Critical Illness Myopathy and Polyneuropathy

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Neuromuscular weakness commonly develops in the setting of critical illness. This weakness delays recovery and often causes prolonged ventilator dependence. An axonal sensory-motor polyneuropathy, critical illness polyneuropathy (CIP), is seen in up to one third of critically ill patients with the systemic inflammatory response syndrome (usually due to sepsis). An acute myopathy, critical illness myopathy (CIM), frequently develops in a similar setting, often in association with the use of corticosteroids and/or nondepolarizing neuromuscular blocking agents. These patients are often difficult to evaluate due to the limitations imposed by the critical care setting and may be further complicated by the presence of both CIP and CIM in varying degrees. This paper reviews the clinical and electrophysiologic features of these disorders, as well as the putative pathophysiology. In the case of CIM, an animal model has provided evidence that weakness in this disorder is caused by muscle membrane inexcitability due to altered membrane sodium currents and loss of myosin thick filaments.

Introduction

The development of severe neuromuscular weakness often complicates recovery from critical illness. In some studies, the development of a neuromuscular cause of weakness occurs in the majority of critically ill patients [1]. The two syndromes that account for the vast majority of cases of acquired weakness in the intensive care unit are critical illness polyneuropathy (CIP), and an acute myopathy known as critical illness myopathy (CIM). Although it was initially thought that CIP was the most common cause of weakness in the ICU, several recent studies have found that CIM is more common in many centers [1,2,3••].

Critical Illness Myopathy

Critical illness myopathy was first described in patients with asthma who were treated with high-dose corticosteroids and neuromuscular blocking agents (NMBAs). The syndrome has been given multiple names, such as acute quadriplegic myopathy, thick filament myopathy, acute necrotizing myopathy of intensive care, rapidly evolving myopathy with myosin-deficient fibers, and critical care myopathy. The term "critical illness myopathy" has been proposed as a single, uniform term for this disorder [4•].

Critical illness myopathy is often only detected after the acute illness has resolved. If the myopathy is detected early during the period of acute illness, the rate of mortality is high due to the severity of the underlying illness. In most patients, the myopathy is first noticed as the patient begins to recover from encephalopathy and/or sedation. At that time it is noted that the patient is not weaning from the ventilator, and upon further examination severe diffuse weakness is often noted. Sensation and reflexes are usually spared. Subsequent recovery occurs over a period of 1 to 3 months and prolongs the hospital course [1,5]. In a prospective study of liver transplant patients, the mean time in the intensive care unit (ICU) for those with CIM was 7 weeks, but it was only 2 weeks for those without CIM [6]. This difference was mostly due to the failure to wean from mechanical ventilatory support. After patients begin to improve and are extubated, recovery can be rapid. In one study, all patients with CIM had near functional independence within 1 month of extubation [5].

The risk factors first associated with CIM were high-dose corticosteroids and nondepolarizing NMBAs. More recently, it has been recognized that sedative drugs such as propofol, which are widely used in the ICU, may be risk factors for CIM [7], as well as for sepsis and the resultant systemic inflammatory response syndrome. In several studies, CIM has occurred in septic patients who have not received corticosteroids and/or NMBAs [2,8,9]. It is the authors' opinion that a number of the agents that predispose to CIM (NMBAs, sedative agents, or even sepsis itself) share the feature of producing prolonged immobility of muscle. In animal studies, it has been demonstrated that loss of muscle activity produces a stereotypic series of changes that contribute to the development of CIM [10]. If loss of muscle activity is a risk factor for CIM, use of sedation instead of NMBAs may not prevent CIM.

Electrophysiologic features

Electrophysiologic studies in patients with CIM are different from the findings in most acute myopathies in that

nerve conduction studies consistently show a decrease in compound muscle action potential (CMAP) amplitudes [2,5,11–13]. In most patients, there is preservation of sensory nerve action potential (SNAP) amplitudes. Unless caution is used, the reduced CMAP amplitude, in conjunction with the presence of spontaneous activity, may result in misdiagnosis of the patient as having a predominantly motor neuropathy [14]. In some patients, nerve conductions may be suggestive of a generalized neuropathy because there are also low SNAP amplitudes. The cause of the reduction in SNAP amplitude is unknown, but may be technical (due to edema), may represent coexistent critical illness polyneuropathy, or may represent electrical inexcitability of nerve. The motor response amplitudes can be seen to increase during clinical recovery of strength [5,13,14]. Sensory and motor response conduction velocities are normal. Distal motor and F-wave latencies, as well as repetitive nerve stimulation, are normal.

