medical Research Council (MRC) sum score (Kleyweg *et al.* 1991)

The Medical Research Council sum score	
Shoulder abductors	Hip flexors
Elbow flexors	Knee extensors
Wrist extensors	Foot dorsiflexors

Scoring: 0–5 for each group. The diagnosis of ICU-acquired muscle weakness is made if the score is $\leq$48

subjects with chronic disease, such as chronic obstructive pulmonary disease, have a reduced ability to sustain a force over time compared to healthy controls (Swallow *et al.* 2007). Despite the detailed and objective nature of these tests, these techniques are challenging to perform in an ICU setting and therefore have limited widespread clinical applicability. The most widely used clinical tool is manual muscle testing (MMT) using the Medical Research Council (MRC) muscle strength sum score (Kleyweg *et al.* 1991; De Jonghe *et al.* 2002; Table 1). However, the ability to perform this test is limited by a number of factors such that the patients are required to be awake, co-operative and motivated, all of which are influenced by sedation, delirium and disease severity. Despite these caveats, the prevalence of ICU-acquired muscle weakness, as defined by an MRC sum score less than 48, has been shown to be present in 25% of patients after only 1 week of mechanical ventilation (De Jonghe *et al.* 2002, 2007). Furthermore, proximal weakness appears to have a greater prevalence than distal weakness, discordant to the traditional diagnosis of ICU-acquired muscle weakness (De Jonghe *et al.* 2007). Finally, hand-grip dynamometry has been shown to be a surrogate marker of generalised ICU-acquired muscle weakness (Ali *et al.* 2008), but suffers from the same limitation as all MMT.

As muscle mass determines function (Seymour *et al.* 2009), a recent focus has been on investigating techniques to accurately and reproducibly measure muscle cross-sectional area. Early assessment of loss of muscle mass could identify those at greatest risk of ICU-acquired muscle weakness and its related functional impairment, allowing the early deployment of treatment, and possibly preventative, strategies. Whilst anthropometric measurements, such as mid-arm and mid-thigh circumference are simple and reproducible, they rely on a balanced state of hydration and are not well correlated with whole lean body mass in the critically ill. These measurements are therefore unreliable as a marker for acute muscle loss (Campbell *et al.* 1995). Alternatively B-mode ultrasonographic measurements of rectus femoris cross-sectional area (RF_{CSA}) is as accurate as magnetic resonance imaging in the assessment of muscle mass changes, with the added benefits of portability, ease of use and lower cost (Arbeille *et al.* 2009). Pilot data suggest that this may be a useful clinical tool for early tracking and detection of muscle loss in critically ill patients, and therefore ICU-acquired muscle weakness (Gruther *et al.* 2008; Seymour *et al.* 2009). However, this technique is limited as muscle wasting can be expected to occur in the absence of a reduction of RF_{CSA}, in particular in critically ill patients who are given significant fluid loading to support failing organs, with the significant fluid shifts resulting in both intracellular and extracellular fluid accumulation. Although tracking muscle loss using RF_{CSA} could be validated by determining its relationship with muscle fibre cross-sectional area, the muscle alkaline-soluble protein (ASP) to deoxyribonucleic acid (DNA) ratio could also be used to validate RF_{CSA}. In addition to the normal range for the ASP:DNA ratio being established, this measurement is unaffected by water content (Soop *et al.* 1989; Forsberg *et al.* 1991). However, our concerns about the total muscle water content may be overemphasised as it has been shown in a longitudinal study in critically ill patients that water content does not change over a period of 7 days (Gamrin *et al.* 1997), although in critically ill patients there is an increase in extracellular water (Gamrin *et al.* 1996; Gatzen *et al.* 1992) accompanied by progressive cellular dehydration (Haussinger *et al.* 1996).

