Muscle Dysfunction in Patients with Lung Diseases
A Growing Epidemic

Esther Barreiro[1,2], Jacob I. Sznajder[3], Gustavo A. Nader[4,5], and G. R. Scott Budinger[3]

[1]Respiratory Medicine Department–Lung Cancer Research Group, Institute of Medical Research of Hospital del Mar (IMIM)-Hospital del Mar, Parc de Salut Mar, Barcelona Biomedical Research Park, Barcelona, Spain; [2]Centro de Investigación en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain; [3]Pulmonary and Critical Care Medicine Division, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; [4]Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden; and [5]Noll Laboratory, Department of Kinesiology, The Pennsylvania State University, University Park, Pennsylvania

The lung is tasked with the provision of oxygen to fuel oxidative phosphorylation and with the removal of its byproduct carbon dioxide and is therefore a key player in organismal metabolism. When viewed from this perspective, it is unsurprising that lung dysfunction is associated with suboptimal function of other metabolic organs, most notably of skeletal muscle. A prevalent example is observed in patients with chronic obstructive pulmonary disease (COPD), which is a leading cause of death worldwide and one of the few major diseases for which mortality continues to climb (1). Skeletal muscle dysfunction, defined as the loss of either muscle strength or endurance, is a prominent comorbidity in patients with COPD that impairs their exercise capacity, quality of life, and disease prognosis (2–8). For example, quadriceps muscle dysfunction, which is primarily characterized by reduced muscle force generation, is observed in one-third of all patients with COPD even at very early stages of their disease, where it is associated with decreased exercise tolerance, a reduced quality of life, and increased mortality (2–8). In patients with COPD, other comorbidities, including muscle wasting, malnutrition, chronic heart failure, exacerbations, and reduced physical activity, can further impair muscle function (4, 7). Sarcopenia, the age-associated loss of skeletal muscle mass and function, is present in as many as 10% of older hospitalized adults (9, 10). Although limb muscle dysfunction is often the most clinically evident problem in patients with COPD, respiratory muscle dysfunction is also present and may contribute to the development and persistence of hypoventilatory respiratory failure in these patients (11, 12). Combined, the presence of respiratory and peripheral muscle dysfunction and underlying sarcopenia results in prolonged hospitalizations and reduced rates of physical activity, creating a vicious circle of progressive muscle dysfunction and morbidity.

Skeletal muscle dysfunction also plays a role in the pathophysiology of the acute respiratory distress syndrome (ARDS). In these patients, skeletal muscle dysfunction develops rapidly and may contribute to weaning failure, prolonged mechanical ventilation, and the risk of readmission after intensive care unit (ICU) discharge and mortality (13–16). In addition, limb muscle dysfunction is observed in the majority of survivors of ARDS and may persist for as long as 5 years after discharge, where it is a major driver of morbidity (17). In patients who require mechanical ventilation for respiratory failure, the acute reduction in the work of breathing allows for precise estimates of the duration of disuse, offering a novel window into muscle dysfunction during critical illness. Recent data suggest that in many patients with critical illness, diaphragmatic dysfunction can be present when mechanical ventilation is initiated, rapidly worsens, and is associated with poor clinical outcomes in critically ill patients with respiratory failure (18, 19).

Despite the clinical importance of muscle dysfunction in patients with lung disease, our understanding of the molecular mechanisms by which lung injury or inflammation results in the development of muscle dysfunction is incomplete (Figure 1). The skeletal muscle is a fascinating organ that exhibits remarkable plasticity, allowing it to undergo dramatic changes in size and function (i.e., atrophy or hypertrophy) in response to local environmental changes. In patients with acute lung injury, the rapid development of muscle dysfunction suggests the presence of endocrine signaling pathways that induce changes in the local environment in the skeletal muscle that promote muscle degradation. For example, in patients with sepsis, a major risk factor for the development of acute lung injury, circulating proinflammatory cytokines released from the injured or inflamed lung induce degradation of cultured muscle cells (20). Although circulating inflammatory cytokines may contribute to the skeletal muscle wasting seen in patients with COPD, their contribution may be less important when compared with other factors associated with muscle loss, including disuse atrophy and malnutrition (4, 21, 22). Although the factors that initiate skeletal muscle dysfunction may differ, both acute lung injury and COPD have been suggested to activate a common molecular program that results in skeletal

