Point:Counterpoint: The major limitation to exercise performance in COPD is: 1) inadequate energy supply to the respiratory and locomotor muscles, 2) lower limb muscle dysfunction, 3) dynamic hyperinflation.

THE MAJOR LIMITATION TO EXERCISE PERFORMANCE IN COPD IS INADEQUATE ENERGY SUPPLY TO THE RESPIRATORY AND LOCOMOTOR MUSCLES

No doubt dynamic hyperinflation and lack of oxidative capacity of skeletal muscles are important causes of exercise limitation in COPD. O'Donnell and Webb and Debigare and Maltais will convince the reader of this by the elegant experiments they have performed. The thesis we will put forward is that during the natural history of COPD the primary factors leading to impairment of exercise performance are an increase in energy demands combined with a decrease in supplies and that both of these result from excessive recruitment of expiratory muscles. We argue that both dynamic hyperinflation and reduced oxidative capacity are secondary adaptations resulting from this primary abnormality.

Increased energy demands during exercise in COPD. Energy demands are increased in COPD because of the high O2 cost of breathing (V\text{O}_2\text{resp}). In health, V\text{O}_2\text{resp} is only 1–3 ml O2/l breathed, whereas in COPD it has been reported variously to average 6.3, 9.7, and 16.4 ml/l breathed with individual values ranging from 3.0 to 19.5 ml/l (8, 17).

The large between patient range in V\text{O}_2\text{resp} probably reflects variation in the work of breathing (W\text{resp}). During exercise, a large variation in W\text{resp} certainly exists. In two studies, COPD patients formed two distinct groups: those that strongly recruited abdominal muscles and those that did not (5, 10). In the first (5), at an exercise workload of 10 W the work performed on the lung averaged 754 cmH2O l/s, while in recruiters but only 277 cmH2O l/s in nonrecruiters, although ventilation was similar. Expiratory muscle activation is the normal response to exercise (1) so the recruiters behaved normally. The problem is that in COPD, it fails to increase ventilation, because expiratory flow becomes limited by high pleural pressures. While abdominal muscle recruitment is beneficial during exercise. Let’s also assume that it was 12 ml O2/l in the former and 20 ml/l in the latter. The maximal exercise workload (W\text{max}) was 20 and 35 W in recruiters and nonrecruiters (P < 0.05), while Ve at W\text{max} was 35.9 and 37.9 l/min, respectively (5). Thus the estimated V\text{O}_2\text{resp} was 430.8 ml/min in recruiters but only 227.4 ml/min in nonrecruiters. From the measured values of V\text{O}_2 at rest and during 10 W exercise and assuming that V\text{O}_2 increased linearly (dV\text{O}_2/dwatt is constant) the V\text{O}_2 at maximal exercise workload (V\text{O}_2\text{max}) was 830.0 and 1,327.5 ml O2/min, respectively, in recruiters and nonrecruiters. Subtracting V\text{O}_2\text{resp} from V\text{O}_2\text{max} reveals that if the respiratory muscles received all their demands there was only 399.2 ml O2 available to locomotor muscles and other body tissues in recruiters but 1,100.1 ml in nonrecruiters. The respiratory muscles demanded 53% of V\text{O}_2\text{max} in recruiters but only 17%, a value close to normal (6), in nonrecruiters.

The nonrecruiters’ breathing pattern was abnormal because abdominal muscles were not recruited during exercise. As a result, their exercise performance was better. However, their resting lung function was worse. Both the FEV1 and FEV1/ FVC were significantly lower in nonrecruiters. This strongly suggests that as COPD progresses, patients eventually realize that abdominal muscles recruitment is bad and somehow they learn to derecruit them. Alas, without abdominal muscle contraction they dynamically hyperinflate. They can exercise a bit more, but not much (15). Thus we believe that dynamic hyperinflation results from a learned response to an inadequate supply of energy to meet demands.

