Physical consequences of critical illness

Patients who survive critical illness are at risk of permanent physical and functional deficits which decrease the health-related quality of life. The reasons for physical morbidity include the nature of and treatment for the inciting critical illness, new decrements in organ function and worsening of pre-existing organ dysfunction, and prolonged physical immobility and long intensive care unit stay.

This review will discuss the varied physical sequelae sustained by patients who have survived an episode of critical illness. Survivors of the acute respiratory distress syndrome (ARDS) have been the focus of the most comprehensive reports on physical dysfunction after critical illness and, as such, will form the basis of this review. The case history below, of a young ARDS survivor, highlights many of the physical consequences of critical illness (*Table 1*).

Case history

This case history, from the Toronto ARDS outcomes cohort (Herridge et al, 2003), illustrates the physical morbidity sustained by a survivor of critical illness, in this case a survivor of ARDS. The patient was a 40-year-old previously healthy female who presented to the intensive care unit (ICU) with hypoxaemic respiratory failure secondary to pneumococcal pneumonia complicated by ARDS. The patient was intubated and mechanically ventilated for 5 weeks in the ICU. Her ICU course was complicated by the development of multiple organ dysfunction requiring pressor support and renal replacement therapy. Three chest tubes were inserted during the ICU stay for pneumothoraces resulting from her complicated ventilatory management.

The patient underwent tracheostomy 3 weeks into the ICU stay and had a protracted wean from the ventilator related to generalized weakness and difficulty clearing secretions. At the time of ICU discharge, the patient had severe weakness and generalized muscle wasting. She was unable to sit up. She could not walk, weight bear or even transfer on her own. After 2 weeks on the medical ward, she was able to stand and take a few steps and was transferred to a rehabilitation facility for ongoing physical therapy. At 4 weeks she was decannulated and discharged to her friend's home. At 3 months following ICU discharge, she continued to have significant proximal muscle weakness with inability to fully abduct her arms. She could not get in and out of cars nor climb stairs because of proximal leg weakness. At 12 months following ICU discharge, she had regained her lost weight, had mild proximal muscle weakness but could now abduct her arms and reported being quite functional. However, because of her need to stand most of the day as a teacher, she was unable to return to work because of residual weakness and fatigue. A more intensive physical rehabilitation programme was organized for her and the patient continued to experience slow and progressive improvement in her weakness. She returned to her original job on a part-time basis 18 months after ICU discharge. At that time, she found her tracheostomy scar stigmatizing and underwent scar revision by a plastic surgeon.

Long-term physical function in survivors of ARDS

Health-related quality of life

In 1994, McHugh and her colleagues prospectively evaluated pulmonary function and quality of life to assess the relationship between pulmonary dysfunction and functional disability. They found that the Sickness Impact Profile (generic quality of life measure of the subject's self-perceived physical and psychological condition) scores were very low at extubation, rose substantially in the first 3 months and then exhibited only slight improvement to 1 year. When quality of life was assessed using a lung-related Sickness Impact Profile score, only a modest proportion of the patient's overall dysfunction was attributed to residual pulmonary problems.

Table 1. Physical outcomes after critical illness

Quality of life below general population, most marked in physical function, may be irreversible
Generalized muscle wasting and weakness
Critical illness neuromyopathy, entrapment neuropathy, heterotopic ossification and joint stiffness
Difficulty with swallowing, phonation related to muscle weakness
Scarring from central line sites, chest tubes
Striae from volume overload
Tracheal stenosis
Hoarseness
Exertional dyspnoea related to increased muscular work of breathing and/or residual pulmonary dysfunction
Taste changes

From Griffiths and Jones (1999), Herridge et al (2003), Cheung et al (2006)

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Weinert and coworkers (1997) identified functional impairment in a cohort of acute lung injury survivors. They administered the Medical Outcomes Study 36-item short-form health survey (SF-36), which yields scores in eight domains including physical and social functioning, role limitations because of emotional or physical problems, mental health, vitality, bodily pain, and general health perceptions (Ware and Sherbourne, 1992). While all domains of the SF-36 were reduced, the largest decrements were in role-physical and physical functioning. While some decreased quality of life was attributed to pulmonary dysfunction, many more patients attributed this to global and generalized disability. Schelling et al (1998) made similar observations about impaired physical functioning and inferred that disability was the result of pulmonary dysfunction, although they did not assess this in their study.