Determinants of muscle mass

Muscle turnover. In healthy subjects muscle catabolism is balanced by anabolism, although this balance may be altered in critical illness (Rennie, 1985) and following resistance exercise (Tipton *et al.* 2003). Changes in the dynamic balance between MPS and MPB result in a net change in protein turnover (Millward, 1980). This balance is influenced by a variety of factors prevalent in the critically ill such as age (de Boer *et al.* 2007; Kumar *et al.* 2009), immobility (Gibson *et al.* 1987; Ferrando *et al.* 1996; Glover *et al.* 2008), inflammation (Biolo *et al.* 2002; Vesali *et al.* 2005, 2009), feeding (Bohe *et al.* 2003; de Boer *et al.* 2007; Tipton *et al.* 2007; Moore *et al.* 2009), insulin (Louard *et al.* 1992; Fryburg *et al.* 1995; Greenhaff *et al.* 2008) and drugs (Gibson *et al.* 1991; Hammarqvist *et al.* 1994; McNurlan *et al.* 1996). The impact of these factors are synergistic. Muscle is consumed during critical illness, providing a pool of amino acids that can be used in hepatic gluconeogenesis as well as in the synthesis of other important factors, such as acute phase proteins and enzymes (Gimson, 1987). Whilst it has been hypothesised that critically ill patients exhibit anabolic resistance (Rennie, 2009), and that the dominant process for a loss in muscle mass is a fall in MPS, studies supporting this view are limited and may have limitations with poor standardisation of time points for MPS assessment compounded by the use of flooding isotope techniques, which can themselves stimulate MPS (Essen *et al.* 1998;

Fredriksson *et al.* 2008). Tracer studies describing MPB in the critically ill are lacking. Whilst indirect evidence exists that the MPB rate in critically ill patients is likely to be increased (Lecker *et al.* 2004; Klaude *et al.* 2007), a definitive statement on the altered balance of MPS and MPB in critically ill patients is not possible.

Intracellular signalling pathways control MPS and MPB, although the exact relationship between different signalling pathways and MPS and MPB remains unclear (Greenhaff *et al.* 2008). In healthy subjects, the catabolic signals are balanced by anabolic signals, although the relative roles of each in the critically ill patient are poorly understood (Greenhaff *et al.* 2008; Murton *et al.* 2008). Despite this, the ubiquitin-proteasome pathway (UPP), which is the pathway suggested to control MPB, has been implicated in a range of physiological states and clinical conditions, albeit in rodent models, many of which affect patients with critical illness (Lecker *et al.* 1999, 2004). MPB in both systemic disease and disuse is regulated by muscle-specific ubiquitin ligases or atrogenes (Jackman & Kandarian, 2004; Kandarian & Jackman, 2006), with accelerated catabolism reported in inflammatory and immobilisation states (Tiao *et al.* 1997; Lecker *et al.* 1999, 2004; Bodine *et al.* 2001*a*; Leger *et al.* 2009). The main so-called 'atrophy genes', encoding atrogin-1, also known as muscle atrophy F-box protein (MAFbx) and muscle ring-finger-1 (MuRF-1), are activated by forkhead (FoxO) transcription factors 1 (FoxO-1) and 3 (FoxO-3) (Sandri *et al.* 2006; Sacheck *et al.* 2007). These atrogenes are rendered inactive by phosphorylation of Akt, a downstream target of insulin-like growth factor 1 (IGF-1) and insulin, which inhibits the de-phosphorylation of FoxO. Animal models of sepsis have shown inhibition of Akt with activation of FoxO and subsequent increase in MAFbx and MuRF-1. However, it should be noted that these atrogenes have also been shown to be regulated independently of the Akt/FoxO axis (Leger *et al.* 2006; Doucet *et al.* 2007) and affected by glucocorticoids (Waddell *et al.* 2008) as well as by nuclear factor κB (NF-κB) (Cai *et al.* 2004) indicating that there are other influences on the relationship between the atrogenes and forkhead transcription factors. In addition to activation of the UPP, and highly relevant to the clinical problem of insulin resistance in critically ill patients, the Akt/FoxO signalling pathway, via FoxO mediated pyruvate dehydrogenase kinase, inhibits muscle carbohydrate metabolism (Crossland *et al.* 2008). This inhibition of Akt and activation of FoxO in these animal sepsis models have been shown to be associated with increased levels of tumour necrosis factor-α, which can be modified by low dose corticosteroids (Crossland *et al.* 2010). IGF-1, which can be activated by repeated muscle contraction, can block transcriptional up regulation of atrogenes (Stitt *et al.* 2004). However, this is obviously an oversimplification of a complex process, particularly given evidence which has shown that blocking the IGF-I receptor does not impair hypertrophy of muscle in response to mechanical overload or indeed activation of the PI3/AKT pathway (Bodine *et al.* 2001*a*,*b*). Furthermore, the IGF-1

