The Systemic Nature of Chronic Lung Disease

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KEYWORDS

• Chronic obstructive pulmonary disease • Pulmonary rehabilitation • Systemic manifestations • Dyspnea • Comorbidity • Exercise

KEY POINTS

- Chronic obstructive pulmonary disease (COPD) can be considered as a multisystem syndrome rather than solely a disease of the lungs.
- Systemic manifestations include skeletal muscle impairment, osteoporosis, mood disturbance, anemia, and hormonal imbalance.
- Pulmonary rehabilitation targets the secondary consequences (systemic manifestations) of COPD.
- The causes of these secondary consequences include inactivity, systemic inflammation, hypoxia, and corticosteroid treatment.
- Individuals with COPD often have a wide range of comorbidities including cardiac disease, obesity, and metabolic syndrome, but this should not prevent referral or acceptance for pulmonary rehabilitation.
- Exercise training is also usually indicated for these comorbidities, but the assessments for safety may need some attention.
- Pulmonary rehabilitation is the only therapy that targets all aspects of the COPD syndrome, and access to the key components of exercise training and education should be equitable, although how this is delivered may vary across the spectrum of disease.

INTRODUCTION

Dyspnea on exertion is the commonest symptom of chronic lung disease. Chronic obstructive pulmonary disease (COPD) is the commonest chronic lung disease, and serves as an illustrative example of how progressive airflow limitation contributes to an inability to match the ventilatory demands of exercise. This inability is due to hypoxia, gas trapping and dynamic hyperinflation,[1] and increased mechanical disadvantage of the respiratory muscles. However, in severe disease the degree of airflow obstruction correlates poorly with exercise ability.[2]

Early trials of rehabilitation were deemed to be unsatisfactory by many because they did not improve lung function.[3,4] The first appropriately designed randomized controlled trial of pulmonary rehabilitation to gain attention compared exercise performance and quality of life with normal care.[5] The degree of dyspnea was reduced and the walking distance increased in patients undergoing pulmonary rehabilitation, but there was no difference in the degree of airflow obstruction. This finding led to the recognition over the next couple of decades that COPD was not solely a disease of the lungs but also was associated with significant systemic alterations, including skeletal muscle impairment, mood disturbance, hormonal imbalance, osteoporosis, and anemia (**Box 1**).

It is now understood that the benefits of pulmonary rehabilitation come from the improvements that can be made on these secondary effects. There is ongoing debate about the exact mechanisms causing these alterations, but physical

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Box 1
Systemic manifestations of COPD

- Skeletal muscle
- Mood disturbance
- Hormonal imbalance
- Others: osteoporosis and anaemia

inactivity leading to deconditioning, systemic inflammation, hypoxia, and medication have all been implicated. COPD is a heterogeneous disease that can be thought of as a syndrome, and it is likely that causes vary between individuals in their predominance.

Pulmonary rehabilitation programs are traditionally composed of hospital-based supervised programs aimed at patients with noticeable dyspnea. However, recent evidence suggests that these secondary manifestations can occur early in the disease,[6] so perhaps physical inactivity should be targeted earlier in the disease to prevent future disablement.

Apart from the secondary manifestations of the disease, patients with COPD may also have multiple comorbidities,[7] which can cause reluctance to refer for rehabilitation. Cardiac disease (ischemic heart disease and chronic heart failure) is more prevalent in COPD than in the rest of the population even after confounding factors have been addressed. Other comorbidities such as abdominal aortic aneurysm can lead to debate over whether exercise training is safe. Obesity and metabolic syndrome are highly prevalent in COPD, perhaps even to a greater extent than in the rest of the population. There is evidence that some comorbidities may be also be part of the secondary consequences of the disease, but for the purposes of this article they are discussed separately.

SYSTEMIC MANIFESTATIONS OF COPD

Skeletal Muscle Impairment

One of the first randomized trials of pulmonary rehabilitation versus normal care noted that despite the improvement in walking distance, the degree of airflow obstruction was unchanged.[5] At a similar time leg fatigue was shown to be a very common limiting symptom to a maximal incremental cardiopulmonary exercise test on a cycle ergometer.[8] Subsequently, several studies have demonstrated that the structure of the quadriceps muscle is altered with a reduction in muscle mass and strength in COPD,[9] and is associated with a higher mortality[10,11] and morbidity, in addition to increased hospital admissions.[12] The muscle quality is also impaired; there is preferential reduction in the type I fiber cross-sectional area in the quadriceps muscle in COPD, and reduced oxidative enzyme concentration,[13–15] mitochondrial density,[16] and capillary density.[14] These adaptations reflect a loss of the aerobic profile of the muscle, which is exemplified during cycling exercise whereby individuals with moderate COPD achieve an earlier anaerobic threshold,[17] and muscle-energy requirements are unable to be met with a resultant decline in phosphocreatine and adenosine triphosphate at very low absolute power.[18] These metabolic impairments of the muscle demand an increase in ventilation on an already burdened system, causing the termination of exercise. Other supporting evidence of a peripheral muscle contribution to exercise limitation in COPD includes quadriceps contractile fatigue after whole-body exercise[19,20] and worsening exercise performance with "prefatigue" of the quadriceps muscles.[21] Lower limb aerobic and strength training are therefore essential components of a pulmonary rehabilitation program.[22,23]

Although most evidence for skeletal muscle impairment has been concentrated on the lower limbs, there is also evidence that the upper limb muscles, both proximal and distal, are weaker than healthy controls.[24]

There is debate about whether there is true weakness of the respiratory muscles in COPD. Inspiratory muscle strength measured by maximal inspiratory pressure is reduced in COPD, but the expiratory muscle strength can be preserved or reduced.[25] Isolated diaphragmatic strength has been shown to be preserved in COPD assessed by twitch transdiaphragmatic pressure when corrected for lung volume.[26] Hyperinflation leads to the muscles being put at a mechanical disadvantage. Regarding fiber type proportion, the opposite phenomenon is seen in the diaphragm muscle fibers compared with the quadriceps fibers as the type one fibers are increased compared with healthy controls.[27] In COPD, diaphragmatic strength is not fatigued by either endurance exercise to symptom limitation or hyperventilation suggesting that it is not a major limiting factor to exercise capacity.[28–30]

Mood Disturbance

Mood disturbance is very common in COPD and is a major contributing factor to morbidity.[31] Anxiety heightens the sensation of breathlessness and compounds the reduced exercise capacity. In itself this can lead to low mood and