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Respiratory Neuropathy as an Important Component of Critical Illness Polyneuromyopathy

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ABSTRACT The attention of neurologists, neurosurgeons, intensive care physicians has been attracted recently by the new PICS (Post Intensive Care Syndrome) symptom complex (PIC) or PIC syndrome — Post Intensive Care Syndrome. One of the most severe options for PIT syndrome is critical illness polymyoneuropathy (CIP). Polyneuropathy (Critical illness polyneuropathies, or CIP) and myopathy (Critical illness myopathies, or CIM) are common complications of critical care. Several syndromes of muscle weakness are combined under the term «Intensive care unit-acquired weakness» or ICUAW. Respiratory neuropathy is a special case of PMCS, where respiratory failure is associated with damage to the neuromuscular apparatus of external respiration. The clinical consequence of respiratory neuropathy is an unsuccessful weaning from ventilator and a long stay of patients in ICU. This systematic review of the literature is an analysis of publications devoted to the main pathogenetic mechanisms of the development of CIP and respiratory neuropathy, diagnostic methods, new therapeutic approaches to the treatment of ICU patients with respiratory neuropathy. The special attention is given to the problem of acute muscle wasting, diagnosis and correction of protein-energy metabolism disorders in patients with respiratory neuropathy.

Keywords: acute cerebral dysfunction, critical illness, polyneuropathy, respiratory failure
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ADP — adenosine diphosphoric acid
AMP — adenosine monophosphoric acid
ATP — adenosine triphosphoric acid
ALV — artificial lung ventilation
CIM — critical illness myopathies
CIP — critical illness polyneuropathies
PdiTw — transdiaphragmatic twitch pressure
PEM — protein-energy malnutrition
PICS — post intensive care syndrome
PMNCC— polymyoneuropathy of critical conditions
RICU — resuscitation and intensive care unit
VADD — ventilator-associated dysfunction of the diaphragm

Improvements in the quality of care for critically ill patients over the past 10–15 years have led to an obvious increase in patient survival in resuscitation and intensive care units (RICU). However, the consequences of a severe pathological process, as well as the use of instrumental methods of prosthetics, when biotechnical systems (microprocesses) replace the vital functions of the body, prolonged artificial lung ventilation (ALV), hemodialysis, extracorporeal membrane oxygenation, prolonged use of a large number of pharmacological agents have led to the formation of new, previously unknown problems, namely, conditions associated with impaired recovery processes after a disease [1, 2].

In recent years, the attention of neurologists, neurosurgeons and resuscitators has been attracted by the new symptom complex PICS (Post Intensive Care Syndrome), a set of somatic, neurological and socio-psychological consequences of stay in RICU conditions [3]. One of the most severe variants of the course of PIC syndrome is the so-called polymyoneuropathy of critical conditions (PMNCC). PMNCC is a syndrome of neuromuscular disorders such as polyneuropathy and/or myopathy acquired as a result of a critical state, clinically manifested by general muscle weakness and is the main reason for difficulties in stopping mechanical ventilation [4, 5]. Critical illness polyneuropathies (CIP) and critical illness myopathies (CIM) are common complications of critical illness. Several syndromes of muscle weakness are also collectively referred to as intensive care unit-acquired weakness, or ICUAW [6].

ALV and muscle immobilization, severe sepsis and multiple organ dysfunction, as well as neuro- and myotoxic poisons are some of the main risk factors for neuromyopathy acquired in RICU. Along with advances in modern intensive care, mortality from critical conditions in the RICU has decreased. However, the price of these successes is an increase in the frequency of occurrence of PMNCC [7, 8].

The prevalence of PMNCC not only affects the prognosis of the underlying disease, but also carries a threat of secondary complications (infection, embolism, etc.), lengthens RICU treatment and rehabilitation, and significantly increases the cost of intensive care [9, 10].

Unlike other conditions that can cause a clinical picture of muscle weakness in RICU patients, PMNCC is an exceptional manifestation of the PIC syndrome, in particular, a complication of bed rest by the mechanism of "non-use of function". A typical clinical picture of PMNCC can be observed in a patient after 2-3 weeks of prolonged mechanical ventilation. The volume of muscle mass and muscle strength are reduced, the patient is unable to raise the arms and legs, or does it with great effort. Symmetrical paresis may predominate in both the proximal and distal segments of the limbs. Pathological flexion of the feet is noted. Paresis of the oculomotor, facial muscles and muscles of the bulbar group is rarely observed. Respiratory muscles are frequently involved, but to a lesser extent than somatic muscles. The patient becomes dependent on ventilation support. When initiating independent respiration, the patient's breathing becomes rapid and shallow, quickly leading to muscle fatigue and hypoxia. Muscle tone and tendon reflexes are symmetrically reduced. In the distal segments of the limbs, a decrease in pain, temperature and vibration sensitivity is determined. The skin of such patients is usually dry, scaly; derivatives of the skin with signs of trophic disorders. The listed symptoms indicate a combination of two syndromes: symmetric peripheral tetraparesis and neuromuscular respiratory failure. The frequency of PMNCC is about 46% among adult RICU patients who are on mechanical ventilation for more than 2 weeks with sepsis and multiple organ failure (MOF) [11,12].

