Intensive Care Unit-Acquired Weakness 13

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13.1 Introduction

Intensive care unit-acquired weakness (ICUAW) is a severe acquired muscle weakness during critical illness and for which there is no other explanation than the critical illness itself [1]. The condition delays rehabilitation and may not be completely reversible. The acute outcome and long-term functional outcome are strongly dependent on age, co-morbidities and the length of intensive care unit stay [2].

13.2 Prevalence and Risk Factors

The prevalence of ICUAW is strongly dependent on the type of patient population studied; e.g. ICUAW occurs more frequently in patients with longer exposure to mechanical ventilation: 33 % of patients mechanically ventilated up to 5 days and 43 % of patients mechanically ventilated up to or more than 7 days develop ICUAW [3], while the frequency rises to 67 % in patients mechanically ventilated up to or more than 10 days [4]. Several risk factors/triggers in addition to mechanical ventilation have been reported: sepsis, bacteraemia, systemic inflammatory response syndrome, multiorgan failure, muscle unloading, steroid treatment, malnutrition, hyperglycaemia/insulin resistance and neuromuscular blockade [5].

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13.3 Clinical Signs

Symmetrical and flaccid weakness of limb muscles, more pronounced in proximal than distal muscles, and weakness of respiratory muscles, which is responsible for difficulties in weaning from mechanical ventilation, are the main features. Facial and ocular muscles are often spared; tendon reflexes are generally reduced, but may be normal. Sensory loss, if present, is usually localised in distal parts of the limbs and is an argument for CIP, but may be due to other causes, such as diabetes. Autonomic dysfunction may be present [6]. While ICUAW is relatively obvious in patients with a primary non-neurological disorder, it may be difficult to notice in patients with the primary lesion in the central nervous system [7]: affection of the peripheral neuromuscular compartment was considered in patients with primary central nervous system disorders when previously spastic patient developed flaccid weakness and an absence of myotatic reflexes, and weaning from mechanical ventilation could not be achieved.

13.4 Diagnosis

ICUAW may be caused by critical illness myopathy (CIM), critical illness polyneuropathy (CIP) or a combination of both [8].

13.4.1 Manual Muscle Testing

According to the American thoracic society practice guideline for the diagnosis of ICUAW [3] and others [9], the Medical Research Council (MRC) manual muscle testing (MMT) is the recommended diagnostic tool for the identification of ICUAW, due to its universal availability. The lack of a universally accepted and validated "gold standard" and inapplicability of MMT in an uncooperative or sedated patient are major limitations, but a more reliable and *universally* available test for muscle strength has not yet emerged [3]. A semi-quantification of muscle strength by MMT, using a six-point MRC scale, was recently proposed [10]: a summed score <48/60 designates "significant weakness", and a score <36/60 indicates "severe weakness"; three muscle groups in all four limbs are evaluated (arm abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion), giving a total score of 60. A simplified version of the MRC scale, consisting of four grades, i.e. 0 = paralysis, 1 = severe weakness (>50 % loss of strength), 2 = slight weakness (<50 % loss of strength) and 3 = normal strength, was developed [11] since MMT using the six-point MRC scale is more time-consuming and discriminating between strength categories at the upper part of the scale is difficult [12]. Although tested on a relatively small number (29) of patients with ICUAW, it has been stated that the simplified version is comparable to the standard MRC scale for the clinical diagnosis of ICUAW [12]. Handgrip dynamometry is an objective outcome measure and can be used as a quick diagnostic test [9], and since it is easily administrated by any

member of the multidisciplinary team, it facilitates early identification of patients who may benefit from therapy [12]. Cut-off scores less than 11 kg in males and less than 7 kg in females indicate significant weakness [12, 13].

