Muscle Metabolism and Exercise Tolerance in COPD*

Michael I. Polkey, PhD

This article explores the hypothesis that dyspnea in patients with COPD arises from an imbalance between the load placed on the respiratory muscle pump and its capacity. Evidence to support this concept is presented, and possible therapeutic approaches are discussed.

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Clinical experience suggests that patients with COPD commonly complain of the symptom of dyspnea. Detailed studies, however, suggest that leg effort may contribute equally to exercise limitation as does dyspnea. In this respect, patients with COPD are similar to healthy subjects, the principle difference being the level of work necessary to generate symptoms. The sensation of dyspnea has been a subject of intensive research for decades. Nevertheless, at the risk of oversimplification, my hypothesis is that exercise limitation results from an imbalance between the load placed on the respiratory system and its capacity (Fig 1). An extreme example of load-capacity imbalance is acute hypercapnic respiratory failure, a recognized complication in COPD patients, but data from our laboratory suggest that treadmill exercise can be sufficient to generate transient respiratory failure in patients with advanced COPD. Thus, during treadmill exercise, the mean pH fell from 7.41 to 7.36 and the mean PaCO₂ rose from 5.4 to 6.3 kPa. Although data suggest that the major problem is that the load on the system is increased rather than diminished capacity, this article will explore both sides of the load/capacity equation and will finish by discussing directions that novel treatment approaches could pursue.

Capacity of the Respiratory Muscle Pump

Early observations suggested that the capacity of the inspiratory muscles to generate a negative intrathoracic pressure was reduced. It was also recognized, however, that the strength of a muscle was related to its length. Thus, a controversy arose among subsequent investigators as to whether diaphragmatic and inspiratory muscle function were more compromised than would be predicted from the hyperinflation associated with COPD.

In an attempt to resolve this question, our group applied the technique of magnetic stimulation of the phrenic nerve roots. That study showed that, allowing for hyperinflation, patients with COPD had a twitch-transdiaphragmatic pressure (TwPdi) that was comparable to that of control subjects. We also showed that, as in healthy subjects, hyperinflation had a negative linear relationship with TwPdi and that this effect was mediated by a reduction in the twitch esophageal pressure (TwPes) [Fig 2]. Thus, we showed that hyperinflation disproportionately reduces the ability of the diaphragm to create a negative intrathoracic pressure, and, indeed, in some patients the diaphragm is expiratory in action.

This observation is relevant because only a few studies have investigated the function of the diaphragm and inspiratory muscles during exercise or hyperventilation, and yet, these are the conditions under which COPD patients are most likely to be symptomatic. We and others have shown that, during exercise, dynamic hyperinflation of up to 1 L can occur. Our data suggest that the diaphragm is then less able to contribute to intrathoracic pressure generation, leaving this task predominantly to the extradiaphragmatic inspiratory muscles. We found that during exhaustive exercise low-frequency diaphragm fatigue does not occur. Since shortened muscles are less susceptible to fatigue, this is perhaps predictable, but it is impressive that the diaphragm can maintain tension generation under these conditions. However, further studies have confirmed that when the inspiratory muscles are studied immediately after treadmill exercise there is a slowing of the relaxation rate, which is evidence of intolerable loading. The use of inspiratory pressure support to unload the muscles during exercise attenuates the slowing of the relaxation rate, extends walking distance, and improves gas exchange.

Thus, exhaustive treadmill walking is associated with excessive loading, and patients can be helped experimentally by the application of inspiratory pressure support. Some studies have examined the diaphragms of COPD patients at a cellular level. These studies have shown a switch from type II muscle fibers to fatigue-resistant type I fibers, with an increase in mitochondria and sarcomere shortening. These adaptations are similar to those seen with training and suggest that the system has attempted to compensate for excessive loading by increasing the capacity of the pump. The novel therapy of lung volume reduction surgery offers the opportunity to reduce static and dynamic hyperinflation, but the published data on lung volume reduction surgery and diaphragm function do not give a clear conclusion as to the significance of this effect.

Respiratory System Load

Clearly, the primary pathology in COPD is expiratory airflow limitation, yet, as shown above, data exist to show that, despite compensatory adaptations, the inspiratory muscle pump is excessively loaded in exercise during COPD. Multiple factors combine to increase the load placed on the pump. Some of these are well-known (Table 1) and are discussed below, but it is increasingly recognized that quadriceps myopathy, which is discussed in detail separately, is an important contributing factor.