Davidson and colleagues (1999) designed a study to determine if there were differences in health-related quality of life (HRQL) in ARDS survivors and comparably ill controls. They used the SF-36 and a pulmonary disease-specific measure (St. Georges Respiratory Questionnaire; SGRQ) to determine the degree to which perceived physical disability in ARDS survivors was related to pulmonary dysfunction. Similar to previous reports, all domains of the SF-36 were reduced and the largest decrement was in the role-physical domain. ARDS survivors had significantly worse scores on the SGRQ than critically ill controls. There appeared to be an ARDS-specific degree of physical disability but it was not clear whether this was solely related to pulmonary dysfunction or whether there were other important extrapulmonary contributors.

Angus et al (2001) used the quality of wellbeing score in a prospective cohort of ARDS survivors to measure quality-adjusted survival in the first year after hospital discharge. The mean quality of wellbeing scores for the ARDS cohort at 6 and 12 months were significantly lower than a control population of patients with cystic fibrosis. When quality of wellbeing was disaggregated into its component subscores, post-hoc analyses showed that the symptom component scores of the quality of wellbeing accounted for 70% of the decrement in perfect health at 6 and 12 months. Although respiratory symptoms were reported in almost half of the patients, the most common complaints were musculoskeletal and constitutional.

In a prospective cohort study of 78 survivors of ARDS, Orme and others (2003) evaluated HRQL and pulmonary function outcomes in patients treated with higher tidal volume *vs* lower tidal volume ventilation strategies. Both groups (higher and lower tidal volumes) reported decreased HRQL in physical functioning, physical ability to maintain their roles (role-physical), bodily pain, general health and vitality (energy) on the SF-36. The pulmonary function abnormalities correlated with decreased HRQL for domains reflecting physical function.

Not only is the observation of impaired physical functioning robust across studies and investigators, it also appears to persist for long periods of time following ICU or hospital discharge. Davidson et al (1999) reported outcomes 23 months after discharge and Cheung and colleagues (2006) have also reported persistent physical dysfunction 2 years after ICU discharge.

HRQL data in ARDS survivors have had an enormous impact on the critical care community and has helped focus attention on long-term morbidity after critical illness. These data have helped doctors begin to understand the heterogeneous nature of reported morbidity and the complexity of the interaction among physical, emotional and cognitive domains in individual patients.

Pulmonary function abnormalities

Many ARDS survivors have persistent pulmonary function impairments that are typically mild to moderate restrictive changes and an associated reduction in diffusion capacity (Lakshminaryan and Hudson, 1978; Elliott et al, 1981, 1987; Schelling et al, 2000). Orme and colleagues (2003) reported that ARDS survivors had abnormal pulmonary function associated with decreased HRQL 1 year following hospital discharge and Schelling et al (2000) reported no additional improvement in pulmonary function after the first year following ARDS.

Neff and colleagues (2003) reviewed 30 studies that evaluated pulmonary function in ARDS survivors. They reported significant variability in the proportion of patients with obstructive (0–33%) and restrictive (0–50%) defects as well as compromised diffusion capacity (33–82%). This spectrum of pulmonary dysfunction may relate to population heterogeneity with respect to evolving definitions or severity of ARDS, severity of lung injury, ICU ventilatory strategy, prior history of lung disease or smoking, and the presence of other pulmonary processes that fulfill the ARDS definition but that have a very different natural history (e.g. bronchiolitis obliterans organizing pneumonia).

Most outcome studies found ARDS survivors are frequently unable to resume their prior lifestyle, but the degree of pulmonary dysfunction does not fully explain their functional limitation. This observation has led investigators to explore other possible contributors to physical disability.

