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ΘΕΜΑ

Metabolic effect of intensive care acquired polyneuropathy

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Contents

Abstract

Background : Intensive Care Acquired Weakness (ICAW) is a major and disabilitating complication of severe critical illness. It's interference with weaning from mechanical ventilation and physical rehabilitation can determine overall prognosis, quality of life and final outcome of ICU patients.

Aim : understanding molecular-cellular mechanisms underlying ICAW.

Design :review study

Methods : PubMed. Literature retrieved experimental studies conducted mainly in human but also animal models.

Conclusions : metabolic alteration pathways taking place in muscle cells during critical illness.

Περίληψη

Υπόβαθρο : η πολυνευρομυοπαθεια της ΜΕΘ (Μονάδα Εντατικής Θεραπείας), είναι μια από τις πλέον σοβαρές επιπλοκές της βαρέας νόσου και της νοσηλείας στην ΜΕΘ. Η συμμετοχή της στην δυσκολία απογαλακτισμού από τον αναπνευστήρα και την ανάγκη για παρατεταμένη φυσική αποκατάσταση, μπορείνα καθορίσει την πρόγνωση, την ποιότητα ζωής και την τελική έκβαση των ασθενών που νοσηλεύονται σε ΜΕΘ.

Στόχος : κατανόηση και μελέτη των μοριακών-κυτταρικών μηχανισμών που υπόκεινται της νόσου.

Μορφή : ανασκόπηση βιβλιογραφίας

Μέθοδοι : αναζητήθηκε σχετική βιβλιογραφία στις βάσεις δεδομένων PubMed που αφορά σε πειραματικά μοντέλα κυρίως ασθενών αλλά και πειραματόζωων.

Συμπεράσματα : αναγνώριση φυσιοπαθολογικών μεταβολικών αλλαγών σε επίπεδο μυϊκών κυττάρων στους βαρέως πάσχοντες ασθενείς.

Introduction

Intensive Care Acquired Weakness (ICAW) is a relevant complication occurring in severely ill patients, mainly diagnosis is clinical, based on physical examination evaluating muscle strength. The feature of generalized symmetrical muscle weakness of both limbs and respiratory muscle involvement usually results from volitional tests, such as Medical Research Council sum score (MRCss) or handgrip dynamometer. Nonvolitional tests including electrical and magnetic neuromuscular twitch stimulation to assess strength and muscle ultrasound to assess muscle mass and architecture. Electrophysiological studies (EPS) of peripheral nerves and muscles can give information about possible pathophysiology pathways of CIP (Critical illness Polyneuropathy), CIM (Critical illness Myopathy) or both.

Patients admitted to the Intensive Care Unit (ICU) frequently develop skeletal muscle dysfunction because of muscle weakness (decreased muscle strength), muscle fatigability (reduced capacity to continue muscle contractions), or other causes such as acquired neuropathy (1,2,3,4,5). Different factors such as immobilization, electrical silencing of muscles due to sedation and neuromuscular blockade may induce muscle wasting, which can be enhanced by inflammation, energy stress, glucocorticoids and trauma. The imbalance between muscle protein synthesis and overwhelming degradation are the main features of muscle loss, with a preferential loss of myosin and myosin related proteins.

This muscle dysfunction often persists after ICU discharge. The majority of critically ill patients treated in ICUs in Northern Europe suffer from

respiratory dysfunction and require mechanical ventilation. Nearly 20% of all mechanically ventilated patients have problems weaning from the ventilator, therefore requiring prolonged ICU treatment (6,7,8). Both respiratory dysfunction and prolonged weaning are thought to be related to respiratory muscle weakness and fatigue. Studies conducted on both human and animal subjectshavefound an association of decreased mitochondrial function in skeletal muscle with shock and organ dysfunction and risk of adverse outcomes of critical illness (9,10,11,12,13,14).

In this review study we try to resume the main molecular mechanisms that contribute and regulate loss of muscle mass and function.