The first indicator that neuromyopathy in RICU patients may not be fully explained by axonal degeneration came from a study that performed nerve and muscle biopsies in critically ill patients with severe CIP and CIM. Nerve biopsy in many patients with electrophysiological signs of neuropathy did not reveal any morphological damage. This conclusion suggests the presence of some kind of functional deficit in the nerves of the affected patients who do not have a pathological correlate. More recently, it was found that nerve excitability was significantly reduced in patients with PMNCC. The presence of a functional deficit in the acute phase of PMNCC increased the possibility of a faster recovery, since the recovery of excitability could occur faster than the recovery of axons [14].

SODIUM CHANNELOPATHY IN THE PATHOGENESIS OF PMNCC

In the study of peripheral nerves of laboratory animals in which sepsis was simulated (rats), decreased excitability was revealed, which could not be explained by changes in input resistance or resting potential. Restoration of normal excitability after short-term hyperpolarization of axons has shown that hyperpolarized shift in voltage dependence on inactivation of sodium channels is the mechanism underlying decreased excitability. These data indicate that it is the dysfunction of sodium channels that occurs in the peripheral nerve that may underlie the pathogenesis of PMNCC [15]. The presence of sodium channelopathy in both muscles and nerves may serve as a mechanism to explain why critical illness is often accompanied by myopathy and neuropathy. This increases the likelihood that sodium channelopathy is present already in the early stages of critical illness [16-18].

DISORDERS OF HIGH-ENERGY PHOSPHATES EXCHANGE IN CRITICAL STATE

The oxidative phosphorylation process is essential for adequate production of adenosine triphosphoric acid (ATP) for energy available in a stable state, but takes some time to respond to changes in ATP demand. Phosphocreatine serves as a rapidly mobilized short-term storage of high-energy phosphates in skeletal muscle. Several studies in critically ill patients indicate significant changes in the levels of these elements in skeletal muscle. In the muscles of the extremities of RICU patients, especially in sepsis, a low-energy charging potential was found with a decrease in ATP, adenosine diphosphoric acid (ADP) and / or phosphocreatine levels and an increase in the content of adenosine monophosphoric acid (AMP), free creatine in the presence of high lactate levels and an increase in the ratio lactate / pyruvate [19].

OXYGENATION OF MUSCLES IN CRITICAL STATE

Disorders of cellular energy metabolism and subsequent bioenergetic insufficiency in trauma and sepsis in RICU patients were initially explained by inadequate tissue perfusion, leading to cellular hypoxia, which was confirmed by a high level of lactate in the blood serum [20]. However, studies on tissue oxygenation have produced mixed results. Thus, in a rat endotoxemia model, 4 hours after the administration of endotoxin in the presence of normal microcirculatory perfusion, oxygen tension in muscles at rest decreased, and tissues remained refractory to an increase in the concentration of inhaled oxygen [21]. A model of 6-hour peritonitis in sepsis rats demonstrated a decrease in oxygen tension in the rectus femoris tissues, an increase in the lactate / pyruvate ratio, and a decrease in ATP and total adenine nucleotides. After 36–42 hours, no signs of cellular hypoxia were detected in skeletal muscle or diaphragm in septic rats with peritonitis, although circulating lactate levels increased significantly [22]. Studies conducted in RICU patients have shown that muscle oxygenation even increases in case of adequate infusion, hemodynamically stable sepsis course, in contrast to patients with local infection, cardiogenic shock, or after coronary artery bypass grafting. Overall, these data indicate that cellular hypoxia is not the main factor for energy disturbances in critical muscle tissue. It is important to note that elevated lactate levels in hemodynamically stable patients may be associated with stimulated aerobic glycolysis rather than tissue hypoxia [23–25].

MORPHOLOGIC AND FUNCTIONAL MITOCHONDRIAL DAMAGE

Recent studies have shown that impairments in oxygen utilization occur earlier than impairments in oxygen delivery, contributing to the development of disorders in cellular energy metabolism, which have been identified as "cytopathic hypoxia" [26].

Deep structural changes in mitochondria occurred quite early in rats subjected to mechanical ventilation and immobilization in the absence of any other influences. Serious changes developed in the diaphragm already after 6 hours of mechanical ventilation, and after 18 hours of mechanical ventilation in the distal muscle of the hind limbs (soleus muscle) [27, 28].