Decreased energy supplies during exercise with expiratory flow limitation. When normal subjects breathe with a Starling resistor in the expiratory line, which limits expiratory flow to ~1 l/s, exercise is limited by severe dyspnea: abdominal pressure (P\text{ab}) increases abnormally; duty cycle decreases; CO2 retention occurs, increasing P\text{ab}, even more (3, 13, 14); the high expiratory pressures and short duty cycle act like a Valsalva maneuver and decrease cardiac output (Q\text{c}) (2); as a result, O2 debt is increased by 52% (22). Expiratory flow limitation (EFL) decreases the shortening velocity of abdominal muscles, and, in accordance with their force velocity characteristics P\text{ab} increases (3). Expiratory muscle recruitment can account for 66% of the variation in Borg scale ratings of difficulty in breathing (14). None of these abnor
malities can be attributed to either dynamic hyperinflation or impaired oxidative capacity of skeletal muscles.

Does this scenario occur in COPD? There is strong evidence that it does. First, there is uniform agreement that lactic acid production occurs at a very low exercise level in COPD. This suggests an imbalance between energy supply and demand, resulting in competition between respiratory and locomotor muscles for limited energy supplies (9, 12, 20). Administration of O₂ improves exercise performance probably by decreasing VO₂resp (7), thereby releasing more energy for locomotor muscles. This improvement should not occur if skeletal muscles were unable to use the energy available to them. Richardson et al. (19) showed that in small muscle mass exercise in COPD there was a 2.2-fold greater mass-specific power output than during whole body exercise. Locomotor muscles have a greater maximal power output in the absence of respiratory-locomotor muscle competition, Oelberg et al. (18) reported a Q'c of only 39% of predicted during exercise in COPD and when heliox was breathed, decreasing VO₂resp and increasing the energy available to locomotor muscles, VO₂ increased by 15% without any change in Q’c (18). If the respiratory muscles in recruits demand 53% of VO₂max, they probably demand the same share of Q’c (6), and if Q’c is only 39% predicted, locomotor muscles must be pretty ischemic. Finally Francois (21) himself reported a plateau in lower limb perfusion while exercise workload increased in COPD.

If inadequate energy to meet demands limits exercise in COPD, why is the oxidative capacity of skeletal muscles reduced? The obvious answer is that disuse and lack of energy supplies (tissue hypoxia) cause the enzymatic changes and mitochondrial abnormalities responsible for decreasing oxidative capacity. Again there is strong evidence that this is so [see Gosker et al. (11) for an outstanding review]. The myopathic changes in congestive heart failure and COPD are almost identical. They do not occur in the diaphragm because there is no disuse of this muscle. There is no reason to believe that myopathy is a primary abnormality in COPD and congestive heart failure and every reason to believe that it is secondary to disuse and tissue hypoxia. Francois refers to this when he states “...a comparable disorder has been described in chronic heart failure. Chronic reduction in oxygen availability at the cellular level...could contribute to...skeletal muscle dysfunction” (16). Francois also recognized the potential importance of respiratory-locomotor muscle competition when he wrote that in COPD “...the respiratory muscles, with [high] VO₂ during exercise...might...compete with lower limb muscles for the available blood flow and O₂.” (21). Yes, reduced oxidative capacity, like dynamic hyperinflation, can limit exercise performance in COPD, but it is secondary to a longstanding imbalance between energy supply and demand.

We believe the long natural history of COPD results in the sequence of events during exercise shown in Fig. 1. The primary event, EFL during exercise, probably occurs when the disease is still mild and exercise is not seriously impaired. This in turn leads to an increase in force generation of expiratory muscles increasing expiratory pressures from which all the pathophysiology described above derives.

REFERENCES

Morphological and biochemical evidences of lower limb muscle dysfunction in COPD. The prevalence of lower limb muscle atrophy in COPD ranges from 21 to 45% depending on the population being investigated and its operational definition (23, 27). Unexpectedly, muscle atrophy can even be present in patients with normal body weight (27). Reduced functional status and low level of physical activity predict poor quality of life (24), high healthcare use (7), and mortality (9) in these patients. A comprehensive understanding of the mechanisms of exercise intolerance is therefore of utmost importance to impact on these adverse outcomes and modify the evolution of the functional impairment associated with COPD.

Respiratory impairment is not sufficient in itself to explain exercise intolerance in COPD. The weak correlation between FEV1 or inspiratory capacity and exercise tolerance implies that other factors must be involved (21, 14). In 1992, Killian and collaborators (15) published a landmark paper that draws attention to the impact of the lower limb muscles on exercise intolerance in COPD. They reported that leg discomfort was a frequent exercise-limiting symptom invoked by these patients after a standardized cycling protocol. The report was the foundation of the rationale used by scientists to investigate lower limb muscle dysfunction in COPD. At that time, no one could have predicted how vast this research area would develop.

