Deterioration of Limb Muscle Function during Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Important features of both stable and acute exacerbation of chronic obstructive pulmonary disease (COPD) are skeletal muscle weakness and wasting. Limb muscle dysfunction during an exacerbation has been linked to various adverse outcomes, including prolonged hospitalization, readmission, and mortality. The contributing factors leading to muscle dysfunction are similar to those seen in stable COPD: disuse, nutrition/energy balance, hypercapnia, hypoxemia, electrolyte derangements, inflammation, and drugs (i.e., glucocorticoids). These factors may be the trigger for a downstream cascade of local inflammatory changes, pathway process alterations, and structural degradation. Ultimately, the clinical effects can be wide ranging and include reduced limb muscle strength.

Current therapies, such as pulmonary/physical rehabilitation, have limited impact because of low participation rates. Recently, novel drugs have been developed in similar disorders, and learnings from these studies can be used as a foundation to facilitate discovery in patients hospitalized with a COPD exacerbation. Nevertheless, investigators should approach this patient population with knowledge of the limitations of each intervention. In this Concise Clinical Review, we provide an overview of acute muscle dysfunction in patients hospitalized with acute exacerbation of COPD and a strategic approach to drug development in this setting.

Keywords: COPD; exacerbations; skeletal muscle; pharmacological interventions; drug development

Skeletal muscle weakness in association with reduced exercise capacity is frequently seen in patients with stable chronic obstructive pulmonary disease (COPD) (1). Sarcopenia is often used to describe this state of abnormally low lean muscle mass combined with reduced muscle strength or function (2). Although this condition is considered to be a feature of aging, it has also been used in the specific context of COPD (3). Cachexia, on the other hand, is a more dynamic disorder in which active fat-free mass loss occurs in association with progressive pathologic processes, such as cancer and COPD (4). Whether due to

sarcopenia or cachexia, skeletal muscle weakness is more prevalent and severe in patients with COPD than in age-matched seniors (1, 4) and is worsened by acute exacerbations of the disease (5). Although clinical consequences of muscle dysfunction in the setting of an acute exacerbation of COPD (AECOPD) are incompletely understood, observations in recent studies have highlighted the importance of the relationship between muscle dysfunction and outcomes after hospitalization for AECOPD. For example, the likelihood of a first or subsequent hospital admission for a COPD

exacerbation is correlated with reduced quadriceps bulk at time of discharge (6) and poor exercise performance (7, 8). Conversely, anabolic stimuli in the form of formal postdischarge pulmonary rehabilitation (PR) reduce both readmission and emergency room visits (9, 10). Despite these findings, the degree to which exacerbations may impact muscle function is variable and likely related to the underlying chronic dysfunction and the severity of illness occurring with the exacerbation, among other factors. Thus, the aim of this review is to focus on contributing factors to limb muscle

(Received in original form May 12, 2017; accepted in final form October 17, 2017)

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CME will be available for this article at www.atsjournals.org.

Am J Respir Crit Care Med Vol 197, Iss 4, pp 433–449, Feb 15, 2018

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Originally Published in Press as DOI: 10.1164/rccm.201703-0615CI on October 24, 2017

Internet address: www.atsjournals.org

weakness and current and emerging therapies for acute muscle dysfunction and to outline clinical trial concepts for drug development in this area.

Chronic Muscle Dysfunction in Stable COPD

Limb muscle dysfunction in COPD negatively affects quality of life, morbidity, and mortality (4). It is characterized by reduced muscle strength and/or endurance (4, 11), with the lower limbs generally being more affected than the upper limbs (12, 13). Reduced skeletal muscle mass, using fat-free mass index (FFMI) as a surrogate measure, is present in 4 to 39% of patients with COPD (14, 15). Although the prevalence generally increases with disease severity, reduced FFMI and quadriceps muscle mass have been reported across all Global Initiative for Chronic Obstructive

Lung Disease spirometric stages (1, 16) and body mass index (BMI) categories (17).

Several cellular signaling pathways that may contribute to the imbalance between muscle protein synthesis and protein breakdown have been implicated in limb muscle mass loss in patients with COPD (Figure 1). These pathways, together with other initiating factors, may lead to the changes observed in the peripheral muscles of this population (Figure 2).

The morphological and biochemical changes in the peripheral muscle may in part be consequences of physical inactivity and can to some extent be reversed by training (18). Indeed, reduced quadriceps volume, capillarity, and strength are already present in mild COPD and are associated with reduced physical activity (16, 19). The chronic use of tobacco may be another contributor to skeletal muscle dysfunction, as smokers without obstructive lung disease have lower weight and lean body mass

(LBM) than never smokers (20). Moreover, smokers or former smokers have weaker quadriceps than never smokers, and annual loss of fat-free mass is faster in patients with COPD who continue to smoke (1, 20, 21).

Acute Dysfunction in Exacerbations of COPD

Although the research on muscle dysfunction in the chronic setting may provide a guide for assessing acute muscle dysfunction, the evidence surrounding the latter is limited. Muscle dysfunction in AECOPD may also have parallels with ICU-acquired weakness (ICUAW), particularly in the area of protein homeostasis (22). It should be noted that there are important differences, as follows: first, patients with COPD always (whether diagnosed or not) have antecedent morbidity. Second, although certain associated characteristics, such as inflammation or