Initial research on mitochondrial repair focused on biogenesis, mainly in tissues other than skeletal muscle (eg, liver), where activation of this process preceded mitochondrial mass recovery and oxidative metabolism and proved to be an important survival factor [29–31]. In biopsies of M. vastus lateralis muscle taken within 42 days after admission to the RICU from patients with sepsis-induced MOF, most of whom survived, it was shown that mitochondrial biogenesis can be partially activated [32]. In another clinical study, early response mitochondrial biogenesis (within 1–2 days after admission to the RICU) was observed in the muscles of survivors, but not in patients with severe sepsis [33]. In a heterogeneous group of critically ill patients, activation of the mitochondrial biogenesis program was observed in postmortem biopsies of the rectus abdominis muscle, but not in in vivo biopsies of M. vastus lateralis muscle taken after 2 weeks in the RICU, and this did not depend on future survival status [34]. Reduced mitochondrial biogenesis was found in muscles taken for 10 days from children with severe burn injury [35]. In the experimental denervated gastrocnemius muscle of rats and mice (immobilization model), a strong decrease in mitochondrial content coincided with a significant

suppression of several key participants in mitochondrial biogenesis several weeks after exposure [36, 37]. Several components of the mitochondrial biogenesis pathway were found to be reduced in gene expression after 24 hours of endotoxemia, which was more pronounced in the anterior tibial and soleus muscles than in the diaphragm [38]. On the other hand, cold injury to the gastrocnemius muscle of the mouse (a model of degeneration and regeneration) has shown that mitochondrial biogenesis plays an important role in muscle regeneration [39].

AUTOPHAGY IN CRITICAL CONDITIONS

Autophagy (from ancient Greek αύτός auto- - "self" and φαγεῖν - "is") is a mechanism of getting rid of all old cellular components that have fulfilled their role (organelles, proteins and cell membranes) when the cell no longer has enough energy support them. It is a regulated, ordered process aimed at breaking down and recycling cellular components. In microautophagy, macromolecules and fragments of cell membranes are simply captured by the lysosome. In this way, the cell can digest proteins when there is a lack of energy or building material (for example, during starvation). But the processes of microautophagy also occur under normal conditions, and in general are not selective. Sometimes organelles are also digested during microautophagy. Thus, in yeast, peroxisome microautophagy and partial nuclear microautophagy, in which the cell remains viable, have been described. In macroautophagy, a portion of the cytoplasm (often containing some organelles) is surrounded by a membrane compartment similar to the cistern of the endoplasmic reticulum. As a result, this area is separated from the rest of the cytoplasm by two membranes. These two-membrane organelles surrounding the organelles to be removed and the cytoplasm are called autophagosomes. Autophagosomes combine with lysosomes to form autophagolysosomes, in which the organelles and the rest of the autophagosome contents are digested. Apparently, macroautophagy is also not selective, although it is often emphasized that with its help the cell can get rid of "expired" organoids, myochondria and ribosomes [40]. The main stimuli to enhance the processes of autophagy in cells can be: lack of nutrients, as well as the presence of damaged organelles and partially denatured proteins and their aggregates in the cytoplasm.

The activation of autophagy in critical conditions has previously been interpreted as a negative reaction that promotes hypercatabolism and wasting. However, the hypothesis that autophagy may be protective for skeletal muscles and other organs during a critical state was initially voiced and deserves consideration in the light of data obtained in studies performed on experimental animals (mice with autophagy selective for various tissues) [41 , 42]. In fact, it has not been previously studied whether autophagy is activated enough to cope with severe cellular damage caused by critical illness. However, a clinical study that took into account the effects of insufficient autophagy confirmed similar adverse changes in skeletal muscle and liver in critically ill patients. They consisted in the accumulation of aggregates of ubiquitin and other substrates of autophagy, such as deformed mitochondria and aberrant concentric membrane structures [43, 44]. Also, the phenotype of autophagy deficiency was observed in skeletal muscles, liver and kidneys in the critical state model against the background of severe burn injury [45]. Fasting is the most potent physiological activator of autophagy, while nutrition and insulin inhibit this mechanism [46]. There are concerns that early delivery of nutrients during critical illness may weaken autophagy activation, thereby reducing the removal of damage that is required for repair. This is supported by critically ill animal experiments (rabbits) showing that early parenteral nutrition (especially when enriched with amino acids) reduces muscle catabolism through suppressed autophagy, thus disrupting muscle fiber integrity and vital organ function, compared with fasting. Muscle biopsy performed in ICU patients showed suppression of autophagy activation in the presence of early (compared to late) onset of parenteral nutrition, but in the absence of any effect on markers of muscle atrophy development [47–49]. However, the effects on autophagy were independently associated with a higher risk of developing clinically significant muscle weakness. Adequate activation of autophagy appears to have been critical for providing protection against mitochondrial dysfunction, liver damage, and renal failure in critically ill models in experimental animals [45, 50, 51].

A critical balance between activation and suppression of autophagy is important for maintaining muscle mass, but more importantly, for maintaining adequate muscle function. Most studies (experimental and clinical) demonstrate insufficient activation of autophagy in a critical condition, but the level of suppression of autophagy activation required to combat the formation of PMNCC is still unknown [6].

