Neurological Sequelae of Sepsis: II) Neuromuscular Weakness

Hubertus Axer[*,1,2], Bernd F.M. Romeike[3], Frank Brunkhorst[2,4], Jan Zinke[1,2], Thomas M. Ringer[1] and Albrecht Günther[1,2]

[1]*Hans Berger Clinic for Neurology, Jena University Hospital, Friedrich-Schiller-University, Erlanger Allee 101, D-07747 Jena, Germany*

[2]*CSCC – Center for Sepsis Control and Care, Jena University Hospital, Friedrich-Schiller-University, Erlanger Allee 101, D-07747 Jena, Germany*

[3]*Department of Neuropathology, Friedrich-Schiller-University Jena, Erlanger Allee 101, D-07747 Jena, Germany*

[4]*Paul-Martini-Clinical Sepsis Research Unit, Jena University Hospital, Friedrich-Schiller-University, Erlanger Allee 101, D-07747 Jena, Germany*

Abstract: Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) have been established as separate entities of muscular weakness in critically ill patients, although both may be associated to each other in some respects. Both are associated to systemic inflammatory response syndrome, sepsis, and severe sepsis. Major signs of nerve and muscle disturbances in critically ill patients are muscle weakness and problems of weaning from the ventilator. Electroneurographic measurements help to detect CIP early in the course of the disease, while muscle biopsy seems to date the diagnostic tool of choice to detect CIM. Sepsis therapy is the major target to prevent the development of CIP and CIM. However, no specific therapy of CIP and CIM has been established in the past. Therefore, management of patients with CIP and CIM is mainly supportive. Neuromuscular weakness cause elongated times of ventilation, elongated hospital stay, elongated times of rehabilitation, and increased mortality. This review provides an overview of clinical and diagnostic features of CIP and CIM, and summarizes current pathophysiological and therapeutic concepts.

Keywords: Sepsis, critical illness polyneuropathy, critical illness myopathy, neuromuscular weakness.

INTRODUCTION

Neurological complications of sepsis and systemic inflammatory response syndrome (SIRS) [1] are common in critically ill patients and comprise the peripheral nervous system, the muscles, and the brain. All these complications cause elongated times of ventilation, hospital stay and rehabilitation, and increased mortality of patients besides their underlying disease. Therefore, it represents a significant economic burden as well as a significant limitation of quality of life for the individual patient. Thus, a neurological examination and evaluation of critically ill patients on ICU is most relevant [2]. This review aims at the description of disturbances of the peripheral nerves and muscles in the course of sepsis. Peripheral muscle force is markedly decreased in sepsis, without evidence for an increased fatigability [3]. Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) have been established as separate entities of muscular weakness [4-10], although both may be associated to each other in some respects.

*Address correspondence to this author at the Hans Berger Clinic for Neurology, Jena University Hospital, Friedrich-Schiller-University Jena, Erlanger Allee 101, D-07747 Jena, Germany; Tel: ++49 +3641 9323454; Fax: ++49 +3641 9323402; E-mail: Hubertus.Axer@med.uni-jena.de

PERIPHERAL NERVES – CRITICAL ILLNESS POLYNEUROPATHY

Definition and Clinical Features

Muscle weakness and atrophy in the course of sepsis have been described in 1892 by Osler [11]. First systematic clinical studies on patients with CIP have been conducted in the 1980s [12,13].

CIP is clinically characterized by a flaccid and symmetrical muscle weakness of the extremities, loss of deep tendon reflexes [9, 10], and atrophy of the muscles. Failure of weaning from the ventilator may be a first sign on ICU. Although the motor failure often predominates [14] distal loss of sensitivity to light touch, pain, temperature, and vibration may also be apparent [10].

Epidemiology

Neuromuscular disturbances are common complications in critically ill patients (about 50%) with mechanical ventilation, sepsis, or multiple organ failure [15]. Incidence rates of CIP depend on the specific patient population studied, diagnostic criteria used, timing of diagnosis, and severity of critical illness [10]. 70% of the patients with sepsis and multiorgan failure develop CIP according to electrophysiologic criteria and 30% have the clinical signs of

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difficulty in weaning from assisted ventilation, weakness of limb muscles, and reduced or absent deep tendon reflexes [16]. About 25% of patients who undergo 7 or more days of mechanical ventilation have clinical signs of CIP [17] and axonal polyneuropathy is related to the severity of multiple-organ-dysfunction syndrome in these patients [18]. It has been demonstrated that the development of CIP during severe sepsis and septic shock (53% of patients) causes a significant elongation of mechanical ventilation and increased the duration of hospital stay [19]. Moreover, CIP has been found to be associated to increased in-hospital mortality [20].

