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Monitoring and evaluation of muscle atrophy: a much needed step in critically ill COVID-19 patients.

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ABSTRACT

INTRODUCTION: Elderly COVID-19 patients admitted to the intensive care unit (ICU) are at high risk of an inflammatory syndrome, hypercatabolic reaction, malnutrition, and physical immobilization. This may result in loss of muscle mass and pulmonary infection leading to prolonged ventilatory support. Factors responsible for muscle mass loss in ICU are (1) microcirculatory disturbances, (2) presence of systemic inflammatory response syndrome (SIRS), (3) sepsis (4) drugs (corticoids, neuromuscular blockers) having inhibitory activity on the nervous system, neuromuscular junction and muscle itself. Mechanism of muscle atrophy in critically ill elderly patients include an imbalance between protein synthesis and degradation. Interventions to manage muscle atrophy for the patients admitted to ICU is also extrapolated to mechanically ventilated COVID-ARDS patients.

PURPOSE: Early recognition of factors contributing to intensive care unit acquired weakness (ICUAW) in COVID-19 patients, inflammation, high catabolic phase, steroid use, and paralysis. The potential interventions to target these specific mechanisms and ameliorate muscle dysfunction in COVID-19 patients.

CONCLUSIONS: Intensive care unit acquired weakness (ICUAW) in critically ill COVID-19 patients is due to severity of illness, co-morbidities, muscle unloading, or ICU treatments, a systemic reaction circulating within the body, or combinations therein. Furthermore, the availability of a culture model of ICUAW could facilitate in expediting the diagnosis of ICUAW and fast track the discovery of putative treatments. We recommend NIV or HFNC ventilation or early weaning from invasive mechanical ventilation in critically ill COVID-19 elderly patients.

KEY WORDS: COVID-ARDS, elderly, immobilization, muscle atrophy, noninvasive ventilation.

INTRODUCTION

COVID-19 acute respiratory distress syndrome (COVID 19 -ARDS) in elderly can be complicated by intensive care unit acquired weakness (ICUAW) resulting in poor outcomes [1, 2]. Prolonged ICU stay frequently involves sedation and immobilization (often in a prone position), resulting in musculoskeletal, pulmonary, cardiovascular, immunological, endocrine, and metabolic complications [3]. Musculoskeletal consequences are especially relevant and include muscle atrophy, decreased strength, reduced protein synthesis, joint contractures, bone density decrease, and pressure ulcers. Critically ill COVID- 19 patients, who required pro- longed sedation frequently develop ICUAW [4]. The term ICUAW comprises critical illness myopathy (CIM), critical illness polyneuropathy (CIP), and a combination of both (CIMP). The management of severe COVID 19-ARDS patients with ICUAW, may require prolonged mechanical ventilation. Prolonged immobilization, unrecognized and untreated delirium or residual effects of small doses of sedative and analgesic agents or other medications in elderly patients with altered drug metabolism contribute to this problem's appearance [5]. The muscular atrophy's clinical picture is characterized by bilateral, symmetrical generalized muscle weakness, which is not associated with a preexisting neuromuscular problem [6]. Muscle weakness, which in severe cases can reduce or abolish the tendon reflexes, to tetraplegia and difficulty in weaning from the ventilator [7]. It remains to be established whether SARS-CoV-2 directly affects diaphragm myopathy or prolonged mechanical ventilation (MV) results in diaphragmatic atrophy and contractile dysfunction, termed ventilator-induced diaphragmatic dysfunction (VIDD). By early recognition of this vulnerability and identification of patients at risk for respiratory failure, the adoption of proactive measures like coordinated approaches and noninvasive ventilation (NIV) strategies in appropriate patients prevent the need for intubation in a patient having COVID-19 ARDS.

The goal of the work: Early recognition of factors contributing to ICUAW in COVID-19 patients, like inflammation, high catabolic phase, steroid use, and paralysis. The potential interventions to target these specific mechanisms and ameliorate muscle dysfunction in COVID-19 patients.