PECULIARITIES OF EXCANGE OF MUSCLE TISSUE PROTEINS IN CRITICAL STATE

Critical illness is usually associated with the loss of muscle protein due to the development of catabolism and a decrease in skeletal muscle mass. As a result, muscle atrophy can contribute to the development of severe weakness, rapid fatigue, impaired glucose tolerance, and a higher incidence of complications and poor outcomes in RICU patients [52–54]. At the cellular level, a decrease in muscle fiber size reflects an imbalance between proteolysis and protein synthesis. This is regulated by complex changes in signaling pathways and gene products that regulate protein breakdown and synthesis [55]. The key difference from simple atrophy, usually observed in bed rest, weightlessness or muscle unloading, and myopathy caused by sepsis, is that critical myopathy is characterized by predominant myosinolysis, which is much more active than the mechanism of simple atrophy (balanced proteolysis of sarcomere proteins) [6].

RESPIRATORY NEUROMYOPATHY AS AN IMPORTANT COMPONENT OF PMNCC

Respiratory neuropathy is distinguished in the structure of the PMNCC as the main problem that determines the development of respiratory failure and an increase in the time required to transfer a patient on prolonged mechanical ventilation to spontaneous breathing. In 60% of cases of PMNCC, the involvement of muscles and nerves of the respiratory group in the pathological process is observed [56, 57].

The clinical signs of respiratory neuropathy:

- inability of the patient to return to spontaneous breathing within 24 hours after the weaning from ventilation;

- the value of the index of frequent and shallow breathing (Tobin's index) (RSBI = f (breath / min) / Vt (l) more than 100 breaths / min / l (normally less than 100 breaths / min / l) [58].

Of particular interest is the fact that difficulty in weaning from mechanical ventilation is often the first sign of the development of PMNCC syndrome. Undoubtedly, the state of the neurorespiratory drive system, the state of the entire complex of the neuromuscular respiratory apparatus is important for successful disconnection from mechanical ventilation. Using neurophysiological methods, it is possible to assess the state of the neurorespiratory drive along its entire length, including the cortex and brain stem, descending motor and ascending sensory pathways, segments of the cervical and thoracic spinal cord, phrenic and intercostal nerves, neuromuscular synapses, diaphragm and other respiratory muscles. For general RICU patients without primary lesion of the central nervous system, it has been proven that PMNCC syndrome due to damage to phrenic nerves prolongs the period of weaning from ventilation [59]. The most important link in the pathogenesis of respiratory neuromyopathy is the so-called "diaphragmatic dysfunction".

DIAPHRAGMATIC DYSFUNCTION IN CRITICAL STATE

The diaphragm is the main inspiratory muscle and its function is critical for optimal breathing. Diaphragmatic dysfunction has long been recognized as an important factor in poor outcomes in various systemic neuromuscular disorders. Recently, it has become increasingly clear that diaphragm dysfunction is present in a large percentage of critically ill patients and is associated with increased morbidity and mortality. It is believed that in RICU patients, diaphragm weakness develops against the background of secondary non-use of the diaphragm (according to the "non-use" principle) during prolonged forced ventilation and as a consequence of the effects of systemic inflammation, including sepsis. Critical-induced diaphragm dysfunction reduces the ability of the respiratory pump to compensate for increased respiratory stress, leading to persistent respiratory failure and poor clinical outcome [60, 61].

PREVALENCE OF DIAPHRAGMATIC DYSFUNCTION IN PATIENTS ON LONG-TERM ALV

Over the past decade, a significant proportion of researchers have focused almost entirely on muscle weakness acquired in the RICU, with little focus on the diaphragm. It has been suggested that this may be associated with a lack of knowledge about the impact of critical illness on the respiratory muscles or the limited availability of tools for assessing and monitoring diaphragm function in RICU patients. However, a number of studies recently carried out by the groups of F. Laghi, A.C. Watson and A. Demoule, showed that severe diaphragmatic weakness develops in a large percentage of patients on artificial ventilation in the RICU [62–64]. Most of the studies cited used objective measurements using the gold standard method to assess the force of contraction of the diaphragm. Transdiaphragmatic pressure is the difference between pressure in the esophagus and pressure in the stomach. When assessing the transdiaphragmatic pressure during muscle contraction (PdiTw, transdiaphragmatic twitch pressure), which is formed during bilateral anterior magnetic stimulation of the phrenic nerve (BAMPS), it was found that in patients on prolonged artificial ventilation, on average, PdiTw is generated only in a volume of 20% of the norm. A large percentage of long-term ventilated patients have lower PdiTw, which is a sign of more severe diaphragm weakness. For example, Supinski and Callahan et al. found that 30% of patients had PdiTw levels less than 5 cm water column, while only 6% of patients had PdiTw levels greater than 15 cm water column; values that are significantly lower than those recorded in healthy volunteers (28–38 cm water column). Additional studies have confirmed that, on average, 60–80% of patients on prolonged artificial ventilation have clinically significant diaphragm dysfunction [62, 63, 65]. Moreover, recently published studies show that in critically ill patients, diaphragm weakness is present 2 times more often than limb weakness [66, 67].

