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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: "THE EFFECT OF CARDIOPULMONARY REHABILITATION ON THE PERIPHERAL SKELETAL MUSCLES IN COPD"

ΜΥΡΤΩ ΧΡΙΣΤΟΦΙΛΗ

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ABSTRACT

COPD is a global scourge affecting a large proportion of the population and a financial burden for modern societies. Its cause still remains unknown and its treatment is mostly symptomatic. Like a respiratory disease COPD affects firstly the ventilation causing hyperinflation, hypersecretion of mucus and dyspnea. However, a very prominent feature of COPD is the deterioration of strength and endurance of the peripheral skeletal muscles. Many, rather complicated, pathways through which COPD affects the peripheral muscles of the patient have been implicated, but nothing is conclusive yet. The ventilation effects of COPD combined with peripheral muscle weakness, lead to reduced physical activity, and decline of the patients' quality of life.

Besides the classic pharmaceutical administration, pulmonary rehabilitation comes to complete the COPD treatment. Pulmonary rehabilitation consists of many different specialties like doctors, phycologists, nutritionists, physiotherapists etc. The cornerstone of pulmonary rehabilitation is considered exercise training. Exercise training includes endurance training, which usually takes place on a treadmill or a cycloergometer, and strength training, which comprises of resistance bands, dumbbells etc. The effects of COPD on muscles have been proven to improve after at least 6 – 8 weeks of training exercise but for the results to last more than 6 – 12 months, the continuation of exercise is necessary. Supplementary to exercise, NMES comes to improve muscle condition, and reduce deconditioning to patients that for any number of reasons cannot undertake exercise training. Different types of exercise like yoga and tai chi have been successfully applied on exercise programs but further investigation is required.

ΠΕΡΙΛΗΨΗ

Μία μάστιγα του σύγχρονου κόσμου στις μέρες μας είναι η χρόνια αποφρακτική πνευμονοπάθεια (ΧΑΠ). Το ΧΑΠ επηρεάζει κατά πρώτο λόγο την υγεία μεγάλης μερίδας πληθυσμού, επιπλέον όμως, επιβαρύνει και οικονομικά τα κράτη. Το ακριβές αίτιο που το προκαλεί παραμένει άγνωστο μέχρι σήμερα και η θεραπεία του είναι ως επί το πλείστων συμπτωματολογική. Σαν αναπνευστική νόσος, επηρεάζει κατά πρώτο λόγο τον αερισμό, προκαλώντας υπερέκκριση βλέννης, υπερδιάταση και δύσπνοια. Ένα πολύ έντονο χαρακτηριστικό του ΧΑΠ είναι η μείωση της μυϊκής δύναμης και αντοχής των περιφερικών σκελετικών μυών. Πολλοί περίπλοκοι μηχανισμοί μέσο των οποίων επηρεάζονται οι σκελετικοί μυς έχουν εμπλακεί, αλλά ακόμα οι επιστήμονες δεν έχουν κατασταλάξει στον ακριβή μηχανισμό. Οι διαταραχές αερισμού ως απόρια του ΧΑΠ σε συνδυασμό με την μειωμένη μυϊκή δύναμη, προκαλούν μείωση της φυσικής δραστηριότητας και επιδείνωση της ποιότητας ζωής των ασθενών.

Εκτός από την κλασσική φαρμακευτική αγωγή που χορηγείται στους ασθενείς με ΧΑΠ, έρχεται η καρδιοπνευμονική αποκατάσταση για να πλαισιώσει την θεραπεία. Η καρδιοπνευμονική αποκατάσταση αποτελείται από μια πληθώρα ειδικοτήτων όπως γιατρούς, ψυχολόγους, διατροφολόγους, φυσικοθεραπευτές κ.α. Ακρογωνιαίος λίθος της αποκατάστασης θεωρείται η άσκηση. Η άσκηση αποτελείται από ασκήσεις αντοχής, που συνήθως λαβαίνουν χώρα σε κυλιόμενους διαδρόμους ή κυκλοεργόμετρα, και ασκήσεις ενδυνάμωσης που περιλαμβάνουν ασκήσεις με λάστιχα, βαράκια κ.α. Έχει αποδειχτεί ότι οι επιπτώσεις του ΧΑΠ στους μυς βελτιώνονται μετά από τουλάχιστον 6 – 8 εβδομάδες άσκησης, αλλά για να κρατήσουν τα αποτελέσματα πάνω από 6 –

12 μήνες θα πρέπει να συνεχιστούν τα προγράμματα άσκησης. Ο υποδόριος νευρομυϊκός ερεθισμός (NMES) χρησιμοποιείται συμπληρωματικά της άσκησης για βελτίωση της μυϊκής λειτουργίας και μείωση της απώλειας μυϊκής δύναμης σε ασθενείς που για διάφορους λόγους δεν δύναται να παρακολουθήσουν προγράμματα άσκησης. Διαφορετικοί τύποι άσκησης όπως το Tai Chi και η Yoga έχουν χρησιμοποιηθεί με επιτυχία σε προγράμματα άσκησης, αλλά απαιτείται επιπλέον διερεύνηση γύρο από το θέμα αυτό.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), is a major, life threatening disease. Currently, COPD is the fourth cause of mortality worldwide [1] and it is estimated that by 2020, it will become the third most common mortality cause and the fifth cause of chronic disability [2].

There are four stages of COPD (table 1) depending on Forced Expiratory Volume in one second (FEV_1) and the ratio FEV_1/FVC (Forced Vial Capacity). The main characteristic of COPD is airflow limitation, which is responsible for many other symptoms like hyperinflation and dyspnea. However, despite ventilatory limitations, a very prominent manifestation of COPD is peripheral muscle weakness which affects one third of COPD patients [3]. In turn, muscle weakness leads to limb muscle dysfunction and exercise intolerance [4], with the lower limbs being more severely affected compared to the upper limbs and respiratory muscles [5]. Muscle weakness was found to be independently associated with low scores of FEV_1, Forced Vital Capacity (FVC) and Peak Expiratory Flow (PEF) [6] and was also associated with morbidity and mortality [7]. The assessment of the quadriceps muscle's strength is a relatively easy and reliable way to estimate peripheral muscle weakness [8]. One third of individuals with COPD have significant quadriceps weakness [5, 9, 10] and 15% have evidence sarcopenia [9] and atrophy of the lower limb muscles and most particularly the quadriceps muscle [5]. Muscle weakness and atrophy lead to an increased use of health care resources [10]. All these manifestations of COPD present some similarities with muscle deconditioning that occurs with aging [4, 9] and reduce the patients' quality of life[11]. Dyspnea, muscle weakness, deconditioning, physical inactivity, inflammation, malnutrition, aging and

oxidative stress are all potential contributors to limb muscle dysfunction [4, 9] (figure 1) along with cigarette smoke, genetics, hypoxia, hypercapnia and acidosis, metabolic derangements including vitamin D, and drugs (especially systemic corticosteroids), other comorbidities, exacerbations, systemic inflammation and nutritional abnormalities [5].

Decondition of peripheral muscles in COPD

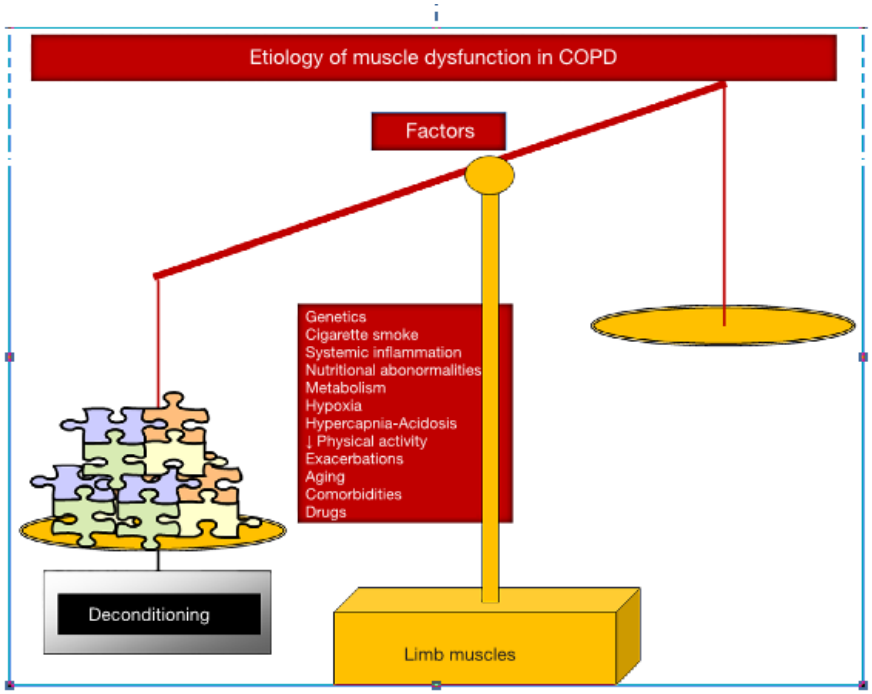


Figure 1. Etiology of muscle disfunction in COPD (Modified from: Barreiro and Jaitovich [10])

Many studies have shown that quadriceps weakness is associated with increased mortality independently of lung function impairment [1, 5, 11], whereas the prevalence of skeletal muscle dysfunction increases depending on disease severity [5, 11]. Muscle weakness in COPD patients compared with healthy subjects (with similarly low activity levels) still present structural and functional differences [4]. What is interesting is that exercise reverses some muscle features but not all and not to the same degree. For example, type I muscle

fiber proportion does not improve to the same degree as the corresponding healthy subjects and this evidence suggests that COPD patients might suffer from some sort of myopathy [4] that cannot be fully reversed.

GOLD STAGE I (mild)	$FEV_1 \geq 80\%$	$FEV_1/FVC \leq 0.7$
GOLD STAGE II (moderate)	$50\% \leq FEV_1 < 80\%$	$FEV_1/FVC \leq 0.7$
GOLD STAGE III (severe)	$30\% \leq FEV1 < 50\%$	$FEV_1/FVC \leq 0.7$
GOLD STAGE IV (very severe)	$FEV_1 < 30\%$	$FEV_1/FVC \leq 0.7$

Table 1. The four stages of COPD (Modified from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf)

Muscle dysfunction affects the COPD patient macroscopically and microscopically. Cross sectional areas of the affected muscle fibers are decreased, type I muscle fibers, capillary to fiber ratio and early lactate release are also reduced [4], oxidation is increased, the delivery and exchange of oxygen is compromised, and cells develop structural changes. Patient's muscles appear cachectic [7] and present reduced endurance, strength and exercise tolerance [5, 11, 13].

Pulmonary rehabilitation (PR) programs are multidimensional aiming to treat a patient comprehensively, since an overall change of lifestyle is required. PR programs include many specialties including pneumonologists, psychologists, nurses, physiotherapists etc. It is known for some time now that exercise training (ET) is the cornerstone of any PR program. The majority, if not all, of recent studies conclude that ET programs are essential for managing muscle dysfunction, dyspnea, exercise intolerance, morbidity, quality of life and mortality. Despite the fact that exercise training is usually recommended for COPD patients whose FEV1 is less than 80% [14], it can be argued that these

programs can improve exercise capacity even in healthy subjects regardless of their COPD stage. Thus, The American Thoracic Society recommends PR for any patient with persistent exercise intolerance [14]. The best type of exercise is yet to be determined as many suggestions have been made and studied including walking, cycling, tai chi [15], NMETS as a complementary treatment and many more. Most studies usually use resistance training and some sort of aerobic training like walking or cycling or the combination of the two. However, a personalized exercise program that takes into consideration the physiological demands and needs of each patient, while at the same time respecting his/her habits and wishes, is probably more appropriate[15].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is a menace of today's world. Its cause is still practically unknown, affected by people's habits like smoking (in modern societies smoking is accused to be the main cause of COPD with a prevalence of 95% [16]) environmental factors (particles in the inhaled air) [17] and genetical factors [16, 18]. Approximately 280 million people suffer from COPD in the world and 2,75 million people die from COPD annually [17] which translates to 25% of all deaths globally[1]. It is a very common disease affecting a great proportion of the population and it has become a humongous economic burden since COPD is a main cause for absence from work [20] and patients were found to use health care resources more [7]. Its effect on the lungs and the human body in general could be paralleled with the normal decline seen with aging however, fundamental differences between the two exist.

COPD patients suffer from lung impairment, firstly due to the destruction of lung parenchyma (emphysema) and secondly from structural abnormalities of the airways like the narrowing of small airways (bronchitis and bronchiolitis) [17, 18, 20] which are smaller than 2mm [21] possibly as a result to an increased thickness met on the walls of the small airways, the formation of follicles and the deposition of collagen in the outer airway [16] (figure 2). In COPD there is an air entrapment mainly due to the reduction of the elastic recoil of the lung and the increased airway resistance resulting in airflow limitation, shortness of breath and exertion [20]. COPD patients exhibit a reduced capacity to produce workload and this is directly correlated with the stage of the disease [22], and exhibit abnormal oxygen uptake and ATP consumption [3]. An abnormally low V_{O2max} defines exercise intolerance [23].