On electromyographic examination, abnormal spontaneous activity, in the form of fibrillation potentials and positive sharp waves, is often seen, particularly in patients with a significantly elevated serum creatine kinase (CK) [2,5,6,12–15]. In some patients, however, there is pronounced spontaneous activity in the setting of only modestly elevated CK. The etiology of spontaneous activity in these patients is unknown, but may be due to a disturbance of membrane excitability and/or muscle fiber necrosis. Reduced insertional activity may be seen in severely weak patients with markedly reduced or absent CMAP amplitudes. This could reflect muscle membrane inexcitability in these individuals. With voluntary muscle activation of significantly weak muscles, one generally sees small amplitude and short-duration motor unit potentials (MUPs) with early full recruitment. Trojaborg *et al.* [3••] performed quantitative electromyogram (EMG) in patients with CIM and found that the MUP duration was significantly less than the normal mean.

Many patients who develop CIM are unable to voluntary activate MUPs due to profound encephalopathy, sedation, or weakness. In patients who cannot activate motor units, distinguishing between neuropathy and myopathy to determine the etiology of decreased CMAP amplitude in a muscle with varying degrees of spontaneous activity is very difficult. In these patients, there may be a role for examining muscle membrane excitability using the technique of direct muscle stimulation. Using direct muscle stimulation, it has been found that muscle in CIM becomes electrically inexcitable [2,3••,12,14]. In patients with CIM, muscle cannot be excited with direct stimulation, whereas in patients with CIP and other acute and chronic neuropathies, a large response can be obtained even when the nerve evoked response is absent [2,12]. The recovery of strength in patients with CIM parallels recovery of muscle membrane excitability, and suggests that weakness in CIM is, at least in part, the result of muscle membrane inexcitability [14]. This observation is also consistent with the common scenario of patients with myopathy who have markedly reduced CMAP amplitudes but have relatively normal muscle morphology on biopsy.

These finding are similar to those in hyperkalemic periodic paralysis, where individual patients have myotonia (hyperexcitability of muscle) at some times and inexcitable muscle at others. The defect in hyperkalemic periodic paralysis was found to be due to abnormal gating of sodium channels, which can lead to both periods of hyperexcitability as well as periods of inexcitability [16]. In this article, we present data suggesting that abnormal gating of sodium channels occurs in CIM. Whether abnormal gating of sodium channels in CIM can explain the pronounced spontaneous activity seen in some patients is not yet known.

Pathophysiology

To understand the mechanism underlying loss of muscle excitability in patients with CIM, we have chosen an animal model in which muscle is denervated and treated with corticosteroids [17,18]. This model recreates key pathologic features associated with weakness in many CIM patients who receive high-dose corticosteroids while paralyzed with nondepolarizing NMBAs. An important difference between the animal model of CIM and affected critically ill patients, however, is that patients often have other major illnesses, including sepsis and multi-organ failure, in addition to receiving corticosteroids and NMBAs. Thus, additional factors other than corticosteroid treatment and functional denervation may also contribute to loss of muscle excitability in patients.

Using the animal model, it has been possible to study loss of electrical excitability of muscle fibers using intracellular electrodes. Studies in the animal model of CIM have demonstrated that individual muscle fibers that are steroid treated and denervated (SD) become electrically inexcitable [19]. SD muscle fibers might become inexcitable as the result of several different types of abnormalities: 1) depolarization of the resting membrane potential might cause inexcitability through inactivation of sodium channels; 2) specific membrane resistance might become so low that the sodium current is insufficient to bring the fiber to threshold; 3) sodium conductance might be reduced through loss of channels from the membrane; and 4) inactivation of sodium channels might occur secondary to a change in the voltage dependence of inactivation. Rich *et al.* [19,20••] have examined these possibilities and found that depolarization of the resting potential, decreased specific membrane resistance, number of sodium channels, and a change in the voltage dependence of inactivation of sodium channels all contribute to decreased muscle excitability. However, the changes in specific membrane resistance and number of sodium channels in the muscle membrane are small and appear to be less important. Depolarization of the resting membrane potential and a shift in the voltage dependence of sodium channel fast inactivation towards more negative potentials appear to be the dominant factors (Fig. 1).