Although many clinicians assume that diaphragm weakness acquired in RICU is temporary and does not directly affect clinical outcome, there are few recent studies suggesting that diaphragm strength is a major determinant of the time it takes to wean from artificial ventilation. In particular, it was shown that the average duration of artificial ventilation is 5 days for more "strong" patients (PdiTw more than 10 cm water column) and statistically significantly increases on average to 12 days for patients with PdiTw less than 10 cm water column ($p < 0.02$). With a low diaphragm force (for example, PdiTw less than 4 cm water column), the duration of artificial ventilation increased, and in most of these patients, the duration of weaning from artificial ventilation averaged 3 weeks [68]. It has also been shown that diaphragm weakness is correlated with higher mortality. In particular, in one study, the incidence of adverse outcomes in the RICU was 49% in patients with diaphragm weakness (PdiTw less than 10 cm water column), and only in 7% of patients with a stronger diaphragm (PdiTw more than 10 cm water column, $p = 0.022$) [69]. In fact, diaphragm weakness was found to be an even stronger predictor of mortality in RICU than the degree of organ dysfunction, severity of lung dysfunction, age, gender, steroid use, or comorbidity [70].

CAUSES OF DIAPHRAGMATIC DYSFUNCTION IN PATIENTS ON ALV

When diaphragm weakness is found in patients on prolonged artificial ventilation, it is always important to first rule out easily treatable electrolyte disorders such as hypophosphatemia, hypomagnesemia and hypocalcemia. Severe diaphragm dysfunction can be present with hypothyroidism, and sometimes respiratory failure due to weakness of the respiratory muscles can be the main manifestation of this disease. Prolonged hyperglycemia, severe protein-energy malnutrition, severe renal failure, use of muscle relaxants, long-term administration of high doses of corticosteroids can reduce muscle strength in a subgroup of patients on mechanical ventilation in the RICU. In most cases, it is believed that diaphragm dysfunction occurs primarily due to artificial ventilation as such (ventilator-associated diaphragmatic dysfunction, VADD). There is also strong evidence that processes other than VADD, including sepsis and other systemic infections, are responsible for the development of muscle (diaphragmatic) weakness associated with RICU stay [71, 72].

VENTILATOR-ASSOCIATED DIAPHRAGM DYSFUNCTION

Ventilator-induced diaphragm dysfunction is a loss of power generated by the work of the diaphragm, which is caused by prolonged artificial ventilation of the lungs. The recent recognition that artificial ventilation may cause diaphragm atrophy has been convincingly made in experimental animal studies. In one of these studies, S. Powers et al. found that rats rapidly developed progressive atrophy of the diaphragm and loss of the ability to stretch the diaphragm during controlled ventilation (CMV). In this work, electromyography confirmed the complete inactivation of the diaphragm, which was achieved using deep sedation [73]. Subsequently, a series of studies showed that atrophy of the diaphragm caused by artificial ventilation also develops in RICU patients undergoing prolonged artificial ventilation [74].

In an earlier posthumous study by A.S. Knisely et al. reduced diaphragm muscle mass and muscle fiber atrophy were found in infants and newborns who received long-term ventilation support [75]. A number of additional studies on humans, performed mainly on organ donors with brain death, have provided convincing evidence of the development of diaphragm atrophy in conditions of prolonged mechanical ventilation [76, 77]. To determine the cellular mechanisms in which mechanical ventilation itself essentially causes atrophy and weakness of the diaphragm, important animal studies have shown that ventilator-assocoated diaphragm dysfunction (VADD) can be closely associated with oxidative stress, activation of several proteolytic pathways (caspases, calpans, and ubiquitin-proteosomal system) and mitochondrial dysfunction in the tissues of the diaphragm, which cause loss of muscle mass and strength. Additional studies indicate that ryanodine receptor dysfunction contributes to the pathology of VADD and that activation of autophagy during VADD, in contrast, provides a protective role [78–82]. More recently, diaphragm tissues have been studied in patients undergoing prolonged artificial ventilation. The authors confirmed many of the data that were found earlier in animal studies, which largely confirms that the same pathophysiological processes occur in patients with weak or absent respiratory drive undergoing mechanical ventilation [74, 77]. There are, however, a few caveats regarding VADD. First, VADD is a diagnosis of exclusion and it should not be assumed that all mechanically ventilated patients have muscle weakness that develops through this mechanism. Second, although animal studies show that it is easy to induce diaphragm weakness when the respiratory drive of this muscle is eliminated by sedation and harsh ventilation modes, VADD does not occur when animals have the opportunity to at least periodically activate the diaphragm during ventilation [83, 84]. These studies also indicate that VADD is rapidly reversible as soon as artificial ventilation in animals is stopped and spontaneous breathing

is allowed, and diaphragm atrophy and weakness are quickly restored to normal within a few hours [85]. As a result, if VADD itself was largely responsible for the diaphragm weakness acquired in the RICU, in theory this problem easy to treat simply by reducing the level of ventilator support (eg, pressure ventilation) over a relatively short period. This rapid reversibility has never been demonstrated in critically ill patients, proving that other mechanisms of diaphragm weakness and respiratory failure play a role in those patients who are difficult to wean from prolonged artificial ventilation [86].