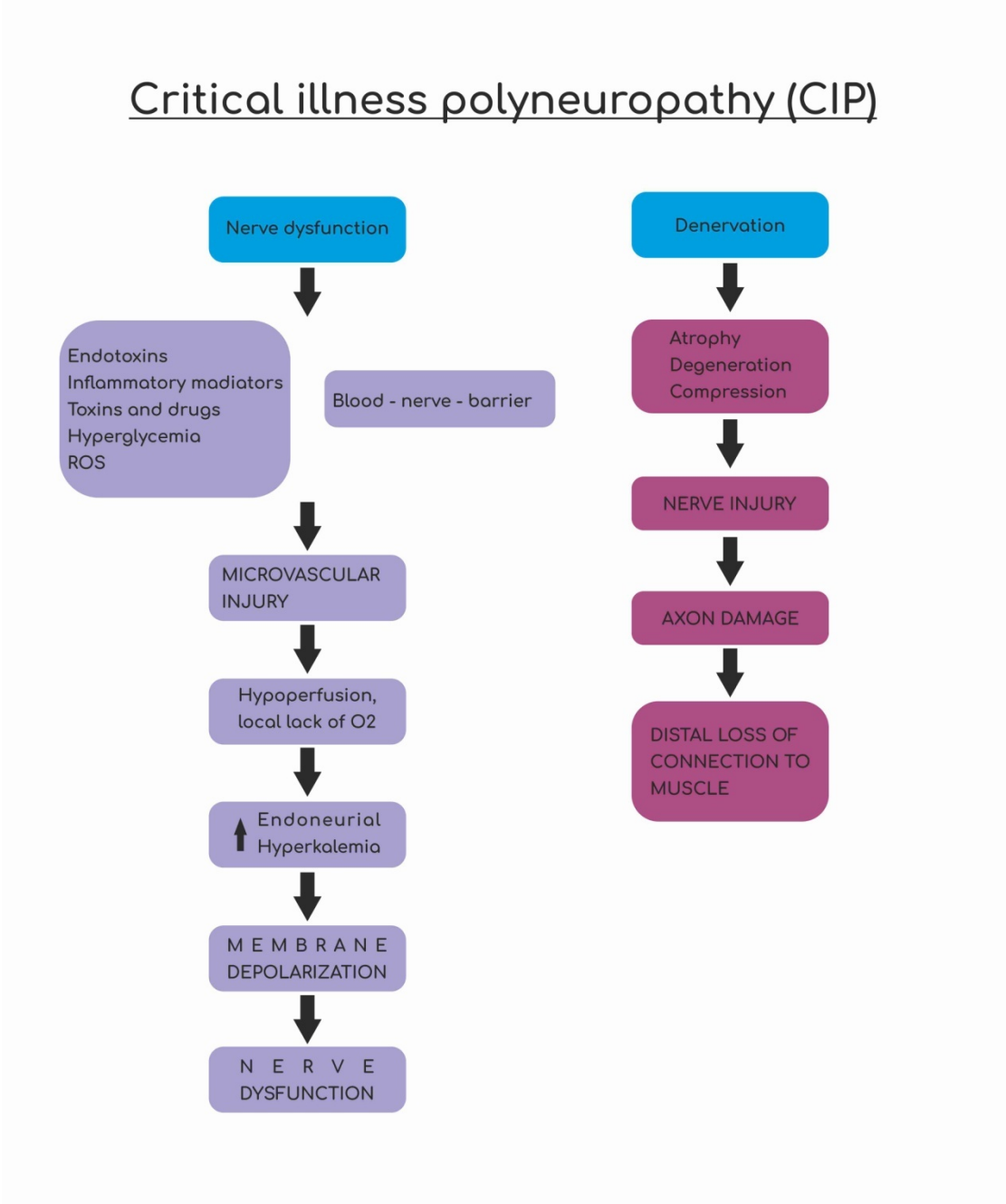
Critical Illness Polyneuropathy and Myopathy

Mechanisms contributing to ICU acquired weakness (ICUAW) include two main processes, those being Critical Illness Polyneuropathy (CIP) and Critical Illness Myopathy (CIM).