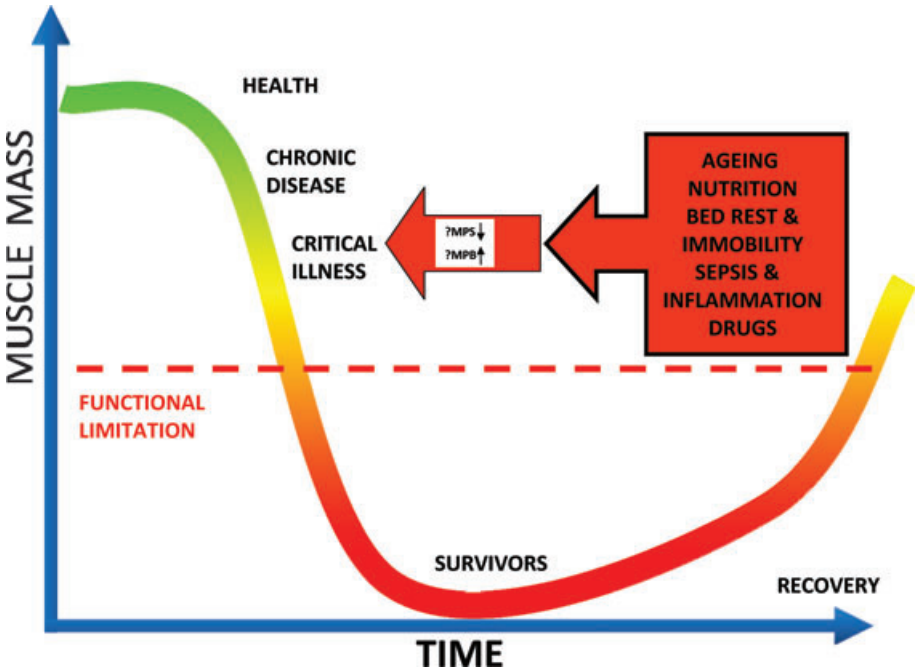

Figure 1. Schematic representation of the factors regulating muscle mass and function in critically ill patients
MPS, muscle protein synthesis; MPB, muscle protein breakdown

receptor is ubiquitous and could result in systemic effects rather than being limited to skeletal muscle, making it a poor target for therapeutic intervention. It must be highlighted that the majority of these data are from animal studies and the few human data, albeit in normal healthy humans, have not demonstrated a direct relationship between anabolic signalling and MPS (Greenhaff *et al.* 2008; Murton *et al.* 2008). Clarification of the final common signalling pathways regulating MPS and MPB in patients during critical illness is important and could provide potential therapeutic targets for novel molecules.

Factors influencing muscle turnover in critically ill patients

Our current understanding of muscle turnover, in regards to adaptation during critical illness, is poorly described. Increasing age affects the response of MPS and MPB to specific stimuli, including resistance training (Kumar *et al.* 2009). Other factors are reported to affect muscle mass in animal models (Sacheck *et al.* 2007), which may have little relevance to human disease. Some factors are likely to have universal effects on healthy subjects and critically ill patients.