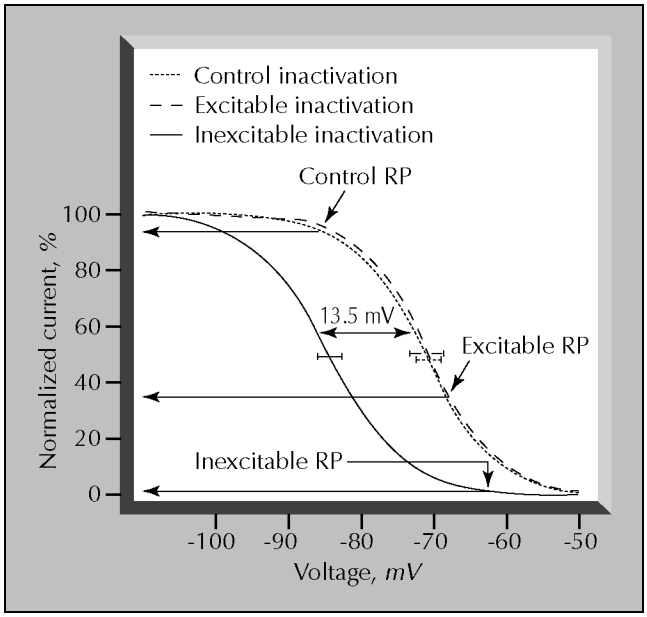

Figure 1. The voltage dependence of sodium channel inactivation determined using patch clamp is shown for control, excitable, and inexcitable steroid treated and denervated (SD) fibers in the animal model of critical illness myopathy. The percentage of sodium current remaining at a given potential is plotted on the y axis, versus the voltage on the x axis. The curves for control fibers and excitable SD fibers are nearly superimposed. In both of these classes of fibers, sodium channels begin to inactivate at a potential of –85 mV; by –71 mV half the sodium channels are inactivated, and significant sodium current remains at –60 mV. The curve for inexcitable fibers is shifted by 13.5 mV towards more negative potentials. In these fibers, sodium channels begin to inactivate at a potential of –100 mV; by –85 mV half the channels are inactivated, and by –60 mV almost no sodium current remains. On each inactivation curve an *arrow* points to the mean resting potential (RP) of the muscle fiber, with a second horizontal arrow drawn to show what percentage of current remains at that potential. At the mean RP, the amount of sodium current remaining in each group of fibers can be calculated: 91% in control fibers, 36% in excitable SD fibers, and 2% in inexcitable SD fibers. Thus, at the RP of inexcitable SD fibers, almost all sodium channels are inactivated and action potentials cannot be initiated. The horizontal error bars on each curve represent the standard error of the mean of the midpoint of inactivation for each curve. (*Adapted from* Rich and Pinter [20••]; with permission.)

In previously described disorders of muscle excitability involving sodium channels, such as paramyotonia congenita and hyperkalemic periodic paralysis, the defect is due to a mutation in the muscle sodium channel gene [16]. In the animal model of CIM, the rats used have no mutation in the muscle sodium channel gene. Likewise, patients who develop CIM have no history of difficulty with muscle excitability. Thus, CIM appears to be a new type of ion channel disease in which the problem is with regulation of sodium channel excitability rather than a genetic mutation leading to abnormal excitability. What is known about mechanisms that might lead to an alteration in the voltage dependence of sodium channel gating in situations where no mutations are present in the gene normally coding for the skeletal muscle sodium channel?

