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Inactivity and Inflammation

Selected Cytokines as Biologic Mediators in Muscle Dysfunction During Critical Illness

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Muscle dysfunction leads to activity intolerance, prolonged hospitalization, and additional days of mechanical ventilation. The etiology of muscle dysfunction in the critically ill patient is multifactoral. Inactivity and inflammation, common phenomena to patients in the intensive care unit, are associated with myopathy and muscle dysfunction. Cytokines are small biological active molecules that regulate inflammation and have a direct effect on muscle wasting. The purpose of this article is to describe selected cytokines (ie, interleukin-1, interleukin-6, interleukin-10, and tumor necrosis factor), explain their role in muscle dysfunction, and explore the role of therapeutic activity as a moderator of muscle dysfunction and cytokine-mediated muscle damage. (KEYWORDS: cytokines, inactivity, inflammation, intensive care unit, muscle dysfunction)

Acquired muscle dysfunction is recognized as a cause of prolonged mechanical ventilation and delayed recovery from critical illness.[1-3] The combination of inactivity and inflammation during critical illness promotes muscle dysfunction. Inactivity from either bedrest or immobilization has direct and profound deleterious effects on muscle strength, endurance, and size, resulting in symptoms of skeletal muscle weakness and generalized fatigue.[4-6] Inflammation, common to critical illness, is also implicated in muscle wasting, activity intolerance, and prolonged critical illness.[6,7] Inflammation is initiated and regulated by cytokines, small biologically active proteins that also have a direct effect on muscle function.[8-9] Inactivity may allow prolonged exposure to myocyte-destructive cytokines or promote an imbalance in cytokines, leading to proinflammatory myocyte degradation. This article describes selected cytokines, explains their role in muscle dysfunction, and explores the role of therapeutic activity as a moderator of muscle dysfunction and cytokine-mediated muscle damage. Understanding the link between muscle dysfunction and its biological mediators is an important first step in identi-

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fying the effects of therapeutic activity on outcomes in the intensive care unit (ICU) patient.

□Muscle Dysfunction and Inactivity

Muscle weakness is common in ICU patients.[1] Respiratory muscles are vulnerable to deconditioning processes and atrophy.[10] Diaphragmatic fatigue and prolonged mechanical ventilation are associated with skeletal muscle wasting in mechanically ventilated patients.[1,2,11,12] When muscle weakness involves respiratory muscles, the duration of mechanical ventilation increases and the potential for reintubation after weaning from ventilatory support increases.[4] Acquired skeletal muscle weakness is an important cause of morbidity for survivors of critical illness.[3,13] Muscle loss leads to impaired functional status, prolonged hospitalization, and the need for rehabilitative intervention.[14,15]

Muscle dysfunction in the ICU is multifactoral. Steroids, neuromuscular blocking agents, several antibiotics, inflammation, immobility, and mechanical ventilator settings designed to rest respiratory muscles during prolonged ventilatory support all contribute to muscle degradation.

Although the hazards of inactivity have been examined in a variety of healthy and hospitalized adults, it was not until the 1980s that inactivity in critically ill patients received investigation. Inactivity in critically ill adults is associated with the occurrence of decubiti, pulmonary complications, deep vein thrombosis, and prolonged ICU and hospital stays.[16-20] Inactivity also leads to muscle dysfunction. Inactivity is associated with muscle atrophy, characterized by loss of myonuclei, decreased myocyte cytoplasm, myosin filament defects, and an increase in several proteolytic enzymes.[5,21] In addition, inflammatory processes lead to production of reactive oxygen species (ROS).[22-24] Molecular ROS factors, in turn, lead to contractile dysfunction—a reduced force of contraction without evidence of structural muscle damage or loss.[22] Ultimately, these processes contribute to decreased muscle strength and endurance.