Emphysema and airway fibrosis

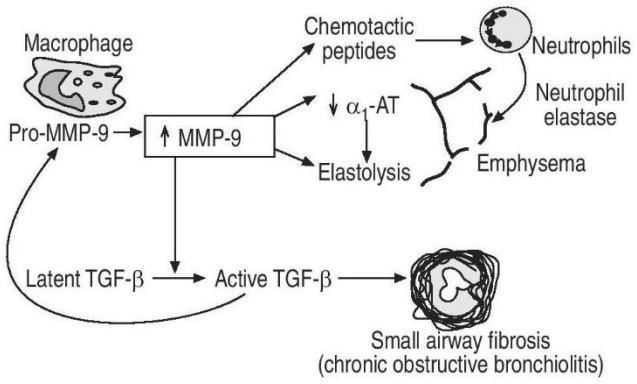


Figure 2. Possible interrelationship between small airway fibrosis and emphysema in COPD. (Modified from: Barnes et al, 2003)

COPD is described by the Global Initiative for Chronic Obstructive Lung Disease as “a preventable and treatable disease...characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious

particles or gases" [20]. Forced expiratory volume in one second (FEV_1), the FEV_1/FVC ratio and Pa_{O2} is used to evaluate lung capacity and help classify the patients to the corresponding stage using the GOLD scale (I, II, III, or IV) (table 1) but evidence suggests that beside the fact that FEV1 is associated with quadricep's strength [24, 25] and greater risk of poor lower extremity function and disability [26], it doesn't describe sufficiently other key symptoms like breathlessness, the impact of COPD on the patients' quality of life [19, 24, 25], and the severity of symptoms [26] whereas Pa_{O2} can appear normal or only slightly decreased even to patients that FEV_1 is reduced to 51% and vital capacity is reduced to 79% [24].

COPD might be a disease of the lungs, however, like most respiratory diseases, has systemic (i.e. extrapulmonary) effects possibly associated with an inflammatory reaction to the airway's alveoli and pulmonary vessels [18]. Inflammatory markers are found in the blood [20] airways, BLA fluid, and pulmonary parenchyma of COPD patients [27]. A very common systemic affect is the skeletal muscle atrophy which leads to weight loss in about 50% of COPD patients with severe COPD and 10-15% with mild, and correlates with poor prognosis independently of FEV_1 [18, 28]. It must be stressed out that COPD limits the exercise capacity and quality of life of patients [18, 28]. An assessment tool predicting disability, like the Short Physical Performance Battery (SPPB) could prove to be useful in distinguishing patients that might develop disabilities affecting their quality of life [29]. The systemic and lung inflammation, despite contributing to muscle atrophy, are also implicated in the pathogenesis of weight loss that occurs or deteriorates by the excessive production of TNF-a by peripheral cytocides [28]. Weight loss on each own was found to be a negative

prognostic factor independent of FEV_1 or Pa_{O2}, however what is most important is that it is reversible [28]. Weight loss is also possibly affected by the low testosterone, the altered hormone regulating pathways, and the reduced leptin in plasma [28]. Other systemic effects include cardiovascular disease, depression [18] and bone loss [18 28, 30] (figure 3).

In COPD there is air entrapment in the lungs which leads to increased residual volume (RV). The increased RV reduces FEV_1 and FVC and at the same time the reduction of elastic recoil of the lung, leads to reduced ratio FEV_1/FVC [31]. This phenomenon creates a dominant feature of COPD which is called hyperinflation [32]. Hyperinflation is either static (occurs at rest) or dynamic (during exercise) [15]. Hyperinflation leads to an increase in residual volume and by extension in functional residual capacity (FRC). Hyperinflation in COPD is created due to the distraction of the inward elastic recoil of the lung parenchyma [15] and the increased airway resistance leading to air entrapment and calling for higher respiratory work load, especially during exercise, where the respiratory demands are higher [15].

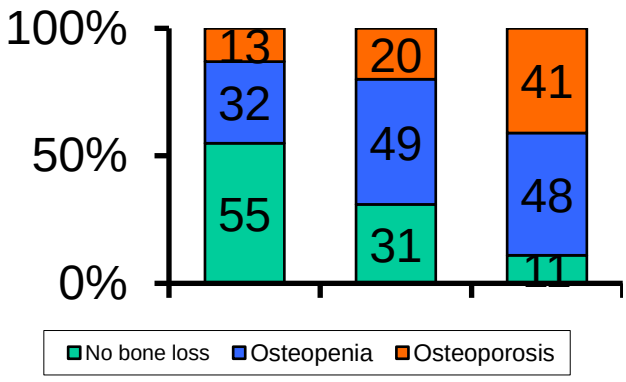


Figure 3. Bone loss in COPD patients (Modified from: Bolton et al, 2004)

COPD pathophysiology

During the years, it has been established that COPD is characterized by a generic, excessive and abnormal inflammatory response of the lungs. This inflammation might be caused by inhaled substances (like cigarette smoke) and particulates or due to the distraction of the lung parenchyma and the substances that are released during the process [18]. This inflammatory response is worst during exacerbations and is maintained even after the cessation of smoking [18]. In cellular level it includes the involvement of cytokines, TNF-a (tumor necrosis factor alpha), IL-6 (interleukin – 6), IL-8 (interleukin – 8), macrophages, GM-CSF (Granulocyte macrophage – colony stimulating factor), neutrophils and more [2, 16, 18].

Cigarette smoke on its own constitutes a major risk factor for developing COPD [17, 28] and a COPD inflammatory activation agent (figure 4). An average of 50% of smokers develop COPD [32]. Nicotine, a main substance of tobacco smoke, alters the expression of TGF – β1 (transforming growth factor beta -1) which is involved in the maintenance of muscle mass, and competes with acetylocholine for its receptor, thus affecting muscle contraction [28]. It is implicated in the endothelium destruction of systemic vessels [18] and the creation of oxidative stress via increase of reactive oxygen species (ROS) [16, 17] and initiating the inflammation of the lungs [18], this in turn, leads to the secretion of inflammatory and proinflammatory cells (cytokines, such as TNF-a, IL-6, IL-1b, macrophages, like macrophage inflammatory protein 1a and GM-CSF etc.) [16, 18] that further “spread” the disease. The number of T – lymphocytes in light and moderate smokers is the same as in no smokers, and the increase in CD8+

(cytotoxic T cell) and decrease in CD4+ (mature T helper cells) drops in heavy smokers as opposed to no smokers. However, according to Agusti and colleagues [28], the abnormality in CD4+ and CD8+ levels disappeared six weeks after the cessation of smoking. Smoking also increases the neutrophil retention in the lungs and the production of neutrophils through the production of granule proteins [16]. Moderate smokers lose FEV1 at a rate of 63% mL/y and 12% of moderate smokers developed COPD, while for heavy smokers, the ratings were 78% mL/y and 26% correspondingly [32]. However, smoking on its own is not enough, since even heavy smokers not all develop COPD. Smoking causes inflammatory response and protease imbalance but to a lesser extent. Consequently, it can safely be stated that the lung impairment in COPD is not simply caused by smoking [16].

Cigarette smoke → macrophages → inflammatory cells

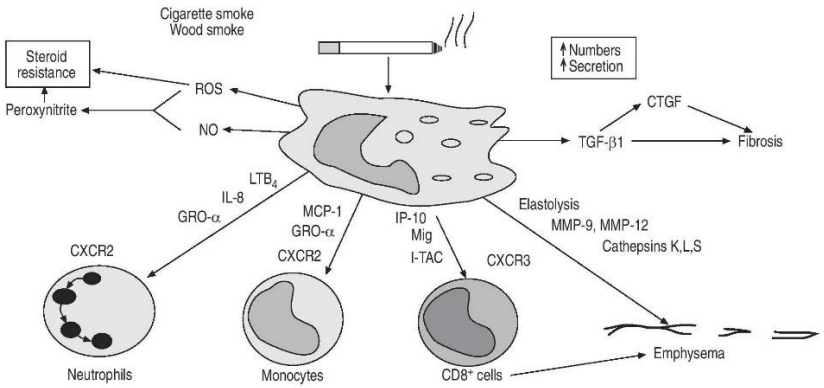


Figure 4. Macrophages may play a pivotal role in COPD as they are activated by cigarette smoke extract and secrete many inflammatory proteins that may orchestrate the inflammatory process. Neutrophils may be attracted by interleukin – 8, growth related oncogene-a and leukotriene B4, monocytes by macrophage chemotactic protein -1 and CD8+ lymphocytes by interferon – γ inducible protein, monokine induced by interferon – γ and interferon – inducible T- cell a chemoattractant. Release of elastolytic enzymes including matrix metalloproteinases and cathepsins cause

elastolysis, and release of transforming growth factor and connective tissue growth factor. Macrophages also generate reactive oxygen species and nitric oxide which together form peroxynitrite and may contribute to steroid resistance. (Modified from: Barnes et al, 2003).

Other factors are involved, some are probably genetic. The connection between COPD and the genetic factors are unknown to our days even so, the connection is very possible [16, 18]. The angiotensin converting enzyme gene (ACE), several transcription factors (myogenic basic helix – loop – helix gene D (MyoD) and myocyte enhancer factor (MEF – 2) are possibly implicated [28] and these factors influence the muscular response to exercise. ACE inhibitors reduce the normal decline in muscle mass because of aging [28]. All genes that are involved in the increased production of inflammatory mediators and enzymes, or in the defective endogenous anti-inflammatory or antiprotease mechanisms might account for for the onset of COPD [16]. The notion that the changes that take place in COPD are affected by the local, possibly cellular, micro – environment, beside the systemic, is supported by the fact that same systemic changes, i.e. hypoxia, cause opposite effects on quadriceps compared to the diaphragm [34]. The diaphragm appears to increase the muscle fibers type I and reduce type IIb as opposed to quadriceps thus becoming more fatigue resistance whereas quadriceps and skeletal muscles in general, demonstrate premature fatigue.

The first manifestation of COPD is air entrapment which leads to an increase in the residual volume and in turn leads to a decrease in vital capacity [31]. COPD patients suffer from three main pathological mechanisms in different relations between them; 1) chronic obstructive bronchiolitis, 2) emphysema and 3) mucus plugging [16] (figure 5).

1) Chronic obstructive bronchiolitis.

It has been acknowledged for some time now that in COPD there is a narrowing of the small airways [17, 18, 20, 21]. Their walls thicken, collagen is deposited in the outer airway wall which makes the airway opening harder [16, 32]. The more severe the disease, the less space inside the airways' lumen exists since the deposition of mucus on the walls thickens [16]. What is more, for unknown reasons, fibrosis is formed around the airways further reducing the lumen's space.

2) Emphysema.

Emphysema compromises, or even destroys, the functionality of the lungs [16, 32]. It progresses parallel with the disease increasing the residual volume and decreasing vital capacity [16]. Emphysema practically modifies the lung's architecture having an impact not only in the affected part of the lung, which underfunctions during ventilation, but also at the healthy part of the lung by compressing normal airways and changing their normal angulations [16] and reducing the lungs recoil capability [31] which is also reduced by the proteolysis of elastin [32].

3) Mucus hypersecretion.

Mucus hypersecretion [31, 32] may come as a result to the extensive bacterial and viral colonization of COPD patients or to the inflammatory process met in COPD. Neutrophils, mast cells, mast cell chymase and serine proteases exist around the submucosal glands and are believed to be at least partly responsible for the mucus secretion [16]. Mucus

hypersecretion also causes the (FEV_1) to drop and is linked to patient's mortality [16].

Disorganization of the parenchyma in COPD patients

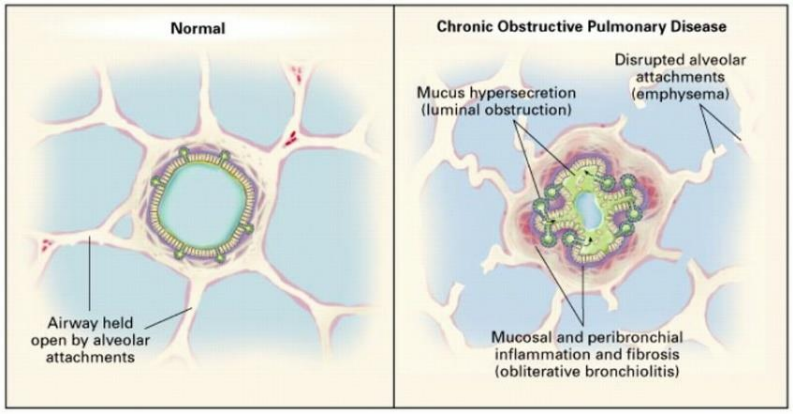


Figure 5. The airway obstruction as it occurs in COPD. (Modified from: Barnes, et al, 2000)

Further below, some cells like neutrophils, macrophage and T-cells which are found in the sputum and BAL fluid and believed to play an important role in the pathophysiological mechanisms of COPD are going to be analyzed. Most of these cells are also incriminated for the secretion of mucus.

Neutrophils are found in abundance in the sputum, BAL fluid, airways and lung parenchyma of COPD patients and are believed to be important in the progress of the disease [16]. Neutrophils are also met in high numbers [18, 32] in the peripheral circulation of COPD patients however it is not clear if this occurs because of the existing lung pathology [16]. Neutrophils are possibly involved in the secretion of mucus and the distraction of alveoli by enabling the emission of serine proteases and matrix metalloproteinases. Despite the fact that a correlation has been found between the number of neutrophils and the drop of

FEV_1, and the number of neutrophils in the sputum and the severity of COPD and the level of lung distraction, the role of neutrophils has yet to be determined[16]. Although the exact mechanism that activates the large number of neutrophils is not known, chemotactic signals from LTB4, IL-8, CXC chemokines could be the stimulant [16].

However, the increased number of neutrophils are more prominent in other respiratory diseases like cystic fibrosis and bronchiectasis. In those diseases the elastolysis is not as protuberant as was expected [16]. Furthermore, the effect of genetic factors to neutrophils' abnormalities or to neutrophils susceptibility to smoking or other agents cannot be excluded [18].

Macrophages, like neutrophils, are increased [32] in the sputum, lung parenchyma, BAL fluid, and airways of COPD patients. In emphysema, they are found in the walls of destroyed alveoli and they make neutrophils produce inflammatory proteins and elastolytic enzymes [16]. Neutrophil elastase prevents the macrophages to take apoptotic neutrophils leading to an increased number of airway neutrophils [27]. All problems created in the phagocytosis may explain, at least partly, the increased number of viral and bacterial colonization in COPD patients [16].