Age. Sarcopaenia, muscle loss associated with ageing, has been shown to occur at a rate of approximately 0.5–2% per annum, although resistance exercise training has been shown to preserve muscle mass (Baumgartner *et al.* 1998; Raguso *et al.* 2006). Interestingly, basal muscle protein turnover rate has not been shown to change with advancing age (Volpi *et al.* 2001). Despite this, a blunted synthetic response has been observed such that training produces less of an anabolic response in older subjects (Kumar *et al.* 2009) with sex differences in MPS apparent in both the post-absorptive and fed states (Smith *et al.* 2008). An increasing proportion of the critically ill patient population are elderly and at high risk of developing muscle wasting during critical illness as a consequence of this blunted MPS response. This is particularly important as frail older sarcopaenic patients who start from a compromised position with a lower muscle mass have a further reduction in muscle mass. Thus, rehabilitation resistance training in this patient group may be even more important, but from previous data is harder to achieve and demonstrate benefit to the muscle.

Immobilisation and bed rest. Mechanical ventilation has traditionally been associated with sedation and bed rest, although this has recently been challenged as a universal paradigm (Schweickert *et al.* 2009; Strom *et al.* 2010). It is established that immobility has a detrimental effect to muscle, both quantitatively and qualitatively. Relatively short periods of immobilisation decrease MPS, and it has been postulated, from the calculation of the degree of involvement of MPS, that there is limited effect on MPB, although the latter has never been directly measured by tracer studies (de Boer *et al.* 2007). However, gene markers of atrophy have been shown to be upregulated in a 2 week immobilisation study, suggesting a simultaneous increase in MPB and reduction in MPS during immobilisation (Jones *et al.* 2004). Furthermore, this altered balance is relatively resistant to programmes in which high dose amino acid feeding is employed (Glover *et al.* 2008). This is in contrast to animal work, where MPB is the dominant process (Sacheck *et al.* 2007; Caron *et al.* 2009). Furthermore, immobilisation has significant effects on peripheral muscle aerobic capacity (Kortebein *et al.* 2008), contractility (Duchateau & Hainaut, 1987), insulin resistance (Hamburg *et al.* 2007) and muscle architecture (Tomanek & Lund, 1974). Microvascular dysfunction occurring in severe sepsis is associated with immobilisation and may have an additive effect on reducing MPS (Hamburg *et al.* 2007; Rennie, 2009).

Systemic inflammation. Sepsis and systemic inflammation are common in critically ill patients, with sepsis reported as the third leading cause of death in the United States (Bone *et al.* 1992; Daniels, 2009). Variation in circulating concentrations of amino acids have been demonstrated in the early stages of sepsis, in addition to decreased MPS (Vesali *et al.* 2005, 2009). The exact role of altered MPB in the critically ill is unclear, with conflicting data from studies (Biolo *et al.* 2002; Vesali *et al.* 2009). Endotoxin administration to healthy volunteers, as a model for systemic sepsis, demonstrated a decrease in MPS with an adaptive decrease in MPB (Vesali *et al.* 2009). In contrast, protein turnover studies performed in 19 patients with severe burn injuries showed an 83% increase in MPB (Biolo *et al.* 2002), although it is appreciated that patients with burn injury and extensive soft tissue loss are not necessarily representative of patients managed in general intensive care.

Defeating muscle failure in critically ill patients

Currently, our knowledge of muscle loss and wasting in critically ill patients is limited (Fig. 1). We have extrapolated animal and healthy human data to identify areas of interest with a focus on determining the relationship between muscle protein signalling and muscle protein turnover. This approach has the potential to identify targets for future drug therapies and other strategies such as neuromuscular electrical stimulation and early physical rehabilitation therapy. We need to validate simple non-invasive tools, such as ultrasound, to track muscle loss and identify those patients at

risk. Encouragingly, data are emerging which suggest that rehabilitation strategies such as neuromuscular electrical stimulation (Gerovasili *et al.* 2009) can preserve muscle mass. However, the underlying pathophysiological mechanisms which control muscle protein turnover remain to be elucidated in this patient population.

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