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Correspondence and requests for reprints should be addressed to G. R. Scott Budinger, M.D., Pulmonary and Critical Care Medicine Division, Feinberg School of Medicine, Northwestern University, 240 East Huron, McGaw Pavilion M-300, Chicago, IL 60611. E-mail: s-buding@northwestern.edu

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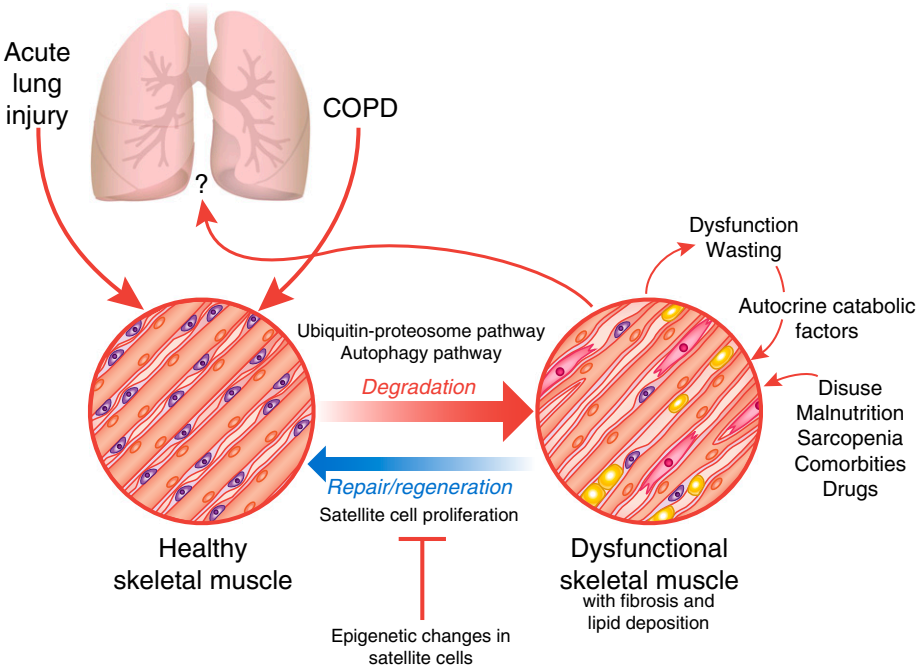

Figure 1. Schematic representation of skeletal muscle dysfunction associated with acute and chronic respiratory conditions. In both patients with chronic obstructive pulmonary disease (COPD) and patients with acute lung injury, the diseased lung induces dysfunction in the skeletal muscle via pathways that are incompletely understood. At the level of the individual myofibers, both acute lung injury and COPD are associated with activation of the ubiquitin–proteasome and autophagy pathways, which induce the degradation of critical skeletal muscle proteins and contribute to the development of muscle dysfunction. In addition, signals originating from the diseased lung or conditions that develop as a consequence of lung dysfunction may impair the regenerative potential of satellite cells at the periphery of the myofiber, perhaps through epigenetic reprogramming, thereby limiting the recovery of muscle function. Skeletal muscle dysfunction is worsened by disuse, malnutrition, preexisting sarcopenia, comorbid illnesses including diabetes and chronic heart failure, and drugs, particularly systemic corticosteroids and statins, culminating in the development of muscle fibrosis and lipid deposition. It is possible that the damaged skeletal muscle releases factors that feedback on the lung to worsen the underlying disease.