The outcome seems difficult to predict from clinical and electrophysiological data [21]. Full recovery from polyneuropathy occurred among the 53% who survived the acute phase of sepsis [16]. However, longer length of stay in ICU, longer duration of sepsis and greater body weight loss have been associated to poor recovery [21]. An overall mortality rate of 26-71% of patients with CIP has been described [22]. The majority of survivors have persistent functional disabilities in activities, quality of life, and restrictions in autonomy and participation 1 year after onset of CIP [23]. Therefore, prolonged rehabilitation treatment is necessary. Severe CIP patients recover slowly because the axon may only regenerate 1 mm per day [24,25]. Neurophysiologic evidence of chronic partial denervation can be found up to 5 years after ICU discharge in more than 90% of long-stay patients [26].

Diagnostic Features

Because the patients have to be cooperative and alert for a complete neurological status, in many cases of critically ill patients the diagnosis cannot be done purely on clinical evaluation.

Therefore, electrophysiological measurements are most helpful to diagnose CIP early in course of the disease. Typical electroneurography (ENG) findings are reductions of amplitudes of compound motor action potentials (CMAPs) as well as sensory nerve action potentials. These are signs of prevailing axonal damage which is typical for CIP (Fig. **1**). In contrast, signs of demyelination in ENG i.e. reductions of conduction velocities play a minor role in ENG findings of CIP. ENG signs of axonopathy may be present as early as 4 days after ICU admission [5]. Moreover, electrophysiological disturbances can be found in the early stage of the inflammatory response 2-5 days after admission to ICU before clinical evidence of neuromuscular damage evolves [27]. While the involvement of motor fibers predominates in most cases [14] also sensory abnormalities are found [28].

In contrast, one of the electromyographic signs of axonal denervation is spontaneous activity (fibrillations and positive sharp waves) in the relaxed muscle (Fig. **2**) and appears earliest about 14 days after axonal damage. Median time to develop denervation in EMG was found to be 21 days after admission to the ICU [14] and therefore can not be used as