13.4.2 Electrophysiological Testing

Electrophysiological testing is usually used in making a diagnosis of ICUAW; concentric needle EMG in 90 % of studies, nerve conduction studies (NCSs) in 84 % of studies and direct muscle stimulation [14] in 19 % of studies [3], but these tools are less universally available in clinical practice; are time-consuming, technically challenging and expensive; and require subspecialists. Nevertheless, electrophysiological tests are minimally invasive, easily reproducible and possibly bedside performed, and the results are available immediately [6]. CIP is an axonal sensorimotor polyneuropathy, which is characterised electrophysiologically by reduced amplitude of sensory nerve action potential (SNAP) and reduced compound motor action potential (CMAP); latency and nerve conduction velocities remain normal or are slightly prolonged; CIM has normal SNAP but, similar to CIP, has reduced CMAP, which is of increased duration [15]. Both CIP and CIM may have abnormal spontaneous activity on needle EMG. The duration of abnormal spontaneous activity is important for differentiation between CIP and CIM – a shorter duration (5–15 days) is an argument for myopathy, since it would need more time to evolve in the case of axonal lesion [7]. If MUPs could be estimated (requires alert and motivated patient), myopathic MUPs and the myopathic recruitment pattern could be detected in CIM [16]. CIP and CIM have some similar electrophysiological characteristics, e.g. a low amplitude of CMAP, which is consistent with functional loss of generators of the compound electrical muscle response, i.e. muscle fibres; this may be brought about by the loss of either axons or muscle fibres [7]. A pattern of recruitment of MUPs and analysis of MUP parameters may help to differentiate between CIP and CIM [7], as well as the duration of CMAP [15] and CMAP on direct muscle stimulation [14]. Unfortunately, direct muscle stimulation is fairly rarely (19 % of studies) used [3]. Nerve conduction studies and EMG cannot always differentiate between CIP and CIM, e.g. in a recent study [17] CIP was detected in 38 % and combined CIP and CIM in 17 %, and 45 % of patients were undetermined. In spite of the limitations, a simplified electrophysiological test has been proposed to be used as a *screening* test for probable CIM/CIP [9, 17]. The peroneal nerve conduction test has been validated in two multicentric studies as a 100 % sensitivity test, compared to complete nerve conduction studies and concentric EMG, in the diagnosis of probable CIM/CIP; no false-negative results were detected, but false-positive results were observed: some patients had peroneal nerve mononeuropathy when analysed by complete nerve conduction studies and EMG, so the specificity of peroneal nerve conduction study was found to be 85 % [17]; it is worth mentioning that patients with diabetes were not included in the study. The peroneal nerve conduction test cannot distinguish between CIP and CIM or combined CIP and CIM, but a suspicion of ICUAW can be confirmed. In addition the test is very

"economic" in terms of time, since it can be performed in 10 min [17] and since it does not require the patient's collaboration, it is a valuable objective method in detecting probable CIP or CIM. A potential useful application of this test could be at the early phase of an ICU stay, when volitional tests are rarely performed, and at the evaluation at ICU/acute hospital discharge – a normal test excludes CIP or CIM and the need for further neurophysiological evaluation, while an abnormal test indicates probable CIP or CIM or some peripheral nerve disorder, such as peroneal nerve mononeuropathy, which should be further evaluated by a neurologist [9].

Since 80 % of subjects with EMG/NCS abnormalities had moderate to severe muscle weakness [3], correlation between electrophysiological studies and clinically detected muscle weakness is considered good. However, most studies used MMT and electrophysiological tests sequentially, not comparing two diagnostic approaches; in spite of this, electrophysiology has aided our understanding of the mechanisms of ICUAW and can aid in determining a patient's ability to respond to certain treatments and should probably not be secondary to MMT (or any diagnostic approach) [3]. Electrophysiological alterations can be detected earlier than the clinical signs and have predictive power: e.g. a reduction of the amplitude of CMAP can precede ICUAW for 48 h in patients with sepsis [18]. Electrophysiological tests are also important with respect to acute outcome: hospital mortality is higher in patients with abnormal NCS/EMG than in those with normal findings [9].

The prevalence of electrophysiological abnormalities in ICU patients is strongly dependent on the population of patients enrolled: it varies from 46 % [1] to 76 % [9], if mostly patients with sepsis, multiorgan failure and prolonged mechanical ventilation are recruited.

Muscle biopsy and nerve biopsy are used infrequently for the diagnosis of CIM/CIP, in 26 and 6 % of studies [3].