CIP is a distal axonal sensory-motorpolyneuropathy affecting both limb and respiratory muscles (15). Electrophysiological studies show a reduction in amplitude of compound muscle action potentials and sensory nerve action potentials (SNAPS) with normal or midly reduced nerve conduction velocity (16,15) in addition to altered proprioception. Electrophysiological evidence of abnormal nerve function, showing abnormalities in action potential, has been associated with early/acute failure to wean patients from mechanical ventilation. Primary axonal degeneration of peripheral motor and sensory

nerve fibers has been documented, as well as, peripheral nerve atrophy and compression neuropathy contribute to loss of functional innervation and muscle dysfunction.

CIM derives from a variable combination of decreased muscle mass and impaired contractility. The muscle atrophy of CIM demonstrates a significantly preferential loss of myosin relative to actin (17,18).



Even though CIP and CIM may represent two separate harmfull procedures that possibly share common mediators, they more likely reflect a gradual continuum of neurogenic and myogenic changes of varying severityin response to critical illness; Nerve impairment leads to muscle atrophy and, vice versa, innervation and neuromuscular junction function can be affected via retrogade signals from diseased muscles (19).

Leading theories regarding the pathogenesis of CIP invoke membrane depolarization defect as the main explanation for axonal damage/dysfunction (20). This would presumably occur early in the course of illness. Impairment of the blood-nerve barrier (BNB) in the absence of ultrastructural damage would be the inciting pathogenetic event (21), axonal depolarization would be due to microvascular alterations leading to hypoperfusion of the nerves' small capillaries and the resulting hypoxia could lead to accumulation of acidic metabolites. Causes of microvascular injury presumably include hypoxemia orcirculating mediators such as endotoxin, or other proinflammatory agents (TNF a, serotonin, histamine) released during sepsis orsystemic inflammatory response syndrome (SIRS) (22,23). This hypothesis is supported by evidence that endothelial cells in the epineurial and endoneurial vessels of critically ill patients with neuromuscular disorders are activated as evidenced by increased expression of E-selectin (24). Interestingly, advanced glycation end-products induce basement membrane hypertrophy in the endoneurialmicrovessels and disrupt the BNB by stimulating the release of transforming GF-b (TGF-b) and vascular endothelial growth factor (VEGF) by pericytes (25).