muscle degradation (23, 24). This program includes activation of the ubiquitin–proteasome system, lysosomal autophagy pathway, and the activation of muscle-specific calpains among others, which result in the degradation of muscle contractile proteins together with underused and damaged organelles, in the process releasing amino acids and other biosynthetic intermediates as well as metabolic substrates into the circulation (13, 15, 25–29). Consistent with this hypothesis, several groups of investigators have found evidence for activation of both the ubiquitin–proteasome and autophagy pathways in muscle biopsies from patients with stable COPD and in patients hospitalized with acute exacerbations of COPD (22, 29–32). In these same studies, indirect evidence of reduced muscle metabolism comes from careful morphologic examination of muscle biopsy specimens for evidence of oxidative injury and alterations of fiber composition and mitochondrial density. In skeletal muscle biopsy specimens from patients with critical illness, many of whom had acute lung injury, and in diaphragmatic biopsies from mechanically ventilated humans undergoing thoracic surgical procedures, investigators observed rapid muscle wasting and up-regulation of the ubiquitin-proteasome pathway (13, 16,).

Although the activation of degradative pathways might explain the acute muscle wasting that occurs with acute lung injury and exacerbations of COPD, these results do not explain the persistence of skeletal muscle dysfunction after the acute illness has resolved, as the normal skeletal muscle is intrinsically able to repair itself after damaging insults (33–35). For example, after high-intensity exercise there can be myofiber damage, necrosis, and inflammation (14). Factors released locally by the damaged fiber and possibly the associated nerve induce the proliferation of myocyte progenitor or satellite cells, a partially differentiated stem cell population, which repair the damaged muscle fiber (35). Although direct evidence is lacking, it is tempting to speculate that these repair processes may be impaired in patients with acute lung injury or COPD. An interesting hypothesis emerges from studies of aged mice, which demonstrate impaired muscle regeneration after injury. Careful experiments suggest these changes may be mediated by epigenetic reprogramming of aging satellite cells (36). A growing body of literature suggests that factors present in the circulation can reverse this epigenetic program to rejuvenate the satellite cell pool (36–38).

In this perspective, we have focused on COPD and acute lung injury largely because of recent studies to examine muscle dysfunction in these populations; however, skeletal muscle dysfunction is likely to play an important role in the pathogenesis of other lung diseases. Several additional key questions remain unanswered. Perhaps most importantly, we need to understand more about the molecular mechanisms by which lung inflammation, inactivity, the systemic administration of corticosteroids and statins, cigarette smoke, respiratory infections, advanced age, hypercapnia, hypoxia, and malnutrition contribute to muscle wasting and muscle dysfunction in patients with acute lung injury and COPD (39–41). This question has obvious implications for the development and implementation of interventions to prevent or reverse skeletal muscle dysfunction: might there be specific populations more likely to benefit from exercise training–based approaches or populations in which augmentation with molecular-based approaches would be beneficial (42)? Second, does the acute muscle degradation associated with critical illness provide fuel and biosynthetic intermediates that support the innate immune response to infection? This question is important for determining the optimal timing of physical or pharmacologic interventions to slow or reverse muscle dysfunction. Third, what are the molecular

mechanisms that underlie the differential susceptibility of individuals with similar impairments in lung function or similar severity of critical illness to the development of skeletal muscle dysfunction? Fourth, do strategies that target muscle function, including exercise, change the course of the underlying lung disease? Although direct evidence is lacking, strategies aimed at minimizing skeletal muscle loss or promoting muscle regeneration might minimize lung injury or accelerate repair. Finally, why do many patients with severe acute or chronic lung diseases fail to recover muscle function after injury? Are muscle progenitor cell populations lost, or is the metabolic or proteostatic reserve reduced in some patient populations (36, 43, 44)?

In summary, given the lungs' central position in organismal metabolism, acute and chronic lung diseases should be viewed as systemic disorders that contribute to dysfunction in other metabolic organs, including the skeletal muscle. Body composition and quadriceps muscle strength should be routinely explored in patients admitted to our ICUs and in patients with chronic lung disease, even at early stages of their disease. Research extending beyond the lung to elucidate the molecular signaling pathways linking lung injury with the loss of muscle mass and function and the failure of normal skeletal muscle regenerative pathways may lead to novel therapies that can be combined with physical therapy interventions to improve morbidity. Meanwhile, we need to expand our use of exercise training, alone or in combination with nutritional support, to improve muscle mass and function in patients in ICUs and patients suffering from chronic lung disease. ■

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