T – lymphocytes are increased in COPD patients compared with healthy subjects. An association was found between alveolar distraction, airflow obstruction and the increased number of T – cells [16]. The CD8+ and CD4+ cells that are found in larger numbers in the airways od COPD patients, under normal circumstances, increase because of an airway infection [32]. Interestingly, the increased concentration of CD4+ and CD8+ in peripheral

blood circulation was linked to better lung function [28]. It is speculated that in COPD they increase because of the bacterial and viral colonies [16] and they cause apoptosis of alveolar epithelial cells [16].

Dendritic cells, placed in strategic places on the surface of airways, are fast activated when a foreign substance is inhaled and activate among other cells macrophages, neutrophils and T – cells causing all the aforementioned effects (figure 6).

Dendritis cells and cigarette smoke

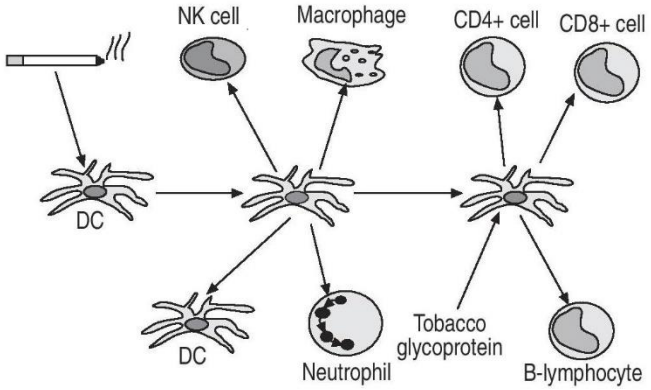


Figure 6. The implication of dendritic cells in the pathophysiology of COPD as they are activated by cigarette smoke and tobacco glycoprotein resulting in recruitment of neutrophils, macrophages, natural killer cell, CD4+, CD8+ T – lymphocytes and B – lymphocytes (Modified from: Barnes et al, 2003).

Lastly, epithelial cells, are accused of activating inflammatory mediators (like TNF-a, IL-1β, GM-CSF, IL-8 etc.), and proteases in COPD. Epithelial cells, are in the first line of defense, and secrete mucus in order to defend the potential patient from bacterial or any other kind of inhaled threat. They also produce anti – oxidants, antiproteases and different kinds of defensive peptides and are involved in tissue repairment [35] (figure 7).

COPD and proteins

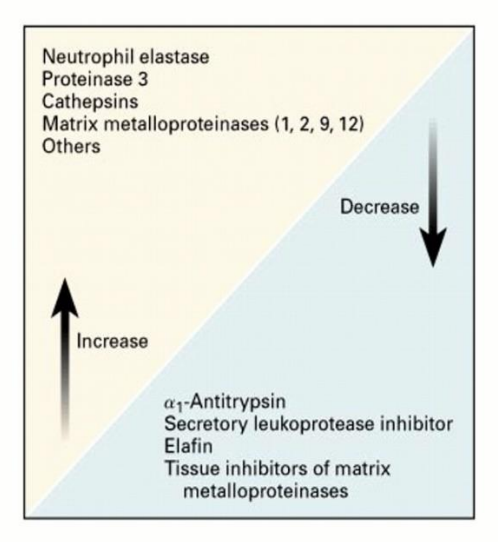


Figure 7. The effect of COPD in micro level (Modified from: Barnes, 2000)

Composition of skeletal muscles and muscle fibers

Each muscle is composed of many motor units. A motor unit is the smallest functional element of a muscle that produces force. It consists of a motoneuron and the muscle fibers it innervates. There are two main categories of motor units: the slow twitch and the fast twitch [36]. The fast twitch muscle fibers are subdivided to fast twitch fatigue resistant, fast twitch intermediate and fast twitch fatigable which differ in size, metabolic status and properties (figure 8). Each muscle fiber type has aerobic profile according to the energy it consumes (I, IIa, IIx, and IIb) or according to myosin heavy chain (MHC) it contains (MHCslow, MHC2A, MHC2X, and MHC2B) [4, 36]. Human muscle fibers formerly identified as type IIb fibers by histochemistry, express the IIx MHC isoform rather than the IIb isoform [4]. So, Type I fibers are slow twitch, have a predominantly oxidative metabolism, and are very resistant to fatigue. Type IIx are fast-twitch fibers, have an anaerobic metabolism, and are low fatigue resistant. Type IIa fibers exhibit intermediate physiological and metabolic

profiles [5]. The different muscle types exhibit a different behavior towards Ca^{2+}. The amount of Ca^{2+} released from the sarcoplasmatic reticulum, the differences in sarcoplasmic reticulum Ca^{2+} reuptake, and the differences in the Ca^{2+} sensitivity of myofibrillar proteins, could account for the difference in the force/ frequency relationship between motor units [4].

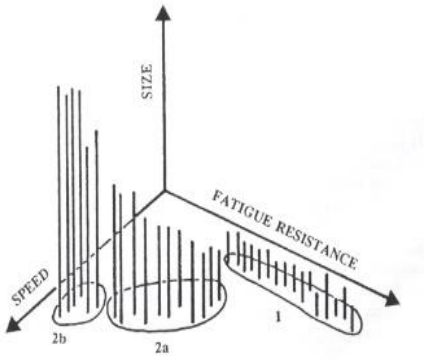


Figure 8. Depiction of the different characteristics of the various muscle fiber types.

Each motor unit generates a certain amount of force depending on the innervation ratio, and cross – sectional areas [4], the arrangement of muscle fibers according to their pennation angle, muscle length, joint angle, and contraction velocity [11]. The cross-sectional area within the unit has a strong relationship with muscle force and its sensibility to Ca^{2+} [4].

During a contraction, a specific order is followed in the muscle fiber recruitment. The first to be recruited are the slow twitch muscle fibers, followed by the fast-twitch fatigue-resistant, then the fast-twitch fatigue intermediate (Fint), and lastly the fast-twitch fatigable (FF) fibers [4].

The motor unit firing and threshold are affected by resistance exercise. The motor unit firing and discharge rate increases significantly and the motor unit

recruitment threshold decreases [4]. The way exercise training affects the muscles of COPD patients is going to be thoroughly analyzed in a later chapter.

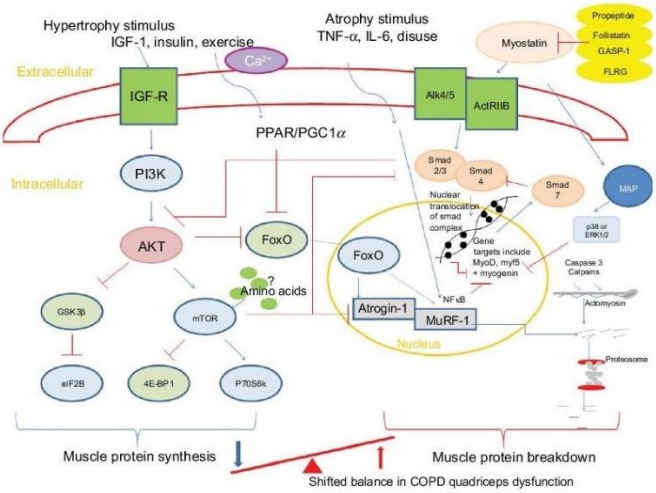
COPD and muscles

Undeniably, COPD negatively affects the muscles of the patients. 4 – 35% of COPD patients have reduced muscle mass [34]. It has been shown that after an acute exacerbation leading to hospitalization, quadriceps force and hand grip force drop significantly [37]. A strong correlation was found between the decrease in quadriceps strength and less improvement in walking time one month after discharge [37] and between muscle mass of COPD patients and mortality and morbidity [38]! Hypoxemia, disuse, aging, nutritional depletion, medication, systemic inflammation, smoking and oxidative stress are the basic factors that cause muscle fatigue and impaired endurance performance [13]. Sedentarism and aging have been accused for much of the symptomatology introduced in the muscles of COPD patients, however, they may cause muscle atrophy but not the muscle fiber swift that is met in COPD [24, 36] and is going to be further analyzed in a following chapter.

COPD is known to cause imbalance in the protein synthesis and breakdown (figure 9.) which leads to muscle atrophy and in turn leads to weakness and regional disorganization of the myofilaments [34]. The reduction in muscle contractile met in COPD influences tropism [39]. The maximum voluntary contraction of COPD patients (with no comorbidities) was found to drop to 43% whereas endurance dropped to 73% compared to healthy subjects [40]. The atrophy of the peripheral skeletal muscles, a main systemic characteristic of COPD, affects the exercise capacity of patients, their quality of life and is associated with reduced health status and mortality [4, 15, 34]. COPD seems to

affect quadriceps more. The fall in quadriceps muscle twitch force was greater [7], increasing the level of fatigue. Interestingly, there was no correlation between muscle resistance to fatigue and lung impairment or physical activity levels [40]. In COPD there is a contractile dysfunction which also leads to muscle weakness. The low levels of potassium, phosphorus, calcium and magnesium seem to contribute to this dysfunction [28].

Muscle protein synthesis and breakdown



→ Muscle atrophy

Figure 9 Summary of pathways controlling muscle protein synthesis (MPS) and muscle protein breakdown (MPB). The role of myostatin has also been included. Myostatin is held in an inactive state by its pro – peptide. Follistatin, and inhibitory binding proteins – growth and differentiation factor – associated serum protein – I (GASP-I) and follistatin-like related gene. (FLRG) as shown. Upon activation it binds to its transmembrane receptor activin receptor type IIB (ActRIIB) which then forms homodimers with activin receptor like kinase 4 or 5 (Alk 4/5). The SMAD signalling pathway is then activated and translocation of this transcription factor complex to the dependent manner. Activation of MAP kinase is mediated via myostatin either via p38 or ERK1/2, which leads to the blocking of genes involved in myogenesis (Modified from: Donaldson et al, 2012).

Muscle weakness is not equally distributed to the muscles of the body. Muscles of the upper arms and respiratory muscles are less vulnerable to the atrophying process compared to the muscles of the lower limbs as were the more distal

muscles compared to the proximal ones while the quadriceps muscle is greater affected compared to the other thigh muscles and directly correlated to mortality [4]. Correlated to mortality is also the reduced cross – sectional areas met at the muscles of the patients and the mid arm muscle area [15]. Quadriceps' muscle strength is reduced by 20% – 30% [2] or according to other findings, up to 40% [17], hamstring cross – sectional area was reduced by 21% and adductor cross – sectional area was reduced by 30%, whereas the cross – sectional areas of elbow flexors and adductor pollicis and the grip strength of COPD patients were unharmed [2].

The muscles of COPD patients are affected macroscopically (stamina, strength and resistance to fatigue etc.) and microscopically (fiber type shift, hypoxia, oxidative stress etc.). The following chapters refer to the effects of COPD on peripheral muscles, as well as the way the skeletal muscles are affected.

How COPD affects muscles in the molecular level

As mentioned previously, COPD affects the muscle system both microscopically and macroscopically. Complicated pathways and signaling mechanisms stimulating anabolic and catabolic properties of the muscles' proteins have been implicated [17] (figure 10). In this section the major contributing factors at a cellular and molecular level are going to be examined.

Protein balance mechanisms

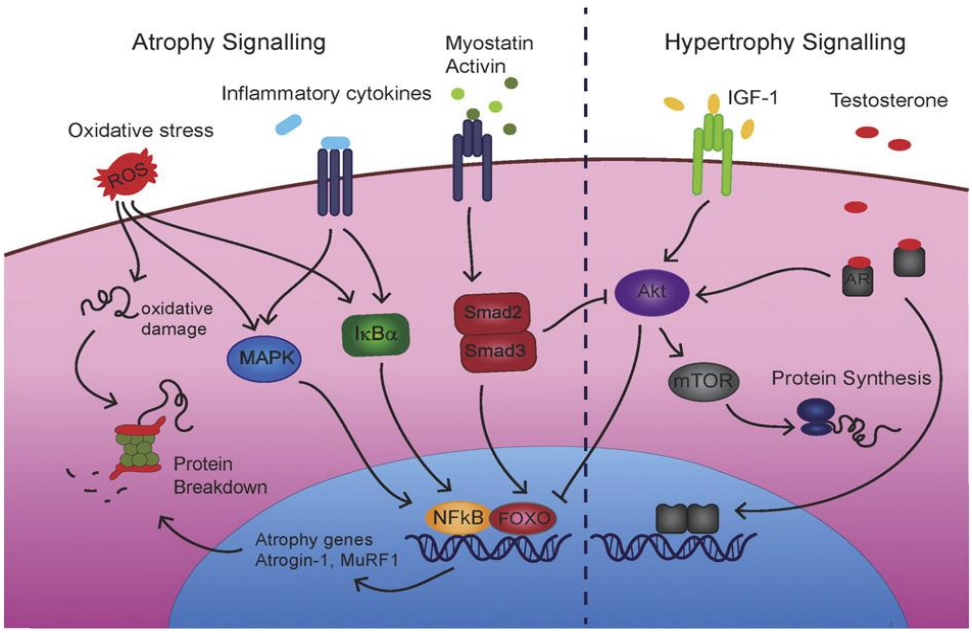


Figure 10. Signalling pathways regulating atrophy and hypertrophy of skeletal muscles. Oxygen reactive species, mitogen-activated protein kinase, FOXO (forkhead box), insulin – like growth factor, protein kinase, Akt etc all contributing to the protein balance (Modified from: Passey et al, 2016).