13.4.3 Muscle Biopsy

On cryostat sections of muscle biopsy obtained 24 h after the onset of symptoms, slight structural abnormalities are present as smudgy purplish staining of muscle fibres with modified trichrome stain [19]. Myofibrillar ATP-ase activity may be reduced (Fig. 13.1a), but immunostaining for myosin heavy chains does not show attenuation or attenuation is minimal. On late biopsies (1–2/3 weeks after the onset of symptoms), histochemical activity of cytochrome–oxidase may be reduced (Fig. 13.1c) and activity of acid phosphatase increased (Fig. 13.1e). Necrotic muscle fibres (Fig. 13.2a), as well as scattered atrophic angular fibres or small group atrophy, may be present (Fig. 13.2b). By electron microscopy on longitudinal view, loss of myosin filaments is observed (Fig. 13.3). Electrophoresis of total muscle homogenate detects a reduction of myosin in relation to actin [20] (Fig. 13.4). There is no predilection for the loss of the specific myosin heavy chain isoform [21] but more severe muscle atrophy is usually observed in fast fibres. No inflammatory changes are detected in CIM [22]. Increased macrophages in endomysium may be found.

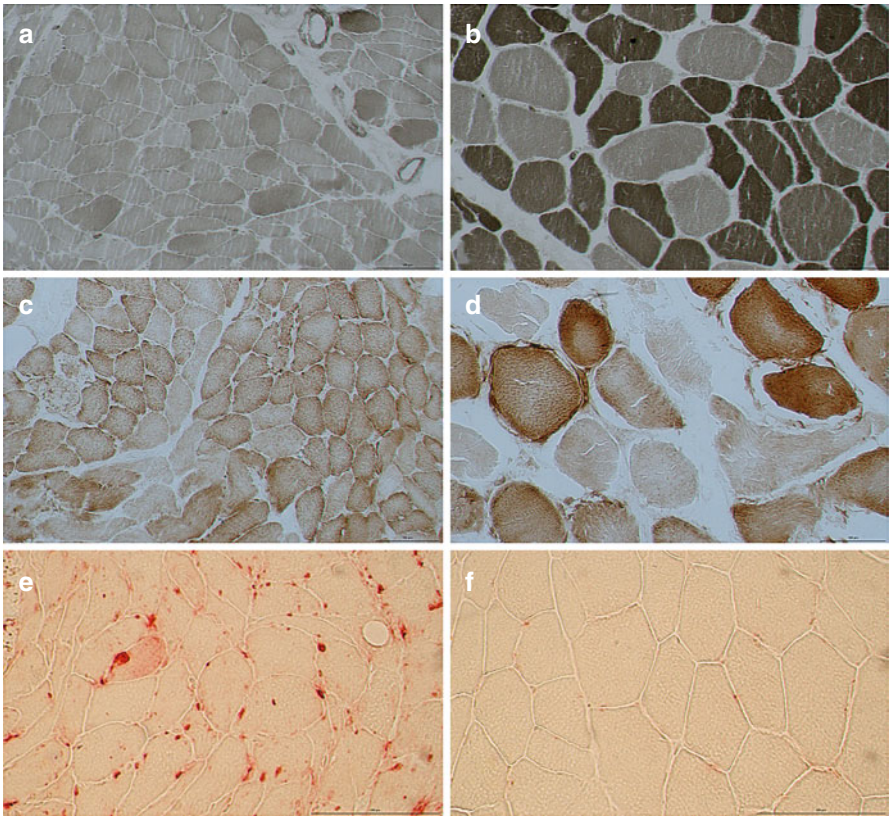

Fig. 13.1 Histochemical demonstration of myofibrillar ATP-ase activity pH 9.4 (**a**), cytochrome–oxidase (**c**) and acid phosphatase (**e**) in CIM compared to control (**b**, **d**, **f**). Enzyme activities of myofibrillar ATP-ase and cytochrome–oxidase are reduced; acid phosphatase activity is increased below the sarcolemma and in the endomysium. Cytochrome–oxidase activity is nearly absent in necrotic fibres. Muscle biopsy of the vastus lateralis muscle in a 59-year-old female patient with CIM (**a**, **c**) and in a 74-year-old female patient with CIM (**e**). Bar 100 µm