Limitation in physical functioning

The Toronto ARDS outcomes group evaluated exercise capacity (distance walked in 6 minutes with continuous oximetry), pulmonary function and conducted an interview, physical examination and HRQL measure in 109 ARDS survivors at 3, 6 and 12 months after ICU discharge (Herridge, 2002; Herridge et al, 2003). Similar to other pulmonary function studies, the ARDS patients had mild restrictive disease and reduced diffusion capacity at 3 months following ICU discharge. By 6 and 12 months they had normal to near normal lung volumes and spirometric measures with a persistent mild reduction in carbon dioxide diffusion capacity – lung

impairment similar to that noted by others. The ARDS survivors had profound muscle weakness and wasting and were only able to achieve 66% of their predicted exercise capacity 1 year post-ICU discharge. This functional disability was reflected in the HRQL assessment in which patients reported profound reduction in the physical functioning and role-physical domains of the SF-36. Impaired exercise capacity was related to burden of comorbid disease, exposure to systemic corticosteroid treatment during the ICU period and the rate of resolution of lung injury, and multiple organ dysfunction during the ICU stay. The precise determinant(s) of the observed muscle wasting and weakness remain unclear.

Critical care weakness

A significant proportion of patients in the ICU develop generalized weakness and this is associated with increased long-term morbidity. ICU-acquired neuromuscular disorders present as diffuse skeletal-muscle weakness with flaccid weakness and reduced or absent deep tendon reflexes that may persist for years after discharge (Latronico et al, 2005a). The most common initial presentation is thought to be failure to wean from the ventilator (Deem, 2006). Many terms have been adopted to define weakness syndromes in the ICU including critical illness polyneuropathy (CIP) and critical illness myopathy (CIM). In most settings, there is considerable overlap between these conditions and so the term critical illness polyneuromyopathy (CIPM) is often used when referring to ICU-acquired weakness.

Incidence: It is difficult to estimate the true incidence of CIPM in ICU settings. Clinicians are often unable to perform an adequate physical examination to assess for neuromuscular weakness and electrophysiological studies may overestimate its incidence because of marked sensitivity of electromyography and nerve conduction studies in this setting. As such, there are limited studies which have systematically evaluated the incidence of ICU-acquired weakness.

In one study, neuromuscular weakness was found in up to 82% of patients with sepsis or multiorgan failure by means of electrophysiology but only half of these patients had clinical evidence of weakness (Berek et al, 1996). In another study of patients with multiorgan failure, 56% of patients had electrophysiological abnormalities, 52% developed mild to moderate weakness, and 26% had diffuse weakness (Bednarik et al, 2003). In another study, 100% of patients with sepsis and coma had CIPM (Latronico, 1996). In general, CIP is more commonly reported than CIM. However, there may be a selective diagnostic bias since diagnosis of CIM requires a muscle biopsy which is rarely performed in this setting.

Risk factors: Sepsis, systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction are often identified as important risk factors for the development of ICU-acquired weakness although there is some controversy surrounding this. One study of patients who developed neuromuscular weakness in the ICU identified the presence of SIRS and high APACHE scores as independent risk factors (de Letter et al, 2001). However, other reports do not support this relationship between sepsis and the development of CIPM (Berek et al, 1996).

Administration of corticosteroids and neuromuscular-blocking agents are other reported risk factors. These were originally described in asthmatics who were receiving high-dose corticosteroids and/or neuromuscular-blocking agents and were subsequently found to have 'acute quadriplegic myopathy'. A prospective cohort study reported that administration of steroids was the strongest predictor of ICU-acquired weakness (Berek et al, 1996). Several studies have shown that late administration of neuromuscular agents, beyond a period of 24 hours, is associated with the development of CIPM (Behbehani et al, 1999).

Hyperglycaemia is also an independent risk factor for the development of ICU-acquired weakness (Van den Berghe et al, 2001). Among the group that received intensive insulin therapy there were fewer cases of CIPM and reduced duration of mechanical ventilation. There is a linear relationship between blood glucose levels and risk of polyneuropathy. It is postulated that hyperglycaemia, insulin deficiency or both contribute to axonal dysfunction and degeneration.

