mucin secretion provoked by the above secretagogues. The results indicate that MARCKS protein plays a major role in mediating human airway mucin secretion.

Response of Human Airway Epithelium *In Vitro* to Inflammatory Mediators*

**Dependence on the State of Cellular Differentiation**

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(CHEST 2000; 117:267S–271S)

**Abbreviations:** HNE = human neutrophil elastase; IL = interleukin; mRNA = messenger RNA; NHBE = normal human bronchial epithelial; NOS = nitric oxide synthase

Airways in patients with COPD or chronic bronchitis contain regions of damaged and regenerating epithelium intermixed with normally differentiated mucociliary areas. Responses of these different regions to the inflammatory milieu present in airways of these individuals may differ, thereby altering further development of additional lesions in the airways. In the studies reported here, we utilized normal human bronchial epithelial (NHBE) cells cultured in an air/liquid interface system as a model of well-differentiated epithelium, and the same cells cultured on plastic and submerged in medium as a model of poorly differentiated, regenerating epithelium. We investigated the responses of these different cell types to inflammatory mediators present in inflamed airways: the cytokine interleukin (IL)-13, human neutrophil elastase (HNE), and "cytomix" (10 ng/mL tumor necrosis factor-α, interferon-γ, and IL-1β). Acute exposure to IL-13 (10 ng/mL, 24 h) caused an increase in steady-state messenger RNA (mRNA) for mucin (MUC5AC) in undifferentiated cells, but did not affect MUC5AC expression in differentiated cells. Secretion of mucin and the secondary cytokine, IL-6, were both decreased in differentiated epithelial cell cultures after exposure to IL-13, but no secretory change was observed in undifferentiated cells. By contrast, chronic exposure to IL-13 (10 ng/mL, 8 days) caused an increase in mucin secretion in differentiated airway epithelial cells, and a decrease in undifferentiated cells. In response to HNE, well-differentiated cells increased steady-state levels of MUC5AC mRNA, but undifferentiated cells increased mRNA levels of another mucin gene, MUC4. Finally, the message level of inducible nitric oxide synthase (NOS) was increased by cytomix only in differentiated NHBE cultures. Undifferentiated cells did not express inducible NOS at all, but rather the constitutive forms of NOS, endothelial NOS and brain NOS. These data suggest that the response of the airway epithelium to inflammatory mediators may be markedly different in undifferentiated versus fully differentiated cells, and these responses may play a role in further exacerbation of airway inflammation. *In vitro* studies utilizing cultured airway epithelial cells must take the state of differentiation of these cells into account when analyzing such responses and extrapolating to the *in vivo* situation.

Skeletal Muscle Function in COPD*

Richard Casaburi, PhD, MD, FCCP

Few effective therapies exist for patients with COPD. Rehabilitative therapy aimed at curing dysfunction of the peripheral muscles may be an appropriate addition to this short list. This review does the following: (1) presents evidence that skeletal muscle dysfunction is present in COPD patients; (2) considers the mechanisms of this dysfunction; (3) describes the role of exercise training in correcting this disorder; and (4) speculates that anabolic hormone supplementation may find a place in COPD therapy. Further research will be necessary to refine these concepts.  

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**Key words:** anabolic; COPD; exercise; growth hormone; muscle; strength; testosterone

**Abbreviation:** IGF = insulin-like growth factor

Advanced COPD burdens the patient with disabling dyspnea and a host of other symptoms and, because of the high worldwide prevalence of cigarette smoking, the number of afflicted individuals is staggering. Consider how few effective therapies we have to offer our patients afflicted with this miserable disease. Inhaled bronchodilators offer distinct, albeit modest, relief to the majority of patients. Thanks in substantial part to the individual for whom this conference is named, Dr. Thomas L. Petty, we recognize that chronic oxygen therapy is of value for the hypoxemic COPD patient. Does the list end with these two therapies? Lung volume reduction surgery, though much discussed, remains both unproven and unlikely to

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be an option for the majority of patients. What of the efforts of our colleagues, the cellular and molecular biologists? It may be uncharitable to point out that, despite almost 15 years of siphoning the vast majority of pulmonary science research dollars into cell and molecular biology pursuits, we have no therapies for COPD in hand.

I would argue that pulmonary rehabilitation and, specifically, rehabilitative exercise training should join this short list of therapies with demonstrated efficacy. This argument is much easier to make today than it was 10 years ago. If we consider COPD to be exclusively a disease of the lung, it is hard to understand how exercise training would be of help. Clearly, exercise training does nothing to improve pulmonary mechanics, pulmonary gas exchange, or pulmonary vascular function. Formerly, it was conceded that exercise programs were primarily of psychological value, of use in motivating patients toward a higher level of activity. The current view, however, is to consider COPD a multiorgan system disease. In particular, there is accumulating evidence that the skeletal muscles (most importantly, the muscles of ambulation) do not function normally and that this dysfunction contributes to exercise intolerance. Exercise intolerance is often the COPD patient’s chief complaint. In this view, rehabilitative exercise training has the goal of treating skeletal muscle dysfunction. Moreover, there are other therapies that might ameliorate skeletal muscle dysfunction, and these might be suitable for administration in the context of pulmonary rehabilitation.