Although the ventilatory system is clearly dysfunctional in COPD, we will demonstrate that peripheral limitation to exercise tolerance is frequent in patients with COPD. To persuade the reader, morphological, biochemical, and clinical evidences demonstrating causal relationship between lower limb muscle dysfunction and exercise limitation will be exposed. We will focus on the tolerance to submaximal exercises, which are particularly influenced by the function and aerobic capacity of the lower limb muscles (3).

Morphological and biochemical evidences of lower limb muscle dysfunction in COPD. The prevalence of lower limb muscle atrophy in COPD ranges from 21 to 45% depending on the population being investigated and its operational definition (23, 27). Unexpectedly, muscle atrophy can even be present in patients with normal body weight (27). Given that muscle strength is mostly determined by muscle mass, muscle weakness is therefore highly prevalent in COPD (4, 11). Patients with COPD also have a poor resistance to isolated leg exercises and increased susceptibility to muscle fatigue (16), two correlates of impaired exercise capacity (1). In parallel, altered muscle energy metabolism as assessed by 31P magnetic resonance spectroscopy (30) has also been correlated to reduced exercise capacity in patients with COPD (30).

Muscle atrophy and impaired energy production are accountable for muscle weakness and increased susceptibility to fatigue, two strong determinants of exercise capacity (13). The physiological link between weakness, leg fatigue, and exercise intolerance was elegantly illustrated by Hamilton and colleagues (12). They evaluated the relationship between the perception of leg fatigue, work capacity, and muscle strength in normal individuals and patients with lung diseases, most of whom had COPD. Three interrelated observations, valid in healthy individuals and patients with lung diseases, were made: 1) for a given power output, the perception of leg fatigue was greater in weaker compared with stronger individuals, 2) peak exercise capacity was reduced in weak individuals, and 3) the strength of the quadriceps was a key determinant of exercise capacity, independent of the impairment in lung function.

Convincing biochemical data also support the thesis that lower limb muscle dysfunction is a major contributor to exercise intolerance in COPD. At the cellular level, several morphological and structural modifications have been observed in the quadriceps of patients with moderate to severe COPD (2). These changes substantially compromise the metabolic performance and work output of activated muscles during exercise. Specifically, the morphological changes observed include reduction in type I fiber proportion (28) as well as reduction in cross-sectional area (CSA) for type I and II fibers (10, 28) that is proportional to the reported reduction in mid-thigh cross-sectional area (4). This former observation suggests that contractile protein deficit is largely responsible for both muscle atrophy and weakness and thus contribute to impaired exercise capacity.

The muscle structural and energetic changes described in COPD involve a reduction in myosin heavy chain I proportion (19) and a decrease in oxidative enzyme activities (10, 17, 18), a strong determinant of muscle endurance (1). Reduced oxidative metabolism correlates significantly with peak exercise capacity independently of lung function impairment (17). Early reliance on glycolytic activity for the energy production results in higher accumulation of inorganic phosphate (30) and premature muscle acidosis from lactate production (18), two biochemical events compromising the ability to sustain repeated muscle contractions and exercise performance. These adaptations seen in COPD are indicative of a muscle tissue that is inappropriately adapted to sustain the metabolic and mechanical requirements of submaximal exercises as seen in daily functional activities and provide a strong muscular basis to lower limb muscle dysfunction and exercise intolerance in COPD.

Clinical evidences of lower limb muscle dysfunction in COPD. Exercise intolerance in COPD is the result of a complex interplay between central (ventilation, dynamic hyperinflation, dyspnea) and peripheral (muscle atrophy and weakness, fatigue) factors. Although the relative contribution of these components to exercise intolerance is difficult to sort out within a single patient, clinical models illustrating the role of the lower limb muscles are available.

Undisputable evidences of peripheral limitation in exercising patients with COPD were provided by Williams and collaborators (29), who found that exercise limitation persisted in single and double lung transplant recipients years after the surgery despite complete restoration of their ventilatory capacity.

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