Figure 1. Schematic overview of anabolic and catabolic signaling in skeletal muscle. A number of underlying mechanisms contributing to imbalance between muscle protein synthesis and protein breakdown have been implicated in limb muscle mass loss in patients with chronic obstructive pulmonary disease (COPD) (4, 43, 104–107). The ubiquitin proteasome pathway is a major driver of muscle proteolysis and includes the forkhead box O (FOXO) transcription factor–regulated muscle-specific E3 ubiquitin ligases muscle ring finger protein 1 E3-ligase (MuRF-1) and atrogin-1 (105, 108). The autophagy–lysosomal pathway is another contributing mechanism to protein degradation in response to atrophic stimuli in the setting of COPD (107). Conversely, the GH–IGF-1–AKT–mTOR axis positively affects protein synthesis and may attenuate protein breakdown via AKT-mediated negative regulation of FOXO. ActRIIB = activin receptor type IIB; AKT = protein kinase B; AR = androgen receptor; GH = growth hormone; GHR = growth hormone receptor; IGF-1 = insulin-like growth factor 1; IGF1R = insulin-like growth factor 1 receptor; IKK = IκB kinase; IR = insulin receptor; JAK2 = janus kinase 2; JNK = Jun N-terminal kinase; mTOR = mammalian target of rapamycin; MyoD = myogenic differentiation 1; NFκB = nuclear factor-κB; P38 = p38 mitogen-activated protein kinase; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; ROS = reactive oxygen species; STAT = signal transducer and activator of transcription.

Figure 2. Factors and consequences in acute and chronic obstructive pulmonary disease (COPD)-related muscle dysfunction. The multiple factors related to muscle dysfunction in chronic and acute settings. Many of these factors are similar for both acute exacerbations of COPD and chronic stable COPD, with the notable exception of tobacco use and comorbidities (18, 21, 43, 54, 109). The large white arrows denote the direction of the impact. *Different muscle compartments show variable levels of cytokines. [†]Level dependent on time frame of illness. IGF-1 = insulin-like growth factor-1.

immobility, are present in both conditions, ICU patients experience an extreme variety of these features. Although clearly more research is required to further elucidate the mechanisms that occur in the context of AECOPD, this article reviews some prominent factors that are believed to contribute to muscle dysfunction in this patient population (Figure 2).

Disuse Atrophy

Muscle disuse causes dysfunction through reduced protein synthesis and increased protein catabolism (23, 24), processes characteristic of inactivity. During hospitalization for AECOPD, which can last a median of 7 days (25), many patients spend less than 10 minutes per day walking (26). Of note, it has also been recently demonstrated that exacerbations treated as an outpatient are also associated with reduced physical activity (27). The specific effects of reduced activity in patients hospitalized for AECOPD can be further extrapolated from observations made in studies of normal healthy individuals submitted to bed rest (28). Within 1 week, reductions in body weight, leg lean mass,

and strength were more pronounced in elderly compared with younger individuals (24). In some cases specifically assessing AECOPD, quadriceps muscle force is reduced, and quadriceps cross-sectional area (Q_{csa}) has been observed to decrease by up to 5% over 5 days of hospitalization (26, 29). Although Greening and colleagues found reduced Q_{csa} in hospitalized patients with AECOPD was linked to rehospitalization, longer hospital stays, and increased mortality (6), the same could not be said for the quadriceps maximal voluntary contraction (QMVC). They found that QMVC was not associated with rehospitalization or death after 1 year. Upper body strength, as measured by handgrip strength (HGS), has been found to be reduced in hospitalized patients with exacerbating COPD (29). The HGS test has also been associated with increased mortality for patients with COPD with values below the 10th centile (30). However, this parameter may be nonspecific, as it is often diminished in the elderly and those with chronic diseases (30, 31). Irrespective of their hospitalization status, patients with COPD who exacerbate

have deterioration of the BMI, obstruction, dyspnea, and exercise capacity (BODE) index score, which does not return to baseline even after 1 year (32). There are numerous other physiological and functional consequences of an exacerbation; however, studies on the best tools to measure these changes in such a setting are lacking. We have summarized methods for the measurement of muscle dysfunction in COPD, with particular focus on those applicable to AECOPD (Table 1) (4, 33).

Energy Imbalance

Weight loss has been observed in hospitalized patients with AECOPD (34) and may be due to reduced protein synthesis as seen in ICUAW (22). In addition, weight loss can worsen during hospitalization for those patients with COPD who are already underweight (35, 36). In stable COPD, a negative balance between energy intake and expenditure has been attributed to increased work of breathing (37, 38). This is further aggravated during a severe exacerbation when the resting energy expenditure (REE) increases partly in response to increased

Table 1. Assessments of Muscle Integrity and Function

Endpoint	Subcategory Endpoint	Method	Test Considerations
Muscle mass	FFMI	DXA (33)	Noninvasive study for clinically stable patient Active participation of patient not required Can be used to derive appendicular muscle mass
		BIA (110)	Noninvasive study Active participation of patient not required BIA is influenced by body water content Measures composition of the whole body
	Muscle CSA or volume	CT imaging (93)	Noninvasive study for clinically stable patient Active participation of patient not required
		MRI (111)	Noninvasive for clinically stable patient Active participation of patient not required
		Ultrasound imaging (6)	Noninvasive study Active participation of patient not required Can be performed at the bedside Potentially more operator dependent than MRI or CT
Muscle phenotype	Oxidative phenotype	31P-MRS (112)	Noninvasive study for clinically stable patient Mainly assessable in research settings Phosphocreatine recovery after exercise
		Fiber-type proportion, mitochondrial density	Invasive study requiring muscle biopsy Active participation of patient not required
	Intramuscular fat infiltration	MRI (113)	Noninvasive study for clinically stable patient Mainly assessable in research settings
Muscle strength	Isometric maximal volatile quadriceps muscle strength	Strain-gauge or computerized dynamometer	Active participation of patient required Recommended in the recent ATS/ERS statement on limb muscle function in COPD as a methodology that can be implemented in clinical practice (4)
	Nonvolatile measurement of quadriceps muscle strength	Magnetic or electrical stimulation of the femoral nerve (114)	Active participation of patient not required Feasible in research settings, but the techniques are not widespread Reported to be safe, reproducible in elderly and severely sick (AECOPD, ICUAW) (114)
	Hand grip strength	Handgrip dynamometer (30)	Active participation of patient required Muscle involvement in COPD preferentially involves lower limb; therefore, this approach may underestimate muscle weakness
Muscle endurance	Quadriceps endurance	Isometric quadriceps endurance using dynamometer (115)	Active participation of patient required
		Repetitive magnetic stimulation (116)	Active participation of patient not required Mainly assessable in research settings
		Myoelectrical assessment of fatigue using EMG	Noninvasive if performed as surface EMG Active participation of patient not required Relationship between EMG signal and power output is not good, leading to concerns regarding the value of this test (117)