The combination of inflammation and inactivity is especially problematic to patients in the ICU. Increased release and action of proinflammatory cytokines contribute to muscle dysfunction through several complex, interrelated pathways (Figure 1). These pathways include: (1) direct stimulation of protein loss in differentiated muscle cells over days-to-weeks; (2) activation of a cas-

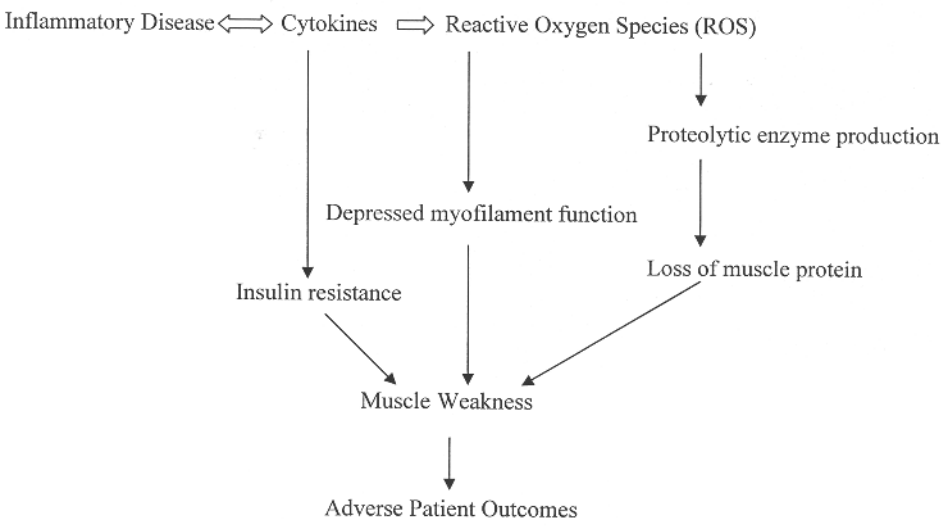

Figure 1. *Mechanisms of cytokine-related muscle weakness. Adapted from Reid & Li. Tumor necrosis factor alpha and muscle wasting: a cellular perspective.* Respiratory Research. *2001;2(5):268-272. Reprinted with permission of Blackwell Publishing.*

cade of postreceptor signaling events that promote oxidative injury (via synthesis of ROS-mediating kinases and calcium regulation); and (3) impedance of insulin receptor signaling in muscles (leading to reduced energy substrate availability and impaired myofibril growth/repair).[22] Inflammation contributes to acute and chronic muscle cell damage and cell death through metabolic derangements in musculature, increased proteolysis, and disturbed regeneration of muscle fibers.[7,13] Elevated levels of proinflammatory factors have been implicated in reduced contractile force even in the absence of muscle damage.[7,22] Inflammation is a normal consequence of injury or infection and a common phenomenon in the ICU. Cytokines initiate inflammation and contribute to muscle dysfunction.

□ Selected Cytokines and Muscle Degradation

Cytokines are small, biologically active molecules that play a key role in the complex regulatory network of inflammation and the immune response.[25,26] First described as products of white blood cells, many cytokines are also produced by parenchymal cells (including myocytes), endovascular cells, and epithelial cells with specific stimuli or through interaction with monocytes, macrophages, and lymphocytes. Cytokines are potent; small amounts cause large effects. Cytokine receptors are ubiquitous: they are found on white cells, endothelial cells, epithelial cells, and parenchymal cells in humans. Once a cytokine binds to a receptor, effects can vary depending on the cell to which it binds. The quantity of cytokine product, the interaction between cytokines, the timing of cytokine release, and location of cytokine production determines the final clinical response.[27,28]

Cytokines include interleukins, tumor necrosis factors, lymphotoxins, colony-stimulating factors, chemokines, and miscellaneous cytokines; more than 200 cytokines have been identified.[25,26,28,29] In general, cytokine synthesis is a self-limiting, tightly regulated, and brief event.[30] Selected interleukins (IL) and tumor necrosis factors (TNF) have been implicated in the severity and progression of several illnesses common to the ICU and are the focus of this article.