PATHOPHYSIOLOGY OF MUSCLE WEAKNESS

The incidence of severe skeletal muscle atrophy and weakness is 25% to 75% in mechanically ventilated patients. [8]. Respiratory muscle weakness in critically ill COVID-19 patients is more prevalent in elderly and in a patient with comorbidities such as obesity, smoking history, physical inactivity, and chronic diseases (such as heart failure, COPD, and neuromuscular disorders). The main contributing factors include (1) microcirculatory disturbances which affect the peripheral nerves and the skeletal muscles, (2) the presence of systemic inflammatory response (systemic inflammatory syndrome SIRS), (3) the sepsis, and (4) the use of drugs with inhibitory activity on the muscular system as well as on the nervous system–neuromuscular junction (corticoids, neuromuscular blockers) [9, 10]. Similar to cardiac tissue, the expression of ACE2 is well-documented in skeletal muscle [11]. Skeletal muscle may be affected by SARS-CoV-2 either through direct infection of resident ACE2-rich cell types or via indirectly through systemic cytokine release. Shi Z et al. [12] detected ACE-2 expression in the human diaphragm and SARS-CoV-2 viral infiltration in the

diaphragm of a subset of COVID-19–ICU patients. They hypothesized COVID-19 infection might lead to severe diaphragm myopathy, which results in diaphragm weakness and might contribute to ventilator weaning failure, persistent dyspnea, and fatigue in patients with COVID-19 who survive their ICU stay [13].

MECHANISM OF MUSCLE ARTOPHY

The possible mechanism of muscle atrophy in critically ill elderly patients is reduced synthesis capacity for myosin and actin, with myosin transcription being even more affected than actin [14, 15]. The atrophic injury appears to result from increased oxidative stress (due to prolonged mechanical ventilation and hypercatabolic reaction), ubiquitin-proteasome system and dysregulated autophagy, disuse and immobilization leading to activation of protein-degradation pathways. The incidence of multilobe lesions in elderly patients is significantly higher than in young and middle-aged patients results in an increased need for mechanical ventilation in the elderly [6]. A meta-analysis of systemic inflammation and muscle strength and muscle mass has revealed that higher levels of circulating inflammatory markers are associated with a marked decrease in skeletal muscle strength and mass [16]. COVID-19 patients are prone to this because of virally driven hyper inflammation [17-19]. Many similarities between CIM and hospitalized COVID-19 patients in the ICU have been reported. These include prolonged ventilation and administration of other ICU interventions, the presence of myalgia, significantly reduced and prolonged duration of CMAP, and significant muscle loss depicted by anorexia in COVID-19 patients [4, 20, 21]. Another commonality between COVID-19 patients and those with ICUAW is the reported cytokines in hyper inflammation discussed below. A subset of proinflammatory cytokines is suggested to stimulate muscle atrophy and weakness during critical illness [22]. Of these, three cytokines, tumour necrosis factor-alpha (TNFα), interleukin 1 (IL-1), and interleukin 6 (IL-6) are the most well investigated in critically ill patients [23]. Others revealed that maximal plasma levels of TNFα were higher in patients who developed ICUAW than control subjects [24]. There is also evidence of elevated TNFα present in blood and diseased tissues of patients with COVID-19 [25], and TNFα levels during hospitalization were an independent predictor of patient survival, disease severity, and death [26]. Moreover, IL-1 is also a potential cytokine driving muscle atrophy seen in critically ill patients. IL-1 infusion for 6 days reduces muscle weight and protein content of the rat gastrocnemius [27], and administration of IL-1 antagonist has been found to preserve muscle mass in a septic rat model [28]. Similarly, a phase 3 randomized controlled trial of the IL-1 blockade, anakinra, showed significant survival benefits in patients with sepsis [29].

In COVID-19 patients with severe infection requiring ICU admission, IL-1 is found to be high [30]. Finally, the role of IL-6 has also been investigated in critical illness. TNFα stimulates IL-6 production, and IL-1β, contributing to the systemic inflammation in critical illness and sepsis [31]. A recent retrospective multicenter study of 150 COVID-19 cases included blood levels of IL-6 and suggested that mortality may be due to hyper inflammation driven by the viral infection [32]. IL-6 serum levels have been reported to be an independent and significant predictor of disease severity and death [26,33]. In some studies, IL-6 receptor blockade like tocilizumab, has been approved for administration in patients with COVID-19 pneumonia and

elevated IL-6 levels [34]. Furthermore, these reports suggest a role of cytokine elevation in skeletal muscle atrophy in systemic inflammation events, such as those seen during sepsis and COVID-19 infection. Specifically, during the first few days of ICU stay, systemic inflammation is increased in patients who developed ICUAW compared to those patients who do not [35] and more severe COVID-19 infection results in higher fatality [26].