*From the Royal Brompton Hospital, London, UK.
Correspondence to: Michael I. Polkey, PhD, Royal Brompton Hospital, Fulham Rd, London SW3 6NP, United Kingdom; e-mail: m.polkey@rbh.nthames.nhs.uk
Patients with COPD have to generate increased minute ventilation to maintain blood gas homeostasis compared with healthy subjects, principally because the destruction of lung tissue generates ventilation-perfusion mismatching. In addition, patients with COPD have an increased physiologic dead space. Thus, the typical minute ventilation in patients with moderately severe COPD could be 10 L/min compared with approximately 5 L/min in healthy adults. Evidence that this load extracts a response from the respiratory muscle pump even at rest is shown both by the finding of increased transdiaphragmatic pressure generation and, more recently, by the demonstration of increased firing rates in the motor units of the diaphragm and extradiaphragmatic inspiratory muscles.

During exercise, the respiratory muscle pump attempts to increase minute ventilation. Since dynamic hyperinflation occurs, patients with COPD cannot increase tidal volume in the same way as healthy subjects (i.e., by

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**Figure 1.** Schematic illustration of the effect of load and capacity on the respiratory muscle pump. If the quadriceps muscles metabolize anaerobically, the increased level of CO₂ needs to be cleared by the ventilatory system, imposing an additional load.

**Figure 2.** The effect of hyperinflation on the function of the diaphragm in four subjects with COPD who were studied by Polkey et al. Although there is an inverse linear relationship between hyperinflation and both TwPdi and TwPes, this causes TwPes to be close to zero in the latter case. TLC = total lung capacity.
that the quadriceps muscles have significant metabolic improvement by improving oxygen delivery, and therefore observation that isolated limb muscle performance can be produced lactate as an end product. The lactate is buffered and at a higher lung volume than healthy subjects. Thus, to attain the minute ventilation necessary to maintain blood gas homeostasis during exercise, COPD patients have to inspire faster, with a greater tidal volume, and at a higher lung volume than healthy subjects.

### Quandriceps Myopathy

Although peripheral muscle weakness has long been a recognized feature of patients with airflow limitation who are treated with steroids,21 it has been appreciated that changes occur in the quadriceps muscles of patients with COPD that cannot be explained readily by steroid therapy. Thus, the quadriceps of patients with COPD are weaker than those of aged-matched control subjects,24 irrespective of recent (ie, the preceding 6 months) steroid exposure.

A histologic examination of biopsy specimens obtained from the quadriceps of patients with COPD has shown a loss of aerobic type I fibers25 and a reduction in oxidative enzymes.26 This suggests that COPD patients should switch into anaerobic metabolism at a lower level of exercise than control subjects, an observation confirmed in an elegant study by Maltais et al.26 Anaerobic metabolism produces lactate as an end product. The lactate is buffered by bicarbonate with the release of CO₂, which in turn imposes an additional load on the respiratory muscle pump. An additional complication of anaerobic metabolism is that it makes the muscle more susceptible to fatigue, and recent data confirm that low-frequency fatigue complicates exercise in patients with COPD.27 The observation that isolated limb muscle performance can be improved by improving oxygen delivery, and therefore that the quadriceps muscles have significant metabolic reserve,28 does not in this author’s view exclude the possibility that anaerobic limb muscle metabolism represents a significant additional load for exercising COPD patients.

The cause of the myopathy remains controversial. Some investigators believe that the quadriceps myopathy is due to immobility, and this viewpoint is supported by the finding that weakness in the quadriceps muscle is greater than that in other muscle groups.24 However, other factors that are hypothesized to contribute to this include undernutrition, androgen deficiency, and inflammatory processes.

Data have suggested that quadriceps function could be related to prognosis in COPD patients. It has long been appreciated that quadriceps strength is related to body weight,29 and it is recognized that a low body mass index in COPD patients confers a poor prognosis.30 Moreover, in those patients who succeed in increasing their body mass index, prognosis is improved.30 It is also recognized that health-care utilization in COPD patients is related to the severity of their COPD.31 Intuitively, it is unlikely that quadriceps weakness is a cause of mortality or morbidity but, rather, that this is simply a marker of more severe disease or of underlying cachetic mechanisms.

### Treatment Options

For patients with established COPD, treatment options aimed at redressing the load-capacity balance should be beneficial.

#### Improving Inspiratory Muscle Function

The following two treatments can have isolated effects on inspiratory muscle function: inspiratory muscle training and surgery (ie, lung volume reduction surgery and transplantation).