1) *Oxidative stress*: Oxidative stress occurs when the direct oxidative stress exposure or indirect production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overcome tissue antioxidant capacity [7, 16]. Oxidative stress may alter and damage the structure and function of membrane lipids, proteins, and ribonucleic acid (DNA), eventually leading to cell injury and death [4, 16]. The oxidative imbalance that leads to oxidative stress is speculated to be involved in COPD pathogenesis [39]. The most important antioxidant in the airways are some enzymes called catalase, other enzymes called superoxide dismutase (SOD) and glutathione which is formed by the enzyme c – glutamylcysteine synthetase, and glutathione synthetase [16]. In the lung, the extracellular anti-oxidants increase their levels as a response to cigarette smoke and oxidative stress whereas the

intracellular anti – oxidants levels are not found particularly increased [16]. ROS and RNS are usually found in low levels in the muscles, however in COPD their concentration increases [7]. ROS and RNS target several enzymes found in the mitochondrial respiratory circle and glycolysis and affect muscle contractility [7]. The increased levels of TNF met in COPD patients, contributes in the upregulation of mitochondrial cytochrome oxidase [28]. Exercise and even exacerbations increase oxidative stress in the blood and muscle tissue of COPD patients [4, 16] while the antioxidant enzymes are reduced in COPD [7]. Oxidative stress is found in the muscles of COPD patients even after only mild exercise [41] or even during resting, where the level of protein oxidation and nitration in the blood and limb muscles of COPD patients are higher [4, 18]. Even smoking induces oxidative stress [18]. The increase of oxidative stress induces proteolysis and the expression of ubiquintin – proteasome (UbP) components [4, 17].

Muscle wasting was related to oxidative stress and inversely correlated to exercise capacity, body composition and quadriceps strength and endurance [5]. It can be ratiocinated that the better the physical activity levels of a COPD patient, the less the oxidative stress either systemic or local. What is interesting though, is that the high levels of ROS partly as a result of the systematic and local inflammation met in COPD, led Maltais and partners [4] logically to the speculation that the increase of ROS would in turn increase oxidative stress; however, Barreiro and Gea [5], found no interrelation between oxidative stress and inflammation.

2) *Hypoxia and hypoxemia*: Hypoxemia is basically the drop of the arterial level of O_2 (Pa_{O2}) and hypoxia the drop of oxygen concentration in the tissues. Pa_{O2} correlates with exercise endurance [7] and is one of the measurements that is used for the diagnosis of COPD [28]. The exact mechanisms though which hypoxia affects muscle mass is not yet known, however, probably through several molecular mediators [5] hypoxia was found to cause defective myogenic processes, increase proteolysis and cause a decline in muscle mass [4, 7, 28]. It is a contributing factor to muscle atrophy and may also compromise muscle oxidative capacity and capillarization [4] and predispose to muscle fatigue [7] which would make sense since hypoxia is suggested to reduce the expression of myosin heavy chains [28]. The effect of hypoxia to muscle mass is also supported by the reduction in muscle mass of healthy subjects that spent time in high altitudes [28]. However, the level of oxygen in the blood was irrelevant to endurance [40].
3) *Ubiquitine proteasome pathway (UbP)*: COPD patients are suggested to have what is called an “anabolic resistance”, meaning that the muscle protein synthesis is in low levels [2]. The combination of oxidative stress, hypoxia, inflammation with muscle disuse, activate the ubiquitine proteasome pathway, causing protein degradation, which is confirmed by the high levels of ubiquitine degraded muscle proteins found in the muscles of COPD patients [34, 42, 43]. UbP also probably causes myogenesis inhibition and decreased protein synthesis [34, 43].

4) *Hypercapnia*: Hypercapnia is the rise of CO_2 levels in the arterial blood stream. It is a common phenomenon in patients with COPD especially

during exacerbations [5]. Hypercapnia causes a drop of pH thus creating oxidative stress and affecting muscle proteins [4] and is also believed to enhance UbP system and reduce protein anabolism [5]. Similarly to oxygen levels, the level of carbon dioxide was not found to affect endurance [40].

5) *O_2 delivery*: Everything in the human body needs O_2 to work properly. Therefore, it is essential that O_2 circulation, delivery and exchange takes place harmoniously, so as everything in the human body to work properly. Everything that affects O_2 delivery or extraction, directly affects, beside everything else, muscle function, O_2 levels, and blood pH. O_2 delivery in the limbs is affected in numerous ways. Firstly, In COPD patients, the blood flow to the peripheral muscles is compromised compared to the blood flow of the respiratory muscles [4]. Secondly, vasoconstriction is found in COPD patients contributing to muscle fatigue [4, 34]. Interestingly though, only 30 – 40% of muscle fatigue was found to be directly related to O_2 issues [44]. In addition, the capillaries are sparser in COPD patients, which affects the gas exchange and the removal of cell respiratory residues like CO_2 and lactate, the accumulation of which contributes to oxidative stress. [4, 5, 19, 45].

   The gas exchange between oxygen and carbon dioxide is affected by the diffusion parameters. Diffusion parameters were found decreased and positively correlated with FEV_1 and vital capacity [24]. Furthermore, COPD patients show higher O_2 requirements which could be attributed to higher energy requirements and ATP consumption apparent by the high concentration of byproducts of glycolysis (glucose-6-phosphate, glucose-1-phosphate, and fructose-6- phosphate as well as phosphofructokinase, and lactate dehydrogenase activities) even in resting muscles [4] and at the same

time high energy phosphates are in low concentrations [2, 4]. Oxygen supply along with oxidative capacity reflect muscle's endurance and fatigability [11].

6) *Capillarization*: COPD patients' quadriceps were found to have fewer and more sparse capillaries [2, 4, 5], correlating to the levels of fatigue after cycling [5]. Reduced capillary bed has been proven to be an early mechanism for systolic arterial blood pressure which occurs to 40 – 60% of COPD patients. What is more, capillary contacts with muscle fibers in general decrease [2, 38] and specifically with type IIa and type I, diminish [34]. Angiogenesis, and of course capillarization is partially regulated by a vascular endothelial growth factor.

7) *Lactate:* Lactate, as a metabolic residue is accumulated in the muscles and affects Krebs cycle in the mitochondria therefore, it can be associated with muscle fatigue [4]. As far as the accumulation of lactate is concerned, it is very possible that an enzyme, called pyruvate dehydrogenase complex (PDC) that is situated on the membrane of the mitochondria plays an important role. This enzyme controls the entrance of pyruvate into the mitochondria where the Kreb's cycle operates. Increased lactic acidosis increases CO_2 production resulting on acidemia and premature muscle acidosis which lead to muscle fatigue [4]. Furthermore, the lower concentrations of adenosine triphosphate and creatine phosphate results to an impaired phosphorylation oxidative capacity which leads to a more anaerobic profile and accumulation of lactate [2]. High concentration of lactate is a limiting factor of exercise.

8) *Inflammation:* In systemic diseases like COPD, a local [7] and / or a general inflammation, also called systemic, is present [28]. Inflammation and pro – inflammatory cytokines markers are noticeable in the lung parenchyma as well as the tissues [28]. In the literature a correlation has been identified between the inflammation and muscle atrophy [4]. The presence of several cytokines (including tumor necrosis factor-alpha (TNFa), interleukin-8 (IL8), IL6 [2, 7, 28], soluble TNF receptors 55 (sTNF-R55) and 72 (sTNF-R75) [7] induced by the inflammation possibly start the UbP system and transcriptional activities like FOXOs [17, 28] and initiate a series of cellular responses like macroautophagy and apoptosis which lead to muscle atrophy. Interestingly, these factors were increased in the blood circulation, but were not detectable in a vastus lateralis biopsy during an exacerbation [37]. In COPD, adhesion inflammatory cells like Mac – 1 (CD11b), are elevated, however, during exacerbations the levels of circulating neutrophils dropped [28]. In COPD in general TNF-a increases [17] but in severe COPD patients, TNF-a was found five time above the normal rates [7]. TNF-a reduces skeletal muscles' oxidative capacity and inhibits mitochondrial biogenesis [7]. During exacerbations TNF-a, cytokines and macrophages level deteriorate [28]. However, no matter how logical the effect of the inflammation sounds, its role is questioned since even during and exacerbations there is not enough data in the literature to support the presence of inflammation in the quadriceps muscle [4, 5].

9) *Growth factors*: A growth factor of interest is Myostatin. Myostatin inhibits myogenesis and is linked to muscle tissue homeostasis and muscle strength. Myostatin inhibits the cell cycle progression and suppresses the

myoblast proliferation [4]. Some researchers report that myostatin levels are increased in COPD patients [2] thus negatively affecting myogenesis, while others report ambiguous results as to whether myostatin levels in COPD patients' muscles increase or not [5, 15]. Another growth factor that is probably involved in the COPD pathology is the insulin – like growth factor 1 (IGF-1) which is affected in COPD [17]. IGF – 1 promotes muscle growth with the intermediation (activation or inhibition) of some kinases (AKT, p70S6, GSK3b) [2, 15]. Except for muscle growth, IGF-1 also suppresses protein degradation [4, 15]. IGF-1 was found to decrease during an acute exacerbation [15].

10) *Energy balance*: The dietary habits of a COPD patient is very important as both energy and protein needs must be met in order to prevent muscle atrophy. A disorder in the energy intake and/ or protein out-take leads to the different body composition phenotypes [4]. However, cachexia, which mainly affects COPD patients should not be confused with malnutrition. Besides cachexia, sarcopenia (loss of muscle mass without overall weight loss) also affects COPD patients [19]. Unfortunately, the higher a COPD patient scores in the GOLD scale, the lower the fat free mass index (FFMI). Skeletal muscle wasting assessed by FFMI occurs up to 40% of COPD patients [17]. FFMI on its own constitutes a mortality predictor even in COPD patients with normal body mass index (BMI). Patients with low body mass index (BMI), presented greater fragmentation of their DNA in their vastus lateralis [5]. COPD patients' BMI was found to be dropping [46] (figure 11), however, BMI was not the most effective way to evaluate muscles' characteristics. A drop in FFM to less than 15 or 16 kgr/m^2 to men and

women respectively was associated with increased mortality [4]. A similar index is intramuscular fat. COPD patients had 35% more intramuscular fat compared with healthy individuals with matched age, gender, body mass index and physical activity [47]. The latter provides proof that changes occurring because of COPD to the skeletal muscles, is not identical to changes occurring in healthy individuals with low physical activity status, and sedentarism might possibly affect, but is not the reason for those changes.

Body mass decrease in COPD patients

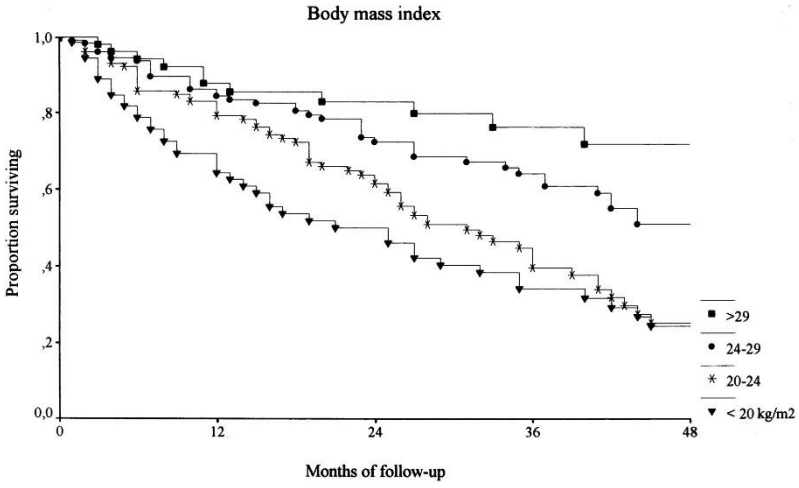


Figure 11. The BMI in COPD patients. (Modified from: Schols et al 1998)

11) *Corticosteroids*: The corticosteroids are a very common category of drugs that COPD patients use extensively. They are used either during an exacerbation, or long term for controlling chronic symptoms [7]. They are found to successfully inhibit IL-8, TNF-a and MMP-9 macrophages, however they fail to inhibit proteases and macrophage induced cytokines [16]. Small dosages for a long period of time, or high dosages for even short periods of

time can promote steroid induced myopathy [7]. They affect muscle fibers, especially type IIx, which after the extensive use of corticosteroids become atrophic [4].

12) *Mitogen Activated Protein Kinases (MAPK)*: In a cellular level, there is a chain of proteins that communicates a signal from the membrane of a cell to the DNA in nucleus of the cell. The MAPK pathway is believed to be involved in COPD patients [17] in the initiation of the UbP pathway which in turn leads to proteolysis [2]. Of all the MAPK proteins the p38 is at the spotlight, since its inhibition is linked with the prevention of muscle atrophy and its stimulation leads to the expression of E3 ligases which are muscle specific [4]. Furthermore, specific muscle proteins like creatinine kinase and myosin (MyHC) were found less in the vastus lateralis of COPD patients with severe muscle wasting [5]. Lastly, overexpression of MAP kinase phosphatase-1 (MKP1) in type IIx fibers was found to increase the synthesis of type I and IIa myosin heavy chains [34].

13) *Calcium*: An imbalance in the regulation of calcineurin could play a role in the fiber type shift. Calcineurin is a calcium-dependent phosphatase. The administration of the specific calcineurin inhibitor cyclosporine A to rats resulted in an increased in type II fiber proportion [34]. Also, in COPD, the intracellular calcium homeostasis regulation is compromised [34]. Vitamin D, which is often found in low concentrations in COPD patients may affect the calcium regulation in the sarcoplasmatic reticulum [2] while the calcium sensitivity of force generation is reduced [42].

14) *Autophagy:* Autophagy, is the process through which unnecessary or dysfunctional proteins are dissembled. A rise in autophagy markers were found in the vastus lateralis of patients with advanced COPD [5].