(Continued)

Table 1. (Continued)

Endpoint	Subcategory Endpoint	Method	Test Considerations
Functional capacity	6-MWT	Submaximal exercise capacity test with patient-determined distance	Minimal equipment requirements Active participation of patient required MCID determined for patients with COPD (118) Requires a hallway of at least 100 ft
	Endurance shuttle walk test	A 10-m hallway course, variable speeds	Minimal equipment requirements Active participation of patient required MCID determined for patients with COPD (119)
	Incremental cycle ergometer test	Cycle ergometer	Active participation of patient required MCID determined for patients with COPD (118)
	PFIT-s	The PFIT-s consists of sit-to-stand assistance, marching on the spot cadence, shoulder flexor and knee extensor strength	Active participation of the patient required Composite score assessing mobility and strength (120) MCID determined for ICU patients
	CPAx	Composite measure of respiratory function, cough, mobility, and strength	Active participation of patient required Functional scoring tool validated for general ICU patients (121) Not specific for the muscle
	TUG	Three main components: rising from a chair, walking, and sitting down (122)	Minimal equipment requirements Active participation of patients required Assesses balance
	4MGS	Measured 4-m time course completed at usual speed	Minimal equipment requirements Active participation of patient required Predicts readmission (123) and has established MCID (7), and also recognized as being of value by the EMA (see below)
	SPPB	Assessment of balance, gait speed, and coordination	Minimal equipment requirements Active participation of patient required Demonstrated relationship with function in COPD (124), 4MGS is a component, as is the sit-to-stand test, which has demonstrated validity in COPD and a functionally relevant cut-off in relation to quadriceps strength (125) EMA considers SPPB may be the preferred instrument to assess physical frailty in many instances (96)

Definition of abbreviations: 31P-MRS = 31P-magnetic resonance spectroscopy; 4MGS = 4-m gait speed; 6-MWT = 6-minute-walk test; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; ATS/ERS = American Thoracic Society/European Respiratory Society; BIA = bioelectrical impedance analysis; COPD = chronic obstructive pulmonary disease; CPax = Chelsea Critical Care Physical Assessment tool; CSA = cross-sectional area; CT = computed tomography; DXA = dual-energy X-ray absorptiometry; EMA = European Medicines Agency; EMG = electromyograph; FFMI = fat-free mass index; ICUAW = ICU-acquired weakness; MCID = minimal clinically important difference; MRI = magnetic resonance imaging; PFIT-s = Physical Function in Intensive Care Test score; SPPB = Short Physical Performance Battery; TUG = timed up-and-go test.

oxygen cost of ventilation, consequently leading to negative changes in body weight and muscle mass (38, 39).

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis positively affects protein synthesis in both the acute and chronic settings (36, 40). In the early phase of an exacerbation, IGF-1 may be elevated in response to hypoxemia or as a stress response and then be reduced in the recovery phase, under the influence of

corticosteroids, a suppressor of the GH/IGF-1 axis (36, 40). In addition, leptin increases during the first days of an exacerbation, while patients are in a low intake/high REE state. Even though leptin should decline as REE decreases and food energy intake increases, in some patients it can remain elevated after 15 days (39, 40). The mechanism for this elevation is believed to be secondary to glucocorticoid use and systemic inflammation (40).

Local and Systemic Inflammation

In reality, leptin is one of many proteins that are altered in response to systemic inflammation during AECOPD (39). In fact, there are alterations of multiple systemic cytokines (tumor necrosis factor- α), acute-phase reactants (C-reactive protein), and other proinflammatory markers, including fibrinogen (39, 41, 42). However, there is limited information regarding the character of the local inflammatory response at the

muscle level (29, 43). Crul and colleagues found similar levels of IL-6 and IL-8 mRNA expression in the vastus lateralis muscle in those hospitalized for AECOPD, stable patients with COPD, and healthy adults (43). However, biopsies were performed on patients with AECOPD on hospital Day 4 and may have been influenced by glucocorticoids. On the other hand, Spruit and colleagues found that local IL-6 and IL-8 levels were inversely proportional to isometric quadriceps strength (29). In addition, increased circulating IL-8 levels were independently associated with the variance observed in handgrip and quadriceps strength in hospitalized patients with AECOPD (29). Given the inconsistent findings, additional studies are needed to evaluate the local effect of inflammatory processes on

muscle function and repair during an exacerbation.

Hypoxia and Hypercapnic Acidosis

Hypoxia has an inhibitory effect on muscle protein synthesis by activating muscle proteolysis via stimulation of calcium-dependent proteases, whereas acidosis stimulates proteolysis mainly via the ubiquitin-proteasome pathway (44). Because of inhibited hydroxylation, HIF-1 α (hypoxia inducible factor-1 α) is elevated in skeletal muscle during hypoxic states (45). The elevation of HIF-1 α causes a downstream cascade of alterations in glucose and oxidative metabolism and DNA alteration affecting myosin heavy chain expression (45). The molecular mechanism for these local changes may be due to reduction of intracellular muscle

pH, resulting in changes in myoelectrical signaling and reduction in muscle fiber conduction velocity (46, 47). Using nuclear magnetic resonance spectroscopy, it has been demonstrated that some patients with stable COPD develop a marked quadriceps acidosis during a sustained contraction (48), which is not seen in the upper limb, suggesting a mechanistic role for changes to muscle morphology. Even though the patients with COPD were sicker than the control subjects in this study, the results suggest potential interaction between hypercapnia, acidosis, and exercise-related fatigue (sustained contraction), which warrants further examination.