CLINICAL FEATURE OF MUSCLE WEAKNESS

The clinical picture of this muscle atrophy is characterized by bilateral, symmetrical generalized muscle weakness which is not associated with a preexisting neuromuscular problem. There is a difficulty in weaning from the ventilator. Levine et al. [36] revealed that 18 to 69 hours of complete diaphragmatic inactivity associated with mechanical ventilation results in decreased in cross-sectional areas of diaphragmatic fibres by half or more. Knisely et al. [37] revealed that the cross-sectional areas of diaphragmatic fibres were much smaller in the infants who received the longer duration of mechanical ventilation ≥12 days. Shanely et al. [38] postulated that MV would result in atrophy of all diaphragmatic fibre types. This was reflected by a decrease in the cross-sectional area of all four diaphragmatic MHC (myosin heavy chain) types. Therefore, the failure to wean patients from MV is a significant clinical problem that prolongs time on the ventilator and increases morbidity and mortality [39]. The diaphragm recovers rapidly during the first 24 hours following MV. Nonetheless, diaphragm force remains depressed at 12 hours after MV's termination but recovered progressively after 24 hours of spontaneous breathing [40].

The complete neurological involvement of COVID-19 is yet to be described. However, neurological sequelae of this disease are derived from the potential direct damage of the virus to the nervous system [41-43] and, as described in our patients, from the severity of the systemic disease itself. Tsai et al. reported four patients with probable SARS secondary to coronavirus who developed neuromuscular problems after the onset of the symptoms, with a final diagnosis of probable CIP [44].

NUTRITIONAL STRATEGIES

Most COVID-19 patients admitted to the ICU are at high risk of malnutrition; Severe respiratory infections induce inflammatory syndrome, physical immobilization and hypercatabolism, with increased energy expenditure linked to ventilatory work, in turn, responsible for increased energy and protein requirements; expose to rapid muscle wasting. Optimized nutrition care of the ICU COVID-19 patients is essential to maintain GI tract function, sustain immune defenses, and avoid severe muscle mass loss and process. There is higher requirement of amino acid and protein in critical illness [45, 46]. Meta-analyses of randomized trial data suggest that glutamine supplementation in the ICU may improve patient recovery [47], although the literature remains conflicted [48]. Anabolic-androgenic steroids, and other hormones such as growth hormone and IGF1, plays a crucial role in muscle protein turnover by specifically stimulating anabolic pathways to promote muscle hypertrophy [49]. It has been found that intensive insulin therapy in critically ill patients have a decreased likelihood of developing CIP and CIM [50] and reduced morbidity and mortality

[51, 52]. In contrast, intensive glucose control has been reported to increase the incidence of hypoglycemia and mortality in adult ICU patients offering no significant benefit in terms of length of ICU stay and days of MV compared to conventional glucose control [53].

High protein intake as compared with standard nutrition was associated with minor improvements in various measures (e.g., grip strength); however, length of stay and mortality measures between the two were comparable [54]. Conversely, increased protein during the first week of ICU stay is associated with accentuated muscle wasting; thus, nutritional supplementation timing also appears to impact outcomes [55]. Critically ill patients who received late parenteral nutrition (after day 8) during ICU stay [56] were found to have more rapid recovery and fewer complications (e.g., infection and cholestasis), compared to early parenteral nutrition (within 48 h). Research has similarly demonstrated that ICU patients' muscle weakness resolves faster in those receiving late parenteral nutrition [57].

EVALUATION AND MONITORING OF MUSCLE WEAKNESS

Presently, there is no gold standard for the early diagnosis of ICUAW. Once muscle weakness is evident, physical examination, ultrasonographic monitoring of diaphragm muscle contractility and its thickness, electromyography, and nerve conduction studies [8] is used to determine the presence of critical illness polyneuropathy (CIP), myopathy (CIM), or a combined critical illness neuromyopathy [8]. The distinction between CIP and CIM depends on electrophysiological or histological evidence of peripheral nerve or muscle fibre dysfunction, respectively [58-60].