15) *Vitamin D*: COPD patients often have low concentrations vitamin D serum. Low levels of vitamin D are associated with reduced muscle strength and increased risk of fall [4]. Vitamin D influences calcium transport into the sarcoplasmatic reticulum and affects calmodulin, actin, and troponin C content and can also up-regulate the expression of IGF-1 [4]. The polymorphism of vitamin D receptors are associated with reduced (Fok I polymorphism) or greater (Bsm I polymorphism) quadriceps strength. This is true only for COPD patients, leading to the assumption that a gene environmental interaction plays a role [2]. Vitamin D deficiency is highly prevalent in patients with COPD Renin-angiotensin system. This system is expressed in skeletal muscle and produces angiotensin II that inhibits the IGF-1 signalization cascade stimulates NF-kB and, as a result, the UbP pathway. The renin - angiotensin system may have implications for the development of limb muscle dysfunction in COPD and interacts positively with myostatin. Myostatin in turn has been associated with a less oxidative muscle phenotype with lower proportion of type I fibers [4].

16) *Peroxisome proliferator-activated receptor-coactivator-1 (PGC-1)*. PGC-1 is another potential pathway for the shift in muscle fibers. PGC-1 mRNA levels in COPD patients' quadriceps were found low. Among other things, this pathway enhances the expression of myoglobin and troponin I both of which proteins are present in type I muscle fibers [34].

17) *Muscle fibers*: Muscle fibers have a tendency to change in response to many different factors like variations in the pattern of neural stimulation, loading conditions, availability of substrates, and hormonal signals. These factors are being perceived by multiple receptors, sensitive for different hormones, cytokines, metabolic sensors for phosphate concentration, oxygen and ROS, calcium – binding proteins and more [36]. It becomes apparent that many of the effects of COPD on muscles, like the increased concentration in ROS, the increase in cytokines, the differentiation in the Ca^{+2} uptake, all tend to lead to a change in the muscle fiber profile.

It is considered a fact nowadays, that muscle fibers' profile in COPD patients change. Muscle fibers change in dimensions and become smaller, which reflects an imbalance in protein turnover with protein loss, and consequent muscle atrophy, and in type, which reflect a reprogramming of gene transcription leading to a remodeling of fiber contractile properties [34, 36], with a tendency to shift from oxidative (type I) to glycolytic (IIb and IIx) [19, 38]. What is very interesting is that the fiber profile changes inversely in the respiratory muscles compared to the muscles of the limbs. In the peripheral muscles of COPD patients, fiber type I seem to atrophy and lessen in favor of muscle fibers type IIb (or IIx) compared with healthy individuals [2, 7, 15, 34]. This change in muscle fiber type is associated with increased mortality and morbidity [38]. But even in the peripheral muscles this structural change is not evenly distributed; the muscles of the upper limbs are less affected compared to the lower limbs [4, 7]. The shift in muscle fiber type seems responsible for resilience to fatigue being compromised at the expense of strength in peripheral skeletal muscles [15, 24]. In COPD patients the

expression of Myosin chains also changes. The coordinated expression between myosin heavy chains and myosin light chain isoforms alters [24]. There is a noticeable loss of myosin heavy chains [42]. It is not clearly stated in the literature if the shift in fiber type can account for the oxidative profile changes met in COPD patients' muscle or the other way around. No matter which happens first though, it results in COPD patients being susceptible to fast fatigue and therefore being unable to sustain any type of exercise for long. The more severe the COPD, and the less the BMI, the less type I fibers are met [4]. Furthermore, muscle fibers were found to be of smaller size in COPD patients contributing to reduction in muscle mass [5]. Moreover, the cross-sectional areas are decreased in COPD patients [4, 7] by 25 – 35% [34]. The cross-sectional area drop that is met in the muscles of COPD patients occurs in all types of fibers [34]. COPD effect on muscle fiber switch defer compared to sedentarism. Kim et al [7] concluded that in both cases type I levels of muscle fibers drops, but in the quadriceps of sedentary adults it drops from the normal distribution of 60 – 65% to 40%, whereas in COPD it drops to 19%. However, their findings are a little bit different compared to Satta et al [24] who report that there was only muscle atrophy and no fiber type swift at all in prolonged bedrest as opposed to COPD. As far as age is concerned, it was found that with age passing there is a decline in muscle fiber type II [34], quite the opposite from what occurs in COPD. A meta – analysis by Gosker et al [48], revealed that there was a strong correlation between FEV_1 and FEV_1/FVC and the proportion of muscle fiber type I and between FEV_1 and the proportion of fiber type IIx, also supported by the

findings of an older study by Satta et al [24], where no relation was found between Pa_{O2} and fiber type I distribution.

18) *Muscle cells' structural abnormalities:* COPD patients show several structural abnormalities in their muscle cells [5]. Membrane and sarcomere are often disorganized, and the density of the mitochondria lessens [5, 7, 19]. Mitochondria have their own genome and produce most of the cell's adenosine triphosphate (ATP). Their function is altered in COPD patients reducing muscle's oxidative capacity. The reduction is consistent with the shift in the muscle fibers in COPD patients (type I shift to type IIx). It has been proven that the density and the function of the mitochondria of the lower limps in COPD patients as well as mitochondrial biogenesis are reduced [4, 7]. Also, in the vastus lateralis, a modification in the phenotype of the heavy chain of myosin was altered (figure 12), supporting the notion that the deconditioning met in COPD patients are not solemnly justified by the low physical activity levels or the sedentarism [49]. The reduced oxidative capacity of mitochondria corelates to the decreased levels of quadriceps endurance and vice versa [7].

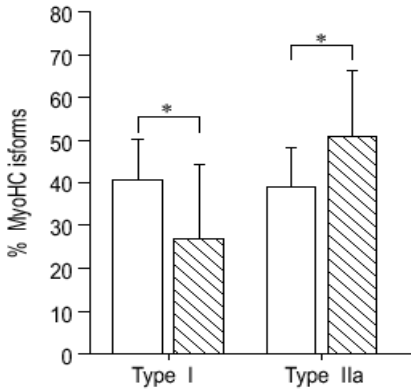


Figure 12. The difference in muscle fiber type between healthy subjects and COPD patients (Modified from Maltais et al, 1999)

How COPD affects muscles macroscopically and functionally.

"Strength is defined as the ability of the muscle to develop maximal force, and endurance is the ability to sustain a submaximal force over time" [5]. "Fatigue is the reversible reduction in force generated by the muscle during a given task" [11].

COPD patients' functionality and quality of life is compromised by a prevalent muscle dysfunction and increased dyspnea [4], translated as a reduction in muscle strength and/ or reduction in muscle endurance [5] and expressed in a constriction of patient's walking capacity, physical activity and exercise intolerance [11]. Furthermore, quadriceps strength is inversely proportional to mortality, and impaired balance and increased risk of falls grows accordingly to weakness [4].

Exercise tolerance is limited by a compromised cardiac output by the reduced venous return and muscle weakness [13] and is also affected by age, smoking nutrition, medication and chronic inactivity [7]. In return, this leads to COPD patients showing limited activity levels and deterioration of their quality of life. However, the lower physical activity levels cannot solemnly explain the excessive muscle weakness (figure 13). During bedrest experiments where the muscle deconditioning is taken for granted, only 50% of muscle strength reduction is explained by the reduction in muscle mass. The rest 50%, possibly, came as a result to reduced neural activation [4]. It goes without saying nevertheless, that the inactive profile that COPD patients adopt affect their lives in many different ways regardless of the reason behind it. Especially as the disease worsens, the patient becomes more and more inclined to stay in and avoid any sort of physical activity, while he becomes more isolated.

Inactivity in COPD is linked to breathlessness

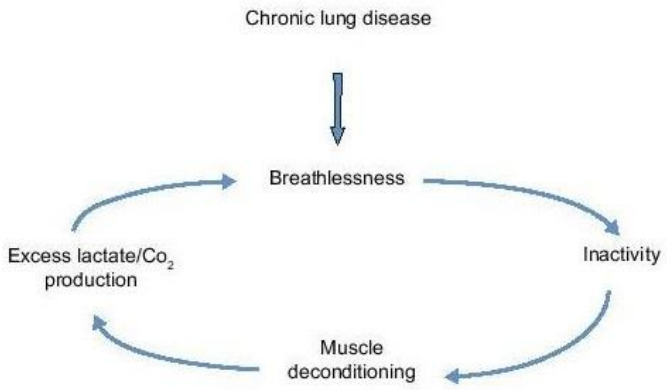


Figure 13. The downward spiral of the disease (Modified from: Donaldson et al, 2012)

What needs to be pointed out is that muscles are affected *independently* of the degree of airway limitation [4, 5] although there is a correlation between muscle fatigue and decreased endurance [5]. Muscle weakness varies between 20-40% while endurance and fatigue vary between 30 – 80% [11] independently from sex [4]. The endurance of the impaired quadriceps muscle of COPD patients was not found to be corresponding to the level of physical activity according to Maltais and colleagues [4], whereas Kim et al [7] found a correlation between physical activity levels and quadriceps muscle endurance. What is more, not all muscles are affected to the same degree. Muscle strength and endurance of the upper arms and respiratory muscles are less affected compared to muscles of the lower limbs [4, 11] and at the same time, strength of the distal muscle groups was less affected compared to strength of proximal muscle groups [4]. Lower limbs lose 20 – 30% more strength compared to the rest of the body which leads to poor exercise performance, increased dyspnea and reduced quality of life [7]. The magnitude of thigh mass loss is greater compared

to the whole body mass [7]. At the same time, during normal walking, the gastrocnemius and the tibialis anterior muscle of COPD patients showed greater signs of fatigue [5]. Endurance drops by approximately 30% in COPD patients of moderate stage [7] and correlates with physical activity levels.

It is known that COPD is characterized by dynamic and/ or static hyperinflation and that the limited expiration capacity is mainly responsible for the hypoxemia. Lower oxygen levels in turn, create a drop of the pH. Endurance was inversely linked to hypoxemia and dynamic hyperinflation [4]. This implies that the higher the hyperinflation and the lesser the oxygen levels the less a muscle can sustain a work load. In other words, in case of hyperinflation, COPD patients demonstrate impaired muscle endurance due to ventilatory constrains [4].

PULMONARY REHABILITATION

So far, it has been demonstrated how much skeletal muscles in COPD are compromised. Not only as far as strength or endurance is concerned but in cellular level as well. This manifestation of COPD affects the patients' quality of life and literally their life since there is a correlation between muscle welfare and mortality. It goes without saying that an intervention to invert such a situation was found to be necessary many years ago. The first research on cardiopulmonary rehabilitation was conducted in 1945 by Epskine and Shires and studied the impact of respiratory, muscle training and massage, in patients that had suffered from embolism. A research of Saltin and partners conducted in 1966 [50] investigated the effects of bedrest and exercise training in a group of healthy, twenty year olds. Their research revealed that only three weeks of bedrest was sufficient for heart rate, systolic blood pressure and body fat to

increase and muscle force to drop. The breakthrough in pulmonary rehabilitation however, came thirty years later, with the publication of two studies of McGuire et al [51, 52], doing a thirty year follow up of the Saltin et al's research. They demonstrated how staying in bed for only three weeks had similar results with thirty years of age passing! In this study the subjects underwent a rehabilitation program for eight weeks after which the effects of bedrest were not only reversed but, in some cases, had improved compared to baseline. A main feature that was examined was maximal O_2 uptake which also increased after training (figure 14a and 14b).

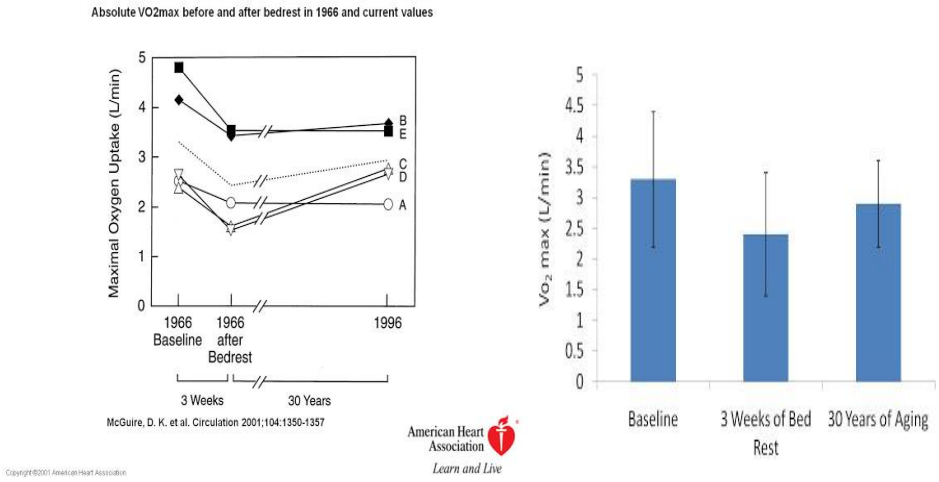


Figure 14a and 14b. The Vo2max, before the three weeks of bed rest, after, and 30 years later.