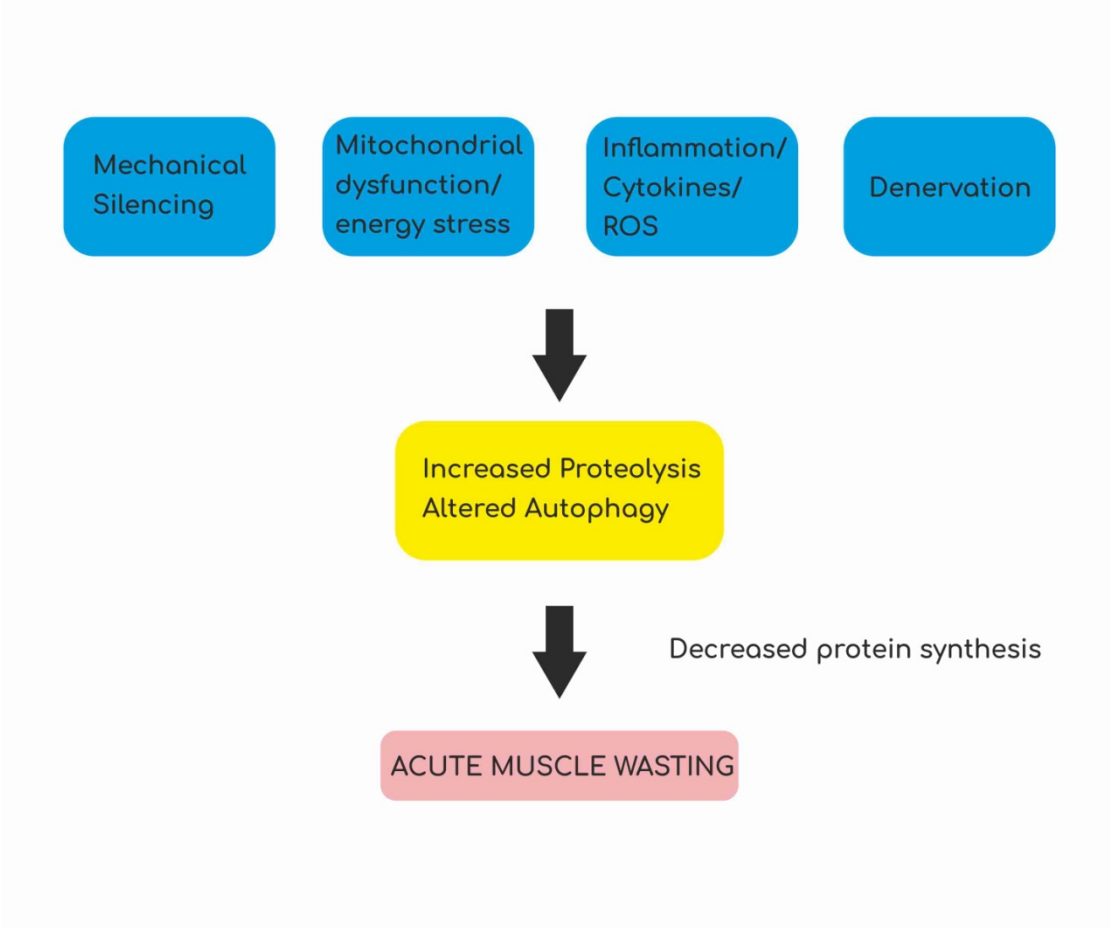
Functional electromyographic changes associated with CIP, can be caused by loss of the endoneurial membrane potential. Depolarization of axons occur due to tissue/endoneurial hyperkalemia (26,27) because axonal slow potassium channels are activated during an action potential and are responsible for generating the late subexcitability phase of the recovery cycle. Voltage-dependent sodium channels have additionally been shown to participate in the regulation of neuron excitability (28). Toxic factors may also directly penetrate the endoneurial membrane, such as passive uptake of glucose, that causes increased generation and deficient scavenging of reactive oxygen species (ROS) in neurons (29). (ROS: Reactive Oxygen Species are toxic metabolites of oxygen, which are produced during the "ischemia-reperfusion" syndrome, often accompanying the treatment of shock and sepsis). Their mass production derives from two sources activated during reperfusion, xanthinoxidase and phagocytic cells. These cytotoxic metabolites cause – through oxidative stress – endothelium and microvascular damage at a very fast rate. Xanthinoxidase activation leads to production of – among else – the most toxic hydroxyl radical "'OH". Simultaneously, in activated phagocytic cells, which adhere to the endothelium of capillary vessels, oxygen consumption increases ten- to twentyfold. This procedure, known as respiratory burst, produces (via reduction of O_2) free superoxide anion "O_2^-", whose dismutation leads to production of hydrogen peroxide "H_2O_2" and hypochlorite "HOCl". These two metabolites, while being basic components of the defense mechanism against bacteria, in this case damage the endothelium, which is very vulnerable to ROS and its protective layer, known as glycocalyx. The compounding injuryfrom these toxic factors would include axonal

degeneration resulting from glucose-induced phosphate depletion. This may be exacerbated by parenteral nutrition (30) as damage of neural microvasculature and impaired transport of axonal proteins can result from oxidative effects of parenterally administered lipids (31). Bolton and colleagues (93,96) hypothesized that sepsis-related disturbance of the microcirculation in peripheral nerves and muscles is a crucial event in the pathogenesis of CIP. This may be mediated by the enhanced expression of E-selectin in the vascular endothelium of the peripheral nerves, induced by pro-inflammatory cytokines (95). Moreover cytokines secreted in sepsis have histamine-like properties that may increase microvascular permeability (94). The resulting endoneuraloedema could induce hypoxemia and energy depletion by increasing intercapillarydistance and other mechanisms. Severe energy deficits would result, inducing primary axonal degeneration.