Other risk factors for ICU-acquired neuromuscular weakness include female sex, severity of illness, greater duration of organ failure or dysfunction, neurological failure, administration of total parenteral nutrition, and use of aminoglycosides and catecholamines (Latronico et al, 2005b).

Muscle wasting is a common feature of ICU weakness. Sepsis, trauma, surgery, immobility, malnutrition and medications are contributors to muscle loss. A study by Plank et al (1998) showed that patients with severe sepsis lost 1.21 kg of protein in the first 10 days of ICU admission. Approximately 70% of this loss was from skeletal and respiratory muscle. Cardiac muscle is relatively preserved (Hill et al, 1997). Over a 30-day ICU admission period, approximately 3 kg of protein is lost and 2% of muscle protein is lost per ICU admission day. This muscle loss contributes to the respiratory, pharyngeal and skeletal muscle weakness that ICU patients often face.

Pre-existing conditions such as diabetes, cancer and neurological conditions can cause neuropathies which can contribute to ICU weakness or they may co-exist with CIPM and go unrecognized. Diabetic patients frequently have distal symmetric sensorimotor polyneuropathy with progressive loss of distal sensation correlating with loss of sensory axons, followed, in severe cases, by motor axonal loss and motor weakness. Furthermore, these patients can also have cranial mononeuropathies. The cranial nerves that are typically affected are cranial nerves III, IV and VI (Dyck et al, 1995; Sands et al, 1997). Paraneoplastic syndromes often affect the peripheral nervous system causing entities such Lambert–Eaton syndrome and myasthenia gravis.

Medications which are often used in the ICU setting, e.g. amiodarone, hydralazine, metronidazole and phenytoin, may also cause peripheral neuropathies. Corticosteroids produce proximal muscle weakness and wasting with acute and chronic use. Neuromuscular agents, especially non-depolarizing neuromuscular-blocking drugs, cause profound muscle weakness that may last months after the drug is discontinued (Murray et al, 2006).

Pathogenesis of CIP and CIM: CIP is an axonal polyneuropathy primarily affecting the lower limbs of critically ill patients. The mechanism for this is thought to be part of the 'organ failure' model of SIRS and sepsis whereby inflammatory mediators and metabolic events contribute to impaired perfusion of nerves resulting in loss or impairment of function (Fenzi et al, 2003). Corticosteroids, neuromuscular agents and hyperglycaemia are thought to potentiate the underlying nerve dysfunction leading to detectable weakness (Latronico et al, 2005a).

CIM pathology exists as two variants. One variant is described as selective thick myosin filament loss under electron microscopy with generalized or selective type II fibre atrophy. The second variant is described as widespread muscle necrosis with vacuolization and phagocytosis of muscle fibres (Latronico et al, 2005a). The pathogenesis is unclear but is thought to involve various mechanisms such as the impairment of voltage-dependent channels, mitochondrial dysfunction and proteolysis.

Diagnosing CIP and CIM: The most common clinical signs of ICU-acquired weakness are difficulty in weaning from the ventilator, muscle weakness and paralysis, and reduced or absent deep tendon reflexes. CIP was most commonly diagnosed, but CIM was present in 50–75% of muscle biopsies (Latronico et al, 2005a).

CIP is diagnosed using electromyography by observing decreased amplitude of nerve action potentials with preserved conduction velocities. Since CIP is an axonal neuropathy, the total number of fibres is reduced, causing a reduction in nerve action potential. However, the surviving fibres have an intact myelin sheath so the nerve conduction velocity remains normal (Latronico et al, 2005a).