This review will summarize the following evidence obtained to date: (1) skeletal muscle dysfunction is present in COPD; (2) the dysfunction may be multifactorial; (3) exercise training can yield physiologic improvements in muscle function; and (4) anabolic hormone supplementation is rational therapy for this disorder. This topic has also been recently addressed in a Statement of the American Thoracic Society and European Respiratory Society, which was composed by an international panel of experts.

**Evidence for Skeletal Muscle Dysfunction in COPD**

1. Several recent studies of the vastus lateralis muscle appear to show that structural and biochemical abnormalities exist in COPD patients, although age- and activity-matched control groups have not always been employed. A lower fraction of type I fibers (and higher fraction of type II fibers) are present. A higher fraction of myosin heavy chain type 2B isoform has been found. These findings would predict relatively poor aerobic function of these muscles. Accentuating the abnormalities in aerobic function, capillary density is decreased, which would result in increased diffusion distances for oxygen transport. Moreover, concentrations of aerobic, but not glycolytic, enzymes are reduced in COPD patients. These findings, along with reports that muscle mass is low (often even if the patient is of normal body weight), are consistent with poor muscle function.

2. Several investigators have shown that lactic acidosis occurs at much lower work rates than in healthy sub-

**Possible Mechanisms of Muscle Dysfunction**

1. Deconditioning almost certainly is a major contributor to the muscle dysfunction seen in COPD patients. These patients generally assume an extremely sedentary lifestyle to avoid the dyspnea that activity brings. Studies of healthy subjects undergoing bed rest or astronauts experiencing prolonged weightlessness have defined the effects of deconditioning. The muscles of ambulation atrophy, muscle capillary density falls, aerobic enzyme concentrations decrease, and a shift in muscle fiber type from type IIA to type IIB is seen. These changes yield substantial decreases in strength and endurance.

2. Malnutrition may contribute to inability to synthesize muscle protein and may be responsible, in part, for the profound muscle wasting seen in some patients. However, recent research indicates that inflammatory mediators are elevated in some COPD patients, and it is speculated that these mediators may be responsible for weight loss and muscle wasting.

3. Adequate levels of anabolic hormones are required for normal muscle growth and development. There are
two well-described anabolic hormone systems. Growth hormone, secreted by the pituitary, has an anabolic effect on muscles principally through stimulating production of insulin-like growth factor (IGF)-1. In men, testosterone is secreted by the testes and has a substantial anabolic effect on muscle. In women, testosterone plays a less well-understood role; circulating levels are roughly tenfold lower than in men. However, some investigators have started to consider the feasibility of testosterone administration to women. In healthy elderly subjects, levels of both IGF-1 and testosterone tend to be lower than in the young. Preliminary evidence reveals a considerable prevalence of substantially reduced levels of these circulating hormones in COPD patients.

4. Corticosteroids are known to cause muscle weakness. Both acute and chronic steroid myopathies have been described. The former is a profound general muscle weakness, uncommonly seen several days after treatment with high doses of IV corticosteroids. Chronic steroid myopathy is a more common occurrence, seen after prolonged administration of lower doses of corticosteroids. The time course of reversal of chronic steroid myopathy is unclear; it seems possible that many months may be required.

5. It is altogether possible that there is a specific myopathy associated with COPD. Chronic hypoventilation or hypercapnia or the effects of cigarette smoking could conceivably damage the muscles. Comorbid conditions may also play a role. Electrolyte imbalance is known to impair skeletal muscle function. Cardiac failure is known to induce changes in muscle structure, although these data have been gathered in patients with congestive heart failure, not cor pulmonale.

Exercise Training Yields Improvements in Muscle Function in COPD

The past 10 years have seen the accumulation of data supporting the concept that exercise programs are capable of inducing physiologic changes in the muscles of ambulation that improve exercise tolerance in COPD. Several pieces of evidence to support physiologic benefit can be cited.

1. Muscle biopsies performed before and after a rigorous endurance training program have demonstrated that concentrations of the enzymes facilitating oxidative metabolism are increased.

2. A given level of heavy exercise can be performed with a smaller increase in blood lactic acid level after a training program. This is associated with a proportionally lower level of carbon dioxide output and of ventilation.

3. After a training program, following the onset of constant work rate exercise, the kinetics of oxygen uptake are faster. This indicates better aerobic function of the muscles.