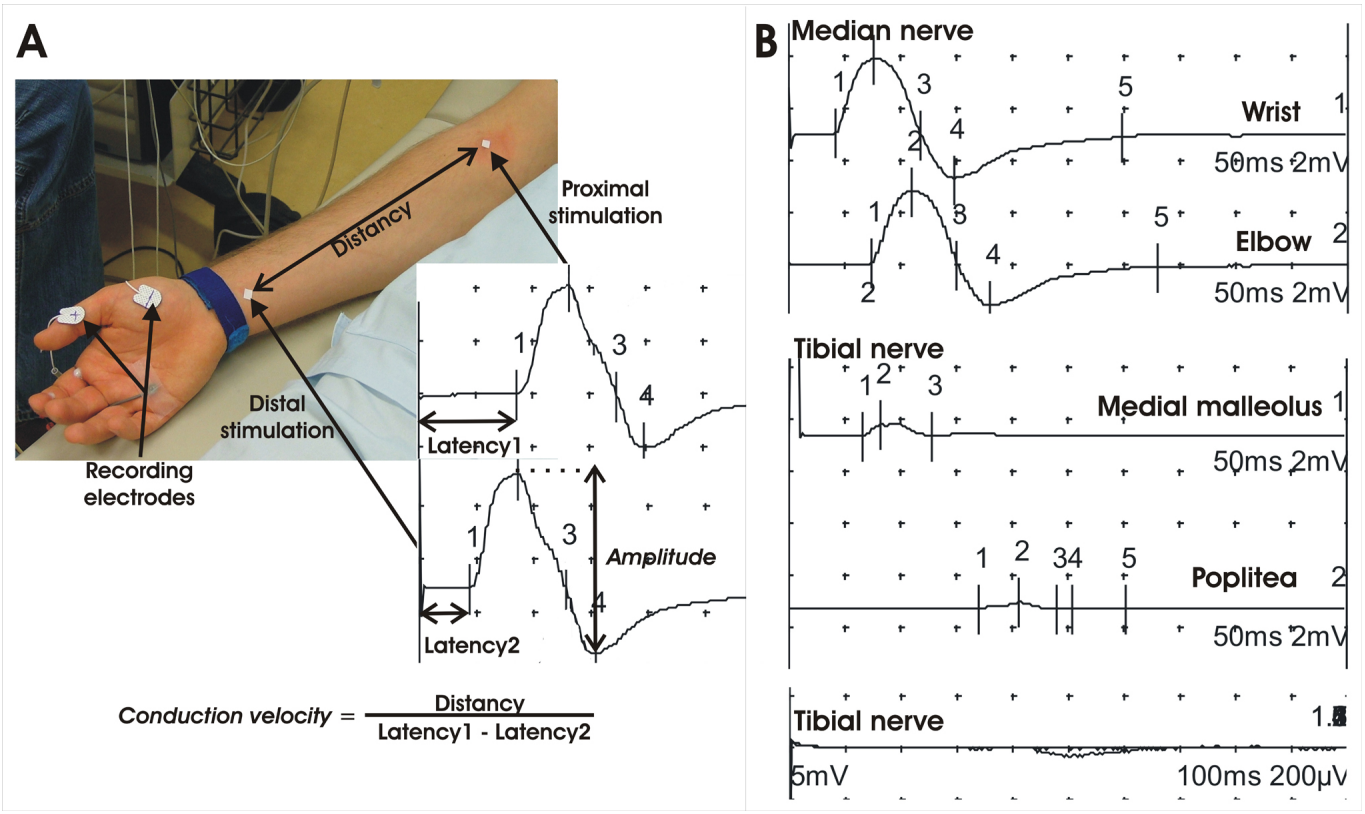

Fig. (1). Electroneurography. **A**) Principle: The nerve is electrically stimulated and a compound motor action potential (CMAP) is recorded from the muscle. Nerve conduction velocity can be calculated from the latencies and the distance between two stimulation sites, its reduction point to demyelinisation. Amplitudes of CMAPs can be measured and its reduction point to axonal loss. **B**) Typical findings of CIP are amplitude reductions of CMAPs or missing CMAPs as sign of axonal neuropathy.