DIAPHRAGMATIC DYSFUNCTION IN SEPSIS

Another potential factor in the development of diaphragm weakness in patients with prolonged artificial ventilation is systemic infection. A number of studies have shown that infection is an important risk factor for the development of severe diaphragmatic weakness in critically ventilated patients. Thus, one of these studies reported that patients on ventilator in RICU with infectious problems had an average PdiTw of only 5.5 cm water column. (25–75%, confidence interval (CI) 4.0–7.9 cm water column), while in uninfected patients the PdiTw value averaged 13.0 cm water column ($p < 0.001$). Demoule et al. found a similar relationship when analyzing this indicator in patients on long-term artificial ventilation - the force of contraction of the diaphragm in infected patients was, on average, two times less than in uninfected patients [67].

Further evidence of a causal relationship between infection and diaphragm weakness was obtained as a result of numerous fundamental experiments in laboratory animals, which showed that severe systemic infection contributes to a significant decrease in diaphragm strength - up to 80% (!) Within 24 hours of artificial ventilation [87, 88]. The pathophysiological mechanisms responsible for this rapid decrease in diaphragm strength include the activation of proteolytic pathways, including calpans, caspases, and proteasomes. Infection induces these pathogenic pathways due to the stimulation of cytokinogenesis, and cytokines, in turn, trigger the mechanism of activation of neutral sphingomyelinase receptors on the cell membrane. Activation of these receptors leads to changes in the metabolism of muscle ceramides, stimulation of the generation of free radicals in mitochondria, and induction of cellular oxidative stress. Oxidative stress is accompanied by damage to subunits of the mitochondrial electron transport chain, contributing to a decrease in muscle strength, as well as activation of proteolytic enzyme pathways, which leads to a decrease in the amount of contractile proteins and a decrease in muscle strength [88–91].

CLINICAL DIAGNOSIS OF DIAPHRAGMATIC DYSFUNCTION IN CRITICAL PATIENTS

In theory, any patient requiring prolonged ventilation should be considered at risk of developing diaphragm weakness. However, there are several specific clinical scenarios that suggest diaphragmatic abnormalities. While not exhaustive, the situations described below may offer a practical approach to early recognition of diaphragm weakness in critically ill patients, as it can be easily detected by a physician at the patient's bedside.

Firstly, this is the presence of the so-called "abdominal paradox", that is, a significant movement of the anterior abdominal wall during inhalation. It is this symptom that is often a clinical sign of the existence of diaphragm weakness or bilateral diaphragmatic palsy. In patients with these symptoms, the inspiratory contraction of the intercostal muscles pulls the soft diaphragm into the chest, resulting in internal movement of the anterior abdominal wall. In a healthy person, on the other hand, during inhalation, the active diaphragm moves downward and prevents internal movement of the anterior abdominal wall. The abdominal paradox is easiest to detect when patients are in the supine position and during weaning from ventilation, especially when pressure support is low. Severe activation of the respiratory muscles can induce diaphragmatic paradox in the absence of true diaphragmatic dysfunction. Therefore, additional testing is often necessary to confirm the presence of true diaphragm weakness when observing this clinical sign [92, 93].

Diaphragm dysfunction should be suspected in all cases of unsuccessful weaning from ventilation, especially when this problem arises, despite the positive dynamics in regression of pulmonary infiltrates and resolution of infectious problems. The likelihood of severe diaphragmatic weakness should also be tolerated in patients with recurrent episodes of unexplained respiratory failure. It is also extremely useful to evaluate simple bedside measures of lung and respiratory function (static respiratory system compliance, inspiratory airway resistance and rapid shallow breathing index - Tobin's index). The combination of relatively good lung mechanics and a high Tobin index is an important prognostic marker for the presence of respiratory muscle weakness [94–96].

A chest x-ray can also sometimes indicate the possibility of a significant pathological condition of the diaphragm. Unilateral or bilateral lifting of half of the diaphragm can be seen in diaphragmatic palsy or severe muscle weakness, and this finding should prompt the use of simple tests, such as ultrasound examination of the diaphragm, to determine how severely impaired its mobility is.

Another clinical situation that requires consideration is patients who do not have a history of disease. but there is respiratory failure with hypercapnia and there are no obvious signs of a pathological process on the chest x-ray. In these cases, patients may have prior undiagnosed primary neuromyopathic processes such as amyotrophic lateral sclerosis, Guillain – Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, carnitine deficiency, Pompe disease, polymyositis. In a number of patients with the above diseases, acute respiratory failure due to weakness of the respiratory muscles can be the main component of the clinical picture of these diseases. Some of these disorders respond to adequate treatment and correction, and failure to diagnose these conditions can be a significant problem [97–99].

ULTROSOUND FOR ASSESSMENT OF DIAPHRAGM DYSFUNCTION IN PATIENTS ON LONG VENTILATION

The study "Bedside Ultrasound Is a Practical and Reliable Measurement Tool for Assessing Quadriceps Muscle Layer Thickness" conducted by M. Tillquist et al. evaluated the results of ultrasound when measuring the thickness of the quadriceps as an indicator of lean body mass. It also concluded that quadriceps ultrasound may ultimately be used to screen patients at risk of developing PMNCC on admission and during hospitalization, and to prevent muscle atrophy [100].