Inspiratory muscle training is widely considered to be a component of pulmonary rehabilitation. Nevertheless, it is of interest that a meta-analysis of training regimes in COPD patients concluded that the data provided little support for this treatment, while, more recently, a controlled randomized study of 30 patients with COPD failed to find an increase in maximal inspiratory pressure in patients with COPD.33 Using phrenic nerve stimulation, we have recently been unable to document an increase in TwPdi following inspiratory muscle training.34

Lung volume reduction surgery and transplantation are therapies for the palliation of dyspnea in patients with advanced COPD.35 Since end-expiratory lung volume is reduced by these procedures, diaphragm function is improved, but the improvements do not follow surgery directly and are not clearly predicted by the magnitude of lung volume change.36,37 Both of these procedures also reduce the load on the system, which also would redress load-capacity imbalance.

#### Load Reduction

Therapy with bronchodilators reduces expiratory flow limitation and therefore limits dynamic hyperinflation during exercise.9 It is this author’s opinion that this mechanism explains many patients’ clear symptom bene-

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Table 1—Causes of Increased Respiratory System Load in COPD Patients*

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<tr>
<th>Respiration</th>
<th>Causes of Increased Load</th>
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<tbody>
<tr>
<td>At rest</td>
<td>Need for increased tidal volume (V/Q mismatch and increased alveolar dead space) Reduced chest wall compliance (higher portion of pressure-volume curve) Increased airway resistance</td>
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<tr>
<td>During exercise</td>
<td>Inspiratory flow rate is increased (because respiratory rate increases and Ti/Ttot shortens) Frequency dependent decrease in lung and chest wall compliance Increased CO₂ generation from anaerobic metabolism in limb muscle</td>
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*V/Q = ventilation/perfusion; Ti/Ttot = inspiratory time/total breathing cycle time ratio.
fits from therapy with bronchodilators, despite the lack of measurable increase in FEV₁ or peak expiratory flow rate.

**Improving Respiratory and Peripheral Muscle Function**

Therapy with methylxanthines and digoxin has been reported to increase contractility, and therapy with β-agonists may protect against fatigue for skeletal muscle *in vitro* (for a discussion see Polkey and Moxham[39]). None of these drug groups have *in vivo* effects at clinical doses.39—41

Anabolic steroids are effective in increasing skeletal muscle mass in healthy subjects,42 especially when combined with exercise. However, a trial of nandrolone decanoate vs nutrition (either alone or together) against placebo failed to show a convincing benefit in COPD patients.43 A second trial of oral stanozolol in COPD also failed to show a conclusive benefit.44

Growth hormones enhance protein synthesis, nitrogen retention, and muscle growth. The value of growth hormone therapy in COPD patients was evaluated in a nutrition-standardized, randomized, controlled study,45 and no clinical benefit was shown.

Nutritional supplementation in COPD patients, if successful, improves prognosis.30 However, it can be difficult for COPD patients to gain weight,46 and repeated studies47 have shown that diaphragm function is not different between normally nourished and undernourished COPD patients.

**Pulmonary Rehabilitation**

Pulmonary rehabilitation is clearly effective when judged by the number of hospital admissions or the use of health-care resources.48 Its mode of action remains unclear, however. It has been shown49 that in patients with mild-to-moderate COPD a high-intensity training program results in a true training benefit (*ie*, for a given workload, less anaerobic metabolism occurs). Moreover, this change is accompanied by increases in the levels of oxidative enzymes,50 suggesting that changes in peripheral muscles can indeed extend exercise tolerance in COPD patients. Interestingly, this effect cannot be replicated in patients with severe COPD51 who mainly benefit by altering their pattern of breathing to minimize dead space.

**Future Directions**

Novel therapies should aim to prevent the conversion of limb muscle from aerobic to anaerobic metabolism. This implies a prevention of the loss of contractile proteins and of the loss of oxidative capacity. Presently, aggressive pulmonary rehabilitation seems to be a risk-free therapy method that is acceptable to patients, but this technique is not applicable to patients with severe COPD, who would most benefit from therapy. An interesting direction has been suggested by the observation that a systemic inflammatory response is present in some patients with COPD. In particular, weight change in response to a refueling program has been shown52 to depend in large part on the presence or absence of a systemic inflammatory response that is manifested by the presence of a soluble tumor necrosis factor receptor. Theoretically, therefore, the suppression of this response could slow a decline in peripheral muscle function in COPD patients.

**REFERENCES**


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