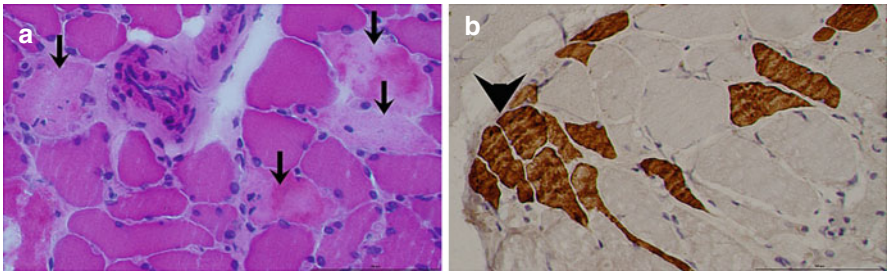

Fig. 13.2 General histopathology of CIM. Haematoxylin–eosin (**a**) and myosin heavy chain 2A (**b**). Necrotic fibres are marked by *arrows* (**a**). Small group atrophy (*arrowhead*) and scattered atrophic fibres mostly of type 2A fast fibres (**b**). (**a**) The same patient as shown in Figs. 13.1a, c and (**b**) the same patient as shown in Fig. 13.1e. Bar 100 µm

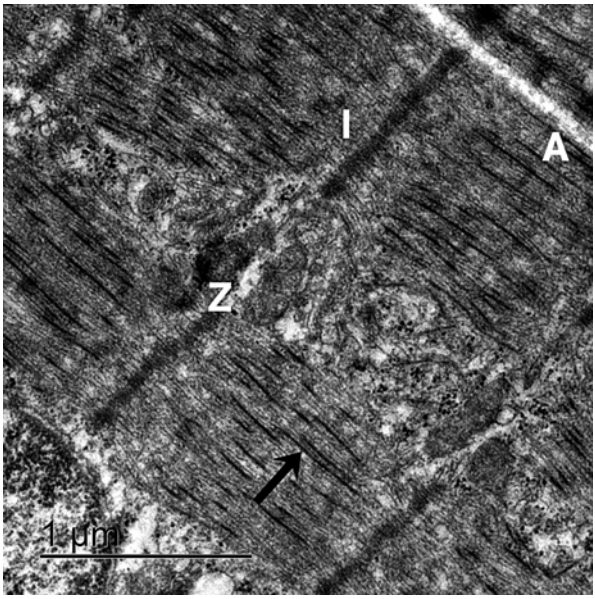

Fig. 13.3 Electron microscopy shows severe loss of myosin filaments (*arrow*) which causes nearly disappearance of *A* band. Actin filaments are preserved and *I* band and *Z* line look normal. The same patient as shown in Fig. 13.1a, c

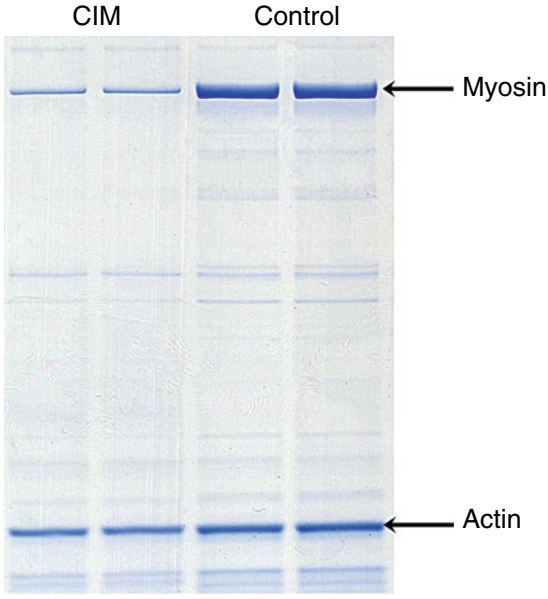

Fig. 13.4 Electrophoresis of total muscle homogenate. Severe loss of myosin in relation to actin. The same patient as shown in Fig. 13.3

Possible "neuropathic elements" can be observed in addition, e.g. small group atrophy or scattered angular fibres (Fig. 13.2b) or even fibre-type grouping; they may reflect a pre-existing chronic condition such as axonal neuropathy (small group atrophy) due to diabetes or previous reinnervation due to radiculopathy (fibre-type grouping) or may be related to distal concomitant axonal damage (scattered angular fibres), if CIM and CIP coexist. Since no reliable marker of acute denervation exists, it is impossible to state whether the scattered angular fibres result from acute denervation (i.e. acute neuropathy) or from chronic neuropathy.