Electrolyte Dysfunction

Electrolyte imbalance, particularly hypokalemia and hypophosphatemia, are

Table 2. Current Therapies for Muscle Dysfunction

Therapeutic Approach	Category	Examples of Interventions	Pros/Cons
Nutritional support	High-protein diet	>1.5 g of protein (4, 38)	May be appropriate after thorough nutritional evaluation; may be nitrogen load
	Complete oral nutrition supplementation	Formulas vary; brands include ENSURE, BOOST	Potential link to reduced readmission, however, hospital formulations vary (34)
	Other nutritional supplements	Creatine (67, 68) Coenzyme Q (68) Vitamin D	Mixed or negative data on effectiveness; insufficient evaluations in hospitalized AECOPD setting
Pulmonary rehabilitation	General	Varies: resistance, cardio; includes limb-specific exercises	Shown to increased exercise capacity and feelings of independence Early initiation may not improve patient-reported outcomes (63) and may be linked to increased mortality (62)
	Upper limb	Supported: arm weight is supported, including cycle ergometry, rear deltoid row, chest press, and biceps flexion with vertical shoulder press (59) Unsupported: requires the activation of muscles that may be involved in respiration and/or in the support of the shoulder girdle during ADLs (e.g., lifting free weights) (59)	Improvement in both performance and endurance but not always dyspnea (59, 61) Potential risks of upper limb training are dynamic hyperinflation, a phenomenon usually seen at >50% of the maximum load obtained (126)
	Lower limb	Exercises for lower limb include heel raises, knee extension with heel touching floor, hip flexion, knee extension with dorsal flexion of ankle (128)	Can improve quadriceps mass and strength, which are linked to mortality outcomes (61, 127)
Neuromuscular electrical stimulation	NMES NMES and PR	NMES only NMES PR	Generally, has been shown to be safe but higher mortality in intervention group in Greening and colleagues study (62)

Definition of abbreviations: ADLs = activities of daily living; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; NMES = neuromuscular electrical stimulation; PR = pulmonary rehabilitation.

recognized causes of muscle dysfunction. Intuitively, one might think these disorders likely in patients who, in addition to aggressive treatment with β -agonist, often require diuretic therapy for comorbidities and whose disease may be worsened by the presence of hypercarbia (49). Few data exist in AECOPD, but it is clear that both hyponatremia and hypokalemia can occur (50, 51), although their impact on muscle force in this context is unknown. Older studies of patients with COPD with respiratory failure (in comparison with control subjects), found reduced intramuscular potassium, phosphorus, and magnesium but increased intramuscular chloride, sodium, and water (51, 52). However, correlation with muscle function tests was not performed, leaving an opportunity for newer studies to evaluate the role of electrolyte abnormalities in muscle dysfunction of AECOPD.

Glucocorticoids

Glucocorticoids, frequently used during AECOPD (53), indirectly reduce protein synthesis through down-regulation of IGF-1 (54, 55). In addition, glucocorticoids have been implicated in the elevation of leptin seen in the early days of an exacerbation (39) and activation of skeletal muscle mitochondrial-mediated apoptotic signaling pathways (56). Although glucocorticoids contribute to a negative nitrogen balance in both acute exacerbations and stable disease (57), corticosteroid use has not directly been linked to a reduction in muscle mass in stable patients (21) or a change in quadriceps strength (58). Furthermore, the correlation between glucocorticoid dose and quadriceps strength is not straightforward (29), thus raising the hypothesis that the effects may be an interaction between the steroids, immobility, and/or inflammation and not simply a steroid effect alone.

Therapies for Muscle Dysfunction in the AECOPD Population

The currently available therapies for muscle dysfunction in AECOPD include PR, neuromuscular electrical stimulation (NMES), and nutritional support (Table 2).

Pulmonary Rehabilitation and Specific Muscle Training

Exercise training for patients with AECOPD can be generalized or limb-specific (upper or lower) with the goal of improving performance, endurance, and strength (4, 59–61). Ultimately, the objective of this aspect of PR in AECOPD may be twofold: to prevent loss and/or induce recovery. A Cochrane review of nine studies in patients with AECOPD found benefits in readmission and mortality in those undergoing inpatient and/or outpatient PR soon after an exacerbation when compared with usual care (60). However, two recent studies in patients with AECOPD and ICU patients suggest the benefits may be limited (62, 63). Greening and colleagues initiated PR during hospitalization and showed fewer benefits and potential concerns for early (inpatient) PR initiation when used in conjunction with NMES (62). Furthermore, they found no difference in QMVC of those who were not readmitted, regardless of study group assignment (62). Notably, there was limited exercise training during hospitalization (average of fewer than three sessions each of aerobic and resistance training) and limited use of PR after hospital discharge in the intervention group. In addition, a randomized trial of standard rehabilitation versus usual care in 300 patients admitted to the ICU because of respiratory failure did not yield any advantage in patient-related outcomes (63). Although the reason for these results is unclear, it may be prudent to initiate PR once the patient's full capacity to participate in rehabilitation returns to a level tolerable of increasing workloads. Despite these controversies, informed opinion suggests that PR is severely underused for multiple reasons, including patient perception of benefit and feasibility of travel (61). Regardless of the goals or methods of PR in the acute condition, the stability and individual needs of the patient should be considered before initiation.

NMES

NMES is the application of electrical current over target muscles stimulating motor neurons and causing a muscular contraction (4). Zanotti and colleagues showed that muscle strength improved with active limb exercises and electrical stimulation in mechanically ventilated patients with COPD (64). The largest study in this area is

that of Greening and coworkers, who assessed 386 subjects, of whom 82% ($n = 320$) were patients admitted with a COPD exacerbation, to either inpatient rehabilitation using a regime incorporating NMES *vide infra* or best supportive care (62). As discussed above, this study failed to demonstrate a benefit for inpatient rehabilitation and revealed higher mortality in the intervention group, which might have been due to reduced uptake of rehabilitation after hospitalization (62). Therefore, one concern for NMES may be the timing of application, given the anabolic/catabolic balance shifts throughout AECOPD (65). Recently, NMES has shown to be useful in outpatients with stable COPD (66) and may yet have a role during early convalescence from AECOPD. More studies are needed to define the population that could benefit from this therapy.