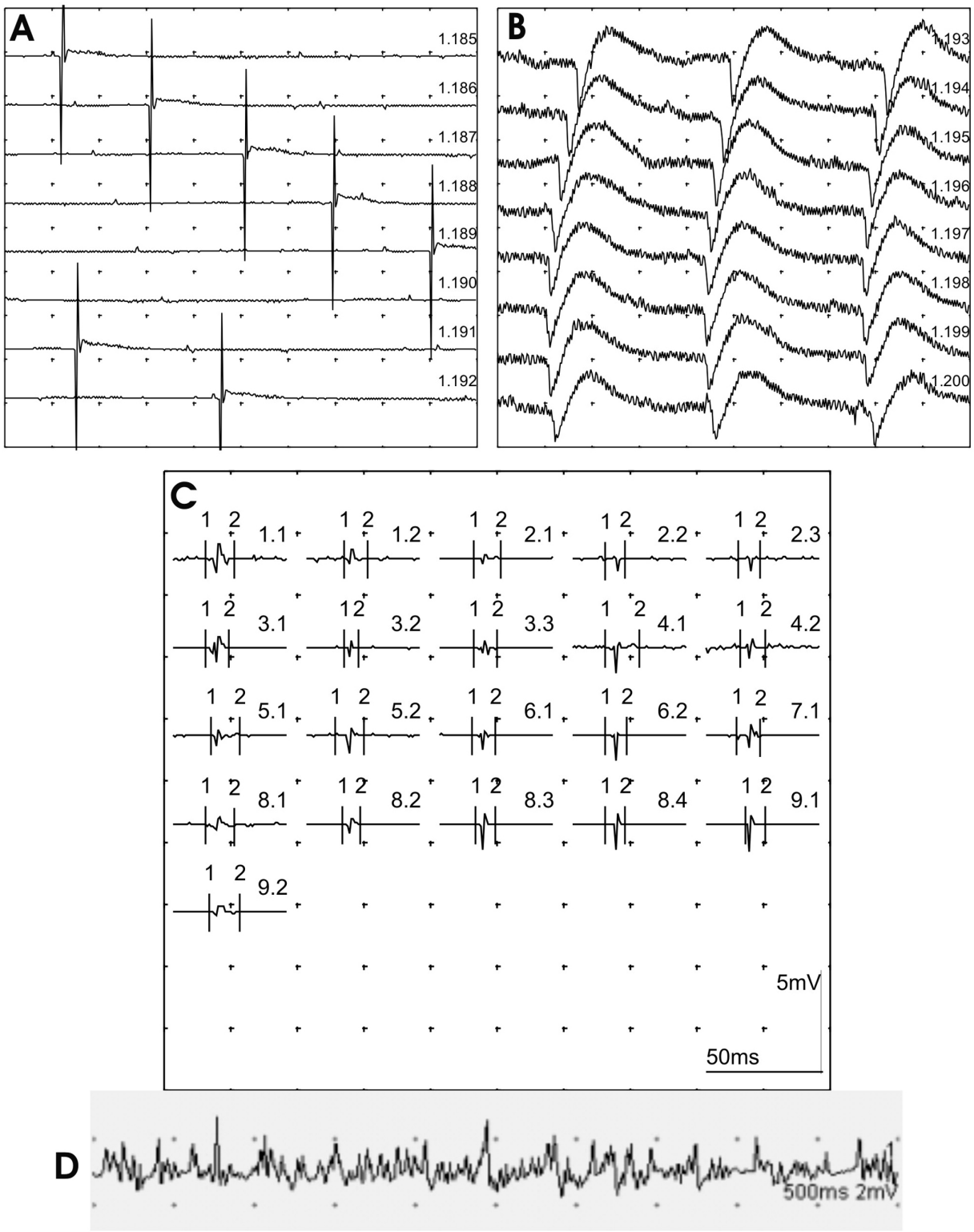

Fig. (2). Electromyography. Spontaneous activity (fibrillations (**A**) and positive sharp waves (**B**)) in EMG may occur in CIM and in CIP. EMG characteristics of myopathic changes are low amplitude and polyphasic motor unit potentials (MUP) recorded on slight voluntary contraction of the muscle (**C**). Another sign is a low amplitude interference pattern under maximum voluntary contraction of the muscle (**D**).

an early detection strategy for CIP. However, spontaneous activity also can be apparent in myopathy and could be found in CIM at earlier time points [24]. Therefore, ENG is the gold standard to assess nerve fiber function in CIP, early in the course of the disease and independent from consciousness and cooperation of the patient.

A clear correlation between motor electrophysiology and histopathological abnormalities could not be demonstrated in all studies [28, 29]. Morphological changes in CIP can be

seen in nerve biopsies e.g. from the suralis nerve. It essentially shows axonal neuropathic changes e.g. loss of fibers with signs of Wallerian degeneration [30]. However, these changes can be seen later in the course of the disease than ENG changes occur. Thus, ENG is superior in the diagnosis of CIP to clinical neurological examination [31] or nerve biopsies, maybe because ENG can also detect functional nerve failure e.g. impairment of axonal transport and transmembrane potential [30]. A recent study showed that reversible neuropathic changes in septic rats were caused by inactivation of sodium channels as an important contributor to reduce excitability [32], which may preceed axonal damage.

Risk Factors and Pathophysiology

The APACHE III score as a quantitative index of disease severity and the presence of SIRS are significantly related with the risk to develop CIP [33]. The Acute Physiology and Chronic Health Evaluation (APACHE) System represents a numerical score between 0 and 299 based on weighted three principal data categories: physiologic measurements; chronic health status; and chronological age.

Mechanical ventilation is another risk factor for CIP [20] as well as the severity of illness at the time of ICU admission [34] and multiorgan failure [35]. Parenteral nutrition has been suggested to be a risk factor for CIP [20,36] as well as side effects of administered drugs e.g. aminoglycosid antibiotics [18, 34].

The pathophysiology of CIP is complex and still unclear [10]. The strong association between sepsis and CIP [37] led to the assumption that both share common pathophysiological principles [16]. A significant correlation between serum concentration of endotoxin and interleukin-2-receptors (IL2-R) and the reduction of compound motor action potentials in electroneurography has been found recently [38]. Significantly elevated levels of tumor necrosis factor (TNF) and interleukin-6 (IL-6) were found in patients with CIP compared to controls [39]. Druschky *et al.* found neurotoxicity in 12 of 16 CIP patients in an in-vitro serum toxicity assay on cultured rat motoneurons [40]. Thus, direct or indirect neurotoxic effects induced by inflammatory cascades have been hypothesized to play a role in the development of CIP.

In addition, a sepsis related disturbance of microcirculation is hypothesized to also play a crucial role in CIP [41]. It has been demonstrated that E-selectin expression is enhanced in the endothelium of microvasculature of peripheral nerves [42]. Other factors are hyperglycemia and cytokines, which influence microvascular permeability [43]. Resulting of endoneural edema and extravasation of inflammatory cells [8] may increase hypoxemia, which leads in addition to direct cytotoxic effects of cytokines to hypoxic damage of nerve axons [44]. Catecholamine support was associated to the development of CIP [37], which may also point to the relevance of microcirculatory disturbances.