A diagnosis of CIM can be confirmed by muscle biopsy, although this is not often done because of its invasive nature. However, direct muscle stimulation may be used to help differentiate between CIM and CIP. A patient with CIP will have reduced or absent action potential when stimulating through the nerve, but normal action potential with direct muscle stimulation. Conversely, there will be reduced or absent action potential with stimulation through the nerve or direct muscle stimulation in CIP (Latronico et al, 2005a). Unfortunately, direct muscle stimulation is not done routinely because of technical demands, so differentiating between CIP and CIM in the ICU is often difficult and not routine practice.

Prevention and treatment: Intensive treatment of sepsis and multiorgan failure and minimizing the use of potential triggering agents such as steroids and neuromuscular-blocking drugs will reduce the incidence of ICU-acquired weakness.

No specific treatments exist for CIP and CIM. However, intensive insulin therapy has been shown to reduce the incidence of CIPM (Van den Berghe et al, 2001). One study showed that using intravenous immunoglobulins may reduce the likelihood of developing ICU-acquired weakness (Latronico et al, 2005a). However, a more rigorous prospective study needs to be done before recommending this widely. Physical therapy and rehabilitation is often used to help accelerate recovery but no studies have looked at the efficacy of this practice.

Patients are often frustrated by their inability to return to their baseline function after a critical illness. Most lay persons are unfamiliar with the concept of CIPM and many health professionals may not have a good understanding of this syndrome, so patients often have no clear explanation for their profound weakness. Educating patients, families and their primary health-care practitioner about the short- and long-term outcomes of ICU discharge and CIPM may allay the anxiety and frustrations about the recovery process. Post-discharge ICU follow-up clinics may also be a vital resource for patients and their caregivers but this awaits future study.

Entrapment neuropathy

Entrapment syndromes may also cause weakness. In the ICU setting the radial, ulnar and common peroneal nerves are often affected secondary to pressure damage while the patient is in the prone position. The clinical manifestations of nerve entrapment include pain, which may be sharp or burning, and paraesthesia. In more severe cases, there may be muscle atrophy, fasciculations and weakness distal to the site of entrapment (Mondelli et al, 1995).

The Toronto ARDS outcomes study observed a 6% prevalence of peroneal and ulnar nerve palsies (Herridge et al, 2003). Although this is only a small proportion of patients, these palsies complicated rehabilitation therapy and precluded return to original work in some cases.

Heterotopic ossification

Heterotopic ossification is the deposition of para-articular ectopic bone and has been associated with polytrauma, burns, pancreatitis and ARDS (Clements and Camilli, 1993; Jacobs et al, 1999). It has been linked with paralysis and prolonged immobilization. There was a 5% prevalence of heterotopic ossification in the Toronto ARDS cohort study with all patients having large joint immobilization, leading to important functional limitation (Herridge et al, 2003). Heterotopic ossification is remediable with appropriate surgical intervention and screening for this may help to improve long-term functional outcomes.

Other physical sequelae

Griffiths and Jones (1999) have done extensive follow-up work in the UK and have had the largest experience with post-ICU longitudinal care delivery to date. They sum-

marized the physical sequelae they observed in heterogeneous populations of critically ill patients in a comprehensive review and additionally cited complications including: tracheal stenosis, reduced cough and pharyngeal weakness related to muscle weakness, joint stiffness, change in taste contributing to anorexia, cardiac and circulatory decompensation, postural hypotension and physical changes including scarring at central line and chest tube sites, and generalized striae related to volume overload.

Conclusions

The physical consequences of critical illness are heterogeneous, although muscle wasting and weakness appear to be ubiquitous findings regardless of the patient population, and are the source of significant functional morbidity and reported decrement in quality of life outcomes. The exact pathophysiology of this physical lesion remains unclear and is the focus of intense research work at present. It is imperative that some understanding of its risk factors and risk modifiers is gained to allow design and testing of appropriate interventions to prevent or ameliorate this long-term physical disability. **BJHM**

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KEY POINTS

- Survivors of critical illness may sustain important and permanent physical and functional disability.
- These may have important consequences for long-term health-related quality of life, return to work and independent living.
- The future challenge is to understand the detailed pathophysiology of these physical lesions and to construct appropriate and timely interventions to ameliorate this disability.