Recently, ultrasound has become a common tool for assessing the function of the diaphragm. This method is attractive because of its non-invasiveness, the availability of equipment in most RICUs and the ability to perform repeated examinations, all this compared to the technically more sophisticated methods used to measure trans-diaphragmatic pressure. The usual approach to diaphragm ultrasonography involves positioning the patient in the supine position, which provides ease of use in critical patients, less overall variability, and greater reproducibility [100, 101].

However, optimal ultrasound of the diaphragm involves measuring parameters during spontaneous breathing and the ventilator is turned off. Evaluation during mechanical ventilation is very difficult to interpret results, especially when the patient is sedated or fully ventilated [102–105]. In general, there are two main methods of ultrasonic assessment of the diaphragm: determining the excursion of the diaphragm and measuring its

thickness. Diaphragmatic excursion is defined using the liver or spleen as an acoustic window with a low frequency curvilinear or phased transducer (1-5 MHz) using two-dimensional brightness or ultrasonography - B-mode and M-mode. The right side of the diaphragm is examined from the anterior hypochondrium, when the sensor is positioned below the right costal margin between the mid-clavicular and anterior axillary lines. The left side of the diaphragm is examined from the inferior intercostal or subcostal approach, in which the sensor is located between the mid and anterior axillary lines. The transducer is angled cranially so that the ultrasonic beam reaches perpendicular to the back of the diaphragm. The direction of movement of the diaphragm towards the sensor (positive deflection in M mode) or away from the sensor (negative deflection in M mode) can be related to the phases of the breathing cycle [101, 106, 107]. Normal ranges of diaphragmatic excursion with calm exhalation and deep inhalation are noted in adults within 0.9–9 cm, while higher values are observed in men. Diaphragm paralysis is represented by a lack of excursion with calm and deep breathing and a complete lack of movement or paradox movements during normal breathing. Likewise, the weakness of the diaphragm is due to a smaller than usual amplitude of deviation during deep breathing and the presence of paradox movement (or in its absence) during forced breathing. Diaphragm thickness estimation can be obtained in the area using 2D ultrasound in B- and M-modes and requires a high frequency linear transducer (6-13 MHz). The transducer is positioned along the mid-axillary line between the VII and VIII or VIII and IX ribs to obtain an ultrasound image in the sagittal plane. The ultrasound view of the diaphragm in the area of application is usually considered as a three-layer structure consisting of two parallel echogenic layers of the diaphragmatic pleura and peritoneal membranes with an interlayer of non-echogenic muscle layer [101, 105].

A recently published study in 107 patients with prolonged mechanical ventilation showed that during the first week of ventilation, the diaphragm thickness decreased by more than 10% in 47 patients (44%), increased by more than 10% in 13 patients (12%) and did not change in 47 patients (44%). It is important to note that despite the absence of significant differences in the results of these 3 groups of patients, this study shows that the diaphragm undergoes changes that can be detected by ultrasound during prolonged ventilation, which allows the authors to suggest that the regulation of respiratory support to maintain an adequate level of activity diaphragm can prevent diaphragm atrophy [108].

Although ultrasound is an evolving technique in ICU settings and is widely recognized as a tool for assessing diaphragm function in ventilated patients, there are important limitations to its use. First, the acquisition and analysis of an ultrasound image is operator dependent and requires training. Moreover, successful imaging can be optimized through a thorough understanding of pulmonary artifacts and the use of correct patient positioning techniques. Thus, in several works devoted to this topic, technical difficulties arising in the analysis of the left side of the diaphragm prompted researchers to limit the assessment of the right side of the diaphragm [102, 109, 110]. Second, the degree of shortening of the diaphragm during contraction is highly dependent on the so-called diaphragm motor outflow, which varies significantly in mechanically ventilated patients depending on the degree of sedation. In addition, the contraction of the diaphragm also depends on the level of "work" load on the diaphragm. For example, when a very “stiff” lung or chest is compressed, the degree of contraction will be much less than a normal airway load. The contraction of the diaphragm will increase when the respiratory load is low and the respiratory drive is adequate and not limited by sedation. On the contrary, weak contraction of the diaphragm may be associated with insufficient drive or high respiratory load and, being isolated, cannot be considered as a direct indicator of the adequacy of diaphragm function [111, 112].

Despite the problems mentioned above, current non-invasive studies of diaphragm function in patients with prolonged ventilation have given a significant impetus to the understanding of the mechanisms that damage the diaphragm during ventilation. However, to date, no randomized controlled trials have been performed on the use of ultrasound diagnostics in critical conditions to assess diaphragmatic dysfunction. Of course, new research is needed to determine if the use of ultrasound diagnostics affects early and long-term treatment outcomes [102].