Two ways in which the voltage dependence of sodium channel inactivation might be altered are through changes in gene expression and post-translational modification. Altered gene expression could cause a shift in the voltage dependence of inactivation in SD muscle. Control muscle contains only the adult isoform (SkM1) sodium channel that inactivates at relatively depolarized potentials [21,22]. In SD muscle, mRNA of a second embryonic sodium channel (NaV1.5; SkM2), which inactivates at more negative potentials, is present at high levels [21–23]. Alternatively, post-translational modifications, such as phosphorylation or glycosylation, might alter sodium channel gating in SD muscle. Both of these processes have been shown to shift the voltage dependence of sodium channel inactivation [24,25]. Whether such regulation is important in skeletal muscle in the living animal is unknown, but abnormalities in a process regulating sodium channel gating could potentially explain not only inexcitability of muscle in CIM, but also hyperexcitability of muscle in diseases such as myotonic dystrophy, where there is no mutation of the skeletal muscle sodium channel gene.

Structural changes in muscle in patients with critical illness myopathy

Although loss of muscle electrical excitability may be the predominant cause of acute weakness in CIM, there are structural changes in muscle that persist even after electrical excitability is re-established. These changes are likely the cause of milder, but more prolonged, weakness that patients have as they recover from their acute illness. Myosin depletion in muscle fibers from biopsy specimens of patients with CIM is the pathologic hallmark of this disorder. Larsson *et al*. [26•] studied patients with CIM and found a decrease in myosin mRNA that correlates with the reduction in myosin protein levels. This finding suggests that abnormalities of gene transcription may play a critical role in the development of weakness. During recovery, there was an increase in myosin mRNA levels that led to reaccumulation of myosin protein. Levels of other structural proteins, such as titin, nebulin, and actin, are also reduced in CIM. Showalter and Engel [27] also found evidence of enhanced expression of calpain, a calcium-activated protease, in atrophic myofibers. Such findings suggest that altered cellular calcium homeostasis may play a role in the loss of myosin, and perhaps other proteins as well.

These studies, as well as the electrical studies discussed previously, demonstrate the difficulty in determining the cause of weakness in CIM. In each study, multiple abnormalities involving multiple mechanisms are found. Thus, to understand the cause of CIM one needs to fully understand regulation of muscle gene expression, modulation of ion channels, and mechanisms governing proteolytic breakdown of muscle proteins.

Decreased excitability in tissues other than skeletal muscle

As described previously, inactivation of sodium channels leads to loss of electrical excitability in skeletal muscle and likely causes acute weakness in CIM. During our studies of ICU patients, we noticed that in some patients with CIM who were recovering from sepsis, SNAP amplitudes were reduced. In several patients, we have observed rapid recovery of SNAP amplitudes that parallel recovery of CMAP amplitude. This led us to hypothesize that there might be widespread loss of excitability in electrically active tissues in critically ill patients. To test this, Rich and McGarvey. [28] performed a study examining electrocardiogram changes occurring in critically ill patients with septic shock to determine whether there was any loss of cardiac excitability similar to that seen in skeletal muscle. In over 80% of the patients studied, there was a significant decrease in QRS amplitude during sepsis [28]. No such reduction in QRS amplitude occurred in a control group of ICU patients. The changes were reversible following recovery from sepsis. It thus appears that both cardiac and skeletal muscle excitability are altered in critically ill patients with sepsis. Studies are planned to determine whether there is also loss of excitability in peripheral nerves and the central nervous system in these patients.

Critical Illness Polyneuropathy

A sensory-motor axonal polyneuropathy commonly develops in the setting of critical illness. This was first described by Bolton *et al*. [29], who called it critical illness polyneuropathy (CIP). During a period of critical illness, with sepsis and multi-organ failure, their patients developed a severe sensory-motor polyneuropathy. CIP was convincingly shown to be a distal sensory and motor axonal neuropathy, differing from the Guillain-Barré syndrome on electrophysiologic and morphologic studies [30]. The clinical, electrophysiologic, and pathologic features have been detailed [29–32], and in the setting of critical illness, these characteristics define a distinctive form of acute polyneuropathy.

Clinical features

The clinical features of CIP are distally predominant limb weakness and reduced reflexes. Failure to wean from artificial respiration is common and may be the first recognized manifestation. Muscle atrophy is present, but is a late finding not seen until the second or third month of illness. Sensory loss can be present, but is usually difficult to demonstrate in patients unable to cooperate with the examination due to coexistent encephalopathy, an even more common complication of critical illness. If there is reduced limb movement after painful stimulation of the distal limb and facial grimacing, limb weakness should be suspected. Cranial nerve involvement is rare and should suggest the possibility of another neuromuscular disorder.