In addition, it has been shown that high blood glucose levels are associated to the development of CIP [16, 34, 45] and a linear relationship has been demonstrated between blood glucose levels and the risk to develop CIP [46]. It has been hypothesized that hyperglycemia and relative insulin deficiency may hamper nerve function caused by direct neurotoxic effects e.g. mitochondrial dysfunction [47] as well as missing neuroprotective and anti-inflammatory effects of insulin [7].

Therapeutical Options

Of course, state of the art therapy of sepsis [48] is the main target to prevent CIP. The treatment of sepsis and septic shock is beyond the scope of this review. However, up to date no specific therapy or preventive measures of CIP are known [9].

It has been found that intensive insulin therapy may reduce CIP by 44% [46] and 48% [47], so substantial evidence exists that intensive insulin therapy reduces the incidence of CIP [49]. However, intensive insulin therapy place patients with severe sepsis at increased risk for serious adverse events related to hypoglycemia [50], which may outweight the beneficial effects regarding CIP. Therefore, to date it cannot per se be recommended.

Intravenous immunoglobulin (IVIG) therapy has been shown to reduce mortality in patients with sepsis and septic shock in small trials [51]. In a retrospective analysis of a small number of patients with severe sepsis and multiorgan failure was found that IVIG treatment affected the development of CIP [52]. However, well designed placebo-controlled studies are still missing.

THE MUSCLE – CRITICAL ILLNESS MYOPATHY

Definition and Clinical Features

The first case of acute quadriplegic myopathy on ICU was described in 1977 by MacFarlane and Rosenthal [53], who described an acute muscle weakness during treatment of status asthmaticus with mechanical ventilation, neuromuscular blocking agents and corticosteroids. CIM shares the symptoms of muscle weakness and muscle atrophy with CIP [54]. Therefore, it cannot be distinguished from CIP based on pure neurologic examination alone [4,10]. In some cases CIP and CIM coexist [55]. Nevertheless, CIM is a primary disease of the muscle, a myopathy. Different forms of CIM can be found [56] using distinct diagnostic procedures.

Epidemiology

Myopathy is common among ICU patients. It is believed that CIM is at least as common as CIP [57] or up to three times more common than CIP [58,59]. Because diagnosis of CIM is difficult and a large overlap to CIP exists, CIM may often be underdiagnosed and, therefore, prevalence data of CIM is difficult to collect [60]. Data allowing to distinguish CIP and CIM revealed similar proportions of patients diagnosed with CIP, CIM, and a combination of both [15]. The long-term outcome of CIM is not as well known as the course of CIP [61]. One retrospective study found that patients with acute myopathy and acute axonal sensorimotor polyneuropathy had similar functional outcomes at 4 months [59]. Nevertheless, it is thought that CIM has a better prognosis than CIP [25] since muscles regenerate faster than nerves [61].

Diagnostic Features

In the electrophysiological assessment CIM may share reductions of amplitudes of compound motor unit potentials

in ENG and spontaneous activity in the EMG with CIP. However, EMG characteristics of myopathic changes are low amplitude and maybe polyphasic motor unit potentials (MUP) [58]. These are recorded on slight voluntary contraction of the muscle. Another sign is a low amplitude interference pattern under maximum voluntary contraction of the muscle (Fig. **2**). However, these measurements demand a cooperative and conscious patient, which is often not the case in critically ill patients.

Therefore, direct muscle stimulation (DMS) has recently been suggested as a diagnostic tool [62-64]. The principle of DMS is the direct electrical stimulation of the muscle fibres, which makes the procedure independent from voluntary muscle contractions. It is a simple, non-invasive, bedside examination and is therefore a promising tool in the differential diagnosis of ICU-acquired weakness.

However, muscle biopsy offers the most reliable tool to diagnose CIM and therefore is actually regarded to be the gold standard to diagnose CIM [54,63]. Different types of myopathic changes have been described [7,56]:

Critical illness myopathy shows histopathological changes including abnormal variation of muscle fibre size, fibre type II myofibre atrophy [65], angulated fibres, rimmed vacuoles, internalized nuclei, fatty degeneration, single fibre necrosis, and fibrosis [30,56]. Thick filament myopathy is characterized by the loss of myosin filaments [66,67]. Although loss of thick filaments also occurs in other myopathies, intraveneous corticosteroid exposure has been suggested as a possible cause [66]. In acute necrotizing myopathy severe myonecrosis occurs with vacuolization and phagocytosis of muscle fibres (56). In these cases elevated serum creatinin kinase (CK) may be found [6].