Cabañes-Martínez L et al. [61] in reported case series of ICUAW as a consequence of COVID-19. Out of 225 patients treated in the ICU, they have reported 11 patients with a clinical and neurophysiological diagnosis of CIM or CIP. Of these 11 patients, seven were diagnosed with critical illness myopathy (63.6%), and four of critical illness neuropathy (36.4%). None of the patients presented both signs of myopathy and neuropathy. However, they haven’t calculated the exact incidence of the presence of neuropathy or myopathy. So it is difficult to pinpoint a well-defined time interval between the acute respiratory distress syndrome by COVID-19 and the appearance of neurological symptoms. The time between the description of weakness and the neurophysiological study's performance is very variable as well. One crucial finding reported by Cabañes-Martínez L et al. [61] is that the degree of spontaneous activity was strikingly severe in the myopathy cases. The possible cause includes the use of corticosteroids, neuromuscular blocking drugs and some antibiotics. However, some reports suggest an increased incidence is due to long-term and intense ventilatory therapy in COVID-19 patients. In our opinion, NCS and EMG play an essential role in diagnosing these patients, and they should be considered at least in those cases in which the diagnosis is unclear.

New biomarkers of muscle mass and function like levels of creatine kinase (CK) and growth and differentiation factor 15 (GDF-15) [62], is elevated in the blood plasma of cardiothoracic ICU patients who developed muscle wasting [63], or were diagnosed with ICUAW [64], and was in the blood serum of critically ill patients with sepsis [65]. They have also been used in routine clinical practice are essential for early

diagnosis, prognosis, and disease monitoring. The inability of CK to identify muscle disease or injury subtypes, CK does not prove useful as a potential biomarker for CIM. Elevated GDF-15 levels were also associated with muscle wasting [63, 64], and in the reduced expression of microRNAs that play a role in regulating muscle differentiation and recovery [64]. Further, GDF-15 levels at admittance were predictive of ICU survival [65]. Consistently, treatment with GDF-15 in vitro led to elevated expression of ICUAW-associated genes, including muscle atrophy-related ubiquitin ligases, MuRF1 and atrogin1 [64]. Several pathological conditions like cancer and sarcopenia are associated with GDF-15. [66], further investigation of the GDF-15 influence in different cell types and disease conditions is warranted.

POTENTIONAL TREATMENTS INTERVENTION STRATEGY

Interventions to manage muscle atrophy for the patients admitted to ICU is also extrapolated to mechanically ventilated COVID-ARDS patients. Intervention divided into three categories: (a) prevention from disuse atrophy and muscle damage, (b) therapeutic to improve respiratory muscle function, (c) rescue interventions. Preventive technique include early mobilization of critically ill patients is intended to encourage muscle loading, shorten the continuous disuse/immobilization experienced in the ICU, stimulate muscle protein synthesis pathways and inhibit catabolism. Heavy sedation is an essential barrier of early mobilization [67, 68]. Early on in the ICU stay, Ceasing sedative infusions is safe and feasible and may be beneficial in decreasing the duration of MV and length of ICU stay [69-71]. Critically ill patients with COVID-19 requiring prolonged sedation have a higher frequency of ICUAW [4]. Avoid using drugs with potential side effects on skeletal muscle, like corticosteroids and muscle relaxants, limit the duration of mechanical ventilation and start early weaning, and provide noninvasive or high-frequency nasal cannula (HFNC) during COVID-19 respiratory distress.[72] Once ICU-acquired weakness has developed therapeutic measures in the form of a combination of respiratory muscle endurance training and strength training should be considered. Endurance training can be instituted using progressive weaning and strength training by using a device for variable inspiratory threshold loading connected to the endotracheal tube.[73] The rescue interventions include (i) use of respiratory muscle positive inotropes, like levosimendan (ii) nandrolone, (iii) Growth hormone stimulation (iv) electric muscle stimulation.