Muscle Atrophy

Loss of muscle mass results froman imbalance between muscle proteolysis and protein synthesis, with proteolysis overwhelming an inadeguate synthetic response. Proteolysis is achieved by several cellular signaling networks, but the predominant proteolytic pathway activated in animal models of muscle atrophy is the ubiquitin-proteasome system (UPS) (46-48). (UPS: Proteins that are intended for degradation are targeted by polyubiquitin attaching to lysine residues). Three enzyme families interact with each other to complete this ATP-dependent procedure. Those are: ubiquitin activating enzymes (E1

proteins), ubiquitin conjugating enzymes (E2 proteins), and ubiquitin ligases (E3 protein). E2 proteins pair with E3 in order to regulate the attachment of ubiquitin to specific protein substrates, which is defined each time by the structure of each E2/E3 pair. This specificity enables the 26S-proteasome to mark selectively proteins for degradation. The 26S-proteasome has two 19S regulatory subunits around its 20S multienzyme core. The 19S subunit on each end identifies an ubiquinated protein, attaches to it and unfolds it and thus cleaves and recycles the binded ubiquitin parts. Subsequently, in its core, the 20S multienzyme degrades the unfolded protein to via peptidase enzymes, producing smaller polypeptides.)



A plethora of processes, active in the critically ill and known to induce muscle atrophy including, but not limited to, muscle inactivity (denervation/unloading/immobility), inflammation, cellular energy stress, and food deprivation, engage the forkhead box O (FoxO) family of transcription factors to stimulate the expression of two critical regulators of UPS-mediated proteolysis: the ubiquitin ligases atrogin-1 and muscle-specific RING finger protein-1 (MURF-1), which are muscle – specific E3 proteins (47,49-54). In human muscle, short-term, but not long term immobilization increased MURF1 mRNA expression in the vastuslateralis of healthy volunteers (55). Studies in the critically ill patients delineating the temporal involvement of enhanced proteolysis in concert with cellular signaling regulating the UPS and their overall correlation with muscle mass and power are necessary to clarify the role UPS-mediated proteolysis plays in acute and sustained CIM.

Protein catabolism and muscle wasting observed in CIM due to proteolytic pathways involving calpain (96) and the ubiquitine-proteasome pathway (97,98) are upregulated due to pro-inflammatory cytokines in conjuction with increased apoptosis (99). As calpain is a calcium-activated protease, altered cellular calcium homeostasis due to endotoxemia and inflammation might play a role (94,100). Also, acute stimulation of the TGF-β/MAPK (transforming growth factor/mitogen-activated proteinkinase) pathway following stress stimuli has been suggested to explain the muscle loss, coupled with the activation of the ubiquitin-proteasome pathway (101). Muscle biopsies in these patients demonstrate a decrease in total aminoacid concentration and, most strikingly, the glutamine levels (102). Decreased levels of anabolic

hormones and increased levels of catabolic hormones may contribute to myofilament loss and apoptosis in CIM (103).

Constantin etal. (104) found that muscle specific E3 proteins (MURF1, MAFbx) and subunits of the proteasome were elevated in vastus lateralis muscle of critically ill patients (assessed by APACHE II scores, no information on mechanical ventilation given). These changes were evident at both the mRNA and protein levels, arguing for their physiological relevance.

Another study (105) demonstrated increased catabolism in vastus lateralis muscle in 63 critically ill ICU patients showing just the opposite: a downregulation of MuRF1 and atrogin-1. Helliwell et al. (106) found fiber atrophy and reduction in myosin ATPase activity in tibialis anterior muscle biopsies from critically ill patients that were accompanied by an increase in immunocytochemical staining of ubiquitin conjugates. Klaude et al. (107) have shown that critical illness increases chymotrypsin-like peptidase activity of membrane-associated proteasomes isolated from human leg muscles. The activity of the proteasomes was by 30% elevated relatively to healthy controls, whereas proteasome activity in the soluble fraction was unaffected by critical illness. A subsequent study by the same group (108) confirmed and extended these findings in patients with sepsis in the ICU. Proteasome activity was elevated by 45-55% in leg muscle biopsies from septic patients. Interestingly, proteasome activity was also elevated by 30% in serratus anterior, a muscle of the rib cage. In rectus abdominalis muscle, a more than twofold increase in chymotrypsin like activity of the 20S-proteasome has been described (109).