Acute necrotising myopathy of ICU is diagnosed, if necrotic fibres are the outstanding feature; necrotic fibres may be related to concomitant toxic myopathy, due to adverse effect of pharmacotherapy, or muscle fibre necrosis may be considered as an advance stage of CIM; acute necrotising myopathy of ICU is often associated with myoglobinuria [22].

Muscle biopsy is useful for the demonstration of characteristic myosin loss and is important with respect to prognosis, since CIM has more favourable short- and long-term outcomes than CIP [23]. An exception is the prognosis for recovery from weakness of acute necrotising myopathy of ICU, which is very poor [22].

Muscle biopsy is not universally available, is invasive and time-consuming. In addition unspecific, mixed myopathic–neuropathic changes may be detected and caution in the interpretation is needed, since neuropathic signs can be chronic, not related to ICUAW. Morphological analysis also takes time and is fairly inconvenient for the demands of an intensive care. Quantification of the myosin/actin ratio in electrophoresis is more appropriate with respect to time, since it can be performed in 1 or 2 days, but further studies are needed in this field to understand the clinical significance of different degrees of myosin loss.

13.4.4 Nerve Biopsy

Nerve histology is initially preserved. Most sensory nerves in early biopsies (day 15 of sepsis) look normal, despite having reduced SNAP [8]. Late biopsies (day 56) demonstrate axonal loss [8], but this is an unspecific change. Axonal loss observed in biopsies of sensory nerves refers to large axonal loss. Small fibre neuropathy was recently demonstrated in skin biopsies of the critically ill [24]. Small fibre neuropathy may be responsible for neuropathic pain, stocking and glove sensory loss, cool extremities and burning pain in the survivors of CIP [6].

Axonal degeneration was also observed in autopsy samples of sympathetic chain and vagal nerve [25], and autonomic dysfunction is frequently observed in the critically ill [6].

13.5 Pathophysiology

CIM and CIP are not isolated events but an integral part of multiorgan dysfunction syndrome in severe illness and a shared pathogenesis for CIM and CIP is likely [2]. A review of proposed pathophysiological mechanisms from clinical studies and animal experiments was recently published [5].

13.5.1 CIM

Skeletal muscle dysfunction in CIM is a combination of reduced muscle mass (muscle atrophy) and impaired contractility [2]. A specific pathomorphological lesion in CIM is early selective loss of myosin myofilaments relative to actin [20, 26]; however myopathies in pure sepsis do not produce severe myosin loss [5]; the same authors [5] proposed that myopathy in pure sepsis should be considered as a subtype of ICUAW, in addition to CIP and CIM, but at present this is still under consideration.

13.5.1.1 Muscle Atrophy

In the critically ill, several processes, such as inactivity, unloading, immobility, inflammation, cellular energy stress or food deprivation, can cause muscle atrophy [2]. Muscle atrophy may contribute to weakness, premature fatigue and glucose intolerance [27]. Muscle atrophy in CIM is the result of increased muscle proteolysis and diminished protein synthesis. The ubiquitin–proteasome system (UPS), studied mostly in patients with sepsis [28, 29], and calpain activation [21, 30, 31] mediate enhanced proteolysis in the critically ill. The role of the caspase family of cysteine proteases in muscle proteolysis in the critically ill is suggested from animal studies [5]. Lysosomal proteases, cathepsins, have been evaluated for their contribution to muscle loss in sepsis [32], but there is no current consensus on the role of cathepsins in CIM [5]. Increased lysosomal (and proteasomal) activation was observed in the diaphragm of prolonged (15–276 h) mechanically ventilated patients [33], and it was concluded that activation of both systems is responsible for fibre atrophy in the critically ill. However, in adult *prolonged critically ill* patients, insufficient autophagy [34] may cause inadequate removal of damaged proteins and mitochondria and may explain prolonged recovery or lack of recovery.

Immobility per se causes a decrease in muscle protein synthesis and is associated with so-called anabolic resistance, i.e. diminished protein synthesis as a response to infusion of amino acids [35]. Older critically ill patients display in addition "anabolic resistance" due to age per se, diminished suppression of muscle proteolysis by insulin [35] and diminished mitochondrial respiratory capacity [36]. It follows that advance age represents high risk for ICUAW.