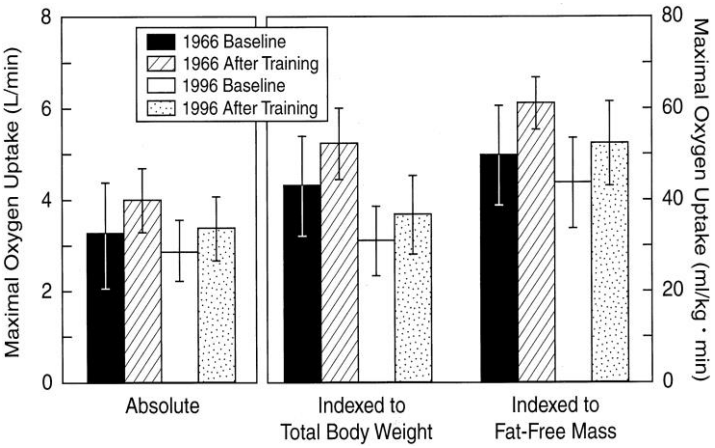


Figure 14c: Maximal oxygen uptake (L/min) from 1966 and the present study reported as absolute values, indexed to present body weight, and indexed to fat-free body mass. (From: McGuire et al. 2001)

Two key features derive from those two studies. One, bed rest, that generally put, could be named “muscle inactivity”, leads to a fast deterioration of the heart, muscle and respiratory system and increase in body fat. And two, muscle training could reverse and even improve those effects (figure 6c). Bed rest could be parallelized to sedentarism as boths main characteristic is muscle inactivity which is often met in COPD patients. The results of McGuire and colleagues researches [51, 52] support that muscle training is believed to be “a”, if not “the”, key component in COPD treatment. However, it must be stressed out that sedentarism and prolonged bed rest may lead to muscle fiber atrophy, but not to muscle fiber alteration as occurs in COPD patients [24].

Since COPD is a complicated systemic disease, pulmonary rehabilitation needs to be multidimensional, referring to the bigger picture and treating each patient differently and comprehensively. Pulmonary rehabilitation (PR) is defined as a “*comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors”* [15].

Besides exercise training, a PR program should include phycological support and dietary consultation [11]. Each PR program ought to be different, best suited to the needs of each patient [15]. The goal is to educate the patient how to self-manage the disease [11, 17, 53] and to change their behavioral attitudes [17]. In this study we are going to focus on muscle training. Muscle training doesn’t directly

affect gas exchange capability or lung mechanics, therefore, we can safely assume that most of the benefits derive from the improvement of the skeletal muscle state [2].

The muscle tissue is very adaptable. Unlike the lung pathology, muscle tissue impairments can be delayed and even reversed up to a point. At this particular quality is where exercise training programs are based on [17]. A PR program benefits all patients independently of the stage of the disease [4, 14, 15], age, sex, or level of dyspnea and functional level [15]. Pulmonary rehabilitation is considered the best non-pharmacological way to relief the burden of COPD symptom.

Exercise training (ET) is considered the golden standard of PR for improving muscle strength [17], for increasing functional capacity [2, 11, 17, 53] and improving symptoms like dyspnea, exercise intolerance and physical activity [2, 14] thus improving quality of life [4, 54] and health status in general [2, 53]. It is beneficial to peripheral muscles creating hypertrophy and muscle regeneration [55]. The quadricep's strength, endurance and fatigability has been shown to improve significantly with exercise training [2]. Since COPD is a disease that hasn't got a cure yet, a very important psychological benefit is that it gives the patient a sense of control over their condition [53]. Looking at the big picture, the financial burden of COPD is heavy. In UK alone, in 2002, the cost was up to 266 million pounds [53]! Therefore, besides the obvious gains for each individual patient, PR programs were found to reduce the cost of health care by reducing hospital admissions, reducing acute exacerbations, and decreasing hospital bed days [53].

Assessments

A patient's ability to perform an exercise is characterized by endurance and strength [15]. Along with reduced exercise capacity, COPD patients also complain about dyspnea [7, 17] and suffer from ventilatory limitations [17] which compromise their quality of life. Muscle strength on its own might be misleading because it reflects the action of fast twitch fibers [11]. Therefore, endurance tests, especially of the quadriceps should be included [40]. All of these elements should be estimated prior to the start of the rehabilitation because firstly this is the only way to assess the progress of the rehabilitation itself, and secondly, the correct amount of training loads or time of exercise for each patient ought to be decided. Endurance correlates with physical activity index, FEV_1, and Pa_{O2} [7].

Endurance

1) *Six minute walk test (6MWT).* The 6MWT is associated with impaired lung function expressed in FEV_1 [1]. The 6MWT requires a 30-m, flat, hard surfaced hallway, where the patient is asked to walk back and forth around cones set at the beginning and end of the 30 meters, as fast as he can, for 6 minutes (figure 15) [56]. The test measures the *distance* that the patient walked. The verbal communication before and during the test, is standardized and considered very important to minimize a potential bias by the tester. Some of the basic instructions that should be mentioned before the test include the patient being encouraged to *"…*walk as far as possible for 6 min" and that they "…probably will get out of breath or become exhausted*"*. Therefore, the patient is *"*permitted to slow down, to stop and to rest if necessary". During the test the tester should only use standard phrases of encouragement every minute with an even tone of voice; for example, "You are doing well. You

have 3 minutes to go". At the beginning and the end of the test the patient's oxygen saturation, heart rate, perceived dyspnea and leg fatigue on a Borg scale are generally documented, as well as the total distance walked (in meters) during the test. It is easy to perform since no special exercise equipment is required and easy to be perceived by the patients [58].

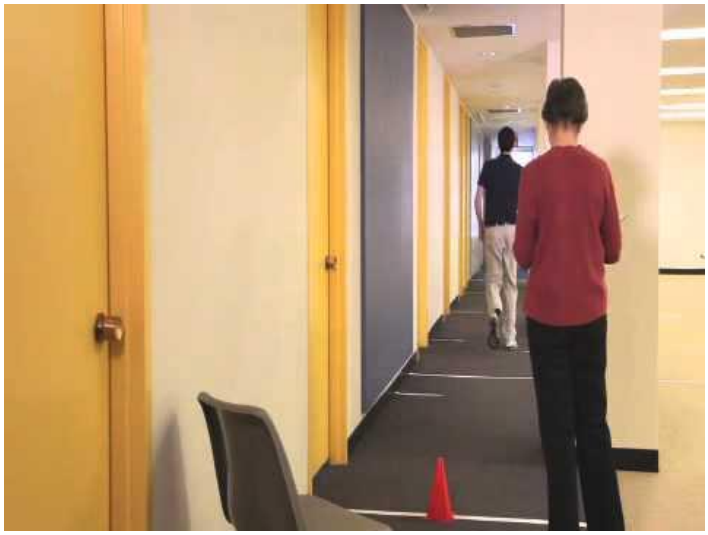


Figure 15. The six minute walk test

2) *Incremental shuttle walk test (ISWT)*. The ISWT is also a field walking test; however, it differs from the 6MWT as it uses an audio signal from a CD player to determine the walking pace of the patient back and forth on a 10 meter course (figure 16). The walking speed increases every minute, and the test ends when the patient is not able to reach the turnaround point within the required time. The *distance* walked is noted as a primary outcome parameter. The ISWT provides better insight of V_{O2} compared to the 6MWT and is able to determine maximum exercise capacity, however, it is a bit more complicated and includes cardiovascular risks [58].

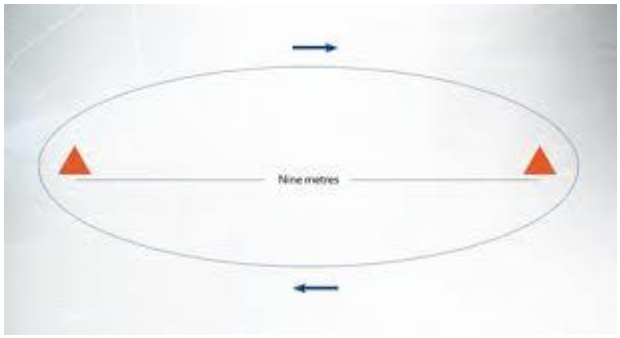


Figure 16. The schematic representation of the Incremental shuttle walk test.

3) *Endurance shuttle walking test (ESWT)*. ESWT is a variation of the ISWT. Patients are asked to walk at a speed equivalent to 85% of the peak speed achieved during the ISWT until exhaustion. Walking *time* is taken as outcome. The ESWT shows major improvements following pulmonary rehabilitation and is more sensitive to changes than the field tests of maximal capacity [58].
4) *Six minute stepper test (6MST)*. The 6MST aims at measuring the *number of steps* performed on a stepper (figure 17) in 6 minutes using a protocol that is equivalent to the 6MWT protocol. A step was defined as a single complete movement of raising one foot and putting it down [59]. The 6MST could be used to individualize aerobic training in patients with COPD [60].

Figure 17. A stepper used for the six-minute stepper test.

5) *Sit to stand tests (STST)*. The STST test determines the functional exercise capacity and status. In these tests, the times a patient is capable of sitting

and standing in a standard chair in 30 seconds and 60 seconds is estimated, or the time it takes a patient to perform a certain amount of repetitions (for example sit and stand for 5 times) (figure 18). These tests are as easy to perform (if not easier) as the 6MWT [58].

Figure 18. The sit to stand test

6) *Cardiopulmonary exercise test (CPET)*. CPET depicts the cardiorespiratory and muscular system. It reflects the entire oxygen transport system starting from the lungs and ending at the skeletal muscles. It is a handy tool for evaluating exercise capacity while it provides with all the necessary information that no other individual organ system function measurement adequately reflects [23]. With CPET, one can objectively determine the functional capacity, possible impairments and their degree, and even undiagnosed exercise intolerance. CPET is considered the gold standard for assessing exercise capacity (and Vo_{2max}) in COPD [15], however it is expensive, performed in limited places and only under doctor's supervision. During the test, the patient is constantly monitored with an EMG and breaths in a mouthpiece apparatus which calculates the respiration's gas volumes. His blood pressure is also measured frequently during the test. All the information go straight to a computer. The test can take place on a treadmill (figure 19b) or on a cycloergometer (figure 19a), with the treadmill having the

advantage since patients are more familiar with its use and more muscle mass in activated (higher need for oxygen by 5 – 10%) [23]. Many different protocols are being used, but are beside the point of this study and are not going to be analyzed further here.

Figure 19a and 19b. a) CPET on cycloergometer b) CPET on treadmill

Strength

Strength assessment is divided in volitional and non-volitional. The volitional assessments are affected by the subject [4], where the non – volitionals are more precise. For measuring the strength of COPD patients, measuring the quadriceps has been proven to be reliable [11] however the assessor should bear in mind that quadricep's strength is susceptible to muscle loss during exacerbations that might last for weeks [5].

Volitional strength assessment includes:

1) *Manual muscle testing (MMT)*. Manual testing with the 0-5 scale from the Medical Research Council is often used in clinical practice, but very insensitive to assess differences in muscle strength of values above grade 3 (active movement against gravity) [61] (table 2).

GRADE 0	No movement is observed
GRADE 1	Only a flicker or a trace of movement is seen or felt in the muscle or fasciculations are seen in muscle
GRADE 2	Muscle can move only if the resistance of gravity is removed.
GRADE 3	Muscle strength is further reduced such that the joint can be moved from full extension to full flexion
GRADE 4	Muscle strength is reduced but muscle contraction can still move against resistance
GRADE 5	Muscle contracts normally against full resistance

Table 2 *The grades of manual muscle testing according to the medical research council*

2) *Handheld dynamometry.* A hand held dynamometer is used to measure isometric muscle force. A steel spring is compressed, which moves a pointer on a scale or shows on a monitor the amount of force exercised, like for example the handgrip dynamometer (figure 20). Handgrip dynamometry has been shown to be reliable and reference values are available [62].

Figure 20. A handgrip dynamometer

3) *Computerized dynamometry* (Cybex, Biodex, Kin-Com etc.) is used to measure isokinetic and isometric strength of various muscle groups at different joint angles and contraction velocities [15] (figure 21)

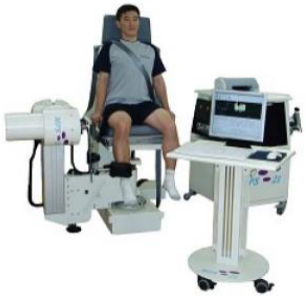


Figure 21. An evaluation of quadricep's strength via a computerized dynamometer.

4) *Strain gauge dynamometer*. A strain gauge dynamometer is used to estimate the isometric force of a muscle. It was proven to be valid and reliable [61].

5) *The one repetition maximum (1RM)*. Muscle strength is usually expressed as the maximal voluntary isometric force of a muscle [58]. The 1RM is considered the gold standard for assessing muscle strength [15]. It is fast, cheap, and doesn't require special training. It is also reliable and well tolerated by the patients [15].

And non – volitional assessment includes:

6) *Supramaximal electrical nerve stimulation*. A Supramaximal electrical nerve stimulation is the application via electrodes to the skin, enough electrical current as to activate all the nerve or muscle fibers in contact with the electrode [64].

7) *Magnetic nerve stimulation*. The magnetic nerve stimulation practically replaces the supramaximal electrical nerve stimulation since the latter is hard to perform and causes discomfort to the patient [15].

Dyspnea

Dyspnea is essential to measure. There are direct and indirect ways of estimating it. The direct methods include The MRC dyspnea scale, the Oxygen Cost diagram, the baseline/ Transitional dyspnea index, the UCSD shortness of breath questionnaire and the Complex breathlessness questionnaires. The indirect methods include the Visual Analogue Scale (VAS), the Borg CR – 10 scale and the modified Borg scale which resembles the VAS. Further on, the basic ones are going to be analyzed, including the St George respiratory questionnaire which mostly defines QoL but also includes dyspnea and is widely used in studies.

1) The Medical Research Council (MRC) scale. The MRC scale was first developed in 1959 and has been widely used ever since (table 3).

Score	Degree of breathlessness depending on activity
0	No breathlessness
1	Not troubled by breathless except on strenuous exercise
2	Short of breath when hurrying on a level or when walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 min walking at own pace
4	Stops for breath after walking 100 yards, or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing/undressing

***Table 3**. The MRC dyspnea scale (Modified from Fletcher et al, 1959)*

2) *Modified Borg scale 1 – 10*. The modified Borg scale, estimates dyspnea. It is very simple and easy to use. It can be expressed with words or pictures creating a very friendly interface for the patients. It was found to be valid and reliable [65] (figure 22).