These physiologic improvements in muscle function only occur after a rigorous program of endurance training. Though physiologically based principles for exercise prescription in COPD patients have not been fully defined, certain principles are likely to be true. As in healthy subjects, programs need to last for 5 to 8 weeks, sessions need to be held 3 to 5 times per week, and sessions need to be 30 to 45 min in duration to achieve a substantial aerobic training effect. Exercise intensity prescription is controversial, but some authors have posited that high fractions of the peak work rate achievable (perhaps 75 to 85%) is an achievable goal. Such training programs have been shown to yield substantial increases in exercise tolerance in patients with both moderate and severe COPD.

Anabolic Hormone Supplementation is Rational Therapy for COPD Patients

In view of preliminary evidence that COPD patients have low circulating levels of IGF-1 and (in men) testosterone, hormone supplementation seems an attractive method to reverse muscle dysfunction. However, not all anabolic stimuli to muscle yield similar effects. For example, endurance and strength training programs have substantially different effects on the exercising muscles. Endurance programs increase capillarity, aerobic enzyme concentrations, and mitochondrial number, but do not cause appreciable muscle fiber hypertrophy. Strength training programs, in contrast, induce dramatic hypertrophy, which increases the potential for force generation for explosive tasks, but do not yield changes that decrease diffusion distances for oxygen. Therefore, strength training increases strength and endurance training increases endurance. From studies in healthy subjects, there is preliminary evidence that both growth hormone and testosterone administration predominantly induce hypertrophy, similar to a strength training adaptation. Though this conclusion is speculative, it seems unreasonable to expect that either growth hormone or testosterone administration will increase exercise endurance. However, decreased strength is commonly seen in COPD patients and strength is required for many everyday activities.

When growth hormone is given to growth hormone-deficient adults, muscle mass increases and strength improves. In healthy young subjects, growth hormone administration causes muscle protein synthesis to increase. In healthy older subjects and patients with HIV-wasting syndrome, growth hormone yields increases in muscle mass. However, studies of functional capabilities have yielded mixed results. In COPD, a 3-week study of thrice-weekly growth hormone administration found evidence of increased muscle mass, but no change in endurance exercise capacity. Because growth hormone must be administered by injection several times per week, because it is quite expensive, and because of equivocal evidence of improved exercise tolerance, questions have been raised regarding the usefulness of growth hormone as therapy for patients with chronic disease.

The administration of testosterone to men whose testicular production is inadequate clearly increases muscle mass and strength. However, the widespread use of anabolic steroids by athletes and body builders has generated nearly a half century of controversy. It was widely believed by the sports medicine community that supra-
physiologic doses of testosterone yield muscle hypertrophy and improved performance. Anecdotal evidence of effectiveness, followed by the publication of > 12 studies conducted mostly in the 1970s, proved inconclusive.49 However, the issue seems to have been settled by a publication of a randomized, well-controlled 10-week trial of supraphysiologic doses of testosterone enanthate delivered in weekly injections.50 Lean body mass and muscle strength increased substantially, and strength training yielded additive effects. Only a few studies have examined the effect of anabolic steroids in patients with chronic disease. In men with AIDS-wasting syndrome, replacement doses of testosterone increased lean body mass, but the change in the 6-min walk distance was not significantly different from the control group.51 Nandrolone (an orally administered anabolic steroid) or placebo was given to 217 men and women with COPD.52 A small increase in lean body mass and a small increase in maximum inspiratory pressure was seen in the nandrolone group. Recently, 6 months of oral stanozolol yielded a mean 1.8-kg increase in lean body mass but no increase in endurance exercise tolerance in 10 underweight COPD patients.53 Before anabolic steroids can be routinely prescribed for patients with COPD, safety concerns must be addressed.54,55 There is a theoretic risk that an occult prostate malignancy might be stimulated to grow faster, although fairly large studies of elderly men are reassuring. Since testosterone stimulates erythrocyte production,56 a tendency toward polycythemia might be exacerbated.

In summary, curing the dysfunction of the peripheral musculature of patients with COPD may in the near future become a routine part of the therapeutic plan. Research into the nature of the defect in muscle function, optimal exercise strategies, and more beneficial anabolic drugs is likely to be productive.

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Chronic Alveolar Hypoventilation Helps To Maintain the Inspiratory Muscle Effort of COPD Patients Within Sustainable Limits*

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Abbreviations: PI = inspiratory pressure; Pmax = maximal inspiratory pressure; Ti/TI = inspiratory duty cycle; TTI = tension-time index of the inspiratory muscles; VA = alveolar ventilation; VCO2 = carbon dioxide output; V̇ṗV̇Ṫ = physiologic dead space ventilation; Z = mechanical impedance

When the load imposed on the inspiratory muscles is excessive relative to the neuromuscular capacity, patients need mechanical ventilation.1 Patients breathing with a tension-time index of the inspiratory muscles (TTI) above a threshold value between 0.12 and 0.15 have been found to be difficult to wean from the ventilator.2 The

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