Review

Exercise Limitation in COPD

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SUMMARY. Exercise tolerance is reduced across all stages of chronic obstructive pulmonary disease (COPD) and this is coupled with numerous negative outcomes. Exercise-limiting factors in patients with COPD can be summarized as 1) imbalance between ventilatory capacity and demand, 2) imbalance between oxygen supply to respiratory and peripheral muscles and demand and 3) peripheral muscle dysfunction. This clinical review article addresses the phenomenon of the impaired exercise capacity in COPD, explores the main underlying pathophysiological mechanisms and attempts to provide the reader with an overview of the way these mechanisms intergrade to generate this deleterious effect. *Pneumon 2013, 26(3):245-256.*

INTRODUCTION

There is evidence for decline in physical activity across all stages of chronic obstructive pulmonary disease (COPD) compared with normal controls[1] and reduced level of physical activity is inversely related to lung function and its rate of decline[2], levels of systemic inflammation[3], hospitalizations[4] and mortality[5]. Gaining an insight into the mechanisms involved in exercise limitation in COPD is therefore of paramount importance and will allow the design of effective therapeutic interventions either in the form of pharmaceutical therapy or rehabilitation programs. Along these lines, this review article addresses the phenomenon of the impaired exercise capacity in COPD, explores the main underlying pathophysiological mechanisms and attempts to provide the reader with an overview of the way these mechanisms intergrade to generate this deleterious effect.

EXERCISE PHYSIOLOGY IN BRIEF

Exercise prompts the mounting of the appropriate amount of oxygen from the external environment to the hemoglobin molecules of red blood cells (ventilation and alveolar-capillary diffusion: the function of the pulmonary system). Oxygen is then transported to the muscle cells (cardiac output and blood flow: the function of the heart and cardiovascular system but also concentration of hemoglobin and the shape and position of the oxygen dissociation curve; the function of the blood). In the muscle

cells, aerobic oxidative phosphorylation takes place to produce energy in the form of adenosine triphosphate (diffusive oxygen transport from the microcirculation to the mitochondria and utilization of oxygen for energy production; the function of the muscles). Carbon dioxide (CO2) which is also co-produced, should then flow in the opposite direction through the same organ systems until it is exhaled to the external environment. Disorders of any of these organ systems or abnormal coordination interaction or between them will result in exercise limitation, i.e., inability to achieve the predicted maximum exercise capacity for a given individual[6,7]. Such is the level of complexity of this cascade that exercise limitation is rarely ascribable to any single structural or functional abnormality, in health or in disease[8].

INTRODUCTION TO EXERCISE LIMITATION IN COPD AND CLINICAL IMPLICATIONS.

In a pathophysiologically heterogeneous clinical entity such as COPD (extending from pure emphysema to pure chronic bronchitis), which is usually accompanied by various comorbidities[9] and sustains the concomitant effects of aging on physical performance the prevailing determinants of impaired exercise capacity typically varies among patients[10-12]. More commonly, exercise intolerance in COPD is multifactorial and its mechanisms are necessarily complex as most likely there exist highly variable combinations of impairment of one or more of the contributing systems that are unique to the individual and can dominate the scene on a given moment in the natural history of COPD[13].

For purposes of simplicity however, exercise-limiting factors in patients with COPD can be summarized as 1) imbalance between ventilatory capacity and demand, 2) imbalance between oxygen supply to respiratory and peripheral muscles and demand and 3) peripheral muscle dysfunction[14]. These adverse factors interfere with the normal in-series system (ventilation, gas exchange, blood flow, hemoglobin, muscle O2/CO2 transport and O2 utilization/CO2 production) from which exercise depends, thereby ultimately preventing adequate oxygen transfer to, and/or utilization of oxygen by mitochondria.