Witt *et al*. [33] prospectively evaluated 43 patients with sepsis and multiple organ failure who had been in the ICU for a mean of 28 days (range of 5 to 89 days). All patients had evidence of encephalopathy. Thirty-five percent had clinical findings consistent with neuropathy, defined as distal weakness and hyporeflexia or inability to wean from the respirator. Twice as many (70%) had electrophysiologic evidence of an axonal polyneuropathy. The severity of the neuropathy correlated with the total time in the ICU, and in those who survived the period of critical illness (50%), recovery was as expected from an acute axonal neuropathy. Those patients who had mild-to-moderate axonal loss recovered fully over months, as a result of collateral sprouting from remaining motor neurons. Those with severe neuropathy requiring axonal regeneration for recovery either had no recovery or had a significant persistent deficit.

The major risk factor for the development of CIP is the presence of the systemic inflammatory response syndrome (SIRS). SIRS is a systemic response that occurs as a result of infection or other injuries, such as burns or trauma. The term sepsis is used when SIRS occurs in the setting of infection. Witt *et al*.'s [33] prospective study of patients with sepsis and multiorgan failure demonstrated clinical CIP in 35%. Lacomis *et al*. [1] evaluated 92 patients in the ICU over a 4.5-year period. In those who developed acute weakness, the most common cause was myopathy (42%), with an acute neuropathy (critical illness polyneuropathy) occurring in 13%. Other prospective studies have yielded a range of values for the incidence of CIP, from 33% to 44% [34,35,36••], and much higher if electrophysiologic techniques are used. This wide range has largely been due to the varying definitions used for CIP and the difficulty in separating it from the acute myopathy that can occur in the same setting [4,14].

DeLetter *et al*. [36••] prospectively evaluated 98 critically ill patients for risk factors for the development of polyneuropathy or myopathy. They combined CIP and CIM cases and termed the disorder CIPNM. The presence of SIRS combined with the Acute Physiology and Chronic Health Evaluation (APACHE)-III score, a quantitative scale of disease severity based on clinical and physiologic data, was a good predictor for the development of neuropathy or myopathy. A high-risk group could be identified by the presence of SIRS and an APACHE-III score greater than 85, in which 72% of patients developed CIPNM. A low-risk group (8% developed CIPNM) was defined by the absence of SIRS and an APACHE-III score less than 70.

Electrophysiologic and pathologic features

Electrophysiologic studies of CIP are those of an axonal neuropathy [30–33,37], with nerve conduction studies characterized by reduced motor and sensory response amplitudes. Some patients with acute weakness have reduced motor response amplitudes with preserved sensory responses [38]. These individuals may have a motor variant of CIP, or more likely have critical illness myopathy

[4,14,39]. Repetitive nerve stimulation studies of neuromuscular transmission are unremarkable, unless there is persistent pharmacologic neuromuscular blockade. Needle EMG examination of limb muscle often is notable for spontaneous activity (fibrillation potentials and positive sharp waves) with the muscle at rest. With voluntary muscle activation, there may be an excess of polyphasic MUPs. In significantly weak muscles, these MUPs are recruited with an increased recruitment ratio. These features on needle EMG examination are consistent with acute denervation. Phrenic nerve conduction studies are often absent in those with severe neuropathy, and needle EMG examination of the diaphragm can demonstrate denervation [40].

Nerve biopsy and postmortem autopsy studies have been consistent with an acute axonal sensory-motor neuropathy. The pathology is that of axonal degeneration of both sensory and motor fibers without evidence of significant inflammation or of primary demyelination [29,31,41]. DeLetter *et al*. [36••] prospectively performed muscle biopsy on 30 patients whom they characterized as having CIPNM. In these biopsy specimens, neuropathic changes were seen in 37% of patients, myopathic changes in 40%, and both in 23%, emphasizing the frequent coexistence of both CIP and CIM.