Since the introduction of the term interleukin, over 27 interleukins have been identified. Interleukins provide signals between (*inter-*) various white cells (*leukins*) to coordinate and integrate the host response to injury and infection.[31,32] They facilitate inflammation, promote white cell proliferation and infiltration, and initiate systemic clinical responses such as fever, malaise, lack of appetite, and sleep.

Interleukins can be proinflammatory, antiinflammatory or have both pro- and antiinflammatory properties.[8] Several interleukins have been studied in critical illness; the roles of interleukins 1 (IL-1), 6 (IL-6), and 10 (IL-10) are of particular interest to practitioners in the ICU as they are associated with pathogenesis, morbidity, and mortality of acute respiratory distress syndrome (ARDS), sepsis, systemic inflammatory response syndrome (SIRS), and compensatory antiinflammatory response syndrome (CARS).[30,33,35] IL-1, IL-6, and IL-10 and their roles in muscle pathology are described below.

Interleukin-1 exists as two distinct forms, IL-1A (alpha) and IL-1B (beta).[36] IL-1A is primarily membrane-bound; it exerts its effects by combining with receptors found on the surface of a cell membrane. IL-1B is secreted and combines with receptors that have been cleaved from a cell membrane and are floating in plasma or interstitial fluid.[8,28] Both forms of interleukin-1 evoke a wide variety of biological effects. IL-1 is a potent proinflammatory cytokine that is able to induce effects by triggering only one or two receptors per cell.[28] This means that only a very small amount of IL-1 causes an immediate and dramatic inflammatory response. The onset of a systemic inflammatory reaction to infection is largely attributable to IL-1.[25] IL-1 induces fever, augments lymphocyte responses to infection, and stimulates acute-phase protein synthesis in response to an invading organism. Locally, IL-1 increases the production of cell adhesion molecules that promote a collection of a critical mass of leukocytes along the endothelium, providing defensive protection from microbial invasion. IL-1 also stimulates hemopoiesis. Under the influence of IL-1, new plasma cells are generated and maturation time is shortened (eg, T cells, B

cells, natural killer cells). In the presence of IL-1, factors that stimulate tissue cell synthesis and migration are upregulated (eg, growth factors, tissue plasminogen activator, cyclooxygenase gene expression, endorphins).[8,31] IL-1B is the major inducer for cyclooxygenase-2 synthesis, leading to the production of prostaglandins, promoting additional peripheral inflammation and increased sensitivity to pain stimuli.[28]

IL-1A and IL-1B have both been reported in patients with idiopathic inflammatory myopathies. Both are toxic to muscle. In addition, IL-1A influences insulin-growth factor leading to myocyte metabolic derangements that inhibit protein synthesis. In vitro, IL-1A promotes muscle proteolysis.[7] IL-1B is synthesized by muscle and may be involved in decrements in muscle mass by promoting apoptosis.[37]

IL-6 is another pleiotropic cytokine—it has multiple effects on multiple sites. Early in inflammation, IL-6 displays proinflammatory properties by activating and stimulating maturation of neutrophils, promoting differentiation and maintenance of natural killer cells, and increasing expression of IL-1 and TNF-a.[28] IL-6 also stimulates the growth and differentiation of B cells as well as stimulating antibody production by B cells.[28] Similar to IL-1, IL-6 is responsible for the induction of acute phase protein production and the release of these substances by hepatocytes.[38] However, IL-6 also has antiinflammatory properties. Over time, IL-6 attenuates the production of TNF-a and IL-1, and promotes the synthesis of other antiinflammatory factors including interleukin-1 receptor antagonist and soluble tumor necrosis factor (TNF) receptor.[39] Several tissues express IL-6 including: T cells, mast cells, epithelial cells, pulmonary epithelial cells, and myocytes.