Nutritional Support and Supplements

Reduced intake of nutrients such as proteins and fats in the first few days of hospitalization has led to suggestion for a high-protein diet (38). In fact, a dietary protein intake of greater than 1.5 g/kg/d has been suggested as a means to prevent weight loss after an exacerbation, on the basis of studies in this population (4, 38). More generally, a recent retrospective study showed that patients with a primary diagnosis of COPD who received complete oral nutritional support while hospitalized experienced a reduction in length of stay by 1.9 days and a 13.1% lower chance of 30-day readmission (34). Because this study was performed using Medicare claims data, the nutrition programs of the hospitals analyzed may vary, limiting the recommendations that can be distilled from the study results. Indeed, Puthucherry and colleagues found that administration of protein for ICUAW was associated with increased muscle wasting (22). However, this study may be of limited applicability to the AECOPD setting, as only a small number of patients with COPD were included (9 out of 63, 14.3%), one-third of all subjects had no antecedent chronic illness, and many experienced multiorgan failure during their ICU course. In addition to oral nutritional support and bulk protein administration, nutrients such as creatine and coenzyme Q10 have been evaluated as potential therapies to treat muscle dysfunction in COPD but have been met

with poor or limited results (67, 68). Finally, although vitamin D appears to be important for skeletal muscle health, as demonstrated by studies in both murine and human models (69, 70), its importance in acute muscle dysfunction in COPD has not been fully evaluated. Because of the mixed data, surrounding nutritional and protein administration for acute muscle dysfunction, nutritional risk screening and phenotyping with biological markers have been suggested before instituting a specific regimen (37).

Emerging Therapies

The major classes of emerging therapeutics for muscle dysfunction are androgens, myostatin inhibitors, GH analogs, and ghrelin receptor agonists (Table 3). Several of these drugs directly increase muscle mass and/or function. However, studies of these therapies have been focused mainly in chronic or subacute debilitating diseases, such as cancer and heart failure, and most lacked the inclusion of structured exercise and nutritional plans.

Androgens and Progesterone

Anabolic steroids affect muscle tissue by inducing protein anabolism via androgen receptors while inhibiting catabolism through neutralization of the glucocorticoid receptor (71). Unlike bulk protein administration during acute illness, androgens do not generate large quantities of urea and heat (71). Nandrolone and oxandrolone have been the best-studied androgens in COPD (72, 73). Oxandrolone was approved for patients with weight loss due to chronic infection, extensive surgery, or idiopathic failure to thrive (73). Oxandrolone increased LBM in an open-label, prospective, multicenter trial of a stable outpatient COPD population with cachexia. However, the applicability of the results of the study is limited because of the lack of a control group and high dropout rate (73). Testosterone has been reported to be low in some patients with COPD, although an association with reduced muscle function has not consistently been shown (72, 73). However, in a four-way study with resistance training in COPD (74), participants who were randomized to receive both training and testosterone gained the most muscle mass. Concerns regarding the side effects of testosterone have limited its use, but this may be mitigated by using

selective androgen receptor modulators. Selective androgen receptor modulators, studied in cancer cachexia, have shown potential to increase weight, strength, and function (75, 76), while minimizing the side effects often seen with testosterone treatment. Finally, megestrol acetate may benefit muscle dysfunction because of its effect on appetite and weight gain, in addition to stimulating ventilation. In one study, the drug increased weight in patients with COPD but, like several other androgens, failed to significantly improve 6-minute-walk distance (6-MWD) (77).

Myostatin Inhibitors

Myostatin, a member of the transforming growth factor- β protein superfamily, is a negative regulator of muscle growth and is elevated in states of cachexia, including COPD (78). There are several drugs in this category, including bimagrumab (BYM338), landogrozumab (LY2495655), AMG/PINTA 745, and trevogrumab (REGN-1033) (Table 3). Bimagrumab (BYM338), which blocks ActRIIB (activin receptor type IIB), has been studied in various disease states, including stable COPD, sarcopenia, and inclusion body myositis (79, 80). In the COPD study, bimagrumab showed statistically significant increase of up to 7% in thigh muscle volume by magnetic resonance imaging at 4, 8, and 24 weeks when compared with placebo (80). There was no improvement in functional outcomes, including the 6-MWD. In a 4-week study of patients with prostate cancer receiving androgen deprivation therapy, AMG 745 caused a 1.5% increase in LBM and 1.7% reduction in body fat when compared with placebo at Day 29 but failed to show any improvement in functional parameters (81).

GH

Once secreted by the anterior pituitary, GH acts via mediators, including IGF-1, to initiate a multitude of biological processes. GH regulation of IGF-1 and its interplay with myostatin have been demonstrated in patients with COPD (42). Despite its potential uses, there is concern for safety, given an important study that demonstrated increased mortality in ICU patients receiving GH (82). The causes of the excess mortality in that study have been debated, but there was a reduction in GH-associated interventional clinical trials in the subsequent years (83). Clinical trials of

GH in respiratory patients have yielded mixed results (84, 85). Pape and colleagues performed an uncontrolled study, finding weight gain and increased maximal inspiratory pressures in patients with COPD treated with recombinant GH (85). In another study, a randomized controlled trial, patients with COPD showed no improvement in strength and endurance compared with placebo and worse 6-MWD (84).