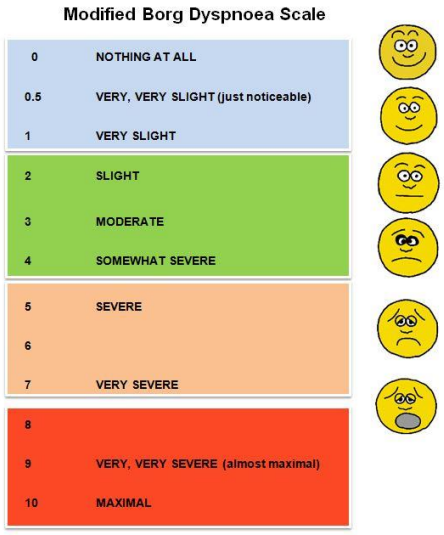


Figure 22. The modified Borg scale for dyspnea.

3) *The Saint George's respiratory questionnaire (SGRQ).* The SGRQ is a bit complicated and lengthy but is broadly used to evaluate dyspnea and health related quality of life, and is considered the gold standard of assessing it [66] (appendix 1).

The effect of pulmonary rehabilitation on the skeletal muscles of COPD patients

It is very clearly demonstrated in the Wasserman's figure bellow (figure 23), how the respiratory, the cardiovascular and the muscle systems directly co-affect one another and how closely they have to "work" together for the oxygen to be delivered. In simpler words, the lungs provide the necessary oxygen, the heart pumps it to the muscles and the muscles use it to provide the

mitochondria with the required energy. As a result, the muscles produce CO_2 which via the blood circulation regulated from the heart, arrives to the lungs where through the process of breathing CO_2 is released to the environment and is replaced by O_2, and the circle starts again. During activities that demand higher oxygen supplies, all three systems have to adjust as for everything to work properly. Pulmonary rehabilitation affects all three systems, and since they are obviously interlinked, by helping one system you improve them all. The muscular system is the main interest of in this study.

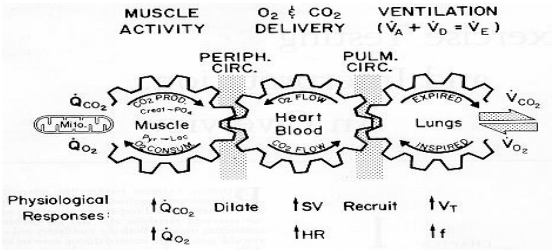


Figure 23. The Wasserman's conceptualization of the three systems during exercise

Pulmonary rehabilitation programs include strength training, also referred to as resistance training, and endurance training, also called aerobic training. The combination of the two different types of programs was found to be more affective [17, 38, 67], each contributing differently in enhancing functionality. Both training modalities, and the combination of those, were found to increase exercise capacity and reduce ventilatory parameters and heart rate [54]. Endurance training is believed to enhance mainly fatigue resistance and exercise tolerance [2, 54] while it has little effect on muscle atrophy and weakness [67]. It contributes in restoring the muscle fiber type imbalance through the modification of muscle fiber type II to type I [2, 55, 68] and increases the oxidative capacity of trained myofibers and the muscles' metabolic capacity [38], enhances

mitochondrial protein content [38] and increases the mitochondrial oxidative enzyme levels and the aerobic threshold and maximum oxygen uptake and decreases the creatine – phosphate recovery time (which also leads to greater exercise tolerance [39]. It also improves the exercise capacity, increases the cross-sectional area and induces the expression of IGF-1 [55, 68] and improves insulin sensitivity [38]. Endurance training consists of walking on ground or treadmill or cycling on a cycle ergometer, but an arm cycle ergometer is also recommended [15]. Endurance programs consisting of walking, are very effective in improving quality of life and exercise tolerance however, the cycloergometer is cheaper and induces less dyspnea [58]. Resistance training, consists of exercises with some sort of resistance like resistance band exercises or dumbbells etc., and increases muscle mass, arm and leg strength and exercise capacity [17, 67] and was found to better improve quality of life of patients [39]. The biggest advantage of resistance training besides enhancing muscle strength and growth, is that compared with endurance training, it does not burden the cardiorespiratory system as much [67]. The oxygen consumption and the minute ventilation is less, leading to a significantly lower level of the feeling of dyspnea [67]. Resistance training also increases the myosin heavy chain gene transcripts and the synthesis rate of muscle proteins [38]. A strength training program was found to be effective in increasing muscle strength and work efficacy [54]. Endurance training, as well as strength training can be performed eccentrically or concentrically. Lengthening muscle exercises lead to higher force generating capacity with low cardiopulmonary cost [69], which constitutes this kind of training very appealing, especially for patients with increased cardiopulmonary limitations. Eccentric ergometer endurance training (EEET)

was found to allow patients to work with five times more workload compared with concentric ergometer endurance training (CEET) with less ventilatory and metabolic requirements, meaning less dyspnea and less lower limb fatigue. Interestingly, there was a noticeable increase in isometric peak strength and thigh mass, but no muscle fiber hypertrophy, no cross-sectional area increase and no increase to the mitochondrial biogenesis regulatory factor (GC-1a) were noticed, as opposed to CEET where no thigh mass increase but there was a significant increase in cross-sectional areas, in type I muscle fibers and the GC-1a factor was increase twice as much as with EEET [69]. This could be partially explained by the two different kinds of muscle growth. Muscles can grow transversally, like in concentric training, or longitudinally, like in eccentric training, or, it could be attributed to gains in coordinative factors, that improve muscle strength [69].

General benefits of pulmonary rehabilitation.

COPD patients that undertook PR programs demonstrated a great deal of improvements. These improvements included reduction of dyspnea [14, 15, 17, 42], resistance to fatigue and, most importantly, quality of life increased [14, 17, 42] and mortality and hospitalization rate dropped [14]. More specifically, after a PR program, skeletal muscles hypertrophy, and regenerate [55], the thigh's lean muscle mass of participants increase [4, 70]. Because it increases for both healthy control and COPD patients' groups, it can be safely assumed that PR programs benefit all who participate for increasing muscle mass and functionality [14, 70], and prove once again how they could be beneficial for all stages of COPD. Quadriceps muscle strength, endurance and fatigability improved, and midthigh cross sectional areas increased [4]. The findings support that there is a variety

in the level each patient benefits from training and the same goes for healthy subjects as well. This phenomenon could be attributed to gene factors [4]. Because the effect of COPD on skeletal muscles are not evenly distributed across the human body, different protocols, concerning upper limb training, lower limb training or both modalities have been used. All three types of exercise have shown improvement as for dyspnea and in SGRQ [42]. However, upper limb endurance training seems to increase upper limb unsupported endurance, lower limb endurance training seems to improve 6MWD and combined endurance exercise training for both upper and lower limbs seem to improve both [42] thus making a combination of upper limb and lower limb training the preferred combination of exercise training.

PR programs were found to enhance the function of the respiratory system. Beside dyspnea, the dynamic hyperinflation was decreased [15]. An increase in V_{O2max} and a greater tolerance to restrictive ventilatory defect [14] leading to an increase in exercise tolerance was noted, depending though on exercise intensity [14] and oxygen consumption [42]. Furthermore, it was shown that physical activity can reduce the decline in FEV_1 [33].

Effects of exercise training in molecular level

As presented earlier, COPD affects the fibers of peripheral skeletal muscles. With ET programs, especially endurance training, independently if it is continuous or intermitted [4], the muscle fiber proportion of type IIx muscle fibers was reduced [4, 11, 68], to the same degree among patients of II – IV stage [4], but not to the same degree among patients of GOLD stage I and stages II, III and IV [68]. Quadricep's muscle mass [70] and cross-sectional areas [4, 11, 17] increased. Modifications like increased levels of muscle lactate, degradation of muscle

phosphocreatine (PCr) and loss of muscle ATP were found at COPD patients in much less work rates compared to healthy individuals [4]. Despite that, COPD patients that undertook endurance exercise training, reduced the decline of Pi/Pcr (the ratio of inorganic phosphate (Pi) to phosphocreatine (PCr) is a validated marker of mitochondrial function in human muscle [72]) during exercise, increased the activity of oxidative enzymes [4] increased oxidative capacity of quadriceps muscle [11] and reduced the lactic acid production [4, 11]. Most studies agree that the capillary to fiber ratio, and the capillarization was increased after an ET program [4, 19, 38, 39] with the exception of a study conducted by Gouzi et al [45] which supports that no significant capillary adaptation was found in COPD patients that undertook ET program (figure 24a and 24b). These different findings maybe underline the differences in molecular level between changes taking place immediately after exercise and in the long run, or could be because skeletal muscle adaptation like muscle hypertrophy or capillarization, that are found to vary extremely between studies, depend on the intensity and the duration of exercise training program [38]. It sounds reasonable that COPD patients could experience certain symptoms earlier compared with healthy subjects, but the bigger picture is that in the end, COPD patients benefit from exercise training.

Capillary density is affected by exercise

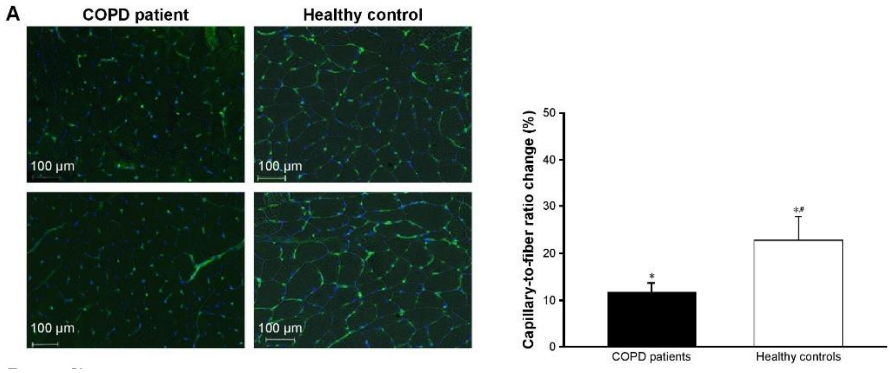


Figure 24. a) The capillaries in COPD and healthy subjects before and after exercise training intervention. b) The capillary to fiber ratio in COPD patients and healthy subjects after an exercise training intervention (Modified from: Gouzi et al, 2016).

In total, protein synthesis and expression seem to increase [70] although 24 hours after the first bout of exercise and for the next 4 – 8 weeks, muscle protein breakdown increased, however, the ratio of phosphorylated protein to total protein expression for all anabolic signaling proteins increased [70]. There is some controversy concerning myostatin levels; in some cases it was found to be stable [70], whereas some other researchers found myostatin levels to drop [4, 5]. However, MyoD (the master regulatory gene for skeletal muscle myogenesis) expression increased after 8 weeks of ET [4, 55, 70]. MyoD correlates with quadriceps force [37] and increased after exercise training only in non – cachectic COPD patients whereas in cachectic COPD patients it remained the same [38]. The protein breakdown that seems to increase, is speculated to be because of the increased catabolic mRNA in the face of protein turnover [70]. MRNA expression of IGF -I and MGF (factors that induce hypertrophy and regeneration) significantly increased [4, 11, 55]. Exercise training suspended the

activation of UbP pathway [4] and resistance training was found to increase the magnitude of post exercise phosphorylation [70].

Exercise training seems to benefit the muscles without stopping the inflammation/ inflammation markers [4, 55] and even more peculiarly, increases muscle mass without an apparent connection to protein expression levels [70].

Exercise training modalities

Although it is very clear that exercise training is a well embedded element of pulmonary rehabilitation for helping COPD patients restoring at least a part from their lost functionality and improve their quality of life, the exact variables of exercise training programs need to be clarified.

It is known for example that the skeletal muscles of the body are not homogeneously affected by COPD [71]. Muscles of the upper arms are less affected compared to lower limbs, distal muscles of a limb are more severely affected compared to the more proximal ones, movements of the arms above shoulder level unsupported are more difficult and provoke greater levels of dyspnea and hyperinflation presumably by making it harder for respiratory muscles to perform and by increasing residual capacity [72].

Lan et al, [14] and later on, Nyberg et al [11], both support that only high intensity exercise can increase V_{O2max} and improve cardiovascular and peripheral muscle function therefore high intensity exercise can be more beneficial.

Moreover, the sequence of exercise modalities need further clarifying. It was suggested that eight weeks of resistance training followed by eight weeks of endurance training were more efficient in the acquisition of peripheral muscle

endurance and patients achieved better resistance training load (by 30%) compared with patients following eight weeks of resistance and endurance training simultaneously [73]. However, overall improvements in exercise performance were similar. Further research is required to explore if indeed the sequence performing the exercise program plays an important role.

All the pulmonary rehabilitation programs ought to be in accordance with each patient's needs and the same goes for the exercise training programs as well. Resistance training can improve muscle strength [11], exercise capacity and quality of life [15] more than endurance programs, however the combination of both was proven to be more efficient [11,17]. There is a wide variety of resistance exercise (free weight lifting, resistance band exercises, dumbbell, lead ball, machine training for arms and legs, isokinetics, etc.) and even multi joint exercises or single joint [15] for the therapist to peak according to the needs and the desired outcome. Walking is preferable to cycling because it causes less quadriceps fatigue, while one-legged cycle training reduces the total metabolic demand and improves aerobic capacity compared with conventional two-legged training in stable COPD patients [15].

Some other issues are the "when" the pulmonary rehabilitation is supposed to start, if it is supposed to continue during an exacerbation or even during hospitalization. PR immediately after an exacerbation reduces hospital (re)admission and mortality [37]. A further study on this matter is necessary in order to draw to any conclusions, however, exercise training in the hospital after an exacerbation is implied to be able to prevent some of the muscle atrophy and impairment of quadriceps, and consequently, of the patient's functionality. Patients were shown to maintain some of the benefits even a month after [4].