Elevated levels of IL-6 are associated with many inflammatory pathologies including arthritis, neoplasms, congestive heart failure, and infection.[32] In critically ill patients, persistent elevation of circulating levels of IL-6 have been linked to elevated mortality risk with sepsis, trauma, and burns.[40,41] In musculature, IL-6 acts as a chemoattractant so that additional cytokine-producing white cells are recruited to muscle fibers. IL-6 promotes infiltration of myocytes with additional inflammatory factors such as prostaglandins, leading to proteolysis, myocyte degeneration, and muscle atrophy.[42,43] As an antiinflammatory cytokine, IL-6 may also work to inhibit proinflammatory effects of IL-1 and TNF.[44] IL-6 may also be linked to the regulation of glucose metabolism of skeletal muscles, promoting homeostasis during exercise.[45]

IL-10 is the prototypical anti-inflammatory cytokine.[46] IL-10 inhibits proinflammatory cytokine production by monocytes/macrophages, neutrophils, and natural killer cells; it also attenuates the synthesis of TNF surface receptors. It is thought to be involved in the negative feedback loop of the inflammatory system, preventing autoamplification.[8,26] IL-10's suppressive effects may be beneficial in autoimmune disease as well as other pathology that results from inflammatory dysregulation such as sepsis or B-cell disease including acquired immunodeficiency syndrome (AIDS).[28] Both excess and scant levels of IL-10 can contribute to adverse outcomes in the ICU patient. Insufficient IL-10 may be associated with systematic inflammatory response system (SIRS) and increased mortality from infection in the ICU.[39,41,47] Low levels of IL-10 predict decreased activity and increased angina in patients with unstable angina.[48] Low levels of IL-10 may lead to excessive inflammation and additional muscle damage; high levels in critical illness may protect against inflammatory myopathy.[49] High levels of IL-10 predict mortality with sepsis syndrome and after successful cardiopulmonary resuscitation.[47,50]

Although high levels of IL-10 have not been linked to muscle damage, moderate-to-high levels of IL-10 may inhibit IL-1 and IL-6, and TNF may mitigate the damage to myocytes when cytokines promote an inflammatory response. It may not be the absolute values of IL-1 or IL-6 that cause myocyte damage but the balance between proinflammatory and antiinflammatory factors that prevent progression of disease and disuse.[49,51-53]

Tumor necrosis factor is an early responder to injury and infection. Its name is derived from its ability to cause hemorrhagic necrosis of tumors. TNF has signaling pathways and receptors that are similar to IL-1, eliciting clinical symptoms of fever, fatigue, anorexia, rigor, and headache.[8,25,34] TNF has two distinct forms: TNF-α and TNF-β. TNF-β is also known as lymphotoxin-a (alpha) (LTa). The

two forms of TNF have similar major effects but TNF-β is not typically detected in circulation.[28] TNF-β is secreted locally, causing paracrine rather than systemic effects. TNF-α, along with IL-1, and IL-6, play central roles in initiating the innate human immune response.[8] TNF-α enhances leukocyte-endothelial cell adhesion, acts on hepatocytes to increase acute-phase protein production, induces neutrophil activation, and initiates the synthesis and release of other inflammatory factors, including IL-6.[28] Excessive TNF-α can cause hyperinflammatory reactions and tissue injury; it is associated with nonsurvivial in septic patients.[34,35] Excess TNF-α is also associated with left ventricular dysfunction and hypertrophy in patients with myocardial infarction.[54,55]

Skeletal muscles express TNF-α receptors and the binding of TNF-α to these receptors has a number of effects on muscle function through adverse alterations in muscle fibers and by inducing muscle metabolism that promotes proteolysis and delays repairs. In muscles, TNF-α overexpresion causes skeletal myopathy and endothelial dysfunction, leading to myocyte apoptosis and decreases in skeletal muscle mass with subsequent weakness.[30] In an animal model, TNF-α decreases force of contraction.[7] TNF-α also has a catabolic effect, leading to protein loss and disruption of myogenesis.[23]

Thus, IL-1, IL-6, and TNF-α have all been implicated in muscle degradation. IL-10 inhibits these potent cytokines and may have a role in mediating myocyte proteolysis and apoptosis from excess IL- 1 and –6 and TNF-α.[49] IL-1, IL-6, and TNF-α all have proinflammatory properties. Inflammation augments proteolysis and is associated with decrements in muscle protein content, resulting in the loss of muscle mass and decrease in strength.[11,15,56] In the presence of inflammation, inactivity may compound the destruction of myocytes. This combination of inactivity and inflammation is likely to occur in critically ill patients.