The earlier study suggests that metformin may be beneficial in targeting both dysregulated autophagy and mitochondrial function, however treatment of fibroblasts or myoblasts with bezafibrate results in pharmacological activation of mitochondrial biogenesis. This may help target dysregulation mitochondrial function in the ICU, especially in energy-demanding interventions such as early mobilization [74]. Therefore it warrants further investigation. Similar considerations apply for the UPS. Bortezomib is the first proteasome inhibitor approved by the Food and Drug Administration (FDA) for clinical use in treating multiple myeloma and has also been reported as an effective inhibitor of muscle atrophy [75]. However, the effects of this drug are not universal for all muscle atrophying conditions. Bortezomib is ineffective for cancer cachexia [75], and a recent study indicated that multiple myeloma patients treated with this drug experienced metabolic myopathy [76]. Alternative proteasome inhibitors such as carfilzomib, ixazomib, and oprozomib have been

generated for the treatment of multiple myeloma, however, their specific role in the treatment of muscle atrophy is unknown.

Corticosteroids are commonly administered during the period of critical illness and ICU stay. In part, glucocorticoids work by inhibiting NF-kB signalling, which in turn inhibits the synthesis of target genes, including IL-1 and IL-6 [77,78]. However, despite its anti-inflammatory effects, association exist between corticosteroid administration and ICUAW, while others have reported increased length of ICU stay and MV with corticosteroid use [79,80]. Similarly, the use of glucocorticoids for the treatment of COVID-19 remains controversial. A meta-analysis revealed that critical patients with severe infection are more likely to require the use of corticosteroids. However, it is associated with higher patient mortality [81].

REHABILITATION

Rehabilitation started shortly after the initiation of mechanical ventilation to improve strength and functional outcomes, decrease ventilation duration, and increase days alive living at home over 6-month follow-up [82,83]. However, there are many challenges in delivering early rehabilitation interventions for critical illness patients due to COVID-19. A multidisciplinary team, including physical therapist (PT), occupational therapist (OT), a speech-language pathologist (SLP), registered nurse, respiratory therapists, psychologist, social worker, and case managers, under the leadership of physical medicine and rehabilitation (PM and R) physician, should navigate the rehabilitation of COVID-19 patient. Policymakers and health-care planners should have a post-acute preparedness plan to meet the rehabilitation needs of COVID-19 survivors. Rehabilitation interventions should be tailored to each patient. Rehabilitation interventions should include, activities of daily living (ADLs), progressive mobility from bed to chair, standing, gait training with and without body weight support and/or robot-assisted gait training, ambulation and robotic arm training, with or without functional electrical stimulation, for activities of daily living (ADLs). Reassess swallowing function if dysphagia persists. Continue swallowing exercises, with or without electrical stimulation of muscles, that aid in swallowing. Assessment for durable medical equipment needs, family training, and education are important components of comprehensive inpatient rehabilitation activities. Rehabilitation of critically ill COVID-19 survivors is important to reduce long-term complications. ICUAW, dysphagia, functional decline, psychological problems, cognitive impairment, and reduced QOL are anticipated complications based on the existing ARDS and SARS literature. Physical rehabilitation interventions include: (1) passive, active assisted, active, or resisted joint range of motion; (2) tilt table, cycle ergometry, and/or NMES; (3) therapeutic exercises; (4) functional mobility; and (5) occupational activities addressing ADL. Use of rehabilitation equipment may be limited due to infection control precautions. Neuromuscular complications might be mitigated with the prevention of hyperglycemia and limiting the use of corticosteroids, minimizing sedation and neuromuscular blockade during critical illness [84, 85]. Randomized trials of physical rehabilitation and mobility in the ICU have demonstrated reduced muscle weakness and are suggested in clinical practice guidelines from the Society of Critical Care Medicine [82, 83, 86].

CONCLUSIONS

Intensive care unit acquired weakness (ICUAW) in critically ill COVID-19 patients is due to severity of illness, co-morbidities, muscle unloading, or ICU treatments, a systemic reaction circulating within the body, or combinations therein. Furthermore, the availability of a culture model of ICUAW could facilitate in expediting the diagnosis of ICUAW and fast track the discovery of putative treatments. We recommend NIV or HFNC ventilation or early weaning from invasive mechanical ventilation in critically ill COVID 19 elderly patients.

SUPPLEMENTARY INFORMATION

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