Ghrelin

Because of controversy surrounding the safety of GH, increasing enthusiasm exists for the use of GH secretagogues, such as ghrelin and ghrelin receptor agonists. Ghrelin stimulates secretion of GH, via growth hormone secretagogue receptor 1a (GHS-R1a), leading to regulation of multiple functions, from food intake to glucose metabolism (86). In humans, ghrelin has been studied in cancer cachexia, sarcopenia of the elderly, chronic heart failure, and COPD (87–91). In patients with COPD, ghrelin improved LBM and muscle strength but had mixed results on functional outcomes such as the 6-MWD (87, 90). SUN11031, another synthetic human ghrelin, was studied by Levinson and Gertner in clinically stable cachectic patients with COPD (89). This study enrolled 192 patients with BMI less than 21 kg/m² and FFMI less than 16 kg/m². Results showed that up to 65% of subjects in both treatment groups gained at least 3% of their body weight after 85 days of treatment (89). Another drug, capromorelin, was tested for 1 year in adults older than 65 years of age with evidence of functional decline on the basis of the Short Form-36 Health Survey and HGS (88). After 12-month treatment, there was a 7% increase in stair climb (vs. 0.9% placebo, $P = 0.02$) and a decrease in tandem walk time.

Finally, anamorelin has shown promise in cancer cachexia. Results of ROMANA 1 and ROMANA 2 (Anamorelin in Patients with Non-small-cell Lung Cancer and Cachexia) studies showed an increase in LBM but no improvements in functional outcomes such as handgrip strength (91).

Considerations for Drug Development to Treat Acute Muscle Dysfunction

Given the learnings from therapeutic studies performed in stable/chronic settings and in

Table 3. Emerging Therapies for Muscle Dysfunction

Class	Drug	Populations*	Tools	Notable Outcomes	Adjunct Therapy	Adverse Events
Androgens and progesterone	Megestrol (multiple) Multiple studies complete/ongoing	COPD , cancer cachexia, HIV/AIDS-related cachexia	DXA Spiro 6-MWT Mahler-Q CRD-Q	↑ Weight after 2 wk, confirmed as fat on DXA (77)	No planned nutrition or PR	Similar to placebo; mostly dyspnea
	Oxandrolone (multiple) Multiple studies complete/ongoing	COPD , Duchenne muscular dystrophy, HIV, cancer cachexia, FTT, chronic infection, surgery	BIA Spiro 6-MWT Karnofsky VAS	↑ Weight, ↑ in LBM at up to 4 mo, nonsignificant ↑ in 6-MWD (73)	No planned nutrition or PR	Edema, ↑ LFTs studies
	Enobosarm (SARM) Multiple studies complete/ongoing	Cancer cachexia	DXA FAACT FACIT-F SCP HGS SCT	↑ Total LBM, ↓ reduction in stair climb time (76)	No planned nutrition or PR	Nausea, anemia, GI disturbances
Myostatin pathway inhibitors	Landogrozumab (LY2495655) (Lilly) Multiple completed studies in various populations	Pancreatic cancer cachexia, hip arthroplasty , muscle atrophy	DXA TUG SCP Leg extension	Trend toward change in aLBM at 12 wk; probability of difference between treatment vs. PBO did not meet statistical significance (128)	Vitamin D supplementation for deficiency; no planned nutrition or PR	Injection site irritation; 7 patients developed anti-LY2495655 antibodies (no clinical significance)
	PINTA/AMG 745 (Atara Biotherapeutics/AMGEN) Discontinued by manufacturer	Prostate cancer cachexia	DXA CT Leg extension SPPB	↑ LBM at 29 d, ↔ SPPB, ↔ leg extension (81)	No planned nutrition or PR	Syncope (1 patient), fatigue, diarrhea, injection site bruising; 1 patient developed anti-AMG 745 antibodies (no clinical significance)
	Bimagrumab (BYM338) (Novartis) Multiple studies ongoing	COPD , IBM, IIM, sarcopenia, mechanical ventilation	DXA 6-MWT TMV	↑ TMV vs. placebo at 4, 8, and 24 wk, ↔ 6-MWD at 24 wk (80)	No planned nutrition or PR	Transient, mild, involuntary muscle contractions

(Continued)

Table 3. (Continued)

Class	Drug	Populations*	Tools	Notable Outcomes	Adjunct Therapy	Adverse Events
Ghrelin receptor agonist	SUN11031 (Daiichi Sankyo) Discontinued by manufacturer	COPD	DXA 6-MWT Spiro SPPB HGS	↓ 6-MWD in low dose vs PBO, ↔ HGS, ↔ SPPB, <i>post hoc</i> analysis of cachexic subjects show statistically significant ↑6-MWD, HGS, SPPB (89)	No planned nutrition or PR	COPD-related symptoms, injection site irritation, headache, weight reduction; MI in 7 subjects (unrelated to drug)
	Anamorelin (Helsinn Therapeutics) Studies completed	Cancer cachexia	DXA HGS FACT	↑ TBM, LBM, and aLBM after 12 wk, ↔ HGS, ↔ FACT (91)	No planned nutrition or PR	Uncontrolled diabetes, hyperglycemia, GI disturbances, edema
	Capromorelin (Pfizer) Discontinued by manufacturer	Sarcopenia (older adults, age 65–84 yr)	6-MWT HGS TWS SCT DXA MMSE SF-36 PAI MOS-SS	↑ SCT after 12 mo, ↔ 6-MWD, nonsignificant ↑LBM after 6 mo (88)	Discontinued by manufacturer	Hyperglycemia (↑ HA1c), insulin resistance, glucosuria, ↑ cholesterol
β-Receptor blocker	Espindolol (MT-102) (PsOxus) (nonselective β-blocker) Multiple studies complete/ongoing	Colorectal and NSCLC cachexia	DXA HGS 6-MWT SCP SPPB EQ-5D	↑ Weight 4 wk (high dose vs. PBO), ↑ HGS, ↑ 6-MWD, SCP, nonsignificant trend toward improved SPPB (high dose vs. PBO) (129)	Multiple studies complete/ongoing	Anemia, cough, dyspnea