□ Activity and Exercise

Activity in the ICU setting can be parsed into therapeutic and nontherapeutic movement. Nontherapeutic movement consists of agitated, nonpurposeful behaviors that are random and have the potential to harm the patient or create an unsafe environment. Therapeutic movement is purposeful and does not injure the patient or create an unsafe condition (such as line dislodgement). Examples of patient-initiated therapeutic movement are gesturing toward a glass of water indicating "I want a drink" or pulling covers up to stay warm. Mobilization is a subset of therapeutic movement that promotes physical fitness, prevents disability, and slows the onset of degenerative processes.[57,58] Mobilization includes multiple turns (as with a bed bath), range of motion, dangling, chair sitting, and walking.

Despite our knowledge of the effects of immobility on muscles and the value of activity, immobilization—bedrest—is a common prescription in the ICU. There are several barriers to mobilization in the ICU (eg, hemodynamic instability, protection against line dislodgement) but few data to indicate whether these barriers are absolute contraindications to early therapeutic activity and mobilization. Instituting mobilization as soon as possible in ICU adults is an effective and inexpensive way to avoid the hazards of immobility. Little is known about the typical level, frequency, and duration of activity in patients; what is known is summarized next.

Nurses advocate introducing activity early in an acute illness to promote patient comfort, improve sensory stimulation, and prevent the complications of bedrest.[6,57] Therapeutic activity in the ICU frequently begins with turning the patient from supine to lateral positions and initiating range of motion (ROM) exercise. Therapeutic activity typically progresses to dangling, chair sitting, and ambulation. Nonetheless, activity also can produce adverse patient responses, including hypoxemia, hemodynamic instability, decreased level of consciousness, and psychological stress. The mechanisms by which activity affects patients remain largely unknown and most studies about therapeutic activity and patient response in the ICU have been limited to observations about a single physiological system (eg, skin integrity). We know that cellular stretching and deformation occurs with muscle contraction and can alter the genetic expression of cytokines; however, little is known about how

activity affects inflammatory mediators and whether these effects have systemic consequences or affect outcomes in ICU patients.

Range of Motion

One common low-intensity form of movement in the ICU for critically ill patients is passive and active ROM. Little is known about the effects of either stretching or ROM and ICU patient response in the muscular system. ROM consists of therapeutic movement about a joint to maintain the integrity of the tendon, ligament, articular cartilage, and muscle. ROM is combined with stretching to lengthen shortened tissue and to decrease muscle stiffness; chronic effects of stretching include adding sarcomeres to muscle mass in deconditioned muscles.[59] ROM does not appear to adversely affect cardiopulmonary parameters in normal subjects.[60] Skeletal muscle is known to be extremely responsive to changes in external stimuli, especially workload and stretch. One study examined whether muscle wasting in critically ill patients can be prevented with stretching alone. Continuous passive motion for three 3-hour periods over 7 days was applied to one leg in five critically ill adults. Protein loss and water gain were less in the treated leg compared to the control leg that received routine nursing care.[61]

Activity and Cytokines

Investigations indicate that activity can affect serum levels of selected pro- and antiinflammatory cytokines.[62] Intense, prolonged activity clearly stimulates cytokine synthesis in healthy athletes. These data seem to indicate that activity (activities that cause epithelial and myocyte stretch and changes in myocyte conformation) can affect levels of TNF-a, IL-1, IL-6 and IL-10.[63-65]

Exhaustive or prolonged exercise produces dramatic increases in TNF-a, IL-6, and IL-10.[66,67] However, moderate exercise has different effects and provides insight into tissue-level mechanisms of myopathy. Moderate exercise can improve blood flow to muscles and joints, inhibiting atrophic changes common to disuse without concomitant alarming increases in either proinflammatory or antiinflammatory cytokines.[11,68-70] Improved circulation to myocytes with mild, therapeutic activity may also prevent infiltration by macrophages into muscles, reducing the local load of potentially destructive cytokines.[12] Finally, activity may prevent ischemia/reperfusion injury with subsequent inflammation.[71,72] Understanding the cytokine milieu and how activity (versus bedrest) affects cytokine production is important to understanding the illness trajectory of ICU patients.