OTHER METHODS FOR DIAGNOSING DIAPHRAGMATIC DYSFUNCTION IN PATIENTS ON LONG VENTILATION

In addition to diaphragm ultrasonography, there are a number of other techniques that are useful in assessing respiratory muscle and diaphragm function in RICU patients. An informative method is to determine the maximum inspiratory pressure (negative inspiratory force). This measurement can be performed with relatively simple equipment and involves connecting a pressure transducer to the inspiratory end of a two-way valve connected to the patient's breathing circuit. The inspiratory end closes and the patient is asked to take several maximum breaths. The main limitation of this procedure is the assumption that the inspiratory effort is truly maximum. When evaluated in sedated or uncooperative patients, this measurement can be extremely unreliable. However, if carefully performed, this measurement method, as well as the criterion, can be a good predictor of the success of weaning from ventilation [70, 113].

The "gold standard" for assessing diaphragm strength is the determination of transphrenic pressure in response to controlled exogenous activation of phrenic nerves on both sides, either by electrical or magnetic stimulation. When this technique is used, the airway is temporarily closed before stimulation to limit contraction of the diaphragm, and diaphragmatic stimulation is applied at the end of expiration when the length of the diaphragm is at its maximum during the respiratory cycle. In addition, the level of current or magnetic field applied to the phrenic nerves is adjusted to “pre-maximal” to ensure that all motor fibers in the phrenic nerve are activated. Classically, this test is performed after the transnasal insertion of small balloon-tipped catheters into the stomach and esophagus. Then transdiaphragmatic pressure is defined as the difference between esophageal and gastric pressure. Unfortunately, these methods are complex and only available in highly specialized centers [66, 67].

Another test is the measurement of phrenic nerve conduction time, which can be used to diagnose unilateral and bilateral diaphragmatic palsy. For example, the complete absence of conduction along the phrenic nerve plus the absence of movement of the diaphragm on ultrasound will confirm the diagnosis of diaphragm paralysis due to damage or pathological condition of the phrenic nerve. There are, however, important technical issues that can limit the interpretation of the results of this test. As a result, this test is technically challenging and should only be performed in experienced laboratories [114].

THE ROLE OF PROTEIN-ENERGY MALNUTRITION IN PATHOGENESIS OF RESPIRATORY NEUROMYOPATHY

Unfortunately, it should be recognized that often in RICU conditions, especially in multidisciplinary hospitals, insufficient attention is paid to the effectiveness of nutritional support. Formal implementation of this technique without taking into account the real needs of the resuscitation patient in energy substrates and protein leads to completely natural severe depletion of the patient with the development of the entire spectrum of consequences and problems directly related to nutritional (protein-energy) insufficiency, namely: nosocomial infections of the respiratory tract (tracheobronchitis and pneumonia), bedsores, urinary infection, the need for long-term ventilation and a long stay of the patient in the RICU and hospital. The most striking clinical manifestation of protein-energy malnutrition is a significant decrease in body weight (body mass index less than 19), as well as the development of hypoproteinemia (total protein less than 65 g/l), hypoalbuminemia (albumin less than 35 g/l), lymphopenia

(absolute number of lymphocytes less than 1800 in 1 mm^3). Hospital wasting is more of a muscle loss syndrome with relative retention of fat in the subcutaneous layer. Loss of muscle tissue due to being in the RICU can adversely affect not only the indicators of clinical outcome, but also the economic costs associated with the presence of the patient in the RICU [13].

The development and progression of protein-energy malnutrition (PEM) is typical for the majority of RICU patients on long-term ventilation. The prevalence of malnutrition in hospitalized patients is 20–69%. However, the prevalence of malnutrition in patients admitted to the RICU is 40–70% [115]. In patients who have PEM, muscle mass usually decreases dramatically due to the activation of catabolic gluconeogenesis. Loss of muscle mass results in impaired wound healing and an increase in infection rates, mortality, morbidity, length of hospital stay and economic costs [116]. Therefore, it is important to identify early patients with PEM and malnutrition already upon admission to the RICU, since early nutritional support can improve the prognosis. There is no gold standard for assessing the nutritional status of critically ill patients on long-term ventilation, but it should be borne in mind that all parameters that can be used in stable non-critical patients have some limitations in patients on long-term mechanical ventilation with manifestations of PIC syndrome [117].

CONCLUSION

Thus, respiratory neuromyopathy is an important component of critical illness polyneuromyopathy, in which the problem of respiratory failure associated with damage to the neuromuscular apparatus of external respiration comes to the fore. The clinical consequence of respiratory neuromyopathy is unsuccessful weaning off mechanical ventilation and a long stay of patients in the RICU. The main links in the pathogenesis of respiratory neuromyopathy are immobilization syndrome, sodium channelopathy, excessive autophagy, diaphragmatic dysfunction, as well as acute muscular atrophy, which is not fully understood by most researchers, which is characteristic of a critical state. Diagnostic methods for respiratory neuropathy can be used more widely in routine clinical practice. An important method of correcting respiratory neuromyopathy is nutritional support personalized in accordance with the results of metabolic monitoring.

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