Definition of abbreviations: 6-MWD = 6-minute-walk distance; 6-MWT = 6-minute-walk test; aLBM = appendicular lean body mass; BIA = bioelectric impedance analysis; COPD = chronic obstructive pulmonary disease; CRD = chronic respiratory disease; DXA = dual-energy X-ray absorptiometry; EQ-5D = EuroQol five dimensions questionnaire; FAACT = Functional Assessment of Anorexia/Cachexia Therapy score; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FACT = Functional Assessment of Cancer Therapy; FTT = failure to thrive; GI = gastrointestinal; HA1c = hemoglobin A1c; HGS = handgrip strength; IBM = inclusion body myositis; IIM = idiopathic inflammatory myopathy; LBM = lean body mass; LFT = liver function test; MI = myocardial infarction; MMSE = Mini Mental Status Examination; MOS-SS = Medical Outcomes Study-Sleep Scale; NSCLC = non-small-cell lung cancer; PAI = Physical Activity Index; PBO = placebo; PR = pulmonary rehabilitation; Q = questionnaire; SARM = selective androgen receptor modulator; SCP = stair-climbing power; SCT = stair-climbing time; SF-36 = 36-item short form health survey; SPPB = Short Physical Performance Battery; TBM = total body mass; TMV = thigh muscle volume; TUG = timed up-and-go test; TWS = tandem walk speed; VAS = visual analog scale.

*Populations in bold were studied in the trial referred to under the “Notable Outcomes” section.

subjects without COPD, we have developed recommendations for drug development targeting muscle dysfunction in hospitalized patients with AECOPD. These recommendations are summarized in Table 4, and further considerations may be found in a recent review by Steiner and colleagues (92).

Inclusion/Stratification

The studies of emerging therapies in the stable COPD setting have shown inconsistent improvement across parameters of muscle dysfunction (Table 3). In an acute setting, it is possible that these drugs may provide greater benefit because of the degree and nature of muscle dysfunction. Therefore, careful consideration needs to be given to the inclusion criteria for a study with a novel intervention. Given current knowledge, it seems sensible to stratify entrance into the study by physical performance, muscle

strength, and/or skeletal muscle composition. On the basis of recent studies, Q_{csa} may be a useful inclusion criterion because of its predictive ability and bedside accessibility (6, 93). Although QMVC was found to be variably impacted in AECOPD and therefore limited as an outcome (62), it may prove to be a good stratification tool to direct therapy toward the most affected individuals. Depending on the severity of the exacerbations, assessment of physical capacity using a tool such as the Short Physical Performance Battery can inform on weakness in the lower limb (94), and the 4-m gait speed component is predictive of readmission in the context of AECOPD.

Outcome Measures

In conjunction with determining the appropriate inclusion criteria for the study, endpoint measurement(s) must be

established. Regulatory endpoints fall into two major categories: objective physiological assessments (pulmonary function tests and exercise capacity) and patient-reported outcome measurements (symptom scores, activity scales, and health-related quality-of-life instruments) (Table 5) (95). The Short Physical Performance Battery, which is widely used in gerontology and relates to quadriceps structure and function in COPD (94), has recently been suggested by the European Medicines Agency for use in clinical trials (96). In addition, submaximal constant work rate endurance time is being prepared for submission for qualification (97).

Another endpoint that may in due course be validated as an outcome is the European Union Innovative Medicine Initiative Patient reported outcome (PROactive) tool (98), which aims to capture the patient experience of physical

Table 4. Recommendations for Clinical Trial Considerations for Muscle Dysfunction in COPD

	Hospitalized, Non-Mechanically Ventilated AECOPD	Mechanically Ventilated AECOPD	Stable COPD
Interventions	Androgens, GH analogs, ghrelin agonists, myostatin inhibitors, NMES		
Endpoint	90-d readmission (30- or 60-d may be considered) Physical function Muscle strength QoL	Ventilator-free days Length of hospitalization Physical function Muscle strength QoL	QoL Physical function Muscle strength
Inclusion/stratification	Muscle strength (QMVC) Muscle mass (CSA, FFMI) Muscle phenotype (BX*) Physical capacity (TUG, 4MGS, 6-MWT)	Muscle strength Muscle phenotype Muscle fiber composition Physical capacity (CPAx)	Muscle strength Muscle mass Muscle phenotype Physical performance
Duration	3 wk to ≥ 3 mo	3 wk to 3 mo	8 wk to ≥ 6 mo
Exercise	Yes	Maybe (ICU dependent)	Yes
Timing	Discharge/postdischarge • Ensure patient can attend initial visit or can be performed in conjunction with rehab facility	Postdischarge	Outpatient
Assessments	Muscle strength Muscle mass Muscle fiber composition	Muscle strength Physical function QoL	Muscle strength Muscle mass Muscle fiber composition Physical function QoL
Nutrition	Controlled	Controlled	Controlled Real world
Other	Age, sex, race/ethnicity, location, additional medications (e.g., oral glucocorticoid, supplements)		

Definition of abbreviations: 4MGS = 4-m gait speed; 6-MWT = 6-minute-walk test; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; BX = biopsy; COPD = chronic obstructive pulmonary disease; CPax = Chelsea Critical Care Physical Assessment tool; CSA = cross-sectional area; FFMI = fat-free mass index; GH = growth hormone; NMES = neuromuscular electrical stimulation; QMVC = quadriceps maximal voluntary contraction; QoL = quality of life; TUG = timed up and go test.

*Fiber-specific interventions.