Risk Factors and Pathophysiology

Although CIM may occur in ARDS patients [68,69], sepsis and SIRS are mainly associated to CIM [33]. Much evidence exists that a dysregulation of sodium channel gating in CIM may contribute to muscle inexitability [70,71]. Electrical inexitability of the muscle membrane has been demonstrated in patients with acute quadriplegic myopathy [64]. Haeseler *et al.* [72] found that endotoxin is able to interact with voltage-gated sodium channels and may lead to reduced muscle membrane exitability during sepsis. Rossignol *et al.* [73] found that chronic inflammation and sepsis can induce a decrease in contractile performances of the muscle in septic rats and accelerated kinetics of atracurium possible related to increased expression of the ryanodine receptor RyR1.

Besides sepsis the use of non-depolarizing neuromuscular blocking agents [74] and the use of corticosteroids seem to be associated to the development of CIM [17,33,55,75], although other studies have not been able to find a significant relationship [35,68]. A recent study [76] on patients with severe ARDS found that early administration of neuromuscular blocking agents improved the 90-day survival and increased the time-off the ventilator without increasing muscle weakness.

Intensive care unit-acquired paresis 7 days after awakening was associated with increased blood glucose and with biological evidence of hypogonadism in men, while an association with hormonal dysfunction was not detected in women [77].

Corticosteroids may also play an important role in muscle wasting in CIM [78]. Muscle wasting [54,79] represents a depletion of muscle proteins due to hypercatabolic conditions. It has been shown that sepsis is associated with a pronounced catabolic resonse in skeletal muscles [80] leading to a degradation of myofibrillar proteins. Cytokines and hormones (e.g. steroids) are able to activate muscle proteolysis [81]. TNF-α acts directly on the muscle cell to induce protein degradation [82]. Both myogenic and neurogenic muscular atrophy share the induction of myofibre-specific ubiquitine/proteosome pathways, while in CIM a strong induction of transforming growth factor ß/MAPK pathways has been demonstrated [83].

Therapeutical Options

There is no specific treatment known for the therapy of CIM [54,84]. Sepsis therapy seems to be the major target to prevent the development of CIM [84]. Management of patients with CIM is supportive, consisting of nutrititional support, physical therapy, and daily trials of decreased ventilatory support [74]. Moreover, it is recommended that the use of non-depolarizing neuromuscular blocking agents and glucocorticoids should only be used in critically ill patients when absolutely necessary [74]. In critically ill patients, glutamine supplementation may be associated with a reduction in complication and mortality rates [85], although the effect on CIM or CIP has not been proven.

A new approach for managing mechanically ventilated patients is the reduction of deep sedation and increased rehabilitation therapy and mobilization early on ICU [86]. There is much support for the ability of mobility interventions to improve outcomes in patients on prolonged mechanical ventilation [87]. However, there is only limited evidence of the best rehabilitation method [87]. Nevertheless, Bailwey *et al.* [88] demonstrated that early activity is feasible and safe in respiratory failure patients. Multi-center studies and randomized controlled trials are still missing in this field.

CONCLUSIVE REMARKS

Major signs of nerve and muscle disturbances in critically ill patients are muscle weakness [2] and problems of weaning from the ventilator [18]. Therefore, comprehensive neurological examinations of critically ill patients at ICU help to identify complications of the nervous system [89]. Electroneurographic measurements help to detect CIP early in the course of the disease [5, 90]. In contrast, electromyography is not reliably able to detect CIM in many cases as it demands a conscious and cooperating patient. Therefore, muscle biopsy seems to date the diagnostic tool of choice to detect CIM and that may be the reason why CIM often is underdiagnosed on ICU. However, often no clearcut differentiation between CIP and CIM can be made. CIP and CIM may coexist and their relative contribution to the weakness may vary [24]. Thus, many clinicians suggest to consider it as a complex entity of polyneuromyopathy [29]. Recognizing CIP or CIM often improves management, although no specific pharmacologic

treatments are known at present [91]. Therefore, it is important to differentiate between CIP and CIM regarding epidemiological, prognostic, and maybe therapeutical considerations [63]. Many efforts of research have to be done in the future to improve early and reliable diagnosis as well as to develop still missing strategies of prevention and therapy.

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