Inhibition of protein synthesis also contributes to muscle loss accompanying critical illness. mTOR1 as a central protein synthesis promotor plays a crucial role by regulating mRNA translation, stimulated by growth factors, nutrients and positive energy balance. Another group of nonlysosomal proteases includes calpains, which role is still to be determined, whether their elevated activationhas an effect in muscle protein degradation. Caspase and cathepsins remain also topics of investigation as regulators of accelerated muscle proteolysis during sepsis.

Autophagy

Autophagy is a cellular process trying to eliminate damaged cell components in order to remodel cellular architecture. Mainly is considered to be the pathway responsible for clearance of damaged organelles and potentially toxic protein aggregates and is found to be impaired in liver and muscle of fed prolonged critically ill patients (64). Dysregulated autophagy results in muscle degradation and loss. Disturbances in other repair mechanisms regarding fusion and fission allow exchange of damaged components leading to dilution of molecular damage or bundling of dysfunctional structures in a single, irreversibly damaged organelle that is subsequently targeted for removal by autophagy (65,66). Impaired repairing compromises mitochondrial biogenesis activation contributing to mitochondrial dysfunction in critical illness (67). Autophagy, actually, has been considered to be protective for skeletal muscle and other organs during critical illness and

changes in skeletal muscle and liver could be the result of an autophagy deficient condition. Accumulation of ubiquitin aggregates and other autophagy substrates, deformed mitochondria and aberrant concentric membranous structures have been observed in skeletal muscle, liver and kidney of severe burn injury critical illness, as well as sepsis and denervation. Fasting is one of the strongest autophagy promotors, whereas fiding and insulin inhibit the process. Studies on patients artificially and continuously fed during critical illness demonstrated reduced muscle catabolism and suppressed autophagy, thus compromising myofiber integrity and vital organ function, compared with fasting. Adequate autophagy activation clearly appeared crucial to offer protection against mitochondrial dysfunction as well as cardiac dysfunction, hepatic injury and kidney failure in animal models. It is fondamental to maintain balance between autophagy activation and suppression in order to preserve muscle mass and quality.

Mitochondrial Dysfunction

Mitochondria are the main producers of cellular energy, so theirdecreased function will compromise cellular performance.Mitochondrial damage and impaired repair mechanisms, such as fusion and fission are involved in ICAW pathophysiology. These processes allow the exchange of damaged components and either dilution of molecular damage over the daughter organelles or bundling of dysfunctional structures by asymmetric fission into a single, irreversibly damaged depolarized organelle, which is fusion-

incompetent and is targeted for removal by mitochondrial autophagy.Mitocondrial fusion and fission are important for another process, called biogenesis, a pathway that generates new mitochondria when damage or increased energy demand occurs.

Studies from biopsies in vastus lateralisof ICU patients which survived from sepsis induced multiorgan failure showed increased biogenesis but insufficient mitochondrial function. Studies on skeletal muscles of patients (14,35,36) are showing an acute effect of shock on the mitochondrial membrane-bound enzymes of the respiratory chain, but evidence to support this observation is limited. As discussed by Brealey et al. (14) this decreased respiratory chain activity is probably related with high mortality seen in acute shock. Fredriksson et al. (37) studied mitochondrial derangements measuring mitochondrial enzyme activities, energy-rich phosphates, and a marker of oxidative stress in leg and intercostal muscle of mechanically ventilated ICU patients with sepsis-induced multiple organ failure (MOF). Compared to controls, the ICU patients had a 40% lower ATP concentration ($P<0,01$), a 34% lower creatinine phosphate concentration ($P<0,01$) and a 43% higher lactate concentration ($P<0,01$) in leg muscle.A twofold decrease in mitochondrial activities were found in both intercostal and leg muscle of ICU patients suffering from sepsis-induced MOF compared with a group of metabolically healthy control patients. In leg muscle the lower enzyme activities were accompanied by a lower concentration of ATP and creatinine phosphate and by a higher lactate concentration indicating a compromised energy production. A high activity of mitochondrial superoxidase dismutase (SOD) in both intercostal and leg muscle of ICU patients suggests an increase

in ROS production. In intercostal muscle of ICU patients, both citrate synthase and complex I activities were lower than in controls. In leg muscle only complex IV activity was significantly lower, but citrate synthase activity showed a trend in the same direction.