Pathophysiology

The pathogenesis of CIP is largely speculative. As noted previously, pathologic specimens reveal acute primary axonal degeneration of sensory and motor nerve fibers without inflammation. Prospective studies have not supported a causative role of drugs, particularly corticosteroids, NMBAs, or aminoglycoside antibiotics [31,34,36••,42•]. No specific toxin, infectious agent, or nutritional deficiencies have been identified in this disorder. The current view is that cytokines and free radicals associated with SIRS adversely affect the microcirculation, producing endoneurial hypoxia and ultimately distal axonal degeneration [43]. This view seems to be supported by the finding that critically ill patients with a high APACHE-III score and SIRS are most prone to the development of CIP [36••].

Systemic inflammatory response syndrome, and particularly sepsis, activate humoral and cellular responses [43]. Humoral responses occur locally in tissues, as antigen-presenting cells produce proinflammatory cytokines such as tumor necrosis factor, interleukin 1, and free radicals. These humoral factors, together with local cellular responses, interact with adhesion molecules on platelets and endothelial cells, producing platelet-fibrin aggregates that may reduce capillary flow. Cytokines released in sepsis have histamine-like effects that may increase microvascular permeability, produce endoneurial edema, and then endoneurial hypoxia. An increase in local tissue nitric oxide or endovascular relaxing factor may cause arteriolar dilatation, further reducing capillary flow. The microvascular structures of peripheral nerve lack autoregulation, which may make nerves particularly vulnerable to these effects [43].

Druschky *et al*. [42•] have found a low-molecular weight neurotoxic agent that may play a role in the pathogenesis of CIP as well. They prospectively studied critically ill patients using an in vitro cell culture assay of neurotoxicity. This assay demonstrated serum neurotoxicity in 12 of 16 patients (75%) with CIP. However, 50% of patients without CIP also showed the same neurotoxic effect in their serum. Further work is needed to define the possible role of this, or other putative neurotoxins, in sepsis.

Conclusions

When CIM or CIP develop in a critically ill patient with the prototypical clinical and electrophysiologic features described here, there is little difficulty in identifying them and making a distinction between the two. However, many patients have features of both disorders and are not as easy to classify [14,44]. Both CIP and CIM present with limb weakness or a failure to wean from ventilatory support. Detailed electrophysiologic studies, including those done during recovery, are usually necessary to determine which is present. Yet the findings most easily identified in the ICU setting, fibrillation potentials and reduced CMAP amplitudes, are common to both disorders. Sensory responses are often limited by edema or may be low amplitude due to pre-existing neuropathy. The assessment of motor unit potential morphology and recruitment may be hampered by poor patient effort due to the presence of encephalopathy. The technique of direct muscle stimulation may be helpful, but only in those with severe CIM. In virtually all patients, however, the identification of a neuromuscular disorder (CIP, CIM, or both) as a cause of delayed recovery can help with management.

The mechanisms involved in the development of critical illness neuropathy and myopathy are likely multifactorial. The use of nondepolarizing neuromuscular blocking agents and corticosteroids are the most clearly established risk factors in CIM; however, sepsis and immobility from any cause may also contribute. How these various factors combine to cause the unique structural and electrophysiologic changes found in muscle from patients with CIM remains unknown. Understanding this complex disorder will shed light on the multiple factors that function in ongoing regulation of both muscle structure and physiology in vivo.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Lacomis D, Petrella JT, Giuliani MJ: **Causes of neuromuscular weakness in the intensive care unit: a study of ninety-two patients.** *Muscle Nerve* 1998, **21:**610–617.
2. Rich MM, Bird SJ, Raps EC, *et al.*: **Direct muscle stimulation in acute quadriplegic myopathy.** *Muscle Nerve* 1997, **20:**665–673.
3. •• Trojaborg W, Weimer LH, Hayes AP: **Electrophysiologic studies in critical illness associated weakness: myopathy or neuropathy—a reappraisal.** *Clin Neurophysiol* 2001, **112:**1586–1593.

A detailed electrophysiologic study in patients with critical illness myopathy utilizing direct muscle stimulation, quantitative electromyography, and motor unit estimation.

4. • Lacomis D, Zochodne DW, Bird SJ: **Critical illness myopathy.** *Muscle Nerve* 2000, **23:**1785–1788.

A review article that suggests diagnostic criteria for critical illness myopathy.