13.5.1.2 Muscle Contractile Dysfunction

Muscle contractility can be suppressed by free radicals, abnormalities of Ca^{2+} sequestering, depletion of cellular energy by mitochondrial dysfunction or abnormalities of muscle membrane excitability.

Chronic inflammatory states can reduce muscle contractile force by increasing free radicals, which depress the myofibrillar function [37].

Uncoupling of excitation–contraction has a negative impact on contraction and might be an accompanying mechanism of CIM for the subpopulation of ICU patients with co-morbidities, such as COPD and CHF in whom the pre-existent abnormalities of Ca^{2+} sequestration exist [2], and these might worsen by stress-induced elevated sympathetic nerve activity in ICU [2].

13.5.1.3 Mitochondrial Dysfunction/Abnormalities

The loss of normal mitochondrial function results in depletion of cellular energy and increased production of free radicals [2]. Complexes I and IV of the respiratory chain in particular are depleted in CIM [38]. Activation of mitochondrial biogenesis seems to be important for short and late outcomes: if compensatory mechanisms of increased mitochondrial biogenesis are activated early, this has a positive effect on survival in critical illness [38]; in critically ill patients with a prolonged clinical course, markers of mitochondrial biogenesis are not upregulated [39].

13.5.1.4 Muscle Membrane Inexcitability

Direct muscle stimulation in humans detects reduced CMAP, compatible with the inexcitability of sarcolemma [40, 41]. Reduction of voltage-gated sodium channels was demonstrated in patients with sepsis in vitro [42]. Sodium channelopathy hypothesis also has support within experimental rat models (sepsis, steroid-denervation experiments) in which inactivation of sodium channels and, consequently, sarcolemma inexcitability were detected [5].

13.5.2 CIP

CIP is a distal axonal sensorimotor polyneuropathy affecting the limb and respiratory muscles. Abnormalities in action potential may occur within hours in humans [17]. Reversible inactivation of sodium channels was demonstrated on an experimental model of CIP in rat [43]. In some patients, weakness subsides when the global health is restored, but a subgroup of patients do not regain normal function even after 1–2 years [2]. As already stated, the current view is that CIP is not an isolated event but an integral part of multiorgan dysfunction syndrome, and the precise mechanisms are not known. Diabetes mellitus as a pre-existing morbidity predisposes to CIP, and the severity of CIP corresponds to serum glucose levels [6].

13.5.2.1 Microvascular Injury and Membrane Depolarisation Defect

Microvascular injury of the nerve, mediated by endotoxins, inflammatory mediators (tumour necrosis factor-α, serotonin and histamine), toxins and drugs, hyperglycaemia and ROS, causes hypoperfusion and lack of oxygen. Accumulation of potassium and acidic metabolites in the endoneurium leads to depolarisation of the nerve membrane and nerve dysfunction [2]. The hypothesis of (micro)vascular injury is supported by increased expression of E-selectin in the endothelial cells of endoneurial microvessels and epineurial small-calibre vessels of critically ill patients [44]. E-selectin mediates the initial step of leucocyte adhesion and extravasation to the endoneurial space, which leads to endoneurial cytokine production and tissue injury during sepsis [44].

13.6 Biomarkers

At present, no validated biomarkers for CIM/CIP are available [6]: creatine kinase may be raised in CIM and slightly also in CIP, but is not a good biomarker; biomarkers of axonal injury, plasma levels of neurofilaments, are elevated in patients with ICUAW, but early diagnosis of ICUAW, before muscle strength assessment, is not possible using neurofilament levels in plasma, and the marker also does not differentiate between CIP and CIM; a possible future candidate may be stress-induced cytokine, growth and differentiation factor-15 (GDF-15) [45].