As mitochondria are the major site of energy production in the cell, the lower mitochondrial enzyme activities are the likely cause of the changes in the energy-rich phosphates. However, a decreased blood flow and thereby oxygen and substrate supplywillalso potentially decrease energy-rich phosphates and increase lactate contents. A decreased blood flow in these patients could be the result of their severe insulin resistance or an ongoing inflammatory response (38,39). ICU patients suffer from a lower mitochondrial density rather a specific inhibition of the measured enzymes. One of the main determinant factors of muscle mitochondrial density is physical activity (40). Critically ill patients lying in the ICU are always bed bound and often sedated, which will most likely influence mitochondrial density. Several human studies have shown thata four to seven weeks period of immobilization decreasesmitochondrial enzyme activity in various muscle types by approximately20% (41, 42, 43, 44, 45). Even though immobilization certainlyaffects mitochondrial enzyme activity in critically ill patients, disease itself most likely plays a larger role.

Garrabou et al. (68) confirmed mitochondrial dysfunction in early sepsis affecting different mitochondrial respiratory chain (MRC) enzymes (complex I, III, IV) and oxygen consumption responsible for energy supply in peripheral blood mononuclear cells (PBMCs) which consequently enhances ROS

production. ROS are highly unstable molecules that attack cellular structures, including nucleic acids, lipids, carbohydrates and proteins causing oxidative stress damage that can lead cells to apoptosis. All of these pathophysiological processes may be linked and may be primarily caused by mitochondrial dysfunction (69).

Muscle Contractile Dysfunction

Oxidative stress, mitochondrial dysfunction, impaired excitation contraction coupling, and muscle membrane inexcitability may all contribute to the impaired force-generating capacity of muscle in acute CIM. Chronic inflammatory states modulate muscle-specific force of contraction by increasing free radical synthesis. Both ROS and nitric oxide (NO) can depress myofibrillar protein contractile function by modifying contractile protein machinery and interfering with myofilament interactions (56-58). Systemic inflammation has been linked to the development of muscle weakness in human disease (59-61). Various proinflammatory mediators such as TNF-a induce oxidative stress in muscle (56,60,62) and inflammation is reported as a factor for acute muscle dysfunction in the critically ill (63,77).

AMPK is a principal energy sensor in eukaryotic cells and is activated by cellular stress (87). Rising AMP and ADP levels activate AMPK. Muscle contraction activates an alternative pathway in response to increasing cellular Ca^{++} (88). AMPK activation has multiple cellular effects and is critical for insulin-independent glucose uptake in muscle through translocation of GLUT-

4 (83-85,89). It interferes with protein synthesis on several levels (90) and directly activates peroxisome proliferator-activated receptor-γcoactivator-1-α (PGC1α), which is important for mitochondrial biogenesis (91). In neurons AMPK regulates membrane excitability via direct interaction with the potassium channel Kv2.1 (92). A muscle-specific AMPK failure taking place in CIM is actually translated as a failure of glucose utilization, trapping of GLUT-4 in perinuclear spaces, and marked down-regulation of the gene encoding PGC1α.

The functional breakdown of AMPK in critical illness may be a consequence of analgesics and sedation because this would shut down the muscle activity-dependent Ca^{++}-triggered pathway of AMPK activation.