Proinflammatory cytokines have been studied in relationship to activity and exercise in community dwelling adults with inflammatory illnesses. Results indicate that exercise and activity decrease proinflammatory serum levels of IL-6 and TNF-a. Physical training modulated proinflammatory IL-6 in patients with chronic heart failure in a 12-week outpatient setting when compared to a detraining (exercise avoidance) in a randomized crossover design; similar training produced no affect on normal, control participants.[73] After 12 weeks of an aerobic exercise program, patients with heart failure experienced a reduction the their baseline TNF-a.[74] Three consecutive days of exercise in participants with sickle cell anemia did not affect serum IL-6 levels.[75] Exercise increased quadriceps sensorimotor function without increasing IL-6 or exacerbating disease activity in rheumatoid arthritis outpatients.[76] There are no data about the effect of exercise on IL-1, IL-6, or TNF in critically ill patients.

The effect of exercise on antiinflammatory interleukins has received less investigation. Prolonged, strenuous exercise in healthy males resulted in a 27-fold increase in IL-10 immediately post exercise.[77] Patients with inflammatory disease who exercise have not been studied. Activity-induced IL-10 is produced by stretching and compressing epithelial cells and in response to high levels of IL-6; the potential for IL-10 synthesis with activity is possible.[46,47]

Chronic stress and chronic illness are associated with increased serum levels of cytokines such as IL-6 and IL-10. In the presence of an increased baseline of inflammatory factors, it is possible that even small amounts of physical activity can increase serum cytokines. Further, the stress of increasing activity from bedrest may contribute

additionally to the synthesis of IL-6 and IL-10. Alternatively, the increased blood flow resulting from increased activity may decrease the local concentration of cytokines and minimize muscle damage. Activity may also restore the balance between proinflammatory cytokines such as IL-1, Il-6, and TNF-a as well as antiinflammatory cytokines such as IL-10. Activity may create a favorable pro- and antiinflammatory balance through direct stimulation of muscle cells. Activity may also promote blood flow to muscles, increasing oxygenation/nutrient delivery, and reducing exposure to toxic locally produced and systemic cytokines.

□Summary

Proinflammatory IL-1, IL-6, and TNF-a have been implicated in muscle damage characteristic to muscle dysfunction; antiinflammatory IL-10 may moderate the level and effects of these muscle-damaging cytokines. Investigating the pattern of selected cytokine levels has the potential to provide unique biologic markers that identify patients at risk for muscle dysfunction resulting in prolonged mechanical ventilation and delayed functional recovery from critical illness. A balance between pro- and antiinflammatory cytokines is important in moderating sickness behaviors and may be helpful in preventing myocyte degradation and apoptosis. Moderate levels of therapeutic activity have the potential to promote skeletal and diaphragmatic muscle strength and endurance. Therapeutic activity may also moderate promote cytokine balance and reduce the time myocytes are exposed to damaging cytokines through increased capillary blood flow.

Nurses are in a unique position to contribute to the investigation of inflammation, activity, and cytokines in the critically ill. Bedside nurses often initiate and maintain programs of activity for hospitalized patients and monitor patient responses to mobilization. Advanced practice nurses can provide information linking molecular mediators with systemic responses in acute and critically ill patients, especially information related to patient outcomes. Research into the relationship between cytokines, activity, and outcomes such as number of ventilator days and need for rehabilitation services after ICU stay could help clarify the optimal timing, level, and duration of activity in critically ill patients.

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