13.7 Prevention and Therapy

- Aggressive treatment of sepsis is considered to be a cornerstone in prevention of ICUAW [6].
- Insulin treatment for normalising glycaemia is complex and difficult to perform optimally. It seems that absolute normoglycaemia is not the optimal choice, since patients treated to strict normoglycaemia had a worse outcome than patients treated to slightly higher blood glucose levels [46]. Continuous monitoring of blood glucose versus intermittent is under discussion and additional research is needed, if continuous monitoring of blood glucose is to become a routine part of daily practice in the management of critically ill patients [6].
- Reducing the duration of immobilisation can be achieved by decreasing the levels of sedation, and overall beneficial effects have been demonstrated [47].
- Early passive and active exercise trainings (such as bedside ergometer) improve muscle strength at hospital discharge [48].
- Electrical muscle stimulation may be used to activate muscles during the period when patients are not able to cooperate, but the evidence remains inconclusive and more research is necessary [6, 49].
- Late parenteral nutrition accelerates recovery compared to early parenteral nutrition [50] since it reduces muscle weakness (but not atrophy) and accelerated

recovery may be mediated by more efficient activation of autophagic quality control of myofibres.

Highlights

- Clinicians should be aware that intensive care muscle weakness can be due to different causes.
- A myopathy or a polyneuropathy can be the underlying mechanism of this flaccid weakness.
- Although the myopathy is acute, the time of onset is difficult to determine.
- Critical illness myopathy can be part of loss of myosin thick filaments or due to generalised reduction of sarcolemma excitability.

References

1. Stevens RD, Marshall SA, Cornblath DR et al (2009) A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med 37(10 Suppl):S299–S308
2. Batt J, dos Santos CC, Cameron JI et al (2013) Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med 187:238–246
3. Fan E, Cheek F, Chlan L et al (2014) An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med 190:1437–1446
4. Mirzakhani H, Williams JN, Mello J et al (2013) Muscle weakness predicts pharyngeal dysfunction and symptomatic aspiration in long-term ventilated patients. Anesthesiology 119:389–397
5. Friedrich O, Reid MB, Van den Berghe G et al (2015) The sick and the weak: neuropathies/myopathies in the critically Ill. Physiol Rev 95:1025–1109
6. Hermans G, Van den Berghe G (2015) Clinical review: intensive care unit acquired weakness. Crit Care. doi:10.1186/s13054-015-0993-7
7. Rodi Z, Filipović T, Švigelj V et al (2009) Critical illness myopathy in patients with central nervous system disorders http://vestnik.szd.si/index.php/ZdravVest/article/view/357. Zdrav Vest 78:289–293
8. Latronico N, Fenzi F, Recupero D et al (1996) Critical illness myopathy and neuropathy. Lancet 347:1579–1582
9. Latronico N, Gosselink R (2015) A guided approach to diagnose severe muscle weakness in the intensive care unit. Rev Bras Ter Intensiva 27:199–201
10. Hermans G, Clerckx B, Vanhullebusch T et al (2012) Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve 45:18–25
11. Vanhoutte EK, Faber CG, van Nes SI et al (2012) Modifying the Medical Research Council grading system through Rasch analyses. Brain 135:1639–1649
12. Parry SM, Berney S, Granger CL et al (2015) A new two-tier strength assessment approach to the diagnosis of weakness in intensive care: an observational study. Crit Care. doi:10.1186/s13054-015-0780-5
13. Ali NA, O'Brien JM Jr, Hoffmann SP et al (2008) Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 178:261–268