Table 5. Selected Patient-reported Outcomes

Outcome Measure	Components	Recall Period	Year Published	MCID	Approved (Agency)	AECOPD Validation
Symptom/activity scales						
EXACT-PRO (130)	Questions: 14 Domains: breathlessness, cough and sputum, chest symptoms Scale: 0 (asymptomatic) to 100 (severely symptomatic)	1 d	2010	Undefined	Yes (FDA, EMA)	Yes
E-RS (131)	Questions: 11 Domains: breathlessness, cough and sputum, chest symptoms Scale: 0 (asymptomatic) to 40 (severely symptomatic)	1 d	2014	1–3 units, varies by domain	Yes (FDA, EMA)	Yes
MMRC* (131)	Questions: 1 Domains: undefined Scale: grade 1 (breathless with strenuous exercise) to 5 (breathless with minimal activity)	Undefined	1952	Undefined	Yes (FDA, EMA)	No
Health-related QoL						
SGRQ-C (95)	Questions: 50 Domains: symptoms, activity, impact of disease on daily life Scale: 0 (no impairment) to 100 (completely impaired)	4 wk, 3 mo, 1 yr	1992	4 units	Yes (FDA)	No
CRQ (132)	Questions: 20 Domains: dyspnea, emotional function, fatigue, and mastery Scale: 1 (severe impairment) to 7 (no impairment) per domain	2 wk	1987	0.5 per domain	No	No
SF-36 (133)	Questions: 36 Domains: physical and mental subscales: physical function, mental health, energy, health perception, physical role limitation, mental role limitation, social function, and pain Scale: 0 (negative health) to 100 (positive health)	1 wk, 4 wk	1992	Undefined	Yes (FDA)	Yes
CAT (131)	Questions: 8 Domains: undefined Scale: 0 (no impact) to 40 (severe impact)	Undefined	2009	1–3	Yes (FDA)	Yes
Multidimensional						
Modified BODE (134, 135)	Questions: 4 areas Domains: FEV ₁ (% predicted), 6-MWT, dyspnea scale score, BMI Scale: 0 (best) to 10 (worst)	N/A	2004	Undefined	Yes (FDA, EMA)	No
PROactive (98)	Questions: D-PPAC: 30, C-PPAC: 35 Domains: amount of activity, difficulty of activity (performed daily or in clinic) Scale: Yet to be established	7 d	2014	Undefined	No	Yes

Definition of abbreviations: 6-MWT = 6-minute-walk test; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, and exercise; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; C-PPAC = Clinical Visit PROactive Physical Activity in COPD; CRQ = Chronic Respiratory Questionnaire; D-PPAC = Daily PROactive Physical Activity in COPD; EMA = European Medicines Agency; E-RS = Evaluating Respiratory Symptoms; EXACT-PRO = The Exacerbations of Chronic Pulmonary Disease Tool-Patient-reported Outcome; FDA = U.S. Food and Drug Administration; MCID = minimal clinically important difference; MMRC = Modified Medical Research Council; N/A = not applicable; QoL = quality of life; SF-36 = 36-item Short-Form Health Survey; SGRQ = St. George's Respiratory Questionnaire; SGRQ-C = COPD-specific SGRQ.

There are several characteristics that the FDA takes into account when reviewing a new or modified patient-reported outcome: concepts being measured, number of items, conceptual framework of the instrument, medical condition for intended use, population for intended use, data collection method, administration mode, response options, recall period, scoring, weighting of items or domains, format, respondent burden, and translation or cultural adaptive availability (136).

*FDA classified as activity scale but also considered in symptom scale.

activity. The consortium conducted a 6-week, multicenter, randomized, two-way crossover study in 236 patients with stable and exacerbated COPD. The scores on the questionnaire correlated with patient quality of life, dyspnea, and exercise capacity (98). Finally, endpoints such as hospital 30- or 90-day readmission can be used as an objective nonphysiological assessment, while having the value of being attractive to payers (e.g., insurance companies) and prognostic indicators of mortality (99, 100).

Timing

The timing of the intervention and duration of administration are important parameters that, although dependent the drug's mode of action, require careful coordination with patient discharge planning. In patients hospitalized with AECOPD, initiating treatment at the time of discharge or shortly after discharge has several advantages. The first advantage is knowing that the patient is to survive hospitalization, given the inpatient mortality rate of 2 to 5% (99, 101). In addition, initiating treatment after discharge allows for confirmation of AECOPD diagnosis and fewer confounding factors, such as use of systemic glucocorticoids.

Duration

Duration of treatment can vary depending on the characteristics of the drug. For

example, bimagrumab increased thigh muscle volume at 8 weeks of treatment (80), although there was no evidence of functional improvement. With due consideration for a medicine's mode of action, a longer treatment period, with a minimum of 3 months, may provide enough time for assessment of physiological, functional, and nonphysiological endpoints. Stable outpatient COPD and mechanically ventilated patients with exacerbated COPD may require longer or shorter lengths of treatment, depending on the goal of the trial.

Adjunct Therapy

Many of the drug studies we reviewed did not include PR or nutritional interventions. For prevention and intervention studies in sarcopenia, the preference is for incorporation of exercise and nutrition because of perceived benefits (102, 103). However, in the recovery phase from AECOPD, PR and nutritional interventions might obscure benefits from a potentially effective medicine. Thus, in early-phase trials designed to provide a "reason to believe," it may be desirable to include an arm that does not contain formal PR or allow PR on the basis of physician discretion, with understanding of the variability it may introduce into the study.

Conclusions

It is now accepted that muscle weakness and consequent limitation to activities of daily living and exercise is a feature of COPD. During a hospitalization for an exacerbation, muscle strength, physical activity, and exercise performance are further impaired and are markers of increased future risk. Therefore, the period around an exacerbation represents a crucial moment to explore interventions that may reverse these processes. In the chronic setting, there have been mixed results in therapeutics for muscle dysfunction. An improved understanding of the contributing factors to acute muscle dysfunction and important clinical trial concepts for drug development in this area may prove a promising therapeutic avenue to reduce morbidity associated with hospitalization for AECOPD. The recent efforts to improve evaluation of outcomes in this population, including the PROactive consortium, will ensure future availability and adoption of drug development tools that are accepted by regulatory agencies to expedite the development of novel therapies focused on muscle dysfunction in the acutely ill patient with COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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