Exercise training after an exacerbation is supposed to improve exercise capacity, quadriceps strength and reduce hospital admission and mortality [4].

During a training program, oxygen, may or may not be used. Oxygen was found to increase muscle energy metabolism and to correct hypoxemia [15]. The use of oxygen increased muscles' exercise tolerance and improves fatigue symptom. It also reduced hyperinflation and the feeling of dyspnea [15].

Exercise training parameters and methods

AN ET program is suggested that it should include at least 12 sessions and last minimum 6 – 8 weeks [17] or 8 – 12 weeks of progressive resistance training. In order for COPD patients to achieve improvement in exercise capacity and quality of life, 2 – 3 times of exercise per week is prerequisite [17], whilst the longer they follow the program, the better the results [4].

The American and European Respiratory Society suggest 20-60 minutes of endurance training per session, at 60% of maximal work rate (a score of 4-8 at Borg scale), 3-5 times a week and the American College of Sports Medicine suggests 8-12 repetitions with the appropriate load 60 – 70% of the maximum repetition(that is, the maximal load that can be moved only once over the full range of motion without compensatory movements) [11], and when the current workload can be performed for one to two repetitions over the desired target, a 2–10% increase in load is recommended [15] or an increase of sets, or a decrease in resting period between sets or exercises [11] at 2 – 3 times a week[14] 1 – 3 sets [11].

The session's length is supposed to last 1 to 4 hours [4] and preferably be of high intensity (>60% of maximal work rate, [11] or ≥80% [37]). Combination of resistance

training programs with endurance training programs are believed to be more effective in improving quadricep's muscle mass and cross-sectional area [4]. A combination of high intensity (≥80%) resistance and endurance training is suggested to be the best and only way to promote muscle hypertrophy in COPD [38]. Patients are encouraged to work out at home as well for better results [17].

As far as increasing endurance is concerned, the American College of Sports Medicine (ACSM) suggests light loads, many repetitions at least 12 to 15 and many sets, 2 – 3 times a week, at moderate to fast speed and rest periods 1 and 2 minutes [11]. The precise percentage of one maximum repetition (RM) is not mentioned by ACSM however Nyberg et al [11] suggest 40 – 65% RM for COPD patients.

Continuous or intermitted exercise?

There are two types of training; intermitted or similarly interval, and continuous. In intermitted exercise training, the higher load (80 – 120% peak capacity) is sustained for a certain period of time, typically 30 – 180 secs [4] or 30 – 120 secs [38], and interchanges with smaller bouts of 30 – 60 sec [4] or 30 – 120 sec [38] of lower intensity (50 – 80% peak capacity). Interval training is basically the same with the only difference that instead of smaller bouts of exercise, the patient stops and rest for that period of time. The main benefits are the same for both types of exercise [74]. In the continuous exercise programs moderate intensity exercise is used [75]. The interval or intermitted exercise training is supposed to allow greater loads with smaller amounts of dyspnea and fatigue [4, 76]. The outcomes are similar despite the fact that patients can endure higher intensity in intermitted/ interval exercise programs [17, 76] and in both cases, the patients gain every benefit from exercise training that has been described earlier, but

the interval and intermitted training exercise is better tolerated from the patients [77].

High intensity interval training (HIIT), was found to prevail over exercise training in general. Although they both increase proteins involved in translation machinery [38], HIIT reversed age related proteasome, promoted changes in transcription and translation regulation of muscle growth and mitochondrial pathways. In healthy adults, it enhanced more changes like aerobic capacity, mitochondrial respiration and lean body mass [38]. HIIT combined the benefits from endurance and resistance training in the skeletal muscles.

Interval training results in fewer symptoms and fewer unintended breaks. It reproduces the effects of continuous training. Interval and continuous training modes generally have comparable improvements in exercise capacity, health related quality of life and skeletal muscle adaptations immediately after training [79].

Other training methods

Tai chi a very popular, modern, training technic is a moderate intensity exercise for COPD patients gaining more benefits compared to conventional pulmonary rehabilitation programs [15]. It has also been suggested that Tai chi can be combined with a “standard” PR program [79]. The rationale behind using a method like Tai Chi is that cognitive and behavioural strategies are being applied during training [79]. This resembles the strategy of PR programs, where not only exercise training, but resetting the mind of the patient is required. Through an experience like Tai Chi training, the patient might be able to create different thinking patterns and cope with COPD symptoms better.

Yoga, also deriving from the east, is an appropriate form of exercise for COPD patients. It has been shown from as early as the 70' that patients practicing Yoga have benefitted and increased exercise tolerance [80]. Especially because of the combination of taking breaths while exercising [15], or possibly because of the better postures sustained [80], Yoga programs improve exercise capacity, fatigue tolerance and life quality, however, they should only be considered complementary to PR.

Great many types of exercise exist like pilates or water exercising that could prove to be beneficial for COPD patients, however further studies are required to reach to a conclusion. Many of these training modalities should be explored, because variety might be the answer for the increased dropout levels of pulmonary rehabilitation programs [53].

Neuromuscular Stimulation (NMES)

Throughout an exacerbation, during hospitalization in the intensive care unit, and in patients suffering from intense shortness of breath, obviously, it is very difficult for any patient to undertake any sort of exercise program. This leads to bed rest and extreme inactivity with all the known effects. Neuromuscular Electrical Stimulation (NMES) could prove to be a solution for the extensive muscle mass loss. In NMES, an electrical stimulation is put upon the skin of the targeted muscles inducing a muscle contraction [2, 15]. The intensity of the stimulation is subjective, according to what each patient can endure [81].

It has been found that NMES enhances the strength of the quadriceps muscle [2, 15, 81, 82], increases the cross sectional area of thigh muscle especially of type II [15] and decreases the loss of cross-sectional areas of type I [15] which leads to an increase in the ratio of type I/ type II muscle fibers and improves muscle

function [15, 17, 82]. It also increased exercise tolerance and capacity [17, 81]. The NMES was found to have little impact on the ventilation and the heart rate [15], however, it's contribution in the long run in the feeling of dyspnea is disputable; Zeng et al [15] concluded that there was no significant impact on the sensation of dyspnea while Passey et al [17] claim the use of NMES reduces dyspnea and improves lung function. This quality of NMES is making it a very useful tool because it might be used on patients in severe health condition to delay the muscle deconditioning, or even to invert the muscle loss or the loss of functionality regardless of the cooperation or the patient [15, 81]. However, the findings concerning quality of life are ambiguous. A meta – analysis that was conducted by Chen et al, [81] concluded that there was no significant difference in the health-related quality of life, whereas Maddocks et al [82] in a randomized control trial concluded that NMES was beneficial for increasing quality of life.

There is still great room for improvement in the NMES literature. A 3 – 5 times a week program, of 30 – 60 minutes of quadriceps electrical stimulation, for 4 – 6 weeks was suggested [2] but still all those variables need to be clarified and further investigated, like the ideal time of treatment or the best frequency and intensity, even the pathways through which NMES helps needs investigated. However, it can prove to be very helpful for enhancing the muscle mass and exercise tolerance in patients in the final stages of COPD or with patients that for any number of reasons have difficulty performing the standard exercise training programs, even in patients in intensive care unit or patients restricted to bad. It is portable, easy to use and has few side effects, which constitutes it as a valuable mean for improving the aforementioned variables.

Patient's attendance rates

A main issue in pulmonary rehabilitation is the attendance rates. The percentages of patients dropping out of PR programs or not even attending are high [83]. In U.K. less than 1.5% of patients that need to undertake PR attend such a program, while globally, it is estimated that this percentage rates between 8,3% - 49.6% of patients. Additionally, 9,7% - 31.8% of patients that undergo PR programs eventuallydrop out [53]. As was mentioned earlier, in order for the results of PR to last, one must not stop exercising.

One of the main problems mentioned by participants, was travel and transportation to the citation of the program. Other problems that reduced the possibility of attendance were living more than 36 miles away, or having to travel more than half an hour, or even if the timing that the PR program took place was inconvenient. Also, patients that did not trust or know well the doctor who recommended PR programs were less likely to attend as well as patients that could not understand the potential benefits from such a program [53]. Several other issues were mentioned like dislike of group activities, exacerbations, fear that regular exercise would deteriorate dyspnea, past negative experiences and more, and some demographic variables like married people were most likely to attend same as house owners or non-smokers [53].

Illnesses, comorbidities, travel and transport difficulties, smoking, depression, lack of perceived benefits, are common reason for participants in PR programs to quit. In addition to those that were the same as before, comes lack of support from family or friends, or living alone, and several other minor issues like the weather, disruption of the normal routine, being dependent on O_2, anxiety, quadriceps torque and more [53].

Amongst the most prominent features, smoking [53, 83] and depression [53, 84, 85] stand out. Depression, smoking and quadriceps strength were the variables used in models with the most success in predicting non – attendance or non – completion of PR programs [53].

KEY POINTS

- The etiology for developing COPD still remains unidentified. Smoking, is a major factor for developing COPD. However, not all smokers develop COPD, meaning that it is not the only cause and possibly works in combination with other factors, genetic and more.
- COPD is a systemic disease, affecting besides the lungs, also the muscles. Peripheral skeletal muscles are not evenly affected, while quadriceps muscle is considered to be representative for all skeletal muscles in COPD. Quadriceps “condition” is associated with mortality and morbidity in COPD patients. Poor clinical outcomes like exercise intolerance and premature mortality can be identified via assessment of limb muscle function.
- Muscles are affected not only in strength and endurance, but also structural changes occur. The density of the capillaries and the ratio of capillaries to fiber are reduced. Muscle fibers change; type II fibers and especially IIx increase at the expense of type I, reflecting the general characteristic of the loss of endurance at the cost of strength. It is very interesting and worthy of note, that this swift from muscle fiber type II to I, that occurs in the peripheral skeletal muscles, takes place in the respiratory muscles *inversely*, that is to say that muscle fibers type II swift to type I, and endurance is more prominent to strength in the respiratory muscles. The

same disease, to the same person, affects a system completely differently. This phenomenon clearly demonstrates that COPD affects muscles differently, or maybe even through different pathways, depending on the microenvironment, and perhaps on other parameters that still remain unknown.

- Lack of physical activity is a prominent feature of COPD probably because of ventilatory limitations, or the decrease in muscle strength and endurance. Exercise increases lean muscle tissue and strength in both COPD patients and healthy controls suggesting that inactivity and deconditioning are key factors underpinning muscle dysfunction in COPD. However, the effects of COPD, no matter how similar, are not to be confused with the effects of sedentarism, or aging. Sedentarism and aging cause muscle fibers to atrophy, not change their oxidative profile. The phenotype of myosin's heavy chains that change in COPD stays the same in healthy subjects with similar activity levels. To further support this argument, abnormalities in the muscle structure took place before even patients became aware they had COPD. Furthermore, no correlation was found between physical activity levels and lung impairment.
- Because the exact cause of COPD is yet unknown, the only way to help patients is by treating the symptoms. Since the symptoms are multidimensional so should the treatment. Pulmonary rehabilitation programs consist of many specialties (doctors, nutritionists, psycologists, ergophysiologists, physiotherapists etc.) in order to cover as many of the needs of the patients as possible. The main purpose of these programs are to *educate* the patients to manage COPD, and usually this involves

changing his / her perspectives. For example, depression and smoking are considered features linked to quitting or not even participating in PR programs, therefore, a holistic approach is necessary.

- The cornerstone of any pulmonary program is exercise training. Exercise training has been proven to increase lean mass, strength, cross sectional areas and capillarization in COPD, as well as strength, endurance, exercise tolerance and fatigue resistance. Exercise training includes resistance training and endurance training. The combination of the two was found to be more efficient. A program starting with only resistance training and then followed by endurance training was proven to be better tolerated by the patients but with similar results as doing endurance and resistance training at the same time. Interval training is better tolerated and has the same results as continuous exercise training. Any exercise training program should last at least 6 – 8 weeks for definite results but for the results to last more than 6 – 12 months, the patient should continue exercising. All patients should be encouraged to work out on their own as well.
- Alternative modalities like NMES have emerged and are offering solutions for critical patients, hospitalized patients or patients that for any number of reasons are not physically capable for participating in exercise training. NMES was found to increase muscle strength, with minimum, or not at all, burden to the cardiopulmonary system.
- Exercise training is starting to expand beyond the strict programs on cycloergometers or treadmills. Tai Chi, Yoga, outdoors walking, offer a variety of options for patients to choose a type of exercise closer to their

taste and perhaps this will increase attendance to PR and decrease drop out.

- Further investigation is required in order to define the exact mechanisms through which COPD affects the muscles. As Maltais et al, [4] aptly point out, strategies for early detection and coping of this disease are required. ET, might be proven to improve exercise capacity, health-related quality of life, as well as to relieve dyspnea and fatigue, however, there is room for improvement, and clarification of the variables governing those programs.

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APPENDIX

Appendix 1. St. George's Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:
Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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UK/ English (original) version 1

continued…

St. George's Respiratory Questionnaire

PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) *one box for each question*:

	most days	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

☐ more than 3 attacks

☐ 3 attacks

☐ 2 attacks

☐ 1 attack

☐ no attacks

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

☐ a week or more

☐ 3 or more days

☐ 1 or 2 days

☐ less than a day

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

☐ No good days

☐ 1 or 2 good days

☐ 3 or 4 good days

☐ nearly every day is

good ☐ every day is

good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

No ☐

Yes ☐

continued…

St. George's Respiratory Questionnaire

PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire

PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire

PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in ***each box*** that applies to you ***because of your breathing***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***:

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

UK/ English (original) version