14. Rich MM, Bird SJ, Raps EC et al (1997) Direct muscle stimulation in acute quadriplegic myopathy. Muscle Nerve 20:665–673
15. Goodman BP, Harper CM, Boon AJ (2009) Prolonged compound muscle action potential duration in critical illness myopathy. Muscle Nerve 40:1040–1042
16. Latronico N, Shehu I, Guarneri B (2009) Use of electrophysiologic testing. Crit Care Med 37(10 Suppl):S316–S320
17. Latronico N, Nattino G, Guarneri B et al (2014) Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. F1000Res. doi: 10.12688/f1000research.3933.3
18. Tennila A, Salmi T, Pettila V et al (2000) Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med 26:1360–1363
19. Carpenter S, Karpati G (2001) Pathology of skeletal muscle. Oxford University Press, New York
20. Stibler H, Edstrom L, Ahlbeck K et al (2003) Electrophoretic determination of the myosin/actin ratio in the diagnosis of critical illness myopathy. Intensive Care Med 29:1515–1527
21. Showalter CJ, Engel AG (1997) Acute quadriplegic myopathy: analysis of myosin isoforms and evidence for calpain-mediated proteolysis. Muscle Nerve 20:316–322
22. Pati S, Goodfellow JA, Iyadurai S et al (2008) Approach to critical illness polyneuropathy and myopathy. Postgrad Med J 84:354–360
23. Guarneri B, Bertolini G, Latronico N (2008) Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatry 79:838–841
24. Latronico N, Filosto M, Fagoni N et al (2013) Small nerve fiber pathology in critical illness. PLoS One. doi:10.1371/journal.pone.0075696
25. Zochodne DW, Bolton CF, Wells GA et al (1987) Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. Brain 110:819–841
26. Danon MJ, Carpenter S (1991) Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. Muscle Nerve 14:1131–1139
27. Puthucheary Z, Montgomery H, Moxham J et al (2010) Structure to function: muscle failure in critically ill patients. J Physiol 588:4641–4648
28. Tiao G, Hobler S, Wang JJ et al (1997) Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. J Clin Invest 99:163–168
29. Constantin D, McCullough J, Mahajan RP et al (2011) Novel events in the molecular regulation of muscle mass in critically ill patients. J Physiol 589:3883–3895
30. Bhattacharyya J, Thompson K, Sayeed MM (1991) Calcium-dependent and calcium-independent protease activities in skeletal muscle during sepsis. Circ Shock 35:117–122
31. Salviati L, Laverda AM, Zancan L et al (2000) Acute quadriplegic myopathy in a 17-month-old boy. J Child Neurol 15:63–66
32. Klaude M, Mori M, Tjader I et al (2012) Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. Clin Sci (Lond) 122:133–142
33. Hussain SN, Mofarrahi M, Sigala I et al (2010) Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. Am J Respir Crit Care Med 182:1377–1386
34. Vanhorebeek I, Gunst J, Derde S et al (2011) Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. doi:10.1210/jc.2010-2563
35. Rennie MJ (2009) Anabolic resistance in critically ill patients. Crit Care Med 37(10 Suppl):S398–S399
36. Peterson CM, Johannsen DL, Ravussin E (2012) Skeletal muscle mitochondria and aging: a review. J Aging Res. doi:10.1155/2012/194821

37. Reid MB, Moylan JS (2011) Beyond atrophy: redox mechanisms of muscle dysfunction in chronic inflammatory disease. J Physiol 589:2171–2179
38. Carre JE, Orban JC, Re L et al (2010) Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med 182:745–751
39. Vanhorebeek I, Gunst J, Derde S et al (2012) Mitochondrial fusion, fission, and biogenesis in prolonged critically ill patients. J Clin Endocrinol Metab. doi:10.1210/jc.2011-1760
40. Rich MM, Teener JW, Raps EC et al (1996) Muscle is electrically inexcitable in acute quadriplegic myopathy. Neurology 46:731–736
41. Lefaucheur JP, Nordine T, Rodriguez P et al (2006) Origin of ICU acquired paresis determined by direct muscle stimulation. J Neurol Neurosurg Psychiatry 77:500–506
42. Haeseler G, Foadi N, Wiegand E et al (2008) Endotoxin reduces availability of voltage-gated human skeletal muscle sodium channels at depolarized membrane potentials. Crit Care Med 36:1239–1247
43. Novak KR, Nardelli P, Cope TC et al (2009) Inactivation of sodium channels underlies reversible neuropathy during critical illness in rats. J Clin Invest 119:1150–1158
44. Fenzi F, Latronico N, Refatti N et al (2003) Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. Acta Neuropathol 106:75–82
45. Bloch SA, Lee JY, Syburra T et al (2015) Increased expression of GDF-15 may mediate ICU-acquired weakness by down-regulating muscle microRNAs. Thorax 70:219–228
46. Finfer S, Chittock DR, Su SY et al (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360:1283–1297
47. Reade MC, Finfer S (2014) Sedation and delirium in the intensive care unit. N Engl J Med 370:444–454
48. Burtin C, Clerckx B, Robbeets C et al (2009) Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 37:2499–2505
49. Maffiuletti NA, Roig M, Karatzanos E et al (2013) Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. BMC Med. doi:10.1186/1741-7015-11-137
50. Hermans G, Casaer MP, Clerckx B et al (2013) Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 1:621–629