In practice, the principal exercise-limiting symptoms stemming from the impaired exercise physiology in COPD are dyspnea and/or leg fatigue. Dyspnea most likely stems from the mismatch between the low ventilatory capacity and high ventilatory work/requirement in patients with COPD[15], whereas exercise-induced leg (muscle) fatigue is believed to be consequent to compromised oxygen transport to the locomotor muscles and/or intrinsic muscle abnormalities[16,17]. In terms of their relevant frequency, evidence suggests that it commonly depends on disease severity. Combined data from clinical studies suggest that COPD patients with GOLD stages III and IV cease exercise primarily due to intense dyspnea sensation (70% of patient population) and to a lesser extend due to leg discomfort (20%) or a combination of dyspnea and leg discomfort (~10%). In contrast, COPD patients with GOLD stage I and II stop exercise primarily due to leg discomfort (40-60%) and to a lesser extend due to intense dyspnea sensation (25%) or a combination of the two symptoms (15-35%)[14]. Therefore, it is possible that in a substantial proportion of patients with advanced COPD, exercise limitation is primarily due to imbalance between ventilatory capacity and demand and to a lesser extend due to inadequate energy supply to locomotor muscles and/or locomotor muscle dysfunction. The opposite seems to hold truth for patients with mild and moderate COPD, although, the presence of ventilator constraints such as resting lung hyperinflation in early disease[18] cannot not be dismissed.

In any case, the development of troublesome symptoms during exercise signifies more advanced stages of the COPD. For example, the presence and intensity of dyspnea is associated with airway and parenchymal abnormalities, increased ventilatory requirements, dynamic hyperinflation, increased respiratory effort-lung volume displacement ratio (see later) and, eventually, reduced exercise performance compared with healthy controls[18,19]. Patients experiencing dyspnea also tend to have more accelerated progression of airflow obstruction while those who are asymptomatic are less likely to have progressive disease[20].

1. Imbalance between ventilatory capacity and demand

As already outlined, the disparity between the decreased ventilatory capacity in COPD, which is manifested by diminished maximum and sustainable voluntary capacity at rest and eventually by the inability to sufficiently increase minute ventilation during exercise, and the increased ventilatory requirements lead to intense dyspnea sensation (Figure 1).

1.a. Reduced ventilatory capacity

In COPD, structural abnormalities of the lung archi-

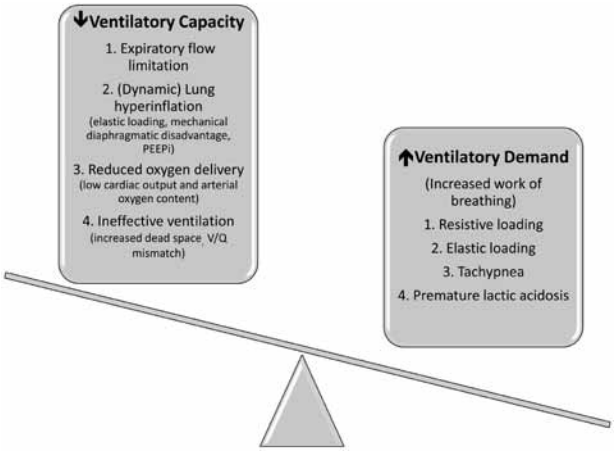

FIGURE 1. The imbalance between ventilatory capacity and demand commonly leads to sensation of dyspnea in exercising COPD patients.

tecture cause mechanical derangements that limit the ventilatory capacity by increasing the work and, consequently, the oxygen cost of breathing. Most of the mechanical constraint that is imposed on COPD patients at exercise derives from the unfavorable sequence of increased airway resistance, expiratory flow limitation (EFL) and lung hyperinflation.

The increased airway resistance due to the combined effects of excessive mucus in the bronchial lumen, thickening of the wall by inflammatory changes (chronic bronchitis) or reduced elastic lung recoil (emphysema) gives rise to EFL, the pathophysiological hallmark of COPD. When EFL is present during resting spontaneous breathing, air trapping occurs and end-expiratory lung volume varies with the mechanical time constant for emptying (i.e., the product of compliance and resistance) of the respiratory system, the inspired tidal volume, and the expiratory time available (i.e. breathing frequency)[12]. *Static lung hyperinflation* refers to the resetting of the respiratory system's relaxation volume to a higher level. The existence of significant lung hyperinflation at rest means that the patient's ability to increase ventilation when the situation demands (e.g., exercise) is seriously curtailed (see later)[12,21]. Additional factors may also contribute to the EFL development in COPD by reducing the expiratory flow reserve in the tidal volume range including lung senescence and breathing at low-lung volume (near residual volume) as is frequently observed in comorbidities such as morbid obesity, chronic congestive heart failure and restrictive diseases of the thoracic cage[21].