Glucose Toxicity

Another important factor, playing a crucial role in the altered pathophysiology of the CIP/CIM (critical illness polyneuropathy/myopathy) ishyperglycemia (70,71). Two prospectively planned subanalyses (72,73) of two large randomized controlled trials (74,75) were performed. The trials evaluated the effect of intensive insulin therapy on a SICU (Surgical ICU) and a MICU (Medical ICU) (aiming at glycemia of 80-110mg/dl) versus conventional insulin therapy in which insulin was started when glycemia rose above 220mg/dl and tempered or stopped at values below 180mg/dl. In the subanalysis, intensive insulin therapy significantly reduced the incidence of CIP/CIM detected on systemic electrophysiological investigation in patients in

the ICU for at least 1 week, from 45% to 25% in the SICU (P<0,0001) and from 51% to 39% in the MICU (P=0,02). Also, the need for prolonged mechanical ventilation, defined as mechanical ventilation for at least 2 weeks, was reduced from 42% to 32% in the SICU (P=0,04) and from 47% to 35% in the MICU (P=0,01). Multivariate analysis attributed the beneficial effect on CIP/CIM to glycemic control, (72) whereas the beneficial effect on prolonged mechanical ventilation was due to the insulin dose and was not completely explained by the benefit on CIP/CIM (73). Although a beneficial effect of intensive insulin therapy is present in patients in who tight glucose control did not totally succeed in lowering glycemic levels to the preset goal (but rather to between 110-150mg/dl), the benefit on CIP/CIM as well as on mortality is most noticeable in the patients with the tightest control (80 to 110mg/dl) (76).

Pronounced hyperglycemia developing in response to illness or trauma and worsened by artificial nutrition, aggravates mitochondrial damage (32,33). Interestingly, it has been determined that the severity of CIP (as well as the duration of ICU stay) corresponds to the serum glucose levels. (34)

Hyperglycemia and insulin resistance are implicated risk factors for CIM (77), because tight glycemic control decreased the incidenceofneuromuscular dysfunction (74,73). However, tight glycemic control was not directly related to protein degradation and muscle atrophy (78). Glucose supply to skeletal muscles closely regulated by at least two mechanisms that are independent and additive (79,80). Glucose transporter-4 (GLUT-4) is stored in vescicles in perinuclear compartments and is rapidly translocated to the sarcolemma after

insulin receptor binding or after muscle contraction (81,82). The insulin-signaling cascade involves proteinkinase B/Akt, whereas contraction-induced GLUT-4 translocation is mediated through phosphorylation of the 5'-adenosinemonophosphate-activated proteinkinase (AMPK) (83-85). Weber-Carstens et al.(86) found that failing GLUT-4 translocation to sarcolemmal membrane is a prominent finding in patients with CIM and cannot be abolished by treatment with insulin, even though insulin-dependent signal transduction seems to be intact up to activation of p-Akt. Additionallyfaulty GLUT-4 disposition and diminished glucose utilization in critical illness may, at least in part, be interpreted as a muscle specific AMPK failure, particularly pronounced in patients with CIM.

Channelopathy

Channelopathy is another mechanism that has been suggested in the pathophysiology of CIM. Electrodiagnostic studies often show evidence of muscle membraneinexcitability. This may be related to the inactivation of sodium channels at the resting potential and a shift in the voltage dependence of channel inactivation (113-116). Interactions of lipopolysaccharide with voltage-gated sodium channels may contribute to muscle membrane inexcitability in sepsis (117). Also altered expression of nitric oxide synthetase has been suggested to possibly affect muscle membrane excitability in CIM, as nitric oxide takes part in the maintenance of muscle fiber resting potential (118). CIM may include alterations in the excitation-

contraction coupling as blood serumfrom patients with CIM were found to affect not only the excitability of muscle fiber membranes but also the release of calcium from the sarcoplasmatic reticulum (SR) (110).

Conclusions

Understanding metabolic alterations and pathways underlying ICUAW can be the key to eventually modify and interfere to the development of this complex entity. This can contribute to decrease ICU mortality and help to early rehabilitation of ICU patients. Comprehension of the pathophysiological mechanisms in ICU acquired weakness also provides prospects for therapeutic interventions. For instance, the gravity of hyperglycaemia's detrimental effect on autophagy in skeletal muscle could lead to the determination of the optimal blood glucose levels for these patients, which remains a mystery. Another therapeutic concept to consider is immune modulation to prevent excessive inflammatory response and avoid ICUAW. As a conclusion, further research on human and animal models is key to present an advance in our understanding of muscle weakness in the critically ill.

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