5. David WS, Roehr CL, Leatherman JW: **EMG findings in acute myopathy with status asthmaticus, steroids and paralytics: clinical and electrophysiologic correlation.** *Electromyogr Clin Neurophysiol* 1998, **38:**371–376.
6. Campellone JV, Lacomis D, Kramer DJ, *et al.*: **Acute myopathy after liver transplantation.** *Neurology* 1998, **50:**46–53.
7. Hanson P, Dive A, Brucher JM, *et al.*: **Acute corticosteroid myopathy in intensive care patients.** *Muscle Nerve* 1997, **20:**1371–1380.
8. Hirano M, Ott BR, Raps EC, *et al.*: **Acute quadriplegic myopathy: a complication of treatment with steroids, nondepolarizing blocking agents, or both.** *Neurology* 1992, **42:**2082–2087.
9. Hoke A, Rewcastle NB, Zochodne DW: **Acute quadriplegic myopathy unrelated to steroids or paralyzing agents: quantitative EMG studies.** *Can J Neurol Sci* 1999, **26:**325–329.
10. Berg DK, Hall ZW: **Increased extrajunctional acetylcholine sensitivity produced by chronic post-synaptic neuromuscular blockade.** *J Physiol* 1975, **244:**659–676.
11. Op de Coul AA, Lambregts PC, Koeman J, *et al.*: **Neuromuscular complications in patients given Pavulon (pancuronium bromide) during artificial ventilation.** *Clin Neurol Neurosurg* 1985, **87:**17–22.
12. Rich MM, Teener JW, Raps EC, *et al.*: **Muscle is electrically inexcitable in acute quadriplegic myopathy.** *Neurology* 1996, **46:**731–736.
13. Zochodne DW, Ramsay DA, Saly V, *et al.*: **Acute necrotizing myopathy of intensive care: electrophysiological studies.** *Muscle Nerve* 1994, **17:**285–292.
14. Bird SJ: **Critical care: myopathies and disorders of neuromuscular transmission.** In *Neuromuscular Function and Disease.* Edited by Brown WF, Bolton CF, Aminoff MJ. Philadelphia: Harcourt-Brace; 2002:1507–1520.
15. Road J, Mackie G, Jiang T, *et al.*: **Reversible paralysis with status asthmaticus, steroids, and pancuronium: clinical electrophysiological correlates.** *Muscle Nerve* 1997, **20:**1587–1590.
16. Ashcroft FM: *Ion Channels and Disease.* London: Academic Press; 2000.
17. Rouleau G, Karpati G, Carpenter S, *et al.*: **Glucocorticoid excess induces preferential depletion of myosin in denervated skeletal muscle fibers.** *Muscle Nerve* 1987, **10:**428–438.
18. Massa R, Carpenter S, Holland P, Karpati G: **Loss and renewal of thick myofilaments in glucocorticoid-treated rat soleus after denervation and reinnervation.** *Muscle Nerve* 1992, **15:**1290–1298.
19. Rich MM, Pinter MJ, Kraner SD, Barchi RL: **Loss of electrical excitability in an animal model of acute quadriplegic myopathy.** *Ann Neurol* 1998, **43:**171–179.
20. •• Rich MM, Pinter MJ: **Sodium channel inactivation in an animal model of acute quadriplegic myopathy.** *Ann Neurol* 2001, **50:**26–33.

A patch clamp analysis of sodium current in an animal model of critical illness myopathy demonstrating that an altered voltage dependence of sodium channel inactivation may underlie electrical inexcitability of muscle in this syndrome.

21. Pappone PA: **Voltage-clamp experiments in normal and denervated mammalian skeletal muscle fibres.** *J Physiol* 1980, **306:**377–410.
22. Rich MM, Kraner SD, Barchi RL: **Altered gene expression in steroid-treated denervated muscle.** *Neurobiol Dis* 1999, **6:**515–522.
23. Ji S, Sun W: **Voltage-dependent regulation of modal gating in the rat SkM1 sodium channel expressed in Xenopus oocytes.** *J Gen Physiol* 1994, **104:**625–643.
24. Bendahhou S, Cummins TR: **Serine-1321-independent regulation of the mu 1 adult skeletal muscle Na+ channel by protein kinase C.** *Proc Natl Acad Sci* 1995, **92:**12003–12007.
25. Zhang Y, Hartmann HA: **Glycosylation influences voltage-dependent gating of cardiac and skeletal muscle sodium channels.** *J Membr Biol* 1999, **171:**195–207.
26. • Larsson L, Li X, Edstrom LI, *et al.*: **Acute quadriplegia and loss of muscle myosin in patients treated with nondepolarizing neuromuscular blocking agents and corticosteroids: mechanisms at the cellular and molecular levels.** *Crit Care Med* 2000, **28:**34-45.

A study examining protein and mRNA levels of muscle structural proteins in muscle biopsies from patients with critical illness myopathy.

27. Showalter CJ, Engel AG: **Acute quadriplegic myopathy: analysis of myosin isoforms and evidence for calpain-mediated proteolysis.** *Muscle Nerve* 1997, **20:**316–322.
28. Rich MM, McGarvey ML: **ECG changes during septic shock. Cardiology 2002,** in press.
29. Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ: **Polyneuropathy in critically ill patients.** *J Neurol Neurosurg Psychiatry* 1984, **47:**1223–1231.
30. Bolton CF, Laverty DA, Brown JD, *et al.*: **Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain- Barre syndrome.** *J Neurol Neurosurg Psychiatry* 1986, **49:**563–573.
31. Zochodne DW, Bolton CF, Wells GA, *et al.*: **Critical illness polyneuropathy.** *Brain* 1987, **110:**819–842.
32. Zifko U, Zipko H, Bolton CF: **Clinical and electrophysiological findings in critical illness polyneuropathy.** *J Neurol Sci* 1998, **159:**186–198.
33. Witt NJ, Zochodne DW, Bolton CF, *et al.*: **Peripheral nerve function in sepsis and multiple organ failure.** *Chest* 1991, **99:**176–184.
34. Berek K, Margreiter J, Willeit J: **Polyneuropathies in critically ill patients: a prospective evaluation.** *Intensive Care Med* 1993, **22:**849–855.
35. Leijten FS, Harinck-De Weerd JE, Poortvliet DC, De Weerd AW: **Critical illness polyneuropathy in multiple organ dysfunction syndrome and weaning from the ventilator.** *Intensive Care Med* 1996, **22:**856–861.
36. •• DeLetter MC, Schmitz PI, Visser LH, *et al.*: **Risk factors for the development of polyneuropathy and myopathy in critically ill patients.** *Crit Care Med* 2001, **29:**2281–2286.

This study prospectively evaluated risk factors for the development of critical illness polyneuropathy or critical illness myopathy. They found that a high-risk group could be identified by the presence of systemic inflammatory response syndrome and more severe critical illness, as measured by the Acute Physiology and Chronic Health Evaluation (APACHE)-III score.

37. Bolton CF: **Electrophysiologic studies of critically ill patients.** *Muscle Nerve* 1987, **10:**129–135.
38. Hund E, Genzwurker H, Bohrer H, *et al.*: **Predominant involvement of motor fibres in patients with critical illness polyneuropathy.** *Br J Anaesth* 1997, **78:**274–278.

39. Teener JW, Rich MM, Bird SJ: **Other causes of acute weakness in the intensive care unit.** In *Critical Care Neurology.* Edited by Miller DH, Raps EC. Boston: Butterworth-Heinemann; 1999:69–89.
40. Bolton CF: **Clinical neurophysiology of the respiratory system.** *Muscle Nerve* 1993, **16:**809–818.
41. Zochodne DW, Bolton CF, Gilbert JJ: **Polyneuropathy in critical illness: pathologic features.** *Ann Neurol* 1985, **18:**160–166.
42.• Druschky A, Herkert M, Radespiel-Troger M, *et al.*: **Critical illness polyneuropathy: clinical findings and cell culture assay of neurotoxicity assessed by a prospective study.** *Intensive Care Med* 2001, **27:**686–693.
A cell culture assay of neurotoxicity may suggest that a low-molecular weight toxin may play a role in the pathogenesis of critical illness polyneuropathy.
43. Bolton CF: **Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations.** *Crit Care Med* 1996, **24:**1408–1416.
44. Breuer AC: **Critical illness polyneuropathy: an outdated concept.** *Muscle Nerve* 1999, **22:**422–424.