During exercise, increased ventilatory demand often leads to further air trapping in flow-limited patients due to the combined effect of increased inspired tidal volume and reduced expiratory time[22]. Accordingly, COPD patients do not have enough time to breathe out all the inspired volume when the subsequent inspiration begins. This temporary and variable additional increase in end-expiratory lung volume that occurs when ventilation is acutely increased is termed *dynamic lung hyperinflation (DH)* and occurs despite the active recruitment of expiratory muscles in a vain attempt to increase expiratory flow[12].

DH has often been regarded as a compensatory mechanism that allows the lungs to reach higher possible volumes thus greater pulmonary stretching and radial airway traction, minimize airway collapsibility and, more importantly, achieve higher expiratory flow rates, reduce the expiratory time required to completely exhale the inspired air volume and ultimately, prevent air-trapping. However, the development of exercise-induced DH imposes major mechanical disadvantages on the respiratory system that synergistically increase the work of breathing, lead to premature fatigue of the respiratory muscle and dyspnea and, ultimately, limit the exercise capacity. Firstly, it shifts the tidal volume to the upper and more flat extreme of the pressure-volume relationship of lung where the inspiratory muscles have to generate greater pressures to pump the same volume (i.e. reduced compliance), thereby increasing elastic loading of the inspiratory muscles [23]. Moreover, since total lung capacity remains unchanged during exercise, an increase in the ratio of end-inspiratory lung volume to total lung capacity indicates a decrease in inspiratory reserve volume and thus restriction in tidal volume expansion that is anticipated to intensify dyspnea sensations[19]. During incremental exercise in COPD inspiratory reserve volume progressively decreases toward the point of exercise termination to values lower than 200 mL whereas healthy age-matched subjects maintain 3-fold higher (600 mL) inspiratory reserve volume at peak exercise[24]. In some patients, this mechanical constraint on tidal volume expansion in the setting of severe pulmonary ventilation/perfusion (V/Q) abnormalities (see later) leads to CO2 retention and arterial oxygen desaturation during exercise[25]. Secondly, owing to DH, the diaphragm is pushed downward and is flattened, so its resting length becomes shorter. The other inspiratory muscles also become shorter, thus causing substantial mechanical disadvantage, decrease of tension generation capability and weakness for the same neural stimulus. Consequently, greater central neural activation is

required and greater effort is necessitated on behalf of the respiratory muscles to produce the same pressure[26]. Thirdly, DH is associated with intrinsic positive end-expiratory pressure (PEEPi). Under such circumstances, inhalation must be initiated from a volume above the relaxation volume and the inspiratory muscles must lower pleural pressure substantially before alveolar pressure becomes subatmospheric and inspiratory airflow is enabled. PEEPi, thus represents an additional inspiratory threshold elastic load that must be overcome for inhalation to be initiated and exacerbates the intensity of dyspnea[27]. Last but not least, DH adversely affects cardiac function (see later).

In terms of the timing that DH develops during exercise and its magnitude, no scientific consensus has been reached yet. Depending in the method of measurement, some studies have shown that DH increases with increasing exercise intensity (ranging between 250 and 500 mL) whereas others that COPD patients hyperinflate only at the end of exercise bouts or that hyperinflation increases mildly (by 150 mL) only at peak exercise or remains either constant or actually falls with increasing exercise intensity as it is commonly seen in healthy subjects[14].

An additional aggravating factor for the exercise ventilatory capacity in COPD patients is the inadequate oxygen supply to the hardly working respiratory muscles due to (a) limitation in the normal increase in cardiac output, (b) reduced arterial oxygen content, and (c) competition for the limited blood flow between the respiratory and locomotor muscles during exercise[14] (see later).

1.b. Increased ventilatory demand

Several studies have confirmed high submaximal ventilation levels during exercise in COPD compared to healthy individuals. Typically, minute ventilation increases progressively with increasing exercise intensity in COPD in such a manner that the relationship between ventilation and work rate or oxygen uptake often has a sharper slope when compared to that recorded in healthy individuals[28].

Many COPD patients adopt a pattern of rapid and shallow breaths both at rest and during exercise compared to normal subjects[19] that reflects the mechanical constraints on tidal volume expansion imposed by DH. In other words, COPD patients rely mainly on respiratory frequency to increase their ventilation. However, rapid breathing reduces the exhalation time thus promoting further air trapping and ultimately, rebounds to cause further DH and decreased lung compliance. In other words, the faster one breathes in COPD, the less the lung compliance becomes reaching levels as low as 0.05 $l \cdot cmH_2O^{-1}$ during intense exercise[29], values usually only seen in pathologically stiff lungs. Eventually, the dependence of lung compliance to the breathing frequency leads to a progressively increased demand for power output on behalf of the respiratory muscles as breathing rate increases; this aggravates dyspnea and limits exercise performance[30].

From an energetic point of view, rapid shallow breathing in COPD is diametrically opposite to the pattern resulting in minimal work. Given the lung hypercompliance due to loss of elastic recoil and the airway obstruction in COPD, a slow deep breathing pattern should result in minimal work. Such a breathing pattern takes advantage of the small pressures required to overcome the elastic recoil of the emphysematous lung, while minimizing the pressures required to produce flow through the obstructed airways. This should diminish dyspnea and improve exercise performance but, unfortunately, very few patients manage to breathe this way[14].

Other factors also contribute to the increased ventilator drive in COPD including increased alveolar dead space ventilation, increased V/Q mismatch, impaired gas exchange, alveolar hypoxia and hypoxemia and the absence of the naturally occurring reduction of physiological dead space during exercise[14]. Furthermore, premature metabolic lactic acidosis has been described during exercise in COPD, representing a powerful additional stimulus to ventilation (see later)[31].

2. Imbalance between oxygen supply to peripheral and respiratory muscles and demand

2.a. Increased oxygen requirement of the respiratory muscles

By this point it should be clear that, for a given exercise workload, COPD patients generate a considerably greater work of breathing than their healthy counterparts owing to the greater ventilation *per se* and also the higher oxygen cost per liter of ventilation.

In healthy individuals, the oxygen cost of breathing is only 1 to 3 mL O2/L breathed[32], whereas in COPD, it has been reported variously to average 6.3, 9.7, and 16.4 mL O2/L breathed with individual values ranging from 3.0 to 19.5 mL O2/L breathed[32,33].

2.b. Impairment in cardiac output due to negative mechanical interactions between respiratory and cardiovascular system

The high expiratory intrathoracic pressure (ITP) gen-

erated by COPD patients against the increased elastic and resistive breathing loads act synergistically with *DH* to produce a range of hemodynamic effects (Table 1). To start with, high ITP above those required to produce maximal expiratory flow rates, not only is wasted in the sense that no extra airflow will be generated in the face of severe EFL but also decreases venous return (preload) to the right ventricle (RV) thus reducing RV stroke volume[34]. The underlying mechanisms of this effect are complex and seem to extend well beyond the increase in right atrial pressure that is induced by high ITP[35].

Increased pulmonary vascular resistance and pulmonary hypertension frequently complicate COPD and this is believed to be multifactorial. Importantly, the hyperinflation-induced elevated alveolar pressures (including PEEPi) and the increased interstitial pressure (owing to increased ITP) extramurally compress alveolar vessels[34]. On passive compression of the vascular bed, the vascular pressures increase above the normal pulmonary venous pressures thus increasing RV afterload and decreasing LV preload. In emphysema, the extensive destruction of pulmonary vascular bed, hypoxic and acidotic vasoconstriction and increased blood viscosity due to polycythemia, all cause increase in vascular resistance. Notably, in advanced disease, irreversible functional and histologic changes occur in the walls of the small pulmonary vessels leading to reduced compliance and endothelial dysfunction[36-41]. Furthermore, the commonly coexisting left ventricular diastolic dysfunction in COPD and the increased pulmonary artery wedge pressure (see later) can cause back pressure changes in pulmonary vasculature and right ventricle[42]. Owing to these mechanisms, RV afterload increases and RV output fails to surge in exercise[43,44] and also, chronic cor pulmonale might ensue. In clinical practice, increased pulmonary vascular resistance is commonly evident at rest in COPD and it is further exacerbated in exercising COPD patients possibly owing to exercise-aggravated lung hyperinflation[45] and vasoconstriction secondary to hypoxemia, acidosis and increased sympathetic tone[46].

TABLE 1. Negative effects of dynamic lung hyperinflation and high expiratory intrathoracic pressure on cardiac function.

1) Reduced systemic venous return → reduced right ventricular (RV) preload.
2) Increased pulmonary vascular resistance due to compression of the vascular bed (superimposed on disease-specific destruction of the vascular bed, hypoxemic/acidotic vasoconstriction, increased blood viscosity, irreversible histological and functional vascular changes, left back pressures) → Increased RV afterload.
3) Reduced LV preload.
4) Increased cardiac transmural pressure and left shift of the interventricular septum → Left ventricular diastolic dysfunction.

The function of the left ventricle (LV) is also affected by ventilatory mechanics in COPD. Exercising COPD patients exhibit decreases in both end-systolic and end-diastolic LV volume[47]. The latter is attributed to the reduced LV preload (owing to reduced systemic venous return and/or decrease in RV output), the increased transmural pressure on the heart exerted by the hyperinflated lungs (thus hampering LV diastolic compliance; the so-called pneumonic cardiac tamponade) and the left shift of the interventricular septum induced by the increased RV pressures and dimensions (the effect of the ventricular interdependence)[37,48]. The left shift of the interventricular septum also contributes to the high pulmonary artery wedge pressure occurring in COPD (the other contributing factor being the increased heart transmural pressure). Finally, the aforementioned reduction in end-systolic LV volume might be the result of the reduced afterload that is produced by the increased expiratory ITP. On the contrary, the large negative inspiratory ITP that alternate with positive expiratory ITP in each respiration in exercising COPD patients seem to promote an opposing effect by increasing left ventricular afterload. As a result, the net-results of the large ITP swings on left ventricular function if by far much more difficult to predict.

Despite the numerous effects of the respiratory mechanics, left ventricular ejection fraction is generally preserved or only moderately reduced in COPD in the absence of concomitant ischemic heart disease or hypertension[36,37]. This combination of preserved LV ejection fraction and reduced systemic venous return produces a reduction in the intrathoracic blood volume (hyperinflation-induced intrathoracic hypervolemia[49]). Also, cardiac output increases normally per unit increase in metabolic rate, suggesting that the tight link between cardiac output and oxygen uptake is preserved. However, peak cardiac output, peak oxygen uptake and stroke volume at high exercise intensities are all lower compared to that of healthy subjects during incremental exercise[14]; the latter being directly associated with the increase in expiratory abdominal muscle recruitment[14]. Interestingly, lightening the work of breathing by helium[50] or bronchodilator [51] administration had beneficial effects on kinetic responses of cardiac output, heart rate, and stroke volume[52].

2c. Reduced arterial oxygen content

Typically, COPD patients manifest hypoxemia which may be moderate (PO_2 often in the high 60s or 70s) or severe (PO_2 often in the 50s or 40s) depending on the prevailing pathological defect (chronic bronchitis versus emphysema respectively). The presence and the extent of hypoxemia is due to the combination of increased physiologic dead space (defined as lung areas of high V/Q ratios) and physiologic shunt (lung areas of low V/Q ratios) in COPD; the former being particularly increased in emphysema and the latter primarily occurring in bronchitis-prevalent disease[38].

The importance of reduced arterial oxygen content as a factor limiting exercise tolerance is illustrated by the fact that administration of supplemental oxygen reduces ventilatory requirement and dyspnea sensation in patients with COPD, reduces exercise-induced arterial hypoxemia and improves leg muscle oxygen delivery and increases exercise capacity altogether[53,54]. Importantly, lightening of the work of breathing by helium administration has also been shown to improve arterial oxygen content during submaximal exercise in COPD[52] and this has been attributed to improved V/Q mismatch secondary to improved lung mechanics and increased alveolar ventilation[52], heliox-induced alveolar hyperventilation [55] and improved oxygen diffusion[56].

2d. Blood flow redistribution

According to the concept of blood flow redistribution, in states of increased respiratory muscle load such as in exercise, the respiratory and locomotor muscles compete each other for their share in the available systemic oxygen delivery and blood flow is redirected form the peripheral muscles to the hard-working respiratory muscles[57]; this phenomenon applies to the whole spectrum of COPD severity. Along with other factors (see later), reduced blood flow to the lower legs contributes to leg fatigability and consequently to exercise limitation in COPD.

In theory, this effect is mediated by an increased sympathetic vasoconstrictor outflow to the limb muscles upon activation of the so-called respiratory muscle fatigue-induced metaboreflex; activation of this reflex follows induction of respiratory muscle fatigue and accumulation of metabolites in the respiratory muscles that activate unmyelinated group IV phrenic afferents, which in turn increase sympathetic vasoconstrictor activity and decrease blood flow to the working locomotor muscles via a supraspinal reflex[58]. In line with this evidence, unloading the respiratory muscles by means of heliox breathing[59], proportional assisted ventilation[60] and inhaled bronchodilators[61] during constant-load exercise in COPD has decreased their perfusion allowing for more blood flow to the skeletal muscles and a greater exercise power at the same total cardiac output[62].

3. Peripheral muscle dysfunction

Peripheral muscle dysfunction in COPD patients primarily involve the lower limb muscles, with quadriceps muscle strength being 20% to 30% lower in patients with moderate to severe COPD as compared to control age-matched healthy subjects[63] and the degree of reduced limb muscle strength seems to correlate with indices of disease severity such as forced expiratory volume in 1 s (FEV1) and resting arterial PO_2[64,65].

The terms "weakness" and "fatigue" are commonly employed by COPD patients to describe the sensory perception of muscle dysfunction. However, it should be mentioned that these terms describe two different sensations, with weakness referring to the lack of physical or muscle strength and the feeling that extra effort is required to mobilize, and fatigue to the feeling of tiredness or exhaustion or a need to rest because of lack of energy or strength. Yet, in practice these terms often are used interchangeably due to their common coexistence, the overlapping nature of their causes, and the subjective element in terms of their perception and expression on behalf of the patients. For simplicity, only the term fatigue is employed in the rest of this article.

Skeletal muscle dysfunction leading to premature sensation of fatigue of the peripheral muscles is an important contributor factor to exercise limitation in COPD patients. The high susceptibility to fatigue is only in part attributable ventilatory constraints; the well-known altered intrinsic muscle characteristics (including abnormal fiber type distribution, reduced muscle fiber size and impaired oxidative capacity) in these patients seem to be critical in the development of exercise-induced muscle dysfunction[66]. Actually, evidence suggests that, only as low as 30% to 40% of the exercise-induced limb muscle fatigue in patients with COPD might be accounted for by pulmonary limitations that affect the supplementation of the working limb muscles with oxygen, whereas the remainder (oxygen delivery-independent portion of quadriceps muscle fatigue) might be explained by the disease-associated intrinsic muscle dysfunctional characteristics of the locomotor muscles[60].

The following paragraphs look into the causes of peripheral muscle dysfunction in COPD (Table 2).

TABLE 2. Peripheral muscle dysfunction in COPD.

1) Reduction in muscle fiber size
2) Disturbances in muscle fiber type distribution
3) Disturbances in muscle oxidative capacity (reduced muscle micro-capillary bed, reduced mitochondrial density, oxygen consumption and oxidative enzyme activity, electron transport chain dysfunction, excessive production of reactive oxygen species)
4) Reduced oxygen supply (blood flow redistribution, impaired cardiac function, hypoxemia)
5) Systemic and locomotor inflammation
6) Muscle disuse
7) Negative nutrition balance
8) Corticosteroids

3a. Reduction in muscle fiber size

Contractile protein deficit is largely responsible for muscle atrophy in COPD. More precisely, the peripheral muscles of patients with COPD develop significant reductions in the phenotypic expression of myosin heavy chain type-I proportion[67] as well as reduction in cross-sectional area (CSA) for type-I and type-II fibers[65,68] and this affect mainly lower limb muscle tissue compared to other body muscles[65].

3b. Disturbances in muscle fiber type distribution

In patients with advanced COPD, there is reduction (up to 20%) in the proportion of myosin type-I (slow-twitch oxidative) muscle fibers and a concomitant increase (up to 10%) in the proportion of type-II (fast-twitch glycolytic) fibers[68]. Although the exact functional consequences of such redistribution in fiber type remains under investigation, type-II fibers present lower mitochondrial density and oxidative capacity and are more dependent on anaerobic activity and, therefore, fatigue-susceptible and along with other factors of the muscle microenvironment (see later) it might be an important contributor to the increased leg muscle fatigability and impaired endurance noted in COPD patients[69].

3c. Disturbances in oxidative capacity

Besides the disturbances of convective oxygen transport pathways discussed previously, muscle tissue in COPD is inappropriately adapted to sustain the metabolic requirements of exercise[11]. Evidence suggests that there is intrinsic myopathic interference to diffusive oxygen transport that reduces the capacity for oxygen utilization below that which is otherwise expected, allowing for the degree of reduction in convective oxygen supply[70]. The observed reduction in muscle diffusive oxygen conductance in COPD is most likely the result of reduced muscle micro-capillary bed supplying mitochondria[71]. Additionally, in patients with COPD, there has been consistently reported reduced mitochondrial density[72] and mitochondrial malfunction (including reduced oxygen consumption, electron transport chain dysfunction, excessive production of reactive oxygen species[73] and reduced oxidative enzyme activity[69,71,74].

To put it all together, local exercise induces muscle oxidative and nitrosative stress that fails to be counteracted by the dysfunctional peripheral muscles (that also sustain the effects of reduced oxygen delivery) and this has been associated with a reduced muscle exercise capacity[75,76] independently of lung function impairment[74]. Moreover, the functionally and structurally altered peripheral muscles in COPD rely prematurely on oxygen-independent glycolytic activity for energy production; in turn, this leads to higher accumulation of inorganic phosphate[77] and premature muscle acidosis from lactate production[71]; these biochemical events are perceived as muscle fatigue, compromise the ability to sustain repeated muscle contractions and thus limit exercise tolerance[11].

3d. Other mechanisms of muscle dysfunction in COPD

Commonly, patients with COPD are on a negative nutrition balance that ultimately leads to loss of muscle tissue. Dietary intake is low in COPD patients loosing weight and this has been attributed to a number or reasons including impaired appetite due to disease-specific symptoms and systemic inflammation, deranged leptin homeostasis, psychological dysfunction and adverse change of breathing pattern and desaturation during chewing and swallowing. On the other hand COPD patients demonstrate increased resting and exercise energy expenditure as a consequence of metabolic and mechanical inefficiency and/or the presence of systemic inflammation[78].

Resistive breathing has referred to as an "immune challenge" for the body initiating due to inducing oxidative stress and subsequently, inflammatory response[79]. Chronic hypoxemia that commonly complicates COPD has also been linked to systemic inflammation. In general, several systemic inflammatory mediators such as tumor necrosis factor alpha, some interleukins, C-reactive protein

(CRP), fibrinogen, lipopolysaccharide binding protein and leucocytes are increased in COPD[80] and although not uniformly proven, they might serve as an important factor in muscle wasting[81,82]. Raised CRP levels related inversely to exercise capacity in advanced COPD[83]. Systemic and/or muscle inflammation along with oxidative stress can independently trigger muscle dysfunction by acting on mitochondria and myofilament properties[14]. Inflammation and oxidative stress are therefore, interrelated mechanisms that could create a closed loop of induction, persistence and amplification of the skeletal muscle abnormalities in patients with COPD.

Interestingly, muscle disuse itself, has also been linked to skeletal muscle atrophy (characterized by a decrease in protein content, fiber diameter, force production, and fatigue resistance) through decreases in protein synthesis and increases in proteolysis, downregulation of various genes[84] and activation of alternative-to-cytokines NF-kB pathways[85]; the latter being reversible with exercise training[86].

Of note, exercise training also partially reverses the abnormal fiber type distribution, increases the CSA, enhances the activity of oxidative enzymes of the muscle fibers, increases capillary density a GOLD stages II- VI[87] and prevents the microvascular inflammatory response to hypoxia[88].

RESPIRATORY MUSCLE STRUCTURE AND FUNCTION

Similarly to peripheral muscles, respiratory muscles undergo significant structural and functional changes in COPD. However, there are important differences in the phenotypic changes between these muscle groups represented by the quadriceps and diaphragm respectively. Precisely, the most obvious difference is the opposite direction of the shift in fiber type distribution. Compared with the quadriceps, the diaphragm of patients with severe emphysema presents an increased proportion of slow-twitch type-I fibers and a lower proportion of fast-twitch type-II fibers[89]. Similar changes have been reported for intercostal muscles. Consistent with the greater proportion of the fatigue-resistant type-I fibers, is an increase in oxidative enzyme activities combined with a decrease in glycolytic enzyme activities resulting in a clear predominance of oxidative metabolism in diaphragm[90,91]. Additionally, the overall mitochondrial respiratory chain capacity and efficiency are enhanced in patients with moderate[92] and severe[93] COPD than in controls with normal lung function. Altogether these alterations might be adaptive mechanisms reflecting an endurance training-like effect resulting from the chronically increased work of breathing seen in COPD.

In contrast, different lines of evidence suggest that adverse, fatigue-promoting diaphragmatic adaptations also coexists. These include chest wall reconfiguration and lung hyperinflation leading to chronic diaphragmatic fiber shortening and suboptimal passive length-tension relationship[94], reduction by 40% to 60% in CSA of all muscle fiber types[89], the loss of myosin heavy chain content due to accelerated muscle protein degradation, dysfunction of the remaining contractile proteins and reduced calcium sensitivity of force generation[95]. Importantly these changes occur early in the disease process[95].

As it evident, multiple, seemingly opposing adaptations co-occur at the diaphragm and the other respiratory muscle in patients with COPD. Possibly, the balance between these adaptations defines the fatigue threshold for these muscles. However, it should also be emphasized that objective diaphragmatic fatigue has not been consistently demonstrated at the limit of tolerance in COPD[26,96].

INTEGRATIVE VIEW OF THE IMPAIRED EXERCISE CAPACITY IN COPD

The following scenario attempts to illustrate in a simplified way the complexity and the contiguous nature of the mechanisms that are involved in the exercise limitation in patients with COPD. Consider a patient with COPD who takes on a physical activity in the form of climbing stairs or fast walking: in order to conduct this physical activity, the lower legs muscles will initially require an increased amount of oxygen supply. However, as already discussed, the capacity for oxygen delivery to the peripheral muscles is significantly compromised and this will lead to the production and premature accumulation of lactic acid, inorganic phosphates and hydrogen ions. This is an additional burden for the peripheral muscles that have largely lost their oxidative capacity due to chronic changes in their structure and function. Combined these factors, accelerate the occurrence of peripheral muscle fatigue (one of the two common exercise-limiting symptoms in COPD) and concurrently, stimulate the respiratory drive. By increasing the respiratory drive, the sensation of dyspnea (the other common exercise-limiting symptom in COPD) intensifies and also the respiratory muscles

(which are already on mechanical disadvantage due to lung hyperinflation and other factors described earlier) are subjected to an even greater mechanical load. The latter further increases the sensation of dyspnea but also raises the demand for blood perfusion and oxygen transport to the respiratory muscles. Consequently, the cardiovascular system is also subjected to greater workload. However, by this moment, the performance of the cardiovascular system is already compromised due to the negative effects of lung hyperinflation and large intrathoracic pressure swings generated by substantial expiratory muscle activity. Under these circumstances, the cardiovascular system will struggle to meet up metabolic requirements (O_2 and energy supply and CO_2 removal) of the respiratory muscles and peripheral muscles. Additionally, blood flow will be redirected from the large peripheral muscle groups to the respiratory muscles. These mechanisms will act synergistically with the inherently reduced arterial content in COPD to further compromise the oxygen supplementation of the peripheral muscles thus aggravating peripheral muscle fatigue. This way, the loop of the events that limit exercise tolerance in patients with COPD closes and the patient will inevitably be made to pause physical activity due to dyspnea and/or leg fatigue depending on the prevailing underlying pathological pathway.

Bearing in mind the vicious cycle of the events that take place during exercise in COPD, it should be comprehensible why a patient with COPD may be willing to avoid exercise at all costs by adopting a sedentary lifestyle. However, in more advanced stages of the disease, even in the absence of physical activity, the increased ventilatory requirements will lead to intense resting dyspnea sensation. At this stage, some patients also unavoidably 'forgo' the attempt to preserve a normal arterial PCO_2 (thus signifying overt ventilatory insufficiency) in a desperate attempt to obtain the advantage of a reduced work of breathing and a correspondingly